The use of assisted autogenic drainage in children with acute and chronic respiratory disease.

By

Lieselotte Corten

CRTLIE001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

DOCTOR OF PHILOSOPHY

in the Department of Health and Rehabilitation Sciences

Division of Physiotherapy

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Supervisors:

Professor B. M. Morrow

Professor J. Jelsma

March 2017

PLAGIARISM DECLARATION

I, *Lieselotte Corten*, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and have used the *American Medical Association* system of referencing. I declare that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

……

Lieselotte Corten

13 March 2017

……

(Date)

ACKNOWLEDGMENTS

The road towards the finalisation of this thesis has been a real adventure. I would like to compare it to the legend of my home town 'Antwerp', where a soldier (me) explored new territory (South Africa) to concquer and expand his land (my knowledge). To be able to do this, he had to cross a river (for me, I travelled to the other side of the world) which was guarded by a giant (PhD) who only let you pass when you sacrificed a hand. The soldier was not going to let the giant cut of his hand, so he battled the giant. He won by cutting of the giant's hand and threw it away. I also had to concquer many obstacles during my great PhD adventure, but luckily I did not have to do this alone. Therefore I would like to take this opportunity to thank everyone who helped me accomplish this adventure. To anyone who I might have forgotten, please do not feel offended, your help has been truly appreciated.

First of all I would like to thank my family for their unconditional support and love, giving me the opportunity to undertake this journey.

Secondly I would like to take the opportunity to thank my supervisors: Prof. Brenda Morrow, for your profound expertise in the field, your endless patience and your help as CF clinic physiotherapist, explaining and teaching the interventions during the CF study. And I also thank Prof. Jennifer Jelsma, for the hours of help with statistical analyses and your expertise in PhD writing. Both of you have shown tremendous confidence in me, which I truly appreciated.

I would also like to express my gratitude to Ms Anri Human for her help as research assistant at Dr George Mukhare Academic Hospital, but most of all for the newly found friendship; and to Dr. Gillian Ferguson for her friendship, enduring my endless complaining and wise words throughout the process.

Of course I also have to thank the Physiotherapy Departments of Red Cross War Memorial Children's Hospital and Dr George Mukhari Academic Hospital for performing all the intervention in the pneumonia research; Mr Sameer Rahim, head of the Physiotherapy Department at Red Cross, for his insight in the working mechanism of the hospital and suggested amendments to the protocol; and Ms Tasneem Ebrahim for the hours, days, weeks, and months in medical records. To all the participants and their parents, I would like to say thank you for being part of the research, without you there would not have been anything to report on.

Finally a huge thank you to my fiancée, Michael, for his endless support throughout these past years. Enduring my mood swings, sharing all the ups and downs, happiness and tears.

Funding: Without funding from the Margaret Roper Sholarship (Division of Physiotherapy, UCT), the Department of Paediatrics and Child Health research award (UCT), and NRF funding from Prof. Jelsma's research fund, this PhD project would not have been possible.

ABSTRACT

Background: Respiratory problems, both acute and chronic, remain an important cause of disease burden for children worldwide. Airway clearance techniques, as part of the management of these conditions, might influence the course of the disease thereby reducing this burden.

Objective: This PhD thesis aimed to explore the epidemiology and management of children with acute respiratory diseases admitted to a paediatric hospital in Cape Town, South Africa; and to determine the usefulness and safety of assisted autogenic drainage in children with an acute (pneumonia) or chronic (cystic fibrosis) respiratory disease. In order to do this, several linked studies were undertaken including a retrospective folder review, two systematic reviews and two pragmatic randomised controlled trials.

Descriptive retrospective folder review:

Objectives: The objectives of this study were to identify the nature and magnitude of the problem of children hospitalised with lower respiratory tract infections at a tertiary paediatric hospital; and to investigate the role of airway clearance therapy in this context.

Methods: A retrospective descriptive research study was conducted using routinely collected data related to the characteristics, management and outcomes of children admitted with acute respiratory disease at the primary research site over six months.

Results: A total of 1357 folders were screened, of which 1208 were eligible for inclusion, accounting for 1440 hospitalisations (including readmissions) between January and June 2015. The median age of the included children was 7.6 months (IQR 2.8-19.0). The majority of children were hospitalised primarily for bronchiolitis (n=662, 46.0%), followed by pneumonia (n=525, 36.5%), unspecified lower respiratory tract infection (n=144, 10.0%), and other diseases (n=3, 0.2%). No primary diagnosis was available for 106 hospitalisations (7.4%), in whom nosocomial infection was considered likely by the researchers.

Comorbidities were present in 52.6% of the patients during at least one of their hospitalisations. The median (IQR) duration of hospitalisation was 2.3 (1.5-5.0) days. The duration of hospitalisation was longest in children hospitalised for presumed nosocomial infections, followed by pneumonia. A longer hospital length of stay was associated with mechanical ventilation, acute comorbidity or

having received airway clearance therapy. The mortality rate was 0.7%, with children hospitalised for presumed nosocomial infections or pneumonia at higher risk for dying.

Airway clearance therapy was given during 83 hospitalisations (5.8%). Four hospitalisations were excluded from this analysis as these children were included in the intervention arm of the pneumonia research study, which could have introduced bias in reporting standard airway clearance therapy practice. Vibrations were the technique most often performed (in 83.1% of the cases who received airway clearance therapy), followed by modified postural drainage (55.4%), percussions/clapping (38.6%), deep breathing exercises (25.3%), active gross motor exercises (20.5%), active cycle of breathing technique (13.3%), thoracic compressions (8.4%), huffing/forced expiratory technique (7.2%), bubble positive expiratory pressure technique (7.2%), assisted autogenic drainage (6.0%), oscillating positive expiratory pressure technique/flutter (3.6%), blowing bubbles (3.6%), and chest wall shaking (1.2%). Treatments were performed daily or bidaily for a median duration of 3.0 days (IQR 1.0-6.0). Children with presumed nosocomial infections or pneumonia, isolated bacterial organisms and chronic comorbidities were more likely to receive airway clearance therapy. Desaturation was reported in six children, three desaturated to levels between 85 and 89% and three below 85%; and one child developed lung collapse an hour post treatment. No other adverse events were reported.

Conclusion: This study showed that a relatively small proportion of children received airway clearance therapy. The majority of children who received airway clearance therapy were hospitalised for pneumonia or acquired an infection while hospitalised for other disorders (presumed nosocomial infections. Conventional airway clearance therapy was used most often, most likely due to the young age of the hospitalised children, limiting the choice of airway clearance techniques. No major adverse events were reported, besides self-limiting desaturation in six children during various techniques; and lung collapse an hour post treatment, unlikely related to airway clearance therapy given the time delay. This novel research in a South African tertiary paediatric hospital provides a better insight in the standard airway clearance therapy used in children with acute respiratory disease. This study highlights the need for research on the use of airway clearance techniques in children with lower respiratory tract infections other than bronchiolitis, and specifically in children with comorbidities, which were highly prevalent in this population group.

Systematic reviews:

Two systematic reviews were conducted; one on airway clearance therapy in children hospitalised with pneumonia and one on autogenic drainage and assisted autogenic drainage in children with

cystic fibrosis; to determine current supportive evidence related to the safety and efficacy of these interventions.

Pneumonia systematic review

Methods: Pubmed, Medline, the Cochrane library, CINAHL, PEDro and Africa-wide information were searched for randomised controlled trials and quasi-randomised controlled trials on airway clearance therapy in children under the age of 18 years hospitalised with acute pneumonia. Further, the reference lists of relevant articles were screened, together with clinicaltrials.gov and pactr.org for ongoing studies.

Results: In total, 202 articles with duplicates were identified. After removal of duplicates, 129 articles remained for further investigation. Seven full text articles were screened, of which two met the inclusion criteria of this review. The two included randomised controlled trials reported on a total of 177 participants between 29 days and 12 years of age. One study compared standard treatment, consisting of antibiotic treatment, fluid therapy and oxygen therapy when needed, to standard treatment with supplementary airway clearance therapy; while the other study compared recommended non-mandatory lateral positioning, cough and diaphragmatic breathing to the use of conventional airway clearance therapy and positive expiratory pressure therapy. One study had an overall low risk of bias, while the other study had a low or unclear risk of bias. No meta-analysis could be performed as data could not able pooled due to the differences in study characteristics and outcome measures. Narrative analysis revealed no differences between the control and intervention group for this review's outcome measures, however, one study reported a longer duration of coughing ($p=0.04$) and rhonchi ($p=0.03$) in the intervention group.

Conclusion: Due to the limited number of included articles and different presentation of outcome measures, it was impossible to reject or accept airway clearance therapy as either an effective or harmful treatment option in children hospitalised with pneumonia.

Cystic fibrosis systematic review

Methods: Pubmed, Medline, CINAHL, PEDro, the Cochrane library, Africa-Wide Information and clinicaltrials.gov were searched; together with the reference lists of relevant articles. Randomised controlled trials, quasi-randomised controlled trials and randomised cross-over trials on autogenic drainage and assisted autogenic drainage in children under the age of 18 years diagnosed with cystic fibrosis were included.

Results: A total of 157 articles with duplicates were identified. After removal of duplicates, 126 references were investigated. Eight abstracts were found potentially relevant and underwent full text review. Seven randomised cross-over trials met this review's inclusion criteria, comparing autogenic drainage with another form of airway clearance therapy. No studies evaluating assisted autogenic drainage were eligible for inclusion. A total of 129 participants (aged four to 42 years) were evaluated in these studies, of which only 47 were younger than 18 years of age. Only one study clearly indicated separate results for the different cross-over periods of the study. Hence we were unable to pool the data in a meta-analysis. This systematic review revealed a weak positive influence of autogenic drainage compared to postural drainage in one paediatric randomised cross-over trial, based on one outcome measure, the Huang score. Furthermore, a tendency towards fewer hospital admissions during one year favouring autogenic drainage compared to postural drainage was seen. This randomised cross-over trial also reported a reluctance of those assigned to the autogenic drainage arm of the study to cross over to the control (postural drainage) intervention, suggesting patient preference for the former intervention. I was unable to identify any true randomised controlled trials evaluating autogenic drainage in the cystic fibrosis population.

Conclusion: Although one study reported a small benefit of autogenic drainage compared to postural drainage; the lack of paediatric-specific randomised controlled trials, the small sample sizes included in the cross-over trials and the unclear risk of bias of most of the included studies made it impossible to determine the efficacy of autogenic drainage in children with cystic fibrosis. Implementation of paediatric-specific randomised controlled trials with adequate sample sizes, appropriate clinical outcome measures and analysis of adverse effects within this field of research is recommended.

Conclusions arising from systematic reviews

No high-level research studies investigating assisted autogenic drainage could be sourced for either systematic review, highlighting the need for well-constructed randomised controlled trials to evaluate the impact of this technique in children with both acute and chronic respiratory disease.

The impact of assisted autogenic drainage in infants and young children hospitalised with pneumonia:

In response to the identified need for further evidence to support the use of assisted autogenic drainage in children with pneumonia, a pragmatic, single-blind, randomised controlled trial was performed evaluating the effects of assisted autogenic drainage as an add-on intervention to standard care in a convenience sample of children admitted to two tertiary hospitals in South Africa, with pneumonia.

Methods: Clinically stable children hospitalised with a clinical diagnosis and/or radiological confirmation of community- or hospital acquired pneumonia, between the ages of one month and eight years, were included in the study. Exclusion criteria were: bronchiolitis; *Pneumocystis jirovecii* pneumonia; active tuberculosis; any cardiac or respiratory comorbidities; recent history (<six months) of pneumothorax or thoracic/abdominal surgery; increased intracranial pressure; pleural effusion with or without intercostal drain; chest deformities; any condition for which mobilisation out of bed was contraindicated; osteoporosis; very premature (≤30 weeks) birth; hospitalised for less than two days; and marked respiratory distress and/or hypoxia. Children removed from mechanical ventilation for more than four days prior to recruitment were also ineligible for the study (for baseline data purposes). The primary outcome was duration of hospitalisation expressed in days.

Results: A total of 896 children were screened for inclusion in the trial. Of these, 862 children were excluded owing to comorbid factors listed in the exclusion criteria. Ultimately, 29 children, median (IQR) age 3.50 (1.47 – 9.57) months, were included in the study. There were no significant differences in pre-specified primary and secondary outcome measures between the intervention and control group at conclusion of the study. However, there was a trend towards shorter duration of hospitalisation in the intervention group compared to the control group on Kaplan-Meier analysis ($p=0.06$), with medium effect size ($d=0.54$). Further, there was a significant decrease in respiratory rate adjusted for age within the intervention group, from the time of recruitment to discharge. Although a statistically significant increase in respiratory rate was found immediately after treatment (from 45 to 46 bpm, $p=0.03$), the clinical relevance of one breath per minute is questionable and the values returned to baseline one hour post-intervention. Finally, this study also showed a shorter duration of hospitalisation for children with unknown compared to viral and bacterial aetiology in the intervention group.

Conclusion: Although there was a trend towards shorter duration of hospitalisation in the intervention group, assisted autogenic drainage was not found to be effective for children with

uncomplicated pneumonia. However, the study was limited by the small sample size, owing to the high exclusion rate. This study is the first of its kind to prospectively investigate the use of assisted autogenic drainage in children with pneumonia. The study highlights the need for future research towards the effectiveness and efficacy of assisted autogenic drainage in children hospitalised with pneumonia and underlying comorbid conditions.

The impact of assisted autogenic drainage in children with cystic fibrosis, a pilot study:

A second pragmatic, single-blind, randomised controlled pilot study was performed evaluating the feasibility of a randomised controlled trial on the effects of assisted autogenic drainage compared to standard airway clearance therapy. A convenience sample of children with cystic fibrosis, attending the outpatient clinic at a tertiary paediatric hospital in Cape Town, South Africa, were enrolled.

Methods: Children between the age of one and eight years of age, with a proven diagnosis of cystic fibrosis, confirmed by sweat testing or genotype analysis, were eligible for the study. Children were excluded if they were awaiting lung transplantation, had severe scoliosis or kyphosis, osteoporosis, recent pneumothorax, thoracic or abdominal surgery in the preceding six months, emphysema or active sarcoidosis, very prematurely born less than 30 weeks of gestation, on TB medication, uncontrolled/untreated asthma, or known to be non-compliant to physiotherapy treatment prior to recruitment. The primary outcome measures were number of hospitalisations and number of pulmonary exacerbations during the one year study.

Results: A total of 37 children were screened for inclusion, of which 16 were eligible and were enrolled in the study (median age 5.75 years, IQR 4.27-6.28). No significant between-group differences were found for a number of primary and secondary outcome measures, however the number of exacerbations during one year revealed a medium effect size (d=0.55) and the number of days receiving antibiotic therapy over one year revealed a small to medium effect size (d=0.48) in favour of the intervention group. Within the intervention group, trends towards improvement in cystic fibrosis clinical score (subjective subtotal and total scores); and health related quality of life visual analogue scale were observed, with large effect sizes (d= 1.07, d= 0.87, and d= 0.86 respectively). Adherence to bidaily therapy was generally poor during the study period and none of the participants in the intervention group solely performed assisted autogenic drainage as per pre-set methodology.

Conclusion: This pilot study revealed great insight in the applicability of the protocol for a true randomised controlled trial. Conclusions cannot be made regarding the effectiveness and safety of

assisted autogenic drainage in children with cystic fibrosis due to the lack of adherence to the prescribed intervention and small sample size. The very poor adherence related to airway clearance therapy in this population is clearly a major concern. Further research is needed to investigate the efficacy and effectiveness of assisted autogenic drainage in children of this population and to tackle issues related to treatment adherence. Assisted autogenic drainage might be a useful technique to add to the airway clearance 'toolbox' for young children with cystic fibrosis as no adverse events were reported and a small to medium effect size for number of exacerbations and days on antibiotic therapy was found, benefiting the intervention group. This is the first controlled clinical study on the use of assisted autogenic drainage in children with cystic fibrosis.

Conclusion:

This thesis is a stepping stone, which will add to the currently small body of knowledge on the use of assisted autogenic drainage in children with acute and chronic respiratory conditions. Owing to the small sample sizes included in the studies presented in this thesis, no definite conclusions can be made regarding the effectiveness and safety of assisted autogenic drainage in children with either pneumonia or cystic fibrosis. Therefore, assisted autogenic drainage cannot currently be recommended as standard clinical practice in children with either of these conditions.

It is recommended that more research needs to be conducted using larger sample sizes in the same population groups, as small benefits of assisted autogenic drainage were noted. Multi-site studies are recommended to increase sample size. In children hospitalised with pneumonia a trend towards shorter duration of hospitalisations with a medium effect size was observed, whilst in children with cystic fibrosis, there was a small to medium effect size in reduced number of exacerbations and days on antibiotic treatment in the intervention group. No adverse events or complications were reported, suggesting safety of this technique. Research investigating the use of assisted autogenic drainage in children hospitalised with pneumonia with underlying comorbid conditions is also warranted.

Notwithstanding the limitations of these studies, the results of this thesis are novel, and will contribute to the global body of knowledge in improving our understanding of the utility of different airway clearance techniques in young children with acute or chronic pulmonary disease.

CONTENT

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAD	Assisted Autogenic Drainage
ACBT	Active Cycle of Breathing Technique
ACT	Airway Clearance Therapy
ACTs	Airway Clearance Techniques
AD	Autogenic Drainage
ARV	Anti-retroviral therapy
ASL	Airway Surface Liquid
ATS	American Thoracic Society
Bpm	breaths/beats per minute
CAP	Community Acquired Pneumonia
CF	Cystic Fibrosis
CFCS	Cystic Fibrosis Clinical Score
CFTR	Cystic Fibrosis Transmembrane Regulator
CI	Confidence Interval
Cl^-	Chloride
CP	Cerebral Palsy
CPAP	Continuous Positive Airway Pressure
EQ-5D-Y	EuroQol 5 Dimensions for Youth
EPP	Equal Pressure Point
ERS	European Respiratory Society
FET	Forced Expiratory Therapy
FEF_{25-75}	Forced Expiratory Flow at 25 and 75%
FEV_1	Forced Expiratory Volume in 1 second

FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GORD	Gastro-Oesophageal Reflux Disease
Hib	Haemophilus influenza type b
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HREC	Human Research Ethic Committee
HRQOL	Health Related Quality Of Life
IQR	Inter-Quartile Range
LRTI	Lower Respiratory Tract Infection
MABC	Movement Assessment Battery for Children
MCC	Mucociliary Clearance
MPD	Modified Postural Drainage
Na^+	Sodium
NMD	Neuro-Muscular Disorder
NS	Not significant
OR	Odds Ratio
PD	Postural Drainage
PDMS	Peabody Developmental Motor Scale
PEF	Peak Expiratory Flow
PEG	Percutaneous Endoscopic Gastrostomy
PEP	Positive Expiratory Pressure
PJP	Pneumocystis Jirovecii pneumonia
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis

RCT	Randomised Controlled Trial
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RV	Residual Volume
SaO_2	Arterial Oxygen Saturation
SpO_2	Transcutaneous Oxygen Saturation
SD	Standard Deviation
TB	Tuberculosis
UDCA	Ursodeoxycholic acid
URTI	Upper Respiratory Tract Infection
TLC	Total Lung Capacity
VC	Vital Capacity

Chapter 1. INTRODUCTION AND THESIS OUTLINE

1.1 BACKGROUND

Respiratory problems, both acute and chronic, remain an important disease burden worldwide;[1] impacting the child, the healthcare system and the community negatively.[2] Pneumonia in particular, an acute lower respiratory tract infection (LRTI), persists as one of the most common causes of death in children younger than five years of age;[3–5] with an incidence rate of 0.27 per child-year in Africa, the highest globally.[6] As children with pneumonia are hospitalised for a significantly longer period of time than children admitted with other LRTIs within the context of this thesis (see Chapter 5), and length of hospital stay determines the cost of treatment,[7] these patients are at risk of increased financial and psychosocial cost of care, stressing the family and the health care system.

It is important to focus on ways to reduce the burden of respiratory disease on the patient,[(1)] which will hopefully reduce the burden on the family, community and healthcare system. It is however, first necessary to quantify this burden, at least within an acute hospital setting. Existing epidemiological research in the South African context has focussed mainly on children with Human Immunodeficiency Virus (HIV), and the aetiology and length of hospital stay in children admitted for treatment of LRTI.[8–10] The guidelines for the management of children with community acquired pneumonia (CAP) in South Africa do not include recommendations regarding the use of airway clearance therapy (ACT) in this population,[11] and there have been no investigations into the clinical application of this modality in hospitalised South African children with pneumonia. Therefore, it is necessary to interrogate current airway clearance practice before introducing new treatment modalities.

Chronic disorders are also burdensome on the patient, their family, and the healthcare system. Cystic fibrosis (CF), is a relatively common inherited chronic, life-limiting, multisystem disorder affecting the respiratory system.[12–16] The management of patients with CF relies on a multidisciplinary approach, including treatment for all exocrine systems in the body. This necessitates adherence to a complex

[(1)] Burden of disease= the impact of a disease, expressed as the time (in years) lost due to the morbidity and/or mortality of the disease. The burden of disease is expressed as disability-adjusted life-years.[466]

treatment regimen, consisting of a number of oral and inhaled medications (with intravenous therapy as required), nutritional supplementation, exercise and regular ACT.[17–20]

The burden of potentially spending more than an hour per day on the management of the disorder may considerably reduce the quality of life of the patient and his/her family.[21,22] Furthermore, these patients need regular follow up at a specialist CF clinic; and all these interventions come with a price, burdening the health care system and family finances even further.[23]

ACT, as part of the management of both acute and chronic respiratory conditions, might influence the course of the disease and hopefully reduce the associated burden. Many airway clearance techniques (ACTs) have been investigated in different patient population groups and a detailed overview of the different ACTs will be presented in Chapter 2. However, as young children cannot perform the more independent modern ACTs,[24] physiotherapists usually use conventional ACTs, such as (modified) postural drainage ((M)PD) in this age group.[25] It is important to investigate the possibilities of using a more modern, time efficient technique in this young age group. Assisted autogenic drainage (AAD), has been suggested as an ACT for use in children with CF.[25] This technique uses the principles of autogenic drainage (AD), however, it is performed by the physiotherapist or caregiver without cooperation or with only minimal cooperation from the child. AD and AAD incorporate breathing at different lung volumes to loosen, collect and evacuate secretions from the lungs.[26,27] During AAD, these different lung volumes are achieved by applying gentle pressure on the child's thorax during inspiration.[28] A complete description of the technique can be found in Chapter 2. As the efficacy of this technique has never been previously investigated, a well-designed research study is required. Therefore, this PhD thesis investigated the use of AAD in both an acute (pneumonia) and chronic (CF) respiratory condition.

1.2 GENERAL AIM AND RESEARCH QUESTIONS OF THE THESIS

This thesis, consisting of several studies, aimed to investigate the usefulness of ACTs, specifically AAD, in children with either acute pneumonia or CF.

The specific research questions addressed in this thesis were:

1) What is the international body of knowledge on the use of ACT for children hospitalised with acute pneumonia?
2) In children hospitalised for a LRTI at a tertiary paediatric hospital in South Africa:
   - What is the patient profile of children who receive ACT compared to those who do not receive ACT?

- What is the nature and frequency of ACT?
- What are predictive factors for receiving ACT?
- Are adverse events reported during ACT and how frequently did they occur?
- Can these adverse events be predicted?

3) Is the use of AAD, as an adjunct to standard nursing care, beneficial for infants and young children admitted to hospital with acute, uncomplicated pneumonia?
4) What is the international body of knowledge on the use of AD and AAD in children with CF?
5) Is the designed research protocol feasible to identify the effect of AAD compared to other ACTs in the home management of children with CF?

1.3 JUSTIFICATION

As mentioned above, both acute and chronic respiratory disorders impose substantial burdens on the patients, their families and the healthcare system. ACT has shown positive effects on mucus clearance in children with CF; however, there is currently insufficient evidence on the use of ACT in children hospitalised with pneumonia.

Damage to the airways and development of chronic lung disease (e.g. bronchiectasis) might occur if pneumonia is not treated appropriately. It is important to promote quick resolution of infection in order to prevent harmful sequelae. ACT is used in clinical practice to facilitate mucus clearance, with potential benefits to pulmonary function, symptoms and disease resolution. By accelerating resolution of the infection, duration of hospital stay might be reduced which would benefit the patient, family and healthcare system; as well as reducing the risk of acquiring additional nosocomial infections and minimising the risk of long-term sequelae. Furthermore, ACT may prevent respiratory complications, such as atelectasis.

Research on the use of ACT in children with CF has shown the importance of the use of ACT as part of the standard management of these children. Conventional ACTs and some modern ACTs have been shown to be effective in older children and adults without superiority of one technique over the other (see Chapter 7). Research on AD in children with CF has also shown small benefits, however, most studies included small sample sizes and often subjective outcome measures.

Unfortunately, in young children, physiotherapists are limited in the number of techniques available. AAD, a passive/assisted technique could be useful in the treatment of young children and is assumed to have few adverse events. However, no research has investigated the efficacy and safety of this

technique. Therefore it is important to provide more evidence-based information on the use of AAD in both acute and chronic respiratory conditions.

1.4 RESEARCH SETTING

The research studies conducted in this PhD thesis took place in two tertiary hospitals and an outpatient clinic of a tertiary hospital in South Africa. Although South Africa is classified as an upper middle-income country,[29,30] it still faces many challenges of a developing country. The overall post-apartheid economy has improved, but the socio-economic status of many people living in South Africa is still low, with a widening of the gap between rich and poor.[31] The country's healthcare system, based on the principles of primary health care, provides free primary care for everyone.[32,33] However, the system is divided into a public and private healthcare sector, with the private sector providing services to approximately 25.3% of the population.[33] The public sector therefore has to cover the majority of the population. With 0.8 physicians per 1000 people, South African doctors are struggling to provide appropriate quality health care for all.[32,34] Primary health care in South Africa is provided by local clinics. District hospitals provide the second line of health care, and finally tertiary hospitals provide specialist interventions and are often linked to an academic institution.

The current studies aimed to reach as many children as possible, by targeting public tertiary hospitals to identify children hospitalised with pneumonia, and a multidisciplinary outpatient clinic of a tertiary hospital specialised in treating children with CF.

1.5 THESIS STRUCTURE

The research questions listed above will be addressed in nine chapters:

A general background chapter, Chapter 2, will first focus on the development of the lungs and the difference in anatomy and physiology of the respiratory system between children and adults, as this has direct bearing on the presentation and approach to ACT in young children. As the incidence and impact of respiratory disease is highest in younger children,[3] the focus of this thesis is mainly on this age group. Thereafter, airway clearance mechanisms and the different ACTs currently available for the management of respiratory conditions are described.

Chapter 3 provides a background to the research on pneumonia, explaining the impact of the disease, the different aetiologies and underlying pathophysiology, the long term sequelae, the impact on health related quality of life (HRQOL) and the management of the disease, including ACT.

Chapter 4 consists of a systematic review on the use of ACTs in children with acute pneumonia. This chapter will therefore address the first research question of this thesis. In the previous chapter, ACT in this population was described; and several studies on the use ACT in children with pneumonia were identified. However, the majority of these studies included small sample sizes, and the study designs lacked rigour. This systematic review therefore aimed to synthesise randomised controlled trials (RCTs) to determine the effect of different ACTs compared to no physiotherapy, sham physiotherapy or alternative therapy in children hospitalised with acute pneumonia.

Children with pneumonia may receive ACT in clinical practice; however, there is little documentation available on the aetiology of disease; prescription, frequency and nature of ACTs used; and length of hospital stay, in the South African context. Most importantly, there is no published data regarding adverse events that may be associated with ACTs in children with pneumonia. Therefore, Chapter 5 presents a descriptive study aimed at gaining a better understanding of the role ACT plays in the management of children with LRTIs within a specialised tertiary hospital in the Western Cape region of South Africa.

As the need for a well-designed randomised controlled trial on the use of AAD in children with pneumonia became clear, Chapter 6 aimed to formulate an answer to research question three, by establishing whether standard nursing care with additional AAD is more effective than standard nursing care alone, in the management of children hospitalised with community or hospital acquired pneumonia.

In the following chapters, the focus shifts towards the chronic respiratory condition under investigation, CF. Chapter 7 provides a narrative background literature review; explaining CF and its impact on the body, the incidence of the disease, the impact on HRQOL and the management of the condition, including both medical and ACT.

Several systematic reviews have been published comparing ACTs to no physiotherapy, and one specific ACT with other ACTs, however no systematic reviews have been published on the use of AD and AAD. The systematic review presented in Chapter 8 therefore pools the body of knowledge and investigates the effects of AD and AAD, compared to no physiotherapy, other types of ACTs or sham physiotherapy in children with CF (research question four).

This systematic review (Chapter 8) revealed that there was no high-level published research on the use of AAD in children with CF, despite this technique being increasingly used in clinical practice. Therefore, a pilot RCT was conducted to establish feasibility of the designed research protocol in

determining whether AAD is more effective than standard ACT when used as a home program in children with CF. This trial is described in Chapter 9.

Finally, the concluding Chapter 10 summarises the thesis findings and provides recommendations for clinical practice and future research.

An overview of the thesis structure with the different chapters is presented in Figure 1-1.

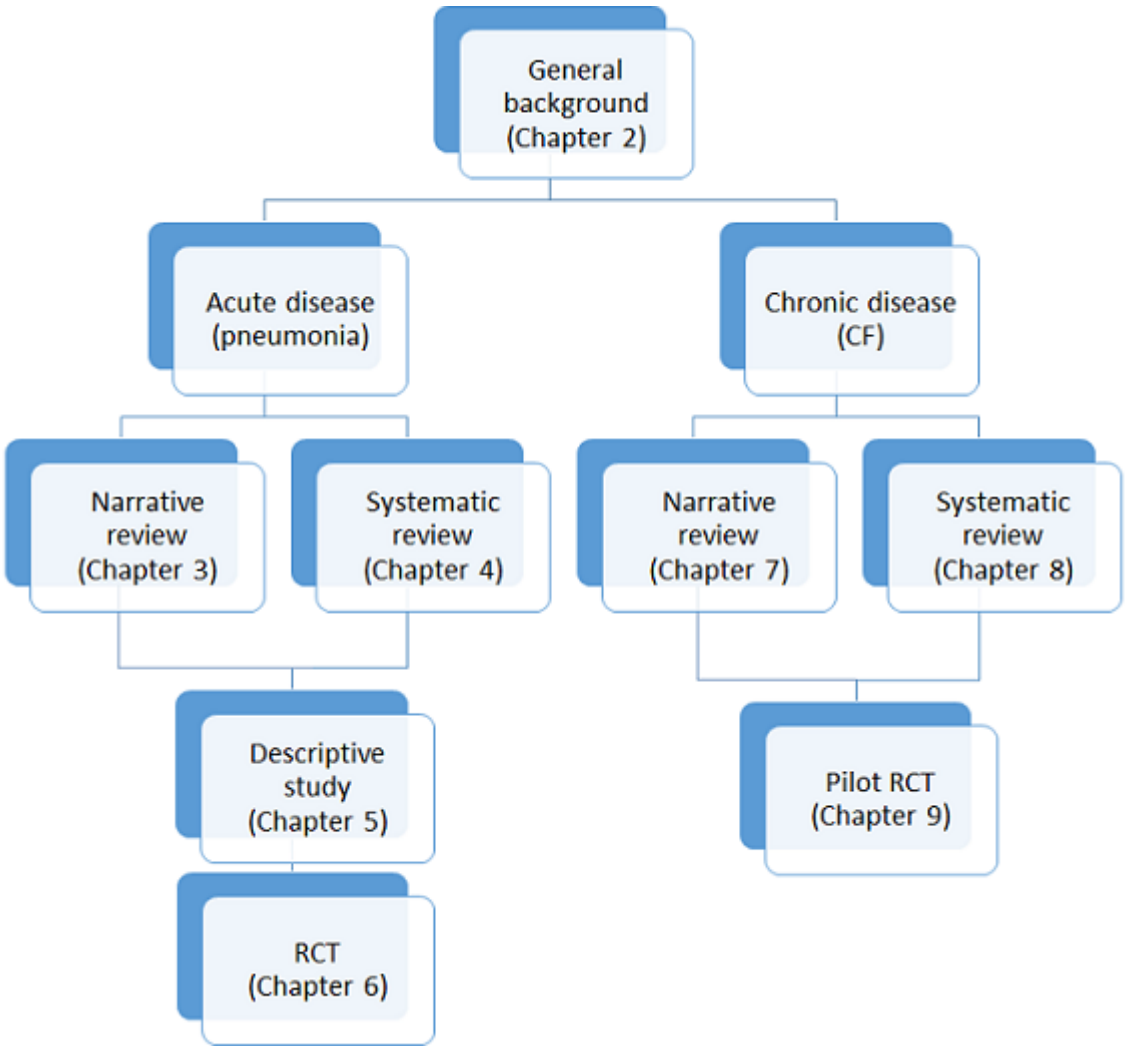


Figure 1-1. Outline of thesis structure

Chapter 2. GENERAL BACKGROUND

2.1 DEVELOPMENT OF THE LUNGS AND IMPACT OF PREMATURITY

Lung development starts from the moment of conception, continues throughout the prenatal period and persists post-natally.[35] Although, lungs of the foetus have a liquid production function and not a gas exchange function, the development of the lungs is nearly completed when the child is born at term.[36] This is to ensure survival of the new-born baby, as the lungs need to take over the role of gas exchange from the placenta once the umbilical cord is cut.[36,37]

After conception, the cells divide into three germinal layers: the endoderm, mesoderm and ectoderm.[37,38] The respiratory system derives from the endodermal layer.[37,38] However, innervation of the respiratory system originates from the ectodermal layer, whereas the muscles supporting the respiratory system arise from the mesoderm.[37] The development of the lungs commences in the embryonic period with the development of the respiratory primordium.[37,38] During the embryonic period, separation of the foregut into the trachea and the oesophagus; the two main bronchi and the segments of the different lung lobes (the lung buds) become visible.[39]

Maturation of the lungs occurs in four different phases:

1) In the pseudo-glandular phase, the bronchial tree to the terminal bronchiole airways are partially formed.[37,39] In this phase, ciliated epithelial cells and goblet cells appear.[37,40] At the same time; in the bronchial wall; bronchial glands, cartilage, and smooth muscles cells emerge.[35–37] Further, the development of the diaphragm is complete.[37]
2) In the canalicular phase, the respiratory bronchioles and alveolar ducts are formed.[35,37,39] Vascularisation of the lungs and formation of primitive alveoli or terminal saccules take place, which enables the gas exchange function of the lungs.[35,37,39]. Furthermore, type I and II pneumocytes begin to develop.[37] Type I pneumocytes are epithelial cells, forming the inside lining of the terminal sacs.[35,37,39] The type II pneumocytes are secretory cells, responsible for surfactant production.[35,37,39] Surfactant is a phospholipid which lines the terminal sacs and reduces the surface tension.[35,37,39] Immature surfactant starts to be produced by the end of this stage, however, it is only during the saccular stage that mature surfactant is produced.[37]
3) In the saccular stage, an increase in terminal sacs appear; type I pneumocytes reduces in thickness, allowing for more efficient gas exchange; and surfactant production increases, reducing the surface tension even further.[35,37,39] This is of great importance to maintain the structure of the small airways and alveoli, which is necessary for gas exchange.[35,39] Laplace's

law states that the pressure in the airways and alveoli is inversely proportional to the radius, when surface tension is constant.[41] Reducing surface tension, by the presence of surfactant, will result in a lower pressure needed to maintain the airway/alveoli open, preventing collapse of these structures, especially in a state of low lung volumes when the radius of the structures will be reduced even further.[41,42]

4) The final stage of lung development, the alveolar phase, commences around 32 weeks of gestational age.[37] During this phase, alveoli are developed.[37,39] Further, the trachea and airways continue to increase in diameter until about five years of age.[36] Postnatally, the lungs continue to develop, with further maturation and increased number of alveoli until about the age of 8-11 years at which time approximately 480 million alveoli are present.[37,43–45]

Prematurely born babies are at risk for developing chronic lung disease, such as respiratory distress syndrome or bronchopulmonary dysplasia, due to the underdevelopment of the respiratory system in utero.[35]

Respiratory distress syndrome, also known as hyaline membrane disease, is caused by underproduction of surfactant in the premature lung.[46] This can lead to bronchopulmonary dysplasia, as children with respiratory distress syndrome are often ventilated for more than 28 days after birth.[46] Bronchopulmonary dysplasia is mainly seen in babies born younger than 30 weeks of gestational age.[47] However, it can also be found in term born children.[48] Further, in children born with low birth weight and/or before 33 weeks of gestational age, recurrent wheezing and asthma is common.[47,49] Prematurely born children can display respiratory problems throughout their lifespan. A decrease in forced expiratory volume in one second (FEV_1) and increased airway resistance has been reported in adolescents who were born prematurely compared to their term born peers.[50]

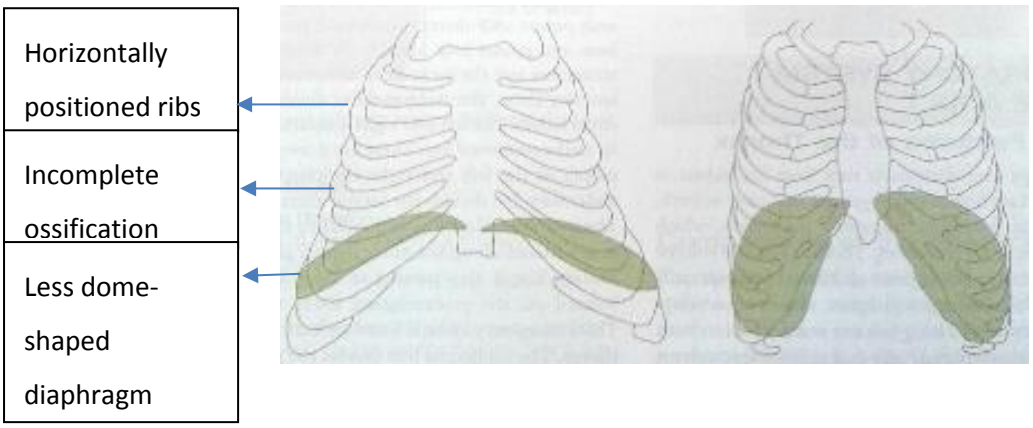
2.2 PAEDIATRIC VERSUS ADULT ANATOMY AND PHYSIOLOGY OF THE LOWER RESPIRATORY TRACT AND THORAX.

The paediatric respiratory system cannot be seen as just a small version of the adult's system,[40] as it differs in both anatomy and physiology. Some important structural and physiological changes occur throughout childhood, which are discussed in this section.

2.2.1 Anatomical changes

In infants, the ribs are more cartilaginous, making them more pliable and deformable.[51] Ossification of the ribcage is only completed at the age of 25 years.[40] A more horizontal positioning of the ribs is found in young children, compared to a more oblique position in children older than 10 years of age

and adults.[40,51] This leads to a flatter position of the diaphragm in young children, influencing the diaphragm's function (Figure 2-1).[40,51] Furthermore, the diameter of the trachea is much narrower in infants than in adults as well being more compliant and consequently easy to compress.[37,51]



[Reproduced with permission; this figure was published in Hicks G. The respiratory system. In: Kacmarek R, Stoller J, Heuer A, eds. Egan's Fundamentals of Respiratory Care. Vol 10th ed. St. Louis: Elsevier Mosby (Copyright); 2013].[37]

Figure 2-1. Anatomical differences of the thorax between young children (left) and adults (right).

2.2.2 Physiological changes

These structural differences lead to changes in physiology. Due to the horizontal rib position in children, the rib cage expansion during inspiration is limited. This rib cage expansion, also known as the bucket handle motion, combined with resistance from the chest wall, which is limited in children, is necessary for an effective pump mechanism of the thoracic cage.[40] This inefficient pump function contributes to the predisposition to atelectasis in new-born babies due to decreased residual lung volume, resulting in a decrease in oxygen reserves.[40] Children compensate to overcome this inefficiency by increasing their respiratory rate (RR), increasing haemoglobin concentration to facilitate gas exchange, and increasing expiratory time by laryngeal braking.[40] Another important difference between infants and adults is the decreased recoil capacity of the lungs in infants due to the reduced elastin.[36] This also leads to an increased risk of developing atelectasis and problems with gas exchange.[36] Furthermore, the decreased diameter of the trachea in infants increases the airway resistance, resulting in an increased risk of lower airway obstruction and atelectasis.[52] Increased compliance of the airways due to the increased proportion of airway cartilage in infants and the underdevelopment of both the pores of Kohn and Lambert's channels, resulting in poor or even absent collateral ventilation in infants, further increases the risk of atelectasis in infants.[53,54]

Incomplete ossification of the ribs leads to an increase in chest wall compliance.[36,40,51] This phenomenon, together with decreased lung compliance, influences the level of functional residual capacity (FRC) in infants compared to adults. As the FRC in infants is located on a lower lung volume, it surpasses the level of the closing capacity (the lung volume at which the small airways and alveoli collapse), predisposing infants to airway collapse during normal expiration and increasing the risk of atelectasis.[54]

The horizontal position of the ribs and the increased compliance of the rib cage, results in infants having to rely more on their diaphragm as the major respiratory muscle, rather than the intercostal muscles, because the intercostal muscles have taken over the stabilising role of the thorax instead of functioning as inspiratory muscles.[55] When intercostal muscles fail to support the rib cage, paradoxical breathing movement can be seen in babies and infants as the thoracic cage will move inwards when muscle forces are applied during inspiration.[36] Further, as the muscle tone of the intercostal muscles during rapid eye movement sleep is decreased, chest wall retraction will increase for which this paradoxical breathing pattern becomes even more apparent.[36,51,55] Over time, the chest wall becomes more rigid, therefore this breathing pattern is not observed in healthy older children and adults.[36,40] However, infants struggle to keep up with large workloads on the respiratory system, as the proportion of type I and type II muscle fibres of the intercostal muscles and diaphragm changes throughout childhood.[51,56] Prenatally, 90% of the muscles consist of type II muscle fibres. This amount decreases to 75% at birth and 50% in children older than two years of age.[51] As type II fibres are fast-twitch, highly contractile and low-oxidative, they are more prone to fatigue than type I fibres which are slow-twitch, low contractile, high-oxidative and more fatigue-resistant.[51,57] This predisposes new-borns and infants to diaphragm muscle fatigue, respiratory failure and decompensation.[51,57,58] Due to the above described change in respiratory muscle function and physiology, and the fact that ventilation improves when infants are placed in an upright position,[59] it could be beneficial to maintain an upright position during any airway clearance interventions in infants, to promote optimal diaphragm use and minimise fatigue.

The development of the respiratory system is completed at the age of 18 years for females and 24-30 years for males.[40] Subsequently, aging has an impact on the respiratory system,[60,61] but this is beyond the scope of this thesis.

2.2.3 Anatomical and physiological changes, and the impact on ACTs in infants and young children

Due to the above anatomical and physiological differences between the paediatric and and adult respiratory system, some of the working mechanisms applied during ACTs might be irrelevant in young children, reducing the efficacy of the technique and limiting the number of available in this population. Furthermore, caution is needed when applying conventional ACT in infants due to the above mentioned anatomical and physiological changes. For example, percussions and vibrations might cause rib fractures, due to the lack of ossification of the rib cage; and airway collapse, due to increased pleural pressure on more compliant airways and absence of collateral ventilation.[54]

2.3 AIRWAY CLEARANCE THERAPY

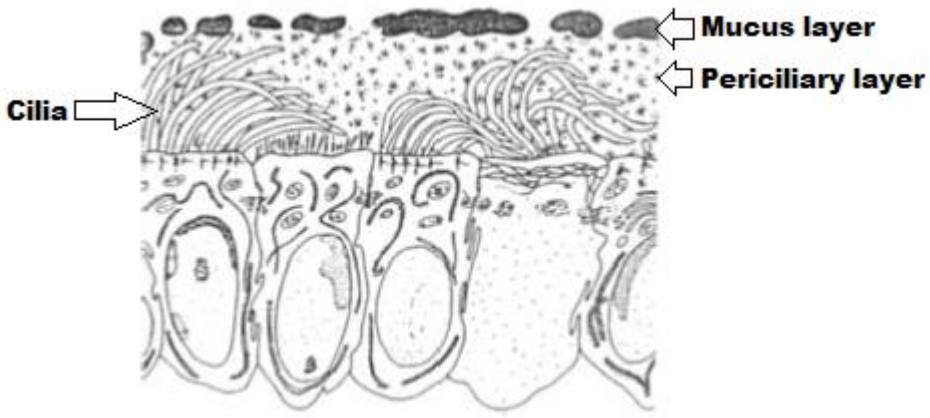
Respiratory diseases are treated with disease-specific interventions, which may include physiotherapy using ACTs to evacuate mucus from the airways and/or to improve ventilation.[62] In this section, normal mechanisms of airway clearance and different ACTs will be described.

2.3.1 Airway clearance mechanisms

2.3.1.1 Mucociliary clearance

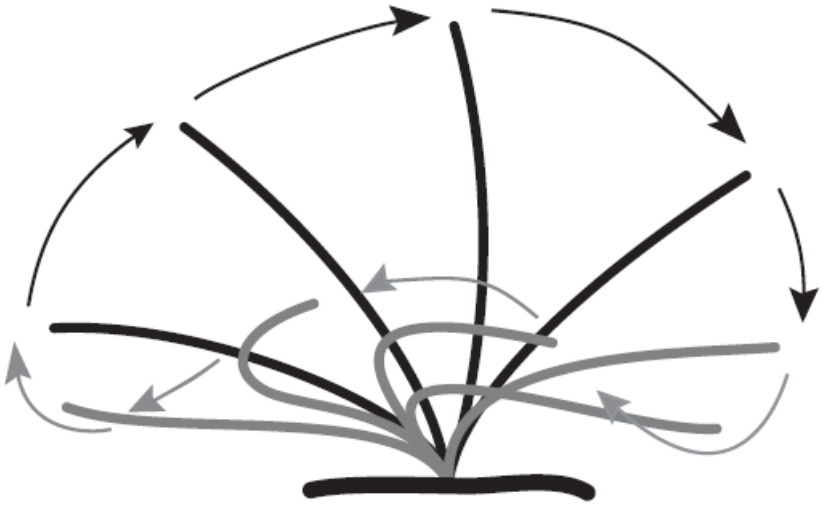
Mucociliary clearance (MCC) protects the lungs by clearing excessive mucus and hazardous micro-organisms from the bronchial tree.[36] The MCC apparatus consist of two layers of fluid, the periciliary layer and the mucus layer (Figure 2-2). The thickness of the periciliary layer is approximately the length of the cilia in the erect position, therefore, the cilia only penetrate the mucus layer in the erect position.[63]

In normal MCC, the periciliary layer is watery, allowing a wave-like movement of the cilia to propel the mucus from peripheral lung regions towards the pharynx.[64,65] The cilia start in the resting position, then move sideways and backwards in a recovery phase to make an effective stroke forwards (Figure 2-3).[66] The mucus is only moved during the effective stroke phase (during which the cilia are fully erected),[67] which propels the mucus to the pharynx where it is swallowed, often unnoticed. Cooperation amongst the cilia is achieved by an almost identical ciliary alignment and therefore a similar stroke direction.[64,68]



[Reproduced with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Cite: Boucher RC (1994). Human airway ion transport. Part one. American Journal of Respiratory and Critical Care Medicine. 150. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.[63]*]*

Figure 2-2. A schematic representation of the mucociliary clearance mechanism



[Reproduced with permission of the European Respiratory Society ©. European Respiratory Journal Dec 2014, 44(6); DOI: 10.1183/09031936.00052014][67]

Black arrows represent the effective stroke phase, grey arrows represent the recovery phase.

Figure 2-3. Schematic representation of the movement of the cilia.

2.3.1.2 Shear forces

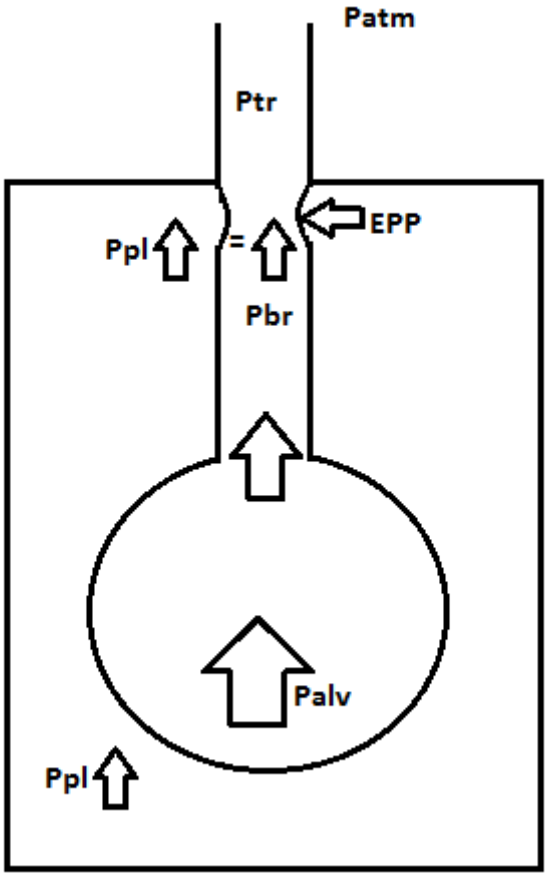
In addition to MCC, a gas-liquid interaction between the mucus layer (fluid) and the airflow (gas) takes place in the airways.[66] This interaction leads to shear forces being applied to the mucus layer.[69] The amount of shear is determined by the airflow velocity, with greater shear forces when air flow velocity is high.[66,69] The diameter of the airways also has an impact on the amount of shear, because the same air flow will create more turbulence if the airways have a narrower diameter.[70] Although the peripheral airways have a narrower individual diameter, the total peripheral airway diameter is

larger than the central airways.[66] Therefore, the turbulence is greater in the central airways than in the peripheral airways. Shear forces are thus greater in the central airways and are one of the main underlying principles of forced expiration and cough.[66] The volume of mucus also influences the airway diameter. A thicker mucus layer (as seen in patients with CF, for example) will lead to a narrowing of the airway diameter, leading to greater shear forces.[71–73]

During relaxed breathing, shear forces are small and occur during both in- and expiration.[66,70] However, due to an increase in intrapleural pressure during expiration, the airway diameter is smaller during expiration, leading to an increase in velocity of airflow.[70,74] Therefore, more shear forces are created during expiration,[70] moving the mucus from peripheral to central airways.[66] In addition, the inspired air warms up in the nasal passage and airways, therefore expanding in the lungs, leading to a greater expiratory flow, enhancing the shear forces from peripheral to central even more.[66]

2.3.1.3 Equal pressure point

Another method by which secretions are moved in the airways is squeezing of the airways. The pressure in the airways is determined by the pressure at the mouth and nose (atmospheric pressure) and the pressure in the alveoli.[66,75] The elastic recoil property of the lungs determines the alveolar pressure during relaxed breathing, whereas the alveolar pressure during a forced expiration is determined by both the elastic recoil properties and pressures generated by the expiratory muscle forces.[75,76] As long as the pressure in the alveoli and bronchi is greater than the pressure outside the airways (pleural pressure), the airways are able to maintain structure. However, the pressure from the alveoli towards the mouth decreases gradually.[75] The point where the pressure in the airways and the pleural pressure are identical, is called the equal pressure point (EPP) (Figure 2-4).[66,76] From this point upwards towards the mouth, the airways are dynamically compressed and mucus transport is elicited.[75,77] The position of the EPP can be changed slightly, by influencing the lung volume at which the expiration takes place, influencing the elastic recoil properties of the lung.[75] This is one of the main principles of mucus transport during forced expiration (see 2.3.2.2 forced expiratory technique (FET)).[66] Further, compression of the airways will lead to narrowing of the airway diameter, increasing shear forces at the point of compression.[66]



Equal pressure point is the point where the pleural pressure (Ppl) equals the pressure in the airways (alveolar pressure (Palv), bronchiolar pressure (Pbr), tracheal pressure (Ptr)). Pressure outside the body, measured at the mouth equals the atmospheric pressure (Patm). (Self-designed by L. Corten)

Figure 2-4. Schematic representation of the equal pressure point

2.3.1.4 Cough

Coughing is a natural airway clearance mechanism. When the glossopharyngeal and vagus nerves are stimulated by secretions in the central airways (especially around the carina), a cough is elicited.[66] The cough mechanism consist of three phases: a deep inspiration; glottic closure to build up intrapleural pressure; and finally forceful expiration with explosive glottis opening.[78,79] Coughing is a very effective way to clear secretions in the central airways,[70] however, closure of the glottis increases intrapleural pressure, changing the pressure on the airways significantly, influencing it EPP and increasing airflow,[79] which might lead to airway closure during expiration. Furthermore, in patients with chronic obstructive lung disease, such as CF, bronchomalacia can be present, increasing compliance of the airways, resulting in further risk of collapse of the airways during forceful

expiration.[70,80] Collapse of the peripheral airways reduces the efficacy of airway clearance due to air trapping distally from the collapse.[81]

2.3.2 Airway clearance techniques

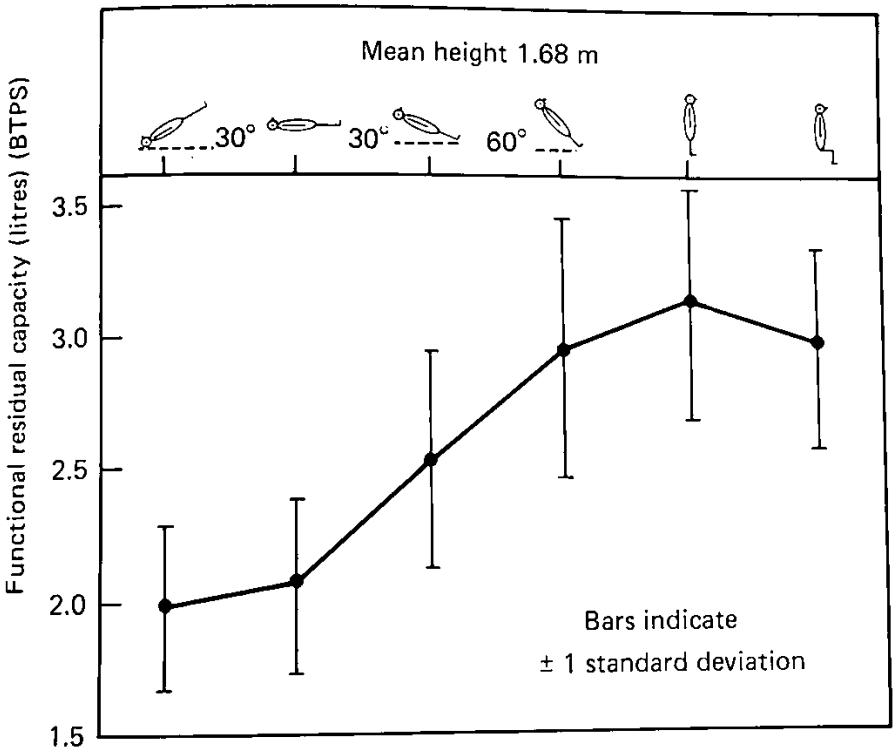
In respiratory disease, the above described natural airway clearance mechanisms could be impaired due to various reasons (See Chapter 3 and Chapter 7 for the pathophysiology of respectively pneumonia and CF). Several ACTs have been developed to remove secretions from the lungs, by facilitating the natural airway clearance mechanisms.

2.3.2.1 Conventional airway clearance techniques

Postural drainage (PD)

During this technique, the patient is placed in different positions, depending on the area where mucus is present in the lungs in order to facilitate mucus clearance from the lungs using gravity.[65,82] The technique is most useful in the central airways, where the influence of gravity is the greatest.[65,82] In the more peripheral airways, gravity alone is not enough to overcome the adhesive forces between mucus and the bronchial wall.[82] Furthermore, tenacious secretions are unlikely to be drained by gravity alone, unless viscocity of secretions is reduced by mucolytics or other forms of ACT.[54,64,83] Caution is needed when using PD, as the technique has several adverse events. The side lying and head-down positions have been associated with an increase in intracranial pressure, bronchospasm, gastro-oesophageal reflux disorder (GORD), hypoxemia, discomfort/pain, cardiovascular and hemodynamic instability.[66,84–86] These adverse events also contribute to poor compliance with home PD therapy, previously advocated for people with CF.[87]

During coughing and huffing (FET) in different positions, the lowest peak expiratory flow (PEF) and maximal expiratory pressure are reported in the head-down position and the highest in the upright position.[88] Furthermore, FRC is lower in the head down position and supine compared to a more upright position (Figure 2-5).[89,90] Therefore, adopting a more upright position during treatment is advised, particularly for young children who are more susceptible to airway collapse due to changes in FRC and related closing capacity, as mentioned previously.[54] As a consequence of the potential adverse events of the head-down position, MPD was introduced, which avoids the head-down tilt position.[91]



[Reprinted from Nunn J. Elastic forces and lung volumes. In: Nunn J, ed. Nunn's Applied Respiratory Physiology. 4th ed. Oxford: Butterworth Heinemann, Elsevier Limited; 1993, with permission from Elsevier][92]

Figure 2-5. Functional residual capacity in different body positions

Percussion, vibration and chest wall shaking

Percussions and/or vibrations applied either manually or mechanically to the thoracic wall are often added to PD treatment to loosen secretions. In the central airways vibrations and percussions may have an influence on the mucus transport as these are not surrounded by air containing lung tissue.[93]

Contradicting results have been reported in the literature regarding the efficacy of these techniques. Vibrations could increase the PEF rate by increasing the pressure in the airways, and altering the thixotropic characteristics of mucus.[94–96] However, other studies failed to identify additional effect of percussion or vibration to PD.[97,98] Disadvantages of these techniques are bronchospasm, decreased arterial oxygen saturation (SaO_2) level and FEV_1 in patients with little expectoration. Even serious hypoxemia can be caused.[99,100] Rib fractures and periosteal reactions may occur in very young children which is a serious complication of these techniques.[101–103]

Assisted cough

When respiratory muscles weakness, e.g. due to neuromuscular disorders (NMDs) or in ventilated patients, results in a weak cough, assistance might be needed for an effective cough. This can be done either manually or mechanically.[104]

During manually assisted cough, a maximal inspiration is followed by a facilitated exhalation manoeuvre.[105] The therapist administers pressure during the expiration phase, by placing the hands on the thorax (thoracic squeeze) and/or abdomen. [105–107] This manoeuvre increases the intrathoracic pressure and expiratory airflow, using the elastic recoil properties of the lungs and thoracic muscles.[105,107] Caution needs to be taken when patients have osteoporosis, due to the risk of rib fractures.[108] Particularly in children with CF, the malabsorption of fat-soluble vitamin D results in vitamin D deficiency, osteopenia, osteoposisis and Rickets disease placing these children at increased risk for rib fractures during ACT.[16,109]

A newer technique for cough augmentation is mechanical in- and exsufflation. These devices apply different pressures to the airways; firstly a positive pressure to insufflate the lungs (imitating inspiration) and afterwards a negative pressure to exsufflate the lungs (imitating expiration), stimulating a cough.[107] An increase in PEF and sniff nasal inspiratory pressure; and a decrease in end tidal carbon dioxide pressure was observed after use of a mechanical in-and exsufflation device.[110] Although adverse events were scarce, it is unclear whether or not these devices are safe as the limited literature available on this topic presented studies which were underpowered to evaluate this outcome measure.[111]

2.3.2.2 Modern airway clearance techniques

Forced expiration technique (FET)

During the FET, one or two forced expirations (huffs) are performed, followed by controlled diaphragmatic breathing.[112,113] Huffing is a manoeuvre similar to coughing but without closure of the glottis. Therefore, FET is considered to stabilize the airways during forced expiration so that airway collapse is prevented and a better airway clearance achieved.[24] Based on the theory of EPP (see section 2.3.1.3), by performing huffs at different lung volumes, different parts of the lungs can be cleared.[114] By inspiring to different lung volumes, different pressures are created in the airways, changing the EPP along the airway. Inhaling deeply before forcefully exhaling evacuates secretions from the central airways, by increasing pressure inside the airways, resulting in the EPP moving more centrally as the increased airway pressure equals the pleural pressure at a more central location. However, when a forced expiration at lower lung volume is performed, the EPP will move more

distally as the pressure in the airways is lower and equals the pleural pressure at a more distal level.[66,112,114] Furthermore, this technique also uses the principle of applying shear forces within the airway through forceful expiration.[66] This techniques requires active participation of the patient, limiting the use to cooperative older children and adults.

Active cycle of breathing technique (ACBT)

The active cycle of breathing technique (ACBT) consists of three components, which affect gas-liquid interactions: 'breathing control', 'thoracic expansion exercises' and 'FET'. These components are repeated several times in a cycle.[24,115] This technique manipulates the EPP to vary airflow patterns and promote shear forces to remove tenacious mucus.[78] ACBT improves ventilation by the use of the interdependence principle.[116] This principle assumes that alveoli are dependent on one another, as they share cell walls. Small pores in the alveolar walls allow for pressure redistribution across neighbouring alveoli.[41] Therefore, ACBT allows air to be redistributed across neighbouring alveoli, improving ventilation.[78] Further, collateral ventilation channels may be recruited to increase the amount of distal air behind secretions.[115] Advantages of the ACBT are the ability to perform the technique independently in older children, no desaturation or other adverse effects have been reported, and no equipment is needed.[117] Unfortunately, though, the patient has to be fully cooperative to perform this technique, therefore it is not applicable in uncooperative patients or infants.[24] Parts of the technique can be performed in children as young as 18 months via fun, playful games and the complete ACBT can be taught in children from the age of four years.[114] However, the efficacy of ACBT in young children might be reduced due to the underdevelopment of collateral ventilation channels, as mentioned previously.[53,54]

Positive expiratory pressure (PEP) technique

Positive pressure is created in the airways by breathing out against a resistance.[24,118] The technique aims to improve mucus clearance by preventing dynamic airway collapse and potentially moving air behind the secretions through collateral ventilation, thereby influencing peripheral airway clearance.[25,66,118,119] Benefits of PEP therapy are no desaturation during low pressure PEP and independent use.[24] However selection of the appropriate PEP level and the application in young children remains unclear and is not well supported by high-level evidence.[24] Patients who are severely ill and cannot maintain breathing control will not be able to perform this technique.[120] In addition high pressure PEP can induce bronchospasm in patients with hyper-reactive airways.[121] Complications such as barotrauma, pneumothorax and arterial rupture may occur, especially when using high pressure PEP.[112,122] Another disadvantage of this technique is the cost of PEP masks. Public health facilities in South-Africa do not have access to these masks. Only PEP valves with mouth pieces

are available, which are not useful in babies and infants (Prof. B. morrow. Personal communication. 2013). In addition, children might not tolerate facemasks placed on their face,[123] leading to reduced adherence with this technique. Furthermore, this technique also relies on the mechanism of collateral ventilation, which is underdeveloped in infants and young children (section 2.2.2)

Oscillating PEP (e.g. Flutter, Acapella, Cornet, Quake)

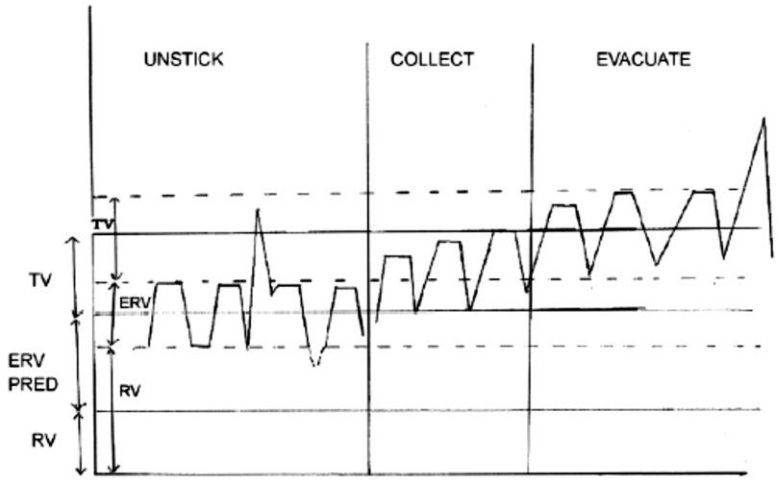
These devices combine PEP with airway oscillations.[118] Oscillations are thought to change the viscoelastic characteristics of mucus so clearance is performed with less effort.[124] This technique also uses shear forces to remove secretions from the lungs, by creating oscillatory expiratory airflow and preventing airway collapse using PEP.[125] Advantages of these devices are the independent use in older children and adults.[125] These techniques have the same limitations for infants and young children as described for PEP in the section above.

Assisted and unassisted autogenic drainage ((A)AD)

These techniques use breathing at three different lung volumes (Figure 2-6);[26,27] and apply the principle of shear forces by producing optimal airflow (without forced expiration) in the small airways to remove secretions from peripheral to central airways, thereby theoretically preventing collapse of the small airways.[26–28] Airflow velocity is greatest when a deep breath in is taken and forceful expiration is performed. However, due to the risk of airway collapse during forceful expiration, AD aims to alter lung volumes rather than using forced expiration to increase airflow velocity. The flow-volume curves when using AD overlap with the flow-volume curve when performing a forced expiratory manouevre.[70] Therefore, unforceful breathing during AD can still remove secretions from the airways.[126] Further, the EPP theory is applied in these techniques.[26] The position of the EPP can be changed slightly, by influencing the lung volume at which expiration takes place. Hence, lung volume and expiratory flow velocity are the main elements in AD and AAD.

In preparing for the technique, it is important to clear the upper airways, to allow mucus to be moved from peripheral to central airways.[26,28] This can be done by huffing and rinsing/blowing the nose.[26] Afterwards, a controlled method of breathing at three different lung volumes is performed during AD.[24,26,127] At each level of breathing, the patient is instructed to breathe in slowly through the nose, hold for 2-3 seconds with an open glottis and then breathe out.[26,28] The preferred amount of air inhaled and exhaled is the patient's functional tidal volume (which is slightly more than their normal tidal volume), while maintaining the required lung volume level.[26,28] Expiration during this technique is performed in an active, but gentle way.[26–28] Firstly, the secretions are 'unstuck' in the peripheral airways by breathing at a low lung volume, then secretions are 'collected' in the central airways by

breathing at mid volume and finally the secretions are 'evacuated' from the lungs by breathing at a high volume.[24,27,28,127] Cough should be avoided during the technique, to prevent secretions from moving back into more peripheral airway generations.[26,28] Only at the end of the session, when a sufficient amount of secretions has been collected in the central airways, should a cough or FET be



used to evacuate the secretions from the airways.[26,128]

[Reprinted from Paediatric Respiratory Reviews, 8 (1), McIlwaine M. Chest physical therapy, breathing techniques and exercise in children with CF, Copyright (2007), with permission from Elsevier][114]

Figure 2-6. Lung volumes during the three phases of autogenic drainage

AD has potential advantages as it can be independently used, no equipment is needed, it is applicable in different settings and in daily life, and it can be combined with MPD.[24,114] In order to effectively perform AD, however, the patient has to be cooperative, not severely ill and some endurance and concentration is needed to learn and apply the technique.[24,114] A training period with visual feedback is recommended.[129] Therefore, the technique is only applicable in children over eight years of age.[70]

In children under eight years of age or children who are not able to perform AD, AAD may be used as it does not require active participation.[25,130]AAD is a modified form of AD, which uses the same principles of airway clearance.[28] However, as the patient cannot actively change the lung volumes towards the desired level, the physiotherapist manually influences the level of breathing.[25,28] In children able to partially execute AD, the technique can be performed as an active assisted technique. During AAD, the child is placed in an upright position. The caregiver manually increases the expiratory flow velocity and prolongs expiration towards residual volume by placing the hands on the child's chest and gently following the breathing of the child while lowering thoracic expansion.[25] The technique may be combined with bouncing to improve loosening of the secretions. Another

reason for bouncing is putting the child at ease. No GORD has been reported during this technique.[130–132]

2.3.2.3 Equipoise in airway clearance therapy

The above described ACTs all have advantages and disadvantages, but none of them have been found to be superior within the CF population.[133–136] In children hospitalised for pneumonia, no comparison between ACTs have been reported. Although modern ACTs have not been found to be more effective than conventional ACTs, they might be more preferred by patients.[134]

Therefore, an individualised ACT program adapted to patient's preference is recommended, as this might increase therapy compliance and adherence.[25]

2.3.3 Outcome measures in airway clearance therapy

Various outcome measures are described in the literature to evaluate ACT.

Sputum

Although often used in research, sputum weight and volume are generally considered poor outcome measures, due to the addition of saliva to the expectorated sputum or swallowing of some secretions.[137,138] In addition, daily fluctuations in sputum production influence this outcome measure.[138,139] The use of sputum rheology could, however, be useful to assess viscoelasticity.[124]

Mucus transport by tracer

Transport rates can be determined by the use of radiolabelled particles (Teflon), radiopaque dust (tantalum powder) or radiolabelled aerosol tracer.[138,139] Radiopaque dust is an invasive technique using high amounts of radiation and therefore often not used.[138,139] Radiolabelled aerosol tracer is a reliable and sensitive technique to measure mucus clearance, however, regional clearance is difficult to assess with this technique, as only two-dimensional pictures are produced. Furthermore, in patients with severe obstruction of the airways the tracer will be unable to reach poorly ventilated lung regions.[139] Although small amounts of radiation are used and half-life is approximately six hours,[140] suggesting radiolabelled aerosol tracer is safe, caution is needed when repeatedly exposing children to radiation. Particularly children with chronic disease who are exposed to a high cumulative radiation dose from recurrent imaging through their lives.[141]

Transcutaneous oxygen saturation (SpO_2)

SpO_2 can be measured by transcutaneous oximetry. This outcome measure is often used in clinical practice and research as it is easy to measure, inexpensive and can be used in acute and chronic conditions.[137] However, the outcome measure might not be reliable, sensitive or specific when SpO_2 is lower than 83% and not be accurate enough for research due to confounding variables such as temperature at the measurement site and haemoglobin levels which can influence the outcome.[142]

Arterial blood gas analysis

The analysis of arterial blood gases, such as oxygen partial pressure and carbon dioxide partial pressure, is highly reliable and valid. The removal of secretions from the lungs and improving ventilation during and after ACT can result in altered arterial blood gases due to improved oxygenation. However, this outcome measure is invasive and therefore not recommended for day to day follow up of the effect of ACT.[142]

Pulmonary function testing / spirometry

Pulmonary function testing is one of the most commonly used outcome measures to evaluate the effect of ACTs.[137] Static and dynamic lung volumes can be influenced by mucus, therefore the interpretation of results need to be made carefully.[139] This outcome measure is neither sensitive nor specific for the evaluation of mucus clearance.[139] Spirometry is primarily a tool to evaluate the secondary effects of ACT rather than an indicator of mucus clearance.[143] Only residual volume expressed as percentage of total lung capacity (RV/TLC) is a likely indicator of mucus clearance.[144] Obstruction caused by secretions results in increased RV due to the inability to completely exhale. Therefore, RV/TLC is an indicator for pulmonary obstruction.[145] Conventional lung function testing is only possible in children older than five years of age.[137] However, more recent studies have shown the possibility of using spirometry lung function testing in children as young as three years of age.[146–148] Spirometry is recommended to be performed at every clinic visit in children with CF, to monitor the progression of lung disease.[149]

Another pulmonary function test, multiple-breath inert gas washout, investigates FRC and ventilation distribution by timing the clearance of a tracer gas from the lungs.[150,151] It is less frequently used to determine closing volume and capacity.[151] This technique is useful in young children as little to no active cooperation is required and non-hazardous gases such as nitrogen or sulphur hexafluoride are used.[152] A mass spectrometer is needed for gas washout analyses, however, specific devices are required per age range.[153] Although several steps have been undertaken to improve reliability due to the high inter- and intra-patient and research site variability;[150] validity and standardisation of this

outcome measure needs to be further investigated before use in clinical practice.[151–153] In infants, the use of nitrogen is not preferred due to higher oxygen requirements during the test procedure, influencing breathing pattern and therefore the outcome;[151,154] the availability of sulphur hexafluoride is also limited, resulting in increased costs.[151,153] The test procedure is more time consuming than spirometry, and normative values still need to be established for each device.[153]

Respiratory resistance can be measured by the use of the forced oscillation technique, during which the child breathes at tidal volume while oscillatory resistance is applied.[152] This technique can also be conducted in young children as little to no cooperation is required.[152] However, this test procedure can also be lengthy, particularly in infants when the child may need to be sedated.[155] Although the forced oscillation technique is easy to perform, contradictory results regarding reliability have been reported. Furthermore, the usefulness of this tool as an outcome measure in infants and young children with CF is questionable.[156]

Chest X-rays

Chest radiograph scores could be used to investigate mucus clearance. In patients with CF, chest X-rays scores are reproducible and can be used as part of the evaluation of patients.[157] However, this assessment is insensitive for acute studies when subjective interpretations need to be made.[137] Radiation exposure needs to be considered, particularly for children with chronic respiratory diseases, where chest X-rays may be taken regularly as part of standard practice.[138,141]

Hospitalisation and number of exacerbations, antibiotic treatments or days on antibiotics

Duration of hospitalisation and number of days on antibiotics or number of exacerbations for children with CF could be influenced by the mucus clearance rate, as reduction of infectious secretions could reduce the need for health care and result in faster discharge from hospital.[138,139] The limitation of these outcome measures is the sometimes subjective criteria on which the outcomes may be based or measured.[137] For example, the decision to discharge a patient could be based on a range of confounders other than simply the resolution of the primary disease, particularly in resource- constrained environments with high demand and limited numbers of paediatric hospital beds.

Health related quality of life (HRQOL)

Although HRQOL is not clearly defined in literature,[158,159] the concept of HRQOL describes the perception of quality of life attributed to health status, which includes disease and disability, and the effect of treatment.[160] Several generic and disease specific tools have been developed to assess this

concept. A valid and reliable tool to measure HRQOL in children is the EQ-5D-Y (Appendix 1).[161] This tool has been found valid for acutely ill children and for the long-term evaluation of HRQOL in children with CF.[162,163] The EQ-5D-Y has been validated and found responsive to change in the thesis' research context.[163] Other valid and reliable tools for evaluating HRQOL in children with acute and chronic diseases are the Pediatric Quality of Life Inventory,[164–166] the Leicester Cough Questionnaire,[167] the St George's respiratory questionnaire,[168] and the Cystic Fibrosis Questionnaire.[169]

Disease severity in patients with CF

Several tools to assess disease severity in the CF population have been described in the literature.

The Shwachman-Kulczycki score assesses progression of chronic illness, by assessing the participant in four domains: general activity; radiological findings; nutrition; and physical examination. A score out of 25 is given for each domain, providing a total possible score of 100. The lower the score, the more severely affected the patient is.[170] A modified version of this tool is described by Doershuk et al.[171] Limitations of this score are the subjective items which reduce the tool's reliability; poor sensitivity for mild disease severity; and categories which are intertwined.[171,172]

Short-term effects of an intervention on disease severity can be measured using the Huang score. This tool consists of three domains: clinical evaluation, radiographic findings, and pulmonary function; which are assessed pre- and post-treatment. Further, results at admission and discharge are compared and complications are recorded.[173] A modified version of this tool was developed by Matouk et al., however, the validity of the tool within a paediatric population has not been established.[172]

The cystic fibrosis clinical score (CFCS) was developed to assess the patient's current clinical status.[174] The tool consist of five subjective criteria and five objective criteria. Each criterion is given a score out of five, resulting in a total possible score of 50.[174] The higher the score, the more severely ill the patient is at the time of assessment. The CFCS is an easy, low-cost tool; and correlates with FEV_1 and forced vital capacity (FVC), for which the tool could be useful as a surrogate for spirometry in young children.[174] This tool has been validated in a paediatric population, however, reliability of the CFCS needs further investigation.[172,174]

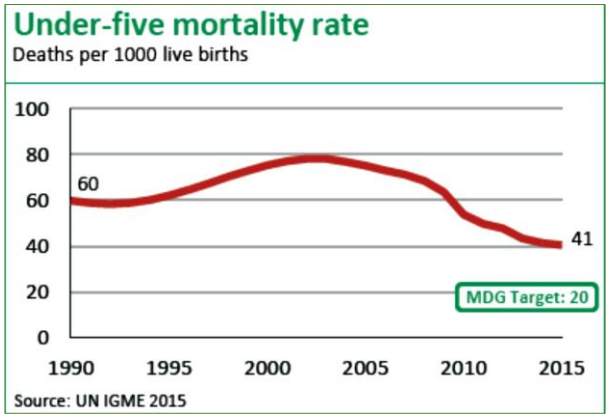
2.4 SUMMARY

Respiratory disease can be either congenital or acquired, and the approach to the management of these conditions differs from adults owing to the physiological and anatomical changes with maturation. ACT might be a valuable addition to the medical treatment of children with different respiratory diseases. Several ACTs are available, of which none has been found to be superior to the others. Limited techniques are applicable in infants and young children, due to the risk of adverse events in this population and the need for active participation in most modern ACTs. A number of outcome measures are available to measure the effectiveness of different ACTs, however, some of the outcome measures were deemed unreliable or invalid. Therefore, caution is needed when selecting appropriate outcome measures.

