

Reasonability of gastro-oesophageal reflux study
requests (contrast swallows and milk scans) for the
detection of gastro-oesophageal reflux disease at
Red Cross War Memorial Children's Hospital
– a retrospective analysis

by

STUDENT: STEFFEN BAU

STUDENT NUMBER: BXXSTE001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements of the degree

Master of Medicine (MMed) in Paediatrics

FCPaeds – Part 3

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of first submission: Monday, 14 April 2014

Date of final revision: Saturday, 12 September 2015

Supervisor: E Goddard, Paediatric Gastroenterology, University Cape
Town

Co-supervisors: A Brink, Nuclear Medicine, University Cape Town
E Banderker, Paediatric Radiology, University Cape Town

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Declaration

I, *Steffen Bau*, hereby declare that the work on which this 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.

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

Signed by candidate

Date:12 September 2015.....

Table of contents

CONTENTS	PAGE
Title page	
Declaration of author	1
Table of contents	2 - 4
Glossary	5
Abstract	6 - 7
Protocol	8 - 15
Research question	8
Background	8 - 10
Aims	10
Method	10 - 12
Statistical analysis	12 - 13
Results	13
Ethical considerations	13 - 14
Conflicts of interest	14
References	14 - 15
Structured literature review.....	16 - 31
Objectives of literature review	16
Literature search strategy	16 - 18
Inclusion and exclusion criteria	18
Summary and interpretation	18 - 27
Literature	18 - 23
Investigation techniques	23 - 25
Timing of investigation	26
Treatment trial	26 - 27
References	27 - 31

CONTENTS	PAGE
Manuscript	32 - 56
Background	32 - 35
Aim	35
Method	35 - 43
Inclusion and exclusion criteria	36 - 37
Methodology of GORD investigations	37 - 38
Reasonability of the study request	39 - 40
Additional definition of criteria.....	40 - 41
Investigation timing	41
Correct modality of study used	42
Analysis	42 - 43
Results	43 - 49
Reasonability of study request	46
Appropriateness of request timing	47
Choice of correct investigation modality	47
Preceding treatment trial	47 - 48
Comparison between modality used and findings	48 - 49
Comparison between findings and indication	49
Discussion	49- 55
Limitations of this study	53 - 54
Identification of gaps and need for further research ...	54 - 55
Conclusion	55
Conflict of interest	55
Acknowledgements	55 - 56
References	56 - 58

CONTENTS	PAGE
Tables and Graphs.....	59 - 70
Table 1	59
Table 2	60
Table 3	61 - 62
Table 4	63
Table 5	64
Table 6	65
Table 7	66
Table 8	67
Graph 1	68
Graph 2	69
Graph 3	70

Glossary

ABBREVIATION	DEFINITION
ALTE	Acute or apparent life threatening event
BAL	Bronco-alveolar lavage
CLD	Chronic lung disease
CMV	Cytomegalovirus
ENT	Ear-Nose-Throat / otolaryngology
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FTT	Failure to thrive
GIT	Gastro-intestinal tract
GOR	Gastro-oesophageal reflux
GORD	Gastro-oesophageal reflux disease
GSH	Groote Schuur Hospital
HIV	Human immunodeficiency virus
IQR	Inter quartile range 25-75% of distribution
LLAM	Lipid-laden alveolar macrophages
LOS	Lower oesophageal sphincter
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
PAXIM	Picture archiving and communication system - radiology image and report review system used at RCWMCH
PEG	Percutaneous endoscopic gastrostomy
pH-metry	Ambulatory 24 hour oesophageal pH monitoring
PPI	Proton pump inhibitor
RSV	Respiratory syncytial virus
RTHC	Road-to-health-chart, the child's record booklet for immunisations, measurements and health treatments
RCWMCH	Red Cross War Memorial Children's Hospital
WHO	World Health Organization

Abstract

Poor weight gain, recurrent vomiting and fussiness, chronic cough and recurrent chest infections are among the wide variety of signs that are often attributed to gastro-oesophageal reflux disease (GORD). The difficulty lies in distinguishing between physiological gastro-oesophageal reflux (GOR) and GORD and none of the tests available can, alone, give conclusive evidence for the latter. Clinicians are often at a loss which investigation to request in order to assess for GOR and assist in a diagnosis of GORD. Our hypothesis was that GORD investigations at Red Cross War Memorial Children's Hospital (RCWMCH) are requested without considering the appropriate modality required and without clear indications for suspecting GORD. This was supported by practical experience and a short preliminary review of request forms. In South Africa no specific guidelines exist regarding the diagnosis of GORD and there is a poor understanding of available tests and their role in aiding the diagnosis. Thus many unnecessary tests are requested.

To review how appropriate the requests for GORD investigations were we analysed all requests made to the departments of nuclear medicine and radiology at RCWMCH for the purpose of GORD investigation between January and April 2011. This analysis was based on a review of the folders and the data of tests performed on all included patients. The two examination modalities involved were gastro-oesophageal radionuclide scintigrams (commonly known as milk scans) and contrast swallows. The specific points assessed were reasonability of the request, appropriate timing of the investigation, use of the correct modality for the question investigated and lastly evaluation of prior treatment with antacids.

We found that most of the studies performed were requested on appropriate grounds and that the timing of the majority of the investigations was reasonable.

We however showed that close to one fifth of patients investigated had the incorrect choice of modality. For most of these, contrast swallows were requested where a milk scan would have been the appropriate modality of investigation. Furthermore we showed that close to a third of the enrolled patients had both modalities requested at some point in time, when the underlying question could, in many cases, have been answered by one investigative modality alone.

We also confirmed the superiority of the milk scan in diagnosing GOR over the contrast swallow in a sub-group that had both investigations performed. We showed that structural abnormalities were found mainly in patients where this was suspected on contrast swallow, indicating that it is not useful to perform a contrast swallow for structural abnormalities if history is not suggestive. Aspiration was detected in our study patients most frequently with contrast swallow in keeping with medical literature.

In view of the radiation exposure, requests should not be made when they are not necessary. Without clinical guidelines too many patients undergo GORD studies without the explicit need to do so. Therefore, this paper suggests a guideline for GORD investigation at RCWMCH. This guideline includes the use of contrast swallow for investigation of dysphagia or odynophagia and for symptoms in keeping with aspiration or incoordinate swallowing. For GORD investigation, a milk scan should be requested. Prior to investigation with milk scan we propose a two to four weeks trial of antacids. We do not recommend a trial of hypoallergenic diet as first line prior to investigation in keeping with current literature.

Protocol

Primary Investigator: Steffen Bau

Student number: BXXSTE001

Supervisor: Liz Goddard

Co-supervisors: Anita Brink, Ebrahim Banderker

Cape Town, 23/10/2012
revised version 11/11/2013

Research question:

Reasonability of gastro-oesophageal reflux study requests (contrast swallow and milk scans) for the detection of gastro-oesophageal reflux disease at Red Cross War Memorial Children's Hospital - a retrospective analysis

Protocol:

Background:

Clinicians, especially in the field of paediatrics, are often faced with the question whether or not symptoms of failure to thrive, recurrent chest infections or even seizure-like spasmodic episodes - known as Sandifer syndrome - in a child may be due to underlying gastro-oesophageal reflux disease (GORD). Gastro-oesophageal reflux (subsequently referred to as reflux) is a condition in which the stomach content leaks back into the oesophagus, bypassing or overcoming the natural barriers for the unidirectional passage of food and liquid from oral to aboral. In very young children this is a frequent condition even if they are well and poses no danger to normal development. The difficulty is to distinguish between normal reflux and GORD, where the regurgitation of stomach content creates actual health problems. Severe GORD can result in failure to thrive, frequent coughing episodes, especially at night and after feeds and to aspiration of gastric content with subsequent respiratory tract disease. In small children apnoea presents as a potentially serious consequence of GORD. Furthermore it can

lead to oesophagitis with increased risk of vomiting, bleeding and subsequent development of strictures.

There are several tools available to support the diagnosis of GORD and to assess its severity. The two most commonly used tests at Red Cross War Memorial Children's Hospital (RCWMCH) are gastro-oesophageal radionucleotide scintigrams, also known as milk scans, and contrast swallows. These tests are often combined in order to make a diagnosis, although each of them measures a different aspect of the pathology and in many cases only one of the aspects is of interest. Simplified, the milk scan shows the function of the oesophagus in swallowing and quantifies the refluxed content and the number of reflux episodes, whereas the contrast swallow shows the structure and possible abnormalities of the oesophagus as well as aspiration on swallowing. In most cases, the question of which modality should be used can be established by taking a thorough history of the child's complaints and reviewing the child's medical records. Quite often though both tests are requested without distinction and without clear indications for suspecting GORD. In view of radiological exposure to the child a clear indication for these investigations is obligatory. It is also worth noting that both modalities are not 100 percent accurate due to the intermittent nature of reflux and there will be false negative results if no reflux episode occurred during the test. This is particularly important for contrast swallows as the observed time frame is only three minutes compared to 30 minutes for milk scans, thus substantially increasing the likelihood of missing a reflux episode. Therefore the conventional modality for detection of GORD is the milk scan. There is no universally accepted gold standard for the detection of reflux in children. Ambulatory 24 hour oesophageal pH monitoring (pH-metry) is often referred to as gold standard in adults, but it has been reported as not reproducible in infants as it only detects acid reflux and misses non-acid reflux common in infants.

The timing of both types of studies also deserves due consideration. Children examined during an acute exacerbation of chest infection produce high negative intra-thoracic pressures, thus increasing a potential for reflux. The differentiation between normal reflux and GORD becomes even more

difficult in this situation. Also, uncooperative children that cry a lot during examination will increase their propensity for reflux due to raised intra-abdominal pressures. Studies should therefore be scheduled preferably in times of reasonable well being of the child.

The departments of nuclear medicine (milk scan) and paediatric radiology (contrast swallow) receive frequent requests for reflux studies involving their respective modality of investigation. Nuclear medicine has had about 420 reflux studies over the past year and paediatric radiology has had about 510 requests in the same period.

Aims:

This analysis aims firstly, to review how many of these studies were requested on reasonable grounds (as defined under Method), and secondly, to correlate the results of each study with the indication(s) for its request.

