Indication for and outcomes of continuous Positive Airways Pressure (CPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) in children admitted to Red Cross War Memorial Children's Hospital (RCWMCH) excluding those with primary respiratory aetiologies

By

Kate Browde

MBBCH, DCH (SA), FCPaed(SA)

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Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Supervisor:

Professor Brenda Morrow

Co-Supervisor:

Associate Professor Mignon McCulloch

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DECLARATION

I, *Kate Browde*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and 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.

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ABSTRACT

Non-invasive CPAP and HFNC use in children Without Primary Lung Pathology: A prospective observational study.

Abstract

Aim

Noninvasive Continuous Positive Airway Pressure (nCPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) are non-invasive ventilation (NIV) modalities appropriate for children in developing countries. There is minimal literature describing nCPAP and HFNC use in children with respiratory compromise secondary to non-pulmonary disease. This study aimed to describe the characteristics and outcomes of all children without primary lung pathology, who received nCPAP and HFNC during their admission to Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

Methods:

This was a prospective observational study of routinely collected data, between August 2015 and January 2016.

Results:

There were 31 cases of nCPAP and one case of HFNC use in 31 patients (median (IQR) age 3.5 (1.8 – 7.6) months.) The majority (n=23; 71.9%) presented with primary diarrhoeal disease. There were two deaths (6.5%), 17 (53.1%) Paediatric Intensive Care (PICU) admissions, and five (15.6%) cases received invasive ventilation (NIV failure). Median (IQR) duration of hospital stay was 11.50 (6.0 – 17.5) days. On multiple logistic regression there were no independent associations with NIV failure. Lower temperature (OR 0.19; 95% CI 0.05 – 0.78; p = 0.02) and receiving inotropes (OR 23.05; 95% CI 1.64 – 325.06; p = 0.02) were independently associated with PICU admission.

Conclusions

nCPAP is used clinically for the management of children with respiratory compromise secondary to non-pulmonary illnesses, particularly diarrhoeal disease. Larger controlled clinical studies are needed to determine the effectiveness and utility of nCPAP in this population. HFNC was not commonly used, and this modality requires further investigation in this population.

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nCPAP	Nasal Continuous Airway Pressure
HFNC	High-flow Nasal Cannula oxygen therapy
RCWMCH	Red Cross War Memorial Childrens Hospital
PICU	Paediatric Intensive Crae Unit
NIV	Non-invasive Ventilation
COPD	Chronic Obstructive Pulmonary Disease
HMD	Hyaline Membrane Disease
FDA	Food and Drug Administration
MEU	Medical Emergency Unit
DHF	Dengue Haemorrhagic Fever
DSS	Dengue Shock Syndrome
HIV	Human Immunodeficiency Syndrome
HUS	Haemolytic Uraemic Syndrome
NPA	Nasopharyngeal Aspirate
RSV	Respiratory Syncytial Virus

1. LITERATURE REVIEW

Background

Non-invasive ventilation (NIV)

The term non-invasive ventilation (NIV) refers to respiratory support provided by an external interface rather than an invasive airway such as an endotracheal tube or tracheostomy (1).

NIV modes include continuous positive airway pressure (nCPAP), bi-level positive airways pressure (BiPAP) ventilation, high flow nasal cannula oxygen therapy (HFNC), and negative pressure ventilation. NIV may be provided through a variety of interfaces including face/nasal masks, mouthpieces, cuirasses, helmets, and nasal cannulae (1). NIV is gaining popularity in adult and paediatric practice, as it might prevent the need for endotracheal intubation (2) and in so doing prevent complications associated with invasive mechanical ventilation, including ventilator-associated pneumonia, lung injuries, subglottic stenosis and nutritional compromise (3). NIV may also reduce the need for deep sedation, thereby maintaining the patient's cough reflex and allowing more effective secretion clearance (4).

A number of adult studies have investigated the use of NIV in various situations, including the management of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), asthma, acute lung injury, cardiogenic pulmonary oedema and chest trauma (2,5). In a recent review, Walkey and Weiner (2013) described NIV use amongst adults in all types of respiratory failure, across all diagnostic categories (6).

The "FLORALI" trial was a multi-centre European trial, which randomly assigned adult patients (n=313) with non-hypercapnoeic hypoxaemic respiratory failure to either HFNC, standard oxygen therapy using a facemask or noninvasive positive-pressure ventilation. Results showed that patients receiving HFNC had the lowest intubation rates and the best 90-day survival compared to

comparison groups (7). There are no similar paediatric trials (3).

Despite fewer formal data supporting its use in children (1), NIV has become more common in this setting, used for the management of acute and chronic respiratory failure, status asthmaticus, hypoventilation syndromes, neuromuscular disorders and chronic upper airway obstruction; and to improve successful extubation rates (8–10). NIV is well established for use in the neonatal setting for all causes of respiratory distress and early stabilization of premature and low birth weight newborns (11).

Most low-income countries cannot provide mechanical ventilator support to children, owing to cost, feasibility, resource limitations, staff shortages and training levels, amongst others. Therefore, simpler yet effective non-invasive methods of providing respiratory support should be considered to improve paediatric care outcomes in these settings (12). In this context, both nCPAP and HFNC can be provided by stand-alone machines, and adapted for use in low-resource settings (12).

nCPAP and HFNC use in children beyond the neonatal period has been reported, where they have been shown to be clinically effective in the management of a range of paediatric respiratory illnesses (13). Both modalities are being used clinically for wider indications (12), but there is a paucity of research specifically investigating the use of nCPAP and HFNC in the setting of respiratory compromise caused by non-pulmonary illnesses.

Continuous positive airway pressure (CPAP)

nCPAP is a mode of noninvasive ventilation where a preset positive pressure is provided continuously, either nasally or via a facemask or mouthpiece (14).

CPAP was initially developed by Dr. George Gregory for use in premature infants with Hyaline Membrane Disease (HMD) in the early 1970's (15). At that time, the mortality rate for infants with HMD was over 50%. During this period Harrison et al, a group of South African researchers, published their findings that grunting

seemed to help infants with HMD to maintain higher saturation levels (16). These researchers observed babies who were grunting and noted that their condition worsened after tracheal intubation, and improved again once they were extubated and allowed to resume grunting. The conclusion was drawn that by performing a modified valsalva manoeuvre during grunting, the babies were able to maintain their functional residual capacity and improve alveolar ventilation. Dr. Gregory used this information and devised a method of providing positive pressure via an endotracheal tube.

Measurable effects of CPAP include increased functional residual capacity, decreased intrapulmonary shunting, increased tidal volume and decreased airway resistance (17). Gregory managed to create these effects with his initial CPAP device: an endotracheal tube connected to an Ayres T-piece, which was connected to a gas inflow line. Fresh gas was introduced into the system near this T-piece, which was connected via corrugate tubing to a reservoir bag. The pressure in the system could be adjusted by varying inflow of gas or the degree of occlusion at the tail end of the reservoir bag.

Certain complications of CPAP have also been described. These include skin erosion at the site of the mask or interface, pneumothorax, abdominal distension, upper airway bleeds (1,18) and noise-induced hearing loss (19).

With the use of CPAP, the mortality rate of infants with HMD has dramatically declined, and CPAP is used as a lung-protective strategy to prevent long term lung damage in preterm infants (20). CPAP has also been shown to be effective in the management of older children with bronchiolitis and other respiratory illnesses (21–25) and has become a mainstay of treatment for many of these conditions.

There are now numerous delivery systems for nCPAP, some of which are straightforward and relatively inexpensive (26). One of these is Bubble CPAP where the positive pressure is achieved by keeping the efferent limb of the exhale tubing under water and the gas flow adjusted to maintain constant

bubbling (12). A study from Ghana (2013) showed that Bubble CPAP is effective in decreasing the respiratory rate of children with non-specific respiratory distress (27).

Certain centres in resource-limited countries are developing their own bubble CPAP devices, sometimes using materials such as recycled plastic bottles, making the devices extremely affordable and yet still effective. A study from Malawi (26) showed that a stand-alone bubble CPAP device could be developed for one fifteenth of the price of the device recently approved by the Food and Drug Administration (FDA).

Considering its efficacy in the management of paediatric respiratory illness and its cost effectiveness, CPAP represents an important development in child health care in the developing world (12).

However, the indications for, and efficacy of CPAP in the management of children requiring ventilatory support secondary to primarily non-pulmonary pathologies, are currently not clearly defined.

<u>High- flow nasal cannula oxygen therapy (HFNC)</u>

Heated, humidified, HFNC is a relatively new therapy first described in the early 1990s (28). It allows the delivery of inspired gas at higher flow rates than regular oxygen cannula therapy (1-8 L/min in infants). HFNC flushes dead space in the nasopharyngeal cavity allowing for better ventilation and oxygenation; provides sufficiently high flow to support inspiration and reduce inspiratory work of breathing; and the added humidification eliminates the effects of drying and cooling (29). The fraction of inspired oxygen (FiO_2) can be adjusted according to the patient's needs and it can also provide some level of CPAP, although the exact level cannot always be predicted (12).

HFNC is being used increasingly commonly in neonatal units, either as a step-down measure from CPAP or as an alternative means of respiratory support in the management of HMD (30). The benefits of HFNC are that it is less

cumbersome than CPAP, more easily applied, and causes less nasal trauma (31). In terms of efficacy, studies have shown no increase in adverse outcomes when replacing CPAP with HFNC in the management of HMD (28,31).

HFNC is also being used more frequently in older children beyond the neonatal age (3), where it has been shown to be as effective as CPAP in the management of bronchiolitis and other respiratory disorders. In a recent retrospective folder review by Metge et al (32), HFNC was compared with nCPAP in infants admitted to PICU with severe acute bronchiolitis for two subsequent seasons. They observed no difference in the length of stay in the PICU, respiratory rate, PCO_2, FiO_2, and duration of oxygen support between the two groups.

Similar to nCPAP, use of HFNC for respiratory support in children without primary pulmonary pathology is not well described.