Chapter 3. PNEUMONIA – NARRATIVE BACKGROUND LITERATURE REVIEW

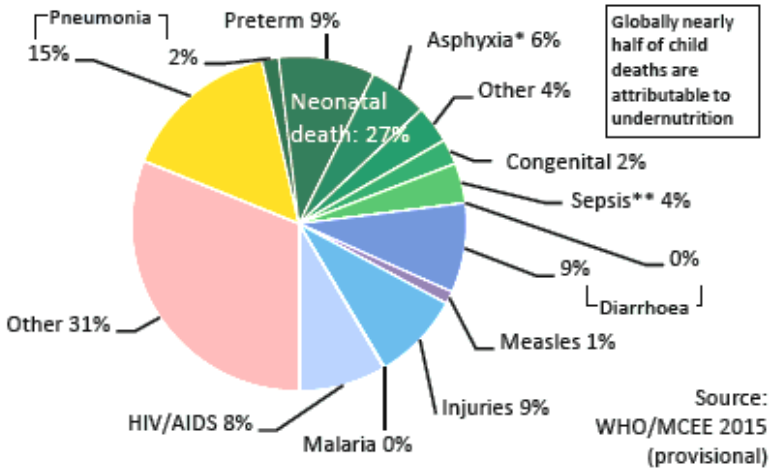
Pneumonia is an acute LRTI, characterised by painful breathing and limited oxygen intake as a result of fluid and suppuration packed in the alveoli.[175,176] When the disease is contracted outside a hospital setting (within the community), it is classified as CAP.[177] Infections contracted within the hospital setting are referred to as hospital acquired or nosocomial pneumonia.[177]

Pneumonia is a global problem, as it continues to be the single leading cause of under five year mortality.[5,178] In 2000, the United Nations set up a plan of action to reduce childhood mortality. This joint action plan was named Millennium Developmental Goal 4 and aimed to reduce childhood mortality by two thirds by 2015.[178] Prevention and management of pneumonia were the major focal points to achieve this goal,[179] however, the decline in mortality was slow and the goal was not achieved by 2015.[179,180] Although, between 1990 and 2008, no progress towards reduction of childhood mortality was seen in South Africa;[181,182] a clear decline in under-five mortality was observed after introduction of highly active anti-retroviral therapy (ARV therapy) (in 2004). However, the mortality rate for children younger than five years of age was still 41 deaths per 1000 live births in 2015, which was below the pre-set goal of fewer than 20 deaths per 1000 live births (Figure 3-1). The majority of childhood deaths (17%) in South Africa are still attributed to pneumonia (Figure 3-2).[183]



[Reprinted with permission from: A Decade of Tracking Progress for Maternal, Newborn and Child Survival. The 2015 Report. Geneva: UNICEF and World Health Organization; 2015. Copyright UNICEF and World Health Organization, 2015][184]

Figure 3-1. Mortality rate for children younger than five years of age in South Africa between 1990 and 2015.



[Reprinted with permission from: A Decade of Tracking Progress for Maternal, Newborn and Child Survival. The 2015 Report. Geneva: UNICEF and World Health Organization; 2015. Copyright UNICEF and World Health Organization, 2015][184]

Figure 3-2. Causes of death in children under five years of age in South Africa in 2015.

3.1 IMPACT OF THE DISEASE: INCIDENCE AND MORTALITY

In low-and middle- income countries, an incidence rate of 0.22 episodes per child-years has been described for CAP.[5] Whereas hospital acquired neonatal infections occur in 20 out of 1000 live births in Africa,[185] with 40% due to pneumonia.[186] The overall incidence rate for pneumonia in Africa is 0.27 episodes per child-years, the highest rate globally.[6]

Although there has been a decrease in pneumonia-related mortality and morbidity over the past years;[5] pneumonia remains the single leading cause of mortality in children younger than five years of age, with a mortality rate of 15-18%.[176,187] The mortality rate is age-dependent, with the highest rate seen in children younger than two years of age (81% of all pneumonia deaths).[6] In South Africa (in 2008), respiratory infections led to 88 000 deaths in children aged 0 to 14 years, of which the majority was due to LRTIs.[188] In 2015, pneumonia (excluding TB) is still the second most common cause of death in children younger than the age of 14 years in South Africa, preceeded by intestinal infections.[189] HIV/AIDS predisposes children to pneumonia, increasing the mortality rate to 37% in this population.[8,188,190] ARV therapy reduces the incidence of pneumonia, but the incidence rates are still higher in the HIV-infected than in the HIV un-infected population.[191,192]

3.2 AETIOLOGY

Pneumonia can be caused by different micro-organisms, either bacterial, viral, or fungal.[176,190] In the African region, *Streptococcus pneumoniae*, *Haemophilus influenza type b* (Hib), and Influenza virus are the most common organisms causing severe pneumonia (18.6%, 3.1%, and 4.1% respectively),

accounting for 32.7%; 12.9%; and 11.1% of pneumonia-related deaths respectively.[6,176,190] In pre-school children, viral aetiology is most common, whilst there is a higher incidence of bacterial pneumonia in older children (10-16 years).[193,194]

Other bacterial causes of pneumonia often seen in very young children (from birth to six days) are *Staphylococcus aureus* and *Klebsiella pneumoniae*.[6] *Salmonella*, *Mycoplasma pneumoniae*, *Mycoplasma tuberculosis*, *Bordetella pertussis* and *Chlamydia pneumoniae* are other less common causes of pneumonia.[6] Viruses, such as respiratory syncytial virus (RSV),[176] para-influenza, bocavirus, rhinovirus, coronavirus, human metapneumovirus and adenovirus are also common causes of pneumonia in childhood.[6,193]

Although a decrease in HIV-prevalence has been reported over the past years in South Africa, the HIV-prevalence in children remains relatively high, with a prevalence of 2.4% in children younger than 14 years of age and 1.7% in children younger than five years of age in 2012.[195] Children with HIV/AIDS are more susceptible to the acquisition of bacterial pneumonia due to immune compromise.[8,196] These children are also more susceptible to infection by opportunistic organisms such as *Pneumocystis jirovecii* and Cytomegalovirus infections.[6,176,196] *Pneumocystis jirovecii* pneumonia (PJP) differs from other aetiologies of pneumonia, as it is a fungal infection most often found in the alveoli of the lungs, and commonly seen in patients with reduced immune support, e.g. HIV-infected and –exposed children or those on immunosuppressive treatment.[196–199]

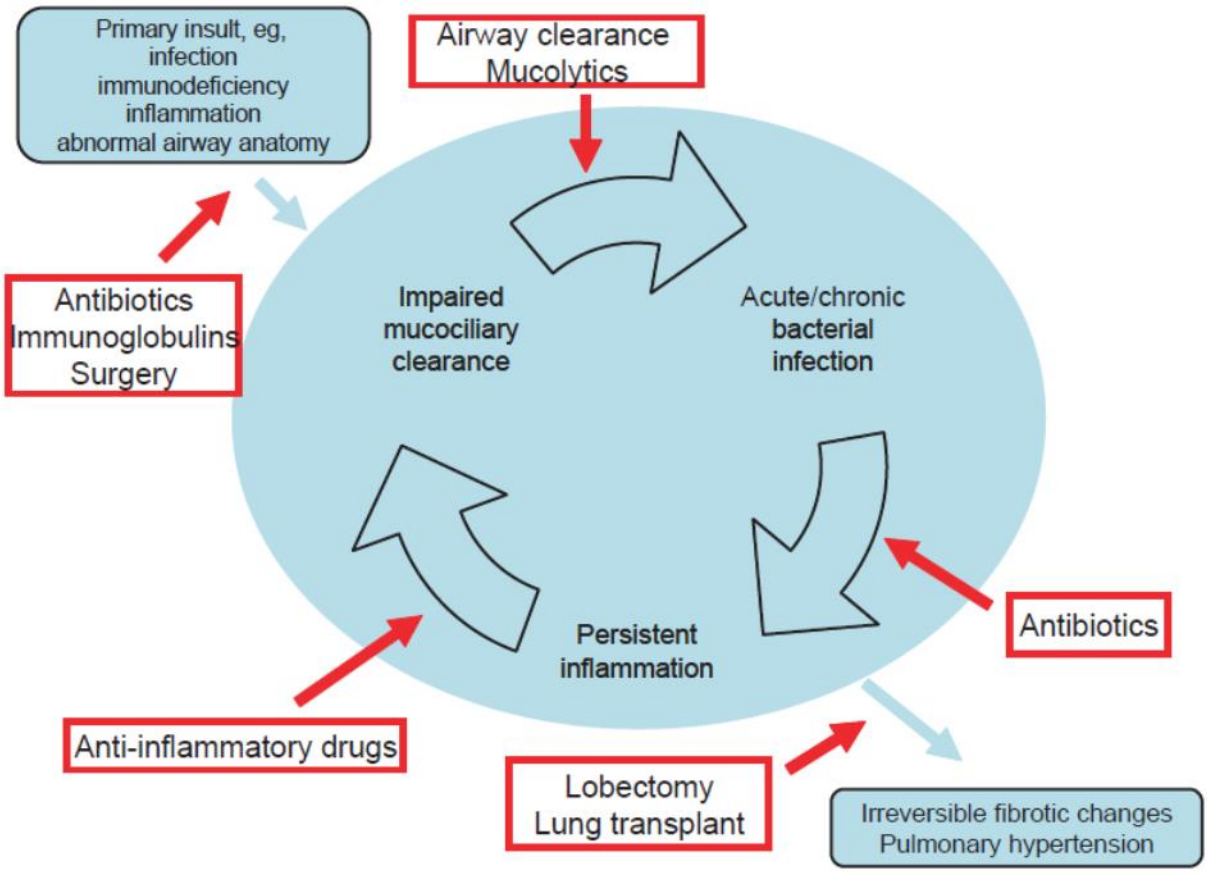
3.3 PATHOPHYSIOLOGY

Infection with any of the above micro-organisms results in an increase in the thickness of the alveolar cell wall, leading to a decrease in gas exchange. Furthermore, an inflammatory process is triggered within the lungs.[193] This inflammatory process results in an increase in the volume and viscosity of pulmonary secretions, ciliary dyskinesia and ineffective cough which may lead to reduced secretions clearance.[70] Subsequent secretion retention predisposes to airway obstruction, inhomogeneity of ventilation and superadded infection.[24] In addition, pneumonia pathogens themselves may influence MCC, impairing its functioning even further.[24,64,200] Pneumonia may influence MCC in two ways: firstly, micro-organisms produce substances which impair MCC and secondly cytotoxic effects on the airway epithelium may occur.[24,64] Reduced MCC may increase the amount of secretions in the lungs, with long term airway obstruction potentially leading to bronchiectasis.[24]

Healthy individuals have natural defence mechanisms against potentially pathogenic micro-organisms. However, children are more vulnerable to respiratory infections due to impaired cough, impaired MCC, alveolar macrophage dysfunction, aspiration, and/or immune dysfunction.[24,200]

3.4 LONG TERM SEQUELAE

About 12% of children with pneumonia progress to severe pneumonia, with a mortality rate of 8.9% for these cases.[6] The risk of long term major respiratory sequelae after childhood pneumonia is 10.4%, with restrictive lung diseases being the most common.[201] Children infected with adenovirus pneumonia specifically can suffer from obstructive lung disease in the long term.[201] In hospitalised children, who are reported to have three times greater risk of sequelae and suffer from more severe sequelae, the development of bronchiectasis has been reported.[201] Bronchiectasis is often related to infection with bacterial agents, such as *Streptococcus pneumoniae* and Hib, as these pathogens often lead to severe pneumonia, causing abnormal clearance or airway damage (Figure 3-3).[24,202]



[Reproduced with permission from: Non-cystic fibrosis bronchiectasis: its diagnosis and management. Stafler P and Carr S. Arch Dis Child Educ Pract Ed. 2010, 95] with permission from BMJ Publishing Group Ltd][202]

Figure 3-3. Development of bronchiectasis

3.5 BURDEN OF DISEASE AND QUALITY OF LIFE

The burden of pneumonia is the highest in infants, with increased disability-adjusted life-year rates compared to other age groups.[203] Furthermore, hospitalisations for pneumonia during infancy decreases HRQOL later on in life.[204]

A study conducted in adults with CAP in the Netherlands, using the CAP score, reported a reduction to pre-pneumonia level in respiratory score after 14 days, whereas the well-being score remained significantly lower than the pre-pneumonia level after 28 days. This well-being level returned to normal after six months. This study also assessed HRQOL, using the Short Form-36, and found that HRQOL was still significantly lower in the dimensions of physical functioning and general health 18 months after enrolment in the study. The presence of comorbid conditions was associated with significantly more impairment, especially in the physical functioning, physical role function, general health perception and vitality domains.[205]

3.6 TREATMENT

Treatment of pneumonia consists of interventions in three domains: (I) protection; (II) prevention, and (III) appropriate treatment.[175,176,190,206]

3.6.1 Protection by promoting good health

Children who do not have strong natural defence mechanisms, due to a weakened immune system, are more susceptible to infections.[190] It is therefore of utmost importance to ensure healthy nutrition.[206] In children younger than five years of age, approximately 35% of all deaths worldwide are related to malnutrition.[206] Children who are underweight have a higher risk of contracting pneumonia with a relative risk ratio of 1.9 for children between weight-for-age z-values of -2 and -3.[6] Further, an increased risk for mortality due to pneumonia is seen in underweight children, with odds ratios (ORs) of 1.2-6.4 (depending on the severity of malnourishment).[6] Therefore, prevention of malnutrition and protection against illness should be prioritised. This can primarily be ensured by exclusively breast feeding until at least six months of age.[6,175,176,206] In 2003, in South Africa, only 8% of all children younger than six months were exclusively breast fed and; in 2008, 33% of children younger than five years of age were underweight.[184] Children who do not receive breastfeeding during the first six months of life have a 15 times higher risk of pneumonia-related death than children who receive breastfeeding during this time.[6,206] Complimentary feeding and nutritional supplements in older infants and children are also vital to further decrease the mortality rate, as

complimentary feeding between the age of six to 24 months reduces mortality for all child deaths by 6%, and vitamin A supplements decrease it further by 23%.[175,206]

3.6.2 Public health considerations

Prevention of pneumonia is crucial in the reduction of child morbidity and mortality. This is usually achieved by vaccinating children against pertussis, measles, Hib, and *Streptococcus pneumoniae*.[5,6,175,176,190,194,207] The implementation of vaccinations has led to a reduction of 15-35% in pneumonia incidence and 30% in pneumonia mortality.[175,206] In South Africa, the application of the pneumococcal conjugate vaccine has led to a vaccine attributable reduction in pneumonia incidence of 1.0-9.1 per 1000 child years, and 5% reduction in mortality.[207,208] In 2014, in South Africa, approximately 70% of children were vaccinated against measles, Hib, pneumococcus, rotavirus, diphtheria, pertussis and tetanus.[184]

A healthy environment is also vital to protect a child from pneumonia.[175] Indoor pollution and crowding (more than seven people in one household), have been found to increase the child's risk of pneumonia.[6,175,176,190,209] By reducing indoor household pollution, the incidence of severe pneumonia decreases by 33%.[206]

3.6.3 Appropriate treatment of pneumonia

Although the reduction of childhood mortality due to pneumonia is one of the worldwide health priorities,[175,190] only 48-54% of children in developing countries are taken to an appropriate healthcare provider.[182,190] In South Africa, in 2003, only 65% of children younger than five years of age were taken to an appropriate health care professional for the treatment of pneumonia.[184] Delayed referral and management of acutely ill South African children might be a result of the tiered health care structure, with limited access to health care facilities.[210,211]

3.6.3.1 Medical treatment of pneumonia

Most children with mild to moderate pneumonia (SpO_2 above 92%, no cyanosis, no difficulties with breathing, no grunting and no apnoea) can be treated in a home-situation, providing the parent/caregiver is able to observe and supervise the child's disease progression.[212] Children with severe pneumonia require hospitalisation.[194,212] Medical management depends on the aetiology of pneumonia, e.g. whether or not to use antimicrobial therapy.

Mild to moderate pneumonia: out-patient setting

The majority of children with pneumonia seen in an out-patient setting present with viral pneumonia and are treated using a symptomatic approach.[193,194] The symptomatic approach in both viral and bacterial pneumonia includes the management of fever by antipyretics.[193,212] In children with bacterial pneumonia, oral penicillin antibiotics e.g. Amoxicillin, are used as first line treatment in the out-patient setting.[175,190,194]

Severe pneumonia: in-patient setting

Hospitalised children with pneumonia, of both viral and bacterial origin, are routinely treated with oxygen support and intravenous fluids to maintain oxygen saturation and hydration levels.[193,212] In addition, antipyretics are used to reduce fever; and mechanical ventilation might be necessary if the child suffers from severe respiratory distress which leads to fatigue or respiratory failure.[212] In addition, children with severe viral pneumonia could be treated with antiviral medication, e.g. Amantadine, Rimantidine, Oseltamivir or Zanamivir for pneumonia caused by Influenza.[193] However, these treatments are only effective when used early in the disease process and are mostly used in children with chronic disorders or immune deficiencies owing to the high cost and risk of drug-resistance.[193,213–216] Bacterial pneumonia is treated with antibiotics, however, the correct choice of antibiotics is vital in preventing emergence of drug-resistance.[212] Identification of pathogens is therefore important, in order to use appropriate narrow-spectrum antibiotics.[212]

3.6.3.2 Airway clearance therapy in pneumonia

Based on the fact that pneumonia can adversely influence MCC and bacterial agents such as *Streptococcus pneumoniae* and Hib can lead to the development of bronchiectasis due to abnormal clearance and/or airway damage,[24] ACT may be an appropriate tool to help evacuate secretions from the airways and/or improve ventilation (see section 2.3.2 for an overview of ACTs). ACT is therefore sometimes prescribed in patients with pneumonia, although the treatment is not recommended by clinical guidelines due to the lack of evidence to support this intervention.[217–220]

Limited evidence is available on ACT in children with pneumonia (see Chapter 4 for a systematic review). Five RCTs,[221–225] two observational studies,[226,227] and one non-controlled/non-randomised study,[228] are available for which the results are presented in Table 3-1.

There is a lack of clear evidence for the use or rejection of ACT in children with pneumonia. Two RCTs and one observational study were published more than 30 years ago, for which the data could be outdated.[224,225,227] In addition, the study by Levine has poor methodological quality, as it is unclear

how randomisation was performed, how allocation concealment was maintained and if outcome assessors were blinded to group allocation.[224] The study by Britton et al. had a pre-set age range of 15-75 years of age, including both paediatric and adult population groups, but considering the mean age for the control and intervention group were 47.4 and 47.2 years respectively and separate data are not available, this study is more relevant to the adult population.[225] The study reported by Stapleton included children of unknown age, with different diagnoses of LRTIs (26 with pneumonia, nine with bronchitis and 20 with bronchiolitis), making it difficult to make conclusions specific to paediatric pneumonia.[227] The study by Plebani et al. is an observational study in only eight patients,[226] and Santos et al. reported a non-controlled and non-randomised study;[228] these study designs are not of sufficiently high quality to make conclusions and generalisability is limited.
The three RCTs may not have included an adequate sample size to evaluate small differences between the groups.[221–223] Therefore, a systematic review, aimed to synthesise the results of these RCTs, was conducted; to determine the effect of different ACTs compared to no physiotherapy, sham physiotherapy or alternative therapy in children hospitalised with acute pneumonia (see Chapter 4).

Although conventional ACT may not be effective in children with acute pneumonia, many of the techniques studied are now outdated. Newer ACTs, including AD and AAD, may be more effective in removing secretions from the peripheral airways, but research into these techniques is characterised by small sample sizes, and therefore more research is needed to make clear and generalizable conclusions.

3.7 SUMMARY

Pneumonia remains the single leading cause for mortality in children younger than five years of age. The disease can be caused by different micro-organisms, impairing the MCC, thickening the alveolar cell wall, and triggering an inflammatory process resulting in an increase in the volume and viscosity of pulmonary secretions, ciliary dyskinesia and ineffective cough. ACT is often prescribed in patients with pneumonia as it might be beneficial to help evacuate secretions from the airways and/or improve ventilation. As contradicting results have been reported in the literature on the use of ACT in children with pneumonia, systematical evaluation of the literature is needed.

Table 3-1. Airway clearance therapy in children with pneumonia

Authors	Study design	N	Age	Aetiology	Intervention	Control	Duration of treatment	Outcome
Britton et al. (1985)[225]	RCT	171	15-75y	Unknown (Primary pneumonia)	PD + vibrations + percussions + external help with breathing (undefined)	Advice on deep breathing and expectoration of secretions + exercises to prevent thrombosis	1x 15-20 minutes /day	• Significant longer duration of fever in the intervention group • No significant difference in duration of hospitalisation, healing time and FEV_1
Stapleton (1985)[227]	Observa-tional	55 I= 34 C= 21	?	Unknown (Acute uncomplicated LRTI)	Percussions + suctioning	Standard care	2-3x 5-15 minutes /day	• No significant difference in duration of hospitalisation • No significant differences in duration of cough or coryza • No significant differences in persistence of rales, wheezes or ronchi
Levine (1987)[224]	RCT	55 I= 32 C= 23	2-12y	Presumed viral Excluded bacterial	PD + percussions + vibrations	Standard care	4x/d	• No significant difference in time till improvement on chest X-ray • Significant longer duration of fever in the intervention group
Plebani et al. (1997)[226]	Observa-tional	8 HIV positive	?	Bacterial	PEP	Therapy used the previous year	2 x 15 minutes /d Study duration= one year	• Significant reduction in the mean number of: - infections per year - antibiotic treatments per year and days of antibiotics per year • Significant improvement in FVC and FEV_1
Paludo et al. (2008)[221]	RCT	89	29d-12y	Unknown (Acute pneumonia)	Standard treatment + PD+ percussion + vibrations + thoracic squeezing + cough stimulation + suctioning	Standard care consisting of oxygen therapy, antibiotics and fluid	2 x 30 minutes/d	• No significant difference in duration of hospitalisation and clinical resolution • Longer duration of cough and rhonchi in the intervention group

I: intervention; C: control

Table 3-1 continued. Airway clearance therapy in children with pneumonia

Authors	Study design	N	Age	Aetiology	Intervention	Control	Duration of treatment	Outcome
Santos et al.[228] (2009)	Non-controlled/ Non-RCT	123	0-11.9y	Unknown (CAP)	Expiratory Flow Increase Technique	Baseline RR, heart rate and SpO_2 from the child	1 x /d	• Significant improvement in SpO_2 after treatment and remained elevated after 20 minutes of rest. RR and heart rate are increased after treatment but returned to baseline after rest
Lukrafa et al.[222] (2012)	RCT	72	1-12y	Unknown (Acute CAP)	Positioning + PEP + thoracic vibrations + cough simulation + suctioning + FET (children 5-12 years)	Cough + positioning in side lying for 5 min + deep diaphragmatic breathing	3 x 10-12 minutes /day	• No significant difference in severity score and duration of hospitalisation
Abdelbasset & Elnegamy[223] (2015)	RCT	50 I= 25 C= 25	29d-5y	Unknown	PD + percussions + vibrations + thoracic squeezing + cough stimulation	Standard care	3x 20 minutes/d	• Significant shorter time to clinical resolution in the intervention group • Significant lower RR in the intervention group at discharge • Significant higher SaO_2 in the intervention group at discharge

I: intervention; C: control

Chapter 4. IS AIRWAY CLEARANCE THERAPY EFFECTIVE IN CHILDREN WITH PNEUMONIA? A SYSTEMATIC REVIEW

4.1 INTRODUCTION

In respiratory disease such as pneumonia, increased volume and viscosity of pulmonary secretions, ciliary dyskinesia and ineffective cough may lead to reduced secretions clearance.[70] This predisposes to airway obstruction, inhomogeneity of ventilation and superadded infection.[24] ACT is therefore often prescribed as part of the treatment of pneumonia, as it might be beneficial for gas exchange, to evacuate secretions from the lungs and decrease work of breathing.[106,218,229]

A systematic review on ACT in adults with pneumonia concluded that ACT should not be given in addition to standard treatment in this population.[230] In a recent systematic review on ACT in children with pneumonia, there was not enough evidence to make a clear conclusion.[231] However, the review included an article on continuous positive airway pressure (CPAP), which I would not classify as ACT.[231,232] Further, one RCT and two non-RCTs did show a positive effect of ACT in children with pneumonia.[223,226,228]

An article based on this review has been published in the South African Journal of Physiotherapy.[(2)]

4.2 AIMS AND OBJECTIVES

To determine the effect of different ACTs compared to no physiotherapy, sham physiotherapy or alternative therapy in children hospitalised with acute pneumonia.

The following hypotheses were tested:
- ACT is more effective than no or sham physiotherapy in improving clinical outcome in children hospitalised with acute pneumonia.
- Certain ACTs are more effective than sham or alternative therapy in improving clinical outcome in children hospitalised with pneumonia.
- ACT is safe to perform in children hospitalised with pneumonia.

[(2)] Corten L, Jelsma J, Morrow BM. Chest physiotherapy in children with acute bacterial pneumonia. South African J Physiother. 2015;71(1):#256. doi:10.4102/sajp.v71i1.256.

4.3 METHODOLOGY

This systematic review used the Cochrane methodology for systematic reviews and conforms the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) (Appendix 2).[233,234] This review's unpublished pre-set protocol described the methodology and inclusion criteria prior to the database searches.

4.3.1 Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs.

Types of participants

Children, under the age of 18 years, hospitalised with acute pneumonia.

Types of intervention

Any ACT, as a single technique or in combination with others compared to no physiotherapy, sham physiotherapy or alternative therapy.

Types of outcome measures

Primary outcome measures:

- Duration of hospital stay (in days)
- SaO_2 or SpO_2 measured before and after intervention
  - transcutaneous
  - arterial blood gas analysis

Secondary outcome measures:

- RR measured before and after intervention
- Duration of oxygen supplementation (in hours)
- Lung function tests (spirometry): vital capacity (VC), FVC, FEV_1, PEF, maximal inspiratory pressure and maximal expiratory pressure measured on enrolment and before discharge
- Any adverse effects
- Mortality

4.3.2 Search methods for identification of studies

Electronic search

Online databases PubMed, Medline, Cochrane library, PEDro, Africa-wide information and CINAHL were searched using predefined search terms (see Appendix 3 for an overview of the search terms). These search terms were also translated into the different included languages.

Articles were included if they were written in English, Dutch, French, German or Afrikaans. Articles were excluded if they were published before 1990 (as the field of ACT has evolved significantly in the past 25 years), written in another language than the ones described above or used a cross-over, non-randomised or pre-experimental design.

Other resources

Reference lists of the identified articles were manually checked. Ongoing research was identified by exploring clinicaltrial.gov and the Pan African Clinical Trials registry (pactr.org). No grey literature was searched due to the problem with reproducibility of this type of literature.[235]

4.3.3 Data collection and analysis

Selection of studies

One reviewer (LC) searched the databases and collected relevant articles based on title and abstract. These were reviewed by a second reviewer (BM). After selection, the full text of each article was reviewed independently by these two reviewers to decide whether the articles were eligible for inclusion in the review. Any disagreement was resolved by consensus.

Data extraction and management

Data extraction was done by two independent reviewers (LC and BM) using a pre-structured data extraction form and included information on the participants (age, gender, condition, severity of symptoms, inclusion/exclusion criteria, comorbid conditions, setting, number randomised, number lost to follow-up); interventions (type of interventions, duration, frequency, intensity, compliance); outcome measurements; results (point estimates, precision, measures of variability, frequency counts for dichotomous variables, number of participants in each group); and study design (randomisation, allocation concealment, blinding) (Appendix 4).

Assessing risk of bias in included studies

The reviewer assessed the following methodological characteristics, based on the Cochrane risk of bias assessment:[233]

1) Generation of sequence:

It was considered low risk of bias when a random number table, computer generated list of random numbers or any other method of randomisation was used. Studies were considered as having high risk of bias when invalid methods of randomisation were used, such as date of birth or allocation by the physiotherapist or physician. When the allocation sequence was not identified, the bias was judged as unclear.

2) Allocation concealment

Low risk was considered when investigators were blinded to group allocation, by the use of coded, opaque and sealed envelopes, on site locked computer files or similar valid means. When the investigator was able to predict allocation, for example by the use of date of birth, the study was classified as high risk of bias. When concealment details were not identified, the bias was considered unclear.

3) Blinding

It is impossible to blind the participant or clinician to physiotherapy treatment, but the physician and data-analyst can be blinded. Therefore the studies were judged as having low risk of bias when investigator and data-analyst were blinded to treatment method. High risk of bias was considered when no blinding or a limited form of blinding was applied. Unclear risk was considered when no information on blinding was available.

4) Incomplete data outcome and intention-to-treat analysis

Low risk of bias was considered when an appropriate intention-to-treat analysis was performed on incomplete data. When no intention-to-treat analysis was conducted, data were considered as having high risk of bias. Risk of bias was considered unclear when no information about intention-to-treat was given.

5) Selective outcome reporting

When primary and secondary outcome measures were reported, the study was considered to have low risk of bias. When no pre-specified outcome measures were identified, the risk of bias was considered high. If not enough information was available to consider the study high or low risk of bias, then the study was classified as having an unclear risk of bias.

6) Other potential threats to validity

When the study was free from other threats, such as baseline imbalance or design-specific risk of bias, then the study was considered to have low risk of bias. High risk of bias was present when there was a potential threat in the study. Unclear risk of bias was considered when insufficient information was available to determine risk of bias.

Measures of treatment effect

It was intended that continuous outcomes would be reported by using the mean difference (or standardised mean differences) and 95% confidence interval (CI). Where insufficient data were provided, or nonparametric measures were reported, the authors were contacted to try and convert data into means (95% CI). Where this was not possible, data were reported as in the source article. Risk ratio and 95% CI were used to report dichotomous outcomes, where possible.

Unit of analysis issues

Long- term studies with repeated measures of outcome were considered eligible for this review, and could be included in later versions, in which case the outcomes would be defined according to set time periods.[236] If studies had more than one intervention group, these groups were planned to be included separately in a meta-analysis, with the control group divided in half.[237]

Dealing with missing data

The original authors of the studies with missing data were contacted. If the author could not be located, a description of the study was included in the narrative review. Where missing data could not be obtained, the studies were considered adequate if more than 85% of participants were included in the outcome analysis, or if fewer participants were included but sufficient measures were taken to ensure or demonstrate that this did not bias the results. Where this was not clear, an intention-to-treat analysis was planned from extrapolated data, where possible.

Assessment of heterogeneity

If different studies measured the same outcome, heterogeneity was planned to be assessed using the chi-squared statistic and the I^2 statistic. Heterogeneity would have been low if I^2 was less than 30%, moderate when I^2 was between 30 and 50% and substantial when it was more than 50%.

Assessment of reporting bias

If a sufficient number of studies were included, a funnel plot was planned to identify reporting bias, and will be used in future reviews when possible.

Data synthesis

If a sufficient number of studies were identified to include in this review, a meta-analysis was planned, using a fixed-effects model, unless substantial heterogeneity was present in which case a random-effects model was planned to be used.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses would be conducted when applicable:

1) Age

2) Gender

3) Duration of treatment

4) Frequency of treatment

5) Severity of the disease

Sensitivity analysis

If an adequate number of studies were included in the review, sensitivity analysis would be performed.

4.4 RESULTS

4.4.1 Results of the search

On 14 July 2016 we performed electronic database searches which identified 202 articles with duplicates (48 in Pubmed, 61 in Medline, 20 in PEDro, 51 in the Cochrane Library, 18 in CINAHL and four in African-Wide Information) (Figure 4-1). One article was identified through searching the reference lists of relevant articles.[225] After removal of duplicates, 129 articles remained for further investigation. After inspection of the titles and abstracts, seven titles were found potentially relevant and the full text was obtained. Full text analysis revealed two articles which met the inclusion criteria.[221,222] One RCT was identified on pactr.org (closed to recruitment, follow up completed) and could be included in future reviews (PACTR201404000706382) (See Chapter 6 for results of this RCT).

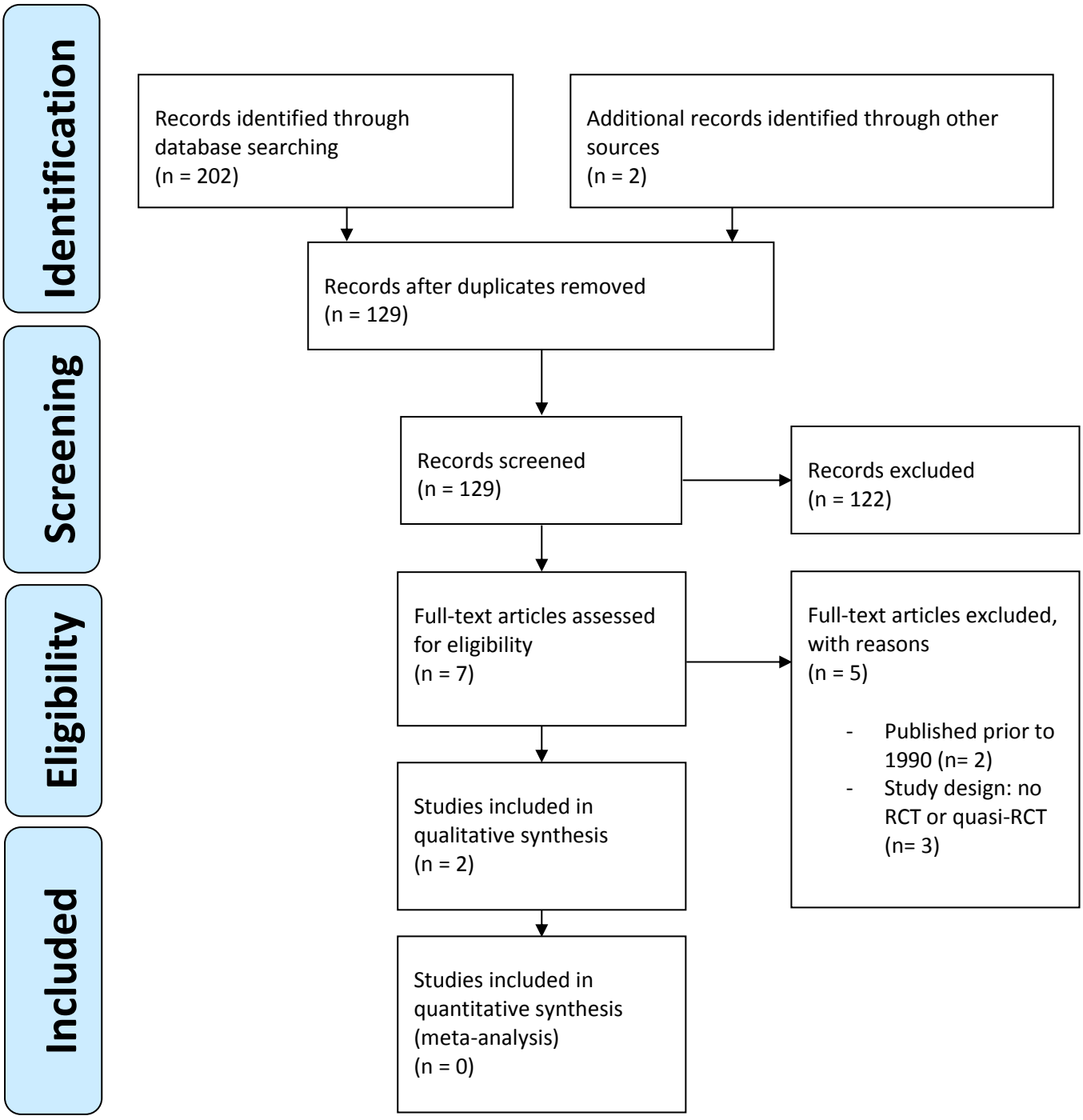


Figure 4-1. PRISMA study flow chart

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

4.4.2 Included studies

See Table 4-1 for characteristics of included studies. Both studies included in this review were RCTs conducted in a hospital setting in Brazil and written in English.[221,222]

Table 4-1. Characteristics of included studies.

Specific characteristics	Paludo et al.[221] (2008)	Lukrafka et al.[222] (2012)
Study design	RCT	RCT
Withdrawal/drop outs, n	9	7
Country	Brazil	Brazil
Research setting	Hospital	Hospital
Health condition	Acute pneumonia	Acute CAP
Severity of symptoms	Mild to moderate	Mild to moderate
Total sample enrolled, n	98	79
Total sample analysed, n	89	72
Age range	29 days - 12 years	1 - 12 years
Inclusion criteria	Acute pneumonia with: presence of cough and/or fever; tachypnoea; consolidations and/or infiltrates on CXR□	Hospitalised with acute CAP (clinically and radiologically diagnosed)
Exclusion criteria	Chest drain; haemodynamic instability (ND‡) bone fragility or rib fractures; any other contra-indication to ACT (ND‡)	Severely ill patients (ICU˜); chest drain; atelectasis detected by CXR□; history of pneumonia or pleural effusion in previous 6 months; other pulmonary disease; heart disease; CP or immune deficiency
Primary outcomes	Time to clinical resolution	Severity score and RR
Secondary outcomes	Length of hospital stay, persistence of respiratory symptoms and signs	Duration of hospitalisation

□CXR= chest X-ray, ‡ND= not defined, ˜ICU= intensive care unit

4.4.2.1 Participants

In total, 177 participants between the age of 29 days and 12 years were enrolled in the two trials. Sixteen were lost to follow up, therefore 161 participants were analysed (95 male and 66 females), with 82 participants in the intervention groups and 79 in the control groups. The study by Lukrafka et al. divided participants in two age groups, children younger than and older than five years of age.[222] This study included participants with acute CAP,[222] while the other study did not specify site of acquisition of acute pneumonia.[221] Both studies included participants with mild to moderate disease, but only one study clearly indicated disease severity in the article text.[222] In the other article disease severity was deduced as mild to moderate from the baseline characteristics of the

participants, as the mean SaO_2 was above 95%. However, mean RR at baseline was above 45 breaths per minute (bpm) which is higher than normal considering the age (Table 4-2).[221]

Table 4-2. Baseline characteristics of included studies

Characteristics	Paludo et al.[221] (2008)		Lukrafka et al.[222] (2012)	
Group allocation	Intervention	Control	Intervention	Control
Analysed, n	47	42	35	37
Male, n (%)	29 (62)	24 (57)	20 (57)	22 (59)
Age, mean (95%CI) or n (%)	44 months (31.6-56.4)	32.2 months (22.5-41.9)	12-59 months: 25 (71.4) 5-12 years: 10 (28.6)	12-59 months: 28 (75.7) 5-12 years: 9 (24.3)
Respiratory rate (*bpm*), mean (SD) (95%CI)	45 (14.3) (40.9-49.1)	45.8 (14.2) (41.6-50.1)	39.1 (9.9) (35.8-42.4)	38,3 (9.9) (35.1-41.5)
Fever, n (%)	45 (96)	37 (90)	7 (20)	8 (22)
SaO_2[221] or SpO_2[222] (%), Mean (SD) (95%CI)	95.0 (2.5) (94.3-95.7)	95.7 (2.3) (95.0-96.4)	96.5 (2.5) (95.7-97.3)	97.1 (2.1) (96.4-97.8)
Pleural effusion, n (%)	5/45 (11)	6/39 (15)	10 (29)	4 (11)

4.4.2.2 Intervention

An overview of the interventions can be found in Table 4-3. One trial compared standard treatment, consisting of antibiotic treatment, fluid therapy and oxygen therapy when needed, with ACTs as an add-on to standard treatment. ACTs included PD (PD positions were guided by chest X-ray findings), thoracic squeezing, percussions, vibrations, cough stimulation and aspiration/suctioning when necessary.[221] ACTs were given bi-daily for an average of 30 minutes per session.[221] The other trial compared recommended non-mandatory lateral positioning, cough and the performance of diaphragmatic breathing for five minutes per day in the control group, with ACTs in the intervention group.[222] In the intervention group, treatment depended on the child's age. Participants younger than five years of age were positioned in high side lying or high sitting positions, and manual thoracic vibrations, thoracic compressions, PEP technique and artificially stimulated cough or suctioning were performed. For participants older than five years of age, the same treatment was applied with the addition of breathing exercises and FET. Treatment was given three times a day for 10 to 12 minutes.[222]

Table 4-3. Description of interventions used in the included studies

Group allocation	Specific characteristics	Paludo et al.[221] (2008)	Lukrafka et al.[222] (2012)
Intervention	Techniques	Standard treatment and ACT: PD, thoracic squeezing, percussions, vibrations, cough stimulation, aspiration/suctioning when necessary. PD positions guided by CXR	<5 year: positioned in high side lying or high sitting, manual thoracic vibrations, thoracic compressions, PEP, artificially stimulated cough or suctioning >5 year: same as above + breathing exercises and FET
	Duration of treatment	±30 minutes/ treatment session	10-12 minutes/ treatment session
	Frequency of treatment	2x/ day until discharge	3x/ day until discharge
	Intensity of treatment	Unclear	Unclear
	Compliance to treatment	Unclear	Unclear
Control	Techniques	Standard treatment: antibiotics, fluid therapy and oxygen therapy as needed	Recommended non-mandatory request: lateral positioning, cough, perform diaphragmatic breathing
	Duration of treatment	Information not available	5 minutes (not mandatory)
	Frequency of treatment	Information not available	1x/ day (not mandatory)
	Intensity of treatment	Unclear	Unclear
	Compliance to treatment	Unclear	Unclear

CXR= chest X-ray

4.4.2.3 Outcome measures

The primary outcome measure of this review "duration of hospital stay", was reported in both trials as a secondary outcome measure.[221,222] The other primary outcome measure of this review, SaO_2/SpO_2 measured before and after intervention, was not assessed in the included studies. The other secondary outcome measures (RR measured before and after intervention, duration of oxygen supplementation, lung function tests measured at enrolment and discharge, any adverse effects or mortality) identified initially, were not reported in the included trials.

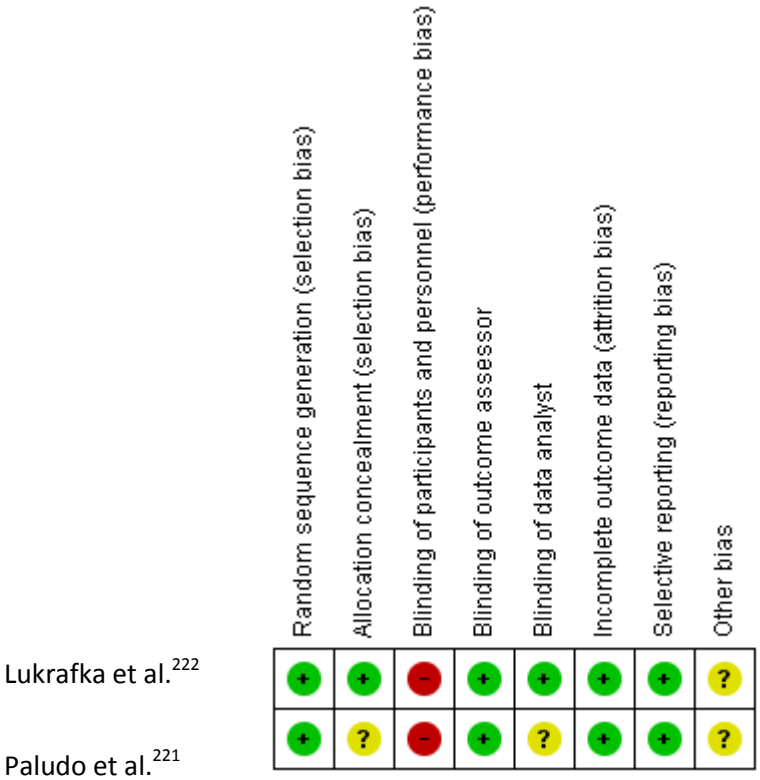
4.4.3 Excluded studies

Five articles did not meet the inclusion criteria and were excluded from this review. Two articles were outdated, with a publication date prior to 1990.[224,225] One of these studies included 55 children with presumed viral pneumonia,[224] whereas the other study included 171 participants between the ages of 15 and 75 years with acute pneumonia.[225] Three studies were excluded because of their

study design.[227,238,239] Stapleton described a case series of 55 children, in which 34 children with acute uncomplicated respiratory tract infections (26 with pneumonia, nine with bronchitis and 20 with bronchiolitis) received ACTs, compared to 21 children who did not receive ACTs.[227] Gilchrist performed a database search of the Cochrane Library, PubMed and PEDro for an answer to the structured clinical question "*In a child with CAP, does chest physiotherapy reduce the length of hospital admission?*".[238] Finally, Lisy presented a summary of the review by Chaves et al.[231,239]

4.4.4 Risk of bias in included studies

A detailed risk of bias analysis can be found in Table 4-4. A summary of the findings is presented in Figure 4-2.



Red = high risk of bias, yellow = unclear risk of bias and green = low risk of bias.

Figure 4-2. Risk of bias summary: review author's judgements about each risk of bias item for each included study

Table 4-4. Risk of bias

Type of bias		Paludo et al.[221]		Lukrafka et al.[222]	
		Authors' judgement	Support for judgement	Authors' judgement	Support for judgement
Generation of sequence		Low risk	Simple randomisation Table of random numbers	Low risk	Computerised random number generator to select blocks of 3 and 4
Allocation concealment		Unclear risk	No specifications on concealment	Low risk	Use of sequentially numbered opaque envelopes
Blinding	Participants	High risk	Participants knew in which group they were assigned	High risk	Participants knew in which group they were assigned
	Outcome assessor	Low risk	Investigators, nurses and physicians were blinded	Low risk	Study radiologist and epidemiologist blinded
	Data-analysts	Unclear risk	No information on data-analysts	Low risk	Data-analysts were blinded
Incomplete data		Low risk	Intention-to-treat principle applied Number lost to follow-up and reason loss to follow-up similar for both groups	Low risk	Intention-to-treat analyses performed Number lost to follow-up and reason loss to follow-up similar for both groups
Selective outcome reporting		Low risk	Primary and secondary outcome measures reported	Low risk	Primary and secondary outcome measures reported
Other potential threats		Unclear risk	Baseline characteristics were similar Groups were treated equally, except for treatment No other information available	Unclear risk	Baseline: tendency of more children with pleural effusion in intervention group Groups were treated equally, except for treatment No other information available

4.4.4.1 Generation of sequences

Both included studies were described as RCTs. One study applied simple randomisation by the use of a table of random numbers.[221] The other study used a computerised random number generator to select blocks of three and four.[222] Therefore the generation of sequence risk of bias was judged as being low for both studies.

4.4.4.2 Allocation

In the article by Paludo et al., no information was available on allocation concealment. Therefore the risk of bias was judged as being unclear.[221] In the article by Lukrafka et al. it is stated that sequentially numbered opaque envelopes were used to conceal allocation, therefore allocation concealment risk of bias was judged as being low for this study.[222]

4.4.4.3 Blinding

As it is nearly impossible to blind participants for treatment when performing ACT, both studies have a high inherent risk of bias. However, outcome assessors could be blinded to allocation. In one study, the investigators, nurses and physicians/paediatricians;[221] and in the other study, radiologist and epidemiologist;[222] were all blinded to allocation, therefore the outcome assessor's risk for bias was judged as being low for both studies. Further, in one study the data-analyst was reported to be blinded to allocation for which the risk of bias was judged as being low.[222] In the other study no information was available on blinding of the data-analyst, so the risk of bias was judged as being unclear for this aspect of the trial.[221]

4.4.4.4 Incomplete outcome data

In both studies, withdrawals were reported and the number of participants lost to follow up was similar for the intervention and control groups. Therefore the risk of bias was judged as being low for both studies. In the study by Paludo et al. nine participants (four in the intervention group and five in the control group) were withdrawn from the study.[221] Four of them were discharged or transferred before the second assessment (two in each group) and five met an exclusion criterion (two in the intervention group and three in the control group). Therefore, 89 from the 98 enrolled participants were analysed during follow-up (47 in the intervention group and 42 in the control group).[221] In the other study seven participants were withdrawn from the study (three in the intervention group and four in the control group) due to the insertion of a chest drain (in four participants, three in the intervention group and one in the control group) or atelectasis detected on the chest X-ray (in three participants in the control group).[222] Analysis was performed on the remaining 72 participants (35 in the intervention group and 37 in the control group).[222] Both studies applied intention-to-treat analysis.

4.4.4.5 Selective reporting

Both studies reported primary and secondary outcome measures, and therefore the risk of reporting bias was judged as being low.

One study selected time to clinical resolution, expressed in days, as their primary outcome measure.[221] They defined it as the number of days the patient needs to achieve: an afebrile state (maximal daily body temperature <37.5°C), absence of severe signs of respiratory distress (chest in-drawing, nasal flaring, cyanosis), and normal RR and SpO_2 ≥95%. The other study chose reduction of RR and severity score between baseline and discharge as their primary outcome measures.[222]

Both studies used length of hospital stay, expressed in days, as one of their secondary outcome measures.[221,222] 'Persistence of respiratory symptoms and signs' (cough, tachypnea, chest in-drawing, wheezing, adventitious sounds on lung auscultation, fever (not further defined), and SaO_2 <95%), expressed in days were the other secondary outcome measures used in the study by Paludo et al.[221]

4.4.4.6 Other potential sources of bias

None of the studies reported sufficient information to judge this risk, therefore the risk of bias was judged as being unclear. In both studies the groups were treated equally, apart from the ACT applied.[221,222] In the one study,[221] baseline characteristics were similar between both groups, but in the other study there was a tendency towards more participants with pleural effusion in the intervention group.[222] No other information was available.

4.4.5 Effects of intervention

No meta-analysis or pooling of data was possible due to different outcome measures used in the two included studies. Duration of hospital stay, whilst a common outcome measure in the included studies, could also not be pooled owing to the absence of the 95% CI of the data, precluding judgement of data spreading.

4.4.5.1 Primary outcome measures

Duration of hospital stay (in days)

Both studies reported length of hospital stay as a secondary outcome measure. In both studies, median number of days in hospital was reported and no significant difference between the groups was found (p= 0.76 and p= 0.11). In the study by Paludo et al.[221] the reported median length of stay was six days of hospitalisation for both groups. After consulting the authors of this article, the following additional information was made available: mean duration of stay for the intervention group was 7.8 days with a 95% CI of 6.6-9.0 days and a mean of 6.8 days for the control group with a 95% CI of 5.9-7.7 days. The other trial reported a median of 8 days in hospital for the intervention group (95% CI 5.1-10.9 days) and 6 days for the control group (95% CI 5.1-6.9 days).[222] We were unable to obtain mean values or 95%CI of duration of hospitalisation for this trial, therefore we were unable to pool data or perform a meta-analysis.

SaO_2/SpO_2 measured before and after intervention (transcutaneous or arterial blood gas analysis)

None of the included studies reported on this outcome measure.

4.4.5.2 Secondary outcome measures

Respiratory rate measured before and after the intervention

Neither of the studies reported on this outcome measure.

Duration of oxygen supplementation (in hours)

Neither study reported data on this outcome measure.

Lung function tests (spirometry): VC, FVC, FEV1, PEF, maximal inspiratory pressure and maximal expiratory pressure measured on enrolment and before discharge

This outcome measure was not assessed in the included studies.

Any adverse effects

None of the included studies reported any adverse effects due to the intervention or disease.

Mortality

Neither study included mortality as an outcome measure.

4.4.5.3 Other outcome measures

See Table 4-5 and Table 4-6 for an overview of the other outcome measures presented in the two included studies.

Except for duration of hospitalisation (reported as a secondary outcome measure), the studies included in this review used different outcome measures in their research. One of the studies reported time to clinical resolution, expressed in days, as their primary outcome measure.[221] No significant difference was seen between the intervention and control group (p= 0.8). The median time to clinical resolution was four days in both groups, with an interquartile range (IQR) of 2.0-7.0 in the intervention group and 3.0-6.0 in the control group. After consulting the authors, mean values and 95% CI were made available. The mean time to clinical resolution in the intervention group was 4.4 days, with a 95% CI of 3.3-5.6 and 4.3 days in the control group, with a 95% CI of 3.4-5.4.[221]

The other study used reduction of RR and severity score, comparing baseline with discharge results, as their primary outcome measures.[222] Both groups showed a significant improvement in outcomes between baseline and discharge (p<0.001), but there were no significant between-group differences for reduction in RR (p= 0.7) and severity score (p=0.6) (Table 4-5).[222]

The study by Paludo et al. reported 'persistence of respiratory symptoms', expressed in days, as another secondary outcome measure.[221] No significant difference between the intervention and control group were reported (Table 4-6), except for a longer duration of coughing (p=0.04) and a longer duration of rhonchi (p=0.03) in the intervention group. The median duration of coughing was 5 days (IQR 4.0-8.0) in the intervention group and 4 days (IQR 3.0-6.0) in the control group. Mean (95% CI) values for this outcome measure were 6.1 days (5.1-7.1) for the intervention group and 4.7 days (3.9-5.6) for the control group. Comparing the duration of rhonchi, the intervention group had a median (IQR) duration of 2 days (0.0-4.0) and the control group 0.5 days (0.0-2.0). Authors further reported a mean duration of ronchi of 2.8 days with a 95% CI of 1.8-3.8 for the intervention group and 1.2 days with a 95% CI of 0.5-1.9 for the control group.[221]

Table 4-5. Other primary outcome measures

Outcome measure	Study and number of participants	Data-presentation	Intervention	Control	p-value
Time to clinical resolution in days	Paludo et al.[221] n=89	Median (IQR) Mean (95%	4.0 (2.0-7.0) 4.4 (3.3-5.6)	4.0 (3.0-6.0) 4.3 (3.4-5.4)	0.84
Reduction of RR (*bpm*)	Lukrafka et al.[222] n= 72	Mean (SD) (95%CI) p-value within	Baseline: 39.1 (9.9) (35.8-42.4) Discharge: 31.6 (6.9) (29.3-33.9) p***<0.001***	Baseline: 38.4 (9.8) (35.2-41.6) Discharge: 32.5 (8.3) (29.8-35.2) p***<0.001***	0.9 0.7
Severity score	Lukrafka et al.[222] n= 72	Mean (SD) (95%CI) p-value within group	Baseline: 2.1 (1.6) (1.6-2.6) Discharge: 0.6 (0.8) (0.3-0.8) p***<0.001***	Baseline: 1.8 (1.1) (1.4-2.1) Discharge: 0.4 (0.6) (0.2-0.6) p***<0.001***	0.2 0.6

P-values are presented as reported in the original article

Table 4-6. Other secondary outcome measures

Outcome measure		Study and number of participants	Data presentation	Intervention	Control	p-value
Persistence of respiratory symptoms (*days*)	Time to normal RR	Paludo et al.[221] n=89	Median (IQR) Mean (95% CI)	3.0 (0.0-7.0) 3.6 (2.4-4.8)	3.0 (1.0-6.0) 3.3 (2.2-4.4)	0.75
	Time to normal SaO_2			1.0 (0.0-2.0) 1.0 (0.5-1.4)	0.5 (0.0-2.0) 0.8 (0.4-1.3)	0.98
	Time to normal lung auscultation			4.0 (3.0-6.0) 4.7 (3.5-5.9)	4.0 (2.0-6.0) 4.1 (3.1-5.0)	0.28
	Duration of fever			2.0 (0.0-2.0) 1.4 (0.8-1.9)	1.0 (0.0-3.0) 1.5 (0.7-2.3)	0.78
	Duration of coughing			5.0 (4.0-8.0) 6.1 (5.1-7.1)	4.0 (3.0-6.0) 4.7 (3.9-5.6)	***0.04***
	Duration of parent's reported wheezing			1.5 (0.0-5.0) 2.9 (2.0-3.9)	1.0 (0.0-3.5) 1.7 (1.0-2.4)	0.29
	Duration of fine crackles			0.0 (0.0-2.0) 1.1 (0.6-1.6)	0.0 (0.0-2.0) 1.2 (0.5-1.8)	0.72
	Duration of coarse crackles			2.0 (0.0-4.0) 2.1 (1.3-2.7)	1.0 (0.0-3.0) 2.0 (1.1-2.8)	0.83
	Duration of wheezes			0.0 (0.0-5.0) 1.7 (1.0-2.5)	0.0 (0.0-4.0) 1.8 (0.8-2.7)	0.62
	Duration of rhonchi			2.0 (0.0-4.0) 2.8 (1.8-3.8)	0.5 (0.0-2.0) 1.2 (0.5-1.9)	***0.03***
	Duration of chest in-drawing			2.0 (0.0-3.0) 1.8 (1.3-2.4)	2.0 (0.0-3.0) 2.0 (1.2-2.8)	0.75

P-values are presented as reported in the original article

4.5 Discussion

4.5.1 Summary of main results

This review included two RCTs, one of which compared standard treatment for pneumonia with additional conventional ACT,[221] and one that compared recommended non-mandatory positioning, cough and diaphragmatic breathing with conventional ACT combined with PEP in all children and FET in children older than five years of age.[222] The latter study did not make a distinction between the two age categories (younger and older than five years) with regards to control group interventions.[222] It is questionable if and how diaphragmatic breathing was achieved with young, uncooperative children.

The intended primary outcome measure of this review, duration of hospitalisation, was investigated in both studies and I have to conclude that ACT did not have an influence on the duration of hospitalisation. However, the study by Lukrafka et al. did report a two day difference between the intervention and control group, with a longer duration of hospitalisation for the intervention group.[222] This study might have been underpowered to detect a significant difference between the two groups. The other outcome measures of this review were not assessed in the included studies,

therefore we cannot comment on the effectiveness of ACT with regards to these outcomes. Conventional ACT was not found to have an influence on time to clinical resolution.[221] There was also no influence of conventional ACT combined with PEP (and FET in children older than five years of age) on the reduction of RR and severity score.[222] Investigation of the outcome measure 'persistence of respiratory symptoms', described in the study by Paludo et al., suggests signs of improvement when using ACT.[221] However, a longer duration of coughing and rhonchi in the participants receiving conventional ACT was also reported.

4.5.2 Overall completeness and application of evidence

The included studies were both RCTs,[221,222] but only one study reported the method of allocation concealment.[222] Not all the review's objectives have been addressed; as the included studies did not comment on adverse events or mortality and I was unable to compare one technique to no physiotherapy or to another type of ACT. Both studies combined multiple ACTs in their intervention group, which makes it impossible to draw conclusions regarding individual techniques. Only one of our pre-set outcome measures, duration of hospital stay, was reported in the studies. The other primary outcome measures, SaO_2/SpO_2 measured before and after intervention and the secondary outcome measures, RR measured before and after intervention, duration of oxygen supplementation (in hours), lung function tests (spirometry): VC, FVC, FEV_1, PEF, maximal inspiratory pressure and maximal expiratory pressure measured on enrolment and before discharge, any adverse effect and mortality were not addressed in the included studies. As different outcome measures were use in the studies with different presentation of results, it was not possible to compare all the data. The study by Lukrafka et al. used severity scores to express baseline and discharge symptoms, but no separate reporting of the symptoms, such as SpO_2 and fever, were available for analysis.[222] The study by Paludo et al. did report the duration of symptoms as median and IQRs, and the authors made mean and 95% CI available for analysis.[221] But due to the lack of comparable data, no meta-analysis was possible in this review. Further, one study described the condition as 'acute pneumonia',[221] while the other study described it as 'CAP'.[222] It is therefore unclear whether the studies described the same condition. Lastly, both studies were conducted in Brazil, which limits the generalisability of the findings.

4.5.3 Quality of the evidence

Two studies, analysing 161 participants who were randomly assigned to the intervention or control groups, were included in this review. The weakness of these studies included risk of bias, multiple ACTs used in the intervention groups, different definitions of the included disease, differing severity

of symptoms and different outcome measures, which makes it difficult to make an overall conclusion. Only one study reported allocation concealment in their article.[222] Due to the nature of the intervention it is impossible to blind the participants of the research, therefore both studies did not comment on this in their studies. The outcome assessors were blinded in both trials, as was the data-analyser in the study by Lukrafka et al.[222] The blinding of data-analysts was not mentioned in the study by Paludo et al. (for which the risk of bias was unclear).[221] There was inadequate information available to eliminate other potential threats to the validity of the studies.

4.5.4 Potential biases in the review process

Six different databases were searched, as well as checking the reference lists of all relevant articles and searching clinicaltrial.gov and pactr.gov registry to identify potential studies for this review. I contacted the authors of the articles to gather more information with regards to mean and 95% CI of all included data, but only one author replied.[221] No articles were excluded due to language, which reduces the risk of selective data reporting. Although, two articles were excluded on the basis of publication date, which might have increased the risk of selective data reporting, the major changes in the field of ACT ought to justify the exclusion of these studies. I might have missed studies reported in non-peer reviewed journals or data-bases, or studies presented at local conferences, which may lead to a potential bias. Grey literature was not searched, therefore, one RCT which compared PD, vibrations, percussions, thoracic squeezing and cough assist with standard care in 50 children between the age of 29 days and 5 years was not included in this review (see Table 3-1).[223] The study reported some improvement in the time to clinical resolution, RR and SpO_2 in the intervention group; however, it is unclear how randomisation was performed and allocation concealment was maintained with potential for introduction of bias.[223] One important potential bias is the identification of the ongoing clinical trial identified through pactr.gov, as this study is one conducted towards this degree (Chapter 6).

4.5.5 Comparison with other studies or reviews

Although two non-RCTs suggested positive effects of ACT (one in a sample of children with CAP,[228] and one on HIV-infected children receiving ARV therapy)[226], a recently published review on ACT for pneumonia in children concludes that although some minor improvements can be found in children receiving ACT, they were unable to pool the data and make generalisable conclusions.[231] However, the review by Chaves et al. differs from this review with regards to the included types of pneumonia and the definition of ACT, as they included a study which used nasal CPAP, a type of non-invasive ventilatory support, and not ACT.[231] Another published review on ACT in adults with pneumonia

included six trials and concluded that osteopathic manipulations and PEP could reduce the length of hospitalisation; PEP might reduce the duration of fever; and osteopathic manipulations could reduce duration of antibiotic treatment.[230] However, the overall conclusion indicated that there was insufficient evidence to support the use of ACT in this population.

4.6 CONCLUSION

4.6.1 Implications for practice

Due to the limited number of included articles and the inability to pool data for meta-analysis, it is impossible to make clear, justified recommendations for clinical practice. Therefore we cannot reject or recommend ACT as a standard treatment option in children with pneumonia.

4.6.2 Implications for research

There is clearly a need for more RCTs in this field of research. The two included RCTs used a combination of several conventional ACTs, none investigating the use of AD or AAD in children with pneumonia. The use of several different ACTs makes it impossible to make conclusions or recommendations on one single treatment. Each treatment should ideally be tested separately, rather than using in a multi-modal approach, and standardised, to identify its influence in the treatment of pneumonia as each ACT has a different mechanism of action (see section 2.3). Furthermore, research is recommended with adequate sample sizes (which could allow sub-analysis of different severity levels of pneumonia); clear, standardised control interventions; appropriate outcome parameters and clear analysis of adverse events and mortality. This need was attempted to be addressed as outlined in Chapter 6.

Chapter 5. THE USE OF AIRWAY CLEARANCE THERAPY IN CHILDREN HOSPITALISED WITH ACUTE LOWER RESPIRATORY TRACT INFECTIONS IN A SOUTH AFRICAN TERTIARY HOSPITAL

5.1 INTRODUCTION

As mentioned previously, ACT is often used in the clinical management of children with LRTI, including pneumonia. However, there is little documentation available on the prescription, frequency and nature of ACT. Most importantly, there is little published data regarding adverse events that may be associated with ACTs in children with LRTI. A better understanding of the use of ACT in clinical practice is warranted.

5.2 AIM AND OBJECTIVES

The overall aim of the study was to develop a better understanding of the role ACT plays in the management of children with LRTI, including pneumonia, admitted to a specialised tertiary paediatric hospital in the Western Cape of South Africa.

The specific objectives were to determine, in children hospitalised with LRTI at a teriary paediatric hospital in Cape Town, South Africa, from January 2015 to June 2015 (from mid-summer to mid-winter):

1) The demographic details, characteristics, medical diagnoses and comorbid conditions.
2) The proportion of children receiving mechanical ventilation and the duration of these interventions; and the proportion of children receiving supplemental O_2 at time of admission.
3) The proportion of children who received ACT during their admission.
4) The nature, frequency and duration of ACT.
5) Which variables were associated with receiving ACT, including:
   - disease severity (determined by RR, heart rate (HR), the need for mechanical ventilation during hospitalisation and/or O_2 supplementation at the time of admission)
   - comorbidities (chronic cardiovascular and lung diseases, prematurity, NMD, cerebral palsy (CP), among others)
6) The incidence and nature of adverse events associated with ACT (these are documented as part of standard practice with each physiotherapy treatment)
7) Which factors are associated with adverse events related to ACT, including:
   - disease severity (determined by RR, HR, the need for mechanical ventilation during

hospitalisation and/or O_2 supplementation at the time of admission)

- comorbidities (chronic cardiovascular and lung diseases, prematurity, NMD, CP, among others)

8) Patient outcomes:
   - length of hospital stay
   - mortality
9) The influence of various variables on these patient outcomes.

5.3 METHODOLOGY

5.3.1 Study design and research setting

A retrospective descriptive study was conducted, based on record review. Folder information of children hospitalised at the research site, with a clinical diagnosis of community- or hospital acquired LRTI, was extracted. The study period was extended to account for a seasonal change in admissions to the institution.

5.3.2 Participants

Children hospitalised with community- or hospital acquired LRTI at any ward at the research site (Intensive Care Unit, medical, surgical and specialist wards), for which the medical files were available, were included in the study.

Participants in the intervention group of the study on the use of AAD in children with acute respiratory disease in South Africa (Chapter 6) were included for research objectives 1) to determine the demographic details, medical diagnoses and complications; 2) proportion of children receiving mechanical ventilation and the duration of these interventions; and proportion of children receiving O_2 supplementation at time of admission; 8) patient outcomes and 9) the influence of various variables on these patient outcomes. However, as these children received bidaily AAD for research purposes, they were excluded from the other analyses.

The sample was population-based, aimed at including the entire population of children admitted with a LRTI during the six-month time frame.

5.3.3 Outcome measures/instrumentation

A standard pre-structured data extraction form was developed (Appendix 5). Table 5-1 lists the different items with reasons for inclusion in extraction form.

Table 5-1. Reason for including items in data extraction form

Category	Item	Reason for inclusion
General information	Folder number	To identify which folders have been completed and to be able to return to the folder when information was incomplete. This item was removed from the excel datasheet after completion of the analyses.
	Date of birth	To be able to calculate the child's age at admission
	Gender	For demographic description of the population and to investigate whether gender influences the chance of receiving ACT
	Prematurity/gestational age	Children born younger than 30 weeks gestational age are more prone to chest infections and chronic lung disease. Therefore this item would be added to the demographic information and used as a variable for predicting the need for ACT
	HIV status	For demographic purposes as the incidence of HIV is still high in South Africa. HIV infected and exposed children are also more prone to chest infections. This item was therefore intended to be used in the logistic regression for predictors of ACT
	History of TB	For demographic purposes regarding medical history and as an influencing factor for receiving ACT
	Asthma	For demographic purposes regarding comorbid conditions, and to identify factors which could influence: - the need for ACT - the likelihood for adverse events due to ACT - duration of hospital stay
	CF	
	Other respiratory disease	
	NMD	
	CP	
	Heart disease	
	Chest deformities	
	Osteoporosis	For analyses of adverse events as this condition can lead to rib fractures during ACT
	History of thoracic or abdominal surgery	ACT could influence the surgical site if the surgery was performed in recent history. Therefore this item was included for adverse event purposes
Current admission	Date of admission	To calculate the age at admission
	Age	For demographic purposes. Furthermore, age will influence vital signs, especially HR and RR, and could influence patient outcomes
	Temperature at admission	For determining disease severity and to be included in the analyses of the association between ACT and disease severity
	RR at admission	
	HR at admission	
	SpO_2 at admission	
	Signs of respiratory distress	
	O_2 supplementation on admission	
	Mechanical ventilation	
	Type of organism (bacterial, viral, mixed, unknown)	To determine disease organism which could be influencing the need for ACT, adverse events and patient outcomes
	Date of discharge	To calculate length of stay
	Days of hospitalisation	As this is one of the study's outcome measures
Adverse events	Pneumothorax	To identify any adverse events related to ACT. Data was recorded as presented in the medical files. Increased intracranial pressure was based on clinical report such as bulging fontanel and altered mental state.
	Increased intracranial pressure	
	Pleural effusion	
	Rib fractures	
	Lung/lobar collapse	
	Atelectasis	
Airway clearance therapy	Was ACT prescribed?	Not all children who have been prescribed ACT receive it. This item will therefore be used to identify for which children ACT is prescribed
	Was ACT given?	As above, therefore this item will identify which children are more likely to receive ACT
	When was ACT started?	To identify the nature and frequency of ACT, as well as to identify when ACT is commenced.
	How often was ACT given?	
	Which techniques were used?	
	Desaturation	To identify this adverse event during ACT

This data extraction form was validated for content by two experts, one in the field of epidemiology and one in the field of paediatric cardiopulmonary physiotherapy. The following items were added to the data extraction form after feedback: 1) history of pneumothorax, 2) other types of LRTI, 3) blood pressure, 4) mortality outcome, and 5) whether or not other forms of physiotherapy were performed.

Data were collected from the patients' medical records. The medical files include all patients' characteristics (e.g. age, gender, disease severity and comorbidit conditions) and whether or not physiotherapy (either ACT or other forms of physiotherapy) was given to the child. It is standard procedure for physiotherapy staff to document their assessment findings, treatment techniques and outcomes of treatment, including adverse events, in the patient's medical file. The following specific adverse events were screened for in the medical files: desaturation during and/or post treatment, pneumothorax, pleural effusion, increased intracranial pressure, lung/lobar collapse, rib fractures and atelectasis.

Magpi, a mobile data collection tool (available from home.magpi.com), was used to extract and digitalise data.

5.3.4 Procedure

Approvals from the Human Research Ethics Committee (HREC) of the University of Cape Town and the medical superintendent at the research site were obtained (Appendix 6). A waiver of the need for written informed consent was obtained from the HREC, as this study was a retrospective, low risk study.

5.3.4.1 Identification of folders

After consulting clinical staff, the following method of identifying folders was found most suitable: eligible patients were identified via Clinicom, using ICD10-codes of the primary admission diagnosis. The folders of patients with the following primary diagnoses were screened: pneumonia, bronchiolitis, LRTI and respiratory distress (see Appendix 7 for a complete list of searched ICD 10-codes). In addition, clinical physiotherapy staff allowed access to their records of patients referred for ACT for the period under study.

5.3.4.2 Quality assurance

A research assistant assisted with extracting folders from medical records and data collection. She received an explanation of the pre-set data extraction form and Magpi data collection tool prior to

data collection. For the first hour of data collection, I was in close proximity so the research assistant could ask questions when necessary. Further, I was always reachable telephonically if there were any queries that needed to be resolved. The research assistant and I both collected data from different folders. At the end of data collection, ten folders were randomly selected from the list of eligible folders and data were extracted once more, by the other data collector, to ensure data were entered consistently. For most cases and outcome measures, 100% agreement was obtained. However, it was noted that HIV status was entered inconsistently. In the cases where the child's HIV status was 'unexposed' as reported by the parents, the research assistant indicated this as 'unknown' HIV status, whereas I indicated this as 'unexposed'. In the case of HIV positive, negative and exposed, good agreement was obtained. Therefore, caution is needed when interpreting HIV unexposed and unknown data. This item has therefore not been used for further analyses in this study.

5.3.4.3 Data capturing

Medical folders were obtained from the medical records office. All folders remained at the medical records office to minimise interference with the daily activities at the research site. Patient details were de-identified. All data were immediately entered into Magpi, which is a password protected online data capturing system. Data were exported from Magpi into a password protected Excel spreadsheet.

5.3.4.4 Data analysis

Data were analysed with Statistica Version 13 (Statsoft Inc, USA). Descriptive statistics were performed for demographic information; the nature, frequency and duration of treatment; incidence and nature of adverse events; and patient outcomes. Proportions were presented as percentages. Data were tested for normality using the Lilliefors test. All numerical data were presented as either mean (standard deviation (SD)) or median (IQR). Chi-square, Fisher exact and Yates test were performed for categorical data. Finally, ORs of various variables for receiving ACT and adverse events were calculated and logistic regression analyses were performed. The influence of various variables on the patient outcome measures were analysed using multiple regression analysis.

5.4 RESULTS

In total, 1756 cases were identified based on primary ICD10 codes and the Physiotherapy Department's patients list (Figure 5-1), of which 399 folders were duplicates, leaving 1357 folders for

screening for eligibility. Fifty-four folders were excluded as the child did not, in fact, have a LRTI (see Table 5-2 for reasons of hospitalisation) and 93 folders were missing or missed the relevant doctors' notes, for which no information could be extracted. Therefore, a total of 1208 patient folders were included in this descriptive folder review. Of these, 1038 patients (85.9%) were hospitalised once between January and June 2015. The remaining 172 (14.2%) were hospitalised multiple times within six months.

Table 5-2. Reasons for hospitalisation of excluded folders

Category	Reason for hospitalisation	N	Percentage
	No LRTI, not further specified	9	16.7
Post-surgery	Cardiac surgery	7	13.0
	Sternotomy	1	1.9
	Thoracic surgery	1	1.9
	PEG surgery	1	1.9
	Hip surgery	1	1.9
	Gunshot wound	1	1.9
	Kasai surgery	1	1.9
Respiratory	Bronchospasm, not LRTI induced	3	5.6
	Chronic lung disease, no acute infection	3	5.6
	Lung abscess	1	1.9
	Bronchiolitis obliterans pulsing	1	1.9
	Upper respiratory tract infection (URTI)	1	1.9
	Asthma exacerbation due to URTI	1	1.9
	Pulmonary oedema due to chronic heart disease	1	1.9
	Trachea stenosis	1	1.9
	Croup, no other LRTI	1	1.9
Neurological	Meningitis	3	5.6
	Herpes encephalitis with URTI	1	1.9
Other	Chicken pox	5	9.3
	Pneumothorax after motor vehicle/pedestrian accident	2	3.7
	TB pericarditis	1	1.9
	Erythrodema	1	1.9
	Follow up kidney transplant	1	1.9
	Measles without LRTI	1	1.9
	Neuromuscular chest pain	1	1.9
	Observation for new treatment technique	1	1.9
	Admitted before the study period	1	1.9
	Folder of the mother of one of the hospitalised children	1	1.9
Total		**54**	**100**

N= 54 excluded folders

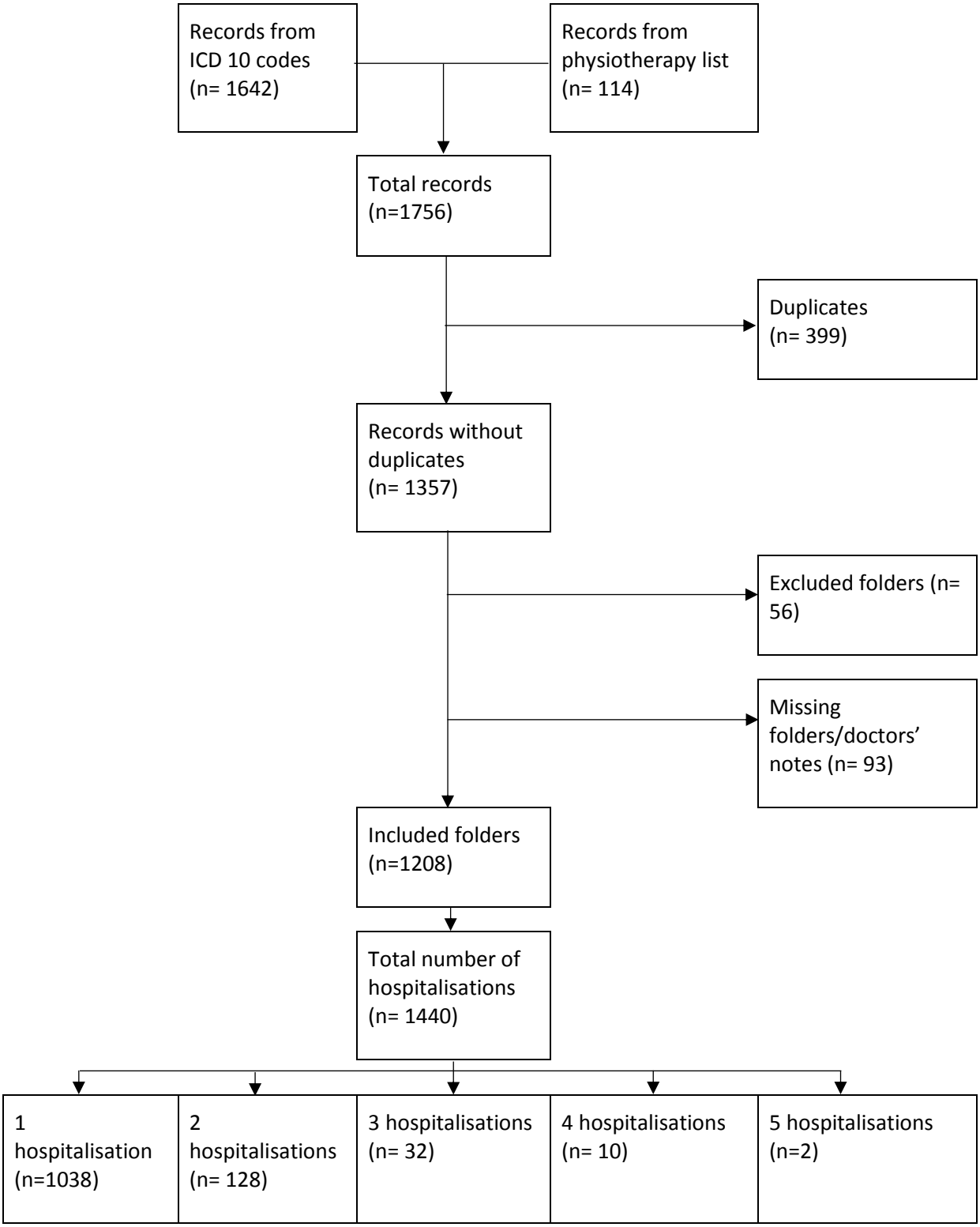


Figure 5-1. Folder review flow chart

5.4.1 Demographic information

The median age of children hospitalised with a LRTI at the research site within the time frame of January to June 2015 was 7.6 months (IQR 2.8-19.0). Frequency distribution in years is presented in Figure 5-2. The majority was male (59.6%), confirmed HIV negative (57.9%) and born at term (≥37 weeks gestational age (64.2%)). Data were based on the first hospitalisation for each patient in the study period (n=1208).