A third aim of the study is to interpret if the timing of the investigation was appropriate.

Furthermore in the literature and guidelines of a number of other countries it has been suggested to give a patient a trial of antacids for an extended period of time prior to investigation. There is no South African guideline for the investigation of GORD. However this paper reviews if in the absence of such a recommendation the patients received such a treatment trial or if such a trial would have been feasible.

Method:

A folder review and review of the respective results and reports on the PAXIM computer system as well as the nuclear medicine database will be conducted to obtain patient history and findings in each case.

The indications that will be considered “reasonable” for investigations are:

- recurrent chest infections – i.e. pneumonia, bronchiolitis (at least more than two episodes requiring hospital admissions in the past year);

- failure to thrive not otherwise explained, defined as crossing of centiles for at least two plots over a three months period or longer, or inadequate weight gain in the neonatal period (average weight gain of less than 15 gram per kilogram per day for term infants after first week of life, for gestational age 33-37 weeks after two weeks and for less than 33 week gestational age after four weeks of life);
- Referral for > 50% lipid-laden macrophages on broncho-alveolar lavage suggesting GORD with aspiration
- not otherwise explained persistent coughing or wheezing episodes (more than three weeks, no recent RSV or pertussis infection at the beginning of coughing / wheezing episode), usually after feeding and at night time;
- referral from ENT after upper gastrointestinal scope suggestive of mucosal changes due to GORD (including erosions, hyperaemia and “cobblestoning” suggestive of reflux laryngitis);
- persistent possetting (effortless vomiting) episodes with no other medical cause found (at least three weeks duration);
- acute life threatening events likely due to aspiration secondary to GORD, involving either apnoea, cyanosis or choking episodes;
- symptoms in keeping with Sandifer syndrome, such as spasticity/dystonia in connection with normal neurological examination, e.g. arching of the back while conscious, often related to feeding times;
- difficulty swallowing (dysphagia) or painful swallowing (odynophagia)
- workup for percutaneous endoscopic gastrostomy (PEG) in presence of neurological deficit or cerebral palsy;
- other:
 - unexplained anaemia with or without evidence of recurrent vomiting / possetting;
 - recurrent episodes of non-cardiac chest pain.

Regarding the timing of the investigation: An examination during time of acute illness suggestive of increased respiratory drive (pneumonia, bronchiolitis, tachypnoea of other reasons) or increased intra-abdominal

pressures (distended abdomen, frequent coughing episodes) will be regarded as inappropriately timed.

This retrospective analysis will include all applications to the nuclear medicine department and the paediatric radiology department of RCWMCH for either reflux study - milk scan or contrast swallow - in order to diagnose GORD from 01 January 2011 until 30 April 2011.

Studies will be excluded:

- if the contrast swallow was done for any other reason than reflux. This refers in particular to requests for a “modified contrast swallow”, which by its nature is commonly used to assess swallowing and aspiration rather than reflux;
- if technical reasons made the result invalid and no repeat study was done in the specified time interval of this research period, e.g. bypassing of the stomach on instillation of radio-labelled milk via naso-gastric tube (too deeply inserted tube) or vomiting of contrast medium.

Results of the nuclear medicine investigation usually state if reflux is present and how severe it is, and displays the value of the trans-oesophageal transit time. It describes the gastric emptying phase and indicates if pulmonary aspiration has been present. This particular study will look only at the diagnosis and severity of reflux. Other reported milk scan findings will not be the focus of this study. Regarding the contrast swallow the diagnoses of reflux as well as aspiration and structural abnormalities that go along with GORD, like hiatus hernia or oesophagitis, will be regarded as positive outcomes. It is important to look at this extended spectrum of outcomes for contrast swallows due to the fact that, as previously mentioned, a contrast swallow is not warranted simply for the diagnosis of GORD, but rather for more complex associated pathophysiological states.

Statistical analysis:

For the data analysis the assistance of a statistician will be sought. The analysis is planned to make use of SPSS 20 statistics software as provided by the University of Cape Town Information and Communication Technology

Services (ICTS), as the primary investigator has previously worked with this software. In collaboration with the statistician the used software might however be changed if it is beneficial for the analysis of the data.

Results:

As a result of this analysis a new request form for reflux diagnosis will be created. The form will ask directly for known signs and symptoms of GORD, as well as findings of this analysis. The referring clinician will be required to tick boxes for each item found in the referred patient. If none of the boxes can be ticked, the referral will be regarded as unreasonable and the requested reflux study will not be performed, unless the reasoning was discussed and agreed to by a senior staff member of paediatric radiology or nuclear medicine respectively. The current request form is attached hereto.

Following completion of the present MMed dissertation, a second follow-up analysis may be conducted in order to assess the changes in request practice after implementation of the altered request form and staff education. A comparison of the total number of requests and the number of reasonable requests, as well as an evaluation of the findings may be done between the two analyses. It is hoped that the implementation of a new form and staff education will prevent many unnecessary investigations for reflux, and thus prevent radiological exposure to children that do not have sufficient grounds for the suspicion of a diagnosis of GORD.

Ethical considerations:

This study is a retrospective folder review of cases that have been assessed for suspected reflux disease using the modalities of milk scans and/or contrast swallows at RCCWMH in the designated time frame. There will be no other involvement of patients for this study. No names or identities will be mentioned in any document. All data will be handled in a completely confidential manner.

This study will have no implication on the work of the involved departments of nuclear medicine or paediatric radiology.

The only financial implication will be the printing costs of the final request form for the investigation of reflux studies as a result of this study upon approval by the departments of nuclear medicine and paediatric radiology. It does not however form part of the costs of the research itself.

Conflicts of interest:

The primary investigator declares no conflicting interests or financial gains related to the proposed study.

References:

- Davies, F. & Gupta, R. 2002. Apparent life threatening events in infants presenting to an emergency department. *Emergency Medicine Journal : EMJ*. 19(1):11-16.
- Fontana, G.A. & Pistolesi, M. 2003. Cough. 3: chronic cough and gastro-oesophageal reflux. *Thorax*. 58(12):1092-1095.
- Indrio, F., Riezzo, G., Raimondi, F., Cavallo, L. & Francavilla, R. 2009. Regurgitation in healthy and non healthy infants. *Italian Journal of Pediatrics*. 35(1):39-7288-35-39. DOI:10.1186/1824-7288-35-39; 10.1186/1824-7288-35-39.
- Jones, A.B. 2001. Gastroesophageal reflux in infants and children. When to reassure and when to go further. *Canadian Family Physician Medecin de Famille Canadien*. 47:2045-50, 2053.
- Mann, M.D. & Wynchank, S. 1994. Chapter 55 - Esophageal function (transport and motility). In *Nuclear Medicine in Clinical Diagnosis and Treatment*. I.P.C.(.P.C. Murray & P.J. Ell, Eds. 2nd ed. Edinburgh: Edinburgh : Livingstone. 377.
- Macfadyen, U.M., Hendry, G.M.A., Simpson, H. 1983. Gastro-oesophageal reflux in near-miss sudden infant death syndrome or suspected recurrent aspiration. *Archives of Disease in Childhood*. 58:87-91.
- McGarvey, L.P. 2004. Cough . 6: Which investigations are most useful in the diagnosis of chronic cough? *Thorax*. 59(4):342-346.
- Moraes-Filho, J.P., Navarro-Rodriguez, T., Barbuti, R., Eisig, J., Chinzon, D., Bernardo, W. & Brazilian Gerd Consensus Group 2010. Guidelines for

the diagnosis and management of gastroesophageal reflux disease: an evidence-based consensus. *Arquivos de Gastroenterologia*. 47(1):99-115.

Paton, J.Y., Nanayakkhara, C.S. & Simpson, H. 1988. Vomiting and gastro-oesophageal reflux. *Archives of disease in childhood*. 63(7):837-838.

Simpson, H. & Hampton, F. 1991. Gastro-oesophageal reflux and the lung. *Archives of Disease in Childhood*. 66:277-283.

Vaezi, M.F. 2005. Atypical manifestations of gastroesophageal reflux disease. *MedGenMed : Medscape General Medicine*. 7(4):25.

Structured Literature Review

Objectives of literature review:

This study is examining the reasonability of GORD investigations at RCWMCH. The two modalities commonly used at this institution are milk scans and contrast swallows. The literature search had to identify the pertinent papers regarding the indications for GORD studies and the appropriateness of the investigation. It had to address in particular both of the investigation modalities mentioned above. Furthermore, oesophageal 24-hour pH monitoring is commonly cited in the literature as a major GORD investigation technique and therefore this literature review also had to cover some of the most important recent articles about this diagnostic tool.

Reasonability of GORD investigations requires a clear definition. Criteria for our definition of reasonability had to be reviewed according to the definitions current in the literature.

Treatment trial with a proton pump inhibitor (PPI) prior to investigation will also be reviewed, as most of the relevant guidelines suggest treatment prior to GORD investigation.

Literature search strategy:

The first literature search was performed using Pubmed on 24 March 2012 for the term "milk scan" and for the combination of terms "barium swallow", "gastro-oesophageal reflux" or "gastro-esophageal reflux" and "diagnosis". The term "paediatric" or "pediatric" was not included into the search as it would have made the search criterion too restrictive with too few relevant articles found.

Further searches were performed with different variants of the terms "milk scan", "scintigraphy", "barium swallow", "contrast swallow", "GORD" or

“GERD”, “reflux”, “gastro-oesophageal” or “gastro-esophageal” and “diagnosis” using the RefWorks search as well as Google scholar. The articles found were examined by title and abstract, followed by scanning of the article text.

In addition, a few of articles were suggested by the co-supervisors of this paper and these were included into the search result.

The search for “milk scan” resulted in 21 articles found and the search for the combined terms including “barium swallow” found 127 articles. These papers were graded as:

- Grade 1 - relevant (diagnosis of GORD is main topic of study)
- Grade 2 - moderately relevant (diagnosis of GORD is at least part of the paper) and
- Grade 3 - not relevant.

For Grades 1 and 2 a further classification was added as to determine whether the paper was using milk scan (A), barium swallow (B) or both modalities (AB).