Management of respiratory distress resulting from extra-pulmonary pathology

Sepsis (resulting in poor oxygenation of tissues with increased oxygen demand) and acidosis (with respiratory compensation) are amongst the main physiological causes of respiratory distress in children (33).

The paediatric section of the 2012 "Surviving Sepsis Campaign" guidelines for treating sepsis and septic shock recommends the use of CPAP or HFNC in the initial resuscitation of children with respiratory compromise or hypoxaemia associated with sepsis or septic shock (34). The authors describe how young children commonly need early respiratory support in circumstances of severe sepsis/septic shock because of their low functional residual capacity, but that intubation and ventilation might actually be deleterious in these settings because increased intrathoracic pressure can lead to compromised venous return and worsening shock. HFNC and CPAP could be used in this setting to increase functional residual capacity and reduce work of breathing, allowing for establishment of intravenous or intraosseous access for fluid resuscitation and peripheral inotrope delivery. By reducing the need for intubation, the use of potentially harmful sedative drugs may also be avoided.

Despite these recommendations, data supporting the use of nCPAP or HFNC for patients in whom the primary pathology is non-respiratory is scarce.

Setting and Current Practice

Red Cross War Memorial Children's Hospital (RCWMCH) is a public tertiary and secondary level hospital in Cape Town, South Africa. It is the only stand alone, specialist children's hospital dedicated entirely to paediatric care in southern Africa. RCWMCH has a total of 275 beds (medical and surgical) of which 15 are "High Care" medical beds and 22 are in the paediatric intensive care unit (PICU). Currently, all children on nCPAP and HFNC are managed either in ward High Care units or in PICU.

An average of 40 000 children per year are seen at RCWMCH, with a large proportion of emergency admissions to the High Care units and PICU coming via the medical emergency unit (MEU). It is estimated that 360 urgent admissions to PICU and 1200 to the high care units are admitted via the MEU.

Because of the highly specialised care available at RCWMCH, a wide variety of illnesses are seen, but the majority of patients are admitted with acute infections, most commonly respiratory or gastrointestinal, depending on the season. For example, in 2013, of 7599 children admitted to the short stay ward at RCWMCH, 2997 (39.4%) of those presented with acute respiratory infections and 1803 (23.7%) presented with acute gastroenteritis. A similar proportion would have been admitted to higher care settings (MEU records).

At RCWMCH, institutional guidelines recommend the use of nCPAP or HFNC (using a stand-alone Bubble-CPAP device for both, with different attachments) as the mainstay of care in children presenting in severe respiratory distress, particularly those with high respiratory rates and respiratory acidosis on blood gas analysis, where intubation and mechanical ventilation are not emergently required. Thus, although pulmonary disease remains the primary indication for

nCPAP or HFNC, these modalities are also used in the management of children with respiratory compromise related to multiple non-pulmonary aetiologies.

In our context, in the summer months a large proportion of patients presenting to the emergency department have gastroenteritis and dehydration as their presenting complaints, with respiratory compromise occurring as a consequence of shock, hypokalaemia or severe metabolic acidosis associated with these conditions. Respiratory compromise is also likely in the face of septic shock or overwhelming sepsis. It is currently standard practice to consider using nCPAP/HFNC for respiratory support in such cases, despite the scarcity of supporting evidence.

Literature Review Objective

The objective of this literature review was to present and synthesise published evidence describing the use and benefits/harms of nCPAP or HFNC in children with respiratory compromise caused by non-respiratory aetiologies such as sepsis, septic shock, electrolyte imbalance and metabolic acidosis.

Search Strategy

The literature review was conducted using Medline/Pubmed search engines, with the final search conducted in November 2016. Search terms included full and abbreviated terms for CPAP; HFNC; and non-invasive ventilation with modifying terms “children” OR “paediatric”; “sepsis”; and “shock”.

Bibliographies of relevant articles were searched in order to identify as wide a range of relevant articles as possible.

Acceptable Studies/Inclusion Criteria

All research articles written in the English language, investigating infants or children receiving nCPAP or HFNC therapy for the management of respiratory compromise secondary to non-pulmonary aetiologies, specifically shock/sepsis, were included in this review.

We excluded adult and neonatal studies, as well as studies focusing on modes of NIV other than nCPAP or HFNC. We also excluded studies investigating NIV for post-extubation respiratory support.

Considering the paucity of high-level scientific evidence supporting nCPAP/HFNC use in this population, methodological aspects were not exclusion criteria.

Results and discussion

Nine studies met the inclusion criteria of this review, and these are summarised in Table 1.

Only one article specifically investigated the use of nCPAP in the management of respiratory compromise caused by non-pulmonary disease, in the setting of sepsis/septic shock (35). In an open prospective randomised controlled study, Cam et al (2002) set out to compare the effectiveness of facemask oxygen therapy compared to nCPAP therapy in children with Dengue Shock Syndrome complicated by respiratory failure.

Dengue Haemorrhagic Fever (DHF) is caused by the Dengue Virus and is transmitted by the mosquito Aedes Aegypti. Patients with grade i DHF present with early bruising, grade ii with spontaneous bleeding into the skin and elsewhere, grade iii with clinical evidence of shock and grade iv with shock so severe that blood pressure and pulse cannot be detected. Grades iii and iv are termed Dengue Shock Syndrome (DSS). Patients with DSS may develop respiratory failure due, at least in part, to increased capillary permeability and alveolar-capillary fluid shifts. Previously, patients with DHF/DSS who did not respond to oxygen supplementation were intubated and ventilated and this led to a number of complications. The study aimed to assess whether the use of nCPAP would help to avoid intubation.

The study was carried out in children younger than 15 years with DSS complicated by acute respiratory failure, admitted to PICU in Ho Chi Minh City,

Vietnam from January 1998 to December 1999. Acute respiratory failure was defined as cyanosis (SaO_2 <93%), RR>50 breaths per minute or severe chest retraction and nasal flaring. Patients with congenital heart disease, those who needed immediate ventilation or who were comatose and those where DSS was complicated by pneumonia were excluded.

Thirty-seven patients were randomly assigned to receive either facemask oxygen therapy or nCPAP. After 30 mins of treatment, the respiratory rate in the nCPAP group decreased significantly (p<0.05) while oxygen saturation and PaO_2 improved in both groups. One patient in the facemask oxygen therapy group did not respond to treatment immediately and was given nCPAP, to which there was a good response. Subsequently, a further 12 of the remaining 18 assigned to the facemask oxygen group, were converted to nCPAP because of treatment failure, to which they positively responded.

In the original nCPAP group, four of 18 required invasive ventilation. This revealed a significantly higher rate of unresponsiveness to treatment in the oxygen mask versus nCPAP group (13/19 vs. 4/18; p<0.01). These results suggest that nCPAP may be more effective than mask-administered supplementary oxygen in reducing the need for invasive ventilation in paediatric DSS.

Considering that DSS is not endemic to the western Cape region of South Africa, the study may not be generalisable to the local population. It is unclear whether results from the above study can be extrapolated to the general paediatric population with, for example, septic shock or metabolic acidosis.

Whilst use of nCPAP and HFNC for children with primary extra-pulmonary conditions has been reported (Table 1), no studies, other than that of Cam et al (2002), have specifically reported efficacy and safety of these NIV modalities for children with extrapulmonary causes of respiratory distress, suggesting the need for further investigation. Instead, studies have included these patients in heterogeneous cohorts, and the sample sizes (where known) are generally too

small to allow meaningful sub-group analysis.

This study therefore set out to describe current practice of HFNC and nCPAP use in the management of children admitted to RCWMCH with primary pathologies other than respiratory illness.

Table 1: Studies of non-invasive CPAP and HFNC in children whose primary diagnoses include non-pulmonary ones

Study	Design, Setting, Study duration	Intervention / control	Study Population	Outcomes	Conclusions/Comments
Cam B et al (2002) (35)	Prospective Randomised Controlled Trial PICU of a childrens' hospital in Ho Chi Minh City, Vietnam January 1998 to December 1999	Nasal CPAP vs. face-mask oxygen	-Children <15 years (n=37; median age 6 years) with confirmed Dengue Shock Syndrome presenting with acute respiratory failure	-Significant decrease in RR after 30 mins in the nCPAP group ($p<0.05$) -13 of the 19 patients in the facemask oxygen group deteriorated and were converted to nCPAP with good effect -4 children in the nCPAP group required mechanical ventilation, and all 4 died -Complications of nCPAP were not recorded	-In children with DSS with respiratory failure, nCPAP might be useful in the management of acute respiratory failure. -While DSS is not primarily a respiratory illness, it remains unclear whether these data can be extrapolated to children with shock/sepsis of other causes.
Kinikar A et al. (2011)(36)	Prospective Observational Cohort Large, tertiary-care public teaching hospital in Pune, India August to November 2009 (during H1N1 "Swine Flu" pandemic)	Nasal Bubble CPAP	-Children 0 -12 years (n=36; median age 18 months) presenting with respiratory distress who were thought to have influenza-like illness -Children with shock refractory to volume and inotropes were excluded -Cases of ARDS and apnoeas were excluded	- RR, HR and pH all improved after 6 hours of bubble CPAP ($p<0.001$,0.015, and 0.003 respectively) -None of the patients required intubation -There were no deaths -No complications reported	-Nasal bubble CPAP appeared safe and useful in the management of children with viraemia. -All patients had associated lung pathology, so results may not be applicable to children without primary lung pathology. -Limited by lack of control group.
Anitha GFS et al. (2016)(37)	Prospective Observational Cohort Critical Care Unit of a government tertiary care hospital in India November 2013 to September 2014	CPAP using a flow-inflating device	-All children (n=214; 78.9% <1 year of age) between 1 month and 12 years admitted to PICU who received CPAP -Underlying conditions included bronchiolitis (30.7%), bronchopneumonia (49%), septic shock / septicaemia (12%), scorpion envenomation (2.6%), and other (5.7%)	-CPAP was successful in 89.7% -22 children failed CPAP and were intubated -Majority of CPAP failures had bronchopneumonia with septic shock -Of the children with septicaemia, CPAP was successful in 23/26 (88%) cases -Complications occurred in 7.8% including pressure sores, abdominal distension, and dry oral and pharyngeal mucosa	-Septic shock/septicaemia was the primary underlying diagnosis in 12% of children receiving CPAP. -In the majority of these patients CPAP was successful and well tolerated. -The study population, sociodemographics and method of NIV used are similar to those at RCWMCH, hence the study is likely generalisable to our population. -Study limited by lack of control group.