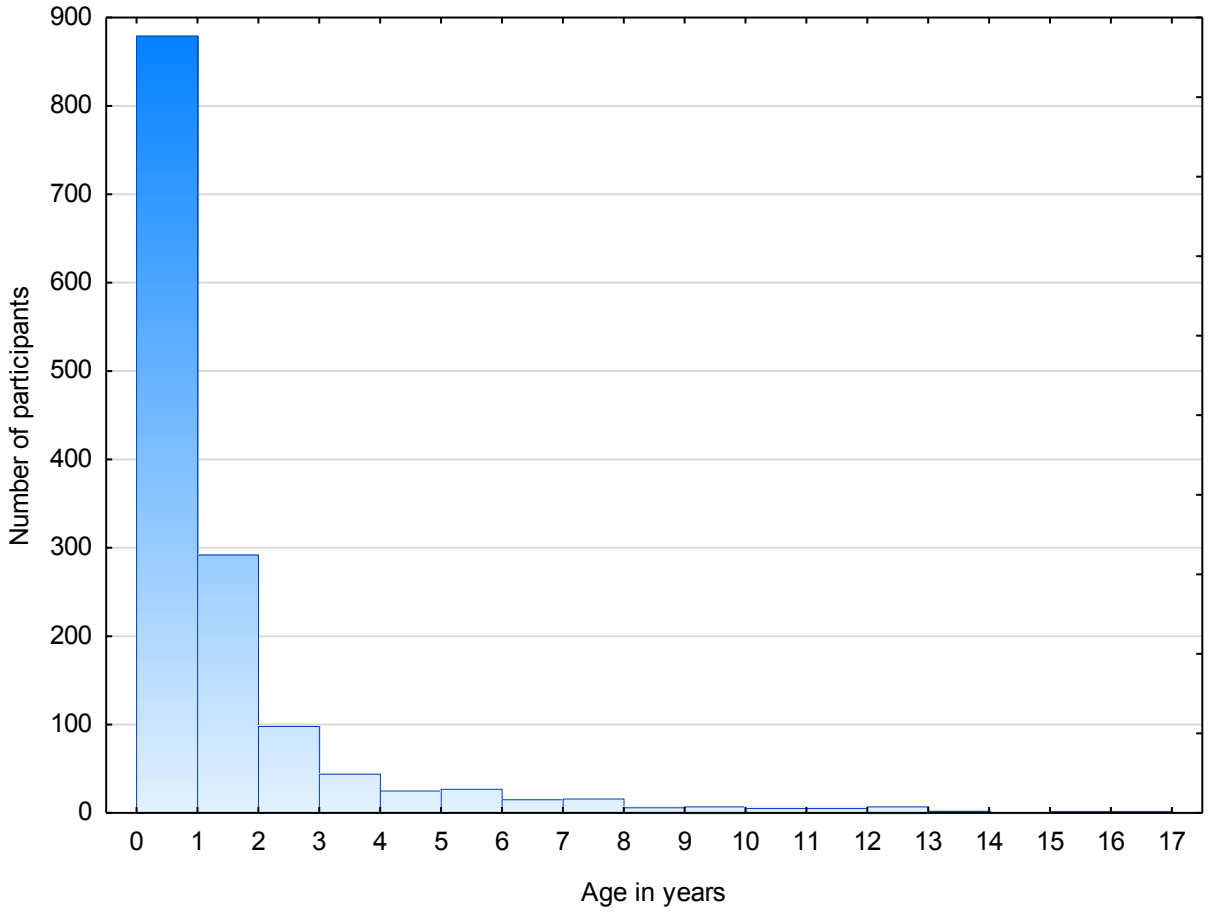


Figure 5-2. Frequency histogram for age in years

Thirty-five children were HIV infected, 29 (82.9%) of whom had received ARV therapy prior to or at the time of admission. No information was available regarding ARV therapy for the other six patients. The median duration of ARV therapy before admission was 63 days (IQR 0.0-117.0).

5.4.2 Health condition

5.4.2.1 Primary diagnosis

Most hospitalisations were primarily for the management of bronchiolitis, followed by pneumonia, unspecified acute LRTI, and other conditions (Figure 5-3). No primary diagnosis was available for 106 (7.4%) hospitalisations, which were presumed to be nosocomial infections by the researchers. An overview of the ICD-10 codes for primary diagnosis can be found in Table 5-3.

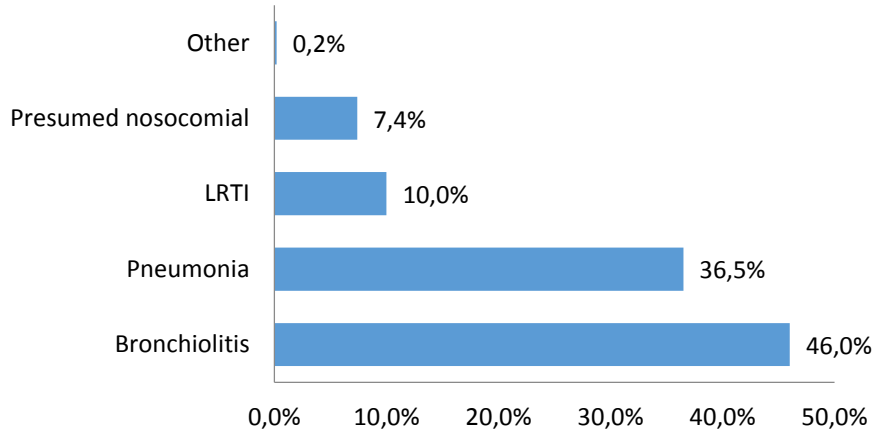


Figure 5-3. Primary diagnoses of the included hospitalisations

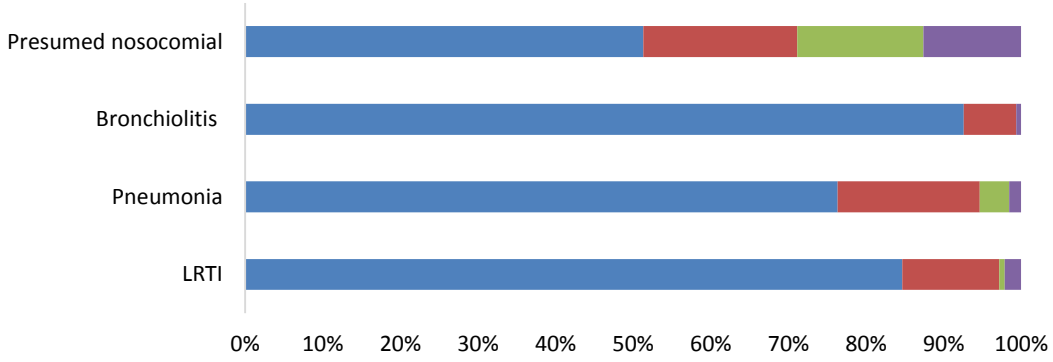
Table 5-3. Overview of ICD-10 codes for primary diagnosis

Aetiology	ICD-10 code	Description	N	Percentage
Bronchiolitis	J21.X	Acute bronchiolitis	1	0.1
	J21.0	Acute bronchiolitis due to RSV	3	0.2
	J21.9	Acute bronchiolitis, unspecified	658	45.7
	Total		**662**	**46.0**
Pneumonia	J12.0	Adenoviral pneumonia	6	0.4
	J12.1	Respiratory syncytial virus pneumonia	2	0.1
	J12.8	Other viral pneumonia	2	0.1
	J12.9	Viral pneumonia, unspecified	1	0.1
	J13.X	Pneumonia due to Streptococcus pneumoniae	1	0.1
	J15.9	Bacterial pneumonia, unspecified	1	0.1
	J18.0	Bronchopneumonia, unspecified	137	9.5
	J18.1	Lobar pneumonia, unspecified	14	1.0
	J18.9	Pneumonia, unspecified	361	25.1
	Total		**525**	**36.5**
Unspecified LRTI	J22.X	Unspecified acute LRTI	144	10.0
	Total		**144**	**10.0**
Other	B01.8	Varicella with other complications	1	0.07
	B01.9	Varicella without complications	1	0.07
	B20.7	HIV disease resulting in multiple infections	1	0.07
	Total		**3**	**0.2**

N= 1440 hospitalisations

5.4.2.2 Associated organisms

Positive sputum or blood cultures were available in 245 hospitalisations (17.0%). Figure 5-4 and Table 5-4 present the prevalence of associated organisms, for each diagnostic category, as identified on sputum or blood culture. One child in the category “other” tested positive for RSV and Cytomegalovirus.



	LRTI	Pneumonia	Bronchiolitis	Presumed nosocomial
Unspecified	84,7%	76,4%	92,6%	53,8%
Viral	12,5%	18,3%	6,8%	20,8%
Mixed	0,7%	3,8%	0,0%	17,0%
Bacterial	2,1%	1,5%	0,6%	13,2%

Figure 5-4. Prevalence of identified organisms per diagnostic category

N= 1440 hospitalisations, presented as 100% stacked histograms per diagnostic category

Table 5-4. Prevalence of viral and bacterial organisms

Category	Organism	Total, n(%)	Bronchiolitis, n	Pneumonia, n	LRTI, n	Presumed nosocomial, n
Viral	RSV	108 (44.1%)	27	57	10	13
	Rhinovirus	92 (38.0%)	18	51	7	17
	Adenovirus	79 (32.2%)	19	36	11	12
	Boca virus	32 (13.1%)	9	16	4	3
	Parainfluenza	25 (10.2%)	5	14	5	1
	Influenza	19 (7.8%)	4	7	4	4
	Enterovirus	17 (6.9%)	2	13	1	1
	Human corona virus	15 (6.1%)	1	10	0	4
	Cytomegalovirus	11 (4.5%)	1	7	0	2
	Human metapneumovirus	3 (1.2%)	0	2	0	1
	Parvo virus	1 (0.4%)	1	0	0	0
	Total viral organisms	**402**	**87**	**213**	**42**	**58**
Bacterial	Mycobacterium tuberculosis	12 (4.9%)	1	7	1	3
	Klebsiella pneumonia	11 (4.5%)	1	4	1	5
	Pseudomonas aeruginosa	9 (3.7%)	0	2	0	7
	Haemophilus influenzae	8 (3.3%)	1	0	1	6
	Staphylococcus aureus	6 (2.4%)	0	1	0	5
	Streptococcus pneumoniae	4 (1.6%)	0	1	0	3
	PJP	4 (1.6%)	0	4	0	0
	Acinetobacter baumannii	3 (1.2%)	0	1	0	2
	Escherichiac coli	3 (1.2%)	0	2	0	1
	Methicillin-resistant Staphylococcus aureus	2 (0.8%)	0	1	0	1
	Moraxella	2 (0.8%)	0	1	0	1
	Enterobacter cloacae	2 (0.8%)	0	0	0	2
	Serratia marcescens	1 (0.4%)	1	0	0	0
	Stenotrophomonas maltophilia	1 (0.4%)	0	0	0	1
	Unspecified gram positive bacteria	10 (4.1%)	0	7	0	3
	Total bacterial organisms	**78**	**4**	**31**	**3**	**40**
Total		**480**	**91**	**244**	**45**	**98**

N= 245 sputum/blood tests, multiple responses per test possible

5.4.2.3 *Chest X-rays*

Chest X-ray findings were reported in the medical file in 1010 cases (70.1%). Data were extracted from the files as reported by the attending physician and are presented in Table 5-5.

Table 5-5. Frequency of chest X-ray findings

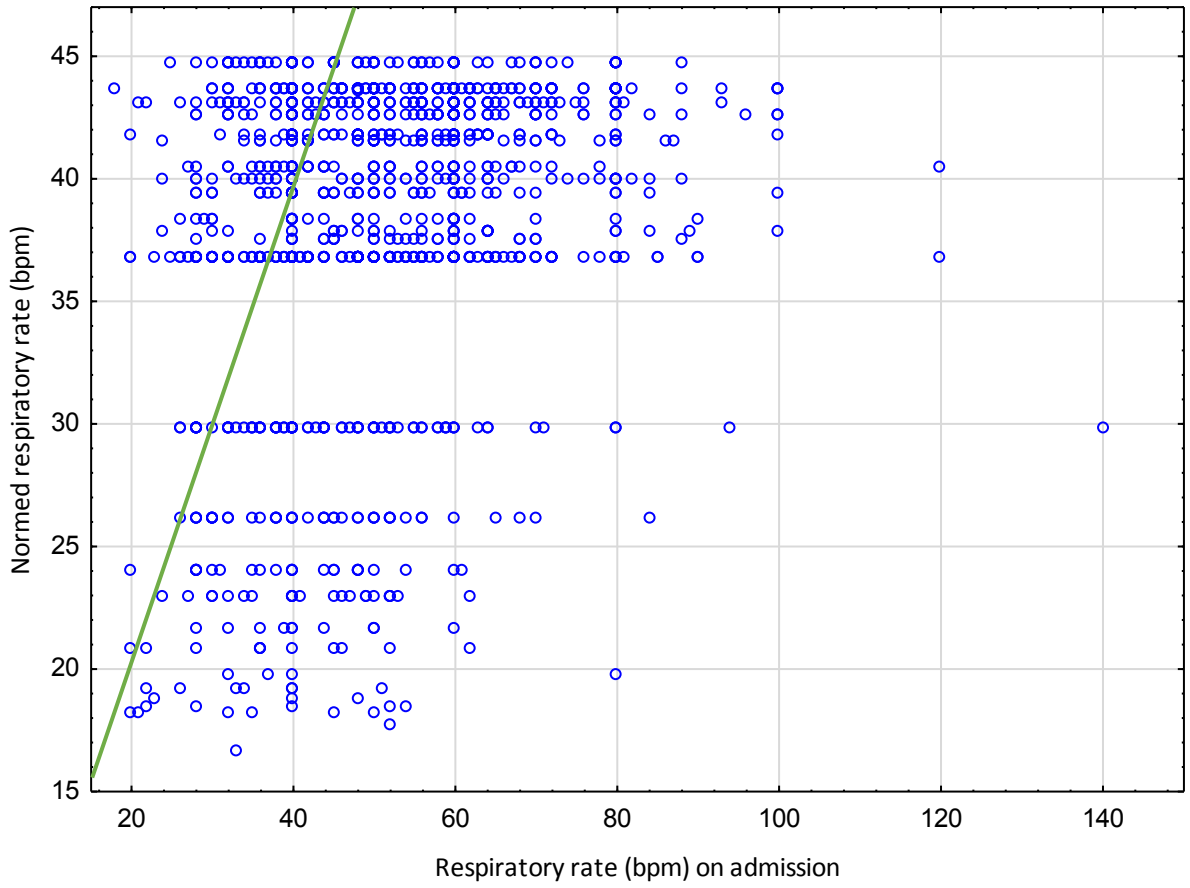
Category	X-ray finding	N	Percentage
Consolidation/infiltrates	Right middle lobe	322	31.9
	Bilateral	263	26.0
	Right upper lobe	194	19.2
	Right lower lobe	172	17.0
	Perihilar	152	15.0
	Left lower lobe	134	13.3
	Multilobar	87	8.6
	Left upper lobe	55	5.4
	Left lingual	24	2.4
	Total consolidation/infiltrates	**1403**	
Other	Hyperinflation	429	42.5
	Air bronchogram	36	3.6
	Diffuse opacification	30	3.0
	Air trapping	25	2.5
	Collapse	24	2.4
	Airspace disease	22	2.2
	Nodes	22	2.2
	Pleural effusion	21	2.1
	Diffuse ground glass opacification	12	1.2
	Total other findings	**621**	
Total		**2024**	

N= 1010 chest X-rays, multiple findings per X-ray possible

5.4.2.4 *Admission information*

Figure 5-5 presents a scatterplot of the absolute values of RR compared to the norm values per age (n= 1237 hospitalisations, n= 203 missing data); and Figure 5-6 presents the HR at admission compared to the norm values per age (n= 1092 hospitalisations, n= 348 missing data), based on the normative data presented in a systematic review by Fleming et al.[240] Signs of respiratory distress were seen in 1360 hospitalisations (94.4%), with tachypnoea the most common (n= 1009, 81.6% of hospitalisations with recorded RR), followed by recessions (subcostal recession (n= 776, 53.9%), unspecified recessions (n= 195, 13.5%) and intercostal recession (n= 167, 11.6%). Other signs of distress reported in the medical files were alar flaring (n= 338, 23.5%), tracheal tug (n= 122, 8.5%),

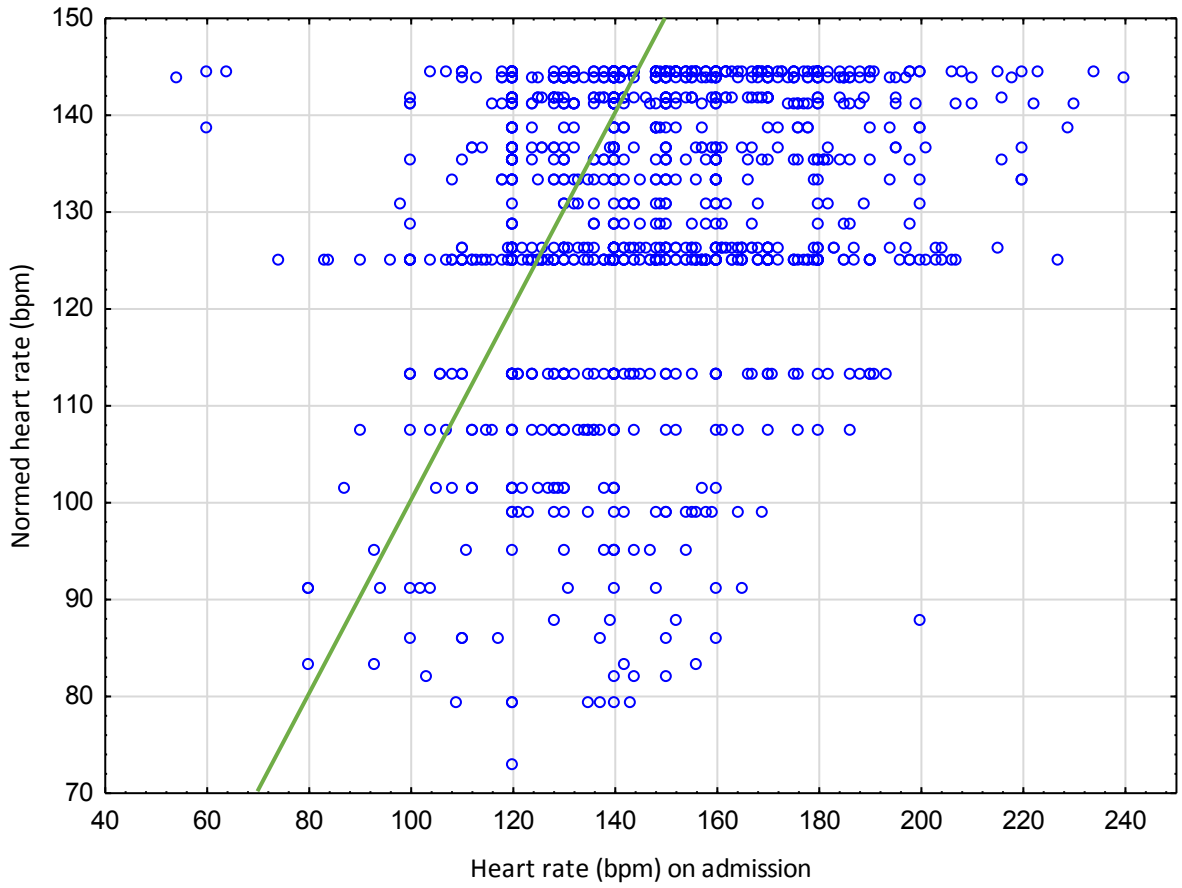
head bobbing (n= 69, 4.8%), cyanosis (n= 6, 0.4%) and feeding problems (n= 6, 0.4%). The median (IQR) temperature at admission was 37.0 (36.7-38.0)°C (based on n= 1334, n= 106 missing); and the median (IQR) SpO_2 in room air was 96.0 (94.0-98.0)% (based on n= 1059, n= 381missing).



Based on n=1237 hospitalisations.[3]

Figure 5-5. RR at admission compared to the RR norm for age.

[3] The green line indicates where the RR at admission is exactly the same as the normed RR. Data points left of this line represents children who have a RR at admission below the norm, whereas data points right of the line are children who have a RR at admission above the norm.



Based on n=1092 hospitalisations.[4]

Figure 5-6. HR at admission compared to the HR norm for age.

5.4.2.5 Mechanical ventilation and oxygen support

Oxygen support at the time of admission was given in 183 cases (12.7%) and recorded in the medical files, (ranging from 1-8 litre/min with 2 litre/min the most frequently applied flow rate (n= 164)). However, no information regarding oxygen support at admission was available in 820 cases. Information for oxygen support during hospitalisation was not extracted from the files.

[4] The green line indicates where the HR at admission is exactly the same as the normed RR. Data points left of this line represents children who have a HR at admission below the norm, whereas data points right of the line are children who have a HR at admission above the norm.

In 258 hospitalisations, children received non-invasive and/or invasive mechanical ventilation (17.9%). An overview of the provided modalities is shown in Table 5-6. The median (IQR) number of days on mechanical ventilation was 3.0 (2.0-5.0) days.

Table 5-6. Frequency of invasive and non-invasive mechanical ventilation modalities.

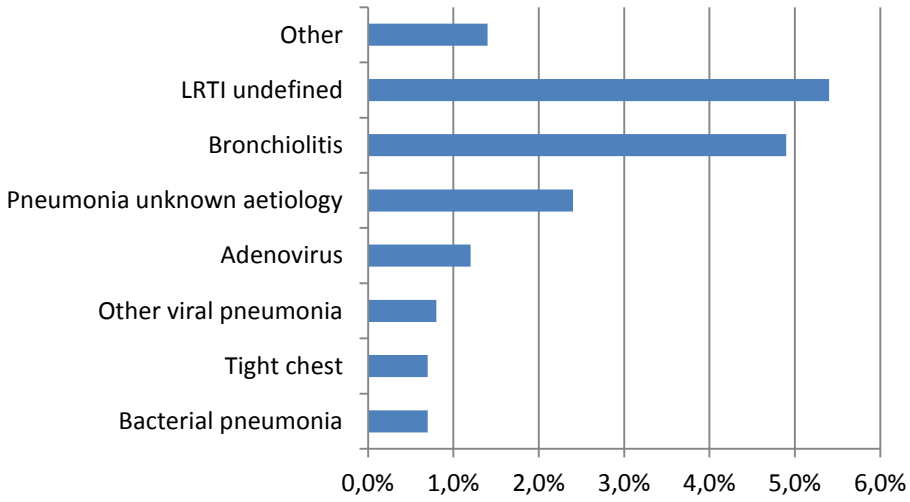
Mechanical ventilation modality	N	Percentage
Continuous positive airway pressure	234	90.7
Intermittent positive pressure ventilation	62	24.0
Pressure control ventilation	12	4.7
High frequency oscillatory ventilation	11	4.3
Bilevel positive airway pressure	11	4.3
Synchronised intermittent mandatory ventilation	3	1.2
Total	333	

N= 258 cases receiving mechanical ventilation during hospitalisation; multiple modalities could have been used in one case.

5.4.2.6 Medical history

Twenty-five children (2.1%) had a history of TB; information regarding TB history was missing for eight children. The episode of TB occurred a median of 8.2 months (IQR 6.3-45.7) prior to the first day of admission in our pre-set timeframe (based on n=15, no information available for 10/25 children).

Most children (82.1%) had not been hospitalised for a prior respiratory disease before their first admission in this study's timeframe (Figure 5-7). Information was missing for 14 cases. For the children who were hospitalised previously, the most recent hospitalisations occurred a median of 8.9 months (IQR 4.8-14.6) before the first admission in 2015.



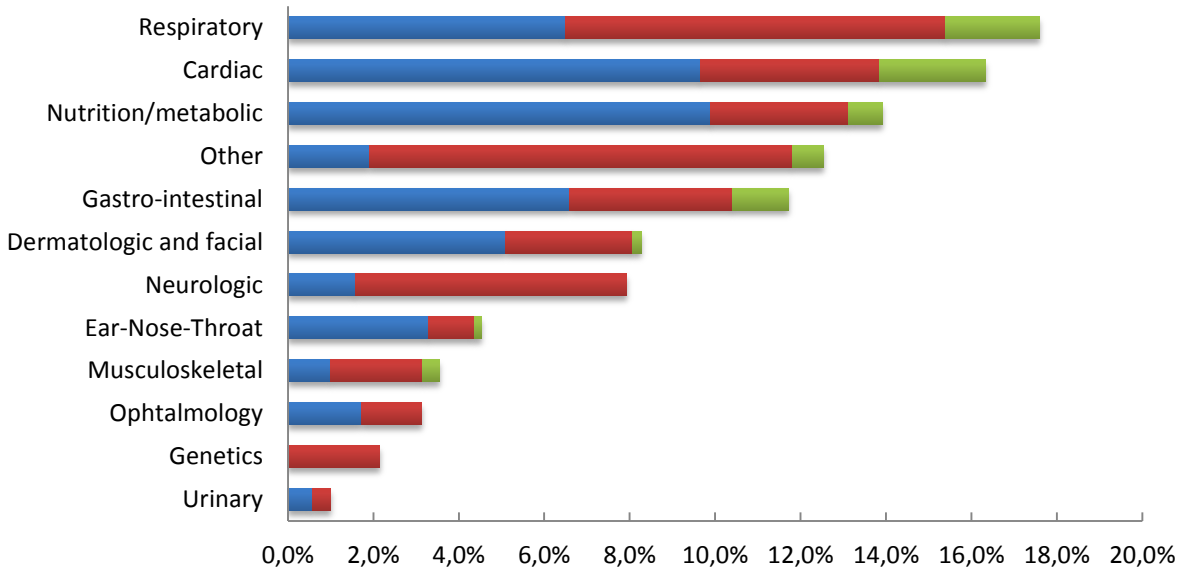
N= 1208 children

Figure 5-7. Frequency and nature of previous hospitalisations due to respiratory disease.

Two patients had a history of pneumothorax. The pneumothorax occurred three to six months prior to the first hospitalisations within the study period in one child, and six to twelve months in the other child. A history of abdominal or thoracic surgery was present in 56 children (4.6%), of which 29 had repair of cardiac anomalies (e.g. atrioventricular septal defect repair, ventricular septal defect repair, atrial septal defect repair, patent ductus arteriosus ligation, aortic stenosis, coarctation repair, anomalous left coronary artery from the pulmonary artery, pacemaker), 20 had a percutaneous endoscopic gastrostomy (PEG) inserted, three underwent a laparotomy, two a colostomy, one had an appendectomy, one a liver transplant, one a pneumonectomy, and one had a posterior urethral valve ablation. Two children had two procedures (PEG cardiac surgery).

5.4.2.7 Comorbidities

Of the total sample, 52.6% of the children had one or more clinically significant comorbidity during at least one of the hospitalisations in our time frame (n= 1208). See Figure 5-8 for an overview of the prevalence of different comorbidity categories. An overview of all comorbidities can be found in Appendix 8. The common chronic and acute comorbidities present in ten or more children are presented in Table 5-7 and Table 5-8.



	Urinary	Genetics	Ophtalmology	Musculoskeletal	Ear-Nose-Throat	Neurologic	Dermatologic and facial	Gastro-intestinal	Other	Nutrition/metabolic	Cardiac	Respiratory
Acute	0,6%	0,0%	1,7%	1,0%	3,3%	1,6%	5,1%	6,6%	1,9%	9,9%	9,7%	6,5%
Chronic	0,4%	2,2%	1,4%	2,2%	1,1%	6,4%	3,0%	3,8%	9,9%	3,2%	4,2%	8,9%
Both chronic and acute	0,0%	0,0%	0,0%	0,4%	0,2%	0,0%	0,2%	1,3%	0,7%	0,8%	2,5%	2,2%

N= 1208 children

Figure 5-8. Prevalence of comorbidities. Percentage of children with comorbidities during at least one hospitalisation.

Table 5-7. Most common chronic comorbidities seen in children hospitalised with a LRTI.

Disease category	Comorbidity	N	Percentage
Respiratory	Asthma		
	Proven	49	4.1
	Suspected	7	0.6
	Upper airway obstruction	27	2.1
	Chronic lung disease, not further specified	11	0.9
Cardiovascular	Patent ductus arteriosus		
	Proven	23	1.9
	Suspected	1	0.1
	Ventricular septal defect	22	1.8
	Atrioventricular septal defect	15	1.2
Neurological	Seizures/epilepsy	35	2.9
	CP	23	1.9
	NMD	13	1.1
Genetic disorder	Trisomy 21	19	1.6
Musculoskeletal	Scoliosis	11	0.9
Gastrointestinal	GORD	51	4.2
Dermatological	Eczema	33	2.7
Other	Developmental delay	45	3.7
	Neonatal jaundice	34	2.8
	Dysmorphic features	14	1.2
	Maternal drug abuse during pregnancy or exposure of the child to toxic fumes caused by drugs	10	0.8

N= 1208 children, one child could present with multiple comorbid conditions

Table 5-8. Most common acute comorbidities seen in children hospitalised with a LRTI.

Disease category	Comorbidity	N	Percentage
Respiratory	URTI	47	3.3
	Allergic rhinitis	16	1.1
	Apnoea	16	1.1
	Pertussis		
	Proven	13	0.9
	Suspected	2	0.1
	Bronchospasm	11	0.8
Cardiovascular	Anaemia	107	7.4
	Sepsis	72	5.0
Neurological	Meningitis	10	0.7
Gastrointestinal	Acute gastroenteritis	91	6.3
ENT	Otitis media	24	1.7
Dermatological	Dermatitis	18	1.3
	Candidiasis/fungal rash	11	0.8
Nutritional/metabolic	Failure to thrive	151	10.5
	Hypothyroidism	10	0.7
Ophthalmological	Conjunctivitis	18	1.3

N= 1440 hospitalisations, multiple comorbid conditions could be present during one hospitalisation

A significant association was seen between primary diagnostic category and the presence of at least one chronic (Yates X^2= 170.5, p<0.001) or acute comorbidity (Yates X^2= 55.7, p<0.001), based on the most common comorbidities. The proportion of children presenting with a primary clinical diagnosis of pneumonia and comorbidities was the highest (Table 5-9 and Table 5-10).

Table 5-9. Association between the presence of a chronic comorbidity and diagnostic category.

Primary diagnosis	Chronic comorbidity		
	Yes	No	Total
Presumed nosocomial	71	35	106
Column%	23.6	3.1	
LRTI	37	107	144
Column%	12.3	9.4	
Pneumonia	116	409	525
Column%	38.5	35.9	
Bronchiolitis	76	586	662
Column%	25.3	51.5	
Other	1	2	3
Column%	0.3	0.2	
Total	301	1139	1440

N=1440 hospitalisations

Table 5-10. Association between the presence of an acute comorbidity and diagnostic category.

Primary diagnosis	Acute comorbidity		
	Yes	No	Total
Presumed nosocomial	42	64	106
Column%	12.5	5.8	
LRTI	34	110	144
Column%	10.0	10.0	
Pneumonia	161	364	525
Column%	47.8	33.0	
Bronchiolitis	99	563	662
Column%	29.4	51.0	
Other	1	2	3
Column%	0.3	0.2	
Total	337	1103	1440

N= 1440 hospitalisations

5.4.3 Airway clearance therapy

Four hospitalisations were excluded for the following analyses as these children were enrolled in the intervention arm of the pneumonia RCT, biasing the airway clearance intervention. Therefore, analysis is based on 1436 hospitalisations. ACT was given in 83 cases (5.8% of the 1436 hospitalisations) in the study timeframe.

5.4.3.1 Description of airway clearance therapy

The majority of ACT interventions (n=63, 75.9%) were started during the first week of hospitalisation. Of these, 17 cases (27.0%) received intervention on the day of admission, 25 (39.7%) on the second day of hospitalisation, six on day 3 (9.5%), five (7.9%) at each of day 4 and day 5, three at day 6 (4.8%) and two at day 7 (3.2%). Twelve interventions (14.5%) were started after one week of hospitalisation, and seven (8.4%) after two weeks of hospitalisation (of whom five were hospitalised for presumed nosocomial infections, one for pneumonia and one for unspecified LRTI).

Approximately half of the patients received once daily treatment (n= 41, 49.4%). One received more than bidaily ACT (1.2%) and the rest received bidaily treatment (n= 40, 48.2%). In one case, no information regarding frequency was available. ACTs were performed for a median (IQR) of 3.0 (1.0-6.0) days per hospitalisation (n=80).

Table 5-11 presents an overview of the performed ACT modalities (used at least once during the respective hospitalisation).

Table 5-11. Frequency of performed ACTs.

Treatment modality	N	Percentage
Vibrations	69	83.1
MPD	46	55.4
Percussions/clapping	32	38.6
Deep breathing exercises	21	25.3
Active gross motor exercises/mobilisation	17	20.5
ACBT	11	13.3
Thoracic compressions	7	8.4
FET/Huff	6	7.2
Bubble PEP	6	7.2
AAD	5	6.0
Oscillating PEP	3	3.6
Blowing bubbles	3	3.6
Chest wall shaking	1	1.2
PEP	0	0.0
AD	0	0.0
Total	**227**	

N= 83 cases receiving ACT, multiple ACTs could be used per case

5.4.3.2 *Adverse events*

SpO_2 decreased during or immediately after ACT in six cases (7.2%) (three desaturated to levels between 85-89% and three to below 85%). Desaturation occurred during side lying on the left side (n=2), suctioning (n=1), suctioning and vibrations (n=1), percussions and vibrations (n=1), and breathing exercises in the sitting position (n=1). One child presented with lung collapse more than an hour after ACT. No other adverse events associated with ACT occurred.

Due to the small number of children presenting with adverse events, no further analyses of this outcome measure was conducted.

5.4.3.3 *Predictors for receiving airway clearance therapy*

A significant association was found between the primary diagnostic category and whether or not ACT was given (Yates X^2= 319.0, p<0.001). ACT was most often given in children hospitalised with presumed nosocomial infections and pneumonia. Children with presumed nosocomial infections were most likely to receive ACT, followed by children with pneumonia (Table 5-12).

Table 5-12. Prevalence of airway clearance therapy based on disease category

Primary diagnosis	Airway clearance therapy				
	No	*Row%*	Yes	*Row%*	Total
Presumed nosocomial	58	54.7	48	45.3	106
Column%	4.3		57.8		
LRTI	140	98.6	2	1.4	142
Column%	10.4		2.4		
Pneumonia	494	96.1	20	3.9	514
Column%	36.8		24.1		
Bronchiolitis	647	98.0	13	2.0	660
Column%	48.2		15.7		
Other	3	100.0	0	0.0	3
Column%	0.2		0.0		
Total	1342		83		1425

Furthermore, a significant association between isolated organisms and receipt of ACT was seen (X^2=171.2, p<0.001). Children with bacterial organisms were more likely to receive ACT (Table 5-13).

Table 5-13. Prevalence of airway clearance therapy based on organism associated with LRTI.

Organism	Airway clearance therapy				
	No	*Row%*	Yes	*Row%*	Total
unknown	1147	97.1	34	2.9	1181
bacterial	16	55.2	13	44.8	29
viral	157	86.7	24	13.3	181
mixed	22	64.7	12	35.3	34
Total	1342		83		1425

The OR was calculated for variables, which might be predictive for receiving ACT (see Table 5-14).

The likelihood of receiving ACT increased greatly when chronic comorbidities were present; when the child had a history of previous TB or was previously hospitalised for a LRTI, when the HR at admission was above normal and when the child was managed with either mechanical ventilation or O_2 therapy on admission.

The variables which predicted a higher odds of receiving ACT were included in a backward stepwise logistic regression model. Those that became non-significant were excluded and the final model is depicted in Table 5-15. The likelihood ratio was 150.5 (p<0.001) which reflected a better fit than the models that included more or fewer variables.

Table 5-14. Odds ratios for receiving airway clearance therapy for various variables.

Variable		Airway clearance therapy					OR	95% confidence interval	
		No	Row%	Yes	Row%	Total		Lower	Upper
Gender	Female	542	93.0	41	7.0	583	0.7	0.4	1.1
	Male	800	95.0	42	5.0	842			
	Total	1342	94.2	83	5.8	1425			
Gestational age	Preterm	246	94.3	15	5.8	261	0.9	0.5	1.6
	Term	871	94.8	48	5.2	919			
	Total	1117	94.7	63	5.3	1180			
Chronic cardiovascular disease	No	1249	94.8	68	5.2	1317	***3.0***	***1.6***	***5.4***
	Yes	93	86.1	15	13.9	108			
	Total	1342	94.2	83	5.8	1425			
Chronic respiratory disease, excluding asthma	No	1282	95.8	56	4.2	1338	***10.3***	***6.1***	***17.5***
	Yes	60	69.0	27	31.0	87			
	Total	1342	94.2	83	5.8	1425			
CP	No	1315	94.5	77	5.5	1392	***3.8***	***1.5***	***9.5***
	Yes	27	81.8	6	18.2	33			
	Total	1342	94.2	82	5.8	1425			
Genetic disorders	No	1304	94.5	76	5.5	1380	***3.2***	***1.4***	***7.3***
	Yes	38	84.4	7	15.6	45			
	Total	1342	94.2	83	5.8	1425			
NMD	No	1338	95.4	64	4.6	1402	***132.4***	***38.2***	***459.0***
	Yes	3	13.6	19	83.4	22			
	Total	1341	94.2	83	5.8	1424			
Seizures	No	1299	94.7	72	5.3	1371	***4.7***	***2.3***	***9.6***
	Yes	42	79.2	11	20.8	53			
	Total	1341	94.2	83	5.8	1424			
History of TB	No	1313	94.7	74	5.3	1387	***5.3***	***2.3***	***12.0***
	Yes	27	77.1	8	22.9	35			
	Total	1340	94.2	82	5.8	1422			
Previously hospitalised for LRTI	No	943	96.6	33	3.4	976	***3.4***	***2.1***	***5.4***
	Yes	396	89.4	47	10.6	443			
	Total	1339	94.4	80	5.6	1419			
Respiratory rate	Normal	215	96.0	9	4.0	224	1.4	0.7	2.9
	Increased	949	94.4	56	5.6	1005			
	Total	1164	94.7	65	5.3	1229			
Heart rate	Normal	286	96.6	10	3.4	296	***2.3***	***1.1***	***4.5***
	Increased	735	92.7	58	7.3	793			
	Total	1021	93.8	68	6.2	1089			
Mechanically ventilated	No	1136	97.1	34	2.9	1170	***8.0***	***5.0***	***12.7***
	Yes	205	80.7	47	19.3	254			
	Total	1341	94.2	83	5.8	1424			
Oxygen supplementation on admission	No	1186	95.3	59	4.7	1245	***3.1***	***1.9***	***5.1***
	Yes	156	86.7	24	13.3	180			
	Total	1342	94.2	83	5.8	1425			

N= 1440 hospitalisations

Significant ORs are presented in red

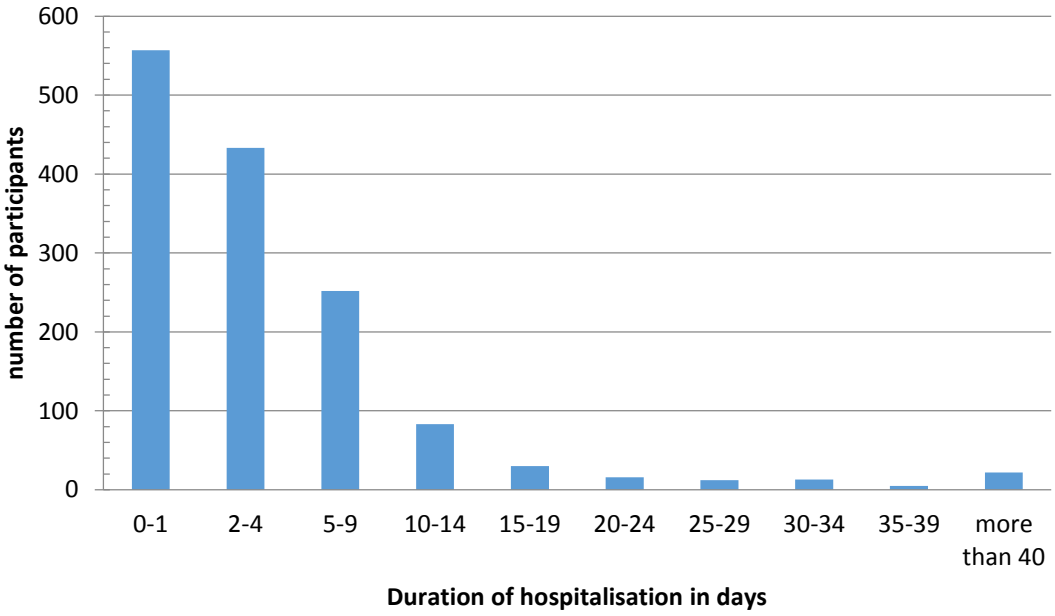
Table 5-15. Final model of logistic regression for predicting variables for receiving airway clearance therapy.

Term	Adjusted OR	95%	C.I.	Z-Statistic	P-Value
Chronic respiratory disease	6.6	3.5	12.4	5.9	***<0.001***
CP	3.9	1.4	10.7	2.6	***0.009***
Genetic disorder	2.8	1.0	7.6	2.0	***0.042***
Chronic heart disease	2.2	1.0	4.7	2.0	***0.042***
NMD	130.8	35.9	476.4	7.4	***<0.001***
CONSTANT	*	*	*	-21.1	***<0.001***

N= 1440 hospitalisations

5.4.4 Patient outcomes

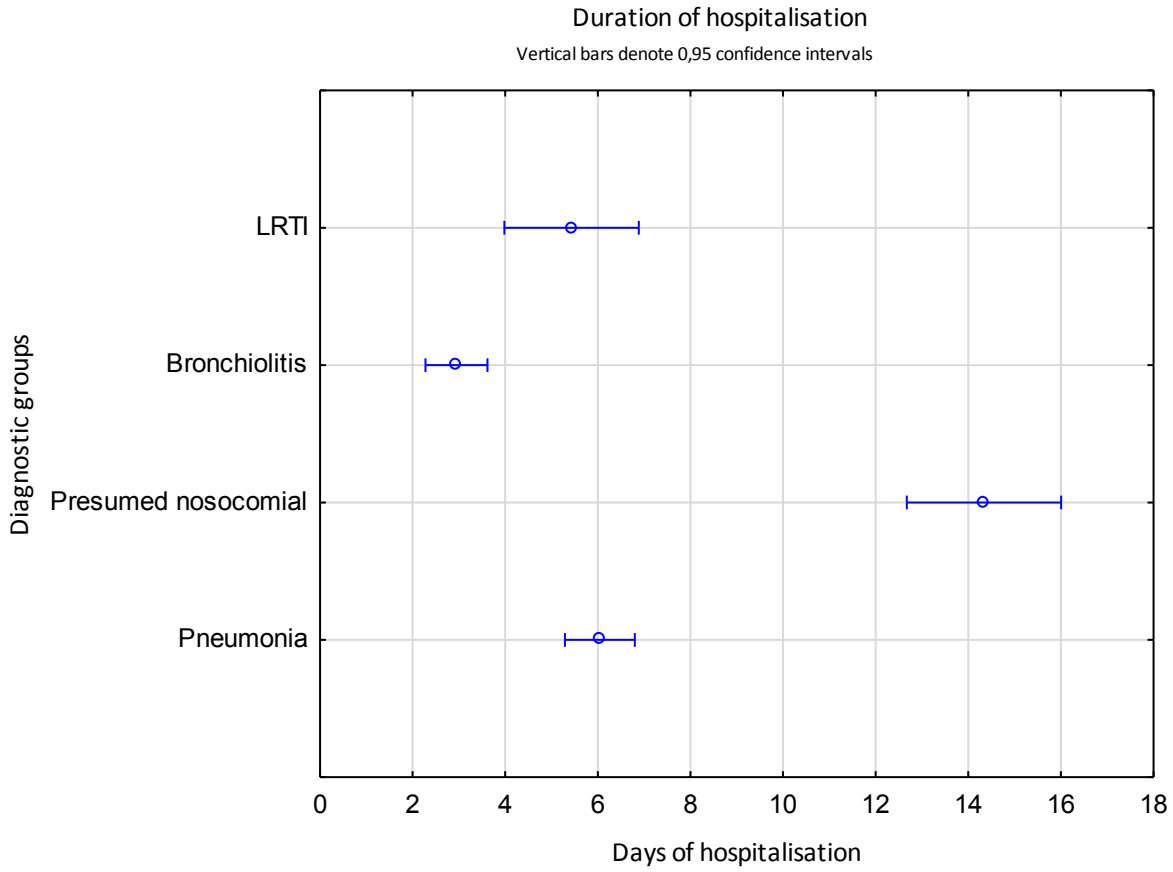
The median (IQR) length of hospitalisation was 2.3 (1.5-5.0) days (Figure 5-9).



N= 1440 hospitalisations

Figure 5-9. Histogram of duration of hospitalisation

A one way ANOVA indicated that there was a significant difference in the mean days of hospitalisation amongst the different diagnostic groups (p<0.001) (Figure 5-10). A post-hoc Tukey test identified this difference as being between presumed nosocomial infections and all other diagnostic categories (Table 5-16). Furthermore children hospitalised for bronchiolitis had a shorter hospital stay than children in the other diagnostic categories.



F(3, 1416)=54.7, p<0.001

Figure 5-10. Days of hospitalisation per diagnostic category.

Table 5-16. Post-hoc Turkey test for diagnostic group and days of hospitalisation

Primary diagnosis	Mean (SD)	Presumed nosocomial	LRTI	Pneumonia	Bronchiolitis
Presumed nosocomial	14.3 (18.5)	-	***<0.001***	***<0.001***	***<0.001***
LRTI	5.4 (12.4)	***<0.001***	-	0.884	***0.012***
Pneumonia	6.0 (8.9)	***<0.001***	0.884	-	***<0.001***
Bronchiolitis	2.9 (4.0)	***<0.001***	***0.012***	***<0.001***	-

Forward stepwise multiple regression analysis was performed to identify factors which influenced the duration of hospitalisation. All relevant factors were entered. After residual analysis was done, nine cases were excluded from analysis. The final model accounted for 52% of the variance (Table 5-17 and Table 5-18). Mechanical ventilation was the factor that influenced the length of hospital stay the most, explaining 28% of variance. It is also seen that children who received ACT stayed in hospital for longer. Furthermore, acute comorbidities were more predictive of a longer hospital stay than chronic comorbidities or disease severity.

Table 5-17. Multiple regression results for length of hospitalisation

Factor	b*	Standard error of b*	b	Standard error of b	t(232)	p-value
Intercept			9,0	3,6	2,5	***0,012***
Mechanical ventilation	0,4	0,1	5,3	0,6	8,5	***<0,001***
Acute comorbidity	0,3	0,0	3,1	0,6	5,5	***<0,001***
Airway clearance therapy	0,2	0,1	3,0	1,1	2,8	***0,006***
CP	0,2	0,0	6,3	1,3	4,8	***<0,001***
Chronic heart disease	0,2	0,0	4,7	1,0	4,8	***<0,001***
Gestational age	0,1	0,0	1,7	0,6	2,8	***0,005***
Tachypnoea	-0,1	0,0	-1,4	0,7	-2,0	0,051
Chronic respiratory disease	0,1	0,0	3,0	1,1	2,8	***0,006***
NMD	0,2	0,1	6,5	2,2	2,9	***0,004***
Chest deformities	-0,1	0,1	-5,7	2,5	-2,3	***0,025***
SpO_2 on admission	-0,1	0,0	-0,1	0,0	-2,0	0,052
Previously hospitalised	-0,1	0,1	-1,2	0,6	-2,0	***0,042***
Age in months	0,1	0,1	0,0	0,0	1,2	0,241

Table 5-18. Forward stepwise multiple regression for factors influencing length of hospital stay

Factor	Step	Multiple R	Multiple R^2	R^2 change	F – to entr/rem	p-value	Variables
Mechanical ventilation	1	0,5	0,3	0,3	94,8	***<0,001***	1
Acute comorbidity	2	0,6	0,4	0,1	29,9	***<0,001***	2
Airway clearance therapy	3	0,6	0,4	0,1	24,1	***<0,001***	3
CP	4	0,7	0,5	0,0	15,4	***<0,001***	4
Chronic heart disease	5	0,7	0,5	0,0	17,1	***<0,001***	5
Gestational age	6	0,7	0,5	0,0	6,1	***0,014***	6
Tachypnoea	7	0,7	0,5	0,0	3,9	***0,048***	7
Chronic respiratory disease	8	0,7	0,5	0,0	4,2	***0,041***	8
NMD	9	0,7	0,5	0,0	3,8	0,054	9
Chest deformities	10	0,7	0,5	0,0	3,2	0,074	10
SpO_2 on admission	11	0,7	0,5	0,0	2,8	0,095	11
Previously hospitalised	12	0,7	0,5	0,0	3,5	0,064	12
Age in months	13	0,7	0,5	0,0	1,4	0,241	13

In total, 10 children (0.7%, n=1424) died while hospitalised during the study period. Information regarding mortality status was not available in the folders of 16 hospitalisations. A significant association between mortality rate and diagnostic category was found (Yates X^2= 45.5, p<0.001). Mortality was higher for children who developed presumed nosocomial infections, followed by pneumonia, compared to other diagnostic categories (Table 5-19). Table 5-20 presents a description of the deceased patients.

Table 5-19. Mortality status per diagnostic category.

Primary diagnosis	Presumed noso-comial	*Row%*	LRTI	*Row%*	Pneumo nia	*Row%*	Bronchi olitis	*Row%*	Other	*Row %*	Total
Alive	100	7.7	139	9.8	514	36.4	658	46.5	3	0.2	1414
Column%	94.3		99.3		99.4		100.0		100.0		
Died	6	60.0	1	10.0	3	30.0	0	0.0	0	0.0	10
Column%	5.7		0.7		0.6		0.0		0.0		
Total	106		140		517		658		3		1424

Table 5-20. Description of the deceased patients

Participant	Primary diagnosis	Age at time of death	Comorbidities
1	Pneumonia	16.5 years	Liver transplant in 2008: chronic liver reject, sepsis, anaemia, acute gastroenteritis
2	Presumes nosocomial	12.4 years	Congenital muscular dystrophy, kyphoscoliosis, GORD, developmental delay
3	LRTI	10.9 years	CP (spastic quadriplegia), seizures, scoliosis, microcephaly, cortical blindness, GORD, upper airway obstruction
4	Presumed nosocomial	7.5 years	CP (spastic quadriplegia), congenital dandy-walker malformation, hydrocephalus, seizures, developmental delay, anaemia, sepsis
5	Pneumonia	5.0 years	Trisomy 21, multiorgan failure, seizures, upper airway obstruction, GORD, history of rickets
6	Presumed nosocomial	4.5 years	Traumatic brain injury due to pedestrian-vehicle-accident, brain stem death
7	Pneumonia	1.8 years	Pulmonary haemorrhage, bronchospasm, acute gastroenteritis, sepsis
8	Presumed nosocomial	3.8 months	SMA I, failure to thrive, acute gastroenteritis
9	Presumed nosocomial	2.8 months	Trisomy 21, atrioventricular septal defect, chylothorax, developmental delay
10	Presumed nosocomial	1.9 months	Trisomy 13, dysmorphic, polydactaly, bilateral cataract, URTI, failure to thrive, atrioventricular septal defect

Table 5-21 shows an association between delivery of ACT and mortality (Yates X^2= 41.96; p <0.001).

Table 5-21. Airway clearance therapy and mortality status.

Mortality status	Airway clearance therapy				
	No	*Row%*	Yes	*Row%*	Total
Alive	1333	94.3	81	5.7	1414
Column%	99,7		93,1		
Died	4	40.0	6	60.0	10
Column%	0,3		6.9		
Total	1337		87		1424

5.5 DISCUSSION

This is the first comprehensive descriptive study of ACT prescription and outcomes in children admitted to a South African hospital with a LRTI.

The majority of children admitted with LRTIs were younger than one year of age, male, HIV uninfected, and born at term. These findings are similar to other studies, where the majority of children hospitalised for bronchiolitis and viral LRTI were also younger than one year of age.[2,241,242] In an aetiological study of children younger than five years of age with an acute LRTI in Thailand, 59% of the affected children were male;[243] and in a study by Foster et al. on children with viral LRTI, 60.8% of the inpatients were male.[242] These results are similar to the proportion found in this current study (59.6%). Other studies have also found that a higher proportion of males were hospitalised for LRTIs than females.[241,244,245] The disproportion among gender could be caused by differences in sex hormones, influencing lymphocyte and macrophage function, hence immune reponse.[246,247] In females, the production of estradiol enhances the immune system, whereas the production of testosterone in males suppresses the immune system.[246] These differences in sex hormones are already present during infancy, although less distinct.[247] Furthermore, male infants have narrower peripheral airways compared to their female peers, contributing to the increased risk to LRTIs.[248]

HIV occurred more often in this current study (2.9%) than in the study by Hasan et al. (0.2%).[243] This could be due to a higher HIV prevalence in South Africa (19.2% of adults in 2015) compared to Thailand (1.1% of adults in 2015), where the study by Hasan et al. was conducted.[249] Although a decline in HIV prevalence in South Africa was observed, from 5.6% in 2002 to 2.4% in 2012 for children between two and 14 years of age, as a result of the "prevention mother-to-child transmission" program;[33,195] the HIV prevalence in the current study (reporting on data from 2015) is comparable to the prevalence of 2012.[195]

The most common primary diagnosis was bronchiolitis, followed by pneumonia and unspecified LRTI. In the current study, the primary diagnosis of pneumonia was made in 36.5% of the cases. This is similar to results found by Forster et al., who identified 59.6% of the inpatients as having bronchiolitis, and 35.1% with pneumonia.[242] A study by Hatipoglu et al. diagnosed 55.6% of their participants with bronchiolitis, and 44.4% with pneumonia.[245] And Wolf et al., investigating children hospitalised with viral LRTI, diagnosed 40% with a primary diagnosis of pneumonia and 60% with other (not further specified) LRTI.[244] Eventually, 53.1% of the children were diagnosed with clinical pneumonia and 42.8% with bronchiolitis in that study.[244] Unfortunately, as the current study did not record discharge diagnoses, no comparison can be made for these latter results.

In the current study, children referred to the clinical physiotherapy staff for ACT without a primary diagnosis of LRTI were classified as presumed nosocomial infections by the researchers. No information regarding LRTI diagnostic category was extracted from the medical files, resulting in the inability to further distinct between hospital acquired pneumonia, bronchiolitis or other LRTI; hence no separate analyses were possible.

Microbiological isolates revealed more associated viral organisms than bacterial organisms. In children hospitalised for bronchiolitis or pneumonia, RSV was the most common isolated viral organism. Adenovirus was most common in children hospitalised for unspecified LRTI; and human rhinovirus was the most common isolate associated with presumed nosocomial infection. In South Africa, human rhinovirus, RSV and adenovirus are most often identified in children with LRTI,[250–252] as confirmed by the current study. In the study by Hasan et al., RSV was the most commonly reported viral agent, followed by rhinovirus.[243] This is the same as the current study's results, although the proportions in the study by Hasan et al. are lower (19.5% and 18.7% respective) than in the current study (44.1% and 38.0% respective). A study conducted on Turkish children with viral LRTI also indicated RSV as the main pathogen (55.6%) in children younger than one year of age, however, they found that parainfluenza was the second most common viral agent in children younger than one year of age and the most common viral isolate in older children in their study.[245] The discrepancies with these viral organisms could be due to the low rate of available sputum/blood cultures, overestimating the proportions of organisms in the current sample. A study conducted in Taiwan found completely different results, with adenovirus and enterovirus the most common viral organisms.[253] Although adenovirus was found to be the most common viral organism in children hospitalised with unspecified LRTI, the other disagreements could be due to the geographical differences in aetiology of disease.

The current study found *Mycobacterium tuberculosis* to be the most common bacterial organism (4.9%), followed by *Klebsiella pneumoniae* (4.5%); however, *Pseudomonas aeruginosa* was more commonly associated with presumed nosocomial infection. Another South African study reported *Acinetobacter Baumannii* as the most common bacterial organism, with *Klebsiella pneumoniae* (20.6%) the second most common identified bacterial organism.[254] Although the incidence rate of the current study for *Klebsiella pneumoniae* was similar to the study by Hasan et al. (4.1%), it was only the seventh most common bacterial agent in their study.[243] A study conducted in Taiwan reported *S. Pneumoniae* as the most common bacterial organism.[253] A limitation of this retrospective study is that specimens were not taken on all patients, in a standardised manner, and therefore accurate aetiological analysis is not possible.

Mechanical ventilation (invasive and non-invasive) was provided for 17.9% of the hospitalisations in the current study, with CPAP being the most commonly administered. This proportion is higher than results found in two studies, where the proportion of children receiving mechanical ventilation was only 1.0-1.7%.[241,244] However, one of these studies only included invasive ventilation,[241] and the other study did not specify the type of mechanical ventilation.[244] Another study reported on the need for intubation, which was required in 1.1% of children.[243] Non-invasive ventilation is used to unload the work of breathing and might facilitate airway clearance. This could have influenced the outcome of ACT as it might limit complications associated with ACT. Furthermore, oxygen supplementation on admission was required in 12.7% of the children hospitalised in the current study. This study did not record oxygen supplementation throughout the study period, precluding comparison with other studies. It is recommended that this intervention be recorded in future studies.

The majority of children in the current study were not hospitalised for a LRTI prior to the current admission. One or more comorbidities were present in just over half the cases, with respiratory problems the most common, followed by cardiovascular disorders. Children admitted for pneumonia were most often affected with both chronic and acute comorbidities. In a study by Wang et al. on Canadian children hospitalised with RSV LRTI, the proportion of comorbidities (22.6%) was lower than that seen in the current study (52.6%).[255] This might relate to different methodologies and comorbidity selection. The study by Wang et al. recorded chronic lung disease, congenital heart disease, immunocompromise, other multisystem diseases, and prematurity;[255] whereas the current study recorded a wider range of comorbidities but excluded prematurity and postnatal age. Furthermore, the current study included any LRTI, not merely RSV LRTI.

ACT was performed in 5.8% of the hospitalisations. The majority of treatments were commenced in the first week of hospitalisation, however seven children only received ACT more than two weeks after admission. Five of whom acquired a nosocomial infection during hospitalisation, which could explain the timing of commencement of ACT. The other two cases were admitted for either pneumonia or LRTI, for which it is unclear why ACT commenced at this time. Vibrations and MPD were performed most often, with 49.4% of the children receiving bidaily treatment. AD and PEP were never given. ACT is not recommended as routine management for children with bronchiolitis, by the American Association for Paediatrics and a South African guideline article by Zar el al., based on the results found in a systematic review by Figuls et al.[256–258] Although the National Institute for Health and Care Excellence agrees with this recommendation for most children, they do specify that ACT can be given to children with bronchiolitis with relevant comorbidities, if these comorbidities require ACT for facilitation of mucus clearance.[259] In the current study, ACT was given less frequently to children

with bronchiolitis or unspecified LRTI. This practice therefore conforms to the guidelines for the management of children with bronchiolitis.

In children with pneumonia, little evidence is available regarding the use of ACT as part of the disease management. Two systematic reviews have been published, including up to three RCTs on this topic, without clear recommendations for or against the use of ACT in these children.[231,260] However, small benefits have been reported in other studies,[223,226,228] indicating the need for further research into this matter. As only 5.8% of the children received ACT in the current study, it is apparent that ACT does not form part of the standard management of children hospitalised with a LRTI at this study site. The children who were most likely to receive ACT were those with bacterial nosocomial infections or pneumonia and those with chronic comorbidities. Therefore, it is recommended that further research be conducted on the use and safety of ACT in children presenting with these conditions.

In the literature, adverse events are rarely mentioned and described; which was also the case in the current study. Six children did however desaturate during ACT. Suctioning was reported to cause desaturation in two children, conventional ACT (consisting of vibrations, percussions and MPD) was associated with desaturation in three children. One child desaturated whilst performing deep breathing exercises in sitting position. One child presented with a lung collapse more than one hour after ACT, and given the time delay it is unlikely that this adverse event was directly related to ACT. Owing to the observation of desaturation during ACT, monitoring of SpO_2 is recommended during the performance of ACT. In the literature, adverse events are rarely mentioned and described. One study conducted in children with bronchiolitis, comparing nasal suctioning to increased exhalation technique with assisted cough, reported a significantly higher rate of children who vomited during ACT and who presented with transient respiratory destabilisation (not further specified).[229] As these two adverse events have not been investigated in the current study and the specific ACT has not been used at the research site, no comparison could be made. Another study on the use of ACT in children with bronchiolitis did mention that no adverse events occurred, however, it is unclear which adverse events were under consideration.[261]
As the rate of adverse events was low in the current study and very little literature is available on this topic, ACT appears to be safe for use in children with LRTI.

Logistic regression revealed that chronic comorbidities (chronic respiratory disease, chronic heart disease, genetic disorders, NMDs, and CP), were the most likely predictors for receiving ACT during hospitalisation. Children with presumed nosocomial infections were more likely to receive ACT,

followed by children hospitalised for pneumonia. This data, however, may have been biased because the majority of children classified as presumed nosocomial infections were included based on physiotherapy referral and not through ICD-10 search identification. Children with nosocomial infections who were not referred for ACT might therefore not have been identified for inclusion in this folder review. In children hospitalised for pneumonia, multiple comorbidities were identified, for which ACT might be indicated. Children with positive bacterial culture were treated more often by the physiotherapists than children with viral isolates. No previous studies have investigated the association between ACT and isolated organisms, therefore, confirmation of the results in a larger prospective study is recommended.

Obstructive disorders, like bronchiectasis, and chronic lung diseases would likely benefit from ACT;[136,262]but the current study found that 60 of 87 children (69%) with chronic respiratory disease (excluding asthma) did not receive any ACT. Unfortunately this study did not gather data to identify the reasons for not providing ACT to these children, however in some conditions, particularly upper airway obstruction, ACT is not indicated.

Children were hospitalised for a median of 2.3 days, however, children with presumed nosocomial infections were hospitalised for a significantly longer duration (14.3 days), followed by children hospitalised for other conditions and pneumonia. Two RCTs on children hospitalised with pneumonia reported a median duration of hospital stay of 6 to 8 days,[221,222] which is similar to the duration of hospitalisation for pneumonia in the current study. A study investigating children hospitalised with viral LRTI, found that children admitted with human metapneumovirus and co-infected with other viruses were hospitalised for the least amount of time (mean (SD) of 2.1 (2.4) days) whereas children with RSV were hospitalised the longest (mean (SD) of 4.6 (5.0)days).[244] This is similar to the current study's overall length of hospital stay of a median (IQR) of 2.25 days (1.5-5.0). However, a South African study found a longer duration of hospitalisation in children hospitalised with human metapneumovirus than RSV (median (IQR) 17 (10.5-33.5) days versus 9.5 (6-17.5) days respectively).[263] Furthermore, a study by Hatipoglu et al. found a median duration of hospital stay of 7.9 days for children with a known viral infection, of which RSV was the most common.[245] Another study, conducted by Wang et al., revealed an overall median duration of hospitalisation of 7 days for children with uncomplicated RSV LRTI, whereas the children admitted with underlying disorders were found to be hospitalised for longer (median 9.5 days).[255] This is shorter than the current study's results, however, hospitalisation was longer for children hospitalised with chronic and acute comorbidities (median (IQR) 5.5 (2.3-11.8) days and 6.3 (2.5-12.3) days respectively) than for children without comorbidities. The shorter overall duration of hospitalisation in the current study compared

to the above mentioned studies might be a result of limited available resources at the research site. As mentioned in Chapter 1, South Africa is a middle-income country with associated financial struggles and a high burden on the public healthcare sector. In addition to clinical outcomes, cost prevention and high demands for hospital beds could be attributing factors for short duration of hospital stay.[264]

The length of hospital stay was associated with whether or not children received mechanical ventilation, had acute comorbidities, received ACT, had CP, NMD, a chronic heart or respiratory disease, a genetic disorder, or tachypnoea on admission. In a study conducted by Rodriguez et al. the predictors for disease severity, which was partially based on length of hospital stay, in children with RSV LRTI were investigated.[265] They found that children younger than six months of age, those born prematurely, with a pre-existing lung disease or congenital heart disease, were more likely to have severe disease.[265] Some of these factors, such as heart disease, prematurity and chronic respiratory disease were also identified in the current study's multiple regression analysis, however, other factors might have been identified as the current study only investigated duration of hospitalisation, not disease severity. Our finding that receiving ACT was associated with increased duration of hospital stay may reflect the increased likelihood of receiving ACT in those who developed nosocomial infections (also associated with increased duration of hospital stay).[266] However, the RCT by Lukrafka et al. also reported a median two days longer hospital stay in children who received ACT, compared to controls, which was not statistically significant, possibly owing to insufficient sample size.[222,267] Therefore, further prospective studies are recommended to confirm these results and to determine causality.

Although very few children in our sample died (mortality rate of 0.7%), children with presumed nosocomial infections or pneumonia were more likely to die than children with other clinical diagnoses. Pneumonia is still the most common cause for mortality in children younger than five years of age worldwide.[176,187] In the current study, the overall mortality rate for children with a LRTI was low at 0.7%; however, a greater proportion of children with presumed nosocomial infection (5.7%) died. The mortality rate for children with a clinical diagnosis of pneumonia was 0.6%. These mortality rates, although slightly higher, are comparable to the rates found in children younger than five years hospitalised with acute LRTI in rural Thailand, with 0.3% overall mortality rate and 0.8% for radiologically confirmed pneumonia compared to 0.2% in children without a confirmed diagnosis of pneumonia.[243] All children, included in the current study, who died during the study period, presented with multiple comorbidities and seven of the ten children were older than four years of age. The cause of death could therefore be versatile and not solely attributed to LRTI. ACT was

associated with an increased mortality rate, which has not been previously reported. However, causality cannot be determined on the basis of this study design. Considering most children admitted with pneumonia had comorbidities, this may explain the higher observed mortality in this group.

A retrospective record review was conducted in the current study, which limited the amount of available information to that which was presented in the medical folders. In addition, the quality of the information could not be verified and a major limitation of this study was the lack of information regarding discharge diagnosis. The reported diagnoses were those made at admission, which are not always correct and may be altered as more information becomes available. Exposure to smoke, which might influence the disease severity and length of hospital stay,[268,269] was not extracted from the medical files, as this is not standardly documented. Furthermore, length of stay in the paediatric intensive care unit was not recorded, which might have been another influencing factor for length of hospital stay.

5.6 CONCLUSION

This descriptive study is the first South African study investigating patient characteristics; ACT practice and adverse events; and patient outcome measures in children admitted to hospital with a LRTI.

This study revealed that a relatively small proportion of children with LRTI received ACT. ACT was mostly applied in children with presumed nosocomial infections, followed by pneumonia, compared to other clinical diagnoses. Few children with uncomplicated bronchiolitis were treated with ACT, which conforms to the guidelines for bronchiolitis management. There is very little literature available on the benefits of ACT in children with pneumonia. Given the paucity of high-level evidence, ACT is therefore used in clinical practice based on the physicians' and physiotherapists' expert opinion. It is therefore recommended that more research regarding ACT in children with nosocomial infections and pneumonia be conducted. This is particularly important considering that the duration of hospitalisation was longer and mortality rate higher in children with nosocomial infections and pneumonia, compared to those admitted with other LRTIs, especially bronchiolitis. This could be associated with increased financial cost and burden for these families. The identification of modalities which could hasten resolution of the disease, as well as identifying interventions which are of no use or harmful, would help to ensure rational and appropriate resource allocation and optimal clinical outcomes.

This study also found that ACT, as performed at this research site, appears relatively safe to perform in children with LRTI, with only six children desaturating and no serious adverse events. However, the study was not designed or powered to determine safety, and further prospective, controlled clinical trials are recommended to confirm this finding. It is recommended that SpO_2 be monitored during ACT, so the treatment can be halted when deemed necessary. Conventional ACTs were the most commonly used techniques by physiotherapists, possibly related to the large proportion of children younger than one year of age, in whom modern ACTs requiring cooperation are more difficult to perform.

As more than half the children included in this study presented with comorbidities, research is warranted to investigate the use of ACT in children hospitalised with LRTI and comorbidities, both chronic and acute.

This is a ground-breaking study, describing the patient population, management and outcomes for children admitted with LRTIs at a tertiary paediatric hospital in Cape Town, South Africa. It highlights the need for more research on ACT especially in children with nosocomial infections and pneumonia.

Chapter 6. THE USE OF ASSISTED AUTOGENIC DRAINAGE IN INFANTS AND YOUNG CHILDREN WITH ACUTE RESPIRATORY DISEASE IN SOUTH AFRICA

PACTR201404000706382

6.1 INTRODUCTION

ACT is often prescribed for children with acute lung disease to assist in clearance of secretions.[143,218] As mentioned previously in this thesis, several studies with mixed results have been published on the use of ACTs in children with pneumonia.[221–224,226–228] New ACTs have recently been introduced for young children, including AAD;[84,121,270–272] but no high-level literature could be found on the use of AAD, although it is used clinically, especially in European countries. Therefore, a RCT was conducted in children hospitalised with acute uncomplicated pneumonia, to investigate the impact of administering AAD as additional treatment to standard care.

AAD is a passive/assisted technique, which could be useful in the treatment of young children and is assumed to have minimal adverse effects.[25,131,132] A quick resolution of pneumonia is important to prevent further damage to the airways, which could lead to bronchiectasis.[201] This could additionally benefit the patient, and health sector both psycho-socially and financially.

6.2 AIMS AND OBJECTIVES

This study aimed to determine whether standard nursing care with additional AAD was more effective than standard nursing care alone in improving clinical outcome measures of children between the age of one month and eight years, hospitalised with community- or hospital acquired pneumonia.

The specific objectives were to establish if there were any significant differences between the following outcomes in the control and intervention group:

- Primary outcome: duration of hospital stay, expressed in number of days from admission to discharge based on the medical practitioner's prescription.

- Secondary outcomes:
  - Short-term outcomes before, during and after treatment: SpO_2 using transcutaneous oximetry; RR; and signs of respiratory distress.
  - Number of children needing intubation or ventilation.

- Number of days to clinical resolution: duration of fever and oxygen supplementation expressed in days.
- Lung function test/spirometry in children older than five years of age.
- Incidence of complications and adverse events.
- Mortality rate.

6.3 METHODOLOGY

6.3.1 Study hypothesis

Null hypothesis: There will be no significant difference in duration of hospitalisation, time to symptom reduction, incidence of adverse events and mortality rate between the control (standard nursing care) and intervention (standard nursing care with additional AAD) groups.

6.3.2 Study design

A RCT, single blinded, pragmatic study design was used. RCTs are the gold standard in experimental research as they reduce bias (especially allocation bias) and have high internal and external validity.[273] The term 'pragmatic' refers to the comparison between a control and intervention group within a real-life setting.[274] Blinding refers to masking participants and outcome assessors to group allocation. As the intervention in the current trial was a physiotherapy intervention, blinding of the participants was impossible, therefore, this study was classified as single blinded.[275] Although the attending physiotherapist (not blinded to group allocation) gathered information pre-, post- and one hour after intervention; the outcome assessor collecting data at admission, recruitment and discharge, and the data analyst were blinded to group allocation thoughout the study.

6.3.3 Research setting

Children, who were hospitalised at two tertiary hospitals in South Africa, with a clinical diagnosis of community- or hospital acquired pneumonia were eligible for the study. The first research site is a 290-bed, tertiary paediatric hospital to which patients from all over Africa, especially low income patients, are referred.[276] Two general medical wards admit 80 to 100 patients per month, with pneumonia and gastro-enteritis as the most common reason for admission. It is estimated that up to 70% of the ward admissions are respiratory related (Prof. B. Morrow. Personal communication, 2013). The second research setting is a 1650-beds tertiary academic hospital associated with Sefako Makgatho Health Sciences University (formerly known as the Medical University of South Africa (Medunsa)). The study took place in their paediatric wards (wards 19, 22 and 23).

6.3.4 Participants

Spontaneously breathing children with a clinical diagnosis of community- or hospital acquired pneumonia and hospitalised at one of the research sites were eligible for enrolment in this study. The planned age range for inclusion was one month to eight years of age.

Inclusion criteria:

- The diagnosis of pneumonia was made by the attending physician, based on the following criteria:
  - tachypnoea defined as a RR ≥20 bpm in children >five years, ≥40 bpm in children between one and five years, ≥50 bpm in children between two and 12 months, and ≥60 bpm in children <two months.[194]
  - fever and/or cough.
  - radiological or clinical confirmation of pneumonia.

- Clinically stable on recruitment: i.e. with none of the following:
  - tachycardia defined as a HR ≥120 beats per min (bpm) in children >five years, ≥140 bpm in children beween three and four years, ≥150 bpm in children between one and two years, and ≥ 160 bpm in children <one year .[194]
  - unstable blood pressure
  - altered mental status
  - SpO_2 <90% on oxygen support.[194]

Exclusion criteria:

- Active TB (to reduce exposure of the research team to active TB; the child was considered for inclusion once the TB had been found inactive),
- Clinical diagnosis of bronchiolitis (a recently updated systematic review concluded that ACTs are not beneficial for young children with bronchiolitis)[257],
- PJP, either suspected or proven (PJP is of fungal origin and pathophysiology is different from bacterial or viral pneumonia (see section 3.2). Furthermore, PJP is generally an interstitial disease without obstructive secretions, resulting in severe hypoxia).[277,278]
- Pleural effusion (children with pneumonia-associated pleural effusions are hospitalised for a longer duration of time, which could be a threat to this research's primary outcome measure)[279],
- Recent pneumothorax in last three months (to reduce the risk of a new pneumothorax),

- Clinical diagnosis or history of asthma (as the pathophysiology of asthma with the presence of wheezing and collapse of the airways might influence AAD and the clinical outcome measurements),
- Increased intracranial pressure (as AAD has not been researched previously and conventional ACTs have been found to increase intracranial pressure,[85] children with an increased intracranial pressure were excluded as a safety precaution),
- Chest deformities (chest deformities could influence the AAD technique, as the lung volumes are altered manually, decreasing the lung volume),
- Osteoporosis (due to the risk of rib fractures)[101],
- Severe hypoxia or respiratory distress on admission and recruitment (SpO_2 ≤90% on oxygen and clinical signs: cyanosis, weak cry, feeding problems, muscle retraction, head nodding, nasal flaring)[194,280]. If the child had more than three of these signs, he/she was excluded from the study. If the child had three or fewer signs, he/she was included in the study (Children were excluded if they were severely distressed, as manually influencing the lung volumes and level of breathing might increase respiratory distress even further). Children who were in severe distress and/or being mechanically ventilated due to pneumonia at the time of admission were considered for enrolment in the study once they had been stabilised after extubation and transferred to the ward.
- CF (these children are standardly hospitalised for two weeks for infection eradication, which influences the duration of hospitalisation),
- Presence of an intercostal drain (as AAD is a manual technique, the physiotherapist places his/her hands on the chest of the child, which could be influenced by the presence of an intercostal drain),
- Thoracic or abdominal surgery during the preceding six months (during AAD, the chest is manually manipulated to reduce lung volumes, which might impact the surgical site and could increase pressure in the thorax and abdomen),
- History of prematurity: ≤30 weeks of gestation (as described in section 2.1, prematurity could severely impact the child's respiratory system for which the outcome measures of the study might be influenced),
- Any other chronic respiratory disease receiving daily physiotherapy as standard practice (as these children cannot be included in the control group, random allocation would not be possible)
- Any cardiac defect (as the adverse effects of AAD are unknown, these children were excluded to prevent increased stress on the heart as a safety precaution)

- Acute or chronic upper airway obstruction and/or stridor (blockage of the upper airways could influence the clearance of secretions from the lungs and might increase respiratory distress when lung volumes are altered)
- Children with a medical condition/complication for which they could not be taken out of bed and placed on the physiotherapist's lap (to standardise the AAD intervention, all children were placed in sitting on the physiotherapist's lap to perform the technique. If a child could not be taken out of bed, the treatment would not be standardised throughout the study)
- Any neurological condition, including but not limited to seizures/epilepsy and NMD (this was a safety precaution for a novel, untested intervention. For patients with seizures/epilepsy, exclusion was based on the risk of inducing a new episode of seizures. Children with NMD were excluded as the majority of these children would already have respiratory compromise due to respiratory muscle weakness and altered chest wall compliance,[281] which could influence this research's outcome measures as well as affect the tolerance towards AAD, jeopardising safety.)
- Hospitalised for less than two days. The study took place in the general wards of the hospitals, where the majority of children are hospitalised for more than two days. No recruitments were done in the short-stay wards to prevent children being enrolled for less than two days of hospitalisation. As the intervention needed to be performed bi-daily for several days before changes were expected, this exclusion criteria was added after initiation of data collection but prior to unblinding the data analyst (as one child was found to be hospitalised for less than two days).

HIV-infected or –exposed children were included in the study. A sub-analysis on this group was planned, however, insufficient sample size was obtained for analysis.

Sample size

The average duration of hospital stay in children admitted for pneumonia was estimated *a priori* to be 7 days (±1.5) (based on results from section 4.4.5.1 and 5.4.4). To detect a clinical relevant difference of one day between control (8 days) and intervention groups (7 days), 49 participants per group were calculated as being needed to obtain a two-sided α of 5% with a power of 90%.

Interim analysis

After enrolment of 23 participants, an interim analysis was done to determine whether the study should continue, with a *priori* boundaries of $p<0.006$ to reject the null hypothesis (efficacy boundary;

if a large treatment effect is detectable before the end of the study); and $p>0.52$ to accept the null hypothesis (futility boundary, if there is little chance of detecting a significant difference between the groups). After interim analysis, data were recoded by an independent researcher to maintain blinding.

The study ran from March 2014 until December 2015. From mid-December 2014 until mid-January 2015, no new recruitments were done owing to staff shortages during the Christmas holidays.

6.3.5 Outcome measures/instrumentation

After considering the benefits and downsides of common outcome measures for the assessment of ACTs as described in section 2.3.3, the following were included in the study:

6.3.5.1 Data collection forms

During recruitment, the researcher collected general information using a standardised case record form (Appendix 9). Information on nursing care was extracted from the child's medical file after discharge. The data on ACT were collected by clinical physiotherapists using a standard evaluation form (Appendix 9). All pre-set data extraction forms were self-designed and validated for content by an expert in the field of paediatric cardiopulmonary physiotherapy. The clinical physiotherapy staff at the research sites provided input regarding applicability of the forms in practice. Research personnel received training regarding completion of the forms prior to the study, to establish a better interrater reliability (see section 6.3.7).