Also a literature search for relevant definition criteria of reasonability was made using Pubmed, RefWorks and Google scholar. These were most commonly specified as the name of the criterion, such as “failure to thrive”, in combination with the term “definition”. The results were then reviewed by title, followed by abstract review where appropriate and lastly by scanning of the article’s full text.

The full text of the relevant articles was retrieved by UCT library electronic database and the outsource link connected to the study where accessible. In some cases an article could be found via Google scholar or Internet search using Google search. In a small number of cases a full text was not available and the judgement whether the article would be useful had to be made on the abstract only. None of these studies were considered of vital importance after review of the abstract, and a pursuit of the full text paper was discontinued.

Lastly some articles were reviewed from the reference list of the previously found articles and added to the reference list for this analysis.

Inclusion and exclusion criteria:

Out of all papers found, only classification grades 1 and 2 were primarily recognised as possible articles of interest for GORD investigation. The decision of relevance was based on the full text review and its importance for this research. For the definitions of the reasonability criteria any full text review that included a definition of the item in question was considered relevant.

Case reports and case series, correspondence letters in journals and articles without available full text were excluded from the literature review. Also articles older than ten years were removed, unless they brought an essential viewpoint that had not been reiterated in newer articles or they included significant first descriptions of central points and concepts.

The remaining articles were mostly clinical reviews and literature reviews on the subject of GORD or GORD investigation, including a number of national or international guidelines. In addition they were comprised of a few cohort studies, an editorial and a prospective study. Many articles focused on the surgical approaches of GORD and only if these articles went beyond the surgical description they were considered for input to this study.

Important findings or discussion points in each article were identified for this paper. A list was prepared with each point and reference to the article the point originated in. This list was then used in the write-up of the paper.

Summary and interpretation

Literature:

GOR is a physiological process. It is defined as a passive movement of gastric content from the stomach into the oesophagus it may or may not be

accompanied with regurgitation or vomiting. GORD is present when it causes severe symptoms and complications. (Vandenplas et al., 2009)

The presence and or absence of severe symptoms and complications distinguish between GOR and GORD. The criteria used to establish if an investigation is reasonable are based on the known complications of GORD. Complications of GORD are broadly defined into two groups; intra-oesophageal complications for example oesophagitis and extra-oesophageal complications such as pulmonary complications and acute/apparent life threatening events (ALTE). (Sherman et al 2009)

Oesophageal complications include:

- Excessive regurgitation,
 - Infants with recurrent vomiting and poor weight gain,
 - Infants with unexplained crying and or distressed behaviour,
 - Children older than 18 months with chronic regurgitation or vomiting,
- Feeding refusal/anorexia,
- Unexplained crying,
- Choking, gagging and coughing during feeding,
- Abdominal pain or heartburn in older children,
- Reflux oesophagitis,
- Structural changes of the oesophagus due to GORD including
 - Oesophageal stricture,
 - Barrett's oesophagus and
 - Adenocarcinoma.

Extra-oesophageal syndromes with a definite association with GORD:

- Sandifer syndrome and
- Dental syndrome.

Extra-oesophageal syndromes with a possible association with GORD:

- Reactive airway disease,
- Recurrent pneumonia,

- Upper airway symptoms, such as chronic cough and cobble stone appearance of the larynx and
- Infants with apnoea or ALTE.

(Sherman et al., 2009; Vandenplas et al., 2009)

Unfortunately no clear cut criteria for when to investigate exist in the literature.

Oesophageal complications:

Vomiting is a common feature in many diseases including most notably acute gastroenteritis, gastro intestinal tract (GIT) obstruction, raised intracranial pressure from different causes, drug treatment side effects especially cytotoxic agents but also many others and substance intoxications. Most of these do not produce chronic vomiting past three weeks duration without other identifiable signs and symptoms. Other causes of chronic vomiting such as chronic gastritis and the exclusion diagnosis of cyclical psychogenic vomiting, however, can be indistinguishable from a diagnosis of GORD and require investigation including GORD studies. (Rudolph et al., 2001) There is no consensus definition of what constitutes persistent or chronic vomiting. However an isolated symptom of vomiting in infants or toddlers without any other health problems would not qualify for GORD investigation. (Jones, 2001) These patients are commonly known as “happy spitters”. (Rudolph et al., 2001)

Failure to thrive (FTT) not otherwise explained is defined as crossing of two main centiles (5%, 10%, 25%, 50%, 75%, 90%, 95%) for at least two plots over a three months period or longer. (Olsen et al., 2007). Isolated FTT did not qualify for GORD investigation, as it is a common feature of many different diseases and underlying conditions (Al Nofal & Schwenk, 2013). The difficulty in defining FTT is that no general accepted definition exists. The term FTT implies negative growth deviation irrespective of the underlying cause and attempts have been made to define it in many different ways most of which are based solely on anthropometry (Olsen, 2006). Olsen et al. (2007) defined seven different criteria for FTT and showed that in a large

cohort study of affluent countries all of these criteria correlate poorly with each other. (Olsen et al., 2007)

Excessive crying is according to Heine et al. (1995) unlikely to be related to GORD if no vomiting is present.

Extra-oesophageal syndromes with a definite association with GORD:

Sandifer syndrome is an uncommon presentation of GORD. The abnormal neuro-behavioural symptoms in keeping with this syndrome include arching of the back or other extensor spasms while conscious, tonic gaze or head movements, torticollis and dystonic posturing (Kabakus & Kurt, 2006). These symptoms are often related to feeding times with increased crying or irritability.

Extra-oesophageal syndromes with a possible association with GORD:

According to Vaezi the strongest association of GORD with any pulmonary condition exists with asthma, although a cause-and-effect relationship is difficult to establish. (Vaezi, 2005) The Brazilian guidelines for diagnosis and management of GORD by Moraes-Filho et al. recommend treatment with PPIs supported by investigation for a GOR component in asthmatics with a suggestive history for GORD. They rate this recommendation as Grades A and B. A successful trial of PPIs may result in improvement in asthma symptoms, frequency and quality of life. (Moraes-Filho et al., 2010)

Concerning the wheezing no guidelines regarding timing for wheeze investigation exists, although Brand et al. are of the opinion that investigations for wheezing are only justified with persistent symptoms from birth, abnormally severe airway obstruction or incomplete resolution. They also report that beneficial effects from demonstrating and treating GORD for wheeze have not been demonstrated. (Brand et al., 2008)

GORD may cause interstitial lung disease, recurrent pneumonia and subsequently chronic lung disease (CLD) and GORD investigation may be indicated in such circumstances. (Vandenplas et al., 2009). The criteria for what comprises recurrent chest infections are problematic in the absence of a general consensus. Respiratory infections are very common in children and to define what just repeated infections are in a normal child and what are recurrent chest infections secondary to underlying pathology is a difficult task. It has been proposed by an Italian Immunology Workgroup in 1988 to consider any child with more than six respiratory infections (upper and lower) as well as three or more lower respiratory infections per year as recurrent chest infections. (Jesenak et al., 2011). Jesenak et al. state that persistent or recurrent pneumonias indicate more severe pathology.

Another difficult to define term is chronic cough. The literature suggests three weeks as a definition criterion (Olsen, 2006; Vaezi, 2005; Irwin et al., 1993; Curley et al., 1988) but elsewhere eight weeks are regarded as a defining criterion in view of the many respiratory infections in early childhood. (McGarvey, 2004; Fontana & Pistolesi, 2003) Cough associated with postural changes or after food intake is most commonly implicated as GORD related and night time symptoms are also commonly reported. However the latter are not necessarily GORD related. (Fontana & Pistolesi, 2003) Some infectious agents are known to produce protracted respiratory symptoms. (deJongste & Shields, 2003) This further complicates the value of the chronic cough criterion for the diagnosis of GORD.

Davies & Gupta found in an analysis of ALTE that apart from GORD other causes included infectious (pertussis, urinary tract infection), neurological (seizures, brain tumour), cardiac- (atrial tachycardia, persistent ductus arteriosus) and drug-related (opioid exposure) apnoeas as well as a number of cases where no diagnosis could be reached. (Davies & Gupta, 2002) However GORD is commonly implicated and investigation for GOR and aspiration in this situation is mandatory if the history is suggestive. (Davies & Gupta, 2002)

Diagnosis of GORD suggested on other special investigations:

Lipid-laden alveolar macrophages (LLAM) on bronco-alveolar lavage (BAL) or tracheal aspirates if intubated, may suggest GORD with aspiration. LLAM are considered suggestive for chronic aspiration. However the finding of LLAM is not specific for pulmonary aspiration as they can also be frequently seen during episodes of chest infections and even in the normal population. (Kitz et al., 2012; Furuya et al., 2007) Published cut-off values are often given as a LLAM index and vary widely from 67 to 200. (Furuya et al., 2007) Other authors use a percentage of oil red O stained LLAM to total number of macrophages as a cut-off point. Basset-Léobon et al. suggested a level of 6% as a cut-off point to discriminate between normal and pathological conditions. (Basset-Leobon et al., 2010)

Patients are occasionally referred for GORD investigation from the otolaryngology department (ENT) after a pharyngeal/laryngeal endoscopy showing mucosal changes suggestive of GORD. There is no consensus about what constitutes signs and symptoms of such reflux laryngitis. Even the diagnosis of reflux laryngitis is not universally recognized in the ENT community. (Karkos et al., 2007) However frequently stated findings suggestive of reflux laryngitis on endoscopy include erythema, oedema and erosions of the arytenoids, posterior glottis, larynx and vocal cords, hypertrophy of the posterior commissure also known as “cobblestoning” and formation of granulation tissue. (Khan et al., 2006) The presence of inflammation or chronic changes of the laryngeal structures in reflux laryngitis is not necessarily suggestive of GORD, nor indicative of its severity if present. (Khan et al., 2006) Nevertheless it indicates the possible exposure of these structures to acid and/or pepsin and therefore warrants investigation for GORD.