Wilson PT et al (2013)(27)	Multicentre randomised Controlled Trial Four rural hospitals in Ghana June -November 2011	Nasal CPAP immediately or one hour after presentation.	-Children aged 3 months to 3 years (n=70; mean age 14 months) presenting to the emergency department with tachypnea or signs of respiratory distress -35 of the patients had positive Malaria smears -Other diagnoses included pneumonia, sepsis and severe anaemia	- Study was stopped early, as it reached the *a priori* set efficacy boundary. -Mean RR in the immediate CPAP group fell by 16 bpm (95%; CI 10-21) -No change was seen in the delayed CPAP group -There were 3 deaths in the immediate CPAP group, all in children with severe malaria. -There were no serious CPAP-related adverse events.	-It is not clear how many patients in the study had primary respiratory diagnoses but a large proportion had respiratory compromise caused by Malaria, which makes this study relevant. -In these patients, immediate CPAP application improved RR, and appeared to be safe.
Spentzas T et al. (2009)(38)	Prospective Observational Study PICU of Le Bonheur Childrens' Medical Centre in Memphis, Tennessee, USA January 2005 - January 2007	HFNC	-Children between 0 and 12 years of age (n=46 analysed; median age 2.8 years) -All patients with respiratory distress; but no record of actual primary diagnoses -22 participants excluded from analysis due to incomplete data (of these, 2 required mechanical ventilation)	-All patients received oxygen via nasal prong or face-mask before being switched to HFNC -Clinical indicators included COMFORT scale, RDS score and SaO2 -All indicators improved on HFNC -5 (10.9%) required mechanical ventilation	-Difficult to extrapolate results as the study did not specify whether the patients had primary respiratory illnesses or not -Study limited by large number of exclusions (including those with NIV failure) -HFNC may improve patient comfort, respiratory distress and SaO2 -HFNC failure rate was approximately 10%
Kelly GS et al (2013)(39)	Retrospective Cohort Review Two tertiary care paediatric emergency departments June 2011 -September 2012	HFNC	- All children <2 years of age (n=498; mean age 7.2 months) with all-cause respiratory distress, who received HFNC within 24 hours of triage were included -Diagnoses included bronchiolitis, pneumonia, status asthmaticus, reflux, septicaemia/septic shock and croup.	-42 (8%) cases required intubation -Initial RR >90th percentile, pCO2 >50mmHg and pH<7.3 were associated with increased risk of HFNC failure	-Septicaemia/septic shock was the underlying diagnosis in 16 patients who received HFNC. 3 of these patients (18.8%) required intubation. -Study limited by lack of control group and heterogeneous sample.

Brink F et al. (2013)(40)	Prospective Observational Study PICU of Royal Childrens' Hospital, Melbourne, Australia July - November 2011	HFNC vs nasopharyngeal CPAP (NP-CPAP)	-All children who were managed with HFNC (n=72; median age 6 months) or NP-CPAP (n=32; median age 5 months) for moderate to severe respiratory distress. -Range of diagnoses included: respiratory, pre- and postoperative cardiac disease, neurological/neuromuscular conditions, immunodeficiency and other.	-Escalation of respiratory support occurred in 26% of HFNC group and 18% of the NP-CPAP group -The need for escalation could be predicted by HR, RR and FiO2 response within 2 hours -Complications of HFNC were abdominal distension (n=2) and mucosal injury (n=1) -nCPAP complications were mucosal injury (n=6); pneumothorax (n=2); and blocked tubes due to secretions (n=2).	-Although there was no specific mention of children with sepsis/shock as cause for respiratory distress, it is assumed that this was the cause of respiratory distress in at least some of the immunocompromised cohort. -It is unclear whether HFNC was successful in this subgroup or not. -There was a trend to better tolerance and fewer complications of HFNC.
Schlapbach LJ (2014)(41)	Retrospective Observational Study Single centre study at PICU of Mater Children's Hospital, Brisbane, Australia January 2005 - December 2012	Pre- vs. post induction of HFNC	-Children under 2 years (n=793) transported into PICU by a specialized paediatric retrieval team -Main causes of respiratory distress included: respiratory, neuromuscular, cardiac, trauma and sepsis	-Significant decrease in invasive ventilation rates on transport after induction of HFNC use (49% to 35%; $p<0.001$) - No patients retrieved on HFNC required intubation during retrieval -There were no cases of pneumothorax or cardiac arrest in those on HFNC.	-18 children with sepsis as their cause of respiratory distress were treated with HFNC. -The outcomes of this sub-group are not reported separately. -Introduction of HFNC during inter-hospital transport was associated with reduced rates of invasive ventilation during transfers. -Limited by historical control group and retrospective nature of the study.
Long E et al. (2016)(42)	Prospective Observational study Royal Childrens' Hospital, Australia April - September 2013	HFNC	-All children presenting to the hospital who received HFNC in the ED (n=71; median age 9 months) -Most common underlying diagnosis was bronchiolitis, other conditions were acute LRTI, asthma, sepsis, apnoea and cardiac disease	-5 (7%) failed HFNC in the ED: 4 were escalated to nCPAP and 1 was intubated - After admission to PICU, a further 16 (23%) needed nCPAP and 7 (10%) were intubated - Overall failure rate was 39% -Adverse events in ED: abdominal distension (n=3); severe air leak progressing to requiring intubation (n=1)	-Included only one patient who required HFNC for sepsis, all others had respiratory disease. HFNC use in this patient was successful. -Limited by lack of control group

PICU=paediatric intensive care unit; CPAP=continuous positive airways pressure; RR=respiratory rate; DSS=Dengue Shock Syndrome; ARDS=Acute Respiratory Distress Syndrome; HR= heart rate; RDS=respiratory distress syndrome; NP-CPAP=nasopharyngeal CPAP; ED=emergency department

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2. PUBLICATION READY MANUSCRIPT

Title Page

Full title:

Non-invasive Continuous Positive Airway Pressure ventilation (nCPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) use in children Without Primary Lung Pathology: A prospective observational study.

Short title:

Non-invasive CPAP and HFNC in non-pulmonary disease

Key words:

CPAP, HFNC, children, sepsis, septic shock, diarrhoeal disease

Authors and affiliations:

K Browde,[1] MBBCh, FCPaed; BM Morrow,[1]PhD

[1]Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa

Corresponding author: Brenda Morrow

5th Floor ICH Building, Red Cross War Memorial Children's Hospital; Klipfontein Rd, Rondebosch, Cape Town, South Africa, 7700

Brenda.morrow@uct.ac.za

+27 (21) 658 5074

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Abstract

Aim

Noninvasive Continuous Positive Airway Pressure (nCPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) are non-invasive ventilation (NIV) modalities appropriate for children in developing countries. There is minimal literature describing nCPAP and HFNC use in children with respiratory compromise secondary to non-pulmonary disease. This study aimed to describe the characteristics and outcomes of all children without primary lung pathology, who received nCPAP and HFNC during their admission to Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

Methods:

This was a prospective observational study of routinely collected data, between August 2015 and January 2016.

Results:

There were 31 cases of nCPAP and one case of HFNC use in 31 patients (median (IQR) age 3.5 (1.8 – 7.6) months.) The majority (n=23; 71.9%) presented with primary diarrhoeal disease. There were two deaths (6.5%), 17 (53.1%) PICU admissions, and five (15.6%) cases received invasive ventilation (NIV failure). Median (IQR) duration of hospital stay was 11.50 (6.0 – 17.5) days. On multiple logistic regression there were no independent associations with NIV failure. Lower temperature (OR 0.19; 95% CI 0.05 – 0.78; p = 0.02) and receiving inotropes (OR 23.05; 95% CI 1.64 – 325.06; p = 0.02) were independently associated with PICU admission.

Conclusions

nCPAP is used clinically for the management of children with respiratory compromise secondary to non-pulmonary illnesses, particularly diarrhoeal disease. Larger controlled clinical studies are needed to determine the effectiveness and utility of nCPAP in this population. HFNC was not commonly used, and this modality requires further investigation in this population.

What is already known on this topic:

- Non-invasive ventilation has become an evidence-based practice for certain conditions in adults and neonates
- In infants and older children with respiratory illnesses, NIV may prevent the need for invasive ventilation
- Bubble nCPAP and HFNC are effective and cheap to administer, making them important health interventions in developing countries

What this paper adds:

- This paper describes the use of nCPAP and HFNC in children with respiratory compromise caused by non-pulmonary illnesses, most commonly diarrhoeal disease
- Independent predictors of the need for intensive care in these children were identified.

Introduction

Non-invasive ventilation (NIV) refers to respiratory support provided by an external interface rather than an invasive airway such as an endotracheal tube or tracheostomy (1). This form of ventilation is gaining popularity in adult and paediatric practice, as it might prevent the need for endotracheal intubation (2) and in so doing prevent complications associated with invasive mechanical ventilation (3).

NIV has been well described in the adult population (2,4), and is used in the management of adult respiratory failure, across all diagnostic categories (5). Compared to other forms of NIV in adults, High Flow Nasal Cannula oxygen therapy (HFNC) is associated with the lowest intubation rates and the best 90-day survival rate (6). NIV is also well established for use in the neonatal setting, in the management of all-cause respiratory distress and for the early stabilization of premature and low birth weight newborns (7). Despite fewer formal data supporting its use in infants and older children (1), NIV is becoming more popular in in this setting, commonly used in the management of acute and

chronic respiratory failure; status asthmaticus; hypoventilation syndromes; neuromuscular disorders and chronic upper airway obstruction; as well as the prevention of extubation failure (8–10).