6.3.5.2 Duration of hospitalisation

The length of hospital stay was expressed in number of days from admission to discharge based on the medical practitioner's prescription (who was blinded to group allocation), as recorded in the medical files. Although the discharge criteria were not pre-defined, the medical practitioner was blinded to group allocation, reducing bias in time of discharge.

- If the child was admitted to the hospital in the morning, this accounted for a full day. When the child was admitted in the afternoon, half a day was taken into account and when the child was admitted in the evening, a quarter of a day was noted.
- If the child remained hospitalised due to other unforeseen problems (e.g. social problems), the day that the child was clinically cleared of his/her pneumonia, based on the medical practitioner's discretion, was used as a proxy for the discharge date.

6.3.5.3 Days to clinical resolution

This outcome measure was based on nursing documentation, completed by the nursing staff who was blinded to group allocation; and expressed as:

- Duration of fever (>37 $^{\circ}$C) in days.
- Days on supplemental oxygen support.

6.3.5.4 Vital signs and oxygen saturation

- RR: absolute values and adjusted for age
  - At baseline, after five days and at discharge, as presented in the medical files by blinded medical personnel
  - Before, immediately after and one hour after every intervention, assessed by the attending physiotherapist (not blinded to group allocation)
- HR: absolute values and adjusted for age
  - At baseline, after five days and at discharge, as presented in the medical files by blinded medical personnel
- Although SpO_2 has been reported as unreliable and insensitive for research purposes (see section 2.3.3);[142] the assessment of SpO_2 was deemed necessary to detect desaturation throughout the study period, especially during ACT (see section 5.4.3.2). Therefore, SpO_2 in room air was measured by transcutaneous oximetry
  - At baseline, after five days and at discharge, as presented in the medical files by blinded medical personnel
  - Before; during; immediately after and one hour after treatment, assessed by the attending physiotherapist (not blinded to group allocation)

Vital signs and SaO_2 were taken once off, with HR and RR measured for one minute. However, these measurements were continuously documented by several members of the medical staff, who flagged great changes in these outcome measures.

6.3.5.5 Lung function testing

Lung function (spirometry) tests (using American Thoracic Society (ATS) criteria) were planned to be performed, assessing RV/TLC, VC, FVC, FEV_1, PEF, in children age five to eight years of age at baseline, after five days and at discharge. This outcome measure would have been assessed by the research assistant or myself (both remained blinded to group allocation throughout the study), using the Microloop.

6.3.5.6 Adverse events and mortality

- The incidence of adverse events were extracted from either the medical files completed by blinded medical personnel or from the physiotherapy data collection form (not blinded to group allocation). Adverse events included hypoxia (SpO_2 ≤90% on oxygen support), acute atelectasis and lung/lobar collapse, based on radiology reports (if available).
- Mortality rate

6.3.6 Interventions

Control group

The control group received standard nursing care, which typically included antibiotic treatment, hydration, oxygen support, regular change of body position and nasopharyngeal or oropharyngeal suctioning if necessary. No ACT was performed in the control group, with the proviso that 'emergency treatment' by a physiotherapist could be requested at any time by the attending paediatrician or physiotherapist. If emergency physiotherapy was deemed necessary, the physiotherapist conducted their treatment of choice. The techniques used, and the duration of the treatment(s) were recorded. As clinical guidelines do not recommend ACT as standard practice for children with pneumonia;[11,217] and a minority of children hospitalised with LRTI at the primary research site received ACT (Chapter 5); a control group not receiving ACT was justified.

Intervention group

The intervention group received standard nursing care as described above, and AAD performed by a physiotherapist, as an adjunct. AAD was planned to be given for five consecutive days, with bi-daily treatment for a minimum of 10 (children younger than five years) to a maximum of 30 minutes (children older than five years) in order to prevent fatigue. The length of therapy was determined by the attending physiotherapist, based on signs of respiratory distress and fatigue, and therefore not standardised. However, length of treatment and reason for halting the treatment was documented on the physiotherapist's data collection forms. Intervention, as described in Chapter 2, was done in the morning and afternoon at approximately the same time daily. To standardise the treatment, all participants were treated in an upright sitting position and no bouncing was performed during AAD treatment. The upright sitting position was applied as this position optimises diaphragmatic function, improves ventilation and reduces fatigue in infants and young children (see section 2.2).

At the end of every treatment session, the participant was required to cough. If no spontaneous coughing occurred, cough was stimulated. Elicitation of a cough was done firstly through

demonstration (mimicking), however, when this was unsuccessful, children younger than nine months of age were suctioned nasopharyngeally (as per standard nursing care) and children older than nine months underwent tracheal stimulation. If children in the intervention group needed more than bi-daily physiotherapy, as determined by the physiotherapist, the additional treatment session was classified as 'emergency treatment', during which the physiotherapist was allowed to use a treatment of choice. The techniques used, and the duration of this additional treatment were recorded. All children remained in their allocated study group, and were analysed in that group, regardless of whether additional 'emergency' physiotherapy treatments were administered or not (intention-to-treat analysis).

6.3.7 Procedure

Approval

Ethical approval was granted by the Faculty of Health Sciences HREC (ref 532/2013, Appendix 10), University of Cape Town. Furthermore, permission to access the hospitals was obtained from the medical superintendent at both research sites (Appendix 10).

Training of research personnel

I was trained in AAD during my MSc in Belgium, as well as further educated (self-study) based on a course designed by Mr Chevailler.[128] A pre-trial workshop was organised and attended by all physiotherapists involved in the study (at both research sites). I led the sessions and travelled between Cape Town and Pretoria to ensure training was identical between the different research sites. The content of the workshop were: explanation of the study protocol, AAD technique as described above and the completion of the forms. A PowerPoint presentation and a practical session were organised to educate the physiotherapists on how and when to perform the AAD technique and how to complete the necessary forms. This workshop was mandatory for all six physiotherapists involved in the study and repeated every six months to ensure consistency between therapists. Correct performance of the technique was evaluated during the AAD workshop as well as during the treatment of a patient, not enrolled in the study. The research assistant who collected baseline and discharge data at the second research site received extra training on how to collect the data and how to interpret inclusion and exclusion criteria. I remained in close contact with the research personnel, for which uncertainties were resolved quickly and did not interfere with the research process.

Recruitment

Recruitment was done on Monday mornings by myself (at the primary research site) and a research assistant (at the second research site). As the study protocol described AAD to be performed for five consecutive days, recruitment could only occur during this limited time frame, to reduce burden on the weekend physiotherapy staff. Eligible participants were identified by screening the patient's medical files or based on the attending medical practitioner's recommendation. Parents received verbal and written explanations of the study procedure and provided written informed consent for their child's participation in the study (Appendix 11). The informed consent form was available in three different languages (English, Afrikaans and isiXhosa). When parents and/or child did not understand the language presented in the consent/assent form, an interpreter explained the study and obtained consent/assent. Parents who were not with their child in hospital on the day of recruitment were telephonically contacted to obtain verbal consent prior to their arrival to hospital to sign the form. If the child was older than five years of age, assent would have been obtained (Appendix 11). After obtaining informed consent, the child was randomly assigned to either the intervention or control group by the use of simple randomisation. Randomisation was done by a computer generated list of random numbers prior to the start of the study (ratio 1:1) and sealed, opaque, sequentially numbered envelopes were created to maintain allocation concealment.

Baseline data

The child's baseline characteristics: day and hour of hospitalisation, RR, HR, SpO_2, temperature, general descriptive characteristics (gender; age; HIV-infected or –exposed; the presence of NMD) and the disease history of the child (including previous episodes of lung infections) were obtained from the medical file during recruitment. If the child was older than five years of age, lung function tests would have been carried out before group allocation. Data were recorded from admission notes and the medical file at the day of recruitment.

During hospitalisation

Before AAD treatment, SpO_2 was noted and RR measured by the attending physiotherapist. During treatment, SpO_2 and general clinical signs of distress were monitored in order for distress and hypoxemia to be prevented or managed. This was done by stopping the therapy until the child recovered, or supplying supplemental oxygen if necessary. Duration of distress or hypoxaemia and clinical signs were documented by the attending physiotherapist. The physiotherapist also indicated the duration of treatment and the reason(s) for halting the intervention. Post-treatment and one hour post treatment assessment of RR and SpO_2 was performed by the physiotherapist. Children

were permitted to receive other (non-respiratory) forms of physiotherapy (e.g. developmental stimulation), which was documented. The number of days the child received oxygen supplementation was noted in the medical file by the nursing staff (blinded to group allocation). After five days all children were re-evaluated by a blinded outcome assessor. If the child was assessed clinically as needing further ACT after the five days of AAD-treatment, any other ACT was given except AAD.

At discharge

Discharge data were documented at the time of hospital discharge and lung function tests would have been taken in children older than five years of age before leaving the hospital. All children enrolled in the study were exposed to the same medical team, who were blinded to allocation. The date of discharge for all participants was determined by this blinded medical team, therefore, no discharge criteria were determined in advance. If the child died, date and time of death were documented. When patients were transferred to another hospital, date of transfer was used as discharge date from the research site. Discharge data were obtained by blinded medical personnel and the research assistant or myself.

6.3.8 Data-capturing and management

All data were de-identified and coded by the use of coded computer files and/or coded paper files saved in sealed envelopes. Data specific to the intervention group (pre-, post- and one hour post-treatment) were recorded on a separate sheet and held by the supervisor in order to maintain the blinding of the outcome assessor and data analyst. After data-collection, data were entered into a password protected Excel spreadsheet and imported to Statistica (Version 12, StatSoft Inc, Tulsa USA) for analysis. Adjustments for age were made for RR and HR by comparing the participant's RR and HR with age norms. The absolute values were divided by the norm values for both outcome measures. Norms were based on a review published by Fleming et al.[240]

6.3.9 Data-analysis

Data were analysed using Statistica (Version 12, StatSoft Inc, Tulsa USA) and as the numbers were too small for application of the Central Limits Theorem, data were tested for normality using the Lilliefors tests. Based on these results, parametric or non-parametric tests were utilised. The Chi

square, Fisher exact or Yates test were used to test for association between groups for dichotomous data, such as gender. Numeric outcome parameters were analysed using the Student t-test or Mann-Whitney U test. An intention-to-treat analysis was performed. Effect size (Cohen's d)[(5)] was calculated for outcome measures which showed a trend towards significant differences between groups. For non-parametric data, the effect size r value was calculated with the formula $r= z/\sqrt{N}$.[282] As the z value is sample size dependent, the r value will eliminate this sample size effect.[282] The r value was converted into a Cohen's d value by the formula $d= 2r/\sqrt{(1-r^2)}$.[282] Interpretation of the effect size was based on Cohen's guidelines for small (d= 0.2), medium (d= 0.5) and large (d= 0.8) effect sizes.[283]

Within-group analyses were conducted using Dependent Student t-tests or Wilcoxon Matched Pairs tests. Change over time analysis was conducted by calculating the difference of the means or medians and the 95% confidence intervals of the difference of means/medians. A Kaplan-Meier analysis was performed to compare the time to discharge between the groups.

Repeated measures were analysed using Friedman ANOVA, with further analysis of significant results by the use of the Dependent Student t-test or Wilcoxon Matched Pairs tests between two dependent groups. Dichotomous repeated data were analysed by the McNemar test. Analysis of the effect of the intervention in children with viral, bacterial and mixed aetiology pneumonia was conducted using the Kruskal-Wallis test. *Post hoc* analysis of significant results was done using a multiple comparison mean rank test.

An intention-to-treat analysis was performed. A significance level of 0.05 was chosen to analyse differences between and within groups. Dependent variables were the different outcome measures as indicated above. The independent variables were age, gender, HIV-infected or –exposed or previous episodes of lung infections.

6.4 INTERIM ANALYSIS AND AMENDMENTS

Owing to the slow recruitment rates, it was deemed necessary to make amendments to the study protocol after six months of commencement. The original protocol only included children admitted with bacterial pneumonia, and this resulted in many children being excluded as their aetiology was

---

[(5)] Cohen's d= (mean1-mean2)/(standard deviation).[283]

not known on the day of recruitment. Therefore, the inclusion criteria were extended to include children with all organisms responsible for pneumonia. Further, the study was expanded to a second research setting in order to increase the number of participants.

An interim analysis was performed after enrolment of 23 participants (13 in the control group and 10 in the intervention group) at the primary research site. No data from the secondary research site were included in the interim analysis. Non-parametric statistics were used for this analysis.

A significant difference in RR adjusted for age at admission was seen between intervention and control groups with p= 0.002 (median (IQR) 1.3 (1.0-1.4) for the control group and median (IQR) 1.5 (1.4-1.8) for the intervention group). However, this difference was resolved by the time of recruitment (p= 0.336).

When looking at the different outcome measures at interim analysis; no significant difference was found for the primary outcome measure, duration of hospitalisation (median (IQR) 7.5 (7.0-11.3) versus 7.3 (6.5-8.5) days for control and intervention groups respectively, p= 0.239). Further, no significant differences were seen for the secondary outcome measures (respective p-values for RR and HR adjusted for age; SpO_2; and duration of fever and O_2 supplementation were 0.975, 0.575, 0.214, 0.620 and 0.967). No adverse events nor fatalities were noted within these 23 participants.

It was decided to continue the study as the significance level of the primary outcome measure was within the pre-set boundaries. Furthermore, there were no recordings of adverse events within either the control or intervention group; and a significant difference at baseline for admission RR adjusted for age was observed, for which continuation of the study was recommended.

The next interim analysis was planned after enrolment of 50 participants, however, the study was halted due to pragmatic considerations prior to achieving this number of participants (see Discussion).

6.5 RESULTS

6.5.1 Participants

A total of 896 children were screened, of which 862 were excluded (Figure 6-1 and

Table 6-1). Thirty-four participants (23 male (67.6%), median (IQR) age 3.5 (1.5 – 9.6) months) were enrolled in the study. Five participants were excluded after enrolment for various reasons (see Figure 6-1). One participant's medical file was missing on the day of enrolment, and only after enrolment a recent history of pneumothorax was identified for which the participant was excluded from the study. Another participant was hospitalised for fewer than two days. The other three participants were excluded owing to the diagnosis of bronchiolitis (n=1) and asthma (n=2) post enrolment. All five participants were allocated to the control group, of whom two (both diagnosed with asthma) received one day of bi-daily emergency physiotherapy prior to exclusion. No participants were lost to follow-up, however, six children were transferred to another hospital (n=2 in the intervention group and n= 4 in the control group), for whom the date of transfer was used as discharge date. Therefore, 29 participants were included in the final analysis (18 male (62.1%), median (IQR) age 3.5 (1.5 – 9.4) months). In the control group, one participant received three sessions of emergency physiotherapy, consisting of percussions, vibrations and suctioning. All other participants in the control group were not exposed to ACT. None of the participants in the intervention group required emergency physiotherapy.

Admission and recruitment characteristics of the analysed participants per group are presented in Table 6-2. Data were skewed for all baseline and recruitment characteristics, except for systolic blood pressure (d= 0.13, Lilliefors not significant (NS)), diastolic blood pressure (d= 0.15, Lilliefors NS) and temperature on admission (d= 0.09, Lilliefors NS); as well as HR adjusted for age at admission (d= 0.10, Lilliefors NS), and recruitment (d= 0.12, Lilliefors NS). Groups were similar at admission and recruitment for all baseline characteristics, except for RR adjusted for age at admission (p=0.013). However, this difference was resolved by the time participants were enrolled in the study. This could have been due to the number of hospitalised days prior to recruitment, which changed the RR adjusted for age at recruitment compared to admission.

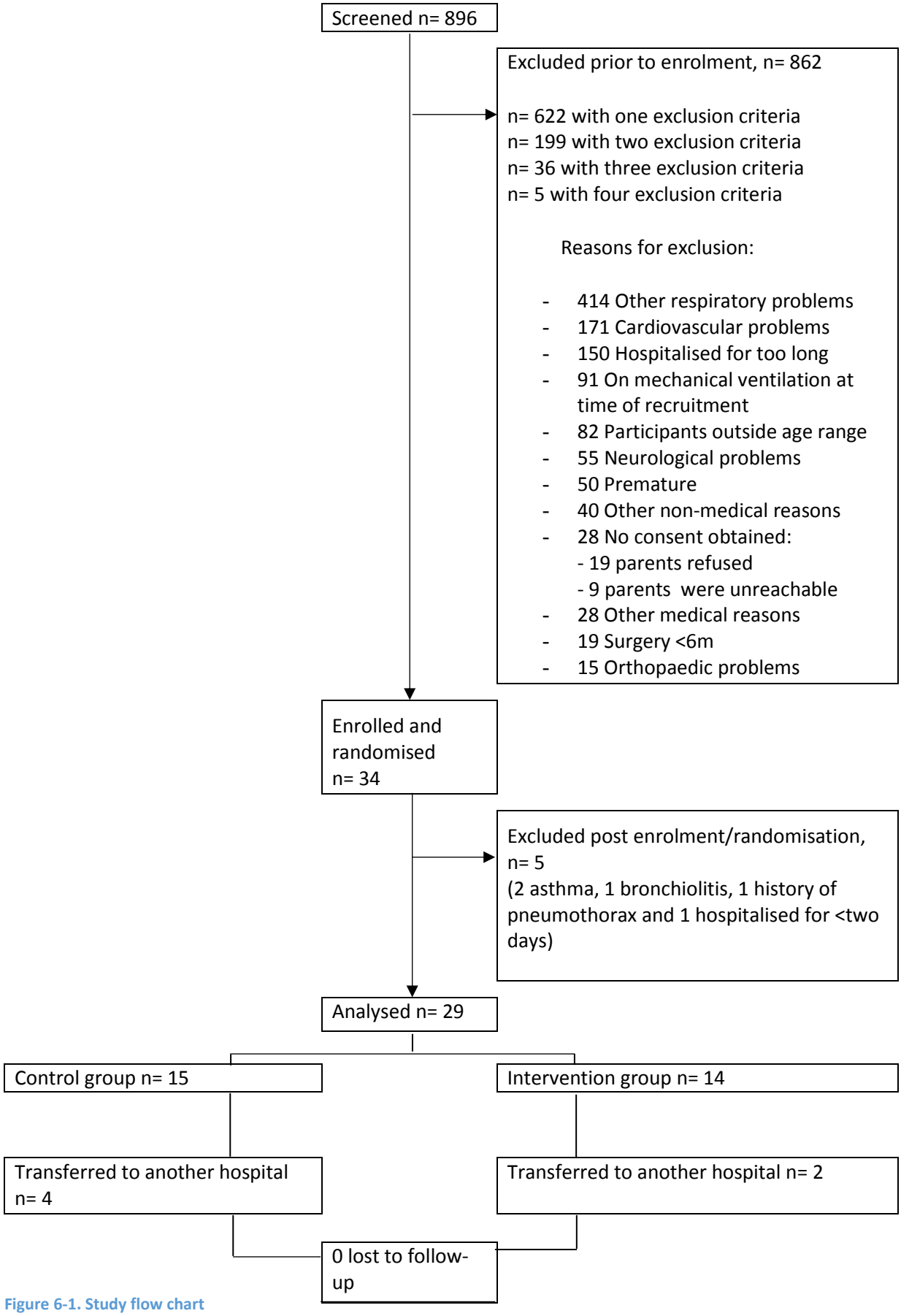


Figure 6-1. Study flow chart

Table 6-1. Reason for exclusion of screened children

Category of exclusion	Specific reason for exclusion
Respiratory problems	- 96 Viral infection prior to expansion of inclusion criteria - 54 Bronchiolitis - 41 PJP (suspicion (n= 28) + diagnosed (n= 13)) - 35 Wheezes + prolonged expiration - 35 Other/unspecified chronic lung disease (suspicion (n= 2) + diagnosed (n= 33)) - 32 Pleural effusion - 28 Asthma (suspicion (n= 12) + diagnosed (n= 16)) - 22 Upper airway obstruction - 16 Intercostal drain - 13 Resolved pneumonia - 11 Pneumothorax - 9 CF (suspicion (n= 5) + diagnosed (n= 4)) - 8 Pertussis (suspicion (n= 6) + diagnosed (n= 2)) - 6 Other unspecified lung disease - 3 Croup - 1 Chronic airway obstruction - 1 Contagious TB - 1 Coughing spells - 1 Stridor - 1 Haemoptysis
Cardiovascular problems	- 40 Patent ductus arteriosus - 32 Ventricular septal defect - 19 Atrial septal defect - 15 Atrioventricular septal defect - 13 Pulmonary hypertension - 12 Stenosis - 11 Tetralogy of Fallot - 11 Patent foramen ovale - 10 Congenital heart deformities/disorders - 9 Cardiomyopathy - 7 Heart failure - 7 Unspecified heart disease - 6 Myocarditis - 4 Cardiomegaly - 4 Heart lesion - 4 Pericardial effusion - 4 Atrio-ventricular valve regurgitation - 3 Double outlet right ventricle - 3 Heart murmur - 2 Boot shaped heart - 2 Atrial switch/defect - 2 Coarctation aorta - 2 Mitral valve atresia/regurgitation - 2 Dextrocardia - 2 Deep venous thrombosis - 1 Transposition of the great arteries - 1 Cor pulmonale - 1 Shone's syndrome - 1 Coronary arterial abnormalities - 1 Sinus of Valsalva aneurism - 1 Mycotic aneurism - 1 Right ventricle outlet tract obstruction - 1 Intaventricular septum aneurism - 1 Bicuspid aortic valve - 1 HR at recruitment above inclusion limit - 1 Atrial tachyarrhythmia due to Broviac insertion - 1 Cardiac arrest prior to enrolment - 1 Blood vessel malformation unspecified
Orthopaedic disorders	- 3 Pectus carinatum - 3 Pectus excavatum - 3 Osteoporosis - 2 Scoliosis - 2 Skeletal dysplasia - 1 Gibbus - 1 Rib fractures

Neurological disorders	-	37 Seizures/epilepsy
	-	14 Increased intracranial pressure
	-	3 meningitis
	-	1 Congenital centronuclear myopathy
Surgery < six months prior to enrolment	-	12 Thoracic surgery less than 6 months ago
	-	5 Abdominal surgery less than 6 months ago
	-	1 Unspecified surgery less than 6 months ago
	-	1 Surgery on day of recruitment
On mechanical ventilation on day of recruitment	-	91 on continues positive airway pressure
Premature	-	50 children with gestational age < 30 weeks
Other medical reasons	-	23 No pneumonia during hospitalisation
	-	4 Unable to be taken out of bed
	-	1 Broncho-oesophageal fistula
Age range	-	42 younger than 1 months
	-	40 older than 8 years
Hospitalisation reasons	-	113 admitted prior to Thursday (without ventilation)
	-	37 off ventilation for too long
No consent obtained	-	15 Parents unreachable
	-	7 Refused
	-	6 No consent on day of recruitment
Other non-medical reasons	-	26 Discharged on day of recruitment
	-	9 Folder missing
	-	3 Transferred on day of recruitment
	-	1 Language barrier
	-	1 Child not in ward

Table 6-2. Participants' baseline characteristics at time of admission and recruitment

Baseline characteristic	Intervention (n= 14)	Control (n= 15)	Statistical value	p-value
Gender, n (%) males	8 (57)	10 (67)	Fisher exact	0.442
Age (*months*), median (IQR)				
- at admission	7.7 (2.0 – 12.5)	3.1 (1.5 – 7.5)	z= -1.6	0.116
- at recruitment	7.8 (2.2 –12.7)	3.2 (1.7 – 7.6)	z= -1.5	0.144
Gestational age (*weeks*), median (IQR)	39.0 (38.0 – 40.0)	39.0 (35.0 – 40.0)	z= -0.4	0.712
Days on mechanical ventilation prior to enrolment, median (IQR)	3.0 (1.5 – 4.0)	4.0 (3.0 – 5.0)	z= -1.2	0.214
SpO_2 (in room air) (*%*), median (IQR)				
- at admission	95.0 (92.0 – 97.0)	93.0 (90.0 – 97.0)	z= -0.2	0.817
- at recruitment	99.5 (96.0- 100.0)	100.00 (98.0 – 100.0)	z= -1.0	0.308
RR adjusted for age, median (IQR)				
- at admission	1.4 (1.3 – 1.7)	1.2 (1.0 – 1.4)	z= -2.5	***0.013***
- at recruitment	1.1 (0.9 – 1.4)	1.1 (1.0 – 1.5)	z= -0.7	0.499
HR adjusted for age, mean (SD)				
- at admission	1.2 (0.2)	1.1 (0.2)	t= -1.4	0.171
- at recruitment	1.0 (0.1)	1.0 (0.2)	t= -0.2	0.836
Systolic blood pressure (*mmHg*) at admission, mean (SD)	100.3 (10.5)	95.6 (21.2)	t= -0.6	0.564
Diastolic blood pressure (*mmHg*) at admission, mean (SD)	60.8 (15.9)	55.50 (12.1)	t= -0.8	0.457
Temperature (*°C*) at admission, mean (SD)	37.8 (0.5)	38.03 (1.3)	t= 0.7	0.514
O_2 supplement (*l/min*) at recruitment, median (IQR)	1.0 (0.0-2.0)	2.0 (0.0-3.5)	z= 0.9	0.369
Signs of distress at admission, n (%)			Yates X^2= 0.5	0.913
- Alar flaring	7 (50)	5 (33)		
- Head nodding	1 (7)	3 (20)		
- ICR	3 (21)	5 (33)		
- SCR	7 (50)	9 (60)		
HIV status, n (%)			Yates X^2= 1.3	0.722
- Negative	11 (79)	11 (80)		
- Exposed	1 (7)	1 (6.7)		
- Positive	1 (7)	1 (6.7)		
- Unknown	1 (7)	1 (6.7)		
Aetiology, n (%)			Yates X^2= 0.5	0.926
- Viral	5 (36)	4 (27)		
- Bacterial	2 (14)	3 (20)		
- Mixed	0 (0)	2 (13)		
- Unknown	7 (50)	6 (40)		

6.5.2 Between groups comparison

All data, except for the outcome measure 'HR adjusted for age at discharge' (d= 0.09, Lilliefors NS) and 'days on oxygen supplementation' (d= 0.13, Lilliefors NS), were skewed. Therefore, non-parametric tests were used to analyse the data, except for these two normally distributed variables.

No significant difference was found between the intervention and control groups for the primary outcome measure 'duration of hospitalisation' (p=0.163) (Table 6-3). Nor was there a significant difference between the number of days enrolled in the study (p= 0.760) (Table 6-3). This last comparison was made to adjust for the days of hospitalisation prior to enrolment in the study. However, Kaplan-Meier analyses of time to discharge revealed a tendency towards a shorter time to discharge for the intervention group compared to the control group (Log-Rank Test WW= -4.1, p= 0,057) (Figure 6-2). A medium effect size was found based on the following calculations:

$r = 1.4/\sqrt{29} = 0.26$

$d = 2x0.26/\sqrt{(1-0.26^2)} = 0.54$

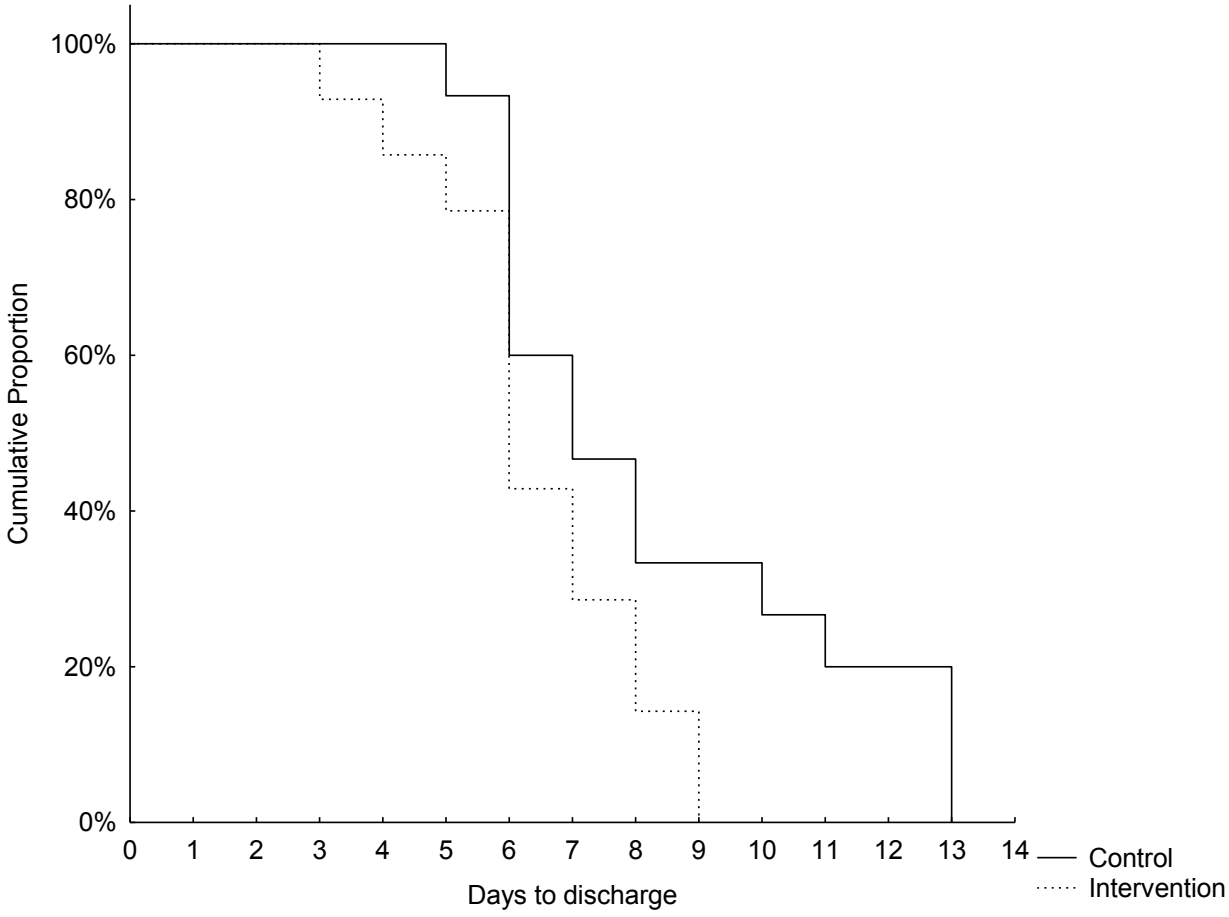


Figure 6-2. Comparison between the intervention and control group for time to discharge, Kaplan-Meier logrank test.

Table 6-3. Comparison between the control and intervention groups for different outcome measures, presented in days.

Outcome measure	Control group (n= 15)	Intervention group (n= 14)	Statistical value	p-value
Days of hospitalisation, median (IQR)	7.5 (7.0-11.3)	7.0 (6.5-8.5)	z= 1.4	0.163
Days of enrolment	3.0 (2.0-6.0)	3.5 (3.0-5.0)	z= 0.3	0.760
Days of fever during hospitalisation	1.0 (1.0-4.0)	2.0 (1.0-2.0)	z= 0.2	0.854
Days on O_2 support during hospitalisation, mean (SD)	4.1 (3.9)	4.2 (2.3)	t= -0.1	0.949

Only eight participants (six in the control and two in the intervention group) were enrolled for five or more consecutive days. Therefore, analyses of results between the control and intervention group after five days of enrolment, as planned and mentioned in the methodology, was not possible.

This study's secondary outcome measures, 'days to clinical resolution' (based on days of fever (p=0.854) and days on oxygen support (p= 0.949) during hospitalisation), SpO_2 (p=0.364), HR and RR adjusted for age (respective p-values 0.941 and 0.585); showed no significant differences between the groups (Table 6-3 and Table 6-4).

No adverse events, mortalities or casualties were reported in either of the groups, therefore no between-groups analyses could be performed for these outcome measures. None of the participants progressed to being intubated and mechanically ventilated during the course of this study. Finally, none of the participants were older than five years of age, therefore, no lung function tests were performed during this study.

No difference in change over time for a number of outcome measures, occurred between the intervention and control groups (Table 6-4).

Table 6-4. Difference within and between groups for all outcome measures assessed at recruitment and discharge.

Outcome measure, data presentation	Control		Intervention		Change over time: median/mean differences (95% CI of the difference)		Difference within group		Difference between groups	
Group or time	Recruitment	Discharge	Recruitment	Discharge	Control	Intervention	Control	Intervention	Recruitment	Discharge
RR adjusted for age, median (IQR)	1.1 (0.9-1.4) (n= 15)	1.0 (0.9-1.1) (n=15)	1.1 (1.0-1.5) (n= 14)	1.0 (0.9-1.3) (n= 14)	-0.1 (-0.4 – 0.2)	-0.2 (-0.5-0.2)	z= 0.9 p= 0.382	z= 2.3 p= ***0.019***	z= -0.7 p= 0.499	z= 0.6 p= 0.585
SpO_2 (%), median (IQR)	99.5 (96.0-100.0) (n= 14)	97.0 (93.0-100.0) (n= 14)	100.0 (98.0-100.0) (n= 13)	99.0 (97.0-100.0) (n= 10)	-2.5 (-6.7 – 1.7)	-1.0 (- 1.9-3.9)	z= 0.7 p= 0.508	z= 0.9 p= 0.398	z= -1.0 p= 0.308	z= -0.9 p= 0.364
HR adjusted for age, mean (SD)	1.0 (0.1) (n= 13)	1.0 (0.1) (n= 14)	1.0 (0.2) (n= 14)	1.0 (0.1) (n= 14)	0.0 (-0.1-0.1)	0.0 (-0.1-0.1)	t= -0.43 p= 0.675	t= -0.32 p= 0.753	t= -0.21 p= 0.836	t= -0.07 p= 0.941

6.5.3 Within groups comparison

Comparison of the data within intervention and control groups, based on recruitment and discharge data, are presented in Table 6-4.

A significant improvement (decrease) in RR adjusted for age occurred in the intervention group (p= 0.019). No statically significant change was seen within the control group for RR, nor were there any differences within either group for the other outcome measures.

6.5.4 Pre-, post- and one hour post- intervention

When comparing the pre-, post- and one hour post-treatment RR in participants receiving AAD, a significant difference was found between the different measures (Friedman ANOVA X^2= 13.7, p= 0.001) (Table 6-5).

Table 6-5. Comparison within the intervention group between the pre-, post-, and one hour post- AAD intervention

Outcome measure	Pre-treatment	Post-treatment	1h Post-treatment	Friedman X^2	p-value
RR median (IQR)	45.0 (40.0-50.0) (n=62)	46.0 (40.0-52.0) (n=62)	43.0 (36.0-50.0) (n= 57)	13.7	***0.001***
SpO_2, median (IQR)	98.0 (95.0-100.0) (n= 51)	98.0 (97.0-100.0) (n=52)	98.5 (96.0-100.0) (n= 50)	2.7	0.256

Further analysis of the results (Wilcoxon matched pairs test) showed a significant increase in RR immediately after treatment (n= 55, z= 2.2, p= 0.029), however the values significantly decreased one hour post treatment (n= 55, z= 2.9, p= 0.003) and returned to pre-treatment values (n= 49, z= 1.4, p= 0.179) (Figure 6-3).

No significant change was seen in SpO_2 amongst pre-, post- and one hour post- treatment measurements in the intervention group (p= 0.256).

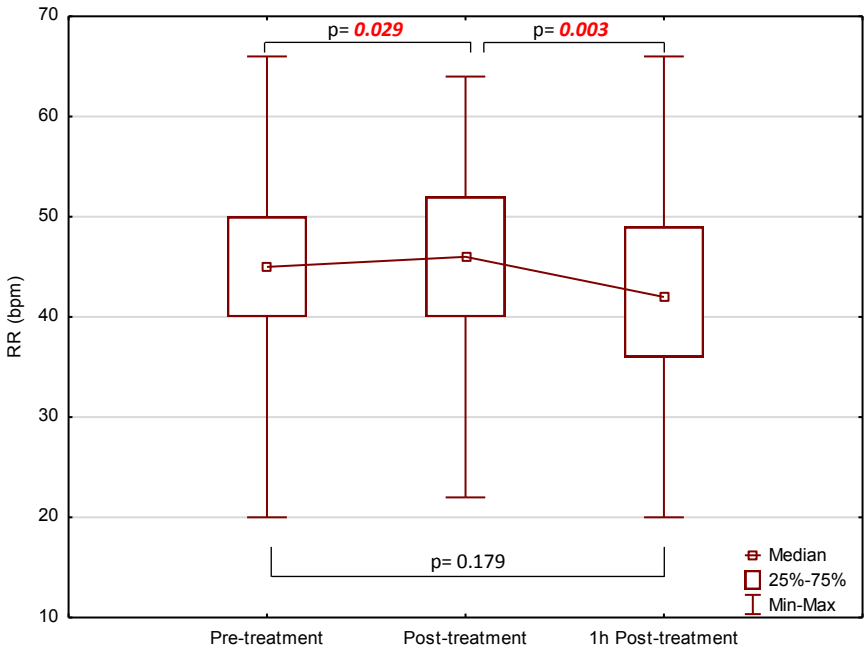


Figure 6-3. Pre-, post- and 1h post-treatment RR for the participants receiving AAD

No significant differences were found for the number of participants presenting with signs of respiratory distress (head nodding, alar flaring and muscle retraction) pre- and post-treatment, in the intervention group (Table 6-6). As none of the participants presented with weak cry, feeding problems or cyanosis; no analyses could be performed for these signs of respiratory distress.

Table 6-6. Analyses of the signs of respiratory distress pre-and post-treatment.

Characteristic Pre-treatment	Post-treatment absent	Post-treatment present	McNemar X^2 for change over time	p-value
Head nodding			1.3	0.248
- Absent	56	0		
- Present	3	3		
Alar flaring			0.0	1.000
- Absent	54	2		
- Present	3	3		
Muscle retraction			0.0	1.000
- Absent	48	4		
- Present	3	7		

6.5.5 Post-hoc analyses

No *post-hoc* analysis for HIV status could be performed due to the limited number of HIV-positive (n=2) and exposed (n= 2) children enrolled in this study.

Post-hoc analyses between the different aetiology groups for the intervention and control group (excluding "mixed" aetiology as only two children, both in the control group, were identified as having both a bacterial and a viral pneumonia) are presented in Table 6-7.

A significant difference was seen between the different aetiology groups in the intervention group for days of hospitalisation (p= 0.008). *Post hoc* analysis showed a significant difference between "unknown" and both "bacterial" and "viral" aetiology (p= 0.031 and p= 0.045 respective), but not between "bacterial" and "viral" aetiology. (Figure 6-4). When groups were combined results were similar (p= 0.004 for "unknown" and "viral" aetiology, p= 0.018 for "unknown" and "bacterial", p= 1.000 for "viral" and "bacterial" aetiology). All other outcome measures did not show a significant difference among different aetiology groups. However in the intervention group, a shorter duration of supplemental oxygen support is seen between the different aetiologies, approaching significance (p=0.055). In the control group, there was a strong tendency to differences between the different aetiology groups for RR adjusted for age (p= 0.050). Except for a trend towards a difference between days on oxygen supplementation between children with "viral" and "bacterial" pneumonia (p= 0.055), *post hoc* analysis did not show any significant differences amongst the different aetiologies for both time on oxygen supplementation in the intervention group and RR adjusted for age in the control group.

Table 6-7. Comparison within groups for the different aetiologies of pneumonia (presented as median and IQR)

Outcome measure	Treatment	Viral N intervention= 5 N control= 4	Bacterial N intervention= 2 N control= 3	Unknown N intervention= 7 N control= 6	Statistical value	P-value
Days of hospitalisation	Intervention	7.8 (7.5-8.5)	9.1 (8.8-10.5)	6.5 (4.5-7.0)	H= 9.7	***0.008***
	Control	10.0 (8.0-12.4)	10.5 (6.3-13.5)	7.0 (6.8-7.0)	H= 5.0	0.083
	Combined	8.5 (7.5-9.5)	9.5 (8.8-10.5)	6.8 (6.0-7.0)	H= 13.6	***0.001***
Days of fever during hospitalisation	Intervention	1.0 (1.0-3.0)	1.0 (1.0-1.0)	2.0 (2.0-2.0)	H= 2.1	0.343
	Control	3.0 (1.0-3.0)	4.0 (0.0-4.0)	1.0 (0.0-1.0)	H= 1.1	0.573
	Combined	1.0 (1.0-3.0)	1.0 (1.0-4.0)	1.5 (1.0-2.0)	H= 0.1	0.955
Days on O_2 supplementation during hospitalisation	Intervention	5.0 (5.0-6.0)	0.0 (0.0-0.0)	4.0 (4.0-6.0)	H= 5.8	0.055
	Control	6.0 (0.0-11.0)	1.0 (0.0-10.0)	2.0 (1.0-4.0)	H= 0.5	0.787
	Combined	5.0 (5.0-7.0)	0.0 (0.0-1.0)	4.0 (2.0-6.0)	H= 4.6	0.099
RR adjusted for age at discharge	Intervention	1.3 (1.1-1.3)	1.0 (0.9-1.0)	0.9 (0.7-1.0)	H= 3.3	0.194
	Control	0.9 (0.9-1.1)	1.0 (0.6-1.0)	1.1 (1.1-1.3)	H= 6.0	0.050
	Combined	1.1 (0.9-1.3)	1.0 (0.9-1.0)	1.0 (0.9-1.1)	H= 1.9	0.387
HR adjusted for age at discharge	Intervention	1.0 (0.9-1.0)	1.0 (0.9-1.1)	1.0 (0.9-1.2)	H= 0.3	0.873
	Control	1.0 (0.9-1.1)	1.0 (0.9-1.2)	1.0 (1.0-1.0)	H= 0.7	0.707
	Combined	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.0)	H= 0.2	0.925
SpO_2 at discharge (%)	Intervention	99.0 (98.0-100.0)	97.0(97.0-97.0)	100.0 (94.0-100.0)	H= 1.1	0.586
	Control	96.0 (95.0-100.0)	98.0 (93.0-100.0)	99.0 (96.0-100.0)	H= 0.5	0.782
	Combined	98.0 (95.5-100.0)	97.5 (95.0-99.0)	99.5 (94.0-100.0)	H= 0.1	0.931

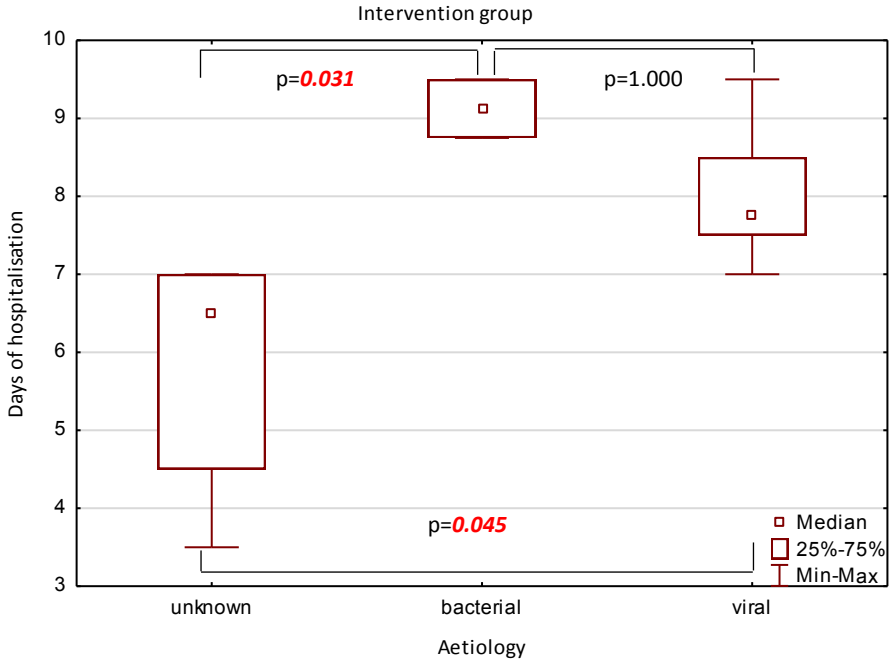


Figure 6-4. Boxplot comparison between the different aetiologies within the intervention group for the outcome measure 'days of hospitalisation'.

Post-hoc power analysis showed a noticeable under powering of the study, with a power of 41%. This analysis used the pre-set mean duration of hospitalisation for the control group and intervention group (8 and 7 days respective), with $\alpha = 0.05$, $\sigma = 1.5$ and the current sample size of 15 and 14 participants in the control and intervention group respectively. As the p-value for the primary outcome measure 'duration of hospitalisation' was still within the pre-set *a priori* boundaries, the study should have continued until the pre-set sample size of 98 participants. However, the study ran from March 2014 until December 2015, during which only 29 eligible participants were identified. Therefore, the researchers deemed it necessary to halt the study for pragmatic reasons.

6.6 Discussion

This study was unable to show significant differences between the intervention group (AAD plus standard nursing care) and control group (standard nursing care), for any of its primary and secondary outcome measures. However, a strong trend towards a faster time to discharge and a significant decrease in RR, adjusted for age, from recruitment to discharge was found within the intervention group. This change in RR adjusted for age was not seen in the control group, and has also not been reported previously. No other within group effects were observed. A statistically significant increase in RR was seen after AAD intervention, however, it is questionable if this increase in RR is clinically relevant, as an increase of only one breath per minute was observed. Further, the RR values returned to

baseline levels one hour post treatment. Finally, a significantly shorter duration of hospitalisation was seen in children hospitalised with pneumonia of "unknown" aetiology compared to "viral" and "bacterial" pneumonia. The shorter duration of hospitalisation might have been the reason for the inability to classify the participants as having either "bacterial" or "viral" aetiology, as no sputum and/blood cultures were conducted or laboratory results were not reported by the time of discharge. A strong trend for a shorter duration of oxygen supplementation in participants with bacterial pneumonia in the intervention group, compared to "viral" and "unknown" aetiology, was seen. Further, in the control group, a strong tendency for a higher RR adjusted for age for participants with "unknown" aetiology was observed. No differences were found for the other outcome measures between pneumonia of "viral", "bacterial" or "unknown" aetiology.

Although admission parameters showed a significant difference between the intervention and control group for RR adjusted for age, this difference was not noticeable by the time of recruitment. To compensate for the time without intervention, the data obtained at recruitment were used for analyses rather than admission data. However, the difference in RR adjusted for age at admission might have influenced the outcome of this study, as the children in the intervention group might have been more severely ill on admission.

Several studies on the use of ACT in children with pneumonia have been published (Table 3-1).[221–223,227,228] However, AAD has never been used in research before, hence no comparison of our results with similar research using the same intervention could be made.

Paludo et al.,[221] Lukrafka et al.,[222] and Stapleton,[227] also reported insignificant differences between the control and intervention groups on the duration of hospitalisation in children. Duration of hospitalisation in the current study (median of 7.5 days and seven days respectively in the control and intervention groups) is in line with the number of hospitalisation days reported in the study by Paludo et al.[221] (median of six days for both groups), who also had a non-intervention control group. However, the study by Lukrafka et al.[222] (median of six days in the control group and eight days in the intervention group) and Stapleton (mean of seven and nine days in control and intervention groups respectively)[227] showed slightly longer duration of stay for the participants receiving physiotherapy intervention than the participants in the control group (see Table 3-1 for an overview of the techniques used in these respective studies). This could be due to the mixed diagnoses included in the study conducted by Stapleton (bronchiolitis, bronchitis and pneumonia)[227]

and the inclusion of participants diagnosed with pleural effusion being enrolled in the intervention group in the study by Lukrafka et al.[222]. This latter study also included a control group who received advice on coughing, diaphragmatic deep breathing and positioning in side lying; which might have influenced the duration of hospitalisation.[222] It is however unclear how the recommendations of coughing and diaphragmatic deep breathing were executed in babies and young children.

No differences in HR and RR adjusted for age between the groups were found in this study. None of the previously conducted studies used HR or RR adjusted for age, and no comparison can therefore be made with this study. However, Lukrafka et al.[222] reported no significant difference between groups at discharge for absolute RR values at the end of the study. This is in contrast with the study by Abdelbasset and Elnegamy, who found a significantly lower RR at discharge in the intervention group compared to the control group.[223]

This current study showed significant improvement in RR adjusted for age within the intervention group, whereas no significant improvement was seen in the control group. On the contrary, in the study by Lukrafka et al.,[222] which reported absolute values for RR, both groups showed a significant improvement in this outcome measure. The improvement of this outcome measure in the control group may be partly explained by the endorsement of deep breathing exercises, positioning and coughing in the control group, for which their outcome measure 'severity score' also significantly improved.[222] By contrast, the current study used a non-treatment control group for which no physiotherapy intervention was given in 14 of the 15 participants. Only one child in the control group received three sessions of emergency physiotherapy intervention, as prescribed by the physician. Similarly, the study by Abdelbasset and Elnegamy, which also compared their intervention with a non-treatment control group, found a greater improvement in absolute RR values in the intervention group, however, this study did not report a statistical value to compare the change over time (mean difference in the intervention and control group was -9.8 and -4.9 respectively).[223] This study also found a significantly quicker resolution of disease; determined by time to normal RR, temperature, SpO_2 and absence of severe signs of respiratory distress; for the intervention group (4 days) compared to the control group (7 days).[223]

No lung function tests were performed in the current study as all included participants were younger than five years of age, which is conventionally used as the cut-off age for reliable lung function results.[137,284] Therefore we were unable to compare our results with the study of Plebani et al.,[226] who enrolled eight HIV-infected participants between the age of 46-94 months and found a significant improvement in lung function results after intervention with a PEP-mask bi-daily for one year. Recent literature does suggest the possibility of conducting spirometry tests in preschool children, after practice and/or under supervision of trained medical staff.[146–148,285] Only one participant in the current study was older than three years, hence, this new cut-off age would not have changed the presentation of our results. However, in future research, the use of spirometric lung function tests could be considered as an outcome measure for children younger than five years of age.

The increase in RR after AAD treatment, which returned to baseline values one hour after treatment, are in line with the results reported by Santos et al.,[228] who also found an increase in RR and HR post-treatment which returned to baseline after rest (see Table 3-1). This phenomenon could possibly be explained by the change in oxygen demand during ACTs, which alters vital signs during treatment.[286] Further, during AAD, airway clearance is performed at three different lung volume stages.[27] Reducing the lung volumes in children might lead to fatigue, which could be the reason for increased RR during and after treatment.[287] However, RR only increased by one breath per minute and the clinical relevance of this small increase is questionable. This current study did not reveal a significant improvement in SpO_2 after treatment, which was reported by Santos et al.[228] We did not record HR before, after and one hour after treatment, as cardiac monitoring is not standard practice in the general medical wards. This is a limitation of this study, and should be included in future trials.

The original protocol of this study focused only on children with bacterial pneumonia. However, due to the numerous unforeseen exclusions of children with “viral” pneumonia, this study’s protocol was amended at the point of interim analysis to include children with all isolates resulting in pneumonia. The initial inclusion criteria might have led to the inability to enrol the pre-set sample size. However, many children hospitalised with viral pneumonia would still have been excluded based on other criteria.

The protocol of this study did not include the identification of presence of pulmonary secretions. This decision was made as determining the presence of pulmonary secretions is largely based on subjective criteria, especially the use of auscultation is unreliable.[142,288,289] Other methods of determining the presence of pulmonary secretions, e.g. chest X-rays, are not part of routine practice at the research site. Furthermore, chest X-rays expose the children to radiation, for which it was deemed necessary to avert unnecessary exposure.[138,141] This is a major limitation of this study as AAD is most effective when pulmonary secretions are present. Other effects of AAD should be considered in future, such as improvement in ventilation, perfusion, and alveolar interdependence.

No subgroup analysis on participants with pneumonia of mixed aetiology (only two children were classified as a combined viral-bacterial pneumonia) could be performed; and participants with different HIV status (only one child in each group was HIV-positive, -exposed and –unknown, majority was HIV-negative) due to the small sample size.

Owing to the many exclusion criteria to warrant safety whilst performing AAD (a novel technique) in this vulnerable participant population, and the limited time for recruitment during the week (on Monday mornings), only 29 participants were included in the study, for which the study power was merely 41%. Ideally, the study should have continued until the pre-specified sample size was reached, as the primary outcome measure 'duration of hospitalisation' was still within the *a priori* boundaries. However, the study was halted after a trial period of one year and nine months due to the slow rate of enrolment, burdening the research personnel. Large amendments would have been necessary, which would have been too time consuming for this thesis. Future research should include larger sample sizes by considering multi-centre (more than two) trials and recruitment on several days during the week. It would be challenging to enrol a larger sample size of children with uncomplicated pneumonia at the research site in a similar time period, owing to the many comorbidities seen in children hospitalised for an extended period with pneumonia at this primary research site (see Chapter 5). Therefore, future research should focus on the use and potential benefits of AAD in children with different comorbid conditions, admitted to hospital with pneumonia. Considering that this is the first research study of AAD in young children, it is recommended that future research be done on the efficacy of this technique amongst different respiratory conditions and different age groups. The results of this current study provide baseline data against which future studies can be compared.

6.7 CONCLUSION

This current study is a stepping stone, aimed at adding to the body of knowledge and addressing the gap in literature on the use of AAD in children with different medical conditions. Although a trend to a faster time to discharge and a significant decrease of RR within the intervention group was observed, this study was unable to prove the clinical usefulness of AAD in children hospitalised with uncomplicated acute pneumonia. No clinically or statistically significant differences were seen between intervention and control groups, therefore AAD cannot currently be recommended as standard practice in children with uncomplicated pneumonia. However, as no adverse events and casualties were reported, the road towards further research on the usefulness of AAD is opened. Future research needs to be conducted using a larger sample size in the same population group, and research investigating the use of AAD in children hospitalised with pneumonia and underlying comorbid conditions is also warranted.

Chapter 7. CYSTIC FIBROSIS – NARRATIVE BACKGROUND LITERATURE REVIEW

7.1 DESCRIPTION OF CF AND IMPACT ON BODILY SYSTEMS

CF is an autosomal recessive hereditary disease (Figure 7-1), affecting the CF transmembrane regulator (CFTR) gene.[290–292] The CFTR gene is located on the long arm of chromosome 7 and contains about 180 000 base pairs of DNA.[15,293] This gene produces the CFTR protein, which is part of the adenosine triphosphate binding cassette transporters.[15] The CFTR protein is responsible for chloride (Cl^-) permeability across the cell wall, by acting as an ion transporter channel for Cl^- and bicarbonate.[15,293] In addition, the protein also assists in the transport of other ions across the cell wall, such as sodium (Na^+).[294] Therefore, when the CFTR protein is defective, both Cl^- and Na^+ conductance will be altered, leading to impaired salt absorption of the cells in secretory organs.[292,294]

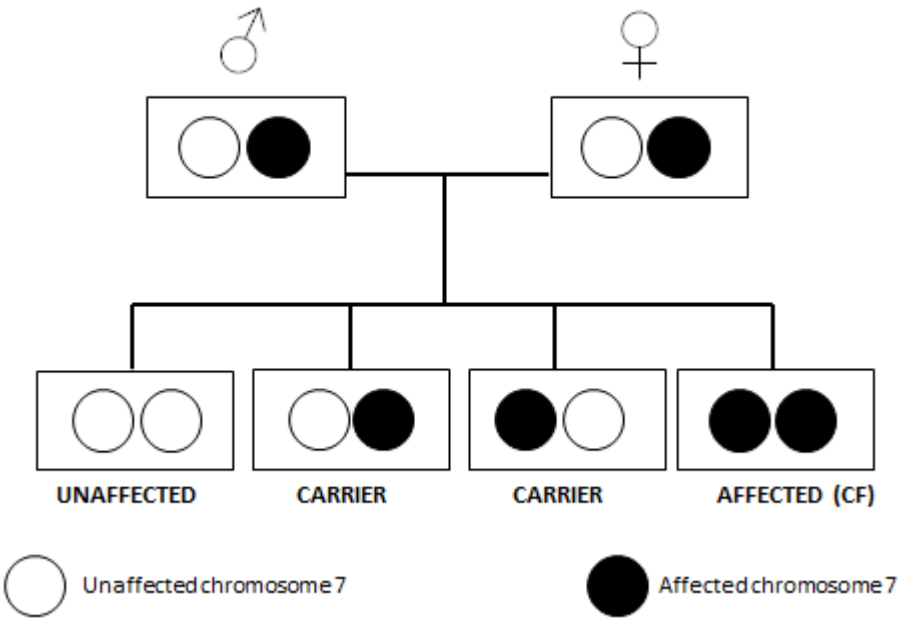
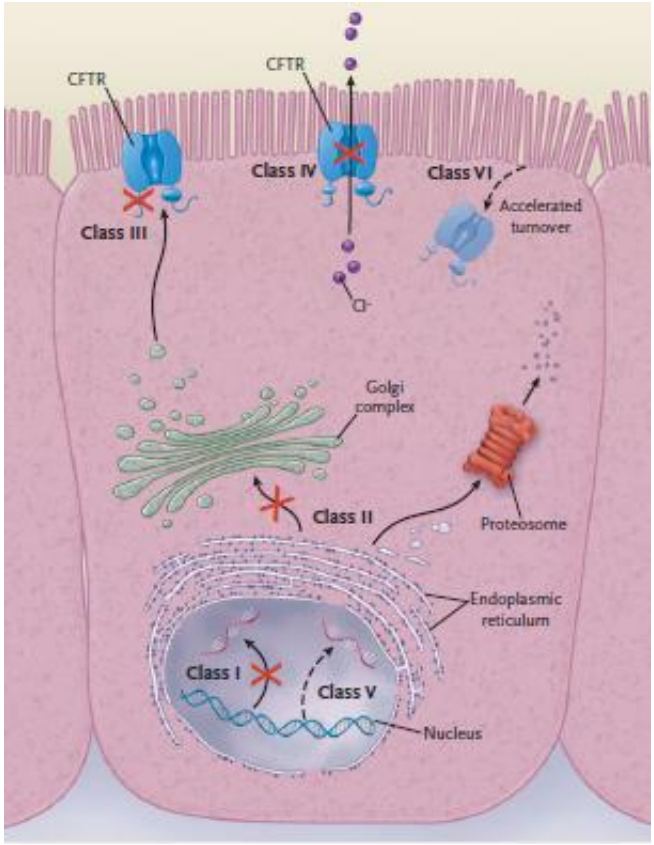


Figure 7-1. Schematic presentation of inheritance CF

Various mutations of the CFTR gene have been linked to CF, with 2009 recorded mutations in 2011.[295] These mutations can be classified in six classes, based on the mechanism of action in the disease process (Figure 7-2).[291,293,296,297] The class I mutations causes an interruption in the production of the CFTR protein due to nonsense alleles in the DNA, leading to incomplete protein production. Class II mutations result in production of the protein, however, due to a default in the protein, it will be destroyed before reaching its end destination in the epithelial cell wall. Class III mutations do produce proteins which reach the epithelial cell wall, however, the protein lacks the Cl^- permeability for which it was designed. Class IV mutations are similar to class III however they are partially functional. Class V mutations causes reduced production of the CFTR protein, whereas class VI mutations result in proper protein production and function; however, proteins are instable and are destroyed faster than normal.[291,293,296,297]



[Reproduced with permission from Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N Engl J Med. 2005;352(19); Copyright Massachusetts Medical Society][293]

Figure 7-2. Schematic representation of the different classes of CFTR dysfunction.

Worldwide, the ΔF508 mutation (class II) is most common, being present in approximately 70% of European Caucasians and 76% of white South Africans with CF.[15,298] It is also found in about 53% of patients from mixed ancestry, but is rare in patients from African and Asian origin.[15,292,299] In native Africans, the 3120 +1G→A mutation has been identified most frequently; and was found to be the second most common mutation in patients from mixed ancestry in South Africa.[15,292]

Because mutation in the CFTR gene may affect all secretory organs throughout the body, CF can be seen as a multi-organ disease.[290,293] Due to the increased Na^+ absorption and defective Cl^- permeability, secretions are dehydrated, becoming thick and sticky.[16,300] Table 7-1 provides an overview of the different affected systems and common presentations of CF disease within these systems.

7.1.1 Gastrointestinal tract

7.1.1.1 Pancreas

Depending on the type of mutation(s), people with CF could be either pancreatic sufficient (mostly with Class IV-V-VI mutations) or insufficient (Class I-II-III mutations).[291] Pancreatic insufficiency is present in approximately 85% of patients with CF and leads to the inability to absorb nutrients, particularly fat (resulting in steatorrhea), fat-soluble vitamins and protein from food; leading to malnutrition.[290,301,302] Further, pancreatic insufficiency could result in CF-related diabetes mellitus due to hyperglycaemia and glucosuria. Therefore, these patients are also at risk for other vascular complications.[301]

7.1.1.2 Intestinal tract

Viscous secretions in the intestinal tract can result in meconium ileus, inability or delayed passing of the first stool, in approximately 10-25% of newborn babies.[16,292,297,301] Furthermore, *distal intestinal obstruction syndrome* can occur in older patients (4-5%), leading to abdominal distention, pain and sometimes vomiting.[16,297,301]

Due to malabsorption of food, patients with CF are at risk of vitamin deficiency, particularly vitamins D, E and K, resulting in associated conditions such as neuropathies, bleeding disorders and osteoporosis.[16]

7.1.1.3 Hepatobiliary tract

Hepatobiliary tract problems in patients with CF can originate from the defective CFTR protein which is involved in the production of ductal bile excretion, but could also be due to other factors such as malabsorption of nutrients and/or adverse effects of medication.[297,303] Most patients with CF have some form of asymptomatic liver dysfunction (e.g. liver enzyme dysfunction).[297,301,303] However, only 5-7% present with symptoms of biliary cirrhosis and portal hypertension.[16,297,301] Common extra-hepatic complications are gallbladder problems such as microgallbladder, present in up to 33% of patients, and distended gallbladder.[297,303]

7.1.2 Reproductive system

In adolescents with CF, puberty is often delayed, mainly due to poor nutritional status. Although adult height has normalised in recent years as a result of improved nutritional management; peak height velocity remains delayed and decreased in patients with CF.[304–306] Delayed onset of puberty influences the onset of sex hormone production, however, in adulthood, normal hormone levels are observed in this population.[307]

Due to the increased longevity of patients with CF, questions related to fertility and reproductive health have become of greater importance in the past decades. Infertility in male patients with CF has been reported in up to 98% of patients, originating prenatally due to *congenital bilateral absence of the vas deferens* or atresia of the ductus leading to azoospermia; or due to poor quality of sperm because of dysfunction of the seminal vesicles resulting in aqueous ejaculates with high acidity levels.[16,308,309]

In women, fertility is less affected; however, increased mucus viscosity of the cervix during ovulation, alterations in uterine fluid control and disease progression of other bodily systems could prevent women from becoming pregnant.[310] For example, deterioration of the respiratory system influences the woman's fertility; female patients with an FEV_1 of less than 50% predicted struggle to fall pregnant.[16,309] Malnutrition can lead to irregular menstrual cycles or amenorrhea.[310,311] Furthermore, structural changes to the reproductive system in women with CF have also been reported.

7.1.3 Sweat glands

Due to the altered Na^+ and Cl^- conductance in the body, patients with CF tend to have elevated Cl^- levels in their sweat.[294,300] This leads to salty tasting sweat, and increased risk of dehydration especially during warm weather and gastroenteritis.[16,293] This distinct

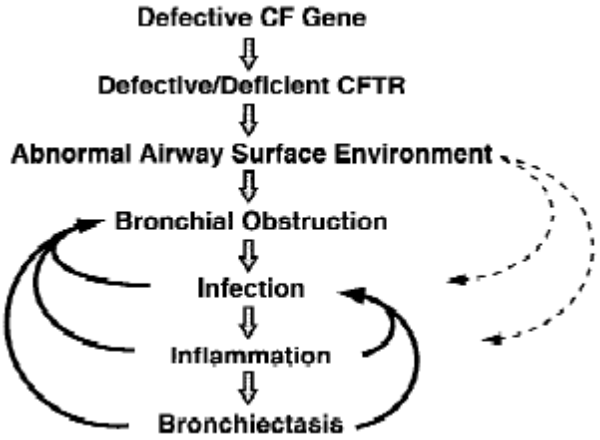
characteristic of CF is used as one of the diagnostic tools for the disease (see section 7.2).[300,312]

7.1.4 Respiratory tract

In healthy people, the MCC mechanism protects the lungs from infections by trapping particles, including potential pathogens, in the mucus layer and evacuating them towards the central airways. Optimal functioning of MCC is dependent on the airway surface liquid (ASL), consisting of the periciliary layer and mucus layer (see 2.3.1.1).[13,63] The thickness of the ASL can be influenced by Na^+ and Cl^- ion transport across the epithelial cell wall.[78] In patients with CF, the impaired Cl^- permeability and Na^+ conductance results in increased absorption of fluids, dehydrating the ASL and increasing the viscoelasticity of the mucus layer.[13,78] Another mechanism that might influence the respiratory defence system is the inhibition of the bactericidal function of the ASL as a result of increased sodium levels in the ASL.[313] This altered airway environment in people with CF leads to a vicious cycle of reduced MCC, leading to secretion retention, airway obstruction, secondary chest infections and inflammation; and can result in irreversible lung damage (bronchiectasis) and respiratory failure (Figure 7-3).[14,291]

Not only the lower respiratory tract is affected in children with CF. Upper respiratory tract manifestations, particularly rhinosinusitis (both chronic and acute) and nasal polyps can occur in these patients.[292,314,315] URTIs can result in LRTIs, inducing the above mentioned vicious cycle.[315,316] Furthermore, upper respiratory tract manifestations in children with CF can lead to sleep apnoea, disturbing the child's sleeping pattern.[317,318]

Lung function testing is part of routine assessment in children with CF.[149] This outcome measure is not merely influenced by severity of lung disease, but also by nutritional status. Children who are underweight for age present with poorer lung function results than their normal weight CF peers,[19,319] highlighting the need for multi-disciplinary management of patients with CF.



[Reprinted with permission from Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. Pediatr Pulmonol. 1997;24(2)][14]

Figure 7-3. Pathogenic scheme for the respiratory system in CF.

Table 7-1. Overview of affected bodily systems and disease presentation in CF

Affected bodily system	Disease presentation	Intervention
Respiratory tract	- Vicious cycle of mucus retention, bronchial obstruction, infection, inflammation and destruction - Upper respiratory tract manifestations, particularly nasal polyps and rhinosinusitis which can lead to sleep apnoea	- Ivacaftor/Lumacaftor when available - Prevention (including vaccination) - Mucolytics - ACTs - Antibiotics - Anti-inflammatories - Bronchodilators - Frequent sputum cultures - Counselling - Nasal irrigation - Endoscopic surgery
Gastrointestinal tract: **1) Pancreas** **2) Intestinal tract** **3) Hepatobiliary tract**	- Malabsorption of nutrients - Steatorrhea - CF-related diabetes mellitus - Meconium ileus - Distal intestinal obstruction syndrome - Fat-soluble vitamin deficiency (D,E,K) - Liver enzyme dysfunction - Biliary cirrhosis - Microgallbladder	- Pancreatic enzyme supplements (e.g. Creon®) - High energy/fat rich diet - Laxatives/bowel washout (e.g. Golytely) - Hypertonic/ hyperosmoloar medium e.g. Gastrografin - Mucolytics - Gastrostomy for supplemental feeding - Vitamin supplements - Ursodeoxycholic acid - Liver transplant
Sweat glands	- Risk of hyponatremia - Hypochloremic alkalosis	- Oral hydration - IV hydration - Salt supplements
Reproductive system	- Decreased fertility in women - Infertility in most males (azoospermia)	- Counselling - Advice on assisted reproductive techniques

7.2 SCREENING AND DIAGNOSTIC TESTING

As CF is a genetic disorder, cascade screening for the carrier gene is recommended in prospective parents, especially when a family history of CF is present.[292,320] Furthermore, blood tests to determine the type of mutation present in the parents is useful to facilitate prenatal screening. [292,320]

At specialist centres, pre-implementation diagnosis can be made.[292,320] By using in vitro fertilisation, embryos can be screened for CF mutations and embryos free of CF can be selected and implanted.[321]

Prenatal screening for CF in couples with increased risk can be done by using amniocentesis or chorionic villus sampling, providing the option to terminate pregnancy when CF is diagnosed.[292,322] Although the safety of these techniques has improved over the years, there is still an increased risk of miscarriage when these invasive techniques are performed (0.1-1%).[322–324] Chorionic villus sampling, removal of a small part of the placenta for testing, is performed early in pregnancy; which may make termination of pregnancy (if that option is chosen) easier to perform than following amniocentesis performed later on in the pregnancy.[292]

Post-natal blood tests for screening of immunoreactive trypsinogen is done in patients with a possible diagnosis of CF.[292,325,326] Diagnosis of CF needs to be confirmed by further diagnostic testing, most commonly done by a sweat test.[149,292,325] As mentioned in the previous section, sweat glands are often affected in patients with CF, due to the altered Cl^- and Na^+ permeability of the secretory glands. Either a sweat conductivity test or electrolyte testing can be performed. The conductivity test is more accessible in South Africa,[292] however, the reliability of this test is lower than the electrolyte test, which analyses the Cl^- levels in the excreted sweat.[292,325] Genetic testing, to identify CFTR mutations, can also be used to confirm the diagnosis of CF, particularly in patients with atypical CF presentation.[320]

When sweat testing is unavailable, faecal pancreatic elastase testing is a reliable test to detect pancreatic insufficiency, in children with positive blood tests.[292,327]

7.3 INCIDENCE AND IMPACT ON HRQOL

CF is most common in the Caucasian population in South Africa, with an incidence of approximately one in every 2000 white children born in South Africa.[292] For the Western

Cape (South Africa), incidence rates up to date until 1996 vary in rural and urban areas. In the Cape Metropole area (urban), an incidence of one in every 2843 live births has been found for the white population, whereas one in every 9778 live births has been reported for non-Cape Metropole areas (rural), resulting in a total incidence of one in every 4007 live births in the white Western Cape population.[328] The rate of the urban Cape Metropole area is in line with an incidence rate of one in 2381 live births in the UK (1947-2003).[12] Incidence rates for CF in the Black African and mixed ancestry population is lower, with one in every 32 000 black babies and one in 14 511 babies of mixed ancestry affected.[292,328] In one study in a Latin-American population, an incidence of one in 11 252 live births was reported.[329]

In South Africa, approximately 1 in 20-32 individuals in the white population, 1 in 55-60 in the population of mixed ancestry and up to 1 in 90 black Africans carry a known CFTR mutation.[292,328]

Life-expectancy in people affected by CF is decreased, but the number of adults with the disease is increasing due to improvements in management e.g. frequent use of antibiotics and more frequent review at multidisciplinary CF clinics.[12,292]

In patients with CF, HRQOL is mostly determined by the patients' personal views on their health status, coping strategies and time consumption of therapy; and less influenced by disease severity.[330,331] However, pulmonary exacerbations do have a clear negative impact on physical and psychosocial HRQOL due to the 'disruptive' effect of exacerbations on the patient's life.[330] Nutritional status has also been found to be associated with HRQOL, as children and adolescents with poor nutritional status, based on BMI-for-age z-scores and percentiles, scored lower on the CF questionnaire.[332] Social stigmatisation can also influence the patient's HRQOL by reducing their positive view on life, therefore leading to increased levels of depression and anxiety.[333] Increased rates of depression and anxiety are reported in patients with CF compared to their healthy peers, with rates of up to 29% for depression in children and 33% for both depression and anxiety in adults.[334,335] Management of depression is becoming of greater importance as part of the management of CF, as depression has proven to negatively influence patient's adherence to therapy.[336,337] The influence of CF on the HRQOL in children living in South-Africa has not yet been studied.

7.4 TREATMENT

7.4.1 General management

As CF is a multi-system disease, a multidisciplinary approach is necessary to tackle all aspects of the disease. Many of the clinical features previously thought to be inevitable can be prevented, delayed or improved by intensive treatment.[292] In this section, a brief overview of the management of common disease presentations are presented. Explanation of different ACTs used in the management of CF can be found in section 7.4.6.

7.4.2 Gastrointestinal tract

7.4.2.1 Pancreas

When patients present with pancreatic insufficiency, pancreatic enzyme supplements (e.g. Creon®, Zenpep) are indicated to facilitate protein and fat absorption.[16,338] The dosage depends on nutritional intake and weight.[339] Normally, this results in an intake with three main meals and two to three snacks per day.[301] Recent studies have found that the previously set limit of 10 000 lipase units/kg/day (to prevent fibrosing colonopathy)[301,340] can be crossed without adverse effect, especially in infants receiving more frequent feeds per day.[341,342] These patients will also have to consume a high energy, fat rich diet to prevent malnutrition.[16,343] In South Africa, Creon® is the sole pancreatic enzyme supplement available, which is expensive and cannot always withstand the warm climate of some parts of the country.[292,344]

Patients with CF related diabetes mellitus need an individually adapted insulin therapy, especially patients suffering from fasting hyperglycemia.[301,345] Insulin injections are given around meals rather than basal insulin injections in patients with CF.[346] Because patients with pancreatic insufficient CF are recommended to increase their energy intake, dietary changes for diabetes are contraindicated.[149,345,347] Therefore, insulin is adapted to the patient's diet rather than changing the nutrition.[345,346]

7.4.2.2 Intestinal tract

Babies suffering from simple meconium ileus are treated with an hyperosmolar solution e.g. Gastrografin®, to extract fluids from the cells and loosen the stool.[16,348–350] However, caution needs to be taken as these solutions might lead to perforation, dehydration/hypovolemia and/or imbalance in electrolytes and fluid.[350–352] Therefore, Gastrografin should be diluted with water to prevent dehydration and electrolyte

imbalance.[351,353] Intravenous fluids might need to be administered during the treatment and additional electrolyte therapy could be needed.[301] When meconium ileus does not respond to these interventions, or the problem is complex, surgery (e.g. enterostomy) might be indicated.[16,348,351]

The management of *distal intestinal obstruction syndrome* usually commences with a trial of laxatives or bowel washouts.[16,301,354,355] In South Africa, Golytely is often prescribed as a laxative.[292,356] Other options are Gastrografin and/or mucolytics when laxatives are insufficient.[301,354,357] When these solutions are not sufficient, surgical interventions (e.g. gastrostomy or laparotomy) might be indicated.[16,301,358]

7.4.2.3 Hepatobiliary tract

First line treatment of hepatobiliary problems are pharmacological agents, especially Ursodeoxycholic acid (UDCA), which impede bile acid, improves bicarbonate excretion, and increases bile flow.[301,359–361] A recent long term study (at least two years of exposure) found UDCA to be safe for administration for a prolonged period of time.[362] Another pharmacological option is Taurine therapy,[363,364] which is often administered in addition to UDCA to stabilize the taurine levels in the liver.[339,360] However, in South Africa, only UDCA is available,[292] but is not accessible in all geographic areas of the country.

Although the administering of fat-soluble vitamins (vitamin A-D-E-K) is recommended by most guidelines,[149,292,365] limited supportive evidence is available to date.[109,366,367] Further, the toxic effect of an overdose of vitamins needs to be taken into account when prescribing vitamin supplements.[302,368]

Finally, when liver failure is present, a liver transplant may be indicated.[16,149] In South Africa, liver transplant is rarely performed due to the limited access to adequate health care, poor socio-economic circumstances, high cost of surgery, and poor outcome as a result of poor follow up treatment.[369] Both internationally and in South Africa, long waiting list for transplants result in a more symptomatic treatment for most patients.[149,370] Eligibility criteria for liver transplant surgery in patients with CF has not been established. Early liver transplant, prior to severe deterioration of nutritional status and lung function, could be beneficial.[371,372] However, recommendations for liver transplant have prioritised patients with severe liver complications, and poor nutritional status and pulmonary function.[373,374]

7.4.3 Reproductive system

Females with mild to moderate CF severity can fall pregnant and carry the foetus full term, despite potentially decreased fertility. Females with severe disease severity could be infertile and/or are at increased risk of pregnancy and childbirth complications.[149,375] Female patients should be referred to appropriate health care professionals to evaluate their fertility and to guide pregnancies, which are considered high-risk.[149,309]

The majority of males are infertile and should be counselled appropriately and referred for alternative reproductive options.[149,309,376]

7.4.4 Sweat glands

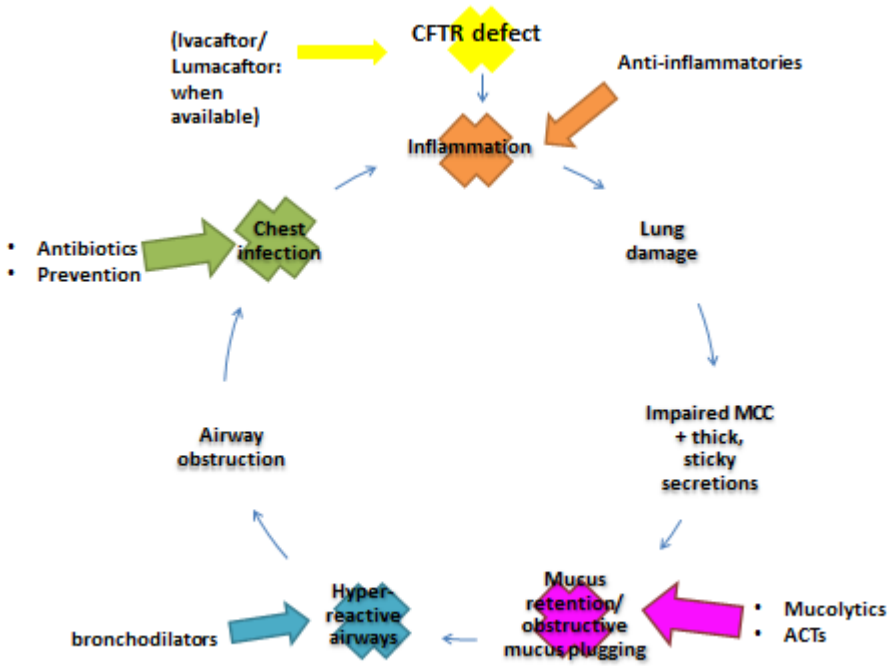
As patients with CF are at increased risk of dehydration, particularly during warm weather and/or episodes of gastroenteritis, it is of great importance to prevent dehydration by increasing oral intake of fluids.[377,378] Patients could also take salt supplements, especially during warm periods and/or periods of illness.[16,378]

7.4.5 Respiratory tract

Decreased longevity in patients with CF is most often due to respiratory complications. Therefore, treatments focused on maintaining or improving respiratory function are of great importance.