Investigation techniques:

There is no defined gold standard of GORD investigation in children. Some authors regard ambulatory 24-hour oesophageal pH monitoring (pH-metry) as the standard technique to diagnose GORD even in children and the

available guidelines of most countries refer to it as the appropriate modality. The investigation with pH-metry is currently still the favoured examination modality worldwide due to a reported specificity of 100% but with a sensitivity of only 60-80% and despite its limitations in the paediatric population. (Vaezi, 2005; Vandenplas et al., 2009) Regarding this cited specificity, it has been well described that the severity of pathologic acid reflux on pH-metry does not consistently correlate with symptom severity or demonstrable complications in infants. (Vandenplas et al., 2009). The European and North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN/ESPGHAN) guidelines consider pH-metry a useful tool to rule out GORD and for evaluation of antacid therapy. Sensitivity and specificity of this method are however not well established. (Vandenplas et al., 2009) Vaezi sets the sensitivity for 24-hour pH monitoring at 70-80% with a false negative rate of up to 50%. (Vaezi, 2005) Vandenplas et al. (2009) also comment on combined pH and impedance monitoring as another method, but indicate that there is at present insufficient data to evaluate whether this method correlates more strongly to symptom severity and GORD complications than isolated pH-metry. (Vandenplas et al., 2009)

The milk scan as an alternative option for GORD diagnosis is limited to measurement of postprandial GOR. It therefore will miss non-feed related GOR episodes that can be observed with pH-metry. It quantifies GOR independently of the oesophageal and gastric pH and at RCWMCH also comments on trans-oesophageal transit time pattern and gastric emptying. (Warrington & Charron, 2007; Vandenplas et al., 2009) Another advantage of the milk scan as compared to pH-metry studies is the possibility to comment on aspiration and to measure its amount. A negative finding however does not rule out intermittent aspiration episodes. A significant disadvantage of the use of milk scans is the lack of standardized techniques and age-specific norms. Sensitivity and specificity are reported as 15% to 59% and 83% to 100%, respectively, when compared with 24-hour oesophageal pH monitoring. (Vandenplas et al., 2009) Most studies compare the milk scan findings directly to findings to pH-metry. Vandenplas et al. (1992) compared both modalities in the same patients simultaneously.

This study showed that there were significantly more GOR episodes found by milk scan compared to pH-metry, but highlighted the fact that the two techniques explore the GORD phenomenon differently. (Vandenplas et al., 1992) To date there is no data correlating the results of the milk scan to symptom severity or demonstrable complications. According to Seibert even one GOR episode found during a one hour milk scan test will be sufficient for a 24 hour pH-metry result to be positive. (Paton et al., 1988) At RCWMCH we use a time interval of 30 minutes instead of the one hour investigation in keeping with the findings of Wynchank. (Wynchank, 1988). Because of the lack of standardisation, the NASPGHAN/ESPGHAN guidelines do not recommend nuclear scintigraphy for routine evaluation of paediatric patients with suspected GORD. (Vandenplas et al., 2009)

Contrast swallows are neither sensitive nor specific for the diagnosis of GORD with high negative results due to the short observation period and high false-positive results secondary to over-interpretation of physiological GOR. There is no place for upper GIT series in GORD investigation. It is however a useful adjunct to diagnose anatomical abnormalities that might present with symptoms suggestive of GORD. (Vandenplas et al., 2009)

Other options for GORD investigation are oesophageal endoscopy including biopsy and oesophageal manometry. The former is an important investigation to identify or rule out other causes of oesophagitis once GORD has been disproven with other modalities, whereas the latter is useful in diagnosing achalasia or motility disorders of the oesophagus mimicking GORD. Both are not first line investigations for GORD. (Vandenplas et al., 2009)

With the emergence of very small probes for combined pH and impedance monitoring this newer technology might replace the use of the pH-metry/milk scan for the purpose of GORD investigation. However, the combined pH and impedance monitoring still has to be evaluated against the same criteria of symptom severity and GORD complications in children as the other two techniques mentioned above.

Timing of investigation:

Coughing and increased abdominal pressure are associated with GOR. Alvin describes the pathogenesis of GOR as lower oesophageal sphincter dysfunction involving the lower oesophageal sphincter (LOS) itself as well as the crural diaphragm and the phreno-oesophageal ligament. He mentions the transdiaphragmatic pressure difference as a contributing factor and describes how cough leads to its increase by deep inspiration prior to the cough and by abdominal pressure increase in the cough phase. He ascribes other potential mechanisms such as transient LOS relaxation or swallow induced LOS relaxation in concert with transdiaphragmatic pressure increase to the GOR development in chronic cough. (Alvin, 2003)]

Treatment trial:

No guidelines exist in the South African context regarding the investigation for GORD. Other countries have suggested a trial of antacids prior to investigation for GORD (Moraes-Filho et al., 2010) as it is known that the introduction of antacids, and in particular the use of PPIs, is one of the most common and most effective treatment options for GORD. (Wang et al., 2013) In refractory GORD, eosinophilic oesophagitis needs to be considered and therefore other guidelines suggest a trial with a hypoallergenic diet in infancy. (Vandenplas et al., 2009) However a recent guideline from ESPGHAN recommends an initial trial for eight weeks of PPIs in histologically confirmed children with eosinophilic oesophagitis prior to a trial/treatment with hypoallergenic diet. (Papadopoulou et al., 2014) Many invasive investigations can be prevented if the symptoms abate or recede on introduction of antacids or on a course of a hypoallergenic diet. (Sherman et al., 2009) Most indications for investigation allow for a preceding trial of antacids of at least two to four weeks duration as suggested by some of the existing guidelines. (Vandenplas et al., 2009) Such a trial could be debatable in cases where a clear indication of the presence and severity of GORD is needed, or where a timely diagnosis would be helpful to avert possible severe consequences, as in investigation of ALTE. For the investigation of ALTE, Davies & Gupta suggest delayed diagnosis for GORD as the finding of

GOR may be misleading with GOR being rather coexistent than causative. (Davies & Gupta, 2002)

A number of publications present different flow charts and approaches to the investigation and treatment of GORD. Vandenplas et al. (2009) give several different flow-charts for investigation of diverse presentations of GORD. (Vandenplas et al., 2009) These are approaches to:

- an infant with recurrent regurgitation and vomiting,
- an infant with recurrent regurgitation and weight loss,
- the older child with heartburn and
- a child with asthma that may be worsened by GORD.

Beattie (2001) and Indrio et al. (2009) each present a stepwise approach for the management of GORD beginning with explanation and reassurance, feeding and positioning adjustments, avoidance of known food exacerbators and reduction in overweight if present. This is followed by antacids and PPIs, possibly prokinetics and surgery. These flow charts were reviewed and utilised for the development of the flow charts presented in this research manuscript.

References:

- Al Nofal, A. & Schwenk, W.F. 2013. Growth failure in children: a symptom or a disease? *Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition*. 28(6):651-658. DOI:10.1177/0884533613506015; 10.1177/0884533613506015.
- Alvin, J. 2003. Cough and gastro-oesophageal reflux. In *Cough: Causes, Mechanisms and Therapy*. K.F. Chung, J.G. Widdicombe & H.A. Boushey, Eds. Edition 1 ed. Oxford: Wiley-Blackwell. 97-106.
- Basset-Leobon, C., Lacoste-Collin, L., Aziza, J., Bes, J.C., Jozan, S. & Courtade-Saidi, M. 2010. Cut-off values and significance of Oil Red O-positive cells in bronchoalveolar lavage fluid. *Cytopathology : Official Journal of the British Society for Clinical Cytology*. 21(4):245-250.

DOI:10.1111/j.1365-2303.2009.00677.x; 10.1111/j.1365-2303.2009.00677.x.

- Beattie, R.M. 2001. Diagnosis and management of gastro-oesophageal reflux. *Current Paediatrics*. 11:269-275.
- Brand, P.L., Baraldi, E., Bisgaard, H., Boner, A.L., Castro-Rodriguez, J.A., Custovic, A., de Blic, J., de Jongste, J.C. et al. 2008. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *The European Respiratory Journal*. 32(4):1096-1110. DOI:10.1183/09031936.00002108; 10.1183/09031936.00002108.
- Curley, F.J., Irwin, R.S., Pratter, M.R., Stivers, D.H., Doern, G.V., Vernaglia, P.A., Larkin, A.B. & Baker, S.P. 1988. Cough and the common cold. *The American Review of Respiratory Disease*. 138(2):305-311. DOI:10.1164/ajrccm/138.2.305.
- Davies, F. & Gupta, R. 2002. Apparent life threatening events in infants presenting to an emergency department. *Emergency Medicine Journal : EMJ*. 19(1):11-16.
- deJongste, J.C. & Shields, M.D. 2003, Cough 2: Chronic cough in children. *Thorax*. 58:998-1003.
- Fontana, G.A. & Pistolesi, M. 2003. Cough. 3: chronic cough and gastro-oesophageal reflux. *Thorax*. 58(12):1092-1095.
- Furuya, M.E., Moreno-Cordova, V., Ramirez-Figueroa, J.L., Vargas, M.H., Ramon-Garcia, G. & Ramirez-San Juan, D.H. 2007. Cutoff value of lipid-laden alveolar macrophages for diagnosing aspiration in infants and children. *Pediatric Pulmonology*. 42(5):452-457. DOI:10.1002/ppul.20593.
- Heine, R.G., Jaquier, A., Lubitz, L., Cameron, D.J.S., Catto-Smith, A.G. 1995. Role of gastro-oesophageal reflux in infant irritability. *Archives of Disease in Childhood*. 73:121-125.
- Indrio, F., Riezzo, G., Raimondi, F., Cavallo, L. & Francavilla, R. 2009. Regurgitation in healthy and non healthy infants. *Italian Journal of Pediatrics*. 35(1):39-7288-35-39. DOI:10.1186/1824-7288-35-39; 10.1186/1824-7288-35-39.