In low and middle income countries, where mechanical ventilatory support cannot be provided to the majority of children owing to resource limitations, simple yet effective non-invasive methods of providing respiratory support should be considered to optimise clinical paediatric outcomes (11). In this context, both noninvasive continuous positive airways pressure (nCPAP) and HFNC can be provided by stand-alone machines, and have been adapted for use in low-resource settings (11).

nCPAP has been shown to be effective in the management of older children with bronchiolitis and other respiratory illnesses (12–16) and has become a mainstay of treatment for many of these conditions. HFNC is also being used more frequently in older children (3), where it has been shown to be as effective as nCPAP (17).

nCPAP and HFNC are also recommended in the initial resuscitation of children with respiratory compromise or hypoxaemia associated with sepsis or septic shock (18). Despite these recommendations, data supporting the use of nCPAP or HFNC for patients in whom the primary pathology is non-pulmonary are scarce.
We found only one article which specifically investigated the use of nCPAP in the management of respiratory compromise caused by non-pulmonary disease, this in the setting of Dengue shock syndrome (19). Other studies have included heterogeneous populations, with sample sizes too small to allow meaningful sub-group analyses (20–27). To the best of our knowledge no other studies have systematically evaluated the use of nCPAP or HFNC therapy specifically in children with non-pulmonary causes of respiratory compromise.

This study therefore aimed to describe the use of HFNC and nCPAP in the management of children admitted to Red Cross War Memorial Children's

Hospital (RCWMCH), Cape Town, South Africa, with primary pathologies other than respiratory illness.

Setting

RCWMCH is a public tertiary and secondary level hospital in Cape Town, South Africa. It is the only stand alone, specialist children's hospital dedicated entirely to paediatric care in sub-Saharan Africa. RCWMCH has a total of 275 beds (medical and surgical) of which 15 are "High Care" medical beds and 22 are in the paediatric intensive care unit (PICU). Currently, children on nCPAP and HFNC are managed both in high care ward units and in PICU.

Approximately 40 000 children per year are managed at RCWMCH. It is estimated that annually 360 children are admitted to PICU and 1200 to high care units via the medical emergency unit (MEU) (MEU records). Because of the highly specialised care available at RCWMCH, patients present with a wide variety of illnesses, but the majority of patients are admitted with acute infections, most commonly respiratory or gastrointestinal, depending on the season.

At RCWMCH, institutional guidelines recommend the use of nCPAP or HFNC, using a stand-alone Bubble-nCPAP device (Fisher & Paykel Healthcare, Auckland, New Zealand) as the standard of care in children presenting in severe respiratory distress where intubation and mechanical ventilation is not emergently required. The interface standardly used for nCPAP is the F&P FlexiTrunk™ midline interface and nasal prongs, whilst appropriately sized Pediatric Oxygen Therapy Nasal Cannulae are used for HFNC (Both Fisher & Paykel Healthcare, Auckland, New Zealand). Although pulmonary disease remains the primary indication for nCPAP or HFNC, these modalities are also used in the management of children with respiratory compromise related to multiple non-pulmonary aetiologies.

In our context, in the summer months, a large proportion of patients present to the emergency department with gastroenteritis and dehydration as their

primary illness, with respiratory compromise occurring as a consequence of shock, hypokalaemia or severe metabolic acidosis. Respiratory compromise is also common in the face of septic shock or overwhelming sepsis. It is currently standard practice to consider using nCPAP/HFNC for respiratory support in such cases, despite the scarcity of supporting evidence.

Study Design and Period

This was a prospective, single centre, observational study of routinely collected data between August 2015 and January 2016.

Participants

All children between 0 and 12 years who received nCPAP or HFNC as part of standard respiratory care, and in whom respiratory compromise was not caused by primary lung pathology, were included in the study.

Neonates requiring respiratory support for HMD or other diseases of the newborn period, children receiving chronic/home-based nCPAP/HFNC, and children with cardiogenic pulmonary oedema were excluded from the study.

Ethics Approval

Permission to conduct the study was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee [Appendix Pg 65-66] and written informed consent was obtained from parents/legal guardians. The study adhered to the provisions of the Declaration of Helsinki (2013)(28).

Method

MEU admissions were reviewed daily by the researcher to identify eligible patients. Patients receiving nCPAP/HFNC therapy in the medical wards or PICU were screened for eligibility daily by the same researcher. Parents/ caregivers were approached for consent after admission of their child but prior to the collection of data from the files. All parents approached gave consent.

Routinely collected admission data was prospectively collected from clinical folders on all eligible patients, using a standardised data collection form. Outcome data were collected at discharge or after death from digital or paper-based hospital records.

Statistical Analysis

Data were entered into an Excel spreadsheet and appropriate parametric or nonparametric descriptive analyses were conducted using Statistica version 12 (StaSoft Inc, Tulsa, USA), after testing for normality (Shapiro Wilks W test). Comparative statistics were conducted using Mann-Whitney U tests, using failure of nCPAP/HFNC (progression to intubation and invasive ventilation) and PICU admission as categorical primary and secondary outcome measures. Mortality was a further planned secondary outcome measure, but owing to small numbers (n=2) was not analysed further. Data found to be associated with the primary and secondary outcomes on univariate analysis ($p < 0.05$) were entered into backward stepwise logistic regression models to determine independent predictive factors. A significance level of $p< 0.05$ was used for this study.

Results

There were 31 cases of nCPAP and one case of HFNC use in 31 patients (median (interquartile range, IQR) age 3.5 (1.8 – 7.6) months; 50% male).

Twenty-three of the 32 cases (71.9%) presented with respiratory distress secondary to diarrhoeal disease or complications thereof. Of these, 18 (78.3%) were shocked and 12 (52.2%) required inotropic support. One patient was admitted twice, on both occasions with shock and respiratory compromise associated with diarrhoeal disease. Seven of the 32 cases (21.9%) were admitted with septicaemia/septic shock. Four of the seven were shocked and only one required inotropes. One child was admitted with acute liver failure and metabolic acidosis with respiratory compensation and increased work of breathing and one with meningitis who was lethargic and required respiratory support. Both were shocked and initiated on nCPAP therapy. A total of 24 (75%) cases were shocked on admission.

13 of the 31 patients (41.9%) were Human Immunodeficiency Virus (HIV) exposed but uninfected, and three (9.7%) were HIV infected.

The only patient who was treated with HFNC had diarrhoeal disease and *Salmonella* sepsis (without shock). HFNC was initiated on the basis of the patient clinically tiring.

One (3.2%) complication of NIV was documented, of nasal skin trauma related to pressure caused by the nCPAP interface.

Primary outcome:
Five (15.6%) patients failed NIV and were intubated and mechanically ventilated. These included the patient with acute liver failure, two cases with diarrhoeal disease and two cases with septicaemia.

Secondary outcomes:
Seventeen (53.1%) cases required ICU admission, with diarrhoeal disease (n=13); septicaemia (n=3); and acute liver failure (n=1).

Two (6.5%) patients died. Both deaths occurred in children who presented with diarrhoeal disease and comorbid chronic illness. One patient had neuroblastoma and previous ventriculo-peritoneal shunt. He demised in the MEU before admission to High Care or PICU but was given fluid boluses and started on nCPAP and inotropes as part of his emergency management. The second patient had congenital Haemolytic Uraemic Syndrome (HUS) with chronic kidney disease and demised after a protracted hospital stay.

Table 1 presents univariate analyses of baseline characteristics and outcomes between primary and secondary outcome measures. Although patients who failed NIV had lower presentation SaO_2 on univariate analysis (Table 1), this association was not present on multiple logistic regression [OR 1.02; 95% CI 0.97 – 1.08; p = 0.6]. Lower temperature (adjusted OR 0.19; 95% CI 0.05 – 0.78; p

= 0.02) and receipt of inotropes (OR 23.05; 95% CI 1.64 – 325.06; p = 0.02) were independently associated with PICU admission.

Positive blood cultures within the first three days were obtained in three (9.3%) cases: one case each of *Pseudomonas aeruginosa* and *coagulase negative Staphylococcus aureus* in patients who presented with diarrhoeal disease and one case of *Streptococcus pneumoniae* in a patient with septicaemia. The coagulase negative *Staphylococcus aureus* was considered likely to have been a contaminant.

Two of the children with septicaemia had nasopharyngeal aspirate (NPA) specimens sent for respiratory viral panel analysis. These were both positive for respiratory syncytial virus (RSV) A and Adenovirus respectively. Four of the children with diarrhoeal disease had NPAs sent of which two were positive for both Adenovirus and Rhinovirus, and two were negative. The patient with acute liver failure had a negative NPA.

Discussion

To the best of our knowledge, this is the first study to systematically describe the clinical use of nCPAP and HFNC in children admitted to hospital with respiratory compromise associated with primarily non-respiratory disease. HFNC was used in only one case, for reasons that are unclear, and this NIV modality therefore requires further research in this population.

The vast majority (71.9%) of children receiving nCPAP/HFNC in this study presented with diarrhoeal disease (many with associated shock) requiring respiratory support. Globally, diarrhoeal disease is one of the leading causes of death in children under five years of age, responsible for more child deaths than AIDS, Malaria and Measles combined (29). There is a particularly high burden of diarrhoeal disease in South Africa (30) , where an estimated 10 109 000 (54%) children live below the poverty line of R671 (approximately $48) per month. In the Western Cape province, in 2013, approximately 486 000 (26%) children were living in income-poor households (31). Diarrhoeal disease is responsible for 20%

of child deaths under five years of age in South Africa (32).