To prevent URTIs progressing to LRTIs; nasal irrigation, topical steroids and antibiotic therapy is recommended.[292,316] Patients with chronic sinusitis might benefit from endoscopic surgery.[292] Symptomatic nasal polyps can be treated with steroids and/or endoscopic surgery.[292,309]

An overview of the interventions and where they intervene in the vicious cycle of lung pathology is presented in Figure 7-4.



[Self-designed by L. Corten]

Figure 7-4. Interventions respiratory tract in CF

Newer gene therapies, Ivacaftor and Lumacaftor, are valuable as they target the CFTR protein defect itself. Ivacaftor is beneficial for patients with the G551D mutation whereas a combination of Lumacaftor/Ivacaftor had been found beneficial for patients with class II Δ508del homozygous mutations.[379–384] Other mutations have not been proven to be responsive to these treatments. Unfortunately, these gene therapies are extremely expensive and not available in South Africa.[385] Therefore, interventions focus on symptomatic treatment of the disease:

1) Prevention of infection

Prevention of infections is important. This can be done by immunisations for vaccine-preventable agents, especially for measles and influenza.[386,387] Further, decreasing exposure to infections is necessary, by e.g. sterilising equipment used at clinics, hand hygiene, and maintaining a two meter distance between patients with CF to prevent patient to patient transmission.[387,388]

2) Inflammation and infection of the respiratory tract

When the patient presents with an acute exacerbation of infection, the use of antibiotics is indicated.[389] When the patient is first infected with CF-related bacteria, particularly *Pseudomonas aeruginosa,* an aggressive eradication regime is required.[292,388,389] At the outpatient CF clinic of a specialised tertiary paediatric hospital in Cape Town, South Africa, the eradication protocol for *Pseudomonas aeruginosa* usually consists of three months of oral antibiotic (usually Cipro), three months of inhaled antibitoic (gentamycin/tobramycin), and azithromycin (Prof. B. Morrow. Personal communication, 2017). Standard management of acute infections (other than *Pseudomonas aeruginosa*) in South Africa, is two weeks antibiotic treatment, either oral (in mild disease) or intravenous (in more severe disease).[292] Antibiotics should not be used long term for prophylactic purposes,[17] however, once a patient is colonised, particularly with *Pseudomonas aeruginosa*, long-term inhaled antibiotics are indicated.[292] Caution is needed to prevent emergence of antibiotic resistant bacteria.[17,390]Azithromycin is often prescribed as it has an anti-inflammatory function in addition to its antibacterial and antiviral effect.[391] Other non-steroidal anti-inflammatory drugs such as Ibuprofen, and corticosteroids, have been shown to slow down the disease progress.[17,292,392] However, gastrointestinal adverse events of Ibuprofen have also been reported.[292] Thus gastrointestinal protective medication will need to be administered in adjunction to non-steroidal anti-inflammatory drugs and regular monitoring of the patient's condition is required.[392] Inhaled and oral corticosteroids, although effective in children with CF accompanied by asthma-induced bronchospasm or allergic bronchopulmonary aspergillosis, might not reach the inflammation in the airways due to thick secretions, reducing the efficacy.[17,292]

3) Inhaled/aerosolised therapy

Ideally, patients should use daily inhaled mucolytics such as hypertonic saline or DNAse, to decrease the viscosity of mucus.[17,83] Inhaled hypertonic saline increases the airway surface liquid by extracting water from the body to loosen the secretions and improve MCC. [393] It is inexpensive and freely available for use in South Africa. DNAse has the added benefit of reducing inflammation in the lungs.[394] However, DNAse is expensive and only available for South African patients on medical aid, unless deemed highly necessary for which motivation for reimbursement can be obtained.[292] Bronchodilators are also often prescribed, to help with mucus clearance by opening the obstructed airways, caused by

hyper-reactive airway bronchoconstriction, resulting in improved penetration of mucolitics, MCC and response to ACTs.[17,395]

4) Airway clearance therapy

Regular ACTs are of great importance in patients with CF to facilitate MCC, to clear secretions from the lungs and therefore prevent mucus plugging, airway obstruction, infection and inflammation, hence slowing the progression to chronic lung disease.[18] See section 7.4.6 for an overview of ACTs in children with CF.

Respiratory treatment for patients with CF commences with a bronchodilator, followed by hypertonic saline or DNAse. Hypertonic saline is preferably administered prior to or during ACT,[396] whereas DNAse can either be admistered 30 minutes before ACT or afterwards, depending on the patient's lung function, preference or timing of ACT during the day.[397] Treatment should end with inhaled antibiotics, long acting bronchodilators and corticosteroids when indicated.[17]

7.4.6 Airway clearance therapy

An overview of available ACTs is presented in Chapter 2. The majority of paediatric studies investigating ACTs in children with CF included children older than six years of age. Very few studies included infants and young children.

7.4.6.1 Postural drainage and modified PD

PD and MPD are useful in infants and young children with CF as no active participation is required.[25]

Although one study found no influence of PD combined with or without percussions compared to cough alone on clearance of a radiolabelled aerosol tracer in adolescents and adults with CF,[398] a significant improvement in sputum expectoration and respiratory function was found when PD was compared to no ACT in this population.[399–402]

A systematic review comparing conventional ACTs (including PD) with other ACTs, did not find any superiority of conventional ACTs over other ACTs; however, evidence is limited and of poor quality, preventing definite conclusions regarding this technique.[134]

Because PD with head-down position induces more gastroesophageal reflux and results in reduced FVC and FEV_1 in children with CF, a modified version of PD has been developed, which does not include inverted positions.[86,91,403,404] Button et al. reported significantly fewer days of upper respiratory tract symptoms and lower antibiotic usage in children with CF using MPD compared to PD during the first year of study.[91] At five years of age, the children in the MPD group had better respiratory function and fewer radiological changes.[91] An increase in the number of GORD episodes compared to baseline data was seen during either PD and MPD treatment, but the increase was significantly lower in children treated with MPD than PD.[91]

PD has been the gold standard treatment for children with CF in the past decades and, along with MPD, has been compared to other ACTs (FET, PEP, oscillating PEP or AD) in children with CF. Results of these studies have been reported below under the respective headings.

7.4.6.2 Forced expiration technique (FET)

FET is often used as an adjunct to other ACTs. The addition of FET to PD results in better clearance of secretions than PD alone;[113] and the same amount of secretion clearance as FET combined with PEP 30 minutes after treatment.[405] In a study by Lannefors and Wollmer, in patients age 12 to 36 years, FET was combined with either PD, PEP or physical activity and no significant differences between the groups were found.[406] Steen et al. compared FET alone to combined therapy with FET and PEP, PD and percussion, and PEP and PD, in patients between the ages of eight to 21 years. No significant differences were seen between the different groups for Chrispin-Norman or Shwachman scores; growth; and pulmonary function tests (FEV_1, FVC, FEF_{25-75}) after one month of intervention.[407] Although FET needs active participation of the patient, it could be implemented in the treatment regime at a younger age by using blowing games.[25]

7.4.6.3 Active cycle of breathing technique (ACBT)

To correctly perform ACBT, the patient has to be cooperative and able to follow commands, therefore it is not recommended in children younger than the age of two years.[24] However, parts of the technique can be taught in children from 18 months through blowing games.[114] A recently published systematic review found ACBT to be as effective as other ACTs in the treatment of paediatric and adult patients with CF (age six to 63 years).[408] In adults (patients older than 16 years), mucus clearance was as effective in patients using ACBT

compared to PD or Flutter.[113,409] Lung function outcome measures were also similar for ACBT and Flutter.[409] In children with an acute exacerbation, ACBT was shown to be superior to high-frequency chest wall oscillation ("Vest" therapy), as it resulted in improved secretion clearance and increased lung function outcome measures.[410] Miller et al. compared ACBT combined with PD with AD in patients between the age of 11 and 32 years; and found no significant difference for sputum weight, ventilation distribution, HR and patient preference. However, ACBT with PD resulted in a better FVC improvement, whereas AD resulted in a greater improvement in FEV_1.[270]

7.4.6.4 Positive expiratory pressure (PEP)

Two reviews on the use of PEP, one in a paediatric (from the age of six years) and one in a mixed paediatric and adult population, indicate that, overall, PEP is not superior to other ACTs in patients with CF.[133,411] However, van der Schans et al. reported an increase in thoracic gas volume after PEP compared to baseline coughing in supine in adolescent and adult patients with CF.[412] In another study, children, aged seven to 17 years, using PEP had fewer hospital admissions, maintained or improved spirometry outcome measures (significant for FVC and trending for FEV_1 ($p=0.08$)) and had a smaller decline in Huang score during a one year trial, compared to patients using Flutter.[413] Further, children and adults on PEP had fewer exacerbations than patients on high frequency chest wall oscillation ("Vest" therapy).[414] PEP was found to be superior to PD in a study by McIlwaine et al. who found a significant improvement in FEV_1 and FVC when using PEP compared to PD in children with CF.[415] Furthermore, a study by Oberwaldner et al. on the use of high pressure PEP compared to PD with percussion found that hyperinflation of the thorax decreased and lung functions improved when PEP was used for ten months and a deterioration of function was seen when returning to PD with percussion.[416] PEP combined with FET was preferred over PEP alone or PD combined with FET in one study.[407]

In infants and young children PEP could be performed by using a facemask.[25] However, accessibility to facemasks in South Africa is poor (Chapter 2).

7.4.6.5 Oscillating PEP (e.g. Flutter, Acapella, Quake, Cornet)

Again, a systematic review on oscillating PEP, in a mixed paediatric and adult population, reports equipoise amongst different ACTs.[135] Mixed results on the use of oscillating PEP in patients with CF are found in the literature. Gondor et al. found a significant improvement in FVC and FEV_1 after the use of the Flutter device compared to PD in children age five to 21

years with CF.[417] Konstan et al. reported greater sputum production with Flutter than with PD.[418] On the other hand, greater sputum production was seen when ACBT was used alone instead of combining Flutter and ACBT,[419] and no difference in sputum production was seen when Flutter was compared to PD or intrapulmonary percussive ventilator therapy in adolescents and adults with CF.[420] McIlwaine et al. found PEP to be more effective than Flutter in maintaining pulmonary function in children with CF in the long term, with a greater decline in FVC and FEV_1 for patients receiving Flutter.[413] One study compared the use of Acapella to PEP mask in children with CF, but found no differences between the two techniques.[421]

Oscillating PEP devices can be used independently in older children, however, as active participation is required to apply the device, these techniques cannot be performed in infants and young children.

7.4.6.6 Assisted and unassisted autogenic drainage((A)AD)

See Chapter 8 for a systematic review on AD and AAD in children with CF.

AD may improve pulmonary function,[121,422] generate greater mucus clearance,[270,271,422] and is preferred over PD.[272] AD also improves SpO_2 and is overall better tolerated by participants.[84] No literature is available on AAD.

As mentioned in Chapter 2, AD is a technique that can be independently performed by patients older than eight years of age, however, due to the complexity of the technique, application in children younger than eight years of age is difficult.[24]

7.4.6.7 Adherence and compliance to airway clearance therapy

In chronic respiratory disease, poor compliance and adherence to ACT is a common problem. About 50% of patients with CF are not compliant with their airway clearance regimen.[423–425] The majority of patients complain about the amount of time that goes into these treatments.[426] The complexity of the interventions is also an important factor for non-compliance,[426] along with patients' socioeconomic status.[427]

It has been reported that self-reported or proxy-reported adherence rates are higher than objectively measured adherence; and adherence to medical interventions is higher than non-pharmacological interventions, including ACTs.[423,428]

7.4.6.8 Equipoise in ACTs

The above described ACTs all have advantages and disadvantages, but none of them have been found to be superior or markedly inferior within the CF population.[18,133–136] Whilst newer, independent ACTs are not better in terms of outcome measures, they may be more preferred than conventional ACTs, which could equate to improved compliance with ACT regimens.[134]

It is recommended, for the standard ACT management of people with CF, that individualised airway clearance programs adapted to, for example patient preference and age, need to be made.[18] This may improve therapy compliance and adherence.[25]

7.4.7 Conclusion

CF is a complex multi-system recessive hereditary disease, requiring a multidisciplinary treatment approach. ACTs are recognised as being beneficial in improving outcome in people with CF, hence they form an essential part of standard management for this population. Comparatively little research has been conducted in the airway clearance management of infants and young children with CF and they have been included only in research on conventional ACTs, as modern ACTs require active cooperation and the ability to follow instructions. AAD is a newer ACT clinically used in infants and young children, although no evidence is yet available. There is little data available on the relative safety and effectiveness of AD, although small studies have suggested AD is well tolerated and effective. As indicated above, no ACT has been found to be superior to others,[133–135] therefore it is plausible that AAD would also be as effective as other treatment options. But if preferred by patients it may be beneficial as compliance to treatment could be improved. Owing to several disadvantages of PEP and PD (see Chapter 2), AAD may be a useful tool for airway clearance in infants and young children.

Chapter 8. ARE AUTOGENIC DRAINAGE AND ASSISTED AUTOGENIC DRAINAGE AS BENEFICIAL AS OTHER AIRWAY CLEARANCE TECHNIQUES IN CHILDREN WITH CYSTIC FIBROSIS? A SYSTEMATIC REVIEW.

8.1 INTRODUCTION

As discussed in Chapter 7, CF is a life-threatening genetic disease for which no definitive cure is yet available. Therefore a symptomatic approach to management is needed. ACT is one component of the multidisciplinary approach in the management of people with CF. Many articles and reviews have been published on the use of different types of ACTs in this population.[24,125,133–136,408,429–431] One recently published review which systematically evaluated the effect of AD in patients with CF did not focus on the paediatric population; only reported on pulmonary function and sputum recovery; and excluded a simplified/modified AD technique.[422] No published articles, to the best of my knowledge, have systematically evaluated the effects of AAD in the management of children with CF.

8.2 AIM AND OBJECTIVES

This systematic review aimed to determine the effect of AD and/or AAD compared to no physiotherapy, other types of ACTs or sham physiotherapy in children with CF, based on the following outcome measures: number of hospitalisations and exacerbations, HRQOL, patient or caregiver preference, adverse effects and mortality.

The following hypotheses were tested:

- AD and/or AAD are more effective than other ACTs in children with CF, for number of hospitalisations and exacerbations during one year.

- AD and/or AAD are preferred to other ACTs by children with CF and/or their caregivers.

8.3 METHODOLOGY

This systematic review used the Cochrane methodology for systematic reviews and conforms to the PRISMA (Appendix 12).[233,234] This review's unpublished pre-set protocol described the methodology and inclusion criteria prior to the database searches.

8.3.1 Criteria for considering studies for this review

Types of studies

RCTs, quasi-RCTs and randomised cross-over trials were included.

Types of participants

Children, under the age of 18 years, diagnosed with CF by positive sweat test and/or genotype analysis.

Types of interventions

AD and/or AAD compared to no physiotherapy, sham physiotherapy or other ACTs. Other ACTs included, but were not limited to:

Conventional ACTs:

- PD and MPD;
- percussions/clapping;
- shaking and vibrations;
- cough;
- rib cage compression, thoracic squeezing or manual assisted coughing;
- a combination of the above techniques.[134]

Modern ACTs:

- ACBT;
- PEP;
- High pressure PEP;
- Oscillating PEP (Flutter, Acapella, Cornet, Quake, Intrapulmonary Percussion Ventilation).

Description of these interventions can be found in section 2.3.1.4 of this thesis.

Types of outcome measures

Primary outcome measures:

- Number of hospitalisations measured at 12 months

- Number of exacerbations measured at 12 months (determined by number of antibiotic treatments per year or diagnosis made by a physician)

Secondary outcome measures:

- HRQOL measured at six and 12 months
- Preference measured at six and 12 months
- Adverse effects measured at three, six and 12 months
- Mortality measured at three, six and 12 months

8.3.2 Search methods for identification of studies

Electronic search

Online databases PubMed, Medline, the Cochrane library, Pedro, CINAHL and Africa wide information were searched with predefined search terms (see Appendix 13 for overview of the search terms). These search terms were translated in the different languages included in this review.

Further, clinicaltrials.gov was searched for ongoing research studies.

Articles were included if they were written in English, Dutch, French, German or Afrikaans. Other languages were excluded. No date limitation was set. Non-randomised cross-over trials and pre-experimental trials were excluded.

Other resources

Reference lists of identified articles were manually checked for relevant studies. No grey literature was searched owing to poor reproducibility of this type of literature.[235]

8.3.3 Data collection and management

Selection of studies

The databases were searched (by LC) and relevant articles, based on title and abstract, were collected. These were reviewed independently by a second reviewer (BM) and articles requiring full text review were selected. These two reviewers independently determined whether the articles were eligible for inclusion in the review. Any disagreement was resolved by discussion and consensus.

Data extraction and management

Data were extracted by two independent reviewers using a pre-structured form including information on participants (age, gender, condition, severity of symptoms, inclusion/exclusion criteria, comorbid conditions, setting, number randomised, number lost to follow-up); interventions (type of interventions, duration, frequency, intensity, compliance); outcome measurements and results (point estimates, precision, measures of variability, frequency counts for dichotomous variables, number of participants in each group); and study design (randomization, allocation concealment, blinding) (Appendix 4).

Assessing risk of bias in included studies

The Cochrane Collaboration's tool for assessing risk of bias was used,[432] to assess the following methodological characteristics:

1) Generation of sequence: Studies were considered to have low risk of bias if a random number table, computer generated list of random numbers or any other valid method of randomisation was used. Studies were considered as having high risk of bias if invalid methods of randomisation were used, such as date of birth or allocation by the physiotherapist or physician. When the allocation sequence was not identified, the bias was judged as unclear.

2) Allocation concealment: Studies were considered low risk of bias if investigators did not know which group allocation was planned. This by the use of coded, opaque and sealed envelopes, on sight locked computer files, or similar valid methods of concealment. If the investigator was able to predict allocation, for example by the use of date of birth, the study was classified as having a high risk of bias. When concealment details were not reported, risk of bias was considered unclear.

3) Blinding: It is usually impossible to blind participants and clinicians to ACT, but the physician and data-analyst could be blinded. Therefore studies were considered to have low risk of bias if investigator and data-analyst were blinded to treatment method. Studies were considered to have high risk of bias if no blinding or a limited form of blinding was applied. Studies had unclear risk if no information on blinding was available.

4) Incomplete data outcome and intention-to-treat analysis: Studies were considered to have low risk of bias if an appropriate intention-to-treat analysis was performed on

incomplete data. When no intention-to-treat analysis was conducted, data were considered to have high risk of bias. Risk of bias was considered unclear if no information about intention-to-treat was given.

5) Selective outcome reporting: When pre-specified (primary and secondary) outcome measures were reported, the study was considered to have low risk of bias. When no pre-specified outcome measures were identified, the risk of bias was considered high. If insufficient information was available the study was classified as having unclear risk of bias.

6) Other potential threats to validity: If the study was free from other threats, such as baseline imbalance or design-specific risk of bias, it was considered to have low risk of bias. High risk of bias was considered if there was a potential threat in the study. Unclear risk of bias was considered if insufficient information was available to determine the risk of bias.

Measuring of treatment effect

Continuous outcomes were reported, where possible, using the mean difference (or standardised mean differences) and 95% CI. Risk ratio and 95% CI was used, where possible, to report dichotomous outcomes. Where insufficient data were available, or data conversion was not possible, data were presented as per the original report. The extracted data were insufficient to perform a meta-analysis (see 8.4 Results). I have therefore described the individual results of included studies in narrative and tabular form, using the effect measures described in the original studies.

Unit of analysis issues

Long- term studies with repeated measures of outcome were included in the review, although none were identified in this version of the review. In future reviews, these outcomes will be defined according to set time periods.[236] If studies had more than one intervention group, it was planned that these groups would be included separately in a meta-analysis, with the control group divided in half.[237]

Dealing with missing data

The original authors of the studies with missing data were contacted. If the author could not be located, a description of the study was included in the narrative review. Where missing data were not obtained, the studies were considered adequate if more than 85% of participants were included in the outcome analysis, or if fewer participants were included

but sufficient measures were taken to ensure or demonstrate that results were unbiased. Where this was not clear, an intention-to-treat analysis was planned for the extrapolated data.

Assessment of heterogeneity

If different studies measured the same outcome, and if there were sufficient data, heterogeneity assessment was planned using the chi-squared statistic and the I^2 statistic. Heterogeneity would be reported as low when I^2 was less than 30%, moderate when I^2 was between 30 and 50% and substantial when it was more than 50%. However, in this review, assessment of heterogeneity was not possible owing to insufficient data.

Assessment of reporting bias

If a sufficient number of studies were included, a funnel plot was planned to identify reporting bias.

Data synthesis

If a sufficient number of studies could be identified to include in this review, a meta-analysis was planned using a fixed-effect model, unless substantial heterogeneity was present in which case a random-effects model was planned. These methods will be employed if sufficient data is available in subsequent updates of this review.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned, to be conducted as applicable:

1) Age
2) Gender
3) Duration of treatment
4) Frequency of treatment
5) Severity of the disease

Sensitivity analysis

A sensitivity analysis was planned if an adequate number of studies were eligible for inclusion in the review.

8.4 RESULTS

8.4.1 Results of the search

This review was up to date as of January 2016. Electronic database searches were conducted, identifying 156 references with duplicates (109 in Pubmed, 21 in Medline, 19 in the Cochrane Library, seven in PEDro and none in CINAHL or Africa-Wide Information). One abstract was found through manually searching the reference lists of relevant articles, however we were unable to obtain the full text of this study.[433] Thirty-one duplicates were removed, which left 126 references for further investigation. After scanning all titles and abstracts, eight abstracts were found potentially relevant and underwent full text review. After full text analysis seven articles met the inclusion criteria for the review (Figure 8-1). However, only one study was purely focused on the paediatric population, with enrolment of children less than 18 years of age.[272] One study included both children and adults, but the author made raw data available for which a separation of populations could be made.[434] The other five studies including mixed population.[84,121,124,271,284]

8.4.2 Included studies

See Table 8-1 for an overview of the included studies.

All studies included in this review were randomised cross over trials.[84,121,124,270–272,434] Six of the included studies were short term studies, with a study period of less than six months (four two day cross over trials,[84,270,271,434] one five day cross over trial,[121] and an eight week cross over trial with a one week washout period between each four week intervention period).[124] One long term study was included, a two year cross over trial, only the first year of which was reported.[272] Three studies were conducted in Germany,[124,271,434] and one each in the United States of America,[84] Canada,[272] Austria,[121] and the United Kingdom.[270] In one study the research was done in an outpatient setting,[121] and in one other study a home-program intervention was used.[272] In the other five articles, it is unclear which research setting was used. One article was written in German,[434] all other articles were available in English.

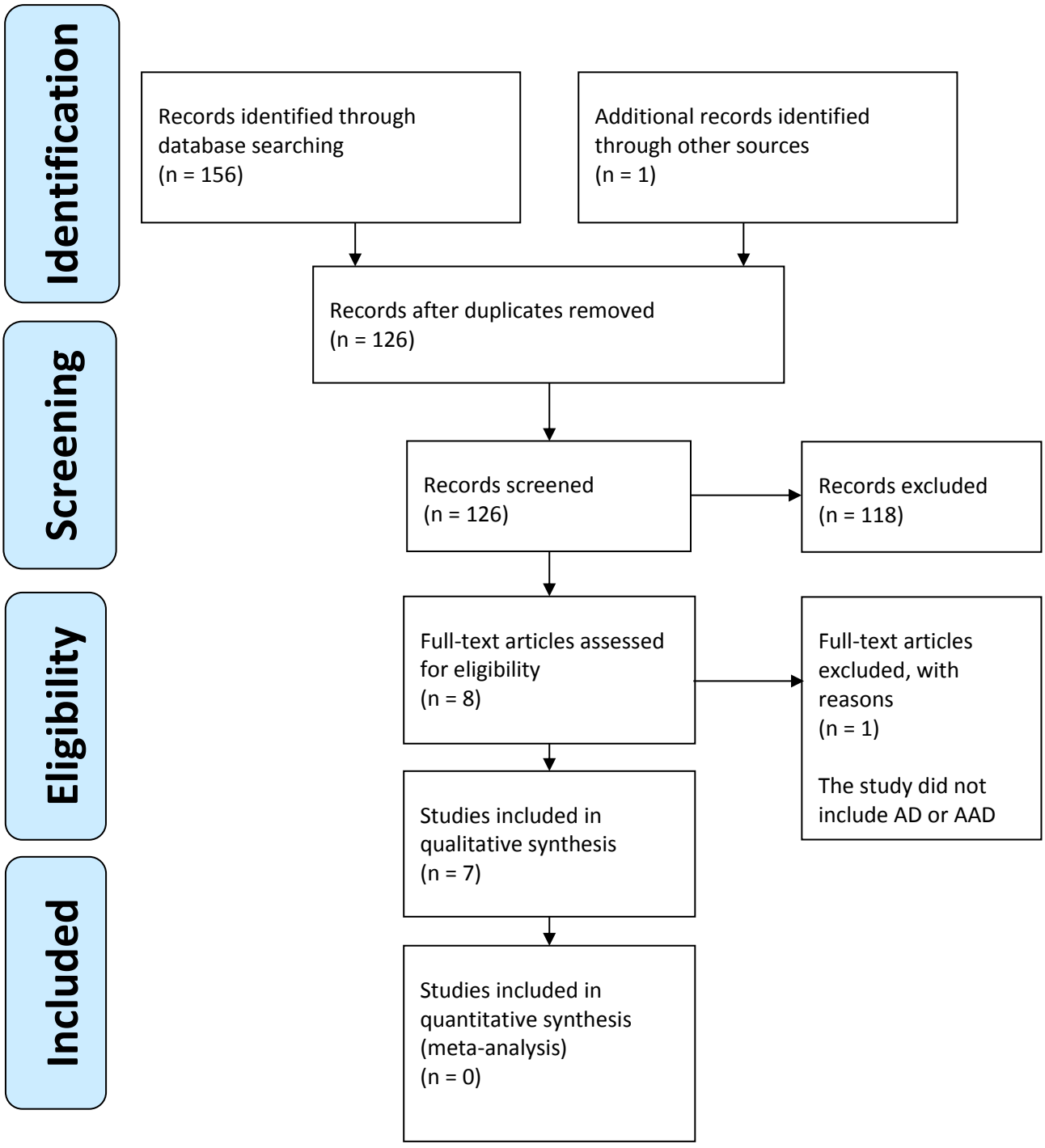


Figure 8-1. PRISMA study flow chart

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 8-1. Description of included studies

Author	- Country - Research setting	Duration of trial	n	Age range	CF diagnosis	Severity of symptoms	Intervention type	Duration and frequency of intervention
App et al.[124]	- Germany - Unknown	8 week cross over; one week washout between 4 weeks of intervention	Enrolled: 17 Analysed: 14	7-41 years	Sweat test	Mild to moderate: Mean FEV_1 = 75 (26.5)% (rang 29.2-117.3)	AD in sitting or lying versus Flutter	Duration: 4 weeks, acute sessions lasted 30 min Frequency: twice a day
Giles et al.[84]	- USA - Unknown	2 day cross over trial	Enrolled: 10 Analysed: 10	12-42 years	Sweat test	Unclear	AD by Schöni[127] versus PD with clapping	Duration: - AD: unclear duration - PD: 3 minutes in 7 positions Frequency: once a day
Lindemann et al. (1990)[271]	- Germany - Unknown	2 day cross over trial	Enrolled: 20 Analysed: 20	4-26 years	Unclear	Unclear	AD versus PEP 10-25 cm H_2O	Duration: 20-30 min Frequency: each treatment was performed once a day
Lindemann (1992)[434]	- Germany - Unkown	2 day cross over trial	Enrolled: 20 Analysed: 20 <18 years: 11 ≥18years: 9	7-28 years	Unclear	Unclear	AD versus Flutter (VRP1-Desitin)	Duration: 20 min Frequency: each treatment was performed once a day
McIlwaine et al.[272]	- Canada - Home-based	2 year cross over trial	Enrolled: 36 Analysed: 33	12-18 years	'proven diagnosis of CF'	Mean (SD) baseline FEV_1 PD: 73.7 (17.7)% AD: 75.9 (19.8)%	AD in sitting versus PD with percussion	Duration: ± 30 min Frequency: twice a day
Miller et al.[270]	- UK - Unknown	2 day cross over trial	Enrolled: 18 Analysed: 18	11-32 years	Unclear	Modified SK□ scores 34-87, clinically stable and not on IV$^{\Delta}$ antibiotics	AD in sitting or supine versus ACBT with PD	Duration: ± 30 min Frequency: twice a day on each day (two days of treatment one week apart)
Pfleger et al.[121]	- Austria - Outpatient	5 day cross over trial	Enrolled: 15 Analysed: 14	9.8-22.4 years	Sweat test	Mean clinical score 62.2 points (range 26-90) Mean X-ray score 3.8 points (range 6-20)	AD versus high pressure PEP versus spontaneous cough	Duration: individually, 50% of time needed to clear lungs Frequency: twice during outpatient visit

$^{\Delta}$IV = intravenous, □SK = Shwachman-Kulczycki

8.4.2.1 Participants

Overall, 136 participants between the age of four and 42 years were recruited for the seven studies.[84,121,124,270–272,434] However, only 47 participants could be identified as younger than 18 years of age: 36 in the study by McIlwaine et al. (18 boys and 18 girls),[272] and 11 in the study by Lindemann (1992) (no gender information available).[434] The other studies did not make a distinction between the different age groups.[84,121,124,270,271] A description of the participant population for each study can be found in Table 8-1. All studies included participants with CF, but only three clearly indicated that CF needed to be proven by a positive sweat test,[84,121,124] whereas in the study by McIlwaine et al. 'proven diagnosis of CF' was mentioned.[272] In the other three studies it is unclear how the diagnosis of CF was made.[270,271,434] Participants in the study by App et al. had mild to moderate disease severity, with a mean (SD) FEV_1 of 75 (26.5)%; ranging from 29.2 to 117.3%,[124] and in the study by McIlwaine et al. the mean (SD) baseline FEV_1 was 73.7 (17.7)% for the PD group and 75.9 (19.8)% in the AD group.[272] Miller et al. used the modified Shwachman-Kulczycki scores to address disease severity, which ranged from 34-87.[270] They also mentioned that participants were clinically stable and did not receive intravenous antibiotics during the study. Finally, Pfleger et al. used the Shwachman-Kulczycki clinical score (mean 62.2 points, ranging from 26 to 90) and chest X-ray scores (mean 3.8 points, ranging from 6 to 20) to describe severity of disease.[121] The other studies did not report disease severity.

8.4.2.2 Interventions

Two trials compared AD with PD combined with percussion or clapping.[84,272] In the study by Giles et al., AD as described by Schoni was used.[84,127] PD in this study was done for three minutes in seven different positions. In each position, manual vibrations and clapping were performed by a therapist. Between each position the participant was instructed to cough or huff. Both treatments were done once, on separate days. In the other study, AD was performed in a sitting position whereas PD was done in five or six different positions depending on the time of the day.[272] In each PD position, percussions were given for three to five minutes by a second person, followed by deep breathing exercises with expiratory vibrations; two or three huffs; encouragement to cough; and finally a short period of relaxed controlled breathing. Treatment during this trial was given bi-daily for 30 minutes as a home-program. The study by Miller et al. was a two-day cross over trial with one week of rest between cross-over periods.[270] This study compared AD with PD combined with the ACBT. AD was done in sitting or supine, and several ACBT cycles were done in standardised

PD positions over a Chesham frame for 7.5 minutes per position. Treatment was given bi-daily for 30 minutes. Two trials compared AD and PEP.[121,271] One of them used a simplified method of AD ("AD is based on a deepened breathing which is adjusted to the localization and quantity of mucus"), compared to PEP (with a mouth pressure of 10-25 cm H_2O) in a two-day cross over trial.[271] Each treatment was given once a day, in a randomised order, for 20 to 30 minutes. This order was reversed on the second day. The other study compared AD and high pressure PEP using a high pressure Danish PEP mask combined with FET.[121] Intensity and duration of treatment are unclear as they were individually chosen. Finally, the last two studies compared AD with Flutter therapy.[124,434] In the study by App et al., the breathing techniques were performed in a sitting or lying position.[124] Each treatment was done twice a day for four weeks, with a total of eight weeks of intervention and one week of washout between the study periods. Before and after each treatment period, the participant received an acute therapy for 30 minutes, which was used to assess the participant. The other study which compared AD with the VRP1-Desitin (Flutter),[434] used the same simplified method of AD as used in the study by Lindemann et al (1990).[271] Each treatment was done for 20 minutes once a day. The second day, the inverse order of treatment was given (two-day cross over trial).

None of the included studies used AAD.

8.4.2.3 Outcome measures

This review's primary outcome measure 'number of hospitalisations measured at 12 months' was only assessed in one study as a secondary outcome measure.[272] This study revealed no significant difference in the mean (SD) number of hospitalisations between treatments (1.0 (0.3) for the PD group, and 0.8 (0.2) for the AD group) for the first year of the study (first period data of the cross-over trial). This study also indicated 16 hospitalisations due to exacerbations occurring in the PD group, compared to 13 in the AD group. This review's other primary outcome: 'number of exacerbations in 12 months, assessed by number of antibiotic treatments or diagnosis of a physician' was not assessed by any study included in this review.

Participant or caregiver preference was only used as an outcome measure in one of the included studies.[270] In this study, the preference was not described after six or 12 months as indicated in this review's outcome measures, but it was assessed after the cross over trial, which lasted 14 days. Of 18 participants, nine preferred AD, eight preferred ACBT and

one did not have a preference. The study by McIlwaine et al. did not report preference as a pre-set outcome measure, however the article could not report results from the second year of the trial due to the clear preference towards AD.[272] Ten of the 17 participants in the AD group refused to cross over to the PD technique during the second year. None of this review's other secondary outcome measures, HRQOL, adverse effects or mortality rate were assessed in any of the included studies.

8.4.3 Excluded studies

One abstract was considered potentially relevant for this review.[435] However, it was subsequently found to be unsuitable as it did not, in fact, include the AD technique.[436]

8.4.4 Risk of bias in included studies

A risk of bias summary can be found in Table 8-2 and Figure 8-2.

8.4.4.1 Generation of sequences

All seven studies were randomised cross over trials. However, only one study specified the method of randomisation, which was by computer generation.[272] Therefore, this study was found to have low risk of bias. The other articles did not specify how the randomisation was done and were therefore classified as having unclear risk of bias.

8.4.4.2 Allocation

Allocation concealment was not specified in any of the articles and therefore there was an unclear risk of bias in this respect.

8.4.4.3 Blinding

As it is extremely difficult to blind participants and physiotherapists during ACT, all studies had a high risk of performance bias. However, it should be possible to blind the outcome assessor in this type of research. Two articles reported blinding of the outcome assessor. In the article by McIlwaine et al. both physicians and the pulmonary function technician were blinded to allocation.[272] In the other study, a blinded investigator weighed the sputum.[121] No information on blinding of the other outcome assessments was reported. Both the above studies were considered to have low risk of detection bias, whereas the other studies were classified as having unclear risk of detection bias.

Table 8-2. Risk of bias

Author	Study bias	Risk	Support for judgment
App et al.[124]	Random sequence generation	Unclear	Random order of treatment, no specifications on sequence generation.
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Both participants and physiotherapist knew in which group the participant was assigned.
	Blinding outcome assessment	Unclear	Not specified
	Incomplete outcome data	Unclear	Unclear if patients were lost to follow up and if an intention-to-treat analysis was performed on incomplete data.
	Selective reporting	Unclear	Outcome measures were pre-specified. However, SpO_2 was only used to report baseline characteristics. It was not mentioned in the results section of the article.
	Other bias	Unclear	Unclear if groups were similar at the start of the research. Both groups were treated equally except for treatment. Two participants, one in each group, were withdrawn for the study due to similar reasons. One other participant dropped out with reason. It is unclear if the other participants were analysed in the group they were randomly assigned to.
Giles et al.[84]	Random sequence generation	Unclear	Random order of treatment, no specifications on sequence generation.
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Both participants and physiotherapist knew in which group the participant was assigned.
	Blinding outcome assessment	Unclear	Not specified
	Incomplete outcome data	Unclear	Unclear if patients were lost to follow up and if an intention-to-treat analysis was performed on incomplete data.
	Selective reporting	Unclear	Outcome measures were pre-specified, however, FEF at 25%, 50% and 75% of VC, and FEF at midportion of VC were not reported in the results section of the article.
	Other bias	Unclear	It is unclear if groups were similar at start of the study and if the groups were treated equally except for treatment. No withdrawals or drop outs were reported, but it is unclear if participants were analyzed in the group they were assigned to.

Table 8-2 continued. Risk of bias

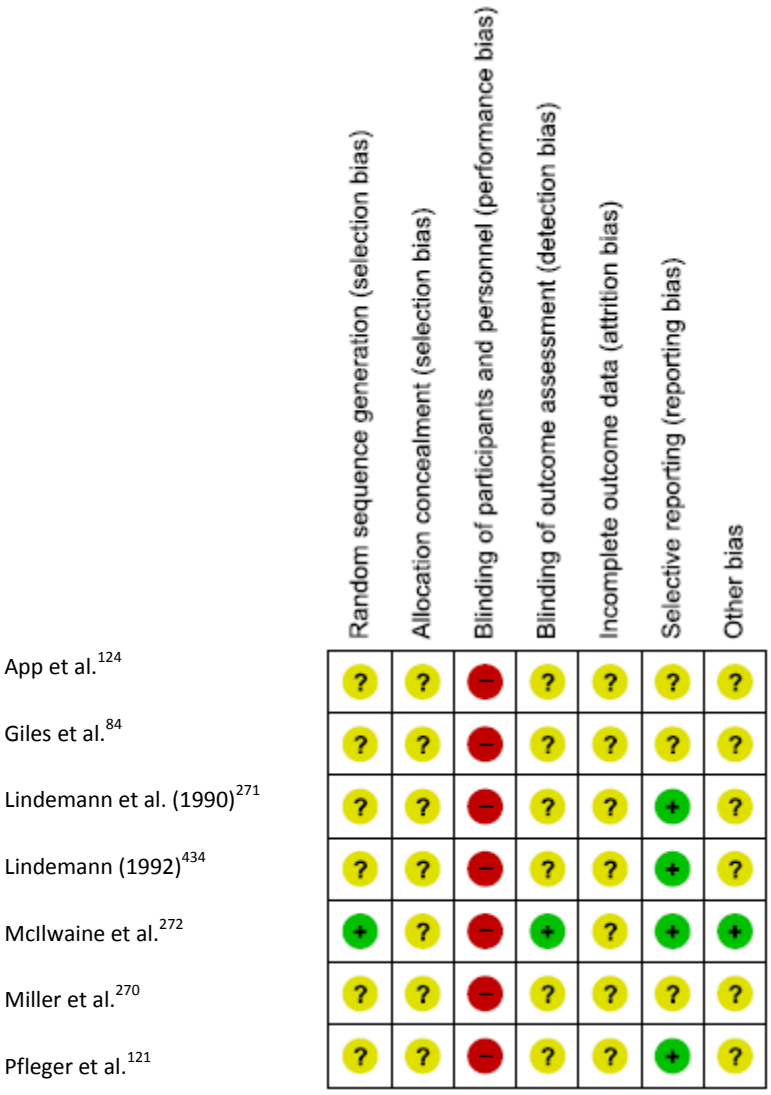
Author	Study bias	Risk	Support for judgment
Lindemann et al. (1990)[271]	Random sequence generation	Unclear	Random order of treatment, no specifications on sequence generation.
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Participants were not blinded to treatment. Unclear if clinicians were blinded to allocation
	Blinding outcome assessment	Unclear	Not specified
	Incomplete outcome data	Unclear	No information available on lost-to-follow up and intention-to-treat analysis
	Selective reporting	Low	Primary outcome was pre-specified, no secondary outcome measures reported
	Other bias	Unclear	Unclear if the groups were similar at start of the study, if participants were analyzed in the group they were randomly assigned to and if the groups were treated equally except for treatment.
Lindemann (1992)[434]	Random sequence generation	Unclear	Random order of treatment, no specifications on sequence generation.
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Participants were not blinded to treatment. Unclear if clinicians were blinded to allocation
	Blinding outcome assessment	Unclear	Not specified
	Incomplete outcome data	Unclear	No information available on lost-to-follow up and intention-to-treat analysis
	Selective reporting	Low	Outcome measure was pre-specified
	Other bias	Unclear	Unclear if the groups were similar at start of the study, if participants were analyzed in the group they were randomly assigned to and if the groups were treated equally except for treatment

Table 8-2 continued. Risk of bias

Author	Study bias	Risk	Support for judgment
McIlwaine et al.[272]	Random sequence generation	Low	A computer randomly assigned participants to a certain group
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Participants and physiotherapist knew in which group the participant was allocated
	Blinding outcome assessment	Low	Both the physicians as the pulmonary function technician were blinded to allocation
	Incomplete outcome data	Unclear	There is no information available on loss-to-follow up and intention-to-treat analysis
	Selective reporting	Low	Primary and secondary outcome measures were pre-specified
	Other bias	Low	Groups were similar at start as participants were matched as pairs before random allocation. Also, both groups were treated equally except for the treatment. All participants, except for 3 drop outs of which the reason for drop out is clearly indicated, were assessed in the group they were assigned to
Miller et al.[270]	Random sequence generation	Unclear	Random order of treatment, no specifications on sequence generation.
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Participants and clinicians knew participant's allocation
	Blinding outcome assessment	Unclear	Not specified
	Incomplete outcome data	Unclear	There is no information available on loss-to-follow up and intention-to-treat analysis
	Selective reporting	Unclear	Outcome measures were pre-specified. However VC, FEV_1 and PEF were not reported in the results section. Also the reason for preference towards a certain treatment option was left out of the article.
	Other bias	Unclear	Unclear if groups were similar at the start of the study, and if participants were analyzed in the group they were randomly assigned to. However groups were treated equally except for treatment.

Table 8-2 continued. Risk of bias

Author	Study bias	Risk	Support for judgment
Pfleger et al.[121]	Random sequence generation	Unclear	Random order of treatment, not specified how sequence generation was done
	Allocation concealment	Unclear	Not specified
	Blinding participants & personnel	High	Participants and physiotherapist knew participant's allocated
	Blinding outcome assessment	Unclear	Sputum was weighed by an investigator blinded to treatment, not specified if other outcome assessors were blinded to treatment
	Incomplete outcome data	Unclear	Although mean age and range of the 10 participants was mentioned in the results section, it is unclear if analysis of the outcome measures were done on all 10 participants as no information is available on loss-to-follow up and intention-to-treat analysis
	Selective reporting	Low	Outcome measures were pre-specified
	Other bias	Unclear	Groups were treated equally except for treatment. However, it is unclear if groups were similar at the start of the study and if participants were analysed in the group they were randomly assigned to



Red= high risk of bias, yellow = unclear risk of bias and green = low risk of bias.

Figure 8-2. Risk of bias summary: review author's judgment about each risk of bias item for each included study.

8.4.4.4 Incomplete outcome data

In three trials participants were withdrawn from the study.[121,124,272] In the study by App et al., two participants, one in each arm of the study, were excluded due to acute bronchopulmonary exacerbation for which intravenous antibiotic therapy was prescribed.[124] One other participant withdraw from the study due to business-related time constraints. It is unclear in which arm of the study this drop-out was assigned. In the study by McIlwaine et al., three participants dropped out, two in the PD group (due to pregnancy and aspergillosis) and one in the AD group (due to non-compliance).[272] Finally in the study by Pfleger et al., one participant had an acute respiratory viral infection, for which this participant was excluded.[121] It is unclear to which group this participant was assigned.

None of the trials reported the use of an intention-to-treat analysis for incomplete data. Therefore an unclear risk of bias in this respect was attributed to all studies.

8.4.4.5 Selective reporting

All included studies reported pre-specified outcome measures. Only one article identified both primary and secondary outcome measures.[272] Two articles reported only one outcome measure.[271,434] All other trials had multiple pre-specified outcome measures, but no distinction between primary and secondary outcome measures were made.[84,121,124,270] The risk of bias for four of these studies was classified as being low, because all pre-set outcome measures were reported in the results section and if not reported in the results section, a reason for omission was provided.[121,271,272,434] The other three studies did not report on all the pre-specified outcome measures, with no reasons provided.[84,124,270] Hence these studies were classified as having an unclear risk of reporting bias.

8.4.4.6 Other potential sources of bias

Only one trial used matched pairs for their research, which ensures groups were similar at the start of the study.[272] This study also indicated that the groups were treated equally, except for the type of ACT and it is clear that participants were analysed in the group they were randomly assigned to. Therefore, this trial was judged to have a low risk of other potential sources of bias. For the other studies included in this review, insufficient information was given to make a good judgement of bias, although it is noted that three studies reported that groups were treated equally except for the physiotherapy treatment.[121,124,270]

8.4.5 Effects of interventions

No meta-analysis was possible due to the variable outcome measures used in the studies, and insufficient reporting of separate period data for both arms of cross-over trials.

8.4.5.1 Primary outcome measures

Number of hospitalisations measured at 12 months

Only one study (based on a paediatric population), included this outcome measure as one of their secondary outcome measures.[272] There was no significant difference between PD and AD in mean (SD) number of hospital admissions. However, the participants performing AD showed a tendency to have fewer hospital admissions during one year (1.0 (0.3) (95%CI 0.8-1.2) for the PD group, and 0.8 (0.2) (95% CI 0.7-0.8) for the AD group). In total, 16 (PD

group) and 13 (AD group) participants were admitted to hospital for pulmonary exacerbations. The significance level for this comparison could not be obtained, but the 95%CIs only overlapped marginally.

Number of exacerbations measured at 12 months

No study explicitly used this outcome measure. McIlwaine et al. reported that all hospital admissions were due to pulmonary exacerbations, but it is unclear how many exacerbations were treated as out-patients.[272]

8.4.5.2 Secondary outcome measures

HRQOL measured at six and 12 months

No included study reported on this outcome measure.

Preference measured at six and 12 months

Although no study reported preference measured at six or 12 months, Miller et al. measured patient's preference after completion of a two day cross over trial, using of a visual analogue scale.[270] Eight participants preferred ACBT, nine preferred AD and one patient had no preference. In the study by McIlwaine et al. participants' preference was not reported, however this study did reflect a strong apparent preference for AD, with 10 out of 17 participants (all younger than 18 years of age) refusing to cross over to PD after one year of intervention using AD.[272]

Adverse effects measured at three, six and 12 months

No study reported adverse effects after three, six and 12 months. Nonetheless, mild desaturation from 93.3 (0.7)% to 91.2 (0.8)% ($p<0.01$) occurred during PD in one study, which was worse when patients were placed in the head down position.[84] Oxygen levels returned to normal 15 minutes after the end of treatment. Conversely, AD was associated with increased SpO_2 levels during treatment (from 93.3 (0.8)% to 94.9 (0.7)%, $p<0.01$), with the higher saturation level maintained at one hour post treatment.

Mortality measured at three, six and 12 months

No study reported on mortality.

8.4.5.3 Other outcome measures

Lung function tests

Five of the included studies reported data on lung function tests.[84,121,124,270,272] However, it

was not possible to pool the data, as they were presented in different ways. McIlwaine et al. was the only study reporting clear paediatric data and used decline in % predicted FEV_1 as the primary outcome measure for their study.[272] When using the regression slope over the first year (lung function test done every three months), there was no significant difference between PD (mean (SD) 2.1 (2.2)) and AD (1.0 (2.3)) for FEV_1 (p= 0.63). Change in FVC and FEF_{25-75} were reported as secondary outcome measures and both showed no significant difference between the groups after one year. The mean (SD) change in FVC and FEF_{25-75} for PD and AD groups respectively were 0.5 (1.7) (PD) versus 2.4 (1.9) (AD) and 5.6 (4.6) (PD) versus -1.9 (3.8) (AD).

Four studies combined paediatric and adult data, with separate data not available. A summary of the results can be found in Table 8-3.[84,121,124,270]

Sputum weight

Six of the included studies reported sputum weight,[84,124,270,434] sputum production,[121] or elimination of sputum as outcome measures.[271] One study reported raw data for each participant, making it possible to distinguish between adult and paediatric data.[434] However, it is unclear which data belongs to which cross over period, therefore it is only possible to report values for the two cross over periods together. In the paediatric population, treatment with the Flutter VRP1-Desitin eliminated a mean (SD) 4.8 (3.5)g of sputum (95%CI 3.4 - 6.3) whereas AD eliminated a mean (SD) 4.3 (2.6)g of sputum (95%CI 3.2 - 5.4). The results for the adult population are given in Table 8-3. No significance levels were available for the separate age data.

For the other five studies, no distinction between adult and paediatric population could be made. Two of these studies reported sputum production collected during the separate periods of the cross-over,[124,271] the other three studies did not make a clear distinction between the different periods of the cross-over. These results are also presented in Table 8-3.

Shwachman- Kulczycki score

See section 2.3.3 for a description of this outcome measure.

Change in Shwachman-Kulczycki score in the paediatric population was reported in one included study and did not differ significantly between the use of AD and PD.[272] The PD group had a mean change in score of 7.5, with a SD of 9.0 and 95% CI 3.1 to 11.9. The AD

group had a mean change in score of 3.1 with a SD of 6.2 and 95% CI 0.2 to 6.1 (I was unable to obtain a p-value for this outcome measure).

Huang score

McIlwaine et al. reported on the change in Huang scores in a paediatric population (see section 2.3.3 for a description of the Huang score), which improved significantly in the AD group, with a mean (SD) change in score of 2.3 (4.3) (95%CI 0.3-4.4), compared to the PD group, which had a mean (SD) change in score of -0.9 (4.9) (95%CI -3.3-1.5)(p= 0.04).[272]

The following outcome measures were used in the studies with mixed populations. A summary of the results are reported in Table 8-3:

Quotient of the change in FVC and sputum recovery,[121]

SpO_2,[84,270]

Time needed to clear the lungs,[121]

Rheological analysis,[124]

Clearance of radiolabelled aerosol,[270]

Ventilation studies.[270]

Table 8-3. Other outcome measures

Outcome	Study, n	Data presentation	AD	Control	Outcome between groups	p-value between groups
FEV_1	App et al.[124] n= 14 (n=7 per group)	Mean (95%CI) (in liter)	Baseline: 2.1 (1.3-2.9) After 4 weeks: 2.0 (1.3-2.7)	Baseline: 2.1 (1.4-2.8) After 4 weeks: 2.1 (1.4-2.8)	No significant difference between techniques	Not reported (NS)
	Giles et al.[84] n= 10	% predicted, in graph format	Not available	Not available	No difference between techniques	Not reported (NS)
	McIlwaine et al.[272] n= 17 (AD) n= 16 (PD)	Mean (95%CI) (change in pulmonary function)	After 1 year: 1.0 (-0.1-2.0)	After 1 year: 2.1 (1.0-3.2)	No difference between techniques	Not reported (NS)
	Pfleger et al.[121] n= 15	% predicted Mean (SD) (within group p-value)	Test 1: 54 (20) Test 5: 56 (19) (p: NS)	PEP: (p< ***0.05***) Test 1: 52 (21) Test 5: 54 (20) PEP-AD: (p< ***0.02***) Test 1: 51 (18) Test 5: 55 (18) AD-PEP: (p: NS) Test 1: 52 (21) Test 5: 54 (19)	No difference between AD compared to PEP or PEP-AD; however, AD was better than AD-PEP for test 5.	Not reported (NS) for AD compared to PEP and PEP-AD p< ***0.05*** for AD compared to AD-PEP
FEF_{25-75}	McIlwaine et al.[272] n= 17 (AD) n= 16 (PD)	Mean (95%CI) (change in pulmonary function)	After 1 year: -1.9 (-3.7-(-0.1))	After 1 year: 5.6 (3.4-7.9)	No difference between techniques	Not reported (NS)
	Miller et al.[270] n= 18	Number of tests out of 36 (18 in the morning and 18 in the afternoon)	>10% improvement: 17 >15% improvement: 11 >20% improvement: 9	>10% improvement: 10 >15% improvement: 8 >20% improvement: 7	No difference between techniques	Not reported (NS)

P-values are presented as reported in the original article

Table 8-3 continued. Other outcome measures

Outcome	Study, n	Data presentation	AD	Control	Outcome between groups	p-value between groups
FVC	App et al.[124] n= 14 (n=7 per group)	Mean (95%CI) (in liter)	baseline: 2.9 (1.9-3.9) After 4 weeks: 2.9 (1.9-3.9)	baseline: 3.2 (2.8-3.6) After 4 weeks: 3.2 (2.8-3.6)	No difference between ACTs	Not reported (NS)
	Giles et al.[84] n= 10	% predicted, in graph format	Not available	Not available	No difference between ACTs	Not reported (NS)
	McIlwaine et al.[272] n= 17 (AD) n= 16 (PD)	Mean (95%CI) (change in pulmonary function)	After 1 year: 2.4 (1.5-3.2)	After 1 year: 0.5 (-0.3-1.3)	No difference between ACTs	Not reported (NS)
	Miller et al.[270] n= 18	Number of tests out of 36 (18 in the morning and 18 in the afternoon)	>10% improvement: 15 >15% improvement: 10 >20% improvement: 4	>10% improvement: 17 >15% improvement: 11 >20% improvement: 8	No difference between ACTs	Not reported (NS)
	Pfleger et al.[121] n= 15	% predicted Mean (SD) (p-value within groups)	Test 1: 69 (21) Test 5: 74 (19) (p< **0.05**)	PEP: (p< ***0.01***) Test 1: 66 (21) Test 5: 73 (20) PEP-AD: (p< ***0.01***) Test 1: 68 (21) Test 5: 73 (20) AD-PEP: (p: NS†) Test 1: 69 (22) Test 5: 71 (21)	No difference between AD compared to PEP or PEP-AD; however, AD was better than AD-PEP for test 5.	Not reported (NS†) for AD compared to PEP and PEP-AD p< ***0.05*** for AD compared to AD-PEP
Peak flow	Giles et al.[84] n= 10	%predicted, in graph format	Not available	Not available	No difference between techniques	Not reported (NS)
RV/TLC	Pfleger et al.[121] n= 15	% predicted Mean (SD) (p-value within groups)	Test 1: 51 (14) Test 5: 49 (14) (p: NS)	PEP: (p< ***0.05***) Test 1: 52 (15) Test 5: 50 (14) PEP-AD: (p< ***0.05***) Test 1: 52 (15) Test 5: 50 (13) AD-PEP: (p: NS) Test 1: 51 (15) Test 5: 51 (14)	No difference between AD compared to PEP or PEP-AD; however, AD was better than AD-PEP for test 5.	Not reported (NS) for AD compared to PEP and PEP-AD p< ***0.01*** for AD compared to AD-PEP

P-values are presented as reported in the original article

Table 8-3 continued. Other outcome measures

Outcome	Study, n	Data presentation	AD	Control	Outcome between groups	p-value between groups
Airway resistance	Pfleger et al.[121] n= 15	% predicted Mean (SD)	Test 1: 225 (108) Test 5: 212 (93) (p: NS)	PEP: (p: NS) Test 1: 241 (117) Test 5: 211 (113) PEP-AD: (p: NS) Test 1: 240 (128) Test 5: 216 (91) AD-PEP: (p: NS) Test 1: 239 (141) Test 5: 219 (97)	No difference between ACTs	Not reported (NS)
ΔFVC/ sputum	Pfleger et al.[121] n= 15	ΔFVC (% predicted/ sputum weight in gram). Mean (SD)	0.5 (0.8)	PEP: 0.3 (0.6)	No difference between ACTs	Not reported (NS)
Sputum weight (in gram)	App et al.[124] n= 14 (n=7 per group)	Mean (95% CI)	Baseline: 2.7 (1.1-4.3) After 4 weeks: 3.6 (1.8-5.5)	Baseline: 2.9 (1.3-4.5) After 4 weeks: 4.5 (2.7-6.4)	No difference between ACTs	Not reported (NS)
	Giles et al.[84] n= 10	Mean (95% CI)	Both arms of the study together: 14.0 (12.1-15.9)	Both arms of the study added up:10.4 (8.5-12.3)	No difference between ACTs	Not reported (NS)
	Lindemann et al (1990)[271] n= 20	Mean (SD) (range)	Day 1: 13.7 (7.1) (4.0-32.0) Day 2: 10.6 (6.4) (0-26)	Day 1: 6.8 (3.9) (0.0-14.0) Day 2: 6.2 (3.4) (1-12)	AD more effective than PEP	Not reported (significant)
	Lindemann (1992)[434] n= 20 n <18 years = 11 n ≥18 years = 9	Total = Mean (range) Pediatric and adults = Mean (SD) (95%CI), in gram	Both arms of the study together: Total: 4.8 (0.0-11.7) Paediatric: 4.3 (2.6) (3.2-5.4) Adults: 5.4 (3.7) (3.8-7.2)	Both arms of the study together: Total: 5.0 (0.0-12.0) Paediatric: 4.8 (3.5) (3.4-6.3) Adults: 5.1 (3.4) (3.5-6.7)	No difference between ACTs	p> 0.05
	Miller et al.[270] n= 18	Mean (SD) difference: -0.4g (1.8)g			No difference between ACTs	Not reported (NS)
	Pfleger et al.[121] n= 15	Means and SD, shown in graph format	AD	> cough < PEP < PEP-AD < AD-PEP	AD produced more sputum than cough, but less then the other ACTs	p< 0.001 p< 0.001 p< 0.02 p< 0.001
Change in Shwachman score	McIlwaine et al.[272] n= 17 (AD) n= 16 (PD)	Mean (95% CI)	3.1 (0.2-6.1)	7.5 (3.1-12.0)	No difference between ACTs	Not reported (NS)
Change in Huang score	McIlwaine et al.[272] n= 17 (AD) n= 16 (PD)	Mean (95% CI)	2.3 (0.3-4.4)	-0.9 (-3.3-1.5)	AD had a better outcome than PD with clapping	p= 0.04

P-values are presented as reported in the original article

Table 8-3 continued. Other outcome measures

Outcome	Study, n	Data presentation	AD	Control	Outcome between groups	P-value
SpO_2	Giles et al.[84] n= 10	Mean (95% CI) (in %) (p-value within groups)	Both arms of the study together: Baseline: 93.3 (92.8-93.8) During: 94.9 (94.5-95.3) (p< ***0.001***) 1h post: 94.5 (94.1-94.9) (p< ***0.001***)	Both arms of the study together: Baseline: 93.3 (92.9-93.7) During: 91.2 (90.7-91.7) (p< ***0.001***) 15 min post: return to baseline	No comparison between groups reported	Not available
	Miller et al.[270] n= 18	n desaturated	0	Morning: 4 Afternoon: 1	No difference between ACTs	p> 0.05
Time needed to clear lungs	Pfleger et al.[121] n= 15	Means and SD, shown in graph format	AD	>PEP =PEP-AD =AD-PEP	PEP cleared the lungs faster than AD; however PEP-AD and AD-PEP did not differ from AD	p< ***0.05*** for PEP compared to AD Other p-values not reported (NS)
Rheologic analysis	App et al.[124]	data in graph format	Not available	Not available	Flutter better than AD	
a) viscoelasticity			AD	>Flutter		p< 0.01
b) MCI[¶]			AD	<Flutter		p= 0.01
c) CCI[ǂ]			AD	<Flutter		p= 0.04
Clearance radiolabeled aerosol	Miller et al.[270] n= 18 (whole lung) n= 18 (central) n= 18 (peripheral) n= 6 (mild) n= 7 (moderate) n= 5 (severe)	Mean (SD) (in %/hour)	Whole lung: 3.9 (1.4) Central lung region: 3.6 (1.4) Peripheral lung region: 5.5 (2.2) Mild disease severity: 3.8 (2.0) Moderate disease severity: 3.3 (0.3) Severe disease severity: 4.7 (1.3)	Whole lung: 3.2 (1.4) Central lung region: 2.9 (1.3) Peripheral lung region: 4.7 (2.0) Mild disease severity: 2.7 (1.2) Moderate disease severity: 2.8 (1.0) Severe disease severity: 4.3 (1.5)	AD cleared the whole lung and central lung regions faster than ACBT, no differences for peripheral lung regions or disease severity	p< ***0.05*** for both whole lung and central lung regions Other p-values not reported (NS)
Ventilation studies	Miller et al.[270] n=9	n	Improvement first breath: 5 No improvement first breath: 4 Faster washout rate: 6 Slower washout rate: 3	Improvement first breath: 5 No improvement first breath: 4 Faster washout rate: 4 Slower washout rate: 3 No change washout rate: 2		Not available

[¶]MCI= mucociliary clearability index, [ǂ]CCI= cough clearability index
P-values are presented as reported in the original article

8.5 DISCUSSION

8.5.1 Summary of main results

No RCTs were identified for inclusion; however, this review included seven randomised cross-over trials which compared AD with Flutter,[124,434] PEP,[271] high pressure PEP,[121] PD (combined with percussions or clapping)[84,272] or ACBT (combined with PD).[270] Although all seven included studies were randomised cross-over trials,[84,121,124,270–272,434] none was bias-free. Further, separation of paediatric and adult data was only possible in two studies. There is therefore insufficient evidence to accept or reject AD as a safe or effective treatment option in children with CF.

Number of hospitalisations measured at 12 months, one of the intended primary outcome measures of this review, was only reported in one of the included studies.[272] Although this study found no difference between AD and PD in a paediatric population, there was a trend towards fewer hospitalisations in the AD group. However, the small sample size prevents any conclusions being made in this regard. The other primary outcome measure of this review, number of exacerbations during 12 months, was not analysed in any of the included studies.

Even though none of this review's secondary outcome measures were assessed in the included studies, two studies did mention participant preference in their research.[270,272] One study in the paediatric population indicated preference towards AD when compared to PD, with the majority of participants assigned to AD during the first period of a randomised cross-over trial refusing to revert to conventional ACTs after completing the first period of cross-over.[272] Miller et al. (adult and paediatric data combined) did not report a clear preference towards either AD or ACBT combined with PD.[270]

Other outcome measures, with various results, were reported in the included studies. Within the paediatric population, a significant improvement in Huang scores was reported when AD was compared to PD as a one year home program.[272] However, the other outcome measures from this study (lung function tests presented as %predicted FEV_1, FVC and FEF_{25-75}; and Shwachman-Kulczycki scores) did not show significant differences between AD and PD after a one year home program.[272] Sputum weight in the paediatric population was reported in one study, but no significance levels were available for the separate (adult versus paediatric) data.[434]

All other included studies combined paediatric and adult data, therefore no conclusions can be made for the paediatric population.[84,121,124,270,271]

8.5.2 Overall completeness and application of evidence

Not all the review's pre-set objectives were addressed, as no studies on AAD were identified, and patient/caregiver preference was only reported in two of the included studies but was not assessed as an outcome measure.[270,272] The majority of studies did not analyse paediatric and adult data separately, and only one study reported on any pre-set primary or secondary outcome measures of this review.[272] Therefore it is impossible to make justified conclusions with regards to this review's objectives. Most of the included articles reported lung function tests,[84,121,124,270,272] and sputum weight/production,[84,121,124,270,271,434] however, most studies did not report data on the different periods of the cross-over trials or used different ways to report outcome measures, which made pooling of the data impossible. Other outcome measures used in the included studies were: SpO_2,[84,270] quotient change in FVC and sputum recovery,[121] time needed to clear the lungs,[121] rheological analysis,[124] clearance of radiolabelled aerosol,[270] ventilation studies,[270] Shwachman-Kulczycki score,[272] and Huang score.[272] Research was conducted in Germany,[124,271,434] Austria,[121] USA,[84] Canada,[272] and the UK,[270] which limits generalisability to developed countries. All but one of the included studies was published more than ten years ago.[272] All other articles were published in the 1990s, which might make the studies less relevant as the management of CF has changed over the past decades towards a multidisciplinary intensive management approach, associated with improved longevity and quality of life.[292]

8.5.3 Quality of the evidence

All seven included studies were randomised cross-over trials,[84,121,124,270–272,434] however, only one study clearly indicated the method of randomisation and none of the studies reported how allocation concealment was maintained.[272] The major problem with the included studies is the risk of bias and the publication date. Lack of blinding was present in all studies. Participants and clinicians are difficult to blind due to the nature of the intervention, however, blinding of the outcome assessors should ideally be reported. This was only the case in two studies.[121,272] No information was available on incomplete data analysis and most studies also did not provide sufficient information to make a clear risk of bias analysis of other potential threats, except for the study by McIlwaine et al. which had a low risk of bias for other potential threats.[272] Selective reporting was found to have unclear

risk of bias in most studies, only those by Pfleger et al. and McIlwaine et al. were judged to have a low risk of bias.[121,272] Overall, risk of bias is questionable and therefore no justifiable conclusions can be made.

8.5.4 Potential biases in the review process

Six different data bases were searched, as well as the reference lists of all relevant articles and clinicaltrial.gov for ongoing clinical trials. Attempts were made to contact the authors of the included articles, however not all authors were contactable or responded and due to the old publication dates, most of the raw data was unavailable. The review included studies that were published in English, Dutch, French, German and Afrikaans. No articles needed to be excluded due to language restrictions. No data limitation was set. All these precautions were set to limit the risk of selective data reporting. It is possible that studies published in non-peer reviewed journals, presented at local conferences or non-published research dissertations were missed, leading to potential bias.

8.5.5 Comparison with other studies or reviews

This systematic review agrees with the conclusion of a previous systematic review on AD in patients with CF, which found a lack of evidence that AD improves lung functions but did find that AD cleared more secretions than spontaneous coughing based on one study.[422] However, the current systematic review reveals that AD clears less or similar amounts of sputum than other techniques based on five studies.[84,121,124,270,434] No reviews on the use of AAD in children with CF are available. Systematic reviews comparing no ACT with any form of ACT,[430,431] and reviews comparing different treatment options in patients with CF,[133–135,429] do include AD as one of the treatment options and reveal similar outcomes for the comparison between different forms of ACT and AD.

8.6 CONCLUSION

8.6.1 Implications for practice

Due to the small sample sizes, the overall unclear risk of bias and the inability to pool data and therefore to perform a meta-analysis, no clear, generalisable conclusions with regards to the use of AD or AAD in children with CF can be made. This treatment modality cannot be accepted nor rejected as either safe or effective for use in clinical practice.

8.6.2 Implications for research

The implementation of paediatric-specific RCTs with adequate sample sizes (to reduce type II error), appropriate clinical outcome measures and analysis of adverse effects (including mortality) is recommended within this field of research. Outcome measures of participant preference, HRQOL and adherence to treatment should be considered. As no research is available on the use of AAD within this population, RCTs should be designed to assess the appropriateness of this technique.

Chapter 9. THE USE OF ASSISTED AUTOGENIC DRAINAGE IN SOUTH AFRICAN CHILDREN WITH CYSTIC FIBROSIS, A PILOT STUDY.

PACTR201501001016415

9.1 INTRODUCTION

ACTs have been shown to have positive effects on mucus clearance in children with CF (see section 7.4.6). However, studies are limited by the small sample sizes and, in many cases, subjective outcome measures. Furthermore, little evidence is available on the use of ACTs in children younger than eight years of age. Development of evidence-based information is a priority for this group of children. As no RCTs have been published on AD or AAD in children with CF (see Chapter 8), this chapter described a pilot study for an RCT on AAD in this population.

9.2 AIMS AND OBJECTIVES

This pragmatic pilot study aimed to assess the feasibility of an RCT protocol, comparing the effect of AAD to standard ACT as a home program in children between the age of one and eight years with CF on: number of hospitalisations and respiratory exacerbations; disease severity; preference by parents and children; HRQOL; weight-, height- and BMI-for-age z-score; lung function tests; and neurodevelopmental level.

The specific objectives of the RCT were to establish differences between the control and intervention group for the following outcome measures:

A) Primary outcome measures:
   - Number of hospitalisations, during one year.
   - Number of respiratory exacerbations, measured by antibiotic prescription during one year.
B) Secondary outcome measure:
   - Preference by the participants and parents/caregivers
   - Parental proxy HRQOL scores
   - Disease severity
   - Weight-, height- and BMI-for-age between start and end of study
   - Quarterly lung function measurements (if applicable)

- Mortality rate
- Relationship between respiratory symptoms and neurodevelopmental level.

9.3 METHODOLOGY

9.3.1 Study hypothesis

There will be no significant difference in number of hospitalisation and exacerbations during one year, HRQOL, lung function tests, preference and mortality rate between the control (standard ACT) and intervention (AAD) groups. It is hypothesised that AAD is as effective as other ACTs in the management of children with CF.

9.3.2 Study design

A pilot RCT, single blinded, pragmatic study design was used. RCTs are the gold standard in performing experimental research as this study design reduces bias (particularly allocation bias) and has high internal and external validity.[273] No RCTs on the use of AAD or AD in children with CF are available, therefore, the current study tested the feasibility of the proposed protocol, for which it is classified as a pilot study.[437] The term 'pragmatic' refers to the comparison between a control and intervention group within a real-life setting.[274] Blinding refers to masking participants and outcome assessors to group allocation. As the intervention in the current trial is a physiotherapy intervention, blinding of the participants is impossible, therefore, this study was classified as single blinded, blinding the outcome assessor and data analyst.[275] Treatment consisted of a taught home-program, executed by the parents during the one year follow up period. The study ran from 15 January 2015 until 30 September 2016. The CF Clinic was closed from mid-December until mid-January, but children still had access to CF care at the hospital in the event of infection, and were able to contact one of the investigators during this period if an adverse event occurred.

9.3.3 Research setting

The study was conducted at a 290-bedded, tertiary paediatric hospital. Patients from all over Africa, especially low income patients, are referred to this institution.[276] The hospital outpatients department runs a weekly multidisciplinary CF Clinic, which manages about 90 children with CF from birth to 18 years of age, resided in the Western Cape of South Africa (Prof. B. Morrow. Personal communication, 2013).

Children with CF who were being followed up at the research site during the study period and met the inclusion criteria were enrolled in this home-based research study. The parent(s) and/or caregiver(s) of the children were taught standard ACT or AAD during routine clinical visits, to be conducted at home, by the parent/caregiver on a bi-daily basis. The children returned to the CF clinic for follow up visits at the discretion of the physician.

9.3.4 Participants

Children diagnosed with CF between the age of one and eight years of age, who were followed up at the research site, were considered for inclusion in the study. Investigation of existing hospital records identified participants suitable to enrol in the study.

Children were included if they had a diagnosis of CF confirmed by sweat testing or genotype analysis. Children were excluded when they had the following:

- awaiting a lung transplant (this intervention is only conducted in severely affected patients, therefore, it might influence this study's outcome measure of disease severity),
- severe scoliosis or kyphosis (as this will influence lung volumes, impacting the ability to perform AAD as well as lung function testing),[438]
- osteoporosis (due to the increased risk of rib fractures during ACTs),[101]
- recent pneumothorax (to prevent a new episode as patients with CF are already at increased risk of recurrent pneumothorax. Furthermore, lung function tests, one of this study's outcome measures, are contraindicated in patients with pneumothorax),[439]
- thoracic or abdominal surgery in the preceding six months (as ACTs will increase pressure in the thorax and/or abdomen, influencing the surgical site),
- emphysema or active sarcoidosis.
- prematurely born at less than 30 weeks of gestation (see section 2.1, prematurity can negatively influence the respiratory system),
- on TB medication (to limit the impact of TB on the study's outcome measures),
- untreated asthma (the pathophysiology of asthma with wheezing and airway collapse, might influence ACTs),
- known to be non-compliant to physiotherapy treatment prior to recruitment (as these patients would not be compliant with either arm of the study)

Children who were not on a physiotherapy regime prior to the study were not eligible until they had received at least two months of standard ACT (to be able to compare standard ACT to AAD in the intervention arm of the study).

Children who had TB in the past but were not on TB medication during the time of the study and children who received asthma medication, such as β2-antagonists or steroids but with the disease under control, were considered for inclusion in the study.

Sample size: due to the small number of children available between the age of one and eight years of age with CF at the research site, this pragmatic pilot study aimed to enrol 30 children (estimated population at the research site) to be randomly assigned to the intervention (n=15) or control (n=15) group. The sample size was limited by the availability of suitable participants within the 18 month time frame of the study.

9.3.5 Outcome measures/instrumentation

After considering the benefits and downsides of common outcome measures for the assessment of ACTs as described in section 2.3.3, the following were included in the study:

9.3.5.1 Data collection forms

Self-designed standardised data collection forms were used throughout the study (Appendix 17). All pre-set data extraction forms were validated for content by an expert in the field of paediatric cardiopulmonary physiotherapy. On day of recruitment, a form regarding general information on the child was completed, using a combination of data from the medical file and oral history from the parent. If data were found to be missing from the medical notes, the necessary information was added to the file. At the end of the study period, another form regarding the participants' health status was completed by a blinded outcome assessor. These forms also included a summary of this study's outcome measures: neurodevelopmental screening, EQ-5D-Y, number of hospitalisations and exacerbations during the one year study period, weight and height.

9.3.5.2 Number of hospitalisation and exacerbations in one year

All exacerbations and hospitalisations were assessed by the attending physician, who remained blinded to group allocation throughout the study period. The physician reported any exacerbation or hospitalisation to the research team and the information was added to the patient's case report file. Number of exacerbations in one year was furthermore determined by days on antibiotic treatment.

9.3.5.3 Parental proxy-HRQOL scores

HRQOL was measured by the use of the EQ-5D-Y, completed by the parent/caregiver of the child, at the start and end of the study. The questionnaire is available in English, Afrikaans and isiXhosa. (Appendix 1).[440] This outcome measure has been validated in the South African context and found valid for children with CF.[162,163] As the parents conducted the interventions as a home-program, they were not blinded to group allocation. The questionnaire was completed at the CF clinic, either in the waiting room or the physiotherapy gym, while awaiting further testing or doctor's appointment.

9.3.5.4 Current clinical status

Current clinical status of the child was assessed by the CFCS, measured at start and end of the study by the attending physiotherapist (not blinded to group allocation). This outcome measure was not assessed by the blinded outcome assessor as the first section of the tool, subjective assessment, was mainly based on parental report who were not blinded to group allocation and increased the risk of unblinding the outcome assessor. A description of the CFCS score can be found in section 2.3.3 of this thesis.[174] This tool has been validated in a paediatric population.[172,174]

9.3.5.5 Neurodevelopmental test

The clearance of pulmonary secretions could improve lung function, resulting in the child being more active during the day, hence improve their motor development. Neurodevelopmental level was assessed by either the Peabody Developmental Motor Scale 2nd edition (PDMS) for children less than five years of age,[441,442] or the Movement Assessment Battery for Children 2nd edition (MABC) for children older than five years of age.[443,444] Both assessment tools are valid and reliable for assessing motor delay in children.[442,445] The MABC consists of eight items in three domains: manual dexterity, aiming and catching, and balance; and has normative values for UK and Dutch children between the ages of three and 16 years.[443,444] The PDMS assesses fine motor and gross motor skills in children younger than 83 months of age, based on five different domains.[441,442] The current study did not apply the visual-motor domain due to time constrains in administering the test. Unfortunately, no developmental screening tool has been validated in the South African context, and no normative values are available for South African children. However, the MABC has been used in research on developmental coordination disorder in South African children.[446–448] These studies applied the Dutch normative values, therefore, the

current study also used the Dutch values. The PDMS only reports American normative values, therefore these normative values were applied in the study. Testing was conducted by a blinded outcome assessor and took place at the physiotherapy gym.

9.3.5.6 Lung function tests (spirometry)

The quarterly spirometry lung function tests in children older than five years of age (FVC, FEV_1, PEF, FEF_{25-75}) were compared. Lung function tests, using the Microloop, were done at every clinic visit, as per standard practice. The best pulmonary function test scores, which adhered to the ATS/European Respiratory Society (ERS) criteria for each quarter was used for analysis. The ATS/ERS criteria for an acceptable blow entail the absence of: cough during the first second or at any time of the measurement when it interferes with the accuracy of the measure; an obstructive mouth piece; leakage; an extra breath during the measurement; an extrapolated volume more than 5% of FVC or 0.150 litre or an unsatisfactory start of the blow; early termination of the blow; or a hesitation or Valsalva manoeuvre. To have a valid lung function test, three acceptable blows should be registered, of which the largest two values for both the FEV_1 and FVC are within 0.150 litre of each other.[284] Lung function tests were conducted by the CF clinic's lung function technologist, who was blinded to group allocation and recorded the results of the test and the quality of the blow in the patients' medical files. These results were extracted from the medical files at the end of the study by a blinded outcome collector.

9.3.5.7 Heigth-, weight- and BMI-for age

Height-, weight- and BMI-for-age z-scores between the start and end of study were determined by weight (fully clothed, excluding winter jackets and shoes) and height (in standing, barefoot) of the participant at time of recruitment and end of study (measured by the assessment tools available at the CF clinic). These measurements are part of standard follow up at the clinic and were obtained by the clinic nurse, who remained blinded to group allocation throughout the study period. Z-scores were calculated by the use of the WHO AnthroPlus software (available from http://www.who.int/childgrowth/software/en/).

9.3.5.8 Preference

Patient's and/or parent's preference of participants in the intervention group was investigated during the second CF-clinic (approximately one to three months after initialising AAD), to prevent recall bias of standard ACT, using an adapted version (to reflect AAD intervention) of a standardized questionnaire designed by Jarad et al.,[449]which was

made available in three languages (English, Afrikaans and isiXhosa). This questionnaire was complete by the parents while waiting for further testing or the doctor appointment in the waiting area or physiotherapy gym. The forms were distributed and collected by the attending physiotherapist, to maintain blinding of the outcome assessor (only one arm of the study completed this questionnaire). At the end of the study, a semi-structured interview was conducted by the clinic social worker (blinded to group allocation) to assess preference and adherence to the study interventions (Appendix 14). The decision to involve the social worker to conduct these end of study interviews was made based on large discrepancies between information gathered by the research staff and other medical personnel. It was considered more objective when personnel not involved in the study collected this information as parents were made aware that this information remained completely anonymous The social worker was found most suitable as she had an established trust relationship with the knew the participants and their parents, and was used to conduct sensitive interviews related to her job.