- Irwin, R.S., French, C.L., Curley, F.J., Zawacki, J.K. & Bennett, F.M. 1993. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest*. 104(5):1511-1517.
- Jesenak, M., Ciljakova, M., Rennerova, Z., Babusikova, E. & Banovcin, P. 2011. Recurrent Respiratory Infections in Children – Definition, Diagnostic Approach, Treatment and Prevention. In *Bronchitis*. I. Martin-Loeches, Ed. 1st ed.119. Available: <http://www.intechopen.com/books/bronchitis/recurrent-respiratory-infections-in-children-definition-diagnostic-approach-treatment-and-prevention>.
- Jones, A.B. 2001. Gastroesophageal reflux in infants and children. When to reassure and when to go further. *Canadian Family Physician Medecin de Famille Canadien*. 47:2045-50, 2053.
- Kabakus, N. & Kurt, A. 2006. Sandifer Syndrome: a continuing problem of misdiagnosis. *Pediatrics International : Official Journal of the Japan Pediatric Society*. 48(6):622-625. DOI:10.1111/j.1442-200X.2006.02280.x.
- Karkos, P.D., Benton, J., Leong, S.C., Karkanevatos, A., Badran, K., Srinivasan, V.R., Temple, R.H. & Issing, W.J. 2007. Trends in laryngopharyngeal reflux: a British ENT survey. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 264(5):513-517. DOI:10.1007/s00405-006-0222-8.
- Khan, A.M., Hashmi, S.R., Elahi, F., Tariq, M. & Ingrams, D.R. 2006. Laryngopharyngeal reflux: A literature review. *The Surgeon : Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*. 4(4):221-225.
- Kitz, R., Boehles, H.J., Rosewich, M. & Rose, M.A. 2012. Lipid-Laden Alveolar Macrophages and pH Monitoring in Gastroesophageal Reflux-Related Respiratory Symptoms. *Pulmonary Medicine*. 2012:673637. DOI:10.1155/2012/673637; 10.1155/2012/673637.
- McGarvey, L.P. 2004. Cough . 6: Which investigations are most useful in the diagnosis of chronic cough? *Thorax*. 59(4):342-346.

- Moraes-Filho, J.P., Navarro-Rodriguez, T., Barbuti, R., Eisig, J., Chinzon, D., Bernardo, W. & Brazilian Gerd Consensus Group 2010. Guidelines for the diagnosis and management of gastroesophageal reflux disease: an evidence-based consensus. *Arquivos De Gastroenterologia*. 47(1):99-115.
- Olsen, E.M. 2006. Failure to thrive: still a problem of definition. *Clinical Pediatrics*. 45(1):1-6.
- Olsen, E.M., Petersen, J., Skovgaard, A.M., Weile, B., Jorgensen, T. & Wright, C.M. 2007. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Archives of Disease in Childhood*. 92(2):109-114. DOI:10.1136/adc.2005.080333.
- Papadopoulou, A., Koletzko, S., Heuschkel, R., Dias, J.A., Allen, K.J., Murch, S.H., Chong, S., Gottrand, F. et al. 2014. Management guidelines of eosinophilic esophagitis in childhood. *Journal of Pediatric Gastroenterology and Nutrition*. 58(1):107-118.
DOI:10.1097/MPG.0b013e3182a80be1;
10.1097/MPG.0b013e3182a80be1.
- Paton, J.Y., Nanayakkhara, C.S. & Simpson, H. 1988. Vomiting and gastroesophageal reflux. *Archives of Disease in Childhood*. 63(7):837-838.
- Rudolph, C.D., Mazur, L.J., Liptak, G.S., Baker, R.D., Boyle, J.T., Colletti, R.B., Gerson, W.T., Werlin, S.L. 2001. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition*. 32(2):S1-31.
- Sherman, P.M., Hassall, E., Fagundes-Neto, U., Gold, B.D., Kato, S., Koletzko, S., Orenstein, S., Rudolph, C. et al. 2009. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *The American Journal of Gastroenterology*. 104(5):1278-95; quiz 1296. DOI:10.1038/ajg.2009.129; 10.1038/ajg.2009.129.
- Vaezi, M.F. 2005. Atypical manifestations of gastroesophageal reflux disease. *MedGenMed : Medscape General Medicine*. 7(4):25.

- Vandenplas, Y., Derde, M.P. & Piepsz, A. 1992. Evaluation of reflux episodes during simultaneous esophageal pH monitoring and gastroesophageal reflux scintigraphy in children. *Journal of Pediatric Gastroenterology and Nutrition*. 14(3):256-260.
- Vandenplas, Y., Rudolph, C.D., Di Lorenzo, C., Hassall, E., Liptak, G., Mazur, L., Sondheimer, J., Staiano, A. et al. 2009. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *Journal of Pediatric Gastroenterology and Nutrition*. 49(4):498-547. DOI:10.1097/MPG.0b013e3181b7f563; 10.1097/MPG.0b013e3181b7f563.
- Wang, Y.K., Hsu, W.H., Wang, S.S., Lu, C.Y., Kuo, F.C., Su, Y.C., Yang, S.F., Chen, C.Y. et al. 2013. Current pharmacological management of gastroesophageal reflux disease. *Gastroenterology Research and Practice*. 2013:983653. DOI:10.1155/2013/983653; 10.1155/2013/983653.
- Warrington, J.C. & Charron, M. 2007. Pediatric gastrointestinal nuclear medicine. *Seminars in Nuclear Medicine*. 37(4):269-285. DOI:10.1053/j.semnuclmed.2007.02.005.
- Wynchank, S. 1988. Aspects of Paediatric Gastro Oesophageal Scintigraphy. *Thesis (M.D. Paediatrics and Child Health) - University of Cape Town*.

Manuscript

Reasonability of gastro-oesophageal reflux study requests (contrast swallows and milk scans) for the detection of gastro-oesophageal reflux disease at Red Cross War Memorial Children's Hospital – a retrospective analysis

Background:

Clinicians in the field of paediatrics are often faced with the question whether or not certain signs and symptoms in children may be due to underlying GORD. These include, but are not limited to, failure to thrive, recurrent regurgitation and vomiting, fussiness and irritability, recurrent chest infections, coughing and wheezing, anaemia, chest pain and even seizure-like spasmodic episodes - known as Sandifer syndrome. (Rudolph et al., 2001)

GOR is a condition in which the stomach content flows effortlessly back into the oesophagus, bypassing or overcoming the natural barriers for the unidirectional passage of food and liquid from oral to aboral. In young children this is a frequent condition that occurs several times a day lasting up to three minutes each (Vandenplas et al., 2009) and poses no danger to normal development. This physiological GOR usually resolves by the age of 18 months. (Indrio et al., 2009; Jones, 2001) The difficulty is to distinguish between physiological GOR and GORD, where the regurgitation of stomach content creates actual health problems. Severe GORD can result in failure to thrive, epigastric or retrosternal pain, frequent coughing episodes and in aspiration of gastric content with subsequent respiratory tract disease. (Beattie, 2001) In neonates and young infants apnoea presents as a potentially serious consequence of GORD. (Davies & Gupta, 2002) Furthermore it can lead to oesophagitis with increased risk of vomiting, bleeding and subsequent development of strictures and/or formation of the premalignant Barrett oesophagus later in life. (Rudolph et al., 2001)

There are several investigations available to support or exclude the diagnosis of GORD and to assess its severity. The two most commonly used tests at RCWMCH in connection with GORD symptoms are milk scans and contrast swallows. The milk scan at RCWMCH quantifies GORD based on height, volume and duration of GOR activity. The milk scan also describes oesophageal transit patterns, calculates gastric emptying volume and is able to detect pulmonary aspiration. The contrast swallow shows the structure and possible abnormalities of the oesophagus and stomach as well as aspiration on swallowing. (Indrio et al., 2009) In most cases the question of which modality should be used can be established by taking a thorough history of the child's complaints and reviewing the child's medical records. (Indrio et al., 2009) Anecdotal experience from practice at RCWMCH and a short preliminary review of a number of request forms indicated however that quite often both tests are requested without distinction and without clear indications for suspecting GORD. In view of radiation exposure to the child a clear indication for these investigations is mandatory. For instance an investigation for GOR when it is apparent and without any evidence of potential GORD complications is not warranted. (Jones, 2001) GORD investigation is a common request at RCWMCH.

In the context of the correct choice of the investigation for GORD it is worth noting that neither modality is hundred percent sensitive nor specific. (Vandenplas et al., 2009) This is due to the intermittent nature of GOR and negative results occur frequently if no GOR episode occurred during the test or false positive results during episodes of non-pathological GOR during the study. (Vandenplas et al., 2009) Contrast swallows are in this regard particularly prone to show negative results, as the observed time frame at RCWMCH is only three minutes compared to 30 minutes for milk scans. Therefore, the conventional means for detecting GOR at our institution is the milk scan. There is no universally accepted gold standard for the detection of GORD in children. In adults pH-metry is often referred to as the gold standard, but it is not reproducible in infants and it only detects acid reflux and misses non-acid reflux which is common in infants. (Indrio et al., 2009; Warrington & Charron, 2007; Mann & Wynchank, 1994) Newer techniques

using combined pH and impedance monitoring can detect acid reflux as well as non-acid reflux, but they are costly and there is insufficient data in children regarding their correlation with GORD symptoms. (Vandenplas et al., 2009)

The timing of milk scans and contrast swallows also deserves due consideration. Children examined during an acute exacerbation of airway disease or infection produce increased negative intra-thoracic pressures, thus increasing a potential for GOR. (Alvin, 2003) The differentiation between physiological GOR and GORD becomes even more difficult in this situation. In addition, children that cry a lot during examination will increase their propensity for GOR due to raised intra-abdominal pressures, as will any other cause of abdominal distension or increased intra-abdominal pressures. (Alvin, 2003) Studies should therefore be preferably scheduled at times of reasonable wellbeing of the child.

A number of countries have published specific guidelines for detection and treatment of GORD as referred to by Moraes-Filho et al. (Moraes-Filho et al., 2010) South Africa has Standard Treatment Guidelines for GORD (The National Department of Health, 2006), however no consensus statement for evaluation and investigation of GORD. The NASPGHAN/ESPGHAN guidelines recommend a two-week trial of a hypoallergenic diet and/or acid suppression prior to investigation for regurgitation and irritability once other causes of vomiting have been excluded. (Vandenplas et al., 2009) Such a recommendation does not exist in the South African context. Regarding the use of extensively hydrolysed or hypoallergenic formula for infants with recurrent vomiting and poor weight gain a recent ESPGHAN guideline for investigation and treatment of eosinophilic oesophagitis (Papadopoulou et al., 2014) recommends a trial of antacid treatment for confirmed disease. This is due to the fact that some of those patients respond to antacids. Therefore a consideration to start antacid treatment as initial treatment of choice before further investigation or dietary changes would be the preferred option. Vaezi (2005) states that in atypical manifestations of GORD empiric treatment should be regarded as the “gold standard” for diagnosis, given the poor specificity of diagnostic testing. He also advocates the bi-daily use of

antacids for at least three months prior to investigation in some conditions like asthma. (Vaezi, 2005)

Aim:

The primary aim of the study was to identify:

1. How many studies were requested on reasonable grounds (as defined under Method),
2. Whether the timing of the requested investigation was appropriate and
3. If the choice of investigation modality was correct for each respective indication.