Considering the burden of disease, limited PICU resources, and poor access to paediatric healthcare centres in South Africa (33); there is a need to identify safe, effective, and affordable means of providing respiratory support to children with complications of diarrhoeal disease, sepsis, and other conditions outside the PICU setting. In this context, nCPAP and HFNC require further study, but are promising in terms of availability and affordability. A study from Malawi (34) showed that a stand-alone bubble nCPAP device could be developed for one fifteenth of the price of the device recently approved by the Food and Drug Administration (FDA). In a recently published study conducted in Cape Town, South Africa, ventilatory management was identified as an important modifiable factor in the initial management of critically ill children presenting to city health clinics, which could impact on morbidity (33). nCPAP and HFNC could feasibly be implemented at such centres. Although no definitive conclusions can be made on the basis of this study, and more research is needed, it is notable that 47% of children were spared PICU admission after nCPAP/HFNC therapy was provided in the ward high care units. This finding may have important implications for low resourced countries with little access to high-level PICU care.

The paediatric section of the 2012 "Surviving Sepsis Campaign" guidelines for treating sepsis and septic shock recommends the use of nCPAP or HFNC in the initial resuscitation of children with respiratory compromise or hypoxaemia associated with sepsis or septic shock (18). Young children with severe sepsis or shock commonly require early respiratory support owing to low functional residual capacity. However, intubation and ventilation in these circumstances may cause harm by increasing intrathoracic pressure with resulting compromised venous return and worsening shock. HFNC and nCPAP could be effective in this setting, by increasing functional residual capacity and reducing work of breathing, thereby allowing for establishment of intravenous or intraosseous access for fluid resuscitation and peripheral inotrope delivery.(18) By reducing the need for intubation, the use of potentially harmful sedative drugs may also be avoided.

The 15.6% NIV failure rate is within the range (11.5% and 19%) described previously in children with sepsis (21,24). In a study investigating nCPAP use in critically ill children in a resource limited setting, Anitha et al (21) found associated shock to be a risk factor for nCPAP failure, while Kelly et al (24) found that those who failed NIV had presented with a higher venous pCO_2, higher initial RR, and a lower venous pH than those in whom NIV was successful. On univariate analysis, Mayordomo et al (35) found that smaller children were at higher risk of NIV failure. We were, however, unable to identify any predictive factors for NIV failure on the basis of such admission characteristics

The complication rate in this study was low, at 3%, but skin breakdown and pressure ulcers have been previously reported as complications of nCPAP (1,35). Therefore care must be taken in applying the interface and frequently checking for pressure areas. Other complications of both nCPAP and HFNC which have been described include pneumothorax and other air leak syndromes (27), abdominal distension, upper airway bleeds (1,35,36) and noise-induced hearing loss (37).

In our setting, PICU admission is largely dependent on resources and availability of PICU beds, therefore not being admitted to PICU does not necessarily always reflect lower acuity of illness. However, we found that lower admission body temperature and the receipt of inotropes were independent predictors of PICU admission, possibly reflecting higher severity of illness in these patients. Studies have shown that scoring systems such as the "Pediatric Early Warning Systems"/ PEWS", which include assessment of temperature and blood pressure, may be able to predict the need for a higher level of care when they are used in the emergency department (38). Our findings support the use of such scoring systems to timeously recognise children who may require PICU admission and increased levels of support.

Limitations

This was a single-centre study with a small sample size, and no control group, which constitute the major limitations of this study. The actual prevalence of HFNC/nCPAP in this population cannot therefore be determined. However, the sample size is comparable to that of previous studies of NIV use in children (19,20,22). Randomized controlled trials with larger, homogeneous study populations are needed to establish the safety and efficacy of nCPAP and HFNC in the management of children with diarrhoeal disease, and other non-pulmonary diseases.

Having had only one researcher recruiting patients throughout the study period, there is a possibility that eligible patients might have been missed. It is possible that children had co-existing, but undiagnosed, respiratory pathology, which might have confounded the results of this study and contributed to patients' respiratory distress. The positive viral screens in a number of respiratory specimens support this suggestion. However, it is not clear how many identified viruses represent colonization or asymptomatic carriage. Respiratory tract secretions were not taken on all patients in a standardised fashion, and no conclusions can therefore be made in this regard.

Conclusion

nCPAP is used clinically for the management of children with respiratory compromise secondary to non-pulmonary illnesses, particularly diarrhoeal disease. In the majority of cases intubation and mechanical ventilation were avoided. Larger controlled clinical studies are needed to determine the effectiveness and utility of nCPAP in this population. HFNC was not commonly used, and this modality requires further investigation in this setting.

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Tables

Table 1: Baseline characteristics and outcomes (n=32 cases)

Variable	All cases (n=32)	Admitted to PICU (n=17)	Not admitted to PICU (n=14)	Intubated (n=5)	Not intubated (n=27)	P (Not admitted to PICU vs. PICU)	P (intubated vs not intubated)
Age (months) (median [IQR])	3.45 (1.8 – 7.6)	2.27 (1.8 – 3.9)	6.12 (1.03 – 10.3)	1.8 (1.73 – 1.80)	5.27 (1.93 – 10.0)	0.26	0.12
Gender M:F	16:16	9:9	7:7	2:3	14:13	1	0.6
HIV exposed n (%)	14 (43.75)	7	7	2	12	0.6	0.8
HIV infected	3 (9.38)	0	3	0	3	0.2	0.96
Shocked	24 (75.0)	16	8	4	20	**0.04**	0.8
Received CPAP	31 (96.88)	17	13	5	26	0.9	0.4
Received HFNC	1 (3.13)	0	1	0	1		
Received fluid bolus	26 (81.25)	16	10	5	21	0.20	0.4
Total fluid bolus (ml/kg) (median [IQR])	32.5 (20.0 – 60.0)	40.0 (20.0 – 60.0)	25.0 (10.0 – 40.0)	20.0 (10.0 – 40.0)	35.0 (20 – 60)	0.36	0.42
Received inotropes	13 (40.63)	11	2	1	12	**0.02**	0.6
PCT (mcg/L) (median [IQR]) n=15	14.25 (4.3 – 35.0)	10.48 (4.3 – 35.0)	19.1 (19.1 – 19.1) (n=1)	4.9 (1.98 – 6.7)	19.55 (4.4 – 35.0)	1	0.30
Creatinine(micromol /L) (median [IQR])	56.5 (29.5 – 114.0)	90.0 (50.0 – 125.0)	38.0 (22.0 – 74.0)	58.0 (35.0 – 90.0)	55.0 (26 – 115)	**0.02**	1
Urea (mmol/L) (Median [IQR])	6.4 (3.5 – 12.9)	10.3 (4.7 – 16.2)	3.9 (3.0 – 8.6)	10.6 (4.7 – 11.1)	6.3 (3.3 – 13.5)	**0.01**	0.42
Cl (mmol/L) (Median [IQR])	115.0 (102.0 – 127.0)	126.0 (104.0 – 139.0)	106.5 (102.0 – 120.0)	114.0 (106.0 – 127.0)	116.0 (102 – 126)	0.10	0.50
K (mmol/L) (median [IQRT])	4.0 (2.4 – 4.8)	4.6 (2.2 – 4.9)	3.4 (2.7 – 4.5)	4.6 (4.5 – 4.6)	3.9 (2.4 – 4.9)	0.49	0.66
Na (mmol/L) (median [IQR])	139.0 (134.0 – 145.5)	140.0 (136.0 – 153.0)	136.0 (133 – 143)	140.0 (134 – 144)	139 (133 – 146)	0.12	0.84
CRP (mg/L) (median [IQR]	14.3 (7.15 – 59.0)	12.0 (7.0 – 57.0)	14.3 (8.85 – 62.95)	17.35 (12.05 – 39.35)	12.95 (6.85 – 62.95)	0.71	0.72
Platelets x 10^9/L (mean ± SD)	397.38 ± 192.32	392.94 ± 160.57	419.5 ± 227.35	405.2 ± 166.62	395.93 ± 199.54	0.71	0.92
Hb (g/dL) (mean ± SD)	9.85 ± 2.96	9.9 ±2.66	9.88 ±3.46	8.92 ± 1.71	10.02 ±3.13	0.98	0.45
WCC x 10^9/L (median [IQR])	17.40 (11.32 – 25.56)	17.8 (14.66 – 23.0)	14.3 (9.39 – 26.6)	17.8 (17.6 – 40.0)	15.4 (10.74 – 24.51)	0.24	0.31
Lactate (median [IQR])	2.2 (1.6 – 6.8)	3.2 (2.0 – 8.0)	1.85 (1.0 – 2.7)	5.25 (1.75 – 8.8)	2.2 (1.2 – 5.5)	**0.04**	0.44
HCO_3 (mean ± SD)	13.1 ±6.94	10.83 ±5.71	15.77 ±7.54	13.65 ± 5.20	12.96 ± 7.25	0.06	0.86
Base deficit (mean ± SD)	15.42 ±9.03	18.62 ±7.81	11.59 ±9.27	15.25 ±6.96	15.45 ± 9.42	**0.04**	0.97
pO_2 (median [IQR])	7.79 (4.75 – 20.7)	7.67 (4.8 – 24.5)	7.6 (4.5 – 17.6)	7.9 (7.67 – 16.9)	7.2 (4.5 – 21.8)	0.62	0.60
pCO_2 (mean ± SD)	3.88 ±1.87	3.76 ±1.97	4.18 ±1.75	3.59 ± 2.45	3.93 ± 1.79	0.53	0.71
pH (mean ± SD)	7.17± 0.19	7.09 ±0.21	7.26 ±0.14	7.14 ±0.25	7.18 ±0.19	**0.02**	0.67
Vitals: SaO_2 (%) (median [IQR])	100 (98 – 100)	100.0 (98 – 100)	100.0 (100 – 100)	95.0 (95 – 99)	100 (100 – 100)	0.46	**0.03**
BP (mean ± SD)	93.88 ±15.63	94.23 ±13.12	94.36 ±19.23	92.0 ±22.35	94.24 ± 14.85	0.98	0.80
RR (mean ± SD)	47.33 ± 16.38	46.65 ±17.64	47.46 ±15.72	38.0 ±24.97	49.12 ±14.19	0.90	0.17
HR (mean ± SD)	156.26 ±26.37	152.88 ±23.95	161.77 ±30.13	137.0 ±18.52	159.96 ± 26.29	0.38	0.07
Temp (° C) (mean ± SD)	36.12 ± 1.68	35.31 ± 1.57	37.11 ±1.33	35.14 ±1.45	36.30 ± 1.68	**0.002**	0.16
Duration of hospital stay (days)	11.50 (6.0 – 17.5)	12.0 (6 – 25)	10.5 (6.0 – 16.0)	14.0 (12 – 23)	8.0 (6 – 17)	0.50	0.12
Length of ICU stay (days) (n=17)		3.0 (2.0 – 7.0)	_	8 (3 – 9)	2 (1 – 4)	_	**0.02**

3. APPENDICES

The Protocol

Indication for and outcomes of continuous Positive Airways Pressure (CPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) in children admitted to Red Cross War Memorial Children's Hospital (RCWMCH) excluding those with primary respiratory aetiologies.