9.3.5.9 Adherence

All parents and participants were asked to keep a record of their adherence to treatment by the use of a calendar and sticker system, to indicate when treatments took place. Parents were asked to record any adverse events on the backside of the calendar.

9.3.5.10 Mortality rate

Mortality rate was based on notes in the medical file, completed by a blinded medical personnel and extracted by a blinded data collector.

9.3.6 Interventions

It is ethically impossible to withhold treatment to children with CF. Therefore, standard treatment, consisting of conventional ACT (MPD, percussion and vibration) and the use of a PEP or Flutter device and/or components of the ACBT, was given to children in the control group. The intervention group received AAD (Table 9-1). There is no literature available on the use of AAD, but the use of AD in children with CF might be beneficial.[272]

Table 9-1. Airway clearance techniques performed during the CF trial

Intervention group	Control group
AAD	MPD + percussion and/or vibration
	(+) ACBT
	(+) PEP device
	(+) Flutter

Control group

The parents of the control group received training and education on bi-daily standard ACT, consisting of MPD (excluding the head-down position), percussions or vibrations. Older children were taught ACBT, and may have been given a Flutter or PEP device, to be done under parental supervision/guidance. The type of control intervention was based on the decision of the physician and physiotherapists of the research site, who follow the South African consensus statement guidelines (which state that "*physiotherapy does not just refer to airway clearance techniques. It involves education and practical application with regard to the holistic assessment and management of the patient both at the time of diagnosis and subsequently as an evolving process throughout the patient's life […] Airway clearance techniques form an integral part of the treatment of CF. This facilitates the loosening, mobilisation and clearance of the often thick and tenacious sputum to prevent airway obstruction and respiratory complications, and to maintain or improve pulmonary function and ventilation. Lung hygiene can be boring, time-consuming and tedious. Therefore it must be effective, efficient, specifically designed for each individual and constantly modified and adjusted. […] In infants, modified postural drainage, percussion and thoracic compressions remain widely used, but other techniques such as infant positive expiratory pressure therapy and assisted autogenic drainage along with physical activity have emerged as feasible alternatives […] From early on in life, components of the active airway clearance techniques should be encouraged[…]"*).[292] Training and education of all parents is standard practice during the CF clinic visits, reinforcing ACT and hopefully optimising compliance to therapy.

For standard ACT, the child was placed in the correct position, as determined by the physician/head physiotherapist and percussions and/or vibrations were performed on the chest wall. If PEP or Flutter was used, again a correct positioning of the child was needed

(usually in sitting) and correct usage of the device was assessed. If ACBT was used, a clear difference between relaxed breathing, thoracic expansion exercises and FET needed to be seen. During FET, the glottis needed to stay open; therefore it was important to teach the parent how to hear when the child closes his glottis.

Intervention group

For AAD, the child was placed in an upright sitting position on the lap of the parent or in front of the parent on a chair. The hands of the parent were placed on the chest of the child and the parent instructed to follow the breathing pattern of the child with his/her hands. When the child breaths out, the parent was told to give light pressure to keep the lung volume to this lower level. This was repeated until secretions are heard or felt. Then the parent should keep the same pressure on the child's chest so that the child keeps breathing on this level until the secretions were gone. If the secretions were moved more centrally, the parent slightly loosened his grip so that the child was able to breathe on a higher lung volume, where the secretions were again felt or heard. Finally the parent let go of the chest wall so that the child could take a deep breath and cough up the secretions.

Training of parents/caregivers

The parents received information on the disease and the importance of physiotherapy. Afterwards the therapist explained the principle(s) of the used technique(s) at the appropriate language level, he/she demonstrated the technique(s) and then the parents showed the therapist how they would perform the technique. The therapist made corrections to the parent's handling if necessary. The parents were allowed to ask questions during the entire teaching session and afterwards time was given to reflect on the handling and asking questions. Finally the parents were asked to demonstrate the technique without feedback from the physiotherapist to make sure they understood it entirely. When the performance was inadequate, the physiotherapist gave more feedback to make sure the parents knew how to perform the treatment. Only when an adequate level of performance (without feedback) was achieved by the parents, they were included in the study.[450–452]

The level of teaching was adapted to the level of education of the parents. The therapy was written down for the parents, with diagrams where necessary. Also the parents were told that they could contact the physiotherapist (BM) when they were not sure how to perform the technique correctly.

Frequency and duration of ACT

Therapy, standard ACT or AAD, was carried out bi-daily, duration depending on the child's age and tolerability (parents were taught how to identify signs of respiratory distress and hypoxaemia and infection). The parents were asked to carry out the intervention every day around the same time, once in the morning and once in the afternoon or evening. This was a one year follow up study.

9.3.7 Procedure

9.3.7.1 Approval

Permission to carry out the study was granted by the Faculty of Health Sciences HREC, University of Cape Town and approval from the medical superintendent at the research site was obtained (Appendix 15). I recruited participants during the weekly CF-clinic, which takes place on Tuesday afternoons. Eligibility of children was determined by screening the patients' medical files or on physician's recommendation. Written informed consent was obtained from the parent(s) and assent was obtained from children older than five years of age (Appendix 16). These forms were available in English, Afrikaans and isiXhosa, and interpreters were used as required.

9.3.7.2 Recruitment

After obtaining permission from the parents (and children), the recruitment data collection form was completed, the CFCS score was assessed by clinic physiotherapist, and the EQ-5D-Y was completed by the parents. Neurodevelopmental tests, done by myself, and lung function tests, performed by the lung function technologist, were then performed. Afterwards the child was randomly assigned to the intervention or control group. Simple randomisation was done prior to commencement of the study, by the use of a computer generated list of random numbers, which randomly assigned the participants to one of two parallel groups (randomisation ratio 1:1). Sealed, opaque, sequentially numbered envelopes were prepared, to conceal group allocation. Once a child was enrolled, the clinic physiotherapist would open an envelope to reveal group allocation. The outcome assessor and data analyst remained blinded throughtout the study period. Patient's information was de-identified and coded by the use of coded computer files and/or coded paper files held in sealed envelopes.

Parents who did not consent on the day of recruitment, preferring to have additional time to consider participation, received the researchers' contact details to obtain more information when required as well as to provide the opportunity for telephonic consent. If the researchers did not get a response prior to the next follow up visit approximately three months later, parents were approached during this follow up appointment.'

Once all this information was obtained and the clinic physiotherapist knew group allocation, this physiotherapist taught the parents how to perform the necessary technique(s) as indicated above.

9.3.7.3 During the study period

Parents and participants in the intervention group were asked to complete a questionnaire regarding therapy preference at the first follow-up visit. At each CF-clinic visit, the parents were asked to hand in their calendar so data could be stored and checked if adherence to treatment was appropriate. If adherence and compliance was poor, the parent was asked to explain why. Concerns raised by the parents were discussed and the importance of ACT was emphasised.

The child was followed up at the CF clinic at the discretion of the physician. During each follow-up visit in the CF-clinic, lung function tests were performed by the lung function technologist. The parents of both control and intervention group were then seen by the physiotherapist and asked to demonstrate the physiotherapy technique(s) to ensure they were well executed and faulty implementation could be corrected. Parents could also ask for more explanation or extra demonstrations when necessary. If the child had an exacerbation, this was reported by the pulmonologist and the information was added to the patient's case report file.

9.3.7.4 End of study

After one year of follow up, lung function tests were repeated and the parents were asked to complete the EQ-5D-Y again.[161,162,440] The PDMS or MABC were used to reassess the neurodevelopment of the children and the CFCS was measured again. Further, the CF clinic's social worker, who was blinded to group allocation, conducted a subjective semi-structured interview with the parent(s)/caregiver(s) regarding physiotherapy management during the study period and the likes and dislikes of the different techniques used during the study period.

9.3.8 Data-capturing and management

During recruitment, the researcher collected general information by the use of a general information sheet (Appendix 17). The child's case report file contained a form with medical information, including weight, height and the results on the PDMS or the MABC. A calendar was used to record the adherence/compliance to therapy, and any adverse events. This data was also used to analyse safety of the technique. All data were de-identified and coded by the use of coded computer files and/or coded paper files.

9.3.9 Data-analysis

All data were entered into an Excel spread sheet and analysed with Statistica (Version 12, StatSoft Inc, Tulsa USA). The data were tested for normality with the Lilliefors test. As the majority of data were skewed and the sample size was small, non-parametric tests were performed. Comparison between the control group and intervention groups on dichotomous data were done using the chi square test and Fisher exact or Yates correction; and numeric outcome parameters were analysed using the Mann-Whitney U test. Effect size was calculated for outcome measures which showed, on initial univariate analysis, to have either a significant difference or a trend towards significant between-groups differences. For parametric data, the Cohen's d value was calculated.[283] For non-parametric data, the r value was calculated with the formula $r= z/\sqrt{N}$.[282] As the z value is sample size dependent, the r value will eliminate this sample size effect.[282] The r value was converted into a Cohen's d value by using the formula $d= 2r/\sqrt{(1-r^2)}$.[282] Interpretation of the effect size was based on Cohen's guidelines for small (d= 0.2), medium (d= 0.5) and large (d= 0.8) effect sizes.[283]

A regression analysis was planned, to compare the relationship between the different variables (use of simple, logistic and forward stepwise analysis), however, due to the small sample size this analysis was not completed. An intention-to-treat analysis was performed. Dependent variables were the different outcome measures as indicated above. The independent variables were age, gender, HIV-infected or –exposed, history of TB, *Pseudomonas aeruginosa* or *Staph. aureus* colonisation, and pancreatic sufficient/insufficient. Chi square tests were used to calculate the patient's or parent's preference.

9.4 AMENDMENTS

In the original protocol, parents and children were asked to complete a diary, indicating when, how long, and which ACTs were given; and what the reason was for terminating the intervention. However, due to the lack of compliance to this diary, evident at the first follow up visit, changes were made. The parents and patients were then asked to adhere to a monthly calendar and sticker system. For each completed treatment, the child was allowed to place a sticker on the calendar, both of which I provided.

Furthermore, an end of study interview was added to the protocol. This interview was performed by the social worker employed at the CF clinic, who was blinded to group allocation. The interview answers were written down by the social worker. No identifying information was available on the documents, in the hope that parents and patients would answer honestly. It was emphasised that the information provided to the social worker would be used for research purposes only and not for patient management.

9.5 RESULTS

9.5.1 Participants

A total of 36 children were screened. Nineteen children were excluded prior to enrolment due to various reasons (see Figure 9-1). One child, allocated to the control group, was excluded post-enrolment as the diagnosis of CF was questioned by the attending physician. Therefore, 16 participants were included in the study (median 5.8 years, IQR 4.3-6.3), of which seven were in the intervention group and nine in the control group. All participants completed the one year clinical trial. None of the participants were lost to follow up. Baseline characteristics of the participants were similar between groups and can be found in Table 9-2. The median duration of enrolment in the study was 359.0 days (IQR 326.0-359.0) for the control group and 360.0 days (IQR 351.0-366.0) for the intervention group ($z= 1.3$, $p= 0.186$).

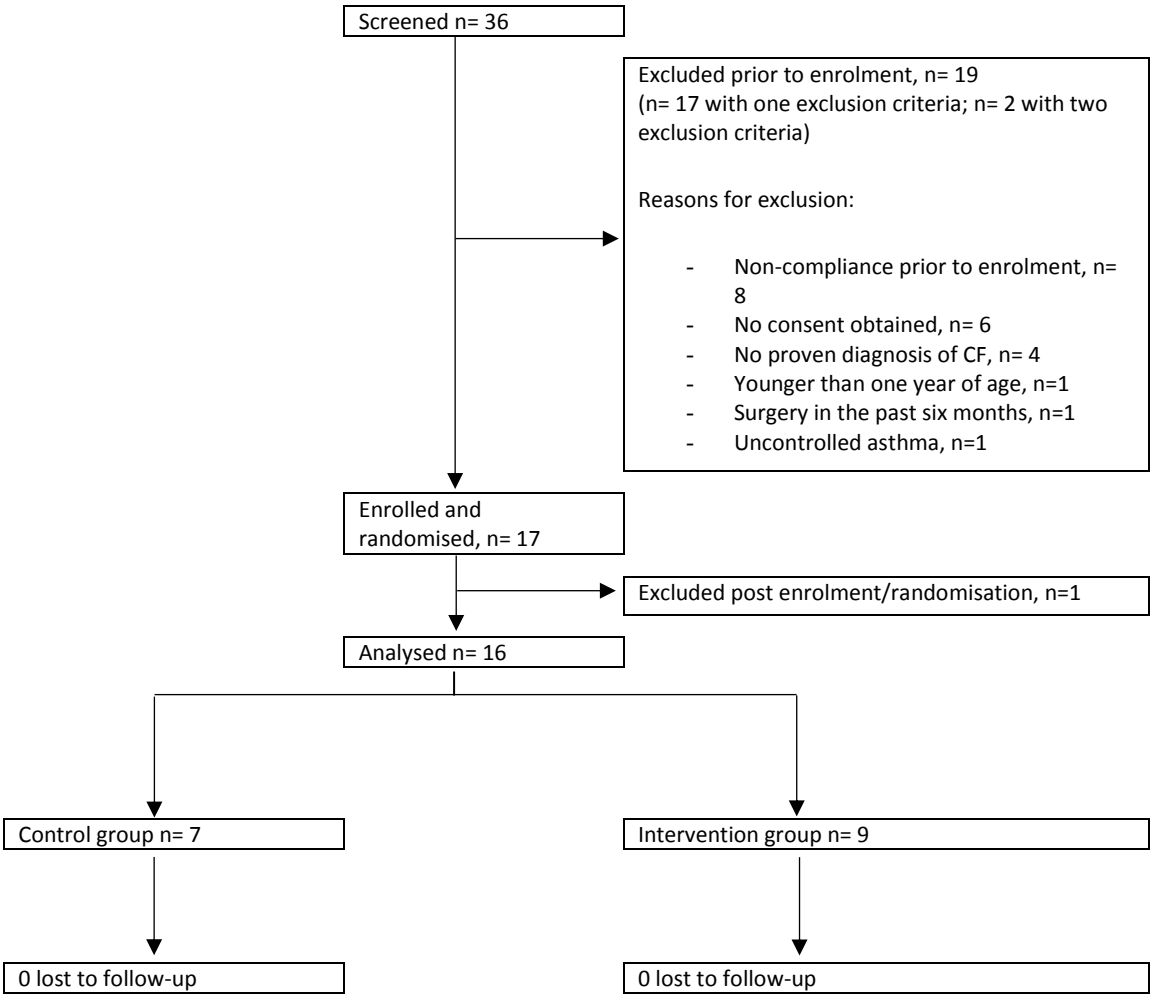


Figure 9-1. Study flow diagram CF pilot study

Table 9-2. Baseline characteristics of participants

Characteristic	Control group, n= 7	Intervention group, n= 9	Statistical value	p-value
Gender, Male (n)	4	5	Fisher exact	p= 0.671
Age (*years*), median (IQR)	5.7 (3.0-6.0)	5.8 (5.5-6.6)	Z= -1.1	p= 0.266
Age diagnosis (*months*), median (IQR)	3.0 (0.0-6.0)	3.0 (1.0-6.0)	Z= 0.0	p= 1.000
Age start physio (*months*), median (IQR)	4.0 (3.0-6.0)	6.0 (2.5-10.5)	Z= -0.6	p= 0.563
Gestation **- Term (n)** **- Preterm (n)** **- Unknown (n)**	 7 0 0	 7 1 1	Yates X^2= 0.1	p= 0.964
History of TB (n)	0	1	Fisher exact	p= 0.563
Asthma (n)	1	3	Fisher exact	p= 0.392
Pancreas insufficient (n)	7	9	X^2= 0.0	P= 1.000
HIV status **- Negative (n)** **- Exposed (n)** **- Positive (n)** **- Unknown (n)**	 6 1 0 0	 7 1 0 1	Yates X^2= 0.3	p= 0.958
Genotype - **ΔF508 (n)** **ΔF508/E585X** **ΔF508/G542X** **ΔF508 homozygous** **ΔF508/unknown** **ΔF508/394delTT** - **3120 (n)** **3120/HG A homozygous** **3120/G A homozygous** **3120/G A heterozygous** - **Unknown (n)**	 5 0 0 3 1 1 0 0 0 0 2	 6 1 1 3 1 0 3 1 1 1 0	Yates X^2= 1.7	p= 0.422
Colonisation/ infection **- St. Aureus (n)** **- MRSA (n)** **- Pseudomonas (n)** **- None (n)**	 4 1 0 2	 8 0 1 0	Yates X^2= 1.0	p= 0.797

9.5.2 Results between groups at 12 months

No significant differences were seen for the primary outcome measures, number of hospitalisations and number of exacerbations, between the intervention and control group (Table 9-3). Nor were there any significant differences between the groups for the other outcome measures (Table 9-3, Table 9-4 and Table 9-5). Although the outcome measures 'number of exacerbations during one year' and 'days on antibiotic therapy during one year' were not significantly different between both groups, the IQRs were only marginally overlapping. Therefore, the effect size was calculated, revealing a medium effect size for the outcome measure 'number of exacerbations during one year' (d= 0.55), with fewer exacerbation during one year in the intervention group and a small to medium effect size for 'days on antibiotic therapy during one year'(d= 0.48), for fewer days on antibiotic therapy in the intervention group.

Due to the small sample of participants performing acceptable lung function tests, based on the quality criteria set by the ATS/ERS,[284] the data of only five participants (of which three were allocated to the intervention group) could be presented in this thesis. Therefore, no statistical analyses were performed for this outcome measure. Data are presented in Figure 9-2 and Figure 9-3. One participant had a clear decrease in both FEV_1 and FVC between the start of the study and lung functions performed three months later; and another participant improved greatly after three months of enrolment in the study. Both participants were enrolled in the intervention arm of the study. The lung function tests of the other participants did not show large changes over time.

Furthermore, only four participants were tested with the PDMS-2, two in each arm of the study. Again no statistical analyses were therefore possible. Data are presented in Figure 9-4. The histograms do not reveal clear differences between the two groups.

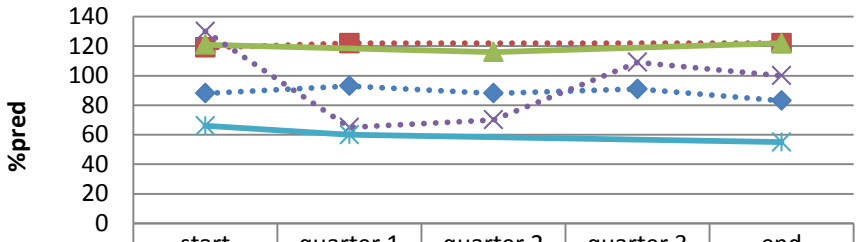
All participants were alive at the end of the study period (100% survival rate).

Table 9-3. Primary outcome measures, presented as median (IQR), between the control and intervention group.

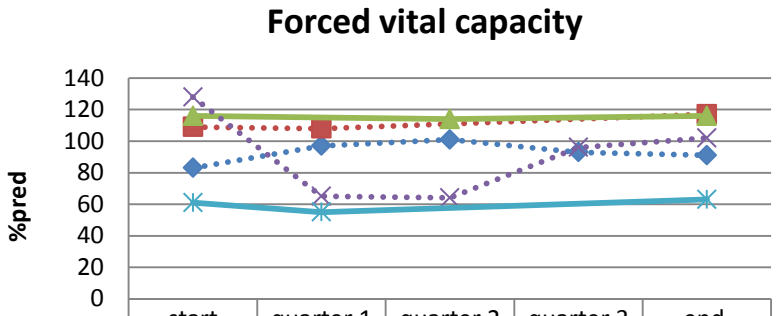
Outcome measure	Control (n=7)	Intervention (n=9)	Statistics (z-value)	p-value
Number of hospitalisations	0.0 (0.0-1.0)	0.0 (0.0-0.0)	-0.3	0.791
Days of hospitalisation	0.0 (0.0-7.0)	0.0 (0.0-7.0)	-0.2	0.832
Number of exacerbations	2.0 (1.0-3.0)	1.0 (1.0-1.0)	-1.1	0.290
Days on antibiotic therapy	20.0 (10.0-97.0)	10.0 (5.0-15.0) (n= 8)	-0.9	0.355

Table 9-4. Movement assessment battery for children 2nd edition results presented as median (IQR)

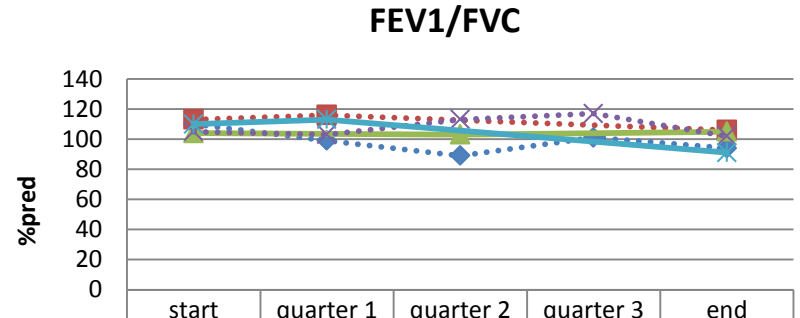
Motor function outcome	Control		Intervention		Change over time: median differences (95%CI)		Between group at baseline and end of study		Within group from baseline to end	
	Baseline n= 5	End n= 5	Baseline n= 7	End n= 7	Control	Intervention	Baseline	End	Control	Intervention
MABC Fine motor %	37.0 (5.0-37.0)	37.0 (25.0-50.0)	50.0 (0.1-98.0)	50.0 (1.0-91.0)	0.0 (-60.0-60.0)	0.0 (-55.6-55.6)	z= 0.4 p= 0.685	z= 0.7 p= 0.516	z= 0.1 p= 0.893	z= 0.1 p= 0.917
MABC Catching and throwing %	16.0 (16.0-63.0)	25.0 (9.0-37.0)	37.0 (25.0-75.0)	16.0 (5.0-50.0)	9.0 (-46.5-64.5)	-21.0 (-66.4,24.4)	z= 0.3 p= 0.745	z= 0.0 p= 1.000	z= 0.7 p= 0.500	z= 0.4 p= 0.675
MABC Balance %	5.0 (5.0-16.0)	25.0 (5.0-25.0)	9.0 (0.5-75.0)	5.0 (0.5-75.0)	20.0 (-21.2-61.2)	-4.0 (-58.0-50.0)	z= 0.2 p= 0.808	z= -0.6 p= 0.570	z= 0.1 p= 0.893	z= 0.5 p= 0.600
MABC Total %	9.0 (5.0-37.0)	16.0 (16.0-16.0)	25.0 (0.5-95.0)	16.0 (0.1-91.0)	7.0 (-43.5-57.5)	-9.0 (-64.3-46.3)	z= 0.2 p= 0.808	z= 0.0 p= 1.000	z= 0.7 p= 0.500	z= 0.9 p= 0.345



	start	quarter 1	quarter 2	quarter 3	end
participant 1	88	93	88	91	83
participant 6	119	122			122
participant 7	121		116		122
participant 8	130	65	70	109	100
participant 11	66	60			55



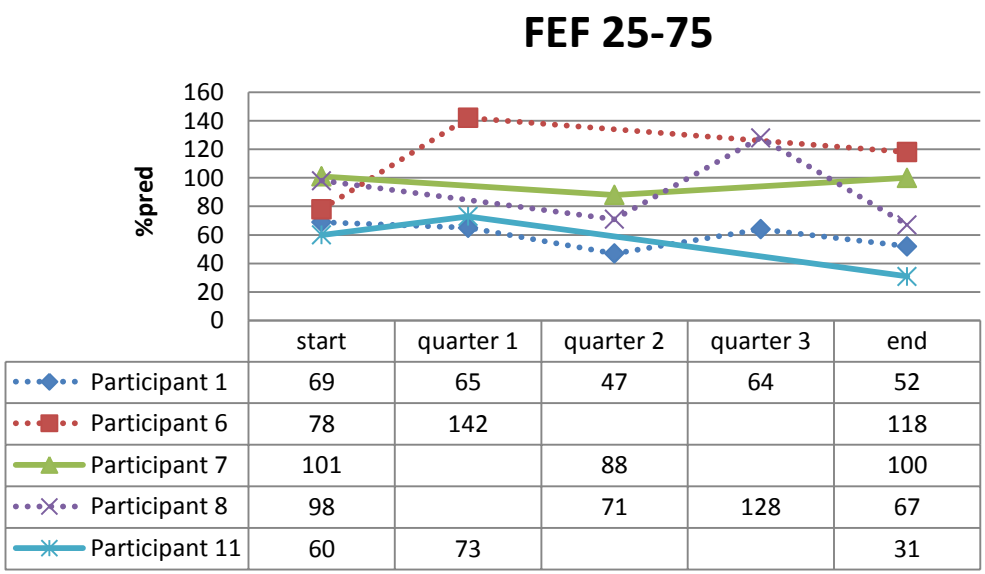
	start	quarter 1	quarter 2	quarter 3	end
Participant 1	83	97	101	93	91
Participant 6	109	108			117
Participant 7	116		114		116
Participant 8	128	65	64	96	102
Participant 11	61	55			63



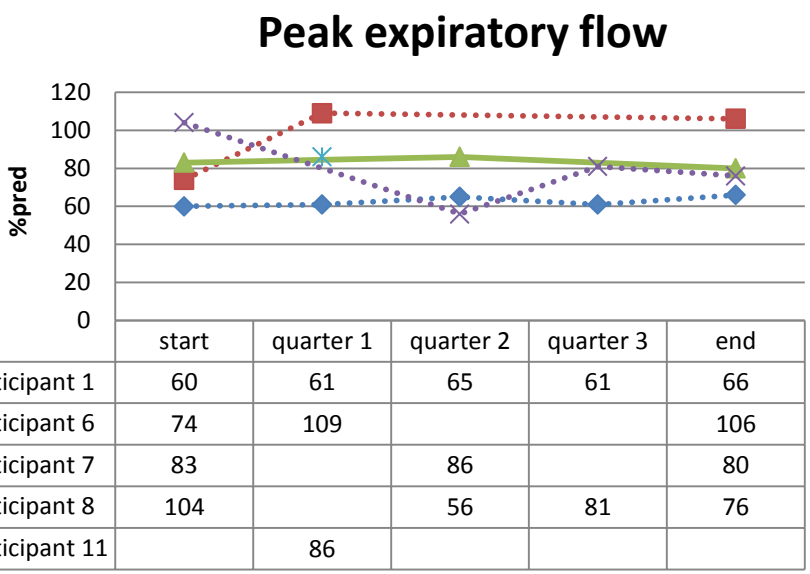
	start	quarter 1	quarter 2	quarter 3	end
Participant 1	110	99	89	101	94
Participant 6	113	116			106
Participant 7	104		103		105
Participant 8	105	103	113	117	102
Participant 11	110	113			91

Figure 9-2. FEV1, FVC and FEV1/FVC presented as %predicted of the five participants who met the quality criteria for lung function tests.

Dotted lines represent the intervention group and solid lines represent the control group.



	start	quarter 1	quarter 2	quarter 3	end
Participant 1	69	65	47	64	52
Participant 6	78	142			118
Participant 7	101		88		100
Participant 8	98		71	128	67
Participant 11	60	73			31



	start	quarter 1	quarter 2	quarter 3	end
Participant 1	60	61	65	61	66
Participant 6	74	109			106
Participant 7	83		86		80
Participant 8	104		56	81	76
Participant 11		86			

Figure 9-3. FEF25-75 and PEF presented as %predicted of the five participants who met the quality criteria for lung function tests.

Dotted lines represent the intervention group and solid lines represent the control group.

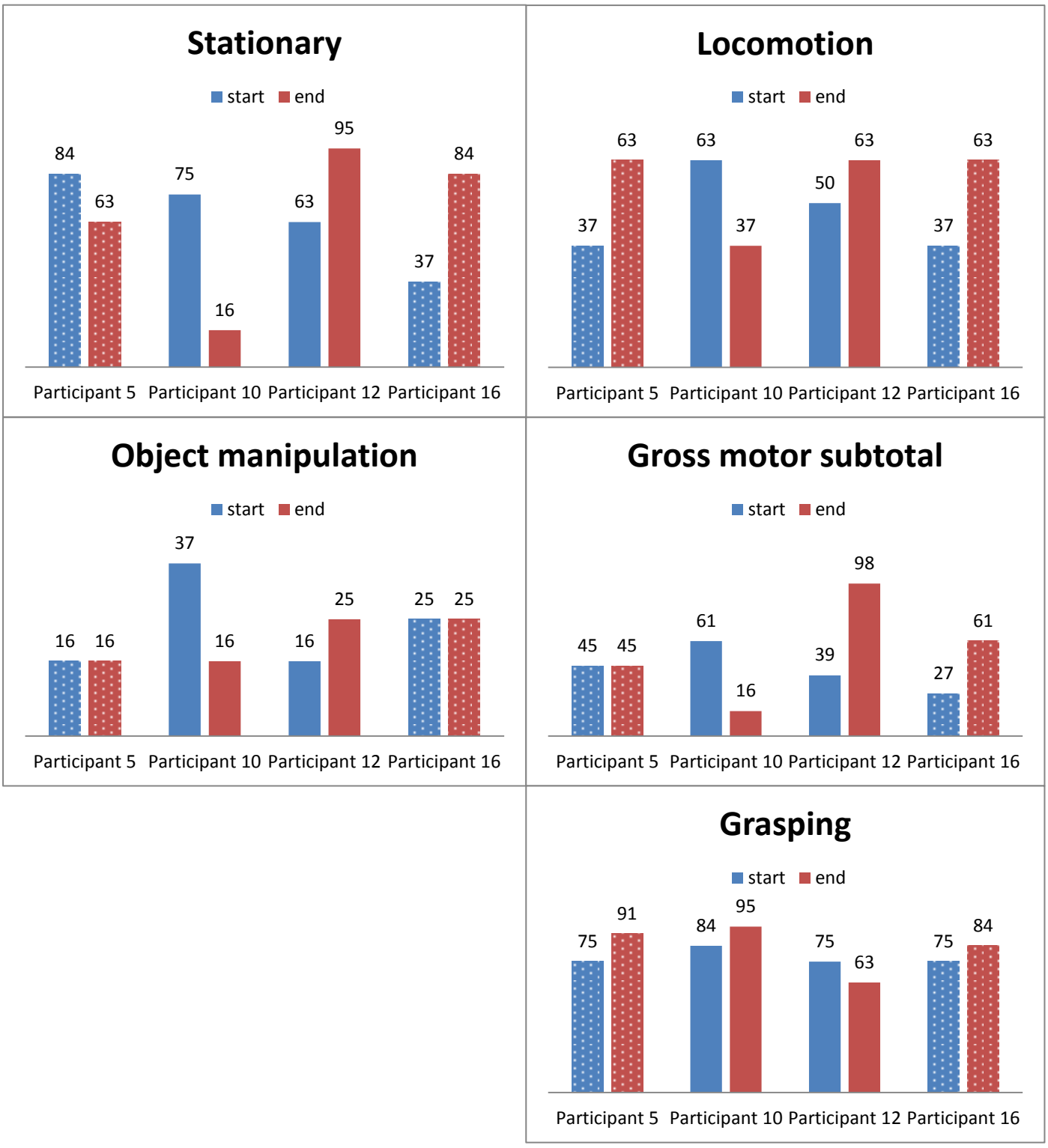


Figure 9-4. Peabody Developmental Motor Scale 2nd edition results, presented as percentage.

Dotted bars represent the participants allocated to the intervention group and solid bars represent the control group.

Table 9-5. Other outcome measures between and within the control and intervention group, presented as median (IQR).

Outcome measure	Control		Intervention		Change over time: Median differences (95%CI)		Between group at baseline and end of study		Within group from baseline to end of study	
	Baseline (n= 7)	End (n= 7)	Baseline (n= 9)	End (n= 9)	Control	Intervention	Baseline	End	Control	Intervention
CFCS subjective	8.0 (7.0-11.0)	8.0 (6.0-12.0)	11.0 (10.0-12.0)	8.0 (6.0-11.0)	0.0 (-4.2-4.2)	-3.0 (-6.0-0.0)	z= 7.8 p= 0.072	z= 0.2 p= 0.832	z= 0.3 p= 0.753	z= 1.7 p= 0.091
CFCS objective	6.0 (6.0-8.0)	7.0 (5.0-8.0)	6.0 (6.0-7.0)	6.0 (5.0-6.0)	1.0 (-1.9-3.9)	0.0 (-1.3-1.3)	z= 0.0 p= 1.000	z= -1.0 p= 0.341	z= 0.3 p= 0.787	z= 0.8 p= 0.418
CFCS total	13.0 (13.0-19.0)	14.0 (11.0-22.0)	17.0 (17.0-18.0)	14.0 (12.0-16.0)	1.0 (-5.1-7.1)	-3.0 (-6.7-0.7)	z= 1.3 p= 0.204	z= 0.1 p= 0.958	z= 0.0 p= 1.000	z= 1.7 p= 0.093
EQ-5D-Y VAS score	91.0 (90.0-99.0)	95.0 (75.0-100.0)	85.0 (80.0-95.0)	92.5 (90.0-10.00) n= 6	4.0 (-19.6-27.6)	7.5 (-6.4-21.4)	z= -1.0 p= 0.315	z= 0.4 p= 0.721	z= 0.1 p= 0.917	z= 1.8 p= 0.068
BMI-for-age z-score	0.3 (-1.0-2.3)	-0.7 (-1.4-1.8)	0.1 (-0.2-0.4)	-0.3 (-0.5-0.1)	-1.0 (-3.9-1.95)	-0.4 (-0.9-0.2)	z= -0.3 p= 0.751	z= 0.4 p= 0.672	z= 0.3 p= 0.735	z= 1.5 p= 0.139
Weight-for-age z-score	-1.2 (-1.5-0.4)	-1.0 (-1.5-1.5)	-1.0 (-1.1-(-0.5))	-0.8 (-1.4-(-0.1))	0.2 (-2.7-3.1)	0.2 (-1.0-1.4)	z= 0.2 p= 0.832	z= 0.0 p= 1.000	z= 0.5 p= 0.612	z= 0.3 p= 0.767
Height-for-age z-score	-0.6 (-1.9-0.2)	-0.3 (-1.6-(-0.1))	-1.3 (-1.5-(-0.8))	-1.0 (-1.6-0.2)	0.3 (-2.-3.2)	0.3 (-1.0-1.6)	z= -0.6 p= 0.525	z= -0.1 p= 0.916	z= 1.2 p= 0.237	z= 1.1 p= 0.260

Table 9-6. EQ-5D-Y dimension

EQ-5D-Y dimension		Control		Intervention	
	n/ntotal	Baseline	End	Baseline	End
Mobility	No problems	7/7	7/7	9/9	6/6
Looking after myself	No problems	6/7	5/7	6/9	3/6
	Some problems	1/7	2/7	3/9	3/6
Doing usual activities	No problems	7/7	6/7	7/9	4/6
	Some problems	0/7	1/7	2/9	2/6
Having pain/discomfort	No problems	5/7	5/7	7/9	6/6
	Some problems	2/7	2/7	2/9	0/6
Feeling worried/sad/unhappy	No problems	7/7	5/7	8/9	5/6
	Some problems	0/7	2/7	1/9	1/6

In the intervention group, the number of children who had some problems with the EQ-5D-Y dimensions remained the same or decreased (for the dimension 'having pain/discomfort') throughout the study. Whereas in the control group a slight increase in children with some problems on the dimensions 'looking after myself', 'doing usual activities' and 'feeling worried/sad/unhappy' was seen (Table 9-6).

9.5.3 Results within groups

Within the control group, no significant changes were seen between baseline and end of study for any of the outcome measures (Table 9-4 and Table 9-5). In the intervention group, a trend towards an increase in the EQ-5D-Y visual analogue scale score (p=0.067), and an improvement in CFCS subjective subtotal (p= 0.091) and total score (p= 0.093) were observed. Large effect sizes for these outcome measures were observed in favour of the intervention group (d= 1.07, d= 0.87, and d= 0.86 respectively).

9.5.4 Subjective questionnaires

9.5.4.1 After one month

Parents and children were asked to complete a written questionnaire with regards to their experience and preference of AAD compared to their previous ACT regime (prior to the study). Seven of the nine participants in the intervention group completed the questionnaire. Results are presented in Table 9-7.

Table 9-7. Experience and preference of the intervention group after one month. Table should be read as follows: "AAD is … than my previous physiotherapy regime".

Participant	Breathlessness	Secretion clearance	Relaxation	Overall experience	Preference
1	Unanswered	Similar	Slightly better	Similar	Previous ACTs
2	Much better	Slightly worse	Slightly worse	Similar	Previous ACTs
3	Similar	Similar	Similar	Similar	Previous ACTs
4	Similar	Slightly better	Similar	Similar	AAD
5	Similar	Slightly better	Slightly worse	Similar	Both techniques
6	Similar	Slightly worse	Slightly worse	Slightly worse	Previous ACTs
7	Similar	Much better	Slightly better	Much better	AAD

Although AAD was not experienced as worse than the previously used ACTs for most aspects of the questionnaire, four of the seven participants would prefer to return to their previously used ACT. The two participants who would prefer to use AAD instead of their previous ACT indicated that AAD was similar or better on all aspects of the questionnaire. One participant would prefer to combine AAD with their previous ACT.

9.5.4.2 End of study interview

An overview of the used techniques, frequency and duration is presented in Table 9-8. Furthermore, likes and dislikes per technique are listed in Table 9-9.

It is clear that, for both groups, percussions and active play were the most preferred techniques during the study period, as they were performed most often, had most likes and least dislikes.

Intervention group

Two participants were not interviewed at the end of the study, as their primary caregivers were not present at the visit. Telephonic follow up calls were inappropriate due to social reasons. Therefore, we can only present the information on seven of the nine participants in the intervention group.

Four of the seven participants used AAD during the trial. The other three did not indicate they used AAD throughout the study period. Further, each of the following techniques was used by one participant: Flutter, vibrations, ACBT, and blowing water; and five of the

participants used additional percussions and active play. Frequency and duration for each technique are presented in Table 9-8.

Non-adherence to ACTs in the intervention group was because the treatment regime was time consuming (n=3) and the child resisted treatment (n=2). One participant indicated that there was no reason for non-adherence. And one participant declined to answer this question.

Control group

In the control group, all participants conducted percussions, two did Flutter, two performed vibrations and one did ACBT. Further, six were engaged in active play/exercise during the day. See Table 9-8 for an overview of frequency and duration of treatment techniques.

Reasons for non-adherence in this group were: treatment regime is time consuming (n=3), child is not productive/ill therefore no treatment was given (n=2), child vomits after treatment (n=1). Three participants did not provide a reason for non-adherence.

Table 9-8. ACTs used during the study period, providing frequency and duration per technique

Technique	Intervention (n=7)			Control (n= 7)		
	n	Frequency	Median time, in minutes, per session (IQR)	n	Frequency	Median time, in minutes, per session (IQR)
AAD	4	Daily (n=3) Not daily (n=1)	7.0 (1.0-15.0)	0	-	-
Flutter	1	Daily	10.0	2	Daily (n=1) 3x/w (n=1)	3.0 (2.0-15.0)
Percussions	5	Daily (n=1) Bidaily (n=1) 3x/d (n=1) Not daily (n=1) When sick (n=1)	10.0 (5.0-16.0) (n=4)	7	Daily (n=1) Bidaily (n=3) 3x/w (n=1) 4-5x/w (n=1) When sick (n=1)	15.0 (5.0-15.0)
Vibrations	1	Not daily	N/A	2	Bidaily	2.0 (2.0-2.0)
ACBT	1	Not daily	N/A	1	Daily	1.0
Active play	5	Daily	105.0 (45.0-180.0) (n=4)	6	Daily	75.0 (60.0-75.0)
Other: blowing water (bubble PEP)	1	Bidaily	N/A	0	-	-

Table 9-9. Likes and dislikes for each ACT used during the study period.

Technique	Likes	Dislikes
AAD	- It works (n=2) - Easy (n=1) - Active technique (n=1)	- Difficult technique (n=2): didn't get it right (n=1) + unsure when to stop (n=1) - Not easy to distract the child (n=1) - Less cough production (n=1) - Child tires easily (n=1) - Child needs to actively cooperate (n=1) - Nothing (n=1)
Flutter	- It works (n=2) - Easy (n=1) - Feel the vibration/feel that is does something (n=1)	- Feels like a duty (n=1) - Child vomits after the technique, especially in the morning (n=1) - Nothing (n=1)
Percussions	- Easy (n=6) - It works (n=2) - Routine/been doing it from the beginning (n=2) - Parent feels what he/she is doing (n=1) - Bonding and adaptable (n=1) - Cough augmentation (n=1) - Sleeps better (n=1) - Relaxing (n=1)	- Nothing (n=6) - Time consuming (n=2) - Scared to hurt the child (n=2) - Feels like a duty (n=1) - Needs to convince child (n=2) - Painful hands (n=1)
Vibrations	- Effective (n=1) - Easy (n=1)	- Time consuming (n=1) - Feels like a duty (n=1) - Not sure how to perform technique (n=1)
ACBT	- It works (n=1) - Easy to motivate the child (n=1)	- Feels like a duty (n=1) - Nothing (n=1)
Active play	- Active (n=3) - Parents are happy when child tires (n=2) - Fun (n=1) - Gets out frustrations (n=1) - No extra effort (n=1) - Independent (n=1) - Clears secretions (n=1) - Keeps child busy (n=1) - Parent can see that the child is healthy (n=1) - Child can be him/herself (n=1)	- Nothing (n=5) - Needs to observe the child (n=1) - Fear of dehydration (n=1) - Child destroys furniture (n=1)
Blowing water (bubble PEP)	- It works (n=1)	- None (n=1)

9.6 DISCUSSION

This study did not reveal any significant differences between the intervention (AAD) and control group (standard ACT) for any of its primary and secondary outcome measures. It did however, give some indication of positive trends in favour of the intervention group. In addition, interesting insights were gained with regard to the outcome measures and the methodology, which can be used to inform the development of protocols which could entail multi-centre implementation.

A small to medium effect of AAD on required antibiotic therapy during one year and a medium effect of AAD on number of exacerbations during one year was seen. Due to the small sample of participants who were able to perform good quality lung function tests, no comparison could be made between or within both groups. Analysis of the raw data did not reveal a clear difference between the intervention and control group. Similarly, no analyses could be performed for the neurodevelopmental outcome measure PDMS-2 due to the limited number of children younger than five years of age. Again, narrative analyses did not reveal a clear difference between both groups. A tendency and large effect sizes for improvement in CFCS subjective and total scores were observed in the intervention group. Although a trend towards a better HRQOL was found within the intervention group, based on the EQ-5D-Y visual analogue scale (with a large effect size) and the EQ-5D-Y dimensions; AAD was not preferred over standard ACT. An important finding of this study, although this was not one of the study's intended outcome measures, was the finding of poor adherence to the study protocol in the intervention arm of the study, as well as poor general adherence to ACT regimens.

As no literature is available on AAD in patients with CF, no comparison can be made with the current study's results. However, several studies have been published on the use of AD in children with CF.[84,121,124,270–272,434] Only one study was purely focused on a paediatric population and compared AD with PD and percussions in a long term randomised cross-over study.[272] The other studies were all randomised cross-over studies, performed in a mixed paediatric-adult CF population. Two of which compared AD with flutter;[124,434] one each compared AD with PD and clapping,[84]ACBT and PD,[270] PEP,[271] and high pressure PEP.[121] For a complete overview of these studies, refer to Chapter 8.

The current study did not find any differences between AAD and standard ACT for the primary outcome measure 'number of hospitalisations in one year'. This is in line with the

results found in a study by McIlwaine et al.[272] This outcome measure might be confounded by other non-pulmonary related variables, resulting in a low hospitalisation rate.The other primary outcome measure of the current study, number of exacerbations during one year, has not been reported in any of the studies on AD in children with CF. However, the study by McIlwaine et al. did mention that more hospitalisations for pulmonary exacerbations were required for participants in the PD with percussions arm of the study, compared to the AD arm.[272] The current study found a small to medium effect size of fewer days on antibiotic therapy in the intervention group. This could suggest that AAD might clear infectious secretions from the lungs, therefore, influencing antibiotic needs. This requires confirmation in controlled trials with larger sample sizes.

Only four of the included participants were hospitalised during the study period, however, 13 participants did experience a pulmonary exacerbation during the study period. Hence 'number of exacerbations' might be a more appropriate outcome measure than 'number of hospitalisations in one year'. Furthermore, it would appear that AAD might have an impact on antibiotic use; therefore 'number of exacerbations' and 'days on antibiotic therapy' might be more responsive measures to use as primary outcomes in future studies.

Lung function testing is often used as an outcome measure for patients with CF, to objectively measure lung disease progression and to guide therapy.[137,149] It is therefore important to take into consideration the quality of the blows, to prevent other variables to interfere with the outcome. Unfortunately in the current study, several participants had at least one lung function test (at start or end of the study) that was of unsatisfactory quality, for which the test scores had to be removed from the analyses. The remaining five participants' results were analysed narratively. One participant had a clear decrease in lung function results after three months of enrolment in the study, which might be attributed to a *Pseudomonas aeruginosa* infection requiring eradication regimen at that time; and one participant improved greatly after three months of enrolment in the study, which might be due to the eradication of *Staph. aureus* which was present at enrolment of the study. No other clear differences between or within the groups were observed. This again is in line with findings of several other studies. FEV_1 was not found significantly different between the intervention and control group in four studies.[84,124,270,272] FVC was investigated in five studies, of which four did not find significant differences between groups.[84,124,270,272] In a study by Pfleger et al., a better % predicted FVC was found for the AD arm of the study when compared to AD followed by high pressure PEP. However, no differences were found

for FVC when AD was compared to high pressure PEP, or high pressure PEP followed by AD in this study.[121] Two studies included FEF_{25-75} as an outcome measure, showing no significant differences between the control and intervention groups.[270,272] None of the studies included PEF as their outcome measures. Therefore, no comparisons of the current study's PEF results can be made. For future research, it is of utmost importance that the quality of the lung function tests is on par with the pre-set criteria of the ATS/ERS. Otherwise, comparison between and within groups will be impossible as the lung function tests could have been influenced by other variables than the participant's lung function. The underlying reason for the current study's invalid measurements is unclear, as this outcome measure was evaluated by a blinded, trained lung function technologist. In literature, the use of spirometry lung function tests in children as young as three years of age has been described and found to be valid.[146,453] Hence, expansion of the lung function testing protocol to younger children might be appropriate for future research. However, caution is needed as it is unclear whether the above mentioned invalid lung function tests could be due to the young age of included children, who might have been unable to perform the test adequately, for which an even younger age category might be inappropriate.

Another outcome measure used in the current study was the EQ-5D-Y to assess the participant's HRQOL by proxy report. The majority of parents reported no problems on the EQ-5D-Y dimensions. No severe problems were reported on any of the items. Parents scored the current health of their children high on the visual analogue scale (medians above 85/100). This could be a result of the chronic nature of the disease, for which coping mechanisms might have led to adaptations in lifestyle and disease perceptions.[163,454] None of the studies investigating AD compared to other ACTs in children with CF reported on HRQOL outcome measures. Therefore, no comparisons can be made with our results. However, HRQOL is affected in patients and parents of patients with CF, as they face many challenges throughout their life. These challenges entail, but are not limited to: stigmatisation; time consuming treatments; increased health care costs; and disrupting effect of a pulmonary exacerbation.[21,22,333] These lead to increased depression and anxiety, which is frequently found in both patient and caregivers lives; and influences adherence to treatment.[334,455] Therefore, the International Committee on Mental Health in Cystic Fibrosis recommends that annual screening for these symptoms should be implemented in routine follow up, so an appropriate intervention can be applied when needed.[337] Hence, it is recommended that in future research, HRQOL tools for both the patient and the caregiver

emerge in research protocols. As proxy-report has not been found to be a valid representation of the child's HRQOL for some assessment tools;[456–458] the child him/herself should complete a questionnaire where possible. The EQ-5D-Y is valid and reliable for children older than eight years of age, and the Pediatric Quality of Life Inventory has been found valid and reliable when completed by children older than five years of age.[161,459] Unfortunately, no tool is available currently for assessing HRQOL in children younger than the age of five years; therefore it is recommended that research is conducted towards developing an easy, valid, child-friendly HRQOL tool which is usable in a younger age group and responsive to small changes in chronic disease.

The current study also used the CFCS, as an outcome measure. This tool has not been reported in any of the studies investigating AD in children with CF. However, one study did report on the Huang and Shwachman-Kulczycki score after one year of intervention in a paediatric CF population.[272] No significant differences for the Shwachman-Kulczycki score were found between the intervention arm receiving AD and the control arm receiving PD with percussions. The Huang score, on the other hand, did differ significantly between both groups, with a better Huang score reported in the AD arm of the study.[272] Although the current study did not find any significant differences between the intervention group receiving AAD and the control group receiving standard ACTs, baseline characteristics show a trend towards more children with an acute illness based on the subjective CFCS results, in the intervention arm of the study. Although all three scores are clinical scores, assessing disease severity, used in patients with CF, the CFCS score has a different content validity than the Huang and Shwachman-Kulczycki score. The CFCS was developed to assess the patient's current clinical status, whereas the Shwachman-Kulczycki score assess the progression of chronic illness and the Huang score the short term effects of an intervention.[170,172–174] Description of the Huang and Shwachman-Kulczycki score can be found in section 2.3.3. The CFCS might not have been the most appropriate outcome measure for a one year intervention, as the current state of the child could be influenced by an acute exacerbation at the time of assessment. However, the current study did find large effect sizes within the intervention group from baseline to end of the study. Future research could therefore opt to use the modified Shwachman score as described by Doershuk et al. in addition to the CFCS, to assess both acute health status and long term chronic disease progression.[171] However, this tool also has flaws such as subjective items reducing the test's reliability, poor sensitivity for mild disease severity, and categories which are intertwined.[171,172] Furthermore, the CFCS score can be used on a more routine

basis, e.g. during each follow up visit, to assess the presence of an exacerbation. Maintaining the score below 25 points or not exceeding five points of the last calculation might provide a more reliable outcome to control exacerbation during ACT.

The median BMI for age z-scores in the current study were within the normal boundaries (z>0) and no significant difference between and within groups were seen. None of the studies investigating AD in children with CF included BMI-for-age z-scores as one of their outcome measures. Therefore, no comparison with the current study can be made. BMI-for-age has been recommended as the preferred method to assess children's growth and nutritional status.[19,365] Children should obtain and maintain a BMI above the 50th percentile,[19] which correlates with a z-score of zero. However, BMI-for-age is unable to identify stunting, therefore, weight-for-age and height-for-age measures are relevant.[460] In the current study, the majority of children were underweight for age, with median z-values >-1. Shorter stature for age was also found, particularly in the intervention group. As the BMI-for-age z-scores were within normal range but reduced weight- and height-for-age z-scores were observed, this study emphasises the importance of including outcome measures focussing on stunting and malnutrition, hence weight-for age and height-for-age, rather than BMI-for-age z-scores.

No severe adverse events or casualties were reported, and the current study had a mortality rate of zero. Again, mortality was not included as an outcome measure in any of the studies on AD in children with CF, for which no comparison could be made. As the current study included a young age range, mortality rate might not have been an appropriate outcome measure as mortality at such a young age is not common; especially considering the increasing life expectancy of people with CF.[12] Adverse events on the other hand are more appropriate in assessing a new intervention in this population. Although this was not an intended outcome measure, no adverse events were reported in either arm of the current study.

Finally, the current study revealed a higher preference for standard ACTs (4/7 participants) than AAD (2/7) in the participants in the intervention group after one month in the study. This is in contrast with the study by McIlwaine et al, where 10 of the 17 participants did not want to return to PD with percussions after completion of the AD arm of the study.[272] In the study by Miller et al, preference was equally divided for AD and ACBT in their two day cross over trial.[270] The discrepancy of the current study's results with these two studies could be

due to the difference in application of the techniques. AD and ACBT are known to be techniques that can be performed independently at any time of the day as no equipment is needed.[24] However, AAD is a passive/assisted technique which requires the caregiver to actively participate in applying the technique.[25,28] Two of the four caregivers who reported to use AAD at the end of the study period did mention that AAD was difficult to administer: they 'did not know how to get it right' or were 'unsure when to stop'. AAD might therefore require more training of the caregiver, which is similar to AD, where the patient also requires multiple training session before effectively being able to apply the technique.[24] For future research, a more intense and comprehensive training program might be needed to train the caregivers in applying AAD. One session with three monthly follow up might not be sufficient to master this more complex technique. AAD could be integrated in the ACT toolkit from an early age, so caregivers and children get used to the technique and might be more comfortable in its application.

As mentioned above, AAD was less preferred than other ACTs such as percussions and vibrations in the current study. However, the adherence to these more preferred ACTs was generally poor, with only four of the 13 participants interviewed at the end of the study performing bidaily ACTs as recommended. Studies on adherence to ACT and general medical treatment in children with CF reported an overall poor adherence to therapy (less than 50%).[423,461] Factors influencing treatment adherence of children with CF and their caregivers include: socio-economic status (with maternal education and income higher than $50 000 identified as positive influencers for adherence);[424,427] mental health (depression and anxiety, in both the child and the caregiver, negatively influencing treatment adherence);[334,336,462] family relationships (supportive parents and a good child-parent relationship positively influencing adherence, whereas oppositional behaviour reduces adherence);[334,426] time-consuming therapy;[426,463] and understanding of the disease progression and necessity of therapy. In the current study, the main reason for non-adherence to ACT was the time consuming nature of the intervention. Furthermore, resistance from the child and the lack of physical signs of illness were indicated as being barriers to adherence. Adherence was intended to be monitored by the use of a diary, however, poor adherence to completion of the diary led to discarding this form of adherence control. Afterwards a less time consuming, more enteraining method of adherence monitoring was applied, using a calendar and sticker method. Unfortunately, even this form of adherence monitoring was not completed by the majority of children and parents. Therefore, information in the current study regarding adherence was obtained via

a subjective interview, performed by a social worker who was not involved in the study but who did know the children and their parents. As this method of data gathering is not objective (self-reported adherence is found to be higher than objectively measured adherence),[423,464] the adherence rates provided in this current study cannot be used for generalisation to a broader population. However, if self-reported treatment adherence is higher than the actual adherence, the rates of adherence to bidaily ACTs in the current study are worrisome; highlighting the need for the use of an objective adherence monitoring tool to objectively quantify the problem in future studies. Several options have been reported in literature, such as telephone calls on a daily basis and electronic devices to monitor adherence.[423,424,464] However, these are not always feasible due to high cost and time constraints.[465] In future research, improving adherence to therapy is essential, which may be obtained by improving training of parents and through more intensive follow up. Cost-effective methods of adherence follow-up should be explored, such as the use of sms, email or online messaging.

9.7 CONCLUSION

This study was the first pilot RCT on the use of AAD in children with CF, which aimed to explore the feasibility of the study protocol. The results of this study can be used as baseline, to which other studies can be compared, adding to the body of knowledge on AAD as an ACT in this population. Conclusions cannot be made regarding the effectiveness and safety of AAD in children with CF due to the small sample size included in this study, and the lack of adherence to the prescribed intervention. However, the magnitude of adherence problems related to ACT in this population is clear. Further research is needed to investigate the usefulness of AAD in children of this population and to tackle issues related to treatment adherence. AAD might be a useful technique to add to the airway clearance 'toolbox' for children with CF as no adverse events were reported and a small to medium effect size for number of days on antibiotic therapy was found, benefiting the intervention group.

Future research should explore multi-center research to increase the study's sample size. Improving the training of the parents/caregivers is required, with a more intensive training session, aiming to increase adherence to therapy. Primary outcome measures such as 'number of exacerbations' and 'days on antibiotic therapy' during one year could be used rather than 'number of hospitalisations'; as they are more responsive to change. Quality of spirometry should be monitored closely, to obtain reliable and valid measures. The use of

lung function testing in children younger than five years of age could be applied, however, training on performance of this outcome measure prior to the study period is recommended. Spirometry results should not be obtained for children unable to perform good quality blows. Disease severity could be measured using the CFCS, for acute health status, and the modified Shwachman score, for chronic disease progress. Furthermore, the use of weight-for-age and height-for-age z-scores could be more responsive than BMI-for-age scores. Adherence to therapy may improve when monitored on a daily basis, using cost-effective alternatives. Furthermore, research towards an easy, valid, child-friendly HRQOL tool which is usable in a younger age group and responsive to small changes in chronic disease should be conducted. The Pediatric Quality of Life Inventory could be useful in children ages five years and older.

Chapter 10. CONCLUSION

10.1 SUMMARY OF RESULTS

Respiratory problems, both acute and chronic, remain an important disease burden worldwide; negatively impacting the child, the healthcare system and the community. Pneumonia in particular persists as one of the most common causes of death in children younger than five years of age; and CF is a relatively common chronic multisystem disorder affecting the respiratory system and reducing life expectancy. ACTs, as part of the management of these conditions, might influence the course of the disease and hopefully reduce the associated burden. Many ACTs have been investigated in different patient population groups, however, very few are useful in infants and young children, as they require active participation. AAD, a modified version of AD, has been used in clinical settings to facilitate airway clearance in infants and young children, however, the efficacy and safety of this technique has not been investigated before.

The first part of this thesis investigated ACTs, including AAD, in an acute respiratory disease, pneumonia. The current body of knowledge on the use of ACTs, including AAD, in children hospitalised with pneumonia was investigated (Chapter 4), to assess the need for future research. Chapter 4 therefore aimed to address the research question:

What is the international body of knowledge on the use of ACTs for children hospitalised with pneumonia?

Only two RCTs were included in this systematic review, revealing no significant differences between the intervention and control groups for length of hospitalisation, time to clinical resolution, reduction of RR and severity score, and persistence of respiratory symptoms. However, this review was unable to pool data for meta-analysis and included only a limited number of articles. Furthermore, positive influences of ACTs in children with pneumonia were shown by one RCT and several non-randomised trials, which were not included in the review; highlighting the need for more evidence-based research within this field. Hence, no clear recommendations can be made for the use of ACTs in the clinical management of children with pneumonia.

Although ACTs are used in the clinical management of children with LRTIs, there is little documentation available on the prescription, frequency and nature of ACTs, particularly in a South African context. Most importantly, there is little published data regarding adverse

events that may be associated with ACTs in children with LRTI. Therefore, a retrospective folder review investigating the patient characteristics and ACT management in a tertiary hospital in Cape Town, South Africa was conducted (Chapter 5), to answer the second research question:

In children hospitalised for LRTI in South Africa: what is the patient profile of children receiving ACT, what is the nature and frequency of ACT, what are the predictive factors for receiving ACT, what are the adverse events associated with ACT and could these adverse events be predicted?

This folder review showed that ACT was only given in 5.8% of the hospitalisations, with conventional ACTs the most frequently used (vibrations (83.1%), MPD (55.4%), percussions/clapping (38.6%), thoracic compressions (8.4%) and chest wall shaking (1.2%). This might be due to the large proportion of infants and young children hospitalised for LRTIs at the hospital, for whom newer ACTs could be challenging due to the need for active cooperation. Other techniques used clinically were deep breathing exercises (25.3%, active gross motor exercises (20.5%), ACBT (13.3%), FET/huff (7.2%), bubble PEP (7.2%), AAD (6.0%), oscillating PEP (3.6%) and blowing bubbles (1.2%). PEP and AD were not performed during the study period. The majority of ACT interventions were commenced during the first week of hospitalisation (75.9%), were performed once or twice per day (49.4% and 48.2% respective), and were carried out for a median of 3.0 days. Children hospitalised for presumed nosocomial infections and pneumonia, with isolated bacterial organisms and a chronic comorbidity (CP, NMD, chronic respiratory disease or genetic disorder), were most likely to receive ACT. Desaturation was reported as an adverse event of ACT in six children during various techniques, particularly conventional ACTs. One child developed lung collapse an hour post treatment. Predictive factors for adverse events could not be analysed due to the small number of children presenting with adverse events.

Only a few children with bronchiolitis received ACT during the study period, which conforms to recommendations made in the literature. However, the folder review did confirm that ACTs are still used in children with pneumonia, particularly the children with associated comorbidities. Furthermore, these children are hospitalised for a longer period than children with bronchiolitis; and have a higher mortality rate.

As mentioned before, no conclusive evidence-based guidelines are available for the use of ACTs in children hospitalised for pneumonia due to the conflicting results in previously

published literature. The folder review suggests that ACTs are probably safe to perform in these children, if SpO_2 is monitored during therapy. Currently, conventional ACTs are most often used to treat infants and young children as other techniques require active cooperation and the ability to follow instructions. AAD has been reported in the literature as a technique that could be used in this population; however, this technique has not been investigated before.

Therefore, Chapter 6 addressed the third research question of this thesis:

Is the use of AAD as an addition to standard care beneficial in children hospitalised with pneumonia?

Due to ethical reasons, children with chronic comorbidities were excluded from the study, as the safety of AAD had not been investigated before. This RCT therefore only included children with uncomplicated pneumonia; and was unable to show any significant difference between the intervention and control groups for length of hospitalisation. However, a trend towards faster time to discharge with a medium effect size for days of hospitalisation favouring the intervention group was seen. Furthermore, a significant decrease in RR within the intervention group was observed. Although a statistically significant increase in RR immediately after AAD was observed in the intervention group, the clinical significance of an increase by one breath per minute is questionable, and the RR returned to baseline within an hour after treatment. Unfortunately, due to the high number of excluded patients, as a result of the strict exclusion criteria, the study was underpowered to make clear conclusions regarding AAD in children with uncomplicated pneumonia.

For the chronic arm of this thesis, CF was the disease of choice as it is a common disorder affecting the respiratory system. ACTs have been found to be beneficial in this population, however, in infants and young children, the number of useful and available tools are limited. The majority of available literature investigates ACTs in children over the age of six years as they are cooperative and able to follow instructions. Again, AAD has been described in this population and is used in clinical practice but needs further investigation to determine effectiveness and safety. As no systematic review was published at the time of commencement of this thesis, Chapter 8 described a systematic review on AD and AAD in children with CF, to address research question four of this thesis:

What is the international body of knowledge on the use of AD and AAD in children with CF?

This systematic review was unable to identify any RCTs for inclusion, however, seven randomised cross-over trials were included. Separation of paediatric and adult data was only possible in two studies. Although there was a trend towards fewer hospitalisations and improvement in Huang score for children performing AD compared to PD, there was insufficient evidence to accept or reject AD as a safe or effective treatment option in children with CF. AD was preferred over PD in one of the paediatric studies, with the majority of participants assigned to AD during the first period of a randomised cross-over trial refusing to revert to conventional ACTs after completing the first period of cross-over. This systematic review was unable to identify any research studies on the use of AAD in children with CF. As no RCTs are available on AD, and AAD has never been researched before, the need for well-designed studies in a paediatric population were recommended.

Therefore, Chapter 9 of this thesis described a pilot RCT in children with CF, to provide an answer to the final research question:

Is the designed research protocol feasible to identify the effect of AAD compared to other ACTs in the home management of children with CF?

A pragmatic pilot study was conducted, the first true RCT, piloting the feasibility of a protocol on the use of AAD in children with CF, aiming at increasing the body of knowledge on AAD as an ACT in this population. No significant differences between the control and intervention groups were observed, although a medium effect size for 'number of exacerbations per year' and a small to medium effect size for 'days on antibiotic treatment during one year' were seen, favouring the intervention group. Within the intervention group trends towards improvement in EQ-5D-Y visual analogue scale and CFCS subjective and total score were observed (large effect sizes). AAD was not preferred over other ACTs used prior to the study period. AAD might be a useful technique to add to the airway clearance 'toolbox' for children with CF; unfortunately, conclusions cannot be made regarding the effectiveness and safety of AAD in children with CF due to the small sample size included in this study, and the lack of adherence to the prescribed intervention. The magnitude of adherence problems related to ACT in this population is clear. Further research is needed to investigate the usefulness of AAD in children of this population and to tackle issues related to treatment adherence. Future research should explore multi-center research to increase the study's sample size.

10.2 RECOMMENDATIONS

Although small benefits of AAD were observed in both children with pneumonia and CF, this thesis cannot recommend the use of AAD as standard practice in these children, based on the findings of this thesis. However, several practical recommendations arise from this thesis:

- In children with LRTI, ACTs seem safe to be administered.
- It is recommended that SpO_2 be monitored during ACT, particularly in infants and young children, so the treatment can be halted when deemed necessary.
- As no adverse events and casualties were reported, AAD could be considered as part of the ACT toolbox for patients with CF. An additional ACT creates more options and hopefully increases adherence to therapy when AAD is more preferred over other techniques.
- Spirometry could be incorporated in the follow up of children with CF from the age of three years onwards, however, it is important that the quality of the spirometry performance is on par with ATS/ERS criteria, producing valid results.
- Weight-for-age and height-for-age needs to be monitored during the routine follow visits for children with CF. BMI-for-age is insufficient to identify stunting and malnutrition in this population.
- More attention towards caregiver training is recommended, ensuring the parent understands the importance of ACT in children with CF, and increase proficiency to optimise adherence to home ACT programs.

This thesis aimed to investigate the effectiveness of AAD in children with pneumonia and CF. Efficacy of AAD could not be established, owing to the small sample sizes and poor adherence to study protocol in the CF study. Therefore, AAD is currently not recommended as standard practice in children with either pneumonia or CF. However, the road towards further research on the usefulness of AAD is opened.

The following recommendations for research are proposed:

- More research regarding ACTs in children with nosocomial infections and pneumonia is warranted; as the duration of hospitalisation was longer and mortality rate higher for these children. The identification of modalities which could hasten resolution of the disease, as well as identifying interventions which

are of no use or harmful, would help to ensure rational and appropriate resource allocation and optimise clinical outcomes.

- Further prospective, controlled clinical trials on the safety of ACTs in children with LRTIs are proposed. Although ACT, as performed at this research site, is relatively safe to perform in children with LRTI; the study was not designed or powered to determine safety.
- As more than half the children included in the descriptive folder review study presented with comorbidities, research is warranted to investigate the use of ACT in children hospitalised with LRTI and comorbidities, both chronic and acute.
- Future RCTs on AAD in the same population groups need to include larger sample size, as small benefits of AAD were noted. Multi-site studies are recommended to increase sample size.
- Inclusion of appropriate clinical outcome measures and analysis of adverse effects (including mortality) is recommended within this field of research. Therefore, following outcome measures are proposed:
    1) 'Number of exacerbations' and 'days on antibiotic therapy' during one year; as they are more responsive to change than 'number of hospitalisations'.
    2) Combination of the CFCS and modified Shwachman score for assessing current health status and chronic disease progression.
    3) Preference of both the parents and child, aimed at improving adherence to treatment
    4) Lung function testing in children younger than five years of age could be applied, however, training on performance of this outcome measure prior to the study period is recommended. Spirometry results should not be obtained for children unable to perform good quality blows.
    5) The Pediatric Quality of Life Inventory might be a better tool to assess HRQOL, as it is valid and reliable in children from the age of five years, and might be more sensitive to small changes in chronic disorders.
- Research towards an easy to administer, child-friendly HRQOL tool for children younger than the age of five years; which is sensitive for change in chronic conditions; is recommended.
- The use of SpO_2 as an outcome measure in a research study, which compares two groups, is not recommended. The outcome might not be reliable and is most likely insensitive to small changes. However, as stated in the clinical recommendations, it

is important to measure SpO_2 during ACT to identify desaturation and halt treatment when necessary.

- Research into treatment adherence and how to tackle the issue in participants with CF is recommended, due to the magnitude of adherence problems related to ACT in this population. Investigation into adherence monitoring tools such as sms, email and online messaging tools are recommended.

Notwithstanding the limitations of the studies presented in this thesis, the results are novel, and will contribute to the global body of knowledge in improving our understanding of the utility of different ACTs in young children with acute or chronic pulmonary disease.

Chapter 11. REFERENCES

1. Zar HJ, Ferkol TW. The global burden of respiratory disease-Impact on child health. *Pediatr Pulmonol*. 2014;49:430-434. doi:10.1002/ppul.23030.

2. Nair H, Simõ EAF, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet*. 2013;381:1380-1390. doi:10.1016/S0140-6736(12)61901-1.

3. Global Burden of Disease Pediatrics Collaboration. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. *JAMA Pediatr*. 2016;170(3):267-287. doi:10.1001/jamapediatrics.2015.4276.

4. Rudan I. Epidemiology and etiology of childhood pneumonia. *Bull World Heal Organ*. 2008;86(5):408-416. doi:10.2471/BLT.07.048769.

5. Rudan I, Brien KLO, Qazi S, Walker CLF, Black RE, Campbell H. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Heal*. 2013;3(1):010401. doi:10.7189/jogh.03.010401.

6. Walker CLF, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381:1405-1416. doi:10.1016/S0140-6736(13)60222-6.

7. Bauer TT, Welte T, Ernen C, et al. Cost analyses of community-acquired pneumonia from the hospital perspective. *Chest*. 2005;128(4):2238-2246. doi:10.1378/chest.128.4.2238.

8. Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis*. 2000;31:170-176. doi:10.1086/313925.

9. Madhi SA, Schoub B, Simmank K, Blackburn N, Klugman KP. Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. *J Pediatr*. 2000;137:78-84.

doi:10.1067/mpd.2000.105350.

10. Zar HJ, Hanslo D, Tannenbaum E, et al. The etiology and outcome of pneumonia in human immunodeficiency virus-infected children admitted to intensive care in a developing country. *Acta Paediatr*. 2001;90:108-112. http://www.ncbi.nlm.nih.gov/pubmed/12797868. Accessed February 10, 2017.

11. Zar HJ, Jeena P, Argent A, Gie R, Madhi SA. Diagnosis and management of community-acquired pneumonia in childhood-South African Thoracic Society Guidelines. *S Afr Med J*. 2005;95(12):977-990. doi:10.1080/10158782.2009.11441336.

12. Dodge J, Lewis P, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J*. 2007;29(3):522-526. doi:10.1183/09031936.00099506.

13. Boucher RC. Airway surface dehydration in cystic fibrosis: pathogenesis and therapy. *Annu Rev Med*. 2007;58:157-170. doi:10.1146/annurev.med.58.071905.105316.

14. Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. *Pediatr Pulmonol*. 1997;24(2):137-142. http://www.ncbi.nlm.nih.gov/pubmed/9292910. Accessed February 11, 2013.

15. Cutting G, Zeitlin P. Genetics and pathophysiology of cystic fibrosis. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:753-762.

16. Egan M, Green D, Voynow J. Cystic fibrosis. In: Kliegman R, Stanton B, St. Geme J, Schor N, eds. *Nelson Textbook of Pediatrics*. Vol 20th ed. Philadelphia: Elsevier; 2016:2098-2113.

17. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689. doi:10.1164/rccm.201207-1160OE.

18. Flume P a, Robinson K a, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care*. 2009;54(4):522-537.

https://www.ncbi.nlm.nih.gov/pubmed/19327189. Accessed December 23, 2016.

19. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. 2008;108(5):832-839. doi:10.1016/j.jada.2008.02.020.

20. Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *J Cyst Fibros*. 2013;12(5):461-467. doi:10.1016/j.jcf.2012.12.009.

21. Quittner AL, Saez-flores E, Barton JD. The psychological burden of cystic fibrosis. *Curr Opin Pulm Med*. 2016:187-191. doi:10.1097/MCP.0000000000000244.

22. Goldbeck L, Zerrer S, Schmitz TG. Monitoring quality of life in outpatients with cystic fibrosis: feasibility and longitudinal results. *J Cyst Fibros*. 2007;6(3):171-178. doi:10.1016/j.jcf.2006.06.005.

23. Van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. *Value Heal*. 2013;16(2):345-355. doi:10.1016/j.jval.2012.12.003.

24. Hardy K. A review of airway clearance: new techniques, indications, and recommendations. *Respir Care*. 1994;39(5):440-452. http://www.rcjournal.com/contents/05.94/05.94.pdf. Accessed February 15, 2012.

25. Lannefors L, Button B, McIlwaine M. Physiotherapy in infants and young children with cystic fibrosis: current practice and future developments. *J R Soc Med*. 2004;97(suppl 44):8-25. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1308795/. Accessed February 6, 2013.

26. Agostini P, Knowles N. Autogenic drainage: the technique, physiological basis and evidence. *Physiotherapy*. 2007;93(2):157-163. doi:10.1016/j.physio.2006.07.005.

27. Chevailler Jean. Autogenic drainage. In: Lawsons D, ed. *Cystic Fibrosis Horizons*. Chichester: John Wiley; 1984:235.

28. International Physiotherapy Group for Cystic Fibrosis. *Physiotherapy for People with Cystic Fibrosis: From Infant to Adult*. Vol 4th ed. IPG/CF; 2009. https://www.ecfs.eu/files/webfm/webfiles/File/Physiotherapy WebPages/blue booklet 2009 website version +1.pdf. Accessed February 27, 2015.

29. United Nations. World economic situation and prospects. In: *Statistical Annex*. 2012:131-140.

30. The World Bank. World Bank Country and Lending Groups. 2016. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed February 23, 2017.

31. International Monetary Fund. South Africa: concluding statement of an IMF staff visit. 2016. https://www.imf.org/en/News/Articles/2016/12/13/MS121316-South-Africa-Concluding-Statement-of-an-IMF-Staff-Visit. Accessed February 23, 2017.

32. Harrison D. An overview of health and health care in South Africa 1994 – 2010: priorities, progress and prospects for new gains. 2009:1-40. http://www.health.gov.za/index.php/2014-03-17-09-09-38/reports/category/102-2010rp. Accessed February 23, 2017.

33. Government Communications. *Pocket Guide to South Africa 2015/16*. Vol 13th ed. (Tibane E, ed.). Pretoria: South African Department of Communication and Information System; 2016. http://www.gcis.gov.za/content/resourcecentre/sa-info/yearbook2015-16. Accessed February 23, 2017.

34. World Health Organization's Global Health Workforce Statistics/The World Bank. Physicians (per 1,000 people). 2016. http://data.worldbank.org/indicator/SH.MED.PHYS.ZS. Accessed February 23, 2017.

35. Whitsett J, Wert S. Molecular determinants of lung morphogenesis. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:1-13.

36. Ochs M, O'Brodovich H. The structural and physiologic basis of respiratory disease. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and*

Chernick's Disorders of the Respiratory Tract in Children. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:35-74.

37. Hicks G. The respiratory system. In: Kacmarek R, Stoller J, Heuer A, eds. *Egan's Fundamentals of Respiratory Care*. Vol 10th ed. St. Louis: Elsevier Mosby; 2013:149-205.

38. Zorn AM, Wells JM. Vertebrate endoderm development and organ formation. *Annu Rev Cell Dev Biol*. 2009;25:221-251. doi:10.1146/annurev.cellbio.042308.113344.Vertebrate.

39. Sadler T. Respiratory system. In: *Langman's Medical Embryology*. Vol 12th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:201-207.

40. Randall D. Development of the respiratory system and respiration. In: Chamley C, Carson P, Randall D, Sandwell M, eds. *Developmental Anatomy and Physiology of Children. A Practical Approach*. Vol 1st ed. London: Elsevier Churchill Livingstone; 2005:165-185.

41. Prange HD. Laplace's law and the alveolus: a misconception of anatomy and a misapplication of physics. *Adv Physiol Educ*. 2003;27(1-4):34-40. doi:10.1152/advan.00024.2002.

42. Otis DR, Johnson M, Pedley TJ, Kamm RD. Role of pulmonary surfactant in airway closure: a computational study. *J Appl Physiol*. 1993;75(3):1323-1333. http://www.ncbi.nlm.nih.gov/pubmed/8226547. Accessed February 10, 2017.

43. Dunhill M. Postnatal growth and development of the lung. *Thorax*. 1962;17:329-333. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1094872. Accessed February 10, 2017.

44. Weibel E, Gomez D. A principle for counting tissue structures on random sections. *J Appl Physiol*. 1962;17(2):343-348. http://jap.physiology.org/content/17/2. Accessed February 10, 2017.

45. Davies G, Reid L. Growth of the alveoli and pulmonary arteries in childhood. *Thorax*. 1970;25(6):669-681. doi:10.1136/thx.25.6.669.

46. Greenough A, Murthy V, Milner A. Respiratory disorders in the newborn. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:358-385.

47. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med*. 2007;357(19):1946-1955. doi:10.1056/NEJMra067279.

48. Abman S. Bronchopulmonary dysplasia. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:386-398.

49. Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. Birth weight and childhood wheezing disorders : a systematic review and meta-analysis. *J Epidemiol Community Heal*. 2015;69:500-508. doi:10.1136/jech-2014-204783.

50. Thunqvist P, Gustafsson PM, Schultz ES, Bellander T, Berggren-broström E. Lung function at 8 and 16 years after moderate-to-late preterm birth: a prospective cohort study. *Pediatrics*. 2016;137(4):e20152056. doi:10.1542/peds.2015-2056.

51. Sarnaik A, Heidemann S, Clark J. Respiratory pathophysiology and regulation. In: Kliegman R, Stanton B, St. Geme J, Schor N, eds. *Nelson Textbook of Pediatrics*. Vol 20th ed. Philadelphia: Elsevier; 2016:1981-1992.

52. Wheeler D, Spaeth J, Metha R, Hariprakash S, Cox P. Assessment and management of the pediatric airway. In: Wheeler D, Wong H, Shanley T, eds. *Pediatric Critical Care Medicine: Basic Science and Clinical Evidence*. Vol 1st ed. London: Springer; 2007:223-252.

53. Rosenberg D, Lyons H. Collateral ventilation in excised human lungs. *Respiration*. 1979;37:125-134. doi:10.1159/000194018.

54. Schechter M. Airway clearance applications in infants and children. *Respir Care*. 2007;52(10):1382-1391. doi:10.07/10.07.1382.

55. Knill R, Andrews W, Bryan AC, Bryan MH. Respiratory load compensation in infants. *J Appl Physiol*. 1976;40(3):357-361. http://jap.physiology.org/content/40/3/357.

Accessed February 23, 2017.

56. Sieck C, Fournier M, Blanco C. Diaphragm muscle fatigue resistance during postnatal development. *J Appl Physiol*. 1991;71(2):458-464. http://jap.physiology.org/content/71/2/458. Accessed February 23, 2017.