Secondary aims:

1. Evaluation of the number of patients who had a treatment trial prior to investigation,
2. Direct comparison between both modalities in the subset of patients who had both investigation modalities performed and
3. Correlation of the results of each study with the indication for its request.

Lastly the intent of this paper was to provide, according to the findings, an updated request form to streamline investigations for GORD and to allow the user to tick off indications for the request with background information.

Method:

In 2011 nuclear medicine performed 426 milk scans and radiology 543 contrast swallows. A specified a time frame of four months between 01 January and 30 April 2011 was our review period. A post-hoc power analysis was performed involving 111 experimental subjects and 77 control subjects. The data indicated that the failure rate among controls is 0.3. True failure rates of 0.12 or 0.51 could be detected in exposed subjects with probability (power) 0.8. The Type I error probability associated with this test of the null hypothesis that the failure rates for experimental and control

subjects are equal is 0.05 (p-value). The minimum difference of -18% or +21% given the pragmatic sample size was exceeded for the category of modality used. The other main categories in this paper would have required a much larger sample size to produce a significant difference, but were judged not to be of clinical value for the aim of this paper.

The details of patients that received milk scans during the study period were provided from the electronic nuclear medicine database. The patients who had contrast swallows during the same period were identified from the radiology booking register.

Inclusion and exclusion criteria:

All milk scans and all contrast swallows or contrast meals performed for the express purpose of GORD investigation during the time interval were included into the review. Contrast investigations labelled as modified contrast swallows and for clear non-reflux indication were excluded. Requests for contrast investigations that had insufficient information to decide if they were performed for GORD diagnosis were not excluded until further information was obtained by folder review.

In conjunction with the folder review of the selected patients, an assessment of the respective results and reports on the radiology image and report review system (PAXIM) as well as the nuclear medicine database was conducted to obtain the provided history and findings in each case. With this increased information another judgement was applied to each case if this truly was a study for the purpose of GORD investigation. This decision was based on request criteria and/or case history and not on the outcome of the tests performed. Thus even if GOR was detected in a study performed for other purposes this study was excluded.

A study was excluded if technical reasons made the result invalid and no repeat study was done in the specified time interval of this research period. These technical reasons included bypassing of the stomach on instillation of

radio-labelled milk or contrast via nasogastric tube (too deeply inserted tube) or vomiting of radio-labelled milk or contrast medium onto the chest with impact on the interpretation of the study.

Methodology of GORD investigations:

All milk scans were performed on the same Philips Axis Dual Head camera (previously known as Picker and then Marconi) using a low energy high resolution (LEHR) collimator (Picker International Inc., Cleveland, Ohio, USA). In most cases a transit study was done before the GOR search. For the transit study the child was given 5ml labelled feed (expressed breast milk/ formula milk or apple juice). The feed was labelled with ^{99m}Tc Tin Colloid using the suggested dose for GORD studies on the EANM dosage card (version 1.5.2008). (Jacobs et al., 2005) The transit studies were performed with the detector upright and the child's back against the camera so that the oesophagus was viewed from the left posterior oblique position. The image was acquired as a dynamic study, 0.5 seconds per frame, for 120 frames using an image matrix of 128 x128. After the transit study the child was given the rest of his/her milk feed before the GOR search. If a child was on nasogastric feeds the labelled feed was given by the nasogastric tube and the tube was removed before the GOR search.

The GOR search with the child supine on the camera was recorded as a posterior dynamic sequence of 5 seconds a frame for 30 minutes (360 frames) and an image matrix of 64 x 64. Three static images were recorded, one immediately before the GOR search, this was a short (60 second) acquisition to check if aspiration occurred during the feed. The second static image was recorded immediately after the GOR search and a third 120 minutes after the feed. The purpose of the second and third static image was to calculate the gastric emptying and to detect aspiration. All the static images were recorded with a 256 x 256 matrix and the duration of the second and third static image was 300 seconds. The milk scan results were reported by two experienced observers.

There is no standardized grading system for GOR severity on milk scan images. At RCWMCH GOR findings are reported according to the frequency, duration, height and volume of GOR episodes and the presence or absence of pulmonary aspiration. Different cut-off points are used for each of these items divided in three age categories. (Table 1)

At RCWMCH contrast swallows, commonly referred to in the literature as “barium swallow”, use a low-osmolar water-soluble contrast medium, as the use of barium is precluded by the risk of post-aspiration pneumonitis and fibrosis. Therefore the term contrast swallow is a more accurate description of this investigation technique.

The water-soluble contrast in a concentration of 150 - 300 mg/ml was administered in aliquots via bottle or failing that via syringe in smaller children, and via cup with straw in older children. During swallowing the oral phase was evaluated for the mechanism of swallowing (deglutition), nasopharyngeal backflow and laryngeal entry. This was followed by a review of the oesophageal motility and its structural integrity. Lastly gastric and duodenal c-loop anatomy were considered. After enough contrast had been given to create gastric distension, the patient was intermittently observed for three minutes in the supine position for the presence of GOR. This concluded the investigation. A radiologist fellow in conjunction with an experienced radiologist reported all contrast swallow results.

In contrast to the milk scan there is an easy guideline to the grading of GOR for contrast swallows. GOR is classified as gross if it reaches the level of the mouth and severe if it reaches above the level of the thoracic inlet. If the maximum height extends above the level of the carina (middle to upper third of the thoracic oesophagus) it is described as moderate and if only the distal third of the oesophagus is reached it is mild GOR. (Jeffery, Rahilly & Read, 1983)

Reasonability of the study request:

The indications that were considered “reasonable” for investigations are:

1. Recurrent chest infections, defined as any infections of the lower airways (pneumonia, laryngo-tracheo-bronchitis or bronchiolitis) that necessitated at least three or more hospital admissions/presentations in the past year,
2. FTT not otherwise explained was defined as crossing of two main centiles (5%, 10%, 25%, 50%, 75%, 90%, 95%) for at least two plots over a three months period or longer,
3. Persistent coughing or wheezing not otherwise explained were classified as episodes lasting for more than three weeks without preceding common infections. The infections considered were mycobacterium tuberculosis, respiratory syncytial virus (RSV), rhinovirus A, adenovirus, influenza A, B and C virus, measles virus causing pneumonia and Bordatella pertussis,
4. Persistent episodes of possetting (effortless vomiting) or vomiting (the forceful expulsion of gastric contents from the stomach) with no other medical causal explanation and present for at least a three week interval,
5. ALTE if they were likely due to aspiration secondary to GORD,
6. Symptoms and signs in keeping with Sandifer syndrome,
7. Workup for bronchiectasis or CLD of unknown origin or progressive nature,
8. LLAM on BAL of more than 10%,
9. Endoscopic findings suggestive for reflux laryngitis,
10. Difficult to control asthma as judged by an allergy specialist,
11. Workup for percutaneous endoscopic gastrostomy (PEG) insertion in a symptomatic patient,
12. Dysphagia/odynophagia,
13. Unexplained normocytic anaemia,
14. Non-cardiac chest pain in older children (heartburn),
15. Previously diagnosed GORD with change in symptoms or failing expected change in symptoms requiring a new investigation and/or

16. Additional investigation for GORD by means of milk scan for suspected GOR finding on contrast swallow.

For both modalities failure to thrive and persistent possetting on their own did not qualify for GORD investigation. In connection with any other criterion or combined they were considered additional evidence for the requirement of GORD investigation.

Studies qualified as exceptional for investigation if none of the above reasonability criteria were fulfilled but the patient had sufficient clinical features to warrant further investigation. The decision about this exceptional qualification was made by a senior consultant of the respective modality.

Additional definition of criteria:

The definition of failure to thrive was based on centiles rather than z-scores as nearly all reviewed folders were still using growth charts predating the newer 2006 World Health Organization (WHO) charts. We did not use the definition of weight-for-height as in the retrospective review height usually was not a frequently available variable.

For persistent wheezing we chose to apply the same time interval as for persistent cough.

ALTE that were likely due to aspiration secondary to GORD was considered when the ALTE involved apnoea, cyanosis or choking episodes without external causative factors such as obstructing food boluses.

Dysphagia or odynophagia can both be signs of reflux oesophagitis and/or stricture formation as a consequence of GORD. However these signs are encountered in other conditions as well. A diagnostic approach includes the ruling out GORD and its consequences.

The workup for PEG insertion generally includes a contrast swallow to exclude anatomical abnormalities and, at RCWMCH, a milk scan to determine the severity of GOR in a symptomatic patient.

Workup for bronchiectasis or CLD of unknown origin or progressive nature was considered a reasonable request as GORD is a valid possibility in cases where the history and other investigations give little information about the aetiology of the bronchiectasis or CLD of the patient.

LLAM indicate aspiration or GORD with aspiration, but are not specific for GORD. In discussion with our laboratory (National Health Laboratory Service) we accepted a LLAM of more than 10% as high enough to warrant GORD investigation.

Investigation timing:

Any GOR examination performed during time of acute illness with increased respiratory drive or increased intra-abdominal pressures was regarded as inappropriately timed. If the underlying condition was chronic then the timing was only considered appropriate if the patient was examined in the best possible state at the time of investigation. Conditions with increased respiratory drive included lower airway disease (such as pneumonia or bronchiolitis) or tachypnoea of other reasons (e.g. acidaemia) and furthermore significant obstruction of the upper or lower airways resulting in visible signs and symptoms of respiratory distress. As conditions with increased intra-abdominal pressures were regarded any surgical and non-surgical condition producing a significantly distended abdomen causing diaphragmatic splinting and/or difficulty in breathing. Frequent coughing episodes at the time of investigation were also considered inappropriately timed for both reasons of increased respiratory drive and raised intra-abdominal pressures as described by Alvin. (Alvin, 2003)

Correct modality of study used:

Each request for GORD investigation was reviewed regarding the indications on the request form and clinical presentation as described in the patient's notes. It was then evaluated according to the listed reasonability criteria for the respective modality.