Investigator: Kate Browde
Supervisors: A/Prof Brenda Morrow
A/Prof Mignon McCulloch

Introduction:

Continuous positive airway pressure (CPAP)

Noninvasive Continuous Positive Airway Pressure (nCPAP) is a mode of noninvasive ventilation where a preset positive pressure is provided continuously, either nasally or via a facemask or mouthpiece(1).

Continuous Positive Airway Pressure (CPAP) was initially developed by Dr. George Gregory for use in premature infants with Hyaline Membrane Disease (HMD) in the early 1970's (2). At that time, the mortality rate for infants with HMD was over 50%. During this period Harrison et al, a group of South African researchers, published their findings that grunting seemed to help infants with HMD to maintain higher saturation levels(3). These researchers monitored babies who were grunting and noted that their condition worsened after tracheal intubation, and improved again once they were extubated and allowed to resume grunting. The conclusion was drawn that by performing the modified valsalva manoeuvre of grunting, the babies were able to maintain their functional residual capacity and improve alveolar ventilation. Dr. Gregory used this information and devised a method of providing positive pressure via an endotracheal tube.

Measurable effects of CPAP include increased functional residual capacity, decreased intrapulmonary shunting, increased tidal volume and decreased airway resistance(4). Gregory managed to create these effects with his initial CPAP device: an endotracheal tube connected to an Ayres T-piece, which was connected to a gas inflow line. Fresh gas was introduced into the system near this T-piece, which was connected via corrugate tubing to a reservoir bag. The pressure in the system could be adjusted by varying inflow of gas or the degree of occlusion at the tail end of the reservoir bag.

There are now numerous delivery systems for nasal CPAP, some of which are straightforward and relatively inexpensive(5). One of these is Bubble CPAP where the positive pressure is achieved by keeping the efferent limb of the exhale tubing under water and the gas flow adjusted to maintain constant bubbling. The depth of the exhale tubing under water determines the amount of CPAP applied to the system(6). Certain centres in resource-limited countries are developing their own bubble CPAP devices, sometimes using materials such as recycled plastic bottles, making the devices extremely affordable and yet still effective. A study was done in Malawi by Brown et al. (5) which showed that a stand-alone bubble CPAP device could be developed for one fifteenth of the price of the device recently approved by the FDA.

With the use of CPAP, the mortality rate of infants with HMD has dramatically declined and CPAP is being used as one of the lung-protective strategies to prevent long term lung damage in preterm infants (7). CPAP has also been shown to be effective in the management of older children with Bronchiolitis and other respiratory illnesses(8–11) and has become a mainstay of treatment for many of these conditions. Being so effective and cheap to administer, CPAP represents a very important development in child health care in the developing world.

<u>High flow nasal cannula oxygen therapy (HFNC)</u>

Heated, humidified, high flow nasal cannula oxygen therapy (HFNC) is a relatively new therapy first described in the early 1990's (12). It allows the

delivery of inspired gas at higher flow rates than regular cannulae (1-8 L/min in infants). The mechanisms of action of HFNC have the following benefits: flushing of dead space of the nasopharyngeal cavity allowing for better ventilation and oxygenation, providing high enough flow adequate to support inspiration and reducing inspiratory work of breathing, and eliminating the effects of drying and cooling(13). The fraction of inspired oxygen (FiO_2) can be adjusted according to the patient's needs and it can also provide some level of CPAP, although the exact level cannot always be predicted.

HFNC is being used more and more commonly in neonatal units, either as a step-down measure from CPAP or as an alternative measure in the management of HMD. The benefits of HFNC are that it is less cumbersome than CPAP, more easily applied, and causes less nasal trauma. In terms of efficacy, studies have shown no increase in adverse outcomes when replacing CPAP with HFNC in the management of HMD(12,14).

HFNC is also being used more frequently in older children and has been shown to be as effective as CPAP in the management of bronchiolitis and other respiratory disorders. In a recent study by Metge et al (15) , HFNC was compared with nCPAP in infants admitted to PICU with severe acute bronchiolitis for two subsequent seasons. Infants with acute bronchiolitis, and one or more of the following, were eligible for inclusion in the study: oxygen requirement to maintain oxygen saturations more than 92%, hypercarbia, acidosis and apnoea. They observed no difference in the length of stay in the PICU, respiratory rate, PCO_2, FiO_2, and duration of oxygen support between the two groups.

<u>Current practice</u>

At Red Cross War Memorial Children's Hospital (RCWMCH), CPAP and HFNC are used commonly for respiratory conditions. There are guidelines issued by the pulmonology department about how and when each should be used. A stand-alone Bubble-CPAP device is used. Unless a child needs to be intubated emergently, CPAP or HFNC are used as the mainstay of treatment for children

presenting in respiratory distress, especially those with high respiratory rates, severe signs of distress or respiratory acidosis on blood gas measurements.

During the time spent in the Emergency Department of RCWMCH, it became obvious that CPAP and HFNC are being used in the management of children with respiratory compromise related to multiple aetiologies, not limited to primary respiratory aetiology, which remains the primary indication for their use. A large proportion of patients presenting to our emergency department in the summer months have gastroenteritis and dehydration as their presenting complaints with respiratory compromise occurring as a consequence of shock, hypokalaemia or severe metabolic acidosis that are associated with these conditions. We noted that CPAP and HFNC are being used very commonly in these patients as respiratory support, sometimes even as prophylactic measures when blood results or blood gases were suggestive of, for example, severe hypokalaemia or metabolic acidosis with respiratory compensation. Respiratory compromise might also occur in the face of septic shock or overwhelming sepsis. CPAP and HFNC are also often used in these conditions in our emergency unit.

In their article "Approach to a Child with Breathing Difficulty", Mathew et al (16), include sepsis (resulting in poor oxygenation of tissues with increased oxygen demand) and acidosis (with respiratory compensation) in the category titled "other" when describing the main physiological causes of respiratory distress in children. Although CPAP and HFNC have been found to be beneficial in the management and prevention of lung injury in preterm infants with respiratory distress (7); and in older children with bronchiolitis and other respiratory diseases (11,17–19); the evidence for the use of CPAP and HFNC in non-respiratory conditions is scarce.

In the 2012 guidelines for treating sepsis and septic shock published in the Journal of Intensive Care Medicine titled: "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012", there is a section dedicated to paediatric considerations(20). The use of CPAP or HFNC is suggested in the initial resuscitation of children with

respiratory compromise or hypoxaemia associated with sepsis or septic shock. The authors describe how young children commonly need early respiratory support in circumstances of severe sepsis/septic shock because of their low functional residual capacity but that intubation and ventilation might actually be deleterious in these settings because increased intrathoracic pressure can lead to compromised venous return and worsening shock. They mention how HFNC and CPAP can be used to increase functional residual capacity and reduce the work of breathing, allowing for establishment of intravenous or intraosseous access for fluid resuscitation and peripheral inotrope delivery. They may also allow for the avoidance of drugs needed for sedation prior to intubation, which may also be counterintuitive in the setting of sepsis, shock, hypokalaemia or hypovolaemia.

Despite this recommendation, we could only identify one article in which the use of CPAP is specifically studied in the context of septic shock syndrome. Cam et al compared the use of oxygen mask therapy with nasal CPAP in the management of children with respiratory failure associated with Dengue Haemorrhagic Fever (DHF) grades 3-4, termed Dengue Shock Syndrome (DSS)(21). The aetiology of the respiratory failure in DSS may be due to increased vascular permeability leading to alveolar oedema, fluid overload, pleural and peritoneal effusions, acute respiratory distress syndrome (ARDS) or cardiac failure. They found that nCPAP was useful in the management of these patients.

With this in mind we plan to investigate the use of HFNC and CPAP in the emergency department, high care wards and Paediatric intensive care unit (PICU) at RCWMCH.

Aims and objectives:

To describe the indications for and outcomes of non-respiratory uses for CPAP and HFNC in children admitted to RCWMCH.

Setting:

Red Cross War Memorial Children's Hospital (RCWMCH) is a public tertiary and secondary level hospital in Cape Town, South Africa. It is the only stand alone,

specialist children's hospital dedicated entirely to paediatric care in southern Africa. RCWMCH has a total of 275 beds (medical and surgical) of which 15 are "High Care" medical beds and 22 are in the PICU. Currently, children on CPAP and HFNC can only be managed in high care or PICU due to nursing constraints.

An average of 40 000 children per year are seen at RCWMCH, with a large proportion of emergency admissions to the High Care units and PICU coming via the medical emergency unit (MEU). It is estimated that 360 urgent admissions to PICU and 1200 to the high care units are admitted via the MEU.

Because of the highly specialised care available at RCWMCH a wide variety of illnesses are seen and children are referred from all over the country, but the majority of patients are admitted with acute infections-generally either respiratory or gastrointestinal, depending on the season. For example, in 2013, 7599 children were admitted to the short stay ward at RCWMCH. 2997 of those presented with acute respiratory infections and 1803 presented with acute gastroenteritis. A similar proportion would have been admitted to higher care settings.