57. Gaultier C. Respiratory muscle function in infants. *Eur Respir J*. 1995;8(1):150-153. doi:10.1183/09031936.95.08010150.

58. Le Souef PN, England SJ, Stogryn HA, Bryan AC. Comparison of diaphragmatic fatigue in newborn and older rabbits. *J Appl Physiol*. 1988;65(3):1040-1044. doi:10.1016/0883-9441(89)90033-6.

59. Stark AR, Waggener TB, Frantz ID, Cohlan BA, Feldman HA, Kosch PC. Effect on ventilation of change to the upright posture in newborn infants. *J Appl Physiol*. 1984;56(1):64-71. http://www.ncbi.nlm.nih.gov/pubmed/6420384. Accessed February 23, 2017.

60. Waugh A, Grant A. The respiratory system. In: *Ross and Wilson Anatomy & Physiology in Health and Illness*. Vol 12th ed. Edinburgh: Elsevier Ltd; 2014:241-272.

61. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging*. 2006;1(3):253-260. doi:10.2147/ciia.2006.1.3.253.

62. Chatwin M, Wakeman R, Wright S. Physical therapies in pediatric respiratory disease. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:299-308.

63. Boucher R. Human airway ion transport. Part one. *Am J Respir Crit Care Med*. 1994;150(1):271-281. doi:10.1164/ajrccm.150.1.8025763.

64. Houtmeyers E, Gosselink R, Decramer M. Regulation of mucociliary clearance in health and disease. *Eur Respir J*. 1999;13:1177-1188. http://erj.ersjournals.com/content/13/5/1177.long. Accessed February 11, 2013.

65. Blake J. On the movement of mucus in the lung. *Eur J Respir Dis*. 1983;64(suppl.

127):162-167. doi:10.1016/0021-9290(75)90023-8.

66. Gosselink R, Decramer M. Behandeling van stoornissen in het mucus transport. In: *Revalidatie Bij Chronisch Obstructieve Longziekten.* Vol 5th ed. Maarssen: Elsevier gezondheidszorg; 2008:145-188.

67. Raidt J, Wallmeier J, Hjeij R, et al. Ciliary beat pattern and frequency in genetic variants of primary ciliary dyskinesia. *Eur Respir J*. 2014;44(6):1579-1588. doi:10.1183/09031936.00052014.

68. Wanner A, Salathé M, O'Riordan T. Mucociliary clearance in the airways. *Am J Respir Crit Care Med*. 1996;154:1869-1902. doi:10.1164/ajrccm.154.6.8970383.

69. Benjamin RG, Chapman GA, Kim CS, Sackner MA. Removal of bronchial secretions by two-phase gas-liquid transport. *Chest*. 1989;95(3):658-663. doi:10.1378/chest.95.3.658.

70. Fink J. Forced expiratory technique, directed cough, and autogenic drainage. *Respir Care*. 2007;52(9):1210-1221; discussion 1221-1223. http://www.rcjournal.com/contents/09.07/09.07.1210.pdf. Accessed February 7, 2013.

71. Clarke SW, Jones JG, Oliver DR. Resistance to two-phase gas-liquid flow in airways. *J Appl Physiol*. 1970;29(4):464-471. http://jap.physiology.org/content/29/4/464. Accessed August 16, 2016.

72. Kim CS, Rodriguez CR, Eldridge MA, Sackner MA. Criteria for mucus transport in the airways by two-phase gas-liquid flow mechanism. *J Appl Physiol*. 1986;60(3):901-907. http://jap.physiology.org/content/60/3/901. Accessed February 23, 2017.

73. Kim CS, Iglesias AJ, Sackner MA. Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *J Appl Physiol*. 1987;62(3):959-971. http://jap.physiology.org/content/62/3/959. Accessed February 23, 2017.

74. Warwick W. Mechanisms of mucous transport. *Eur J Respir Dis*. 1983;64(suppl 127):162-167. https://www.ncbi.nlm.nih.gov/pubmed/6578055. Accessed February 11, 2017.

75. Zach MS. The physiology of forced expiration. *Paediatr Respir Rev*. 2000;1(1):36-39. doi:10.1053/prrv.2000.0010.

76. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. *J Appl Physiol*. 1967;22(1):95-108. http://jap.physiology.org/content/jap/22/1/95.full.pdf. Accessed July 27, 2016.

77. Chatburn R, Daoud E. Ventilation. In: Kacmarek R, Stoller J, Heuer A, eds. *Egan's Fundamentals of Respiratory Care*. Vol 10th ed. St. Louis: Elsevier Mosby; 2013:225-249.

78. Button BM, Button B. Structure and function of the mucus clearance system of the lung. *Cold Spring Harb Perspect Med*. 2013;3:a009720. doi:10.1101/cshperspect.a009720.

79. Ross B, Gramiak R, Rahn H. Physical dynamics of the cough mechanism. *J Appl Physiol*. 1955;8(3):264-268. doi:10.1016/0022-460X(71)90105-2.

80. Herlitz GN, Sternberg DI, Palazzo R, Arcasoy S, Sonett JR. Treatment of bronchomalacia in cystic fibrosis by silicone stent. *Ann Thorac Surg*. 2006;82(6):2268-2270. doi:10.1016/j.athoracsur.2006.05.006.

81. Mair E, Parsons D. Pediatric tracheobronchomalacia and major airway collapse. *Ann Otol Rhinol Laryngol*. 1992;101(4):300-309. doi:10.1177/000348949210100403.

82. Wong J, Keens T, Wannemaker E. Effects of gravity on tracheal mucus transport rates in normal subjects and in patients with cystic fibrosis. *Pediatrics*. 1977;60:146-152. http://pediatrics.aappublications.org/content/60/2/146. Accessed February 16, 2013.

83. Shak S, Capon DJ, Hellmiss R, Marsters SA, Baker CL. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. *Proc Natl Acad Sci U S A*. 1990;87(23):9188-9192. doi:10.1073/pnas.87.23.9188.

84. Giles D, Wagener J, Accurso F, Butler-Simon N. Short-term effects of postural drainage with clapping vs autogenic drainage on oxygen saturation and sputum recovery in patients with cystic fibrosis. *Chest*. 1995;108(4):952-954.

doi:10.1378/chest.108.4.952.

85. Naylor JM, Chow C-M, McLean AS, Heard RC, Avolio A. Cardiovascular responses to short-term head-down positioning in healthy young and older adults. *Physiother Res Int*. 2005;10(1):32-47. doi:10.1002/pri.22.

86. Button B, Heine R, Catto-smith A, Phelan P. Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis. *Arch Dis Child*. 1997;76(2):148-150. doi:10.1136/adc.76.2.148.

87. Lapin C. Conventional postural drainage and percussion: is this still the golden standard? *Pediatr Pulmonol*. 1994;(suppl 10):87-88. doi:10.1002/ppul.1950180706.

88. Badr C, Elkins M, Ellis E. The effect of body position on maximal expiratory pressure and flow. *Aust J Physiother*. 2002;48(2):95-102. doi:10.1016/S0004-9514(14)60203-8.

89. Blair BE, Hickam JB. The effect of change in body position on lung volume and intrapulmonary gas mixing in normal subjects. *J Clin Invest*. 1955;34(3):383-389. doi:10.1172/JCI103086.

90. Ibañez J, Raurich JM. Normal values of functional residual capacity in the sitting and supine positions. *Intensive Care Med*. 1982;8(4):173-177. doi:10.1007/BF01725734.

91. Button B, Heine R, Catto-Smith A, et al. Chest physiotherapy in infants with cystic fibrosis: to tip or not? A five-year study. *Pediatr Pulmonol*. 2003;35(3):208-213. doi:10.1002/ppul.10227.

92. Nunn J. Elastic forces and lung volumes. In: Nunn J, ed. *Nunn's Applied Respiratory Physiology*. Vol 4th ed. Oxford: Butterworth Heinemann, Elsevier Limited; 1993:36-60.

93. Radford R, Barutt J, Billingsley J, et al. A rational basis for percussion augmented mucociliary clearance. *Respir Care*. 1982;27:556-563.

94. McCarren B, Alison JA, Herbert RD. Vibration and its effect on the respiratory system. *Aust J Physiother*. 2006;52(1):39-43. doi:http://dx.doi.org/10.1016/S0004-

9514(06)70060-5.

95. McCarren B, Alison JA, Herbert RD. Manual vibration increases expiratory flow rate via increased intrapleural pressure in healthy adults: an experimental study. *Aust J Physiother*. 2006;52(4):267-271. doi:http://dx.doi.org/10.1016/S0004-9514(06)70006-X.

96. Holody B, Goldberg HS. The effect of mechanical vibration physiotherapy on arterial oxygenation in acutely ill patients with atelectasis or pneumonia. *Am Rev Respir Dis*. 1981;124(4):372-375. http://www.atsjournals.org/doi/abs/10.1164/arrd.1981.124.4.372. Accessed February 11, 2017.

97. Eid N, Buchheit J, Neuling M, Phelps H. Chest physiotherapy in review. *Respir Care*. 1991;36(4):270-282. http://europepmc.org/abstract/med/7047185. Accessed February 26, 2013.

98. van der Schans CP, Piers D a, Postma DS. Effect of manual percussion on tracheobronchial clearance in patients with chronic airflow obstruction and excessive tracheobronchial secretion. *Thorax*. 1986;41(6):448-452. doi:10.1136/thx.41.6.448.

99. Selsby D. Chest physiotherapy. *BMJ*. 1989;298(March):541-542. doi:10.1136/bmj.298.6673.541.

100. Campbell A, O'Connell J, Wilson F. The effect of chest physiotherapy upon the FEV1 in chronic bronchitis. *Med J Aust*. 1975;1(2):33-35. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1128356. Accessed February 26, 2013.

101. Chalumeau M, Foix-L'Helias L, Scheinmann P, Zuani P, Gendrel D, Ducou-le-Pointe H. Rib fractures after chest physiotherapy for bronchiolitis or pneumonia in infants. *Pediatr Radiol*. 2002;32(9):644-647. doi:10.1007/s00247-002-0755-y.

102. Wood B. Infant ribs: generalized periosteal reaction resulting from vibrator chest physiotherapy. *Radiology*. 1987;162(3). doi:10.1148/radiology.162.3.3809498.

103. Gorincour G, Dubus J, Petit P, Bourliere-Najean B, Devred P. Rib periosteal reaction: did you think about chest physical therapy? *Arch Dis Child*. 2004;89(11):1078-1079. doi:10.1136/adc.2004.052290.

104. Bach JR. Mechanical insufflation/exsufflation: has it come of age? A commentary. *Eur Respir J*. 2003;21(3):385-386. doi:10.1183/09031936.03.00098702.

105. Finder JD. Airway clearance modalities in neuromuscular disease. *Paediatr Respir Rev*. 2010;11(1):31-34. doi:10.1016/j.prrv.2009.10.007.

106. Balachandran A, Shivbalan S, Thangavelu S. Chest physiotherapy in pediatric practice. *Indian Pediatr*. 2005;42:559-568.

107. Boitano LJ. Management of airway clearance in neuromuscular disease. *Respir Care*. 2006;51(8):913-922. http://rc.rcjournal.com/content/51/8/913. Accessed February 11, 2017.

108. American Association for Respiratory Care. AARC clinical practice guideline: directed cough. *Respir Care*. 1993;38(5):495-499. http://www.rcjournal.com/cpgs/dccpg.html. Accessed February 12, 2017.

109. Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database Syst Rev*. 2009;(4):CD007298. doi:10.1002/14651858.CD007298.pub2.

110. Fauroux B, Guillemot N, Aubertin G, et al. Physiologic benefits of mechanical insufflation-exsufflation in children with neuromuscular diseases. *Chest*. 2008;133(1):161-168. doi:10.1378/chest.07-1615.

111. Morrow B, Zampoli M, van Aswegen H, Argent A. Mechanical insufflation-exsufflation for people with neuromuscular disorders. *Cochrane database Syst Rev*. 2013;12(12):CD010044. doi:10.1002/14651858.CD010044.pub2.

112. Williams MT. Chest physiotherapy and cystic fibrosis: why is the most effective form of treatment still unclear? *Chest*. 1994;106(6):1872-1882. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1305881/. Accessed March 6, 2013.

113. Pryor JA, Webber BA, Hodson ME, Batten JC. Evaluation of the forced expiration

technique as an adjunct to postural drainage in treatment of cystic fibrosis. *Br Med J*. 1979;2(6187):417-418. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=486968. Accessed February 26, 2013.

114. McIlwaine M. Chest physical therapy, breathing techniques and exercise in children with CF. *Paediatr Respir Rev*. 2007;8(1):8-16. doi:10.1016/j.prrv.2007.02.013.

115. Pryor J. Physiotherapy for airway clearance in adults. *Eur Respir J*. 1999;14(1):1418-1424. http://erj.ersjournals.com/content/14/6/1418.long. Accessed March 6, 2013.

116. McIlwaine M. Physiotherapy and airway clearance techniques and devices. *Paediatr Respir Rev*. 2006;7(Suppl. 1):220-222. doi:10.1016/j.prrv.2006.04.197.

117. Pryor JA, Webber BA, Hodson ME. Effect of chest physiotherapy on oxygen saturation in patients with cystic fibrosis. *Thorax*. 1990;45(1):77. doi:10.1136/thx.45.1.77.

118. Myers T. Positive expiratory pressure and oscillatory positive expiratory pressure therapies. *Respir Care*. 2007;52(10):1308-1326.

119. Falk M, Kelstrup M, Andersen J, et al. Improving the ketchup bottle method with positive expiratory pressure, PEP, in cystic fibrosis. *Eur J Respir Dis*. 1984;65(6):423-432. https://www.ncbi.nlm.nih.gov/pubmed/6381081. Accessed February 13, 2017.

120. Pisi G, Chetta A. Airway clearance therapy in cystic fibrosis patients. *Acta Biomed Atenei Parm*. 2009;80(2):102-106. http://www.mattioli1885journals.com/index.php/actabiomedica/article/view/1204. Accessed February 26, 2013.

121. Pfleger A, Theissl B, Oberwalder B, Zach M. Self-administered chest physiotherapy in cystic fibrosis: a comperative study of high-pressure PEP and autogenic drainage. *Lung*. 1992;170(6):323-330. doi:10.1007/BF00177578.

122. Zach MS, Oberwaldner B. Effects of positive expiratory pressure breathing in patients with cystic fibrosis. *Thorax*. 1992;47(1):66. doi:10.1136/thx.47.1.66-b.

123. Rand S, Hill L, Prasad SA. Physiotherapy in cystic fibrosis: optimising techniques to improve outcomes. *Paediatr Respir Rev*. 2013;14(4):263-269. doi:10.1016/j.prrv.2012.08.006.

124. App E, Kieselmann R, Reinhardt D, et al. Sputum rheology changes in cystic fibrosis lung disease following two different types of physiotherapy: flutter vs autogenic drainage. *Chest*. 1998;114(1):171-177. doi:10.1378/chest.114.1.171.

125. Marks J. Airway clearance devices in cystic fibrosis. *Paediatr Respir Rev*. 2007;8(1):17-23. doi:10.1016/j.prrv.2007.02.003.

126. McIlwaine MP, Chilvers M, Lee Son N, Richmond M. Analysis of expiratory flow rates used in autogenic drainage. Are they sufficiently high to mobilize secretions? *J Cyst Fibros*. 2014;13:S29. doi:10.1016/S1569-1993(14)60091-6.

127. Schöni M. Autogenic drainage: a modern approach to physiotherapy in cystic fibrosis. *J R Soc Med*. 1989;82(suppl 16):32-37. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1291917&tool=pmcentrez&rendertype=abstract. Accessed February 6, 2013.

128. Chevailler Jean. *Autogenic Drainage. Unpublished Course Notes.* De Haan, Belgium; 1992.

129. Spence S, Anderson B, Hardy K. Use of biofeedback to teach autogenic drainage (abstract). *Pediatr Pulmonol*. 1990;Suppl S5:A332. doi:10.1002/ppul.1950090506.

130. Van Ginderdeuren F, Malfroot A, Dab I. Influence of “assisted autogenic drainage (AAD)”, “bouncing” and “AAD combined with bouncing” on gastro-oesophageal reflux (GOR) in infants. *J Cyst Fibros*. 2001:112.

131. Van Ginderdeuren F, Malfroot A, Verdonk J, Vanlaethem S VY. Influence of assisted autogenic drainage (AAD) and AAD combined with bouncing on gastro-oesophageal reflux (GOR) in infants under the age of 5 months. *J Cyst Fibros*. 2003;2(suppl 1):A251. doi:10.1016/S1569-1993(03)00027-4.

132. Van Ginderdeuren, F Vandenplas Y, Deneyer M, Vanlaethem S, Buyl R, Kerckhofs E. Influence of bouncing and assisted autogenic drainage on acid gastro-oesophageal

reflux in infants. *Pediatr Pulmonol*. 2017;[Epub ahea. doi:10.1002/ppul.23677.

133. Elkins M, Jones A, van der Schans C. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis (Review). *Cochrane Database Syst Rev*. 2009;(1). doi:10.1002/14651858.CD003147.pub3.

134. Main E, Prasad A, van der Schans C. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. *Cochrane Database Syst Rev*. 2005;(2). doi:10.1002/14651858.CD002011.pub2.

135. Morrison L, Agnew J. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2009;(1). doi:10.1002/14651858.CD006842.pub2.

136. Van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev*. 2000;(2). doi:10.1002/14651858.CD001401.

137. Homnick DN. Making airway clearance successful. *Paediatr Respir Rev*. 2007;8(1):40-45. doi:10.1016/j.prrv.2007.02.002.

138. Rubin BK. Designing clinical trials to evaluate mucus clearance therapy. *Respir Care*. 2007;52(10):1348-1358. http://www.rcjournal.com/contents/10.07/10.07.1348.pdf. Accessed February 13, 2017.

139. Van der Schans CP. Physiotherapy and bronchial mucus transport. *Eur Respir J*. 1999;13:1477-1486. doi:10.1034/j.1399-3003.1999.13f37.x.

140. Thomson ML, Pavia D, McNicol MW. A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung. *Thorax*. 1973;28(6):742-747. doi:10.1136/thx.28.6.742.

141. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr Radiol*. 2006;36(Suppl. 14):121-125. doi:10.1007/s00247-006-0191-5.

142. Marques A, Bruton A, Barney A. Clinically useful outcome measures for

physiotherapy airway clearance techniques: a review. *Phys Ther Rev*. 2006;11(4):299-307. doi:10.1179/108331906X163441.

143. Wallis C, Prasad A. Who needs chest physiotherapy? Moving from anecdote to evidence. *Arch Dis Child*. 1999;80(4):393-397. doi:10.1136/adc.80.4.393.

144. Regnis J, Robinson M, Bailey D, et al. Mucociliary clearance in patients with cystic fibrosis and in normal subjects. *Am J Respir Crit Care Med*. 1994;150(1):66-71. doi:10.1164/ajrccm.150.1.8025774.

145. Ruppel GL. What Is the Clinical Value of Lung Volumes? *Respir Care*. 2012;5757(1):26-38. doi:10.4187/respcare.01374.

146. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society / European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. 2007;175:1304-1345. doi:10.1164/rccm.200605-642ST.

147. Nystad W, Samuelsen S, Nafstad P, Evardsen E, Stensrud T, Jaakkola J. Feasibility of measuring lung function in preschool children. *Thorax*. 2002;57:1021-1027. doi:10.1136/thorax.57.12.1021.

148. Eigen H, Bieler H, Grant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med*. 2001;163:619-623. doi:10.1164/ajrccm.163.3.2002054.

149. Smyth AR, Bell SC, Bojcin S, et al. European cystic fibrosis society standards of care: best practice guidelines. *J Cyst Fibros*. 2014;13(S1):S23-S42. doi:10.1016/j.jcf.2014.03.010.

150. Anagnostopoulou P, Egger B, Lurà M, et al. Multiple breath washout analysis in infants: quality assessment and recommendations for improvement. *Physiol Meas*. 2016;37(3):L1-L15. doi:10.1088/0967-3334/37/3/L1.

151. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and singlebreath tests. *Eur Respir J*. 2013;41(3):507-522. doi:10.1183/09031936.00069712.

152. Rosenfeld M, Allen J, Arets BHGM, et al. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc*. 2013;10(2):1-11. doi:10.1513/AnnalsATS.201301-017ST.

153. Subbarao P, Milla C, Aurora P, et al. Multiple-breath washout as a lung function test in cystic fibrosis: a cystic fibrosis foundation workshop report. *Ann Am Thorac Soc*. 2015;12(6):932-939. doi:10.1513/AnnalsATS.201501-021FR.

154. Singer F, Yammine S, Schmidt A, et al. Ventilatory response to nitrogen multiple-breath washout in infants. *Pediatr Pulmonol*. 2014;49(4):342-347. doi:10.1002/ppul.22841.

155. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J*. 2003;22:1026-1041. doi:10.1183/09031936.03.00089403.

156. Nielsen KG, Pressler T, Klug B, Koch C, Bisgaard H. Serial lung function and responsiveness in cystic fibrosis during early childhood. *Am J Respir Crit Care Med*. 2004;169(11):1209-1216. doi:10.1164/rccm.200303-347OC.

157. Brasfield D, Hicks G, Soong S-J, Peters J, Tiller R. Evaluation of scoring system of the chest radiograph in cystic fibrosis: a collaborative study. *Am J Roentgenol*. 1980;134(6):1195-1198. doi:10.2214/ajr.134.6.1195.

158. Karimi M, Brazier J. Health, health-related quality of life, and quality of life: what is the difference? *Pharmacoeconomics*. 2016;34(7):645-649. doi:10.1007/s40273-016-0389-9.

159. Bakas T, McLennon SM, Carpenter JS, et al. Systematic review of health-related quality of life models. *Heal Qual Life Outcomes*. 2012;10(1):134-145. doi:10.1186/1477-7525-10-134.

160. Ferrans C, Zerwic J, Wilbur J, Larson J. Conceptual model of health-related quality of life. *J Nurs Scholarsh*. 2005;37(4):336-342. doi:10.1111/j.1547-5069.2005.00058.x.

161. Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the

EQ-5D-Y: results from a multinational study. *Qual Life Res*. 2010;19(6):887-897. doi:10.1007/s11136-010-9649-x.

162. Eidt-Koch D, Mittendorf T, Greiner W. Cross-sectional validity of the EQ-5D-Y as a generic health outcome instrument in children and adolescents with cystic fibrosis in Germany. *BMC Pediatr*. 2009;9:55. doi:10.1186/1471-2431-9-55.

163. Scott D, Ferguson GD, Jelsma J. The use of the EQ-5D-Y health related quality of life outcome measure in children in the Western Cape, South Africa: psychometric properties, feasibility and usefulness - a longitudinal, analytical study. *Health Qual Life Outcomes*. 2017;15(1):12. doi:10.1186/s12955-017-0590-3.

164. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: reliability and validity of the Pediatric Quality of Life Inventory ™ Version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001;39(8):800-812. http://www.jstor.org/stable/3767969. Accessed March 8, 2017.

165. Varni JW, Burwinkle TM, Seid M. The PedsQL™ 4.0 as a school population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3(6):329-341. doi:10.1007/s11136-005-1388-z.

166. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes*. 2007;5:1. doi:10.1186/1477-7525-5-1.

167. Birring S, Prudon B, Carr A, Singh S. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58(4):339-343. doi:10.1136/thorax.58.4.339.

168. Padilla A, Olveira G, Olveira C. Validity and reliability of the St George's Respiratory Questionnaire in adults with cystic fibrosis. *Arch Bronconeumol*. 2007;43(4):205-211. doi:10.1157/13100539.

169. Quittner AL, Buu A, Messer M a, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest*. 2005;128(4):2347-2354.

doi:10.1378/chest.128.4.2347.

170. Shwachman H, Kulcyncki LL. Long-term study of one hundred patients with cystic fibrosis made over a five to fourteen year period. *Am J Dis Child*. 1958;96(1):6-15. doi:10.1001/archpedi.1958.02060060008002.

171. Doershuk C, Matthews L, Tucker A, et al. A 5 year clinical evaluation of a therapeutic program for patients with cystic fibrosis. *J Pediatr*. 1964;65:677-693. doi:doi:10.1016/S0022-3476(64)80152-9.

172. Hafen GM, Ranganathan SC, Robertson CF, Robinson PJ. Clinical scoring systems in cystic fibrosis. *Pediatr Pulmonol*. 2006;41:602-617. doi:10.1002/ppul.20376.

173. Huang N, Keith H, Palmer J, Hsuan F. A scoring system for short-term evaluation of patients with cystic fibrosis: a possible means for assessment of antibiotic efficacy. In: Warick W, ed. *1000 Years of Cystic Fibrosis*. Minesota: Collected Papers Annuals of Internal Medicine, University of Minnesota; 1981:207-215.

174. Kanga J, Kuhn R, Craigmyle L, Haverstock D, Church D. Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation. *Clin Ther*. 1999;21(8):1343-1356. doi:10.1016/S0149-2918(99)80035-6.

175. World Health Organization/UNICEF. Global action plan for the prevention and control of pneumonia. 2009. http://www.who.int/maternal_child_adolescent/documents/fch_cah_nch_09_04/en/index.html. Accessed February 11, 2013.

176. World Health Organization. Pneumonia, fact sheet N°331. 2015. http://www.who.int/mediacentre/factsheets/fs331/en/index.html. Accessed February 6, 2013.

177. Alcon A, Fabregas N, Torres A. Pathophysiology of pneumonia. *Clin Chest Med*. 2005;26(1):39-46. doi:10.1016/j.ccm.2004.10.013.

178. World Health Organization. MDG 4: reduce child mortality. 2015. http://www.who.int/topics/millennium_development_goals/child_mortality/en/. Accessed July 14, 2016.

179. Gaffey MF, Das JK, Bhutta A. Millennium Development Goals 4 and 5: past and future progress. *Semin Fetal Neonatal Med*. 2015;20:285-292. doi:10.1016/j.siny.2015.07.001.

180. Molyneux M, Molyneux E. Reaching Millennium Development Goal 4. *Lancet*. 2016;4:e146-e147. doi:10.1016/S2214-109X(16)00009-7.

181. Countdown Coverage Writing Group. Countdown to 2015 for maternal, newborn, and child survival: the 2008 report on tracking coverage. *Lancet*. 2008;371:1247-1258.

182. Bhutta Z, Chopra M, Axelson H, et al. Review Countdown to 2015 decade report (2000 – 10): taking stock of maternal, newborn, and child survival. *Lancet*. 2010;375:2032-2044. doi:10.1016/S0140-6736(10)60678-2.

183. Victora CG, Requejo JH, Barros AJD, et al. Countdown to 2015: a decade of tracking progress for maternal, newborn, and child survival. *Lancet*. 2016;387(10032):2049-2059. doi:10.1016/S0140-6736(15)00519-X.

184. World Health Organization/UNICEF. *A Decade of Tracking Progress for Maternal, Newborn and Child Survival. The 2015 Report*. Geneva: UNICEF/World Health Organization; 2015.

185. Zaidi AKM, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet*. 2005;365:1175-1188. doi:10.1016/S0140-6736(05)71881-X.

186. Nagata E, Brito AS, Matsuo T. Nosocomial infections in a neonatal intensive care unit: incidence and risk factors. *Am J Infect Control*. 2002;30(1):26-31. doi:10.1067/mic.2002.119823.

187. World Health Organization. Part 2: causes of death. In: *The Global Burden of Disease: 2004 Update*. Vol 1st ed. ; 2008:7-17.

188. World Health Organization. Mortality and burden of disease estimates for WHO member states in 2008 by sex and age. 2011. http://www.who.int/healthinfo/global_burden_disease/estimates_country/en/inde

x.html. Accessed July 8, 2013.

189. Statistics South Africa. *Mortality and Causes of Death in South Africa, 2015: Findings from Death Notification*. Pretoria; 2017. http://www.statssa.gov.za/publications/P03093/P030932015.pdf. Accessed March 8, 2017.

190. World Health Organization/UNICEF. *Pneumonia: The Forgotten Killer of Children*. New York: UNICEF; 2006. http://www.who.int/maternal_child_adolescent/documents/9280640489/en/. Accessed February 6, 2013.

191. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43(1):90-98. doi:10.1086/504871.

192. Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. *J Infect Dis*. 2005;191(12):2038-2045. doi:10.1086/430356.

193. Crowe J. Viral pneumonia. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:453-460.

194. Bradley J, Byington C, Shah S, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e1-e52. doi:10.1093/cid/cir531.

195. Shisana O, Rehle TM, Simbayi L, et al. *South African National HIV Prevalence, Incidence and Behaviour Survey, 2012*. Vol 1st ed. Cape Town: HSRC Press; 2014.

196. Kattan M, Zar H. Respiratory disorders in pediatric HIV infection. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:920-933.

197. Catherinot E, Lanternier F, Bougnoux M-E, Lecuit M, Couderc L-J, Lortholary O. Pneumocystis jirovecii pneumonia. *Infect Dis Clin North Am*. 2010;24:107-138. doi:10.1016/j.idc.2009.10.010.

198. Sokulska M, Kicia M, Weso M, Hendrich AB. Pneumocystis jirovecii — from a commensal to pathogen: clinical and diagnostic review. *Parasitol Res*. 2015;114:3577-3585. doi:10.1007/s00436-015-4678-6.

199. McNally LM, Jeena PM, Gajee K, et al. Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. *Lancet*. 2007;369(9571):1440-1451. doi:10.1016/S0140-6736(07)60670-9.

200. Singh Y. Pathophysiology of community acquired pneumonia. *Suppl to JAPI*. 2012;60:7-9. http://www.japi.org/january_special_2012/03_pathophysiology_of_community.pdf. Accessed July 14, 2016.

201. Edmond K, Scott S, Korczak V, et al. Long term sequelae from childhood pneumonia; systematic review and meta-analysis. *PLoS One*. 2012;7(2):e31239. doi:10.1371/journal.pone.0031239.

202. Stafler P, Carr SB. Non-cystic fibrosis bronchiectasis: its diagnosis and management. *Arch Dis Child Educ Pract Ed*. 2010;95(3):73-82. doi:10.1136/adc.2007.130054.

203. Tong N. Priority medicines for Europe and the world. “A public health approach to innovation”. update on 2004 background paper. 2013. http://www.who.int/medicines/areas/priority_medicines/BP6_12Osteo.pdf. Accessed March 2, 2017.

204. Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. *Pediatr Pulmonol*. 2014;49(4):318-325. doi:10.1002/ppul.22842.

205. El Moussaoui R, Opmeer B, de Borgie C, et al. Long-term symptom recovery and health-related quality of life in patients with mild-to-moderate-severe community-acquired pneumonia. *Chest*. 2006;130(4):1165-1172. doi:10.1378/chest.130.4.1165.

206. World Health Organization/UNICEF. *Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025. The Integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)*. WHO Library Cataloguing-in-Publication Data; 2013.

207. Madhi SA, Levine OS, Hajjeh R, Mansoor D, Cherian T. Vaccines to prevent pneumonia and improve child survival. *Bull World Health Organ*. 2008;86(5):365-372. doi:10.2471/BLT.07.044503.

208. Klugman K, Madhi S, Huebner R, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003;349(14):1341-1348. doi:10.1056/NEJMoa035060.

209. Dherani M, Pope D, Mascarenhas M, Smith KR, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: a systematic review and meta-analysis. *Bull World Health Organ*. 2008;86(5):390-398. doi:10.2471/BLT.07.044529.

210. Jones CHD, Ward A, Hodkinson PW, et al. Caregivers' experiences of pathways to care for seriously Ill children in Cape Town, South Africa: a qualitative investigation. *PLoS One*. 2016;11(3):1-15. doi:10.1371/journal.pone.0151606.

211. Hodkinson P, Argent A, Wallis L, et al. Pathways to care for critically Ill or injured children: a cohort study from first presentation to healthcare services through to admission to intensive care or death. *PLoS One*. 2016;11(1):1-16. doi:10.1371/journal.pone.0145473.

212. Marostica P, Stein R. Community-acquired bacterial pneumonia. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:461-472.

213. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Heal Technol Assess*. 2003;7(35). doi:10.3310/hta7350.

214. Rothberg MB, Fisher D, Kelly B, Rose DN. Management of influenza symptoms in healthy children. *Arch Pediatr Adolesc Med*. 2005;159(11):1055.

doi:10.1001/archpedi.159.11.1055.

215. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. *Genet Divers RNA Viruses*. 1992;176:119-130. doi:10.1007/978-3-642-77011-1_8.

216. Moscona A. Global Transmission of Oseltamivir-Resistant Influenza. *N Engl J Med*. 2009;360(10):953-956. doi:10.1056/NEJMp0900648.

217. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66 Suppl 2:ii1-ii23. doi:10.1136/thoraxjnl-2011-200598.

218. Principi N, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax*. 2011;66(9):815-822. doi:10.1136/thx.2010.142604.

219. Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Adjunctive therapies for community-acquired pneumonia: a systematic review. *J Antimicrob Chemother*. 2008;62(4):661-668. doi:10.1093/jac/dkn283.

220. Moreno-Pérez D, Andrés Martín A, Tagarro García A, et al. Community acquired pneumonia in children: treatment of complicated cases and risk patients. Consensus statement by the Spanish Society of Paediatric Infectious Diseases (SEIP) and the Spanish Society of Paediatric Chest Diseases (SENP). *An Pediatría*. 2015;83(3):217.e1-e217.e11. doi:10.1016/j.anpede.2015.08.002.

221. Paludo C, Zhang L, Lincho C, Lemos D, Real G, Bergamin J. Chest physical therapy for children hospitalised with acute pneumonia: a randomised controlled trial. *Thorax*. 2008;63(9):791-794. doi:10.1136/thx.2007.088195.

222. Lukrafka J, Fuchs S, Fischer G. Chest physiotherapy in paediatric patients hospitalised with community-acquired pneumonia: a randomised clinical trial. *Arch Dis Child*. 2012;97(11):967-971. doi:10.1136/archdischild-2012-302279.

223. Abdelbasset W, Elnegamy T. Effect of chest physical therapy on pediatrics hospitalized with pneumonia. *Int J Heal Rehabil Sci*. 2015;4(4):219-226.

doi:10.5455/ijhrs.000000095.

224. Levine A. Chest physical therapy for children with pneumonia. *J Am Osteopath Assoc*. 1978;78(2):122-125.

225. Britton S, Bejstedt M, Vedin L. Chest physiotherapy in primary pneumonia. *Br Med J*. 1985;290(6483):1703-1704. doi:10.1136/bmj.290.6483.1703.

226. Plebani A, Pinzani R, Startari R, Brusa D, Padoan R. Usefulness of chest physiotherapy with positive expiratory pressure (PEP)-mask in HIV-infected children with recurrent pulmonary infections. *Acta Paediatr*. 1997;86(11):1195-1197. doi:10.1111/j.1651-2227.1997.tb14844.x.

227. Stapleton T. Chest physiotherapy in primary pneumonia. *Br Med J (Clin Res Ed)*. 1985;291(6488):143. doi:10.1136/bmj.291.6488.143-b.

228. Santos C, Ribeiro M, Ribeiro J, Morcillo A. Respiratory physiotherapy in children with community-acquired pneumonia. *Can J Resp Ther*. 2009;45(3):23. http://www.cjrt.ca/download/2009-volume-45-number-3/?wpdmdl=76. Accessed April 26, 2013.

229. Gajdos V, Katsahian S, Beydon N, et al. Effectiveness of chest physiotherapy in infants hospitalized with acute bronchiolitis: a multicenter, randomized, controlled trial. *PLoS Med*. 2010;7(9):e1000345. doi:10.1371/journal.pmed.1000345.

230. Yang M, Yuping Y, Yin X. Chest physiotherapy for pneumonia in adults. *Cochrane Database Syst Rev*. 2010;(10). doi:10.1002/14651858.CD006338.pub2.

231. Chaves G, Fregonezi G, Dias F, et al. Chest physiotherapy for pneumonia in children (Review). *Cochrane Database Syst Rev*. 2013;Sep 20(9):CD010277. doi:10.1002/14651858.CD010277.pub2.

232. Zhao S. Nasal continuous positive airway pressure for the treatment of severe pneumonia in children from the plateau area: clinical analysis of 47 cases. *Chinese J Contemp Pediatr*. 2010;12:226-227. http://www.cjcp.org/EN/abstract/abstract12218.shtml. Accessed July 14, 2016.

233. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [Updated September 2009]*. The Cochrane Collaboration; 2009. www.cochrane-handbook.org. Accessed July 15, 2014.

234. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed1000097.

235. Mahood Q, Van Eerd D, Irvin E. Searching for grey literature for systematic reviews: Challenges and benefits. *Res Synth Methods*. 2014;5:221-234. doi:10.1002/jrsm.1106.

236. Deeks J, Higgins J, Altman D. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Intervention*. Vol 1st ed. Chichester: John Wiley; 2008:243-296.

237. Ramsay C. How do you include trials with more than two groups into a single meta-analysis. *Methodol Cochrane Eff Pract Organ Care Gr*. 2003. http://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/FAQmultiplegroups2003.pdf. Accessed March 15, 2013.

238. Gilchrist F. Is the use of chest physiotherapy beneficial in children with community acquired pneumonia? *Arch Dis Child*. 2008;93(2):176-178. doi:10.1136/adc.2007.127290.

239. Lisy K. Chest physiotherapy for pneumonia in children. *Am J Nurs*. 2014;114(5):16. doi:10.1097/01.NAJ.0000446761.33589.70.

240. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377:1011-1018. doi:10.1016/S0140-6736(10)62226-X.

241. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-1446. doi:10.1001/jama.282.15.1440.

242. Forster J, Ihorst G, Rieger CHL, et al. Prospective population-based study of viral lower respiratory tract infections in children under 3 years of age (the PRI.DE study). *Eur J Pediatr*. 2004;163(12):709-716. doi:10.1007/s00431-004-1523-9.

243. Hasan R, Rhodes J, Thamthitiwat S, et al. Incidence and etiology of acute lower respiratory tract infections in hospitalized children younger than 5 years in rural Thailand. *Pediatr Infect Dis J*. 2014;33(2):e45-e52. doi:10.1097/INF.0000000000000062.

244. Wolf DG, Greenberg D, Kalkstein D, et al. Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. *Pediatr Infect Dis J*. 2006;25(4):320-324. doi:10.1097/01.inf.0000207395.80657.cf.

245. Hatipoglu N, Somer A, Badur S, et al. Viral etiology in hospitalized children with acute lower respiratory tract infection. *Turk J Pediatr*. 2011;53(5):508-516. http://www.turkishjournalpediatrics.org/uploads/pdf_TJP_966.pdf. Accessed February 6, 2017.

246. Bouman A, Jan Heineman M, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update*. 2005;11(4):411-423. doi:10.1093/humupd/dmi008.

247. Muenchhoff M, Goulder PJR. Sex differences in pediatric infectious diseases. *J Infect Dis*. 2014;209(suppl 3):S120-S126. doi:10.1093/infdis/jiu232.

248. Tepper RS, Morgan WJ, Cota K, Wright A, Taussig LM. Physiologic growth and development of the lung during the first year of life. *Am Rev Respir Dis*. 1986;134(3):513-519. http://www.atsjournals.org.ezproxy.uct.ac.za/doi/abs/10.1164/arrd.1986.134.3.513. Accessed March 3, 2017.

249. UNAIDS. AIDSinfo. HIV prevalence. 2015. http://aidsinfo.unaids.org/. Accessed February 5, 2017.

250. Morrow BM, Feldman C, Green R. Acute viral bronchiolitis in South Africa: intensive care management for severe disease. *South African Med J*. 2016;106(5):446-448. doi:10.7196/samj.v106i5.10436.

251. White DA, Madhi SA, Jeena P, et al. Acute viral bronchiolitis in South Africa: viral aetiology and clinical epidemiology. *South African Med J*. 2016;106(5):443-445. doi:10.7196/SAMJ.2016.v106i5.10444.

252. Lonngren C, Morrow BM, Haynes S, Yusri T, Vyas H, Argent AC. North-South divide: distribution and outcome of respiratory viral infections in paediatric intensive care units in Cape Town (South Africa) and Nottingham (United Kingdom). *J Paediatr Child Health*. 2014;50(3):208-215. doi:10.1111/jpc.12458.

253. Chou C-A, Lin T-I, Chen Y-S, et al. Comparisons of etiology and diagnostic tools of lower respiratory tract infections in hospitalized young children in Southern Taiwan in two seasons. *J Microbiol Immunol Infect*. 2016;49(4):539-545. doi:10.1016/j.jmii.2014.08.029.

254. Ghani AS., Morrow BM, Hardie DR, Argent AC. An investigation into the prevalence and outcome of patients admitted to a pediatric intensive care unit with viral respiratory tract infections in Cape Town, South Africa. *Pediatr Crit Care Med*. 2012;13(5):e275-e281. doi:10.1097/PCC.0b013e3182417848.

255. Wang EEL, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr*. 1995;126(2):212-219. doi:10.1016/S0022-3476(95)70547-3.

256. American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502. doi:10.1542/peds.2014-2742.

257. Figuls Mr, Gine-Garriga M, Rugeles C, et al. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Libr*. 2016;2(2):CD004873. doi:10.1002/14651858.CD004873.pub5.

258. Zar HJ, Madhi SA, White DA, et al. Acute viral bronchiolitis in South Africa: strategies for management and prevention. *South African Med J*. 2016;106(4):330-332. doi:10.7196/SAMJ.2016.v106i4.10437.

259. Caffrey Osvald E, Clarke JR. NICE clinical guideline: bronchiolitis in children. *Arch Dis*

Child - Educ Pract Ed. 2015:1-3. doi:10.1136/archdischild-2015-309156.

260. Corten L, Jelsma J, Morrow BM. Chest physiotherapy in children with acute bacterial pneumonia. *South African J Physiother*. 2015;71(1):#256. doi:10.4102/sajp.v71i1.256.

261. Postiaux G, Louis J, Labasse H, et al. Evaluation of an alternative chest physiotherapy method in infants with respiratory syncytial virus bronchiolitis. *Respir Care*. 2011;56(7):989-994. doi:10.4187/respcare.00721.

262. Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr*. 2008;20:272-278. doi:10.2223/JPED.49.

263. Morrow BM, Hatherill M, Smuts HEM, Yeats J, Pitcher R, Argent AC. Clinical course of hospitalised children infected with human metapneumovirus and respiratory syncytial virus. *J Paediatr Child Health*. 2006;42(4):174-178. doi:10.1111/j.1440-1754.2006.00825.x.

264. Argent AC, Ahrens J, Morrow BM, et al. Pediatric intensive care in South Africa: an account of making optimum use of limited resources at the Red Cross War Memorial Children's Hospital. *Pediatr Crit Care Med*. 2014;15(1):7-14. doi:10.1097/PCC.0000000000000029.

265. Rodriguez DA, Rodriguez-Martinez CE, Cardenas AC, et al. Predictors of severity and mortality in children hospitalized with respiratory syncytial virus infection in a tropical region. *Pediatr Pulmonol*. 2014;49(3):269-276. doi:10.1002/ppul.22781.

266. Green N, Johnson AP, Henderson KL, et al. Quantifying the burden of hospital-acquired bloodstream infection in children in England by estimating excess length of hospital stay and mortality using a multistate analysis of linked, routinely collected data. *J Pediatric Infect Dis Soc*. 2015;4(4):305-312. doi:10.1093/jpids/piu073.

267. Venditti M, Falcone M, Corrao S, Licata G, Serra P. Outcomes of patients hospitalized with community-acquired, healthcare-associated, and hospital-acquired pneumonia. *Ann Intern Med*. 2009;150:19-26. doi:10.7326/0003-4819-150-1-200901060-00005.

268. Ahn A, Edwards KM, Grijalva CG, et al. Secondhand smoke exposure and illness

severity among children hospitalized with pneumonia. *J Pediatr*. 2015;167(4):869-874. doi:10.1016/j.jpeds.2015.06.049.

269. Wilson KM, Pier JC, Wesgate SC, Cohen JM, Blumkin AK. Secondhand tobacco smoke exposure and severity of influenza in hospitalized children. *J Pediatr*. 2013;162(1):16-21. doi:10.1016/j.jpeds.2012.06.043.

270. Miller S, Hall D, Clayton C, Nelson R. Chest physiotherapy in cystic fibrosis: a comparative study of autogenic drainage and the active cycle of breathing techniques with postural drainage. *Thorax*. 1995;50(2):165-169. doi:10.1136/thx.50.2.165.

271. Lindemann H, Boldt A, Kieselmann R. Autogenic drainage: efficacy of a simplified method. *Acta Univ Carolinae Medica*. 1990;36(1-4):210-212. https://www.ncbi.nlm.nih.gov/pubmed/2130697. Accessed February 14, 2013.

272. McIlwaine M, Wong L, Chilvers M, Davidson G. Long-term comparative trial of two different physiotherapy techniques; postural drainage with percussion and autogenic drainage, in the treatment of cystic fibrosis. *Pediatr Pulmonol*. 2010;45(11):1064-1069. doi:10.1002/ppul.21247.

273. Portney L, Watkins M. Epidemiology. In: Mehalik C, ed. *Foundations of Clinical Research. Application to Practice*. Vol 2nd ed. New Jersey: Prentice-Hall Inc; 2000:317-344.

274. Patsopoulos N. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011;13(2):217-224. http://www.dialogues-cns.org/publication/a-pragmatic-view-on-pragmatic-trials/. Accessed July 19, 2016.

275. Portney L, Watkins M. Experimental control. In: Mehalik C, ed. *Foundations of Clinical Research. Application to Practice*. Vol 2nd ed. New Jersey: Prentice-Hall Inc; 2000:153-176.

276. Western Cape Government. Red Cross War Memorial Children's Hospital: overview. 2013. http://www.westerncape.gov.za/redcrosshospital. Accessed April 5, 2013.

277. Bassat Q, Lanaspa M, Machevo S, et al. Hypoxaemia in Mozambican children <5

years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models. *Trop Med Int Heal*. 2016;21(9):1147-1156. doi:10.1111/tmi.12738.

278. Morrow BM, Samuel CM, Zampoli M, Whitelaw A, Zar HJ. Pneumocystis pneumonia in South African children diagnosed by molecular methods. *BMC Res Notes*. 2014;7:26. doi:http://dx.doi.org/10.1186/1756-0500-7-26.

279. Van De Water JM. The treatment of pleural effusion complicating pneumonia. *Chest*. 1970;57(3):259-262. doi:10.1378/chest.57.3.259.

280. Usen S, Weber M, Mulholland K, et al. Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. *BMJ*. 1999;318(7176):86-91. doi:10.1136/bmj.318.7176.86.

281. Panitch HB. The pathophysiology of respiratory impairment in pediatric neuromuscular diseases. *Pediatrics*. 2009;123 Suppl(May 2009):S215-S218. doi:10.1542/peds.2008-2952C.

282. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen*. 2012;141(1):2-18. doi:10.1037/a0024338.

283. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Vol 2nd ed. Hillsdale, New Jersey, New Jersey: Lawrence Erlbaum Associates; 1988.

284. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805.

285. Jat KR. Spirometry in children. *Prim Care Respir J*. 2013;22(2):221-229. doi:10.4104/pcrj.2013.00042.

286. Weissman C, Kemper MB, Harding J. Response of critically ill patients to increased oxygen demand: hemodynamic subsets. *Crit Care Med*. 1994;22(11):1809-1816. http://journals.lww.com/ccmjournal/Abstract/1994/11000/Response_of_critically_ill_patients_to_increased.17.aspx. Accessed July 16, 2016.

287. Macklem PT. Respiratory muscles: the vital pump. *Chest*. 1980;78(5):753-758.

doi:10.1378/chest.78.5.753.

288. Elphick HE, Lancaster G a, Solis A, Majumdar A, Gupta R, Smyth RL. Validity and reliability of acoustic analysis of respiratory sounds in infants. *Arch Dis Child*. 2004;89(11):1059-1063. doi:10.1136/adc.2003.046458.

289. Morrow B, Angus L, Greenhough D, et al. The reliability of identifying bronchial breathing by auscultation. *Int J Ther Rehabil*. 2010;17(2):69-75. doi:10.12968/ijtr.2010.17.2.46332.

290. Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med*. 2006;173(5):475-482. doi:10.1164/rccm.200505-840OE.

291. Ratjen FA. Cystic fibrosis: pathogenesis and future treatment strategies. *Respir Care*. 2009;54(5):595-602. http://rc.rcjournal.com/content/54/5/595.short. Accessed October 4, 2014.

292. South African Cystis Fibrosis Association., South African Cystic Fibrosis Association. *The South African Cystic Fibrosis Consensus Document*. Vol 4th ed. The South African Cystic Fibrosis Association; 2012.

293. Rowe S, Miller S, Sorscher E. Cystic fibrosis. *N Engl J Med*. 2005;352(19):1992-2001. doi:10.1056/NEJMra043184.

294. Reddy MM, Light MJ, Quinton PM. Activation of the epithelial Na+ channel (ENaC) requires CFTR Cl- channel function. *Nature*. 1999;402(6759):301-304. doi:10.1038/46297.

295. CFMD/CFTR1 team. Cystic fibrosis mutation database. 2011. http://www.genet.sickkids.on.ca/cftr/ConsortiumDataPage1.html. Accessed December 12, 2016.

296. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell*. 1993;73(7):1251-1254. doi:10.1016/0092-8674(93)90353-R.

297. Wilschanski M. Patterns of gastrointestinal disease associated with mutations of CFTR. *Curr Gastroenterol Rep*. 2008;10(3):316-323. doi:10.1007/s11894-008-0062-3.

298. Goldman A, Labrum R, Claustres M, et al. The molecular basis of cystic fibrosis in South Africa. *Clin Genet*. 2001;59:37-41. doi:10.1034/j.1399-0004.2001.590106.x.

299. Masekela R, Zampoli M, Westwood AT, et al. Phenotypic expression of the 3120+1G>A mutation in non-Caucasian children with cystic fibrosis in South Africa. *J Cyst Fibros*. 2013;12(4):363-366. doi:10.1016/j.jcf.2012.11.003.

300. Quinton P. Cystic fibrosis: a disease in electrolyte transport. *FASEB J*. 1990;4(10):2709-2717. http://www.fasebj.org/content/4/10/2709.long. Accessed October 4, 2014.

301. Ahmed N, Durie P. Nonpulmonary manifestations of cystic fibrosis. In: Wilmott R, Boat T, Bush A, Chernick V, Deterding R, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. Vol 8th ed. Philadelphia: Elsevier Saunders; 2012:781-795.

302. Brei C, Simon A, Krawinkel MB, Naehrlich L. Individualized vitamin A supplementation for patients with cystic fibrosis. *Clin Nutr*. 2013;32(5):805-810. doi:10.1016/j.clnu.2013.01.009.

303. Curry MP, Hegarty JE. The gallbladder and biliary tract in cystic fibrosis. *Curr Gastroenterol Rep*. 2005;7(2):147-153. doi:10.1007/s11894-005-0053-6.

304. Johannesson M, Gottlieb C, Hjelte L. Delayed puberty in girls with cystic fibrosis despite good clinical status. *Pediatrics*. 1997;99(1):29-34. doi:10.1542/peds.99.1.29.

305. Bournez M, Bellis G, Huet F. Growth during puberty in cystic fibrosis: a retrospective evaluation of a French cohort. *Arch Dis Child*. 2012;97(8):714-720. doi:10.1136/archdischild-2011-301069.

306. Aswani N, Taylor CJ, McGaw J, Pickering M, Rigby AS. Pubertal growth and development in cystic fibrosis: a retrospective review. *Acta Paediatr*. 2003;92(9):1029-1032. doi:10.1080/08035250310004333.

307. Reiter EO, Stern RC, Root AW. The reproductive endocrine system in cystic fibrosis. *Am J Dis Child*. 1981;135(5):422-426. doi:10.1001/archpedi.1981.02130290020009.

308. McCallum T, Milunsky J, Cunningham D, Harris D, Maher T, Oates R. Fertility in men with cystic fibrosis: an update on current surgical practices and outcomes. *Chest*. 2000;118(4):1059-1062. doi:10.1378/chest.118.4.1059.

309. Kerem E, Conway S, Elborn S, et al. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros*. 2005;4(1):7-26. doi:10.1016/j.jcf.2004.12.002.

310. Hodges CA, Palmert MR, Drumm ML. Infertility in females with cystic fibrosis is multifactorial: evidence from mouse models. *Endocrinology*. 2008;149(6):2790-2797. doi:10.1210/en.2007-1581.

311. Stead R, Hodson M, Batten J, Adams J, Jacobs H. Amenorrhea in cystic fibrosis. *Clin Endocrinol (Oxf)*. 1987;26(2):187-195. doi:10.1111/j.1365-2265.1987.tb00776.x.

312. Toh HS, Batchelor-McAuley C, Tschulik K, Compton RG. Electrochemical detection of chloride levels in sweat using silver nanoparticles: a basis for the preliminary screening for cystic fibrosis. *Analyst*. 2013;138(15):4292-4297. doi:10.1039/c3an00843f.

313. Smith JJ, Travis SM, Greenberg EP. Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. *Cell*. 1996;85(2):229-236. doi:10.1016/S0092-8674(00)81099-5.

314. Berkhout MC, Van Rooden CJ, Rijntjes E, Fokkens WJ, El Bouazzaoui LH, Heijerman HGM. Sinonasal manifestations of cystic fibrosis: a correlation between genotype and phenotype? *J Cyst Fibros*. 2014;13(4):442-448. doi:10.1016/j.jcf.2013.10.011.

315. Mainz JG, Naehrlich L, Schien M, et al. Concordant genotype of upper and lower airways P aeruginosa and S aureus isolates in cystic fibrosis. *Thorax*. 2009;64(December 2005):535-540. doi:10.1136/thx.2008.104711.

316. Aanaes K. Bacterial sinusitis can be a focus for initial lung colonisation and chronic lung infection in patients with cystic fibrosis. *J Cyst Fibros*. 2013;12(suppl 2):S1-S20. doi:10.1016/S1569-1993(13)00150-1.

317. Spicuzza L, Sciuto C, Leonardi S, Rosa M La. Early occurrence of obstructive sleep apnea in infants and children with cystic fibrosis. *Arch Pediatr Adolesc Med*.

2012;166(12):1165-1169. doi:10.1001/archpediatrics.2012.1177.

318. Ramos RTT, Salles C, Gregório PB, et al. Evaluation of the upper airway in children and adolescents with cystic fibrosis and obstructive sleep apnea syndrome. *Int J Pediatr Otorhinolaryngol*. 2009;73(12):1780-1785. doi:10.1016/j.ijporl.2009.09.037.

319. Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr*. 2013;162(3):530-535.e1. doi:10.1016/j.jpeds.2012.08.040.

320. Dequeker E, Stuhrmann M, Morris MA, et al. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations. *Eur J Hum Genet*. 2009;17:51-65. doi:10.1038/ejhg.2008.136.

321. Harton GL, Magli MC, Lundin K, Montag M, Lemmen J, Harper JC. ESHRE PGD Consortium/Embryology Special Interest Groupbest practice guidelines for polar body and embryo biopsy for preimplantation genetic diagnosis/screening (PGD/PGS). *Hum Reprod*. 2011;26(1):41-46. doi:10.1093/humrep/deq265.

322. Davis LB, Champion SJ, Fair SO, Baker VL, Garber AM. A cost-benefit analysis of preimplantation genetic diagnosis for carrier couples of cystic fibrosis. *Fertil Steril*. 2010;93(6):1793-1804. doi:10.1016/j.fertnstert.2008.12.053.

323. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45(1):16-26. doi:10.1002/uog.14636.

324. Royal College of Obstetricians and Gynaecologists (RCOG). Amniocentesis and chorionic villus sampling. In: *Green Top Guideline No.8.* Vol 4th ed. London: RCOG Press; 2010. http://www.jsog.org/GuideLines/Amniocentesis_and_chorionic_villus_sampling.pdf. Accessed February 23, 2013.

325. Wagener J, Zemanick A, Sontag M. Newborn screening for cystic fibrosis. *Curr Opin Pediatr*. 2012;24:329-335. doi:10.1097/MOP.0b013e328353489a.

326. Castellani C, Massie J, Sontag M, Southern KW. Newborn screening for cystic fibrosis. *Lancet Respir Med*. 2016;4(8):653-661. doi:10.1016/S2213-2600(16)00053-9.

327. Laterza L, Bruno G, Agnes A, et al. Pancreatic function assessment. *Eur Rev Med Pharmacol Sci*. 2013;17(Suppl 2):65-71. http://www.europeanreview.org/article/6337. Accessed February 23, 2017.

328. Westwood T. The epidemiology of cystic fibrosis in the Western Cape province. *South African J Child Heal*. 2007;1(2):78-81. doi:http://www.sajch.org.za/index.php/SAJCH/article/view/48/9.

329. Valle E, Burgos R, Valle J, Egas Béjar D, Ruiz-Cabezas J. Analysis of CFTR gene mutations and cystic fibrosis incidence in the Ecuadorian population. *Invest Clin*. 2007;48(1):91-98. https://www.ncbi.nlm.nih.gov/pubmed/17432547. Accessed December 15, 2016.

330. Britto M, Kotagal U, Hornung R, Atherton H, Tsevat J, Wilmott R. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest*. 2002;121(1):64-72. doi:10.1378/chest.121.1.64.

331. Staab D, Wenninger K, Gebert N, et al. Quality of life in patients with cystic fibrosis and their parents: what is important besides disease severity? *Thorax*. 1998;53(9):727-731. doi:10.1136/thx.53.9.727.

332. Shoff SM, Tluczek A, Laxova A, Farrell PM, Lai HJ. Nutritional status is associated with health-related quality of life in children with cystic fibrosis aged 9-19years. *J Cyst Fibros*. 2013;12(6):746-753. doi:10.1016/j.jcf.2013.01.006.

333. Oliver KN, Free ML, Bok C, McCoy KS, Lemanek KL, Emery CF. Stigma and optimism in adolescents and young adults with cystic fibrosis. *J Cyst Fibros*. 2014;13(6):737-744. doi:10.1016/j.jcf.2014.04.005.

334. Smith BA, Modi AC, Quittner AL, Wood BL. Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance. *Pediatr Pulmonol*. 2010;45(8):756-763. doi:10.1002/ppul.21238.

335. Yohannes AM, Willgoss TG, Fatoye FA, Dodd M, Pt D, Webb K. Relationship between anxiety, depression, and quality of life in adult patients with cystic fibrosis. *Respir Care*. 2012;57(4):550-556. doi:10.4187/respcare.01328.

336. Hilliard M, Eakin M, Borrelli B, Green A, Riekert K. Medication beliefs mediate between depressive symptoms and medication adherence in cystic fibrosis. *Heal Psychol*. 2015;34(5):496-504. doi:10.1037/hea0000136.

337. Quittner AL, Abbott J, Georgiopoulos AM, et al. International committee on mental health in cystic fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax*. 2015;(Published online first):1-9. doi:10.1136/thoraxjnl-2015-207488.

338. Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. *J Cyst Fibros*. 2016;15:675-680. doi:10.1016/j.jcf.2016.02.010.

339. Haack A, Aragão GG, Novaes MRCG. Pathophysiology of cystic fibrosis and drugs used in associated digestive tract diseases. *World J Gastroenterol*. 2013;19(46):8552-8561. doi:10.3748/wjg.v19.i46.8552.

340. FitzSimmons S, Burkhart G, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med*. 1997;336(18):1283-1289. doi:10.1056/NEJM199705013361803.

341. Kashirskaya NY, Kapranov NI, Sander-Struckmeier S, Kovalev V. Safety and efficacy of Creon® Micro in children with exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros*. 2015;14(2):275-281. doi:10.1016/j.jcf.2014.07.006.

342. Borowitz D, Gelfond D, Maguiness K, Heubi JE, Ramsey B. Maximal daily dose of pancreatic enzyme replacement therapy in infants with cystic fibrosis: a reconsideration. *J Cyst Fibros*. 2013;12(6):784-785. doi:10.1016/j.jcf.2013.05.011.

343. Anthony H, Bines J, Phelan P, Paxton S. Relation between dietary intake and nutritional status in cystic fibrosis. *Arch Dis Child*. 1998;78(5):443-447. doi:10.1136/adc.78.5.443.

344. South African Cystic Fibrosis Association. About cystic fibrosis. 2017. http://www.sacfa.org.za/about-cystic-fibrosis/. Accessed February 21, 2017.

345. O'Riordan SM, Robinson PD, Donaghue KC, Moran A. Management of cystic fibrosis-related diabetes. *Pediatr Diabetes*. 2008;9(Part 1):338-344. doi:10.1111/j.1399-5448.2008.00437.x.

346. Scheuing N, Thon A, Konrad K, Bauer M, Karsten C. Carbohydrate intake and insulin requirement in children, adolescents and young adults with cystic fibrosis-related diabetes: a multicenter comparison to type 1 diabetes. *Clin Nutr*. 2015;34:732-738. doi:10.1016/j.clnu.2014.08.016.

347. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12):2697-2708. doi:10.2337/dc10-1768.

348. Carlyle BE, Borowitz DS, Glick PL. A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon. *J Pediatr Surg*. 2012;47(4):772-781. doi:10.1016/j.jpedsurg.2012.02.019.

349. Noblett H. Treatment of uncomplicated meconium ileus by Gastrografin enema: a preliminary report. *J Pediatr Surg*. 1969;4(2):190-197. doi:10.1016/0022-3468(69)90390-X.

350. Kao S, Franken E. Nonoperative treatment of simple meconium ileus: a survey of the Society for Pediatric Radiology. *Pediatr Radiol*. 1995;25(2):97-100. doi:10.1007/BF02010315.

351. Karimi A, Gorter RR, Sleeboom C, Kneepkens CMF, Heij HA. Issues in the management of simple and complex meconium ileus. *Pediatr Surg Int*. 2011;27(9):963-968. doi:10.1007/s00383-011-2906-4.

352. Maneksha F, Betta J, Zawin M, Poppers P. Intraoperative hypoxia and hypotension caused by Gastrografin-induced hypovolemia. *Anesthesiology*. 1984;61:454-456. http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1955686. Accessed

December 23, 2016.

353. O'Halloran SM, Gilbert J, McKendrick OM, Carty HM, Heaf DP. Gastrografin in acute meconium ileus equivalent. *Arch Dis Child*. 1986;61(11):1128-1130. doi:10.1136/adc.61.11.1128.

354. Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *J Cyst Fibros*. 2011;10(suppl 2):S24-S28. doi:10.1016/S1569-1993(11)60005-2.

355. Koletzko S, Stringer DA, Cleghorn GJ, Durie PR. Lavage treatment of distal intestinal obstruction syndrome in children with cystic fibrosis. *Pediatrics*. 1989;83(5):727-733. http://pediatrics.aappublications.org/content/83/5/727. Accessed December 23, 2016.

356. Cooke M. An approach to constipation in children. *South African Pharm J*. 2007;74(2):46-51. http://journals.co.za/docserver/fulltext/mp_pnt/11/2/mp_pnt_v11_n2_a12.pdf?expires=1488227673&id=id&accname=guest&checksum=841EC94F9D147D5DAB98E987238DC0CD. Accessed February 23, 2017.

357. Zahra M, Frederick C, Thomas R, Iqbal V, Borowitz D. Gastrografin enemas for treatment of distal intestinal obstruction syndrome in children and adults with cystic fibrosis. *J Pharm Nutr Sci*. 2014;4:76-80. doi:10.6000/1927-5951.2014.04.02.1.

358. Speck K, Charles A. Distal intestinal obstruction syndrome in adults with cystic fibrosis: a surgical perspective. *Arch Surg*. 2008;143(6):601-603. doi:10.1001/archsurg.143.6.601.

359. Cotting J, Lentze MJ, Reichen J. Effects of ursodeoxycholic acid treatment on nutrition and liver function in patients with cystic fibrosis and longstanding cholestasis. *Gut*. 1990;31(8):918-921. doi:10.1136/gut.31.8.918.

360. Colombo C, Battezzati PM, Podda M, Bettinardi N, Giunta A. Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. *Hepatology*. 1996;23(6):1484-1490. doi:10.1002/hep.510230627.

361. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology*. 2002;36(3):525-531. doi:10.1053/jhep.2002.36088.

362. Colombo C, Crosignani A, Alicandro G, et al. Long-term ursodeoxycholic acid therapy does not alter lithocholic acid levels in patients with cystic fibrosis with associated liver disease. *J Pediatr*. 2016;177:59-65. doi:10.1016/j.jpeds.2016.05.008.

363. Darling P, Lepage G, Leroy C, Masson P, Roy C. Effect of taurine supplements on fat absorption in cystic fibrosis. *Pediatr Res*. 1985;19(6):578-582. doi:10.1203/00006450-198506000-00015.

364. Thompson G. Excessive fecal taurine loss predisposes to taurine deficiency in cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 1988;7:214-219. http://journals.lww.com/jpgn/Abstract/1988/03000/Excessive_Fecal_Taurine_Loss_Predisposes_to.10.aspx. Accessed December 23, 2016.

365. Borowitz D, Baker RD, Stallings V, et al. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2002;35(September):246-259. doi:10.1097/01.MPG.0000025580.85615.14.

366. Jagannath V, Fedorowicz Z, Thaker V, Chang A. Vitamin K supplementation for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;(1):CD008482. doi:10.1002/14651858.CD008482.pub4.

367. Bonifant C, Shevill A, Chang A. Vitamin A supplementation for cystic fibrosis. *Cochrane database Syst Rev*. 2014;(5):CD006751. doi:10.1002/14651858.CD006751.pub4.

368. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD. Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. *J Clin Endocrinol Metab*. 2014;99(4):1132-1141. doi:10.1210/jc.2013-3655.

369. Millar AJW, Spearman W, Kahn D. Paediatric liver transplantation in South Africa in 2009. *South African Med J*. 2009;99(5):308-309. http://www.samj.org.za/index.php/samj/article/view/3306. Accessed February 23, 2017.

370. Muller E. Organ donation and transplantation in South Africa – an update. *Contin Med Educ*. 2013;31(6):220-222. http://www.cmej.org.za/index.php/cmej/article/view/2764/3004. Accessed February 23, 2017.

371. Milkiewicz P, Skiba G, Kelly D, et al. Transplantation for cystic fibrosis: outcome following early liver transplantation. *J Gastroenterol Hepatol*. 2002;17(2):208-213. doi:10.1046/j.1440-1746.2002.02671.x.

372. Fridell JA, Bond GJ, Mazariegos G V., et al. Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. *J Pediatr Surg*. 2003;38(8):1152-1156. doi:10.1016/S0022-3468(03)00260-4.

373. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros*. 2011;10(suppl 2):S29-S36. doi:10.1016/S1569-1993(11)60006-4.

374. Zuckermann M, Loveland JA. Selection and work-up for liver transplantation. *South African Med J*. 2012;102(11):876-878. doi:10.7196/SAMJ.6146.

375. Thorpe-Beeston JG, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis-single centre experience 1998-2011. *BJOG An Int J Obstet Gynaecol*. 2013;120(3):354-361. doi:10.1111/1471-0528.12040.

376. Jungwirth A, Diemer T, Dohle G., Giwercman A, Kopa Z, Krausz C. Guidelines on male infertility, European Association of Urology. *Eur Urol*. 2012;62:324-332. doi:dx.doi.org/10.1016/j.eururo.2012.04.048.

377. Sayer R, Sinha I, Lowdon J, Panickar J. Preventing hyponatraemic dehydration in cystic fibrosis: a cautionary note to take coconut water with a pinch of salt. *Arch Dis Child*. 2014;99(1):90. doi:10.1136/archdischild-2013-305177.

378. Scurati-Manzoni E, Fossali EF, Agostoni C, et al. Electrolyte abnormalities in cystic fibrosis: systematic review of the literature. *Pediatr Nephrol*. 2014;29(6):1015-1023. doi:10.1007/s00467-013-2712-4.

379. Whiting P, Al Maiwenn, Burgers L, et al. Ivacaftor for the treatment of patients with

cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess (Rockv)*. 2014;18(18):1-106. doi:10.3310/hta18180.

380. Van Goor F, Hadida S, Grootenhuis PDJ, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A*. 2009;106(44):18825-18830. doi:10.1073/pnas.0904709106.

381. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724. doi:10.1378/chest.11-2672.

382. Elborn J, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *Lancet*. 2016;4(8):617-626. doi:10.1016/S2213-2600(16)30121-7.

383. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respir Med*. 2014;2(7):527-538. doi:10.1016/S2213-2600(14)70132-8.

384. Van Goor F, Hadida S, Grootenhuis PDJ, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci U S A*. 2011;108(46):18843-18848. doi:10.1073/pnas.1105787108.

385. Cohen D, Raftery J. Paying twice: the “charitable” drug with a high price tag. *Br Med J*. 2014;348:g1445. doi:10.1136/bmj.g1445.

386. Le Moigne V, Gaillard JL, Herrmann JL. Vaccine strategies against bacterial pathogens in cystic fibrosis patients. *Med Mal Infect*. 2015;46(1):4-9. doi:10.1016/j.medmal.2015.11.013.

387. Saiman L, Siegel JD, LiPuma JJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infect Control Hosp Epidemiol*. 2014;35(suppl 1):S1-S67. doi:10.1086/676882.

388. Ciofu O, Hansen CR, Hoiby N. Respiratory bacterial infections in cystic fibrosis. *Curr*

Opin Pulm Med. 2013;19(3):251-258. doi:10.1097/MCP.0b013e32835f1afc.

389. Döring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros*. 2012;11(6):461-479. doi:10.1016/j.jcf.2012.10.004.

390. Samson C, Tamalet A, Thien HV, et al. Long-term effects of azithromycin in patients with cystic fibrosis. *Respir Med*. 2016;117:1-6. doi:10.1016/j.rmed.2016.05.025.

391. Principi N, Blasi F, Esposito S. Azithromycin use in patients with cystic fibrosis. *Eur J Clin Microbiol Infect Dis*. 2015;34(6):1071-1079. doi:10.1007/s10096-015-2347-4.

392. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis. *Cochrane Database Syst Rev*. 2016;(4). doi:10.1002/14651858.CD001505.pub2.

393. Donaldson SH, Bennett WD, Zeman KL, et al. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *Am J Respir Crit Care Med*. 2004;170(3):241-250. doi:10.1164/rccm.200305-648OC.

394. Konstan MW, Ratjen F. Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *J Cyst Fibros*. 2012;11(2):78-83. doi:10.1016/j.jcf.2011.10.003.

395. Colombo JL. Long-acting bronchodilators in cystic fibrosis. *Curr Opin Pulm Med*. 2003;9(6):504-508. doi:10.1097/00063198-200311000-00010.

396. Elkins M, Dentice R. Timing of hypertonic saline inhalation for cystic fibrosis. *Cochrane Database Syst Rev*. 2016;(12):CD008816. doi:10.1002/14651858.CD008816.pub3.

397. Dentice R, Elkins M. Timing of dornase alfa inhalation for cystic fibrosis (review). *Cochrane Database Syst Rev*. 2016;(7):CD007923. doi:10.1002/14651858.CD007923.pub4.

398. Rossman C, Waldes R, Sampson D, Newhouse M. Effect of chest physiotherapy on the removal of mucus in patients with cystic fibrosis. *Am Rev Respir Dis*.

1982;126:131-135. doi:10.1136/thx.45.1.77.

399. Lorin M, Denning C. Evaluation of postural drainage by measurement of sputum volume and consistency. *Am J Phys Med*. 1971;50:215-219. http://journals.lww.com/ajpmr/Citation/1971/10000/EVALUATION_OF_POSTURAL_DRAINAGE_BY_MEASUREMENT_OF.1.aspx. Accessed February 26, 2013.

400. Desmond K, Schwenk W, Thomas E, Beaudry P, Coates A. Immediate and long-term effects of chest physiotherapy in patients with cystic fibrosis. *J Pediatr*. 1983;103(4):538-542. doi:10.1016/S0022-3476(83)80579-4.

401. Tecklin JS, Holsclaw DS. Evaluation of bronchial drainage in patients with cystic fibrosis. *Phys Ther*. 1975;55(10):1081-1084. https://www.ncbi.nlm.nih.gov/pubmed/1161802. Accessed February 26, 2013.

402. Braggion C, Cappelletti LM, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross-over randomized study. *Pediatr Pulmonol*. 1995;19(1):16-22. doi:10.1002/ppul.1950190104.

403. Button B, Heine R, Catto-Smith A, Phelan P. Postural drainage in cystic fibrosis: is there a link with gastro-oesophageal reflux? *J Paediatr Child Health*. 1998;34(4):330-334. doi:10.1046/j.1440-1754.1998.00236.x.

404. Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Chest physiotherapy, gastro-oesophageal reflux, and arousal in infants with cystic fibrosis. *Arch Dis Child*. 2004;89(5):435-439. doi:10.1136/adc.2003.033100.

405. Mortensen J, Falk M, Groth S, Jensen C. The effects of postural drainage and positive expiratory pressure physiotherapy on tracheobronchial clearance in cystic fibrosis. *Chest*. 1991;100(5):1350-1357. doi:10.1378/chest.100.5.1350.

406. Lannefors L, Wollmer P. Mucus clearance with three chest physiotherapy regimes in cystic fibrosis: a comparison between postural drainage, PEP and physical exercise. *Eur Respir J*. 1992;5(6):748-753. http://erj.ersjournals.com/content/erj/5/6/748.full.pdf. Accessed December 23, 2016.

407. Steen H, Redmond A, O'Neill D, Beattie F. Evaluation of the PEP mask in cystic fibrosis. *Acta Paediatr*. 1991;80(1):51-56. doi:10.1111/j.1651-2227.1991.tb11729.x.

408. Mckoy NA, Wilson LM, Saldanha IJ, Odelola OA, Robinson KA. Active cycle of breathing technique for cystic fibrosis. *Cochrane Database Syst Rev*. 2016;2016(7). doi:10.1002/14651858.CD007862.pub4.

409. Milne S. A pilot study comparing two physiotherapy techniques in patients with cystic fibrosis. *South African J Physiother*. 2004;60(2):3-6. http://www.sajp.co.za/index.php/sajp/article/view/183/180. Accessed December 23, 2016.

410. Phillips GE, Pike SE, Jaffé A, Bush A. Comparison of active cycle of breathing and high-frequency oscillation jacket in children with cystic fibrosis. *Pediatr Pulmonol*. 2004;37(1):71-75. doi:10.1002/ppul.10358.

411. McIlwaine M, Button B, Dwan K. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2015;(6):CD003147. doi:10.1002/14651858.CD003147.pub4.

412. Van Der Schans CP, Van Der Mark TW, De Vries G, et al. Effect of positive expiratory pressure breathing in patients with cystic fibrosis. *Thorax*. 1991;46(1):252-256. doi:10.1136/thx.46.4.252.

413. McIlwaine M, Wong L, Peacock D, Davidson G. Long-term comparative trial of positive expiratory pressure versus oscillating positive expiratory pressure (flutter) physiotherapy in the treatment of cystic fibrosis. *J Pediatr*. 2001;138(6):845-850. doi:10.1067/mpd.2001.114017.

414. McIlwaine MP, Alarie N, Davidson GF, et al. Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. *Thorax*. 2013;68:746-751. doi:10.1136/thoraxjnl-2012-202915.

415. McIlwaine M, Wong L, Peacock D, Davidson G. Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. *J Pediatr*. 1997;131(4):570-574.

doi:10.1016/S0022-3476(97)70064-7.

416. Oberwaldner B, Evans JC, Zach MS. Forced expirations against a variable resistance: a new chest physiotherapy method in cystic fibrosis. *Pediatr Pulmonol*. 1986;2(6):358-367. doi:10.1002/ppul.1950020608.

417. Gondor M, Nixon P, Mutich R, Rebovich P, Orenstein D. Comparison of Flutter device and chest physical therapy in the treatment of cystic fibrosis pulmonary exacerbation. *Pediatr Pulmonol*. 1999;28(4):255-260. doi:10.1002/(SICI)1099-0496(199910)28:4<255::AID-PPUL4>3.0.CO;2-K.

418. Konstan M, Stern R, Doershuk C. Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. *J Pediatr*. 1994;124(5):689-693. doi:10.1016/S0022-3476(05)81356-3.

419. Pryor JA, Webber BA, Hodson ME, Warner JO. The Flutter VRP1 as an adjunct to chest physiotherapy in cystic fibrosis. *Respir Med*. 1994;88(9):677-681. doi:10.1016/S0954-6111(05)80066-6.

420. Newhouse P, White F, Marks J, Homnick D. The intrapulmonary percussive ventilator and flutter device compared to standard chest physiotherapy in patients with cystic fibrosis. *Clin Pediatr (Phila)*. 1998;37(7):427-432. doi:10.1177/000992289803700705.

421. West K, Wallen M, Follett J. Acapella vs. PEP mask therapy: a randomised trial in children with cystic fibrosis during respiratory exacerbation. *Physiother Theory Pract*. 2010;26(3):143-149. doi:10.3109/09593980903015268.

422. Morgan K, Osterling K, Gilbert R, Dechman G. Effects of autogenic drainage on sputum recovery and pulmonary function in people with cystic fibrosis: a systematic review. *Physiother Canada*. 2015;67(4):319-326. doi:10.3138/ptc.2014-64.

423. Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros*. 2006;5(3):177-185. doi:10.1016/j.jcf.2006.03.002.

424. Modi A, Cassedy A, Quittner A, et al. Trajectories of adherence to airway clearance

therapy for patients with cystic fibrosis. *J Pediatr Psychol*. 2010;35(9):1028-1037. doi:10.1093/jpepsy/jsq015.

425. Abbott J, Dodd M, Bilton D, Webb A. Treatment compliance in adults with cystic fibrosis. *Thorax*. 1994;49(2):115-120. doi:10.1136/thx.49.2.115.

426. Modi AC, Quittner AL. Barriers to treatment adherence for children with cystic fibrosis and asthma: what gets in the way? *J Pediatr Psychol*. 2006;31(8):846-858. doi:10.1093/jpepsy/jsj096.

427. Oates GR, Stepanikova I, Gamble S, Gutierrez H, Harris WT. Adherence to airway clearance therapy in pediatric cystic fibrosis: socioeconomic factors and respiratory outcomes. *Pediatr Pulmonol*. 2015;50(12):1244-1252. doi:10.1002/ppul.23317.