A milk scan investigation for GORD was considered the correct modality if it fulfilled any of the reasonability criteria except for dysphagia/odynophagia, as this may suggest a structural abnormality rather than GORD.

A contrast swallow investigation was considered the correct investigation modality if it fulfilled at least one of the following criteria:

1. Persistent coughing or wheezing episodes if present since birth or related to food intake,
2. FTT,
3. Persistent episodes of vomiting related to food intake with no other medical causal explanation and present for at least a three week interval,
4. Dysphagia/odynophagia,
5. ALTE if they were likely due to aspiration,
6. Workup for PEG insertion,
7. Workup for bronchiectasis or CLD of unknown origin or progressive nature, especially if clinically suggestive of tracheo-oesophageal fistula or aspiration and/or
8. LLAM on BAL of more than 10%.

Analysis:

Some of the subjects received more than one GORD investigation either with the same or with the alternative modality in the specified time interval. For our analysis, the difference in numbers of studies performed to numbers of patients enrolled provided the problem of partially dependent variables. We analysed the data for the number of studies where appropriate and resorted to analysis of the number of patients where the former would have caused a

confounding error. To determine which of the studies performed for the same patient should be analysed, we scrutinized the question asked and the main modality useful for answering this question. We then eliminated the less important study or studies for that particular patient for the analysis per patient. We specified in the result section for each result if it was analysed per number of studies or per number of patients.

The availability of data from milk scans and contrast swallows in the same patient provided us with an opportunity to compare the results of both modalities directly. We therefore performed a sub-analysis of these specific patients.

For our data analysis we accepted according to general convention a p-value of less than 0.05 as statistically significant. All continuous variables were analysed using the Shapiro-Wilk test to examine deviations from the normal distribution. The distribution of all the datasets was skewed ($p < 0.001$). Therefore all the statistical analyses employed non-parametric methods (Mann-Whitney U rank sum test) and were summarized using the median and interquartile range (IQR). All categorical data were analysed by means of descriptive statistics, comparing proportions. Either the Fisher's exact test or Pearson's Chi-square test were used where appropriate.

The analysis of all data was performed using the Stata/IC software, version 11.2 for Mac, in consultation with the biostatistics department of the University of Cape Town.

Results:

In the specified four month time frame 125 milk scans for GORD investigation and 148 contrast swallows for definite or presumed GORD investigation were performed. In total a number of 273 studies were performed between the two imaging departments.

In seven instances the information gained from the folder and request form was inadequate to provide judgement on the nature of the request as a GORD diagnostic test and these were therefore excluded. Furthermore 17 GORD studies requested by other institutions than RCWMCH and Groote Schuur Hospital (GSH) were excluded, as the yield of background information was insufficient to perform a judgement on the research questions for these investigations. In addition 57 patients were referred for contrast studies for reasons other than GORD investigation and were subsequently excluded. (Table 2) A total 192 studies where the primary aim of investigation was GORD was therefore available for analysis after the initial folder and request form review. The breakdown of the rationale and numbers for exclusion is given in Graph 1.

None of the accepted GORD studies were primarily excluded on technical reasons. In four cases neither the report nor the actual study was found on any system and these studies were therefore excluded from analysis. A total of 188 studies, 111 milk scans and 77 contrast swallows, performed on 161 patients were left for review.

Despite the acceptance of 188 studies for 161 patients as GORD investigation, not all of them provided enough detail to judge all six proposed research questions adequately. Some studies/patients had to be removed from the analysis of a particular aim. Subsequently the total numbers for each aim differ slightly from the total number of accepted studies:

The reasonability was judged on 187 investigations. For one milk scan that had been evaluated as a true GORD request a judgement on reasonability could not be performed due to insufficient background information on folder review. This study was excluded from the analysis of reasonability.

The clinical notes for five studies provided insufficient data to comment on the correct timing leaving a remainder of 183 studies for analysis.

For the judgement on the correct choice of investigation modality all studies supplied adequate information.

Regarding the use of an antacid trial prior to investigation 155 patients out of the total 161 were providing sufficient information. For one study there was insufficient information to assess if a trial of antacids had been performed prior to its request and was therefore excluded from this analysis. A further five patients had non-quantifiable descriptions of treatment duration so that an appropriate judgement could not be carried out. These were also excluded.

For the comparison of modality used and GOR found three contrast swallows did not comment on GOR and the study could not be found on the system for review. They were subsequently excluded leaving 74 contrast swallows for analysis.

Two patients had insufficient information for comparison between investigation findings and indication of request. One of these was requested for presumed persistent GORD but the contrast swallow result did not comment on reflux and the study could not be found on the system to review the result. Both patients were removed from analysis. Thus 159 patients were available for review.

Of all 161 patients 26 patients had more than one study performed in the specified time interval. (16.1% of all patients) To avoid confounding error in the analysis most of the following results had to be analysed by the number of patients rather than the number of studies performed. For the analysis per patient we eliminated 27 studies, one study each for 25 patients and two studies for the remaining patient. In total 18 contrast swallows and nine milk scans were removed for observations analysed by number of patients. One of the removed milk scans was a repeat of a previous milk scan. Therefore 25 patients were investigated with both modalities within the research period (Table 3).

A further 23 patients had the other modality of investigation requested at some stage outside of the study period. One of these was never performed and one was cancelled after the contrast swallow showed significant GOR. Therefore a total of 48 patients (29.8%) had received or were booked for investigations with both modalities at some point. Three of these patients underwent both investigations for the workup for PEG insertion, as it the current practice at RCWMCH. The subgroup of 25 patients that had both study types performed within the study period were used in comparison analysis.

In the observed studies per patient, there was a significant age difference between the modalities ($z=-3.87$; $p<0.001^*$). For milk scans the age ranged from less than one month to nine years and nine months, the median age of patients was five months (IQR 13 months). In comparison the age for contrast swallows extended from one month to twelve years and nine months, median of 17.5 months (IQR 56 months). The median age of all study participants was eight months. (IQR 24 months) There was no difference in gender in the patients allocated to the two modalities (Chi-square=0.43; degrees of freedom 1; $p=0.51$).

Reasonability of study request:

According to the reasonability criteria set out in the method section 16 out of 110 milk scans (14.4%) were inappropriately requested. However five of the inappropriate requests would have been granted after review by a nuclear physician despite the non-fulfilment of entry criteria, on a basis of exceptional qualification. Likewise 13 out of 77 contrast swallows (16.9%) were inappropriately requested with five of these qualifying as exceptional. This leaves eleven milk scans versus eight contrast swallows, in total 19 requests that were inappropriately requested. No significance was shown on Chi-square testing. (Table 4)

* Mann-Whitney U test

Appropriateness of request timing:

The majority of the 188 investigations were correctly timed with seven out of 107 milk scans (6.5%) and three out of 76 contrast swallows (3.9%). No statistical significance was shown. (Table 4)

Choice of correct investigation modality:

There was a significant difference between both modalities with regard to the choice of the correct study type for the indication on the request form and/or history. (Table 4) After exclusion of the 19 inappropriately requested studies on reasonability grounds 100 milk scans and 69 contrast swallows remained for analysis of correct modality choice. In total 32 of 169 studies (18.9%) were requested using the incorrect modality. Contrast swallows were incorrectly chosen in 27 of 69 studies (39.1%) compared to only five incorrectly chosen milk scans (5%) out of a total of 100 milk scans performed. The number of incorrectly requested contrast swallows analysed by number of studies was significantly higher than the number of incorrectly requested milk scans. (Chi-square=30.98, degree of freedom 1, $p < 0.001$)

Preceding treatment trial:

An antacid trial prior to investigation was performed in 24 out of 155 patients. (15.5%), all of which used proton pump inhibitors (PPIs) as the antacid of choice. There was no significant difference in the two modalities between the numbers of performed versus not performed antacid trials. (Chi-square=0.14, degree of freedom 1, $p = 0.70$) (Table 4)

Of the 24 patients with PPIs given prior to the investigation the antacid trial duration ranged from three weeks to five years and two months with a median of three months. (IQR 7 months)

Of the same 24 patients with PPI trial, 20 (83.3%) had a degree of GOR diagnosed compared to 90 patients out of 130 that did not have an antacid

trial (69.2%). For one patient the contrast swallow did not comment on GOR. There was no statistical difference between these two groups. (Chi-square=1.97, degree of freedom 1, p=0.16)

Comparison between modality used and findings:

A significant difference was demonstrated between the modality used and GOR found during the study. Ninety-four out of 111 milk scans (84.7%) had a degree of GOR compared to 38 out of 74 contrast swallows (51.4%). (Chi-square=24.13; degree of freedom 1; p<0.001) The severity grading in both modalities can be reviewed in Table 5. The severity categories between milk scan and contrast swallow did not differ significantly. (p=0.13^{*})

The difference in the presence of GOR between milk scans and contrast swallows in the sub-group of 25 patients that had both investigations done during the specified time interval reached significance. (p=0.025^{*}) Milk scans observed a degree of GOR in 22 of 25 cases (88%) whereas contrast swallow showed GOR in 14 of 25 cases (56%). (Table 6) The severity spectrum finding was similar in both modalities. (p=0.12^{*}) In eight cases the milk scan and contrast swallow showed the same result. However, in six cases the contrast swallow showed more severe GOR than the milk scan while in the remaining eleven cases the milk scan showed more severe GOR than the contrast swallow. (Table 6)

In this sub-group of patients where both investigations were employed, aspiration was detected in eight patients. One patient had aspiration on both modalities, the other seven only on contrast swallow. The distribution between the modalities reached significance. (p=0.049^{*}) In this group structural abnormalities were found on contrast swallow in four cases (Table 7).