Methods:

Study design: Prospective observational study.Duration : 6 months or 100 consecutive patients.

Participants:

Inclusion criteria:

Any child admitted to RCWMCW with a clinical diagnosis other than a primary respiratory pathology, receiving CPAP or HFNC as part of standard clinical management.

Exclusion criteria

- Children receiving CPAP/HFNC for complications of bronchiolitis,asthma, or a primary clinical diagnosis of pneumonia or other primary respiratory illnesses

- Neonates
- Children receiving home-based CPAP/HFNC for the management of chronic respiratory conditions
- Cardiogenic pulmonary oedema
- Children receiving CPAP/HFNC for the management of sleep apnoea.

Data collection and research procedures:

MEU admissions will be reviewed daily by researcher to identify eligible patients and patients receiving CPAP/HFNC therapy in the medical wards or PICU will be screened for eligibility daily by same researcher.

Admission data will be prospectively collected from patient clinical folders on all eligible patients, using a standardised data collection form (Appendix A) and outcome data will be collected at discharge or after death from hospital records, the PICU database and Clinicom.

The data to be collected for study purposes is routinely documented as standard of care for all patients so will be available in their files and clinical records.

Since the study participants' files will only be reviewed for outcome data after discharge or death, there will be little chance of identifying clinical omissions or errors while the patient is still admitted. However should these be identified by the investigator at any stage, the relevant ward consultant would be alerted.

Outcome measures:

Number of patients receiving CPAP/HFNC for non-respiratory illnesses, proportion of patients admitted to PICU, proportion of patients intubated and invasively ventilated, duration of hospital and PICU length of stay, and mortality. Failure of CPAP or HFNC will be considered for patients who are intubated and ventilated invasively.

Ethical considerations, Risks and benefits:

No intervention will be conducted as part of this study, which is purely observational in recording outcomes of current standard practice.

It is therefore considered that this study affords minimal risk to participants. Participant protection will be ensured by de-identifying all data (using codes instead of names), and password-protecting the database, which will only be accessible by the investigators. No identification of any participants will occur on any output arising from this research.

Despite this, in order to maintain respect for person and autonomy, we will obtain written informed consent from parents to inform them about the study being conducted and to request their consent to use information obtained from their child's files (Appendix B). The consent form will assure them of the anonymity and privacy afforded to them by de-identification of the patient and use of a password-protected database.
The consent form will be available in English, isiXhosa and Afrikaans, and consent will be taken in the language of choice, with the use of interpreters where necessary.

Permission to conduct the study will be obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee and research will adhere to the provisions of the Declaration of Helsinki (2013).

Reimbursement:
Will not be offered to study participants.

Analysis
Data will be entered into an Excel spreadsheet and appropriate parametric or nonparametric descriptive analyses will be conducted using Statistica version 11 (StaSoft Inc, Tulsa, USA), after testing for normality (Shapiro Wilks W test). Comparative statistics will be conducted (Mann-whitney U or T-tests according to distribution) using failure of CPAP/HFNC and mortality as categorical outcome measures. Data found to be associated with these outcomes on univariate analysis ($p < 0.05$) will be entered into a forward stepwise logistic

regression model to determine independent predictive factors. A significance level of $p < 0.05$ will be used for this study.

Conflicts of interest:

None to declare

Limitations:

Since there is only one researcher collecting data and patients might be started on CPAP/HFNC at any time in numerous different places, patients might be missed.

Since there might be both respiratory and non-respiratory pathology in certain patients, data might be difficult to interpret in these cases.

This is an observational study without a control group, and therefore we will not be able to determine cause and effect related to outcomes. It will, however, form the basis for future prospective interventive studies.

Appendix A

Data collection form

1 Folder Number:

2. Identifier code:

3. DOB:

4 Age and sex

5. Date of admission:

6. Date of discharge:

7. Date of death:

8. Primary presenting complaint:

9.Main Presenting signs:
1.
2.
3.

10. Vital signs:
Temp:
HR:
RR:
BP:
Sats:

11. Shocked?

Yes

No

12. Gas done

Yes

No

13. First Gas result:

pH:

pCO2:

pO2:

BE:

HCO3:

Lactate:

Sats:

14. Blood results on presentation:

Na:

K:

Cl:

Urea :

Creatinine:

WCC:

Hb:

Platelets:

Other:

15. CPAP or HFNC

16. Reason documented for initiating respiratory support:

17.Fluid boluses:

Yes

No

18. Inotropes:

yes

No

19. Admitted to:

High Care

ICU

Other

20. Subsequent gases:

1.Date

Time

pH

pCO2

pO2

BE

HCO3

Lactate

Sats

2.Date

Time

pH

pCO2

pO2

BE

HCO3

Lactate

Sats

3.Date

Time

pH

pCO2

pO2

BE

HCO3

Lactate

Sats

21. Subsequent relevant blood results:

22. Culture results:

Blood:

NPA:

CSF:

23. Complications:

24. Required intubation?

Yes

no

25. Length of ICU stay

26. Length of hospital stay

27. Mortality

Appendix B

INFORMED CONSENT FORM FOR THE PARENT(S)/GUARDIAN(S) OF CHILDREN RECEIVING RESPIRATORY SUPPORT WITH CPAP/HFNC FOR NON-RESPIRATORY INDICATIONS.

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, Dr. Kate Browde (MMED- student at the University of Cape Town), am doing research on devices that help children with breathing problems. The study is called "Indication for and outcomes of continuous Positive Airways Pressure (CPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) in children admitted to Red Cross War Memorial Children's Hospital (RCWMCH), excluding those with primary respiratory aetiologies".

We would like to invite your child to participate in this study, by allowing us to use medical information about your child and his/her illness. Before you decide whether you are happy for us to use this information, please read the following information, which we will also explain and discuss. Please feel free to ask questions about anything you do not fully understand.

What is the reason for the study and how will it be done?

Children often struggle to breathe when they become very sick. Breathing problems are not only caused by infections or illnesses in the lungs. We want to find out how many children need breathing support for other reasons, for example, extreme fatigue (tiredness), severe infections, organ failure, electrolyte abnormalities etc.

With the information we obtain from this study, we can encourage further research on the topic and inform doctors in other hospitals on how best to use this type of respiratory support for other sick children.

The study will be done by identifying children who require breathing support for illnesses that are not only in their lungs. We will later look at the files of these children and see how they progress, what other interventions were necessary for them and how long they stay in hospital.

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 at Red Cross War Memorial Children's Hospital, he/she will receive standard care. This means that there will be no change in the care your child will receive if you agree to participate in the study-he/she will be treated the same as all other patients.

What are the possible benefits and/or risks to your child?

There are no direct benefits to participate in the study.

Potential harms – there are no major harms expected other than a possible breach of confientiality. However, we will strive to avoid this by using numbers instead of names and having passwords for all our databases.

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, it will in no way affect the care your child received at red Cross.

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 investigators will know what information belongs to your child.

Payment for involvement

Participation in this research does not involve extra costs for you, and you will not receive payment if you agree to your child being enrolled.

Contact details

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.

Dr Kate Browde
021 658 5111
kbrowde@gmail.com

Prof Brenda Morrow
021 658 5074
brenda.morrow@uct.ac.za

Prof Mignon McCulloch
021 658 5354
mignon.mcculloch@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 agree to us using your child's information for this research study, we ask you to sign this staement of consent:

I have read the above information, and it has been fully explained 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 _____

Witness (in the case of the parent being unable to read/sign)_____

Date_____

References:

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Ethics approval and Renewal

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

21 April 2015

HREC REF: 141/2015

A/Prof B Morrow
Paediatrics & Child Health
5th Floor, ICH Building
Red Cross War Memorial Children's Hospital

Dear A/Prof Morrow

PROJECT TITLE: INDICATION FOR AND OUTCOMES OF CONTINUOUS POSITIVE AIRWAYS PRESSURE (CPAP) AN HIGH FLOW NASAL CANNULA OXYGEN THERAPY (HFNC) IN CHILDREN ADMITTED TO RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH) EXCLUDING THOSE WITH PRIMARY RESPIRATORY CONCERNS (FC-candidate-K Browde.

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 13th April 2015.

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 April 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)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student Kate Browde will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB0000 1938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/07/17
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	16/8/2016

HUMAN RESEARCH ETHICS COMMITTEE
15 AUG 2016
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol Information

Date form submitted	15 August 2016		
HREC REF Number	141/2015	Current Ethics Approval was granted until	30/7/2016
Protocol title	Indication for and outcomes of continuous Positive Airways Pressure (CPAP) and High Flow Nasal Cannula oxygen therapy (HFNC) in children admitted to Red Cross War Memorial Children's Hospital (RCWMCH) excluding those with primary respiratory aetiologies		
Protocol number (if applicable)			
Principal Investigator	Brenda Morrow		
Department / Office Internal Mail Address	5th Floor ICH Building, Red Cross War Memorial Children's Hospital		

1.1 Does this protocol receive US Federal funding?	☐ Yes	X No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	X No

2. List of documentation

This study was approved until April 2016, data collection was completed in January 2016 and no study activities have occurred since that time. The data are now to be analysed.

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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Journal of Paediatrics and Child Health

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Thank you for your interest in *Journal of Paediatrics and Child Health*. Please read the complete Author Guidelines carefully prior to submission, including the section on copyright. To ensure fast peer review and publication, manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once you have prepared your submission in accordance with the Guidelines, manuscripts should be submitted online at http://mc.manuscriptcentral.com/jpch
We are looking forward to your submission.

EDITORIAL AND CONTENT CONSIDERATIONS

Aims And Scope

Journal of Paediatrics and Child Health is the official journal of the Paediatrics and Child Health Division (The Royal Australasian College of Physicians) in affiliation with the Perinatal Society of Australia and New Zealand, the Paediatric Research Society of Australia and the Australasian Association of Paediatric Surgeons, and publishes original research articles of scientific excellence in paediatrics and child health. Research Articles and Editorial Correspondence are published, together with invited Reviews, Annotations, Editorial Comments and manuscripts of educational interest.