428. Rapoff M. *Adherence to Pediatric Medical Regimens*. Vol 2nd ed. (Rapoff M, ed.). New York: Springer Science Business Media; 2010. doi:10.1007/978-1-4419-0570-3.

429. Mckoy N, Saldanha I, Odelola O, Robinson K. Active cycle of breathing technique for cystic fibrosis. *Cochrane Database Syst Rev*. 2012;(12). doi:10.1002/14651858.CD007862.pub3.

430. Warnock L, Gates A, van der Schans C. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev*. 2013;(9). doi:10.1002/14651858.CD001401.pub2.

431. Warnock L, Gates A. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis (Review). *Cochrane Database Syst Rev*. 2015;(12):Art. No.:CD001401. doi:10.1002/14651858.CD001401.pub3.

432. Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Intervention*. Vol 5.1.0 [upd. The Cochrane Collaboration; 2011. www.handbook.cochrane.org. Accessed January 22, 2017.

433. Davidson A, McIlwaine P, Wong L, Nakielna E, Pirie G. Comparative trial of positive expiratory pressure, autogenic drainage and conventional percussion and drainage techniques (abstract 137). *Pediatr Pulmonol*. 1988;suppl 2:132.

434. Lindemann H. The value of physical therapy with VRP 1-Desitin (’Flutter') [Zum Stellenwert der Physiotherapie mit dem VRP 1-Desitin ('Flutter')]. *Pneumologie*. 1992;46(12):626-630. https://www.ncbi.nlm.nih.gov/pubmed/1494580. Accessed October 4, 2014.

435. Reix P, Aubert F, Kassai B, Bige V, Bellon G. Better satisfaction of cystic fibrosis paediatric patients with autogenic drainage associated to exercise compared to conventional chest physiotherapy [abstract]. *J Cyst Fibros*. 2009;8(Suppl 2):S73 abstract 293. doi:http://dx.doi.org/10.1016/S1569-1993(09)60288-5.

436. Reix P, Aubert F, Werck-Gallois M-C, et al. Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial. *J Physiother*. 2012;58:241-247. doi:10.1016/S1836-9553(12)70125-X.

437. Portney L, Watkins M. The research question. In: Mehalik C, ed. *Foundations of Clinical Research. Application to Practice*. Vol 2nd ed. New Jersey: Prentice-Hall Inc; 2000:113-135.

438. Johari J, Sharifudin M, Ab Rahman A, et al. Relationship between pulmonary function and degree of spinal deformity, location of apical vertebrae and age among adolescent idiopathic scoliosis patients. *Singapore Med J*. 2016;57(01):33-38. doi:10.11622/smedj.2016009.

439. Lord RW, Jones AM, Webb AK, Barry PJ. Pneumothorax in cystic fibrosis: beyond the guidelines. *Paediatr Respir Rev*. 2016;20:30-33. doi:10.1016/j.prrv.2016.06.012.

440. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res*. 2010;19(6):875-886. doi:10.1007/s11136-010-9648-y.

441. Palisano RJ, Kolobe TH, Haley SM, Lowes LP, Jones SL. Validity of the Peabody Developmental Gross Motor Scale as an evaluative measure of infants receiving physical therapy. *Phys Ther*. 1995;75(11):939-948. doi:10.1093/ptj/75.11.939.

442. Folio M, Fewell R. *Peabody Developmental Motor Scales: Examiner’s Manual*. Vol 2nd ed. Texas: Pro-ED; 2000.

443. Croce R, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. *Percept Mot Skills*. 2001;93:275-280. doi:10.2466/PMS.93.5.275-280.

444. Van Waelvelde H, De Weerdt W, De Cock P, Smits-Engelsman BCM. Aspects of the validity of the Movement Assessment Battery for Children. *Hum Mov Sci*. 2004;23(1):49-60. doi:10.1016/j.humov.2004.04.004.

445. Henderson S, Sudgen D, Barnett A. Movement Assessment Battery for Children - Second Edition (examiner's manual).

446. Jelsma D, Ferguson GD, Smits-Engelsman BCM, Geuze RH. Short-term motor learning of dynamic balance control in children with probable Developmental Coordination Disorder. *Res Dev Disabil*. 2015;38:213-222. doi:10.1016/j.ridd.2014.12.027.

447. Smits-Engelsman BCM, Jelsma LD, Ferguson GD, Geuze RH. Motor learning: An analysis of 100 trials of a ski slalom game in children with and without developmental coordination disorder. *PLoS One*. 2015;10(10):1-19. doi:10.1371/journal.pone.0140470.

448. Ferguson GD, Naidoo N, Smits-Engelsman BCM. Health promotion in a low-income primary school: children with and without DCD benefit, but differently. *Phys Occup Ther Pediatr*. 2015;35(2):147-162. doi:10.3109/01942638.2015.1009230.

449. Jarad N, Powell T, Smith E. Evaluation of a novel sputum clearance technique--hydro-acoustic therapy (HAT) in adult patients with cystic fibrosis: a feasibility study. *Chron Respir Dis*. 2010;7(4):217-227. doi:10.1177/1479972310376082.

450. Wuang Y-P, Ho G-S, Su C-Y. Occupational therapy home program for children with intellectual disabilities: a randomized, controlled trial. *Res Dev Disabil*. 2013;34(1):528-537. doi:10.1016/j.ridd.2012.09.008.

451. Novak I, Cusick A, Lowe K. A pilot study on the impact of occupational therapy home programming for young children with cerebral palsy. *Am J Occup Ther*. 2007;61(4):463-468. doi:10.5014/ajot.61.4.463.

452. Raynolds N. Teaching parents home care after surgery for scoliosis. *Am J Nurs*. 1974;74(6):1090-1092. doi:10.2307/3469682.

453. Beydon N. Pulmonary function testing in young children. *Paediatr Respir Rev*. 2009;10(4):208-213. doi:10.1016/j.prrv.2009.03.001.

454. Jelsma J, Ramma L. How do children at special schools and their parents perceive their HRQoL compared to children at open schools? *Health Qual Life Outcomes*. 2010;8:72. doi:10.1186/1477-7525-8-72.

455. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. *Thorax*. 2014;69(12):1090-1097. doi:10.1136/thoraxjnl-2014-205983.

456. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. *Health Qual Life Outcomes*. 2006;4:58. doi:10.1186/1477-7525-4-58.

457. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. *Qual life Res*. 2008;17:895-913. doi:DOI 10.1007/s11136-008-9350-5.

458. Havermans T, Vreys M, Proesmans M, De Boeck C. Assessment of agreement between parents and children on health-related quality of life in children with cystic fibrosis. *Child Care Health Dev*. 2006;32(1):1-7. doi:10.1111/j.1365-2214.2006.00564.x.

459. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes*. 2007;5:1. doi:10.1186/1477-7525-5-1.

460. Konstan MW, Pasta DJ, Wagener JS, VanDevanter DR, Morgan WJ. BMI fails to identify poor nutritional status in stunted children with CF. *J Cyst Fibros*. 2017;16(1):158-160. doi:10.1016/j.jcf.2016.11.005.

461. Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest*. 2014;146(1):142-151. doi:10.1378/chest.13-1926.

462. Barker DH, Quittner AL. Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics*. 2016;137(2):e20152296. doi:10.1542/peds.2015-2296.

463. Chappell F, Williams B. Rates and reasons for non-adherence to home physiotherapy in paediatrics. *Physiotherapy*. 2002;88(3):138-147. doi:10.1016/S0031-9406(05)60547-0.

464. Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. *Chest*. 2011;140(2):425-432. doi:10.1378/chest.09-3074.

465. Quittner AL, Espelage DL, Ievers-Landis C, Drotar D. Measuring adherence to medical treatments in childhood chronic illness: considering multiple methods and sources of information. *J Clin Psychol Med Settings*. 2000;7(1):41-54. doi:10.1023/A:1009545319673.

466. World Health Organization. Global burden of disease. http://www.who.int/topics/global_burden_of_disease/en/. Accessed March 2, 2017.

APPENDICES

Appendix 1. EQ-5D-Y

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility (walking about)

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

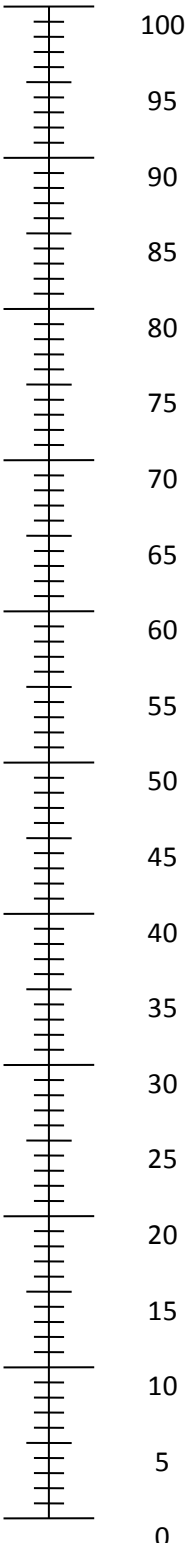
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

The best health you can imagine



The worst health you can imagine

We would like to know how good or bad your health is TODAY.

This line is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Please mark with an X on the line to show how good or bad your health is TODAY.

Appendix 2. PRISMA checklist for the systematic review on the use of ACTs in children with pneumonia

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P36
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P V
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P36
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P36
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P37
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P37
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P38
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P38
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P38
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P38
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P38

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P39
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P40-41
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P41
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P41
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P42-43
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P44-46
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P47-50
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P50-53
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P 53-54
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P 54-55
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P56
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P ii

Appendix 3. Search term used in the systematic review on the use of ACTs in children with pneumonia

Intervention	Population	Disease
chest physiotherapy	child*	pneumonia
chest physical therapy	infant*	lung infection
respiratory physiotherapy	baby	lower respiratory tract infection
respiratory physical therapy	babies	chest infection
airway clearance techniques	toddler*	Pulmonary infection
airway clearance therapy	paediatric*	
breathing therapy	pediatric*	

Search terms between columns were combined with 'AND'

Search terms within one column were combined with 'OR'

Appendix 4. Data extraction form for the systematic reviews

Name investigator: …… Date: ……

Title: ……..

Author(s): ……..

Source: ……

Study design:

1. Where the patients random assigned to the different groups?
   [ ] Yes
   [ ] No
   [ ] No information available

2. The person who recruited the patients did not know in which group the patient is randomly assigned?
   [ ] Yes
   [ ] No
   [ ] No information available

3. Where patients blind to treatment?
   [ ] Yes
   [ ] No
   [ ] No information available

4. Where the clinicians blind to treatment?
   [ ] Yes
   [ ] No
   [ ] No information available

5. Where the investigators blind to treatment?
   [ ] Yes
   [ ] No
   [ ] No information available

6. Where the data-analysts blind to treatment?
   [ ] Yes
   [ ] No
   [ ] No information available

7. Where the groups similar at start of the study?
   [ ] Yes
   [ ] No, but this is corrected during analysis
   [ ] No, and no correction was done during analysis
   [ ] No information available

8. Is data available about follow-up?
   [ ] Yes
   [ ] No

   Is selective loss-to-follow-up excluded?
   [ ] Yes
   [ ] No
   [ ] No information available

9. Was intention-to-treat analysis performed on incomplete data?
   [ ] Yes
   [ ] No
   [ ] No information available

10. Which outcome measures are reported?
    [ ] Primary
    [ ] Primary and secondary
    [ ] Non pre-specified outcome measures
    [ ] Not enough information available

11. Are all included patients analysed in the group they were randomly assigned to?
    [ ] Yes
    [ ] No
    [ ] No information available

12. Are the groups equally treated, except for treatment?
    [ ] Yes
    [ ] No
    [ ] No information available

Participants:

		Intervention group	Control group	Total
Number of subjects	Male			
	Female			
	Total			
Age	Mean			
	SD			
Number lost to follow-up				

1. Condition: ……
2. Severity of symptoms: ……
3. Inclusion criteria: ……
   ……
   ……..
4. Exclusion criteria: ……
   ……
   ……..
5. Comorbid conditions: ……
   ……..
6. Setting: ……

Intervention:

	Intervention group	Control group
Treatment description		
Duration of treatment		
Frequency of treatment		
Intensity of treatment		
Compliance to treatment		

Results:

DICHOTOMOUS OUTCOMES:

Outcome: …….

Follow-up: ……. weeks / months / years

Group	Outcome present	Outcome absent	Total
Intervention			
Control			

Chance that event occurs in intervention group	
Chance that event occurs in control group	
Absolute risk reduction (ARR)	
Number needed to treat (NNT)	
Relative risk (RR)	
Relative risk reduction (RRR)	

CONTINUOUS OUTCOMES:

Outcome 1: ……..

Follow-up: ……. weeks / months / years

Group	Mean (SD) baseline	Mean (SD) discharge	Range	Number (n)
Intervention				
Control				
Difference between groups:				
Difference within groups:				
95% CI **Baseline:** **Discharge:**				

Outcome 2: ……..

Follow-up: ……. weeks / months / years

Group	Mean (SD) baseline	Mean (SD) discharge	Range	Number (n)
Intervention				
Control				
Difference between groups:				
Difference within groups:				
95% CI **Baseline:** **Discharge:**				

Outcome 3: ……..

Follow-up: ……. weeks / months / year

Group	Mean (SD) baseline	Mean (SD) discharge	Range	Number (n)
Intervention				
Control				
Difference between groups:				
Difference within groups:				
95% CI **Baseline:** **Discharge:**				

Outcome 4: ……..

Follow-up: ……. weeks / months / years

Group	Mean (SD) baseline	Mean (SD) discharge	Range	Number (n)
Intervention				
Control				
Difference between groups:				
Difference within groups:				
95% CI **Baseline:** **Discharge:**				

Appendix 5. Data extraction form for the descriptive folder review

A. General information

1. Folder number ……
2. Date of birth …../……/……..
3. Gender M F
4. Gestational age? ……
5. HIV status: Positive Negative Exposed
   If positive, when diagnosed? ……..
   If positive, since when HAART? ……..
6. History of TB: Y N
   If yes, when? ……..
7. Asthma: Y N
   If yes, since when medication: ……..
   Which medication? ……..
8. Cystic fibrosis: Y N
9. Chronic respiratory disease? Y N
   If yes, which disease? ……..
10. Neuromuscular disorder: Y N
    Type?

Muscular	Peripheral	Motor neuron	Others
Duchenne	Charcot-Marie-Tooth	SMA I	Myastenia gravis
Becker	Dejerine-Sottas	SMA II	……
Congenital	Freidreich's ataxia	SMA III	……
Emery-Dreifuss		Spinal-bulbar muscular atrophy (Kennedy disease)	……
Limb girdle			……
Myotonic (Steinerd)			……

11. Cerebral palsy: Y N
    Type: Spastic Ataxic Dystonic Choreo-athetoid
    Hemiplegia: R or L Diplegia Quadriplegia
12. Heart disease: Y N
    If yes, which one? …….
13. Osteoporosis: Y N
14. History of Tx or abdominal surgery: Y N When? …….
15. Chest deformities: Excavatum Carinatum None
16. Other comorbidities: Y N
    If yes, which ones? ……

B. Information with regards to hospitalisation

1. Date of admission: ……..
2. Temperature at admission …….°C
3. Respiratory rate at admission: …….bpm
4. Heart rate at admission: …….bpm
5. Blood pressure at admission: ……/…….
6. Oxygen saturation at admission: ……..%
7. Signs of respiratory distress at admission: circle which are present
   Cyanosis Alar flaring Head bobbing SCR ICR
   Tracheal tug Feeding problem Weak cry
8. Oxygen support at admission: Y N …….l/min
9. Ventilation required during admission: Y N
10. Type of ventilation: CPAP BiPap IPPV HFOV SIMV PCV …….
11. Days on ventilation: ……
12. Date of discharge/death: ……/……/…….
13. Days of hospitalisation ……
14. Mortality (circle): alive / died

15. Organism of LRTI:

Viral	Bacterial	Unknown
RSV	Staph. aureus	
Influenza	Pseudomonas aureginosa	
Parainfluenza	Streptococcus pneumoniae	
Metapneumo	Other Streptococcus	
Adeno	PJP	
Boca	Mycobacter tuberculosis	
Rhino	Bordetella pertussis	
Entero	Other Gram +	
Parvo	Other Gram-	
Human corona	Klebsiella	
CMV		

C. Complications/adverse events during hospitalisation (Y = yes, N = no, N/A = info not available)

1. Pneumothorax: Y N N/A When? ……
2. Increased intracranial pressure: Y N N/A When? ……
3. Pleural effusion: Y N N/A When? ……
4. Lung/lobe collapse? Y N N/A When? ……
   Which lung/lobe? ……..
5. Atelectasis? Y N N/A When? ……..

D. Chest physiotherapy

1. Was chest physiotherapy prescribed? Y N N/A When? ……
2. Reason? ……
3. Was chest physiotherapy given? Y N N/A
4. When did treatment start? ……..
5. How often was physio given? Daily Bidaily >2x/d
6. Techniques used? (M)PD Percussion/clapping Vibrations PEP
   ACBT Oscillating PEP Bubble PEP AD AAD
   Others/specify: ……..

E. Adverse events during or immediately post chest physiotherapy

1.	Desaturation during chest physiotherapy?	Y	N	N/A	SpO_2: …… %
2.	Pneumothorax:	Y	N	N/A	When? ……..
3.	Increased intracranial pressure:	Y	N	N/A	When? ……
4.	Pleural effusion:	Y	N	N/A	When?…….
5.	Rib fracture:	Y	N	N/A	When?…….
	Location?	……			
6.	Lung/lobe collapse?	Y	N	N/A	When?……
	Which lung/lobe?	…….....			
7.	Atelectasis?	Y	N	N/A	When?……

Appendix 6. Approval forms to conduct the descriptive folder review

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 September 2015

HREC REF: 717/2015

A/Prof B Morrow
Paediatric Medicine
Paediatric Critical Care and Children's Heart Disease
Red Cross War Memorial Children's Hospital

Dear A/Prof Morrow

PROJECT TITLE: USE OF CHEST PHYSIOTHERAPY IN CHILDREN HOSPITALISED WITH ACUTE PNEUMONIA IN A SOUTH AFRICAN TERTIARY HOSPITAL (PhD-candidate-L Corten)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th September 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student L Corten will be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.

HREC 717/2015

Western Cape Government
Health

DR A BOOYSEN
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Tony.Booysen@westerncape.gov.za
Tel: +27 21 658 5867 Fax: +27 21 658 5006/5166

Ms L Corten
Physiotherapy Student
UCT

Dear Ms Corten

PROJECT TITILE: USE OF CHEST PHYSIOTHERAPY IN CHILDREN HOSPITALISED WITH ACUTE PNEUMONIA IN A SOUTH AFRICAN TERTIARY HOSPITAL

It is a pleasure to inform you that approval has been granted to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Kindly submit a copy of your final report to the RCWMCH Research Committee, For Attention Dr Tony Booysen.

Yours faithfully,

DR A BOOYSEN
MANAGER: MEDICAL SERVICES

DATE: 16 October 2015

Appendix 7. ICD-10 codes for identification of patients for the descriptive folder review

(as found on http://www.health.gov.za/icddoc.php under section ICD-10_MIT_2014 Changes Add Delete Modify 1 Jan 2014)

	Chapter description	Group code	Group description	ICD 10_3 code	ICD 10 code description	ICD 10 code	WHO description
VIRAL PNEUMONIA	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J10	Influenza due to other identified influenza virus	J10.0	Influenza with pneumonia, other influenza virus identified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J11	Influenza, virus not identified	J11.0	Influenza with pneumonia, virus not identified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12	Viral pneumonia, not elsewhere classified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.0	Adenoviral pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.1	Respiratory syncytial virus pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.2	Parainfluenza virus pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.3	Human metapneumovirus pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.8	Other viral pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J12	Viral pneumonia, not elsewhere classified	J12.9	Viral pneumonia, unspecified
BACTERIAL PNEUMONIA	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J13	Pneumonia due to Streptococcus pneumoniae	J13	Pneumonia due to Streptococcus pneumoniae
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J14	Pneumonia due to Haemophilus influenzae	J14	Pneumonia due to Haemophilus influenzae
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15	Bacterial pneumonia, not elsewhere classified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.0	Pneumonia due to Klebsiella pneumoniae

	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.1	Pneumonia due to Pseudomonas
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.2	Pneumonia due to Staphylococcus
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.3	Pneumonia due to Streptococcus, Group B
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.4	Pneumonia due to other streptococci
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.5	Pneumonia due to Escherichia coli
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.6	Pneumonia due to other aerobic Gram-negative bacteria
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.7	Pneumonia due to Mycoplasma pneumoniae
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.8	Other bacterial pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J15	Bacterial pneumonia, not elsewhere classified	J15.9	Bacterial pneumonia, unspecified
PNEUMONIA OTHER AETIOLOGY	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J16	Pneumonia due to other infectious organisms, not elsewhere classified	J16	Pneumonia due to other infectious organisms, not
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J16	Pneumonia due to other infectious organisms, not elsewhere classified	J16.0	Chlamydial pneumonia
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J16	Pneumonia due to other infectious organisms, not elsewhere classified	J16.8	Pneumonia due to other specified infectious
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17	Pneumonia in diseases classified elsewhere
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17.0	Pneumonia in bacterial diseases classified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17.1	Pneumonia in viral diseases classified elsewhere
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17.2	Pneumonia in mycoses

	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17.3	Pneumonia in parasitic diseases
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J17	Pneumonia in diseases classified elsewhere	J17.8	Pneumonia in other diseases classified elsewhere
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18	Pneumonia, organism unspecified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18.0	Bronchopneumonia, unspecified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18.1	Lobar pneumonia, unspecified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18.2	Hypostatic pneumonia, unspecified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18.8	Other pneumonia, organism unspecified
	Diseases of the respiratory system (J00-J99)	102 (J09-J18)	Influenza and pneumonia	J18	Pneumonia, organism unspecified	J18.9	Pneumonia, unspecified
BRONCHIOLITIS	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J21	Acute bronchiolitis	J21	Acute bronchiolitis
	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J21	Acute bronchiolitis	J21.0	Acute bronchiolitis due to respiratory syncytial virus
	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J21	Acute bronchiolitis	J21.1	Acute bronchiolitis due to human metapneumovirus
	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J21	Acute bronchiolitis	J21.8	Acute bronchiolitis due to other specified organisms
	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J21	Acute bronchiolitis	J21.9	Acute bronchiolitis, unspecified

ACUTE LRTI	Diseases of the respiratory system (J00-J99)	103 (J20-J22)	Other acute lower respiratory infections	J22	Unspecified acute lower respiratory infection	J22	Unspecified acute lower respiratory infection
RESPIRATORY DISTRESS AND PNEUMONIA IN NEWBORNS	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P22	Respiratory distress of newborn	P22	Respiratory distress of newborn
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P22	Respiratory distress of newborn	P22.0	Respiratory distress syndrome of newborn
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P22	Respiratory distress of newborn	P22.1	Transient tachypnoea of newborn
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P22	Respiratory distress of newborn	P22.8	Other respiratory distress of newborn
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P22	Respiratory distress of newborn	P22.9	Respiratory distress of newborn, unspecified
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23	Congenital pneumonia
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.0	Congenital pneumonia due to viral agent

	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.1	Congenital pneumonia due to Chlamydia
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.2	Congenital pneumonia due to Staphylococcus
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.3	Congenital pneumonia due to Streptococcus, Group B
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.4	Congenital pneumonia due to Escherichia coli
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.5	Congenital pneumonia due to Pseudomonas
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.6	Congenital pneumonia due to other bacterial agents
	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.8	Congenital pneumonia due to other organisms

	Certain conditions originating in the perinatal period (P00-P96)	167 (P20-P29)	Respiratory and cardiovascular disorders specific to the perinatal period	P23	Congenital pneumonia	P23.9	Congenital pneumonia, unspecified
OTHERS	Certain infectious and parasitic diseases (A00-B99)	011 (B00-B09)	Viral infections characterized by skin and mucous membrane lesions	B01	Varicella [chickenpox]	B01.2	Varicella pneumonia (J17.1*)
	Certain infectious and parasitic diseases (A00-B99)	011 (B00-B09)	Viral infections characterized by skin and mucous membrane lesions	B05	Measles	B05.2	Measles complicated by pneumonia (J17.1*)
	Certain infectious and parasitic diseases (A00-B99)	013 (B20-B24)	Human immunodeficiency virus [HIV] disease	B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	B20.6	HIV disease resulting in *Pneumocystis jirovecii* pneumonia
	Diseases of the respiratory system (J00-J99)	108 (J85-J94)	Suppurative and necrotic conditions of lower respiratory tract	J85	Abscess of lung and mediastinum	J85.1	Abscess of lung with pneumonia
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.0	Streptococcus, group A, as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.1	Streptococcus, group B, as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.2	Streptococcus, group D, as the cause of diseases classified to other chapters

Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.3	*Streptococcus pneumoniae* as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.4	Other streptococcus as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.5	Unspecified streptococcus as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.6	*Staphylococcus aureus* as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.7	Other staphylococcus as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95.8	Unspecified staphylococcus as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96	Other specified bacterial agents as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.0	*Mycoplasma pneumoniae* [*M. pneumoniae*] as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.1	*Klebsiella pneumoniae* [*K. pneumoniae*] as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.2	*Escherichia coli* [*E. coli*] as the cause of diseases classified to other chapters
Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.3	*Haemophilus influenzae* [*H. influenzae*] as the cause of diseases classified to other chapters

	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.4	*Proteus (mirabilis)(morganii)* as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.5	*Pseudomonas (aeruginosa)*as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.6	*Bacillus fragilis* [*B. fragilis*] as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.7	*Clostridium perfringens* [*C. perfringens*] as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B96	Other specified bacterial agents as the cause of diseases classified to other chapters	B96.8	Other specified bacterial agents as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97	Viral agents as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.0	Adenovirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.1	Enterovirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.2	Coronavirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.3	Retrovirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.4	Respiratory syncytial virus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.5	Reovirus as the cause of diseases classified to other chapters

	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.6	Parvovirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.7	Papillomavirus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B97	Viral agents as the cause of diseases classified to other chapters	B97.8	Other viral agents as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B98	Other specified infectious agents as the cause of disease classified to other chapters	B98	Other specified infectious agents as the cause of disease classified to other
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B98	Other specified infectious agents as the cause of disease classified to other chapters	B98.0	Helicobacter pylori [H.pylori] as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	020 (B95-B98)	Bacterial, viral and other infectious agents	B98	Other specified infectious agents as the cause of disease classified to other chapters	B98.1	Vibrio vulnifucus as the cause of diseases classified to other chapters
	Certain infectious and parasitic diseases (A00-B99)	021 (B99)	Other infectious diseases	B99	Other infectious disease	B99	Other infectious disease

Appendix 8. Comorbidities seen in children hospitalised with a LRTI

1) Respiratory comorbidities

Chronic respiratory comorbidities

Chronic comorbidity	N	Percentage
Asthma: proven	49	4.1
suspected	7	0.6
Upper airway obstruction	27	2.2
Chronic lung disease, not further specified	11	0.9
Bronchiolitis obliterans	8	0.7
Hyaline membrane disease	7	0.6
Bronchiectasis	6	0.5
CF	5	0.4
Chronic obstructive pulmonary disease	4	0.3
Obstructive sleep apnoea	4	0.3
Recurrent LRTI	4	0.3
Chronic respiratory failure, requiring nocturnal BiPap	3	0.2
Chronic cough	2	0.2
Pulmonary haemorrhage	2	0.2
Colonised with Staph. Aureus	2	0.2
Congenital lung disease	2	0.2
Left sided empyema	1	0.1
Atelectasis	1	0.1
Elevated right hemidiaphragm	1	0.1
Diffuse lung disease	1	0.1
Colonised with MRSA	1	0.1
Bronchopulmonary dysplasia	1	0.1
Restrictive lung disease	1	0.1
Destroyed right lung	1	0.1
Total	**151**	

N= 1208 children, multiple comorbidities could be present in one child

Acute respiratory comorbidities

Acute comorbidity	N	Percentage
URTI	47	3.3
Allergic rhinitis	16	1.1
Apnoea	16	1.1
Pertussis: proven	13	0.9
suspected	2	0.1
Bronchospasm	11	0.8
Croup	2	0.1
Aspiration	2	0.1
Sinusitis	2	0.1
Respiratory acidosis	1	0.1
Respiratory arrest	1	0.1
Pneumonitis	1	0.1
Coryza	1	0.1
Acute respiratory distress syndrome	1	0.1
Compression bronchus intermedius	1	0.1
Persistent left upper lobe collapse	1	0.1
Pneumatocele	1	0.1
Total	**119**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

2) Cardiovascular comorbidities

Chronic cardiovascular comorbidities

	Chronic comorbidity	N	Percentage
Chronic cardiac	Patent ductus arteriosus: proven	23	1.9
	suspected	1	0.1
	Ventricular septal defect	22	1.8
	Atrioventricular septal defect	15	1.2
	Patent foramen ovale	8	0.7
	Cardiac failure	8	0.7
	Cardiomyopathy	4	0.3
	Atrial septal defect	4	0.3
	Tetralogy of Fallot	3	0.2
	Heart murmur	3	0.2
	Pulmonary hypertension	3	0.2
	Double outlet right ventricle	2	0.2
	Cor pulmonale	2	0.2
	Shone syndrome	1	0.1
	Dextrocardia	1	0.1
	Congenital cardiac block	1	0.1
	Cyanotic heart lesion	1	0.1
	Cardiomegaly	1	0.1
	Acyanotic heart lesion	1	0.1
	Barth syndrome	1	0.1
	Severe dilated left atrium and ventricle	1	0.1
	Right ventricular outflow tract problems	1	0.1
	Total	**107**	
Chronic valvar	Pulmonary stenosis	5	0.4
	Mitral valve abnormalities/regurgitation	2	0.2
	Pulmonary atresia	2	0.2
	Bicuspid atrioventricular valve	1	0.1
	Atrioventricular valve regurgitation	1	0.1
	Total	**11**	
Chronic vascular	Coarctation aorta	3	0.2
	Anomalous left coronary artery from the pulmonary artery	2	0.2
	Truncus arteriosus	1	0.1
	Interrupted inferior vena cava	1	0.1
	Transposition great arteries	1	0.1
	Lymphatic venous malformation	1	0.1
	Total	**9**	
Chronic blood disorders	Sickle cell anaemia	3	0.2
	Microcystosis	2	0.2
	Acute lymphoblastic leukemia (acute or history)	2	0.2
	Acute non-lymphoblastic leukemia	1	0.1
	Idiopathic thrombocytopenic purpura	1	0.1
	Total	**9**	
Other chronic disorders	Pulmonary hypertension	4	0.3
	Left isomerism	1	0.1
	Total	**5**	
Total		**141**	

N= 1208 children, multiple comorbidities could be present in one child

Acute cardiovascular comorbidities

Acute cardiovascular problems	N	Percentage
Anaemia	107	7.4
Sepsis	72	5.0
Pericardial effusion	6	0.4
Deep venous thrombosis	3	0.2
Hypotension	1	0.1
Total	**189**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

3) Neuromuscular disorders

Chronic neuromuscular comorbidities

	Chronic Comorbidity	N	Percentage
Neuromuscular disorders	SMA (I – II)	7 (4 – 3)	0.6
	Congenital myopathy	5	0.4
	Congenital muscular dystrophy	1	0.1
	Total	**13**	
Cerebral Palsy	Spastic (quadriplegic – unknown distribution)	15 (10 – 5)	1.2
	Spastic dystonic quadriplegic	3	0.2
	Hypotonic	3	0.2
	Dystonic hypotonic (unknown distribution)	1	0.1
	Hemiplegic (left)	1	0.1
	Total	**23**	
Other chronic neurological condition	Seizures/epilepsy	35	2.9
	Hydrocephalus	5	0.4
	Dandy walker malformation	4	0.3
	Intraventricular haemorrhage	4	0.3
	Hypoxic brain injury	3	0.2
	Hypoxic ischemic encephalopathy	3	0.2
	Traumatic brain injury	3	0.2
	HIV encephalopathy	3	0.2
	Microcephaly	2	0.2
	Agenesis corpus callosum	2	0.2
	Cortical blindness	2	0.2
	Leukencephalopathy	1	0.1
	Neurofibromatosis	1	0.1
	Othara syndrome	1	0.1
	Ataxia	1	0.1
	Hypotonia	1	0.1
	Chronic periventricular leukomalacia	1	0.1
	Colpocephaly	1	0.1
	Total	**73**	
Total		109	

N= 1208 children, multiple comorbidities could be present in one child

Acute neuromuscular comorbidities

Acute neurological comorbidities	N	Percentage
Meningitis	10	0.7
Febrile seizures/seizures due to acute illness	5	0.3
Change in tone due to acute illness	2	0.1
Benign extra cranial hydrocephalus of infancy	1	0.1
Guillain Barre Syndrome	1	0.1
Occipital abscess	1	0.1
Total	**20**	

N= 1440 hospitalisations, multiple comorbidities could be present in one hospitalisation

4) Genetic disorders

Comorbidity	N	Percentage
Trisomy 21	19	1.6
Cystinosis	1	0.1
Goldernhar syndrome	1	0.1
Klinefelter syndrome	1	0.1
Wolf-Hirsschorn syndrome	1	0.1
Prader-Willi syndrome	1	0.1
Achondroplasia	1	0.1
Barth syndrome	1	0.1
Trisomy 13	1	0.1
Neurofibromatosis	1	0.1
Total	**28**	

N= 1208 children

5) Musculoskeletal comorbidities

Chronic musculoskeletal comorbidities

	Chronic comorbidity	N	Percentage
Chronic skeletal comorbidities	Scoliosis	11	0.9
	Pectus carinatum	3	0.2
	Pectus excavatum	3	0.2
	Kyphoscoliosis	3	0.2
	Polydactyly (n=1 digit removed as neonate)	2	0.2
	Spina bifida occulta	1	0.1
	Vertical talus	1	0.1
	Hemivertebra	1	0.1
	Narrowed craniocervical junction	1	0.1
	Congenital missing ribs	1	0.1
	Limb reduction, defect left forearm	1	0.1
	Valgus deformity knees	1	0.1
	Flattened chest, barrel shaped on left side	1	0.1
	Total	**30**	
Soft tissue/muscular comorbidities	Burns	5	0.4
	Muscle wasting	2	0.2
	Fixed flexion deformity right index finger	1	0.1
	Absent left pectoralis major	1	0.1
	Contractures	1	0.1
	Clubfoot	1	0.1
	Total	**11**	
Total		**41**	

N= 1208 children, multiple comorbidities could be present in one child

Acute musculoskeletal comorbidities

Acute comorbidities	N	Percentage
Rickets	4	0.3
Femur fractures	3	0.2
Hip dislocation	3	0.2
Rib fractures	1	0.1
Osteoporosis	1	0.1
***Staph. aureus* septic arthritis left shoulder**	1	0.1
Total	**13**	

N= 1440 hospitalisations

6) Gastrointestinal comorbidities

Chronic gastrointestinal comorbidities

Chronic comorbidity	N	Percentage
Gastro-oesophageal reflux disorder	51	4.2
Hepato(spleno)megaly	5	0.4
Chronic gastroenteritis	2	0.2
Pancreas insufficiency	2	0.2
Short bowel syndrome	1	0.1
Chronic liver rejection	1	0.1
Central liver placement	1	0.1
Total	**63**	

N= 1208 children, multiple comorbidities could be present in one child

Acute comorbidities	N	Percentage
Acute gastroenteritis	91	6.3
Constipation	2	0.1
Blood in stool	1	0.1
Hepatitis	1	0.1
Multiple bowel perforations	1	0.1
Total	**96**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

7) Ear, nose and throat (ENT) comorbidities

Chronic ENT comorbidities

Chronic comorbidities	N	Percentage
Hearing impairment/loss/deafness	7	0.6
Chronic otitis media	3	0.2
Subglottic stenosis	2	0.2
Vocal cord paresis	1	0.1
Laryngomalacia	1	0.1
Pinna malformation grade 1	1	0.1
Peri-auricular tag	1	0.1
Total	**16**	

N= 1208 children, multiple comorbidities could be present in one child

Acute ENT comorbidities

Acute comorbidities	N	Percentage
Otitis media	24	1.7
Pharyngitis	8	0.6
Enlarged adenoids/adenoidectomy	7	0.5
Tonsillitis	6	0.4
Tympanic membrane perforation	1	0.1
Enlarged adenoids	1	0.1
Otitis externa	1	0.1
Total	**48**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

8) Dermatological and facial comorbidities

Chronic dermatological/facial comorbidities

Chronic comorbidities	N	Percentage
Eczema	33	2.7
Cleft lip/palate	3	0.2
Seborrhic dermatitis	2	0.2
Chronic dermatitis	1	0.1
Total	**39**	

N= 1208 children

Acute dermatological/facial comorbidities

Acute comorbidities	N	Percentage
Dermatitis	18	1.3
Candidiasis/fungal rash	11	0.8
Scabies	8	0.6
Erythema	3	0.2
Varicella	3	0.2
Tinea Capitis	3	0.2
Undefined rash	2	0.1
Urticaria	2	0.1
Molluscum face	2	0.1
Cellulitis	2	0.1
Genital warts	1	0.1
Axilliary abscess	1	0.1
Syphillis	1	0.1
Petechiae due to viral infection	1	0.1
Vesicles on legs	1	0.1
Post inflammation hyperpigmented macules	1	0.1
Mongolian spots	1	0.1
Measles	1	0.1
Herpes gingiro-stomatitis	1	0.1
Haemanglioma	1	0.1
Occipital blisters	1	0.1
Dermoid mass	1	0.1
Pityriassis sicca alba	1	0.1
Breast abscess	1	0.1
Impetigo	1	0.1
Rubella	1	0.1
Total	**70**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

9) Nutritional and metabolic comorbidities

Chronic nutritional/metabolic comorbidities

Chronic comorbidity	N	Percentage
Growth faltering/slow weight gain	10	0.8
Overweight/obesity	9	0.7
Malnutrition	6	0.5
Food allergies	6	0.5
Diabetes	4	0.3
Metabolic acidosis	1	0.1
Hyperparathyroidism	1	0.1
Total	**37**	

N= 1208 children, multiple comorbidities could be present in one child

Acute nutritional/metabolic comorbidities

Acute comorbidity	N	Percentage
Failure to thrive	151	10.5
Hypothyroidism	10	0.7
Total	**161**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

10) Ophthalmological comorbidities

Chronic ophthalmological comorbidities

Chronic comorbidity	N	Percentage
Strabismus	8	0.7
Visual impairment/blind	4	0.3
Cataract	3	0.2
Ptosis	2	0.2
Chronic dry eye	1	0.1
Total	**18**	

N= 1208 children, multiple comorbidities could be present in one child

Acute ophthalmological comorbidities

Acute comorbidity	N	Percentage
Conjunctivitis	18	1.3
Eye discharge	2	0.1
Retinal haemorrhages	1	0.1
Total	**21**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

11) Urinary comorbidities

Chronic urinary comorbidities

Chronic comorbidity	N	Percentage
End stage renal disease	2	0.2
Dysplastic kidneys	2	0.2
Vesilo-ureteric reflux	1	0.1
Neuropathic bladder	1	0.1
Total	**6**	

N= 1208 children

Acute urinary comorbidities

acute comorbidity	N	Percentage
Urinary tract infection	3	0.2
Hydronephrosis	2	0.1
Renal cyst	1	0.1
Nephrotic syndrome	1	0.1
Total	**7**	

N= 1440 hospitalisations

12) Other comorbidities

Chronic other comorbidities

Chronic comorbidities	N	Percentage
Developmental delay	45	3.7
Neonatal jaundice	34	2.8
Dysmorphism	14	1.2
Maternal drug abuse during pregnancy or exposing the child to toxic drug fumes	10	0.8
Umbilical hernia	5	0.4
Allergies	3	0.2
Lymphadenopathy	3	0.2
Hypospadias	2	0.2
Rapid plasma regain (RPR) exposed	2	0.2
Lympho(histio)cystosis	2	0.2
Asplenia	2	0.2
Immunodeficiency	2	0.2
Foetal alcohol syndrome	2	0.2
Intellectually impaired	2	0.2
Sexual assault	1	0.1
Multi organ failure	1	0.1
Autism spectrum disorder	1	0.1
Mitochondrial disease	1	0.1
Insomnia	1	0.1
Anorectal malformation	1	0.1
Speech delay	1	0.1
Hypoalbuminaemia	1	0.1
Sacral dimple	1	0.1
Haemophagocytosis	1	0.1
Cortes syndrome	1	0.1
Vestibular anus	1	0.1
Chylothorax	1	0.1
Blind ending sacral sinus	1	0.1
Total	**142**	

N= 1208 children, multiple comorbidities could be present in one child

Acute other comorbidities

Acute comorbidities	N	Percentage
Hyponatraemia	6	0.4
Hypokalaemia	4	0.3
Disseminated TB	3	0.2
Inguinal hernia	2	0.1
Dehydration	2	0.1
Dental caries	2	0.1
Undescended testes	2	0.1
Electrolyte disturbance	2	0.1
Hypophosphatemia	1	0.1
Hypocalcaemia	1	0.1
Hypoglycaemia	1	0.1
Submandibular lymph nodes	1	0.1
Headache	1	0.1
Elevated auto-antibodies	1	0.1
Ulcer tongue	1	0.1
Disseminated cytomegalovirus	1	0.1
Acute transaminitis	1	0.1
Distended abdomen	1	0.1
Cryptorchidism	1	0.1
Oedematous legs	1	0.1
Poisoning (salicylate and toxic levels ibuprofen/paracetamol)	1	0.1
Total	**36**	

N= 1440 hospitalisations, multiple comorbidities could be present during one hospitalisation

Appendix 9. Data extraction forms used in the study on AAD in children hospitalised with pneumonia

Recruitment form

1) Name: ……..

2) Date of birth: ……/……/……

3) Date of admission: ……/……/……

4) Age at admission: ……

5) Gender: M F

6) Prematurity: Y N

Gestational age? ……

7) Acute TB: Y N

If yes, since when medication? ……

Which medication? ……

8) History of TB: Y N

If yes, when? ……..

9) Previous episodes of lung disease: Y N

If yes, when? ……

10) HIV-infected: Y N

If yes, when diagnosed? ……
If yes, since when HAART? ……

11) HIV-exposed: Y N

12) Asthma: Y N
If yes, since when medication: ……
Which medication? ……

13) Cystic fibrosis: Y N

14) Other respiratory disease? Y N
If yes, which disease? ……..

15) Neuromuscular disorder: Y N
If yes, which one? …….

16) Chest deformities: Y N
If yes, which one? ……

17) Recent pneumothorax (≤3m): Y N

18) Thoracic or abdominal surgery: Y N
(≤6m)

19) Severe heart disease? Y N
Type of heart disease? …….

20) Osteoporosis: Y N

Medical record baseline

1) Increased intracranial pressure: Y N

2) Intercostal drain: Y N

3) Pleural effusion: Y N

4) Mechanical ventilation: Y N
Type of mechanical Ve? ……..

5) Previously on mechanical Ve? Y N
Type of mechanical Ve? …….
Days on mechanical Ve: ……days
Hours on mechanical Ve: ……hours

6) O2 supplement:
on admission Y N l/min: …….
on recruitment Y N l/min: …….

7) Oxygen saturation Admission:…….% Recruitment:……%

		Admission		Recruitment	
8)	Distress/hypoxia:				
	Oxygen saturation ≤ 90% on O2:	Y	N	Y	N
	Cyanosis:	Y	N	Y	N
	Weak cry:	Y	N	Y	N
	Feeding problems:	Y	N	Y	N
	Head nodding:	Y	N	Y	N
	Nasal flaring:	Y	N	Y	N
	Muscle retraction in neck:	Y	N	Y	N

9) Respiratory rate at admission ……breaths per minute ….. bpm

10) Heart rate at admission: …….beats/min …..bpm

11) Blood pressure normal elevated decreased
Blood pressure ……/……..

12) Mental status normal abnormal

13) X-ray: lobar diffuse

14) Osteoporosis on X-ray: Score? …….

15) Sputum/blood culture: positive negative

16) Organism of infection: ……..

17) Fever Y N
Temperature at admission: ……°C
Temperature site anal axillar

18) Lung function tests
RV/TLC ……..
VC ……..
FVC ……..
FEV1 ……..
PEF ……..

Physiotherapy form

Pre-treatment (for every treatment! = for each AAD, emergency physio and standard physio treatment):

1) Treatment date: …./……/……..

2) Treatment hour: ……

3) Respiratory rate: ……breaths per minute

4) Oxygen saturation ……

5) Distress/hypoxia:
   Oxygen saturation ≤ 90% on O2: Y N
   Cyanosis: Y N
   Weak cry: Y N
   Feeding problems: Y N
   Head nodding: Y N
   Nasal flaring: Y N
   Muscle retraction Y N

6) O2 supplement: Y N l/min? .....

7) Palpation of secretions: Y N
   Region (top, mid, base, left, right)? ……

8) Auscultation of secretions: Y N
   Region (top, mid, base, left, right)? ……

9) Spontaneous cough: Y N
   If yes, productive cough? Y N

10) Wheezing: Y N

Treatment:

1) Emergency physio: Y N Standard physio: Y N
   If yes, which technique is used? ……

2) Duration of treatment: ……
   Reason for stop? ……

3) Oxygen saturation between (min)……and (max)……

Post-treatment, immediately after:

1) Respiratory rate: ……breaths per min

2) Oxygen saturation ……%

3) Distress/hypoxia:

Oxygen saturation ≤ 90% on O2:	Y	N
Cyanosis:	Y	N
Weak cry:	Y	N
Feeding problems:	Y	N
Head nodding:	Y	N
Nasal flaring:	Y	N
Muscle retraction	Y	N

4) O2 supplement: Y N
   l/min? .....

5) Palpation of secretions: Y N
   Region (top, mid, base, left, right)? …….

6) Auscultation of secretions: Y N
   Region (top, mid, base, left, right)? ……..

7) Spontaneous cough: Y N
   If yes, productive cough? Y N

8) Wheezing: Y N

Post-treatment, after 1h:

1) Respiratory rate: …….breaths per minute

2) Oxygen saturation: ……%

Other physiotherapy treatment sessions:

1) Reason for treatment: ……

2) Type of treatment: ……

3) Start date treatment: ……

4) Frequency of treatment: ……

5) Duration of treatment session: ……

6) End date treatment: ……

After 5 days

1) Days of fever: ……..

2) Respiratory rate: ……..breaths per minute

3) Lung function tests
   RV/TLC ……
   VC ……
   FVC ……..
   FEV1 ……
   PEF ……..

4) Oxygen saturation ……..%

5) Duration of O2 supplement ……(hours)

6) Atelectasis/collapse: Y N
   If yes, when? ……

Discharge information Pneumonia

1) Date of discharge: ……/……/……..

2) Days of hospitalisation: ……..

3) Days of fever: …….

4) Respiratory rate: ……..breaths per minute

5) Lung function tests
   RV/TLC ……
   VC ……
   FVC ……
   FEV1 ……
   PEF ……

6) Oxygen saturation …….%

7) Duration of O2 supplement ……(hours)

8) Atelectasis/collapse: Y N
   If yes, when? ……

Appendix 10. Approval documents for the study on the use of AAD in children hospitalised with pneumonia

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: jinsey.samuels@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

07 November 2013

HREC REF: 532/2013

A/Prof B Marrow
Paediatric Medicine
Red Cross War Memorial Children's Hospital

Dear A/Prof B Marrow

PROJECT TITLE: THE USE OF ASSISTED AUTOGENIC DRAINAGE IN CHILDREN WITH ACUTE RESPIROTORY DISEASE IN A DEVELOPING COUNTRY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312

Western Cape Government
Health

DR T A BLAKE
MANAGER MEDICAL SERVICES
thomas.blake@wessterncape.gov.za
0216585788/0828225553
18 JULY 2014

MS L CORTEN

Dear Ms Corten,

RESEARCH: **The use of assisted autogenic drainage (AAD) in children with acute respiratory disease in a developing country.**

The use of assisted autogenic drainage (AAD) in South-African children with cystic fibrosis.

This letter confirms the approval for the above proposed research at the Red Cross War Memorial Children's Hospital.

Yours faithfully,

DR T A BLAKE
CHAIRPERSON
HOSPITAL RESEARCH REVIEW COMMITTEE

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Dr. George Mukhari
Academic Hospital

Office of the Director Clinical Services
Enquiries : Dr. P. Shembe
Tel : (012) 529 3880
Fax : (012) 560 0099
Petunia.Shembe@gauteng.gov.za

To : A/ Prof. Brenda Marrow
: Department of Paediatric Medicine
: F45 Old Main Building, Groote Schuur Hospital
: Observatory
: Cape Town
: 7925

Date : 06 September 2014

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Hospital hereby grants you permission to conduct research on "The use of assisted Autogenic drainage in children with Acute respiratory disease in a developing country at Dr. George Mukhari Academic Hospital."
The hospital is aware that you have already obtained Clearance from the University of Cape Town

This permission is granted subject to the following conditions:

☑ That the Hospital incurs no cost in the course of your research

☑ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.

☑ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

Yours sincerely

DR. C. HOLM
ACTING DIRECTOR CLINICAL SERVICES

Informed Consent Form for the parent(s)/guardian(s) of children between the ages of 0 and 8 years with acute pneumonia, hospitalised in Red Cross Children's hospital, Cape Town.

This Informed Consent Form has two parts:

- Part I: Information Sheet (to share information about the study with you)
- Part II: Certificate of Consent (for signatures if you agree that your child may participate)

You will be given a copy of the full Informed Consent Form.

PART I: Information sheet

I, Lieselotte Corten (PhD- student at the University of Cape Town), am doing research on different breathing techniques in children with lung disease. One of my research topics is the use of "Assisted Autogenic Drainage" in children hospitalised with acute pneumonia.

What is the reason for the study and how will it be done?
Pneumonia is a disease of the lungs which is usually treated by giving antibiotics and oxygen and/or suctioning of phlegm if necessary. Sometimes, physiotherapy is used to clear phlegm from the lungs to help the child breathe easier. A new physiotherapy technique, called Assisted Autogenic Drainage, may help children to breathe better and get the phlegm out of their lungs. This technique uses deepening of breathing to loosen up and remove the phlegm from the lungs. During the physiotherapy session, your child will be put on the physiotherapist's lap while the therapist places his/her hands on the child's chest and gives light pressure. We selected this technique because children do not have to actively help during the treatment and therefore it can be a useful tool for young children. The aim of this research is to test if using this technique can shorten the length of the hospital stay and resolve the pneumonia more quickly. We cannot assume that this technique will be effective in children with pneumonia unless we test it on children with this disease. We therefore invite your child to take part in this research because he/she has pneumonia and is less than 8 years old.

What does the study mean for your child?
The study will take place during the time your child is in the hospital. While your child is hospitalised in Red Cross War Memorial Children's Hospital, he/she will receive standard care given by the nurses in the ward (this means he/she will get oxygen support, his/her position will be changed regularly and suction of phlegm will be done if necessary), or standard nursing care plus physiotherapy twice a day for 5 days, using Assisted Autogenic Drainage, for up to 10 to 30 minutes. As we do not know if the physiotherapy is better than the standard nursing care, we need to make a comparison. Children taking part in this

research will be put in one of the two groups by chance. This is like flipping a coin: e.g. with heads the child will be placed in group 1 and tails in group 2. Only the physiotherapist knows if your child will receive physiotherapy or not. All the other healthcare workers should not know which treatment your child is given. It is important not to tell the doctors which treatment your child is getting. This is the best way to test treatments without being influenced by what we think or hope might happen. We will then compare which of the two treatments has the best results. You may stay with your child during the procedures. During your child's hospital stay, we will do some tests to follow up your child's disease status. Your child's body temperature will be measured daily by the nurses. This is routine practice in the hospital. Also an X-ray of your child's chest will be taken when he is admitted to hospital. This is again standard practice for children with pneumonia. We will use these X-rays to make some observations. We will also count how many times your child breathes per minute (the physiotherapist or nurse will watch your child and count the number of breaths your child takes during one minute) and we will test the level of oxygen in your child's body by putting a small device on your child's finger or ear, which will than give a number that we will write down in your child's file. These tests will be done at admission, after 5 days and at discharge from the hospital and before, during and after each treatment session. The test won't take longer than five minutes. If your child is between 5 and 8 years of age, we will also conduct lung function tests. This means that your child will need to do some breathing exercises while breathing through a small tube into a machine, which gives us an idea of how well your child's lungs are working. This test will be done at admission, after 5 days and at discharge. The test will take 15 minutes on average. None of the tests used in our research are painful for your child. These tests will be done on a regular basis as long as your child stays in the hospital.

What are the possible benefits and/or risks to your child?

It is unknown which risks/benefits are related to physiotherapy in children with bacterial pneumonia. We do not know which complications are associated with Assisted Autogenic Drainage, but the technique is adapted to the child's tolerance. Physiotherapy can lead to some distress, but we will watch your child closely for any signs of distress. (We will look if your child his/her lips or nails become blue, if he/she is starting to have a weak cry, if he/she gets tired, if his/her head is starting to wobble, if your child is breathing with a widened nose or if we see that your child has overworked muscles in his/her neck) Suctioning may be necessary if the child cannot clear their phlegm by coughing alone. We will only use suctioning when it is really necessary, as this is uncomfortable and can damage the lungs or increase blood pressure.

At the start and end of the study, your child may be asked to do a lung function test. Your child may experience some light-headedness or fatigue, but the test is not harmful. The other tests in this study are not harmful.

We do not know the benefits of Assisted Autogenic Drainage, but Autogenic Drainage which is used in older children and adults works well in clearing the lungs. At the moment, we do not know if the children receiving physiotherapy will benefit from this treatment. Therefore, there are no direct benefits to participate in the study.

Voluntary participation

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive will continue and nothing will change, except your child will definitely not receive Assisted Autogenic Drainage. You may also choose to change your mind later and stop participating, even if you agreed earlier. The services you and/or your child receive at the clinic will continue.

Confidentiality

The information that we collect from this research project will be kept confidential. Any information about your child will have a number on it instead of his/her name. Only the physiotherapists will know what information belongs to your child. Participation in this research does not involve extra costs for you. No compensations for travel costs will be given.

Insurance

If you took part in study procedures exactly as the investigator told you to and as a result you become ill or are injured as part of the research, you may need to receive medical treatment. If this happens, the costs of any reasonable and necessary medical treatment will be covered by insurance held by the University of Cape Town through its no fault insurance policy, which covers this study, provided you have followed the directions of the investigator and her staff. You are not giving up any of your legal rights by participating in this study. When you sign this form, you only indicate that your study investigator has informed you about this research study and that you agree to take part in it.

Contact

If you have any questions or worries after reading this form or at any other time during or after the study, please do not hesitate to contact us. You may contact the University of Cape Town Faculty of Health Sciences Human Ethics Committee (HREC) if you have any questions or concerns regarding your child's rights or welfare as a research participant.

Lieselotte Corten
071 588 37 29
crtlie001@myuct.ac.za

Brenda Morrow
021 658 5074
Brenda.Morrow@uct.ac.za

Human Research Ethic Committee (HREC)
Prof Marc Blockman, Chair
Old Main Building, Groote Schuur Hospital
021 406 6338
Marc.Blockman@uct.ac.za

PART II: Certificate of consent

If you consent, we ask you to sign this letter.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study.

Print Name of Participant_____

Print Name of Parent or Guardian_____

Signature of Parent or Guardian _____

Date _____

Assent form for children older than 5 years of age, hospitalised with bacterial pneumonia.

PART I: information sheet

My name is Lieselotte Corten and I am studying at the University of Cape Town. I am doing an investigation into the use of physiotherapy in children with who are hospitalised with pneumonia (a lung infection).

I am trying to find out more about the use of physiotherapy compared to only the care that nurses give to you. You are being asked to join this study because you have pneumonia and because you are younger than 8 years of age. The study will take place during the time you are in the hospital. You can be put in the group of children who only receive the care from the nurses, or you can be put in the group of children who will get physiotherapy. We don't know yet in which group you will be placed in.

But if you decide you want to be in this study, this is what will happen:

If you are in the group that will only get the care from the nurses, the nurses can give you oxygen so you will be able to breathe better and they will change your position (side lying on the left or the right or sitting upright). It is also possible that they will need to help you with getting the phlegm out of your lungs, this they will do with a small tube which they put in your mouth. This is not pleasant and we will only do that when you need it.

If you are in the group that also gets physiotherapy, you will get the same care by the nurses as described above and you will also get 5 days of physiotherapy by a physiotherapist. The physiotherapist will come twice a day, once in the morning and once in the afternoon or evening to give the therapy. During this therapy, you will be sitting on his/her lap. The physiotherapist will place his/her hands on your chest and will give some pressure. This does not hurt but it is necessary to perform the treatment correct. You don't have to do anything. The physiotherapist does everything for you. So he/she will give some pressure so you will not be able to take a deep breath. The physiotherapist will do this until he/she feels or hears your phlegm. If he/she hears or feels them, the physiotherapist will hold the pressure on your chest until the phlegm is gone. Then he/she will let go the pressure a little bit until he/she feels or hears the phlegm again. Then he/she will hold the pressure again until the phlegm is gone. This is repeated three times. Eventually the physiotherapist is going to let go of your chest so you can take a deep breath and maybe cough the phlegm out. The physiotherapist is going to repeat this a few times, for about 10 to 30 minutes.

We will also have to do some tests on you. The nurses will take your temperature every day. They will use a thermometer and they will put it under your arm or sometimes we need to put it in your bottom. Also an X-ray of your chest will be taken when you enter the hospital. This is done to all children with pneumonia. We will use these X-rays to make some observations We will also have to measure the oxygen in your body, this we do by placing a small device on your finger or ear. This little device will show us a number which

we will write down in your file. And we will also count how many times per minute you breathe. For this test you don't have to do anything, you probably won't even know the nurse or physiotherapist is counting how many times you breath per minute. These tests will be done when you are admitted to the hospital, and then before, during and after each physiotherapy treatment and again after 5 days in the hospital and before you go home. These tests will not take more than 5 minutes. And you will also have to do some lung tests, this means you have to blow in a small tube, which is linked with a machine that shows us different numbers which tells us about how well your lungs are working. This test is only done when you enter and when you leave the hospital. The test will take about 30 minutes. All these tests are not painful; they can be a bit unpleasant. All these test will be repeated regularly while you are in the hospital.

Can something bad happen to me?
We want to tell you about some things that might hurt or upset you if you are in the study.

We don't know yet what bad things can happen during the physiotherapy that you will get, but you can get some blue lips or nails and find it difficult to breathe. The physiotherapist is going to watch you really closely so he/she can immediately stop the therapy if something like that happens. And you can always tell him/her if you don't feel good. Also the suctioning of the phlegm, what the nurses do, can be uncomfortable but it will only be done when it is really needed.
You will need to do a lung function test at the start and the end of the study. You may feel a bit light in your head or a bit tired, but the test will not do anything bad to you.

Can anything good happen to me?
We don't know if being in this research study will help you feel better or get well. But we hope to learn something that will help other people someday.

Do I have other choices?
You can choose not to be in this study

Will anyone know I am in the study?

We won't tell anyone you took part in this study. When we are done with the study, we will write a report about what we found out. We won't use your name in the report. The only person who knows you are in the study is the physiotherapist.

What if I don't want to be in the study?
If you don't want to be in this study, we will tell you about the other things we can do for you. Even if you decide not to be in this study, we will still take care of you.

You don't have to be in this study. It's up to you. If you say yes now, but you change your mind later, that's okay too. All you have to do is tell us.

Who can I ask questions about the study?

You can always ask questions or tell us about your worries.
The persons you can contact about this are:

Lieselotte Corten
071 588 3729
crtlie001@myuct.ac.za

Brenda Morrow
021 658 5074
Brenda.Morrow@uct.ac.za

PART II: certificate of assent

If you want to be in this study, please sign or print your name.

☐ Yes, I will be in this research study. ☐ No, I don't want to do this.

_____ _____ _____

Child's name signature of the child Date

_____ _____ _____

Person obtaining Assent signature Date

Appendix 12. PRISMA checklist for the systematic review on AD and AAD in children with CF

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P 141
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P VI
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P 141
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P 141
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P 141
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P 142
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P 143
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P 143
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P 143
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P 144
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P 143

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P 144-145
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P 145
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P 146
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P 146
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P 147-148
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P 147 +149-152
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P 152-158
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P 158-165
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P 166-167
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P 167-168
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P 168-169
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P ii

Appendix 13. Search terms for the systematic review on AD and AAD in children with CF

Intervention	Control	Population	Condition
autogenic drainage	chest physiotherapy	Child*	cystic fibrosis
assisted autogenic drainage	chest physical therapy	infant*	CF
passive autogenic drainage	respiratory physiotherapy	baby	mucoviscidosis
AD	respiratory physical therapy	babies	
AAD	airway clearance techniques	toddler*	
	airway clearance therapy	paediatric*	
	breathing therapy	pediatric*	
	conventional physiotherapy		
	conventional airway clearance therapy		
	conventional airway clearance technique		
	postural drainage		
	modified postural drainage		
	percussions		
	clapping		
	vibrations		
	chest wall shaking		
	coughing		
	active cycle of breathing technique OR ACBT		
	Forced expiratory therapy OR FET		
	Positive expiratory pressure therapy OR PEP		
	Oscillating PEP		
	High pressure PEP		
	Rib cage compressions		
	Thoracic squeezing		
	Flutter		
	Acapella		
	Intrapulmonary vibrations OR IPV		
	Quake		

Search terms between columns were combined with 'AND'

Search terms within one column were combined with 'OR'

Appendix 14. Interview guideline for preference and adherence

1) Which technique(s) did you use during the study to 'clear your lungs'?
   - ☐ AAD (the new technique)
   - ☐ Flutter (device with ball that vibrates when breathing/blowing in the device)
   - ☐ Percussions (clapping on the chest and back by parent)
   - ☐ Vibrations
   - ☐ Active cycle of breathing (deep breathing exercises without a device)
   - ☐ Active play
   - ☐ Other: ……

2) How often did you do this treatment per day? If not daily, how often did you do it per week? When more than 1 technique was used, please specify per technique how frequently it was used.

3) How much time did you spend on 1 treatment session (specify per technique if possible)?

4) What did you like about the technique (for each technique separately)?

5) What did you dislike about the technique (for each technique separately)?

6) What is the reason you were unable to perform the treatment twice a day?

Appendix 15. Approval documents for the study on the use of AAD in children with CF

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: linsey.samuels@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

07 November 2013

HREC REF: 648/2013

A/Prof B Morrow
Paediatric Medicine
Red Cross War Memorial Children's Hospital

Dear A/Prof Morrow

PROJECT TITLE: THE USE OF ASSISTED AUTOGENIC DRAINAGE IN SOUTH AFRICA CHILDREN WITH CYSTIC FIBROSIS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

DR T A BLAKE
MANAGER MEDICAL SERVICES
thomas.blake@westerncape.gov.za
0216585788/0828225553
18 JULY 2014

MS L CORTEN

Dear Ms Corten,

RESEARCH: **The use of assisted autogenic drainage (AAD) in children with acute respiratory disease in a developing country.**

The use of assisted autogenic drainage (AAD) in South-African children with cystic fibrosis.

This letter confirms the approval for the above proposed research at the Red Cross War Memorial Children's Hospital.

Yours faithfully,

DR T A BLAKE
CHAIRPERSON
HOSPITAL RESEARCH REVIEW COMMITTEE

Informed Consent Form for the parent(s)/guardian(s) of children between the ages of 0 and 8 years with cystic fibrosis, receiving a home-program and being followed up in Red Cross Children's hospital, Cape Town.

This Informed Consent Form has two parts:

- Part I: Information Sheet (to share information about the study with you)
- Part II: Certificate of Consent (for signatures if you agree that your child may participate)

You will be given a copy of the full Informed Consent Form

PART I: Information sheet

I, Lieselotte Corten (PhD- student at the University of Cape Town) am doing research within breathing techniques in children with different diseases. One of my research topics is the use of "Assisted Autogenic Drainage" in children receiving a home-program for cystic fibrosis.

What is the reason for the study and how will it be done?
Cystic fibrosis is a disease that affects the whole body, and therefore also the lungs. Physiotherapy is part of the treatment for this disease. The current physiotherapy treatment consists of positioning, percussion (clapping) and breathing exercises. There is a new chest physiotherapy technique developed, Assisted Autogenic Drainage, which uses deepening of breathing to loosen up and evacuate the phlegm from the lungs. We selected this technique as children do not have to actively help during the treatment and therefore it might be a useful tool in young children. The aim of this research is to test this new technique to see if it helps the children better than the current therapy. We selected this technique because children do not have to actively help during the treatment and therefore it can be a useful tool for young children. We cannot assume that this technique will be effective in young children with cystic fibrosis unless we test it on this disease. We invite your child to take part in this research because he/she has cystic fibrosis and is less than 8 years old.

What does the study mean for your child?
The children participating in this research will receive a home-program consisting of chest physiotherapy twice a day (performed by you), either the standard physiotherapy or the new treatment for 10 to 30 minutes, depending on the physician's and physiotherapist's decision and how your child responds. As we do not know if the new treatment is better than the standard treatment we need to make a comparison. Children taking part in this research will be put in one of the two groups by chance. This is like flipping a coin, with heads is the child participating in group 1 and tails in group 2. Only the physiotherapist knows which treatment is given during this home-program. It is important not to tell the doctors which treatment your child is getting. This is the best way to test treatments

without being influenced by what we think or hope might happen. We will then compare which of the two treatments has the best results.
We will collect some information of your child during one year, like how many times they need to be hospitalised or how many days they need antibiotics. We will collect this information from your child's medical file. We will also ask you (and your child) to fill in a questionnaire concerning your child's well-being at the beginning and end of the study period. You will have to mark which answer best describes your child's health at that time. This questionnaire will take about 10 minutes to complete. We will also do a test to see how your child's development is going. This test is not painful, it is a test where the child can do some playing activities and we will observe how he/she is performing these tasks. This test can take up to 30 minutes. Also your child's height and weight will be measured every time you come to the clinic. Once a year a chest X-rays is taken, this is standard practice for managing children with CF. We will use these X-rays to look for changes. Also, if your child is older than five years of age, lung function tests are done annually, as part of the standard practice. This means that your child will be asked to do some breathing exercises while breathing through a small tube into a machine, which gives us an idea of how well your child's lungs are working. Again we will use these results to look for differences. If your child is in the group receiving assisted autogenic drainage, we will also ask you to fill in an extra questionnaire on which treatment you preferred. We will ask you to fill in this questionnaire during the first follow-up visit and at the end of the study, and will not take more than 5 minutes. Again you are asked to indicate which answer suits you the best.
During the first CF-clinic, you will be asked to spend about two hours more in hospital, because we need to get some more information about your child, we will have to do the test for your child's development. We will try and do most of this while you are waiting to see the doctor. During this test, you can fill in the questionnaire we ask you to fill in. You will also be taught the treatment that needs to be given to your child and we will explain how to fill in the diary. The following visits won't take much more time than usually. The last visit during the study period will again take more time, about 40 minutes, because we need again to test your child's development and you will be asked again to fill in the different questionnaires.

What does this study mean for you?
As parent or legal guardian of your child, you will be asked to perform the chest physiotherapy at home, twice a day and fill in a diary on these treatments. We will teach you how to do the treatments by showing you an animated video to explain what cystic fibrosis is and why physiotherapy is important in this disease. Afterwards the physiotherapist will explain the treatment to you, he/she will demonstrate how to perform the treatment and then you will do it together with the physiotherapist. You can ask questions at any time. We will assess if you perform the technique correctly by asking you to show us how to do the technique on your child. We will not give feedback at the time you are performing the technique. Every time your child comes to the CF-clinic, you will be asked to perform the technique, to make sure it is executed as it should. This is not to criticise you, but to make sure that we receive the best results for our study and that your child receives the best treatment at home.

What are the possible benefits and/or risks to your child?
It is unknown which risks/benefits are related to different chest physiotherapy techniques in children with cystic fibrosis. Conventional chest physiotherapy has been shown to improve lung function in children with cystic fibrosis if continued for a long period of time. Risks of postural drainage and percussion (standard chest physiotherapy) are a decrease in oxygen levels in the blood (your child can have dizziness), discomfort/pain and/or gastro-oesophageal reflux, which means that your child may be nauseous or vomit. We will try to limit these risks by giving clear instructions on what you need to pay attention for during your treatment: is your child getting tired, does his/her lips or nails become blue, is he/she starting to get a weak cry, is his/her head starting to wobble, is he/she breathing with a widened nose or do you see the muscles in his/her neck retract. We do not know which complications are associated with Assisted Autogenic Drainage, but the technique is adapted to the child's tolerance. The tests used in this study are not harmful in any way.

We do not know the benefits of Assisted Autogenic Drainage, but Autogenic Drainage which is used in older children and adults works well in clearing the lungs. We do not know if the children who receive the new technique will have more benefits than the children who receive the standard chest physiotherapy. Therefore, there are no direct benefits to participate in the study.

Voluntary participation
Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive at this clinic will continue and nothing will change, except your child will definitely not receive Assisted Autogenic Drainage. You may also choose to change your mind later and stop participating, even if you agreed earlier. The services you and/or your child receive at the clinic will continue as before.

Confidentiality
The information that we collect from this research project will be kept confidential. Any information about your child will have a number on it instead of his/her name. Only the physiotherapist will know what information belongs to your child. Participation in this research does not involve extra costs for you. No compensations for travel costs will be given.

Insurance
If you took part in study procedures exactly as the investigator told you to and as a result you become ill or are injured as part of the research, you may need to receive medical treatment. If this happens, the costs of any reasonable and necessary medical treatment will be covered by insurance held by the University of Cape Town through its no fault insurance policy, which covers this study, provided you have followed the directions of the investigator and her staff. You are not giving up any of your legal rights by participating in this study. When you sign this form, you only indicate that your study investigator has informed you about this research study and that you agree to take part in it.

Contact

If you have any questions or worries after reading this form or at any other time during or after the study, please do not hesitate to contact us. You may contact the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC) if you have any questions or concerns regarding your child's rights or welfare as research participants.

Lieselotte Corten
071 588 3729
crtlie001@myuct.ac.za

Brenda Morrow
021 658 5074
Brenda.Morrow@uct.ac.za

Human Research Ethic Committee (HREC)
Prof Marc Blockman, Chair
Old Main Building, Groote Schuur Hospital
021 406 6338
Marc.Blockman@uct.ac.za

PART II: Certificate of consent

If you consent, we ask you to sign this letter.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study.

Print Name of Participant_____

Print Name of Parent or Guardian_____

Signature of Parent or Guardian _____

Date _____

Assent form for children older than 5 years of age with cystic fibrosis.

PART I: Information sheet

My name is Lieselotte Corten and I am studying at the University of Cape Town. I am doing an investigation into the use of physiotherapy in children with cystic fibrosis.

I am trying to find out more about the use of a new physiotherapy technique compared to the physiotherapy techniques you use now. You are being asked to join this study because you have cystic fibrosis and because you are younger than 8 years of age. You can be put in the group of children who keep using the physiotherapy you already use, or you can be put in the group of children who will get the new physiotherapy treatment. We don't know yet in which group you will be placed in.

But if you decide you want to be in this study, this is what will happen:

Your mum or dad is going to give you physiotherapy twice a day, once in the morning and once in the afternoon or evening. The therapy will not take more than 30 minutes. We will follow you up during one year.

If you are in the group that keeps doing the physiotherapy you already do, not much will change. We will teach your mum or dad how to do the physiotherapy with you. We will teach them in which position you need to be to do the therapy and how you need to breathe. Maybe they also need to tap you on the chest during the techniques. Sometimes we also give you a small device, called PEP-device of Flutter, through which you need to breathe.

If you are in the group that gets the new physiotherapy treatment, you will sit in front of your mum or dad and your mum or dad will place his/her hands on your chest and will give some pressure. This does not hurt but it is necessary to perform the treatment correct. You don't have to do anything. Your mum or dad will have to do everything. So he/she will give some pressure so you will not be able to take a deep breath. He/she will do this until he/she feels or hears you phlegm. If he/she hears or feels them, your mum or dad will hold the pressure on your chest until the phlegm is gone. Then he/she will let go the pressure a little bit until he/she feels or hears the phlegm again. Then he/she will hold the pressure again until the phlegm is gone. This is repeated three times. Eventually your mum or dad is going to let go of your chest so you can take a deep breath and maybe cough the phlegm out. Your mum or dad is going to repeat this a few times.

We will also have to do get some information from you and your parents. We will see how many times you will be in hospital this year and how many times you need medicine. This information we will get from your doctor's file. You and your mum or dad need to fill in a questionnaire about how you feel at the start of the study and at the end. This questionnaire will only take about 10 minutes to fill in. You need to point out which sentence you and your mum find the best to explain how you feel. We will also test how

well you are developing, you will play some games for about 30 minutes and we are going to watch how you do this. Every year an X-ray is taken, this is normal in children with CF. We will look at these X-rays to see if we can find some changes. Every year you also need to do a lung test, this means you have to blow in a small tube, which is linked with a machine that shows us different numbers which tells us about how well your lungs are working. We will use these numbers to look for differences. And finally we will also measure your height and weight every time you come to the CF-clinic. If you have been getting the new technique, we will also ask you and your parents to fill in an extra questionnaire on which treatment you like the most. This questionnaire will only take 5 minutes and again you need to point out which sentence explains the best how you feel.

Can something bad happen to me?
We want to tell you about some things that might hurt or upset you if you are in the study.

If you get the standard physiotherapy, the therapy you are currently getting, it is possible that you feel nausea or maybe you have to vomit. The oxygen level in your body can go down so you may feel a bit dizzy or it can hurt you a bit. We don't know yet what bad things can happen during the new physiotherapy technique, but you can get some blue lips or nails or find breathing more difficult. We are going to teach your parents how to see these things so they can immediately stop the therapy if something like that happens. And you can always tell him/her if you don't feel good. The tests we will do, will not do anything bad to you.

Can anything good happen to me?
We don't know if being in this research study will help you feel better or get well. But we hope to learn something that will help other people someday.

Do I have other choices?
You can choose not to be in this study

Will anyone know I am in the study?

We won't tell anyone you took part in this study. When we are done with the study, we will write a report about what we found out. We won't use your name in the report. The only person who knows you are in the study is the physiotherapist.

What if I don't want to be in the study?
If you don't want to be in this study, we will tell you about the other things we can do for you. Even if you decide not to be in this study, we will still take care of you.

You don't have to be in this study. It's up to you. If you say yes now, but you change your mind later, that's okay too. All you have to do is tell us.

Who can I ask questions about the study?

You can always ask questions or tell us about your worries.
The persons you can contact about this are:

Lieselotte Corten
071 588 3729
crtlie001@myuct.ac.za

Brenda Morrow
021 658 5074
Brenda.Morrow@uct.ac.za

PART II: certificate of assent

If you want to be in this study, please sign or print your name.

☐ Yes, I will be in this research study. ☐ No, I don't want to do this.

_____	_____	_____
Child's name	signature of the child	Date
_____	_____	_____
Person obtaining Assent	signature	Date

Appendix 17. Data collection forms for the study on AAD in children with CF

Recruitment form CF: Subjective assessment

1) Name: …….

2) Date of birth: ….../…../……

3) Date of recruitment: ….../…../……

4) Age at recruitment: …….

5) Gender: M F

6) Age at diagnosis: …….
   Age started physio: …….

7) Prematurity: Y N
   Gestational age? ……..

8) Acute TB: Y N
   If yes, since when medication? …….
   Which medication? ……

9) History of TB: Y N
   If yes, when? ……

10) HIV-infected: Y N
    If yes, when diagnosed? …….
    If yes, since when HAART? …….

11) HIV-exposed: Y N

12) Asthma: Y N
    If yes, since when medication: ……..
    Which medication? ……..

13) On lung/heart transplant list: Y N

14) Neuromuscular disorder: Y N
    Type of NMD? ……

15) Severe kyphosis: Y N
    Severe scoliosis: Y N
    Other chest deformity? Y N Which one? ……

16) Recent pneumothorax (≤3m): Y N

17) Thoracic or abdominal surgery: Y N
    (≤6m)

18) Osteoporosis: Y N

19) Ephysema: Y N

20) Active sarcoidosis: Y N

21) Developmental delay: Y N
If yes,IQ/developmental age? ……..

22) Pancreas: sufficient insufficient

<u>Medical record at commencement of the study CF</u>

1) Genotype …….

2) X-ray score: …….

3) Colonised with:
- ☐ Pseudomonas aeruginosa
- ☐ Staphylococcus aureus
- ☐ MRSA
- ☐ Haemophilus influenza
- ☐ RSV
- ☐ Adenoviruses
- ☐ Viral influenzae
- ☐ Aspergillosis
- ☐ Other: ……..
- ☐ Nothing

4) First isolation: ……..

5) Medication:
- ☐ Eradication regimen
- ☐ Chronic inhaled gentamicin
- ☐ Chronic inhaled colistin
- ☐ Azimothrycin
- ☐ Others: ……
- ☐ None

6) Osteoporosis on X-ray: Y N Score? …….

7) EQ-5D-Y score: …….

8) Neurodevelopmental test: PDMS-2 Mov. ABC
score: ……

9) Weight: …….

10) Height: ……..

11) Weight for height ratio: ……..

Medical record at the end of the study CF

1) X-ray score: ……..

2) During study period, infected with or colonised with:
   - ☐ Pseudomonas aeruginosa
   - ☐ Staphylococcus aureus
   - ☐ MRSA
   - ☐ Haemophilus influenza
   - ☐ RSV
   - ☐ Adenoviruses
   - ☐ Viral influenzae
   - ☐ Aspergillosis
   - ☐ Other: ……..
   - ☐ Nothing

3) First isolation: ……

4) Medication:
   - ☐ Eradication regimen
   - ☐ Chronic inhaled gentamicin
   - ☐ Chronic inhaled colistin
   - ☐ Azimothrycin
   - ☐ Others: ……
   - ☐ None

5) EQ-5D-Y score: ……..

6) MABC/PDMS score: ……

7) Number of hospitalisations ……..
   Days of hospitalisations ……..

8) Number of exacerbations ……
   Days of antibiotic usage ……

9) Weight: ……

10) Height: ……..

11) BMI-for age z-score: ……..