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The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated,

manuscripts are peer reviewed by two anonymous reviewers and the Editors. Final acceptance or rejection rests with the Editors.

Manuscripts should be written so that they are intelligible to the professional reader who is not a specialist in the particular field. Where contributions are judged as acceptable for publication on the basis of scientific content, the Editors or the Publisher reserve the right to modify typescripts to eliminate ambiguity and repetition and improve communication between author and reader.

Ethical Considerations

Authors must state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Brazil 2013) available at http://www.wma.net/en/30publications/10policies/b3/index.html.

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In general, submission of Instructive Cases and Case Notes should be accompanied by the written consent of the subject (or parent/guardian) prior to publication; this is particularly important where photographs are to be used or in cases where the unique nature of the incident reported makes it possible for the patient to be identified. While the Editors recognise that it might not always be possible or appropriate to seek such consent, the onus will be on the authors to demonstrate that this exception applies in their case.

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Authors should declare any financial support or relationships that may pose conflict of interest. If there is none, this should be stated.

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Annotations

Annotations should be no more than 1500 words with a maximum of 12 references. Authors must supply a maximum of 5 key words and an unstructured abstract. Authors must supply three brief 'Key Points' summarising the main points raised in the manuscript. Authors must also provide 3 multiple choice

questions (preferably 'A-type' single best of 5 alternatives with brief explanations for each answer) based on their Annotation. Please ensure that brief explanations are provided for both correct and incorrect answers.

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Editorial Comments should be no more than 1500 words with a maximum of 12 references. Authors must supply a one-line summary of the key point raised and provide a reference to the manuscript(s) the paper comments on.

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Original Articles should be no more than 2500 words with a structured abstract that states in 250 words or fewer the purpose, basic procedures, main findings and principal conclusions of the study. Divide the abstract with the headings: Aim, Methods, Results, Conclusions. Authors must supply up to three brief points 'What is already known on this topic' and up to three brief points stating 'What this paper adds'.

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Review Articles should be no more than 2500 words with a maximum of 50 references. Abstracts can be either structured or unstructured, at a maximum of 150 words. The abstract should not contain abbreviations or references. Authors must supply three brief 'Key Points' summarising the main points raised in the manuscript. Authors must also provide 3 multiple choice questions (preferably 'A-type' single best of 5 alternatives with brief explanations for each answer) based on their Review. Please ensure that brief explanations are provided for both correct and incorrect answers.

Case Reports

The *Journal of Paediatrics and Child Health* has amended its Case Report section. New Case Notes/Reports will now only be considered for publication in the Letters to the Editor section. In order to suit this format, manuscripts need to be formatted as a Letter to the Editor and be approximately 400 words in length, with no more than one figure or table, and a maximum of four references.

Clinical Trials

Clinical Trials must be registered with the appropriate governing body.

Instructive Cases

Instructive Cases involve a clinical problem or issue of clear educational benefit. There is an initial case report, then a brief discussion with appropriate references. No abstract or key words are required (when the website requests an Abstract, type N/A for 'not applicable'). A Summary listing learning points should be included at the end of the Instructive Case. Instructive Cases should be no more than 1200 words in length, with no more than 3 figures or tables and a maximum of 8 references. Authors must also provide 3 multiple choice questions (preferably 'A-type' single best of 5 alternatives with brief explanations for each answer) based on their Instructive Case. Please ensure that brief explanations are provided for both correct and incorrect answers.

Letters to the Editor

Letters to the Editor should be no more than 400 words in length, with no more than one figure or table, and a maximum of four references.

Heads Up

Heads Up submissions should be a summary, approximately 200 words, of a recent paper of interest. This should not be the abstract but a short digest of the results, putting them in context of what the paper adds. Please attach a file with a single graph or histogram (preferably not a table) from the paper to make the most important point visually (not essential). A photograph or illustration (subject to copyright) would also be suitable. The names of authors of Heads Up pieces will be published.

Journal Club

Journal club articles should be no more than 2500 words. They should reflect what happens at journal clubs where doctors come with a clinical question, search for evidence, critically appraise the best evidence and then apply it to their patient, reflecting how the research could have been conducted better. The paper should be divided into the headings: Clinical scenario, Structured clinical question, Search strategy, Table (of relevant papers found in the search), Critical appraisal of all relevant papers (using standard critical appraisal guidelines), followed by a brief discussion of how to do the research better, how to apply the information to the patient and the clinical bottom line.

Citations	Study population	Study design and evidence	Level of	Results	Comments
–	–	–		–	–

Image of the Month

Please send a photograph or other image, together with a short clinical question and a brief answer. For an example, please follow these links: Question and Answer. If the photograph is identifiable, please send written permission from a parent and/or child or confirm that verbal approval has been obtained. Privacy is the responsibility of the author(s).

Position Papers

Position Papers express the consenses view of an organisation, e.g. about the management of a condition. Any recommendations should be evidence-based and should state the Level of Evidence (using NHMRC criteria). They should be up to 2,500 words long with a maximum of 50 references.

Viewpoint

Viewpoint is available for papers expressing a personal practice or personal view on medical or non-medical topics that are relevant to the readers. They can be up to 2,500 words long and referenced if appropriate.

Ethical Debate

Ethical debate is available for papers describing an ethical dilemma in clinical practice. They may argue only one perspective or two different viewpoints. They can be up to 2,500 words long and reference if appropriate.

Brief Communications

Brief Communications are used to fill gaps in the JPCH and will be indexed. They are supposed to be entertaining, humorous, informative, thought-provoking or all of the above. They should be relevant, in a broad sense, to paediatrics and those who work in child health. They should be no longer than 600 words. Examples include humorous or poignant stories or instructive mistakes. Consent will be needed if the subject of the Brief Communication is identifiable.

Fillers

FIllers are used to fill gaps in the JPCH, but are not indexed. They are supposed to

be entertaining, humorous, informative, thought-provoking or all of the above. Examples of Fillers include cartoons and poems. Consent will be needed if the subject of the Filler is identifiable.

PREPARATION OF MANUSCRIPTS

Pre-acceptance English-language editing

Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. Visit our site to learn about the options. All services are paid for and arranged by the author. Please note using the Wiley English Language Editing Service does not guarantee that your paper will be accepted by this journal.

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Style of the Manuscript

Manuscripts should follow the style of the Vancouver agreement detailed in the International Comittee of Medical Journal Editors' revised 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication', as presented at http://www.ICMJE.org

Spelling

The journal uses UK spelling and authors should therefore follow the latest edition of the *Concise Oxford Dictionary*.

Units

All measurements must be given in SI units.

Abbreviations

Abbreviations should be used sparingly and only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation.

Scientific names

Upon its first use in the title, abstract and text, the common name of a species should be followed by the scientific name (Genus, species and authority) in parentheses. However, for well-known species, the scientific name may be omitted from the article title. If no common name exists in English, the scientific name should be used only.

Trade names

At the first mention of a chemical substance, give the generic name only. Trade names should not used.

Drugs should be referred to by their generic names, rather than brand names.

Equations

Equations should be numbered sequentially with Arabic numerals; these should be ranged right in parentheses. All variables should appear in italics. Use the simplest possible form for all mathematical symbols.

Parts of the Manuscript

The manuscript should be submitted in separate files: title page; main text file; figures.

Title page

The title page should contain (i) a short informative title that contains the major key words. The title should not contain abbreviations (ii) the type of manuscript (e.g. Original Article, Instructive Case, Editorial Correspondence: Case Note), (iii)

the full names of the authors and (iv) the addresses of the institutions at which the work was carried out together with (v) the full postal and email address, plus telephone numbers, of the author to whom correspondence about the manuscript, proofs and requests for offprints should be sent. The present address of any author, if different from that where the work was carried out, should be supplied in a footnote.

Main text

As papers are double-blind peer reviewed the main text file should not include any information that might identify the authors. The main text of the manuscript should be presented in the following order: (i) abstract and key words, (ii) text, (iii) acknowledgements (iv) references, (v) tables (each table complete with title and footnotes), (vi) figure legends. Figures and supporting information should be submitted as separate files. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter.

Abstract and Key words

Please refer to the section 'Manuscript Categories' for details about which article types require abstracts. *Key words* should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list.

Text

Authors should use subheadings to divide the sections of their manuscript: Introduction, Materials and Methods, Results, Discussion.

Acknowledgements

The source of financial grants and other funding should be acknowledged, including a frank declaration of the authors' industrial links and affiliations. The contribution of colleagues or institutions should also be acknowledged. Thanks to anonymous reviewers are not allowed.

References

The Vancouver system of referencing should be used. In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text.

Cite the names of all authors when there are six or fewer; when there are seven or more list the first three followed by *et al*.

Names of journals should be abbreviated in the style used in *Index Medicus*. Reference to unpublished data and personal communications should not appear in the list but should be cited in the text only (e.g. A Smith, unpubl. data, 2000).

Journal article

1 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N. Engl. J. Med.* 1976; **294**: 687–90.

Online article not yet published in an issue

An online article that has not yet been published in an issue (therefore has no volume, issue or page numbers) can be cited by its Digital Object Identifier (DOI). The DOI will remain valid and allow an article to be tracked even after its allocation to an issue.

Hall, A. and Jones G. V. (2008) Effect of potential atmospheric warming on temperature-based indices describing Australian winegrape growing conditions. *The Australian Journal of Grape and Wine Research* doi: 10.1111/j.1755-0238.2008.00035.x

Book

2 Kaufmann HE, Baron BA, McDonald MB, Waltman SR, eds. *The Cornea*. Churchill Livingstone, New York, 1988.

Chapter in a Book

3 McEwen WK, Goodner IK. Secretion of tears and blinking. In: Davson H, ed. *The Eye*, Vol. 3, 2nd edn. Academic Press, New York, 1969; 34–78.

Appendices

These should be placed at the end of the paper, numbered in Roman numerals and referred to in the text. If written by a person other than the author of the

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