In addition to the results of the eight patients with aspiration noted in the subgroup who had both investigations a further four studies out of the total

* Fisher's exact test

188 studies reported aspiration. One of these was shown on milk scan and was confirmed with a contrast swallow outside of the study period, and the other three were findings on contrast swallow only. The analysis of all the studies showed a significant difference in detection of aspiration between contrast swallows and milk scans. ($p=0.004^*$)

In addition to the four structural abnormalities described in the subgroup analysis four more were described in the primary study group of 188 studies. The eight structural abnormalities are described in detail in Table 7. One milk scan suggested a possible hiatus hernia but this was not confirmed on a subsequently performed contrast swallow outside the study period.

Comparison between findings and indication:

The indications for the request of studies per patient were summarized in seven categories. The suspicion or follow-up of GORD constituted the most common indication followed by apnoea, a combination of GORD and aspiration, other anatomical issues related to GORD, other functional issues related to GORD, suspicion or review of aspiration alone and lastly workup for Nissen's fundoplication and/or PEG. (Table 8) The analysis of GOR found by indication showed no significance. ($p=0.139^*$) The sub-group analysis for the 25 patients with both investigations also showed no significance for GOR found by indication. ($p=0.144^*$)

Discussion:

About a third of the patients (29.8%) enrolled in the study had GORD investigations performed with both modalities at some point or at least requests made for both modalities. Of all patients included in this review, 16.1% (26 out of 161) had two or more investigations in the four months study period. This complicated the analysis in terms of double counting and partially dependent variables. Where appropriate we analysed the data per studies performed and where double counting or partially dependent

* Fisher's exact test

variables would have been a problem we calculated the statistics per patient as described under the method section. In the results section of this paper each result specifies whether it refers to analysis of the number of studies or the number of patients. However, the performance of both test modalities in the same patient provided us with the opportunity to compare the results of both tests against each other.

Out of the 187 reviewed for reasonability of request 29 (15.5%) were requested inappropriately according to the criteria set out. Ten would still have been performed after discussion with a senior staff member, dropping the total inappropriate request number to 19 (10.2%). These exceptions would have been granted on the basis of suggestive GOR history despite non-fulfilment of any of the individual criteria. These 19 inappropriately requested GORD tests proved to be statistically insignificant. (Table 4)

Most studies performed in the assessed time interval were appropriately timed. Ten of 183 studies (5.5%) did not fulfil the timing criterion and this was statistically insignificant. (Table 4) .

Even though the total numbers of inappropriately requested milk scans and contrast swallows were relatively low (10.2% and 5.5% respectively) one would ideally aim to have the lowest possible number of inappropriately requested investigations to reduce radiation dose to patients.

There was a significantly higher number of inaccurately requested contrast swallows compared to milk scans. A total of 32 out of 169 studies (18.9%) were an inappropriate choice of modality. We presume this to be a consequence of clinicians not fully understanding the use of available GORD investigation modalities. This highlights the need for an investigation protocol or guideline for GORD and related conditions.

There is no national guideline regarding a treatment trial of antacids and therefore only 15.5% of all patients received a trial prior to investigation. However this analysis showed that 90 of the 130 patients without a preceding

trial had a positive GOR result (69.2%). It is likely that some of these would have responded to a trial of antacids and therefore the radiation exposure for testing could have been avoided.

There was no significant difference between the indication for the request (request category) and whether GOR was found or not. (Table 8)

Not surprisingly a significant difference between the modality used and the finding of GOR was demonstrated. The milk scan showed a positive result for GOR more often than the contrast swallow (84.7% vs. 51.4% respectively), although the proportion of severity of GOR for each modality was similar. This is in keeping with the limitation of contrast swallows in diagnosing GOR. An additional explanation is that the patients examined by milk scan were significantly younger than the patients examined by contrast swallow. (five months versus 17.5 months) As GOR is more frequently encountered in the younger infant the milk scan is more likely to find patients with GOR. However it needs to be pointed out that these GOR findings on either modality could represent either true GOR or false positive results. Furthermore the non-detection could be explained by sampling error, which is by comparison larger in contrast swallows due to the ten times shorter observation period. As currently a gold standard for the paediatric population is not available this study cannot distinguish between true positive and false positive GOR results and missed detection by false negative test.

Using the data of the patients that had both investigations performed in the observed four month time interval, there was no difference between the severities of GOR found with either modality. A review of the individual patients indicates that in 76% of patients the milk scan showed more severe results or the same severity compared to the contrast swallow. According to our data the contrast swallow tends to show a greater severity than the milk scan where there is nasopharyngeal backflow or a very irritable child on examination, or where the intake of radioactive-labelled feed for the milk scan was insufficient due to poor intake or large volume vomitus. (Table 6)

Milkscans are requested to evaluate for possible aspiration. The detection of aspiration in our study population was significantly more frequent using a contrast swallow. This finding was significant despite the small number of patients in the group that had both examinations performed in the set time frame. This is in keeping with the literature as according to the NASPGHAN/ESPGHAN guidelines reported sensitivity for microaspiration on milk scan is low. (Vandenplas et al., 2009)

Of all the patients in the study population with identified structural abnormalities, all but one had a history suggestive of structural abnormalities and were correctly investigated by contrast swallow. In one case a suggestive history was not present and the appropriate investigative modality would have been a milk scan. However, a contrast swallow was performed in this patient, which incidentally showed an aberrant subclavian artery.

None of the extended definition criteria on its own showed any significance between the modalities of milk scan and contrast swallow apart from the “not otherwise explained persistent cough or wheeze episodes” with a predominance of such reported indications in the milk scans ($p=0.029^*$). Some of the indications were reported in very small numbers therefore possibly missing detection of significance due to sample size. This included five referrals from ENT that all received a milk scan (two for inflammation and three for oedema) and six referrals for Sandifer syndrome that all also received milk scans. A few other investigations were also present only in small numbers but equally distributed between the modalities. These were referrals for LLAM with three each per modality, referrals for dysphagia/odynophagia with four referrals for milk scan versus three for contrast swallow and a total of six investigations for PEG investigation with three in each modality. Another two cases were referred for epigastric pains with one in each modality. No cases were investigated during the study period for unexplained anaemia

* Fisher’s exact test

The intention of this paper was to provide an updated request form to streamline investigations for GORD. However, during the course of the work on this paper, RCWMCH changed its request mode from a paper-based to an online-based request format for all its investigations. This new request system does not currently allow for further modification of a specific request in its drop-down menu. Therefore we were unable to pursue the idea of a new request form. We have, instead, taken a different approach and suggested a possible guideline for the investigation of GORD at RCWMCH using flow diagrams addressing the three most common indications for GORD investigation, possetting/vomiting, chronic cough and chronic chest infection. (Graph 2 and 3) These flow diagrams also contain some features such as patient and parent education and life-style changes that have not been discussed in this paper, but find suggestion elsewhere in the referenced literature.

Alternative techniques such as pH-metry or pH-impedance monitoring find no mention in our proposed guideline as they are not readily available at our institution. Endoscopy and manometry are also excluded from this guideline as they are not primary GORD investigations and are only performed for special indications.

Limitations of this study:

This was a retrospective review of clinical folders and some of the information needed was not available for analysis.

The reasonability criteria had some limitations. Examples included recurrent chest infections, FTT and chronic cough or wheeze:

Recurrent chest infections are a common complication of GORD and the definition used in this paper includes only lower respiratory infections requiring hospitalisation or documentation of an outpatient hospital review. This is problematic as not every chest infection might require hospitalisation or presentation to a hospital. In our context many mild or early chest infections are dealt with at primary level institutions. However if these

presentations were recorded in the hospital notes, the criterion would still have been fulfilled. In many cases presentations to primary level institutions were not recorded or poorly documented. Some referrals only stated “multiple” chest infections without further quantification. These referrals with uncertain terms were removed from analysis of the particular criterion.

The criterion of FTT is also problematic in a retrospective folder review, as patients often don't have enough measurements charted to scrutinize the trend appropriately. The availability of accurately filled road-to-health-charts (RTHC) would make such an assessment easier, but only rarely have copies of this document been found during the folder review. A weight-for-height approach was not possible as too few folders had the height noted.

Chronic cough and wheeze was defined as a cough/wheeze of at least three weeks duration with the addition of ruling out bacteria and viruses that are known to cause protracted episodes of coughing or wheezing. This poses the question of how to deal with patients that did not have investigations for these infectious agents at the beginning of their symptoms or for whom these investigations showed false negative results. A number of the patients with prolonged wheeze or cough will have had one of these infections but not have been investigated initially. They would therefore have been enrolled into the study. Some patients who were excluded on the grounds of positive microbiological cultures may in fact still have GORD. Also if any of the patients with these initial infections have developed chronic lung disease they could potentially qualify for GORD analysis on the investigation for chronic lung disease criterion.

The diagnosis of GORD is a difficult one to make as a degree of GOR is normal and no highly specific and/or sensitive tests exist to distinguish GORD from physiological GOR.

Identification of gaps and need for further research

To date there is no data correlating the results of the milk scan to symptom severity or demonstrable complications. This remains to be investigated. If the results of such a research project correlate better with symptom

severity than pH-metry, the milk scan age specific normal values used in that study could be validated at other centres.

Conclusion

The detection of GORD is a difficult task due to the many different ways in which it can present and due to the limitations of the techniques currently used to assess it.

This study showed that the majority of GORD investigations in the examined period were appropriately requested and also appropriately timed. However this study also supports our assumption that a considerable number of studies are unnecessarily performed. The numbers of patients referred inappropriately for a contrast swallow were significantly higher than inappropriate milk scan referrals.

In keeping with some of the international guidelines, we recommend that a course of antacids be prescribed prior to GORD investigation and that the duration of such an empiric treatment could range from two to four weeks. We do not recommend the use of hypoallergenic formula as initial empiric therapy.

Conflict of interest:

The author of this paper has no conflicting interests to declare.

Acknowledgements:

I am grateful to my supervisor and co-supervisors for being available whenever I had questions regarding the design, analysis and write-up of this paper. Furthermore, I want to give special thanks to my co-supervisors for providing me with background information and understanding of the technologies involved and for help in reviewing results that were not available in the folder and not reported on the computerized review systems. I also

want to express thanks to Henri Carrera (biostatistician) for being available to answer my questions on the analysis of the data presented in this paper. Lastly I want to thank Dr Nura Afshani for revising the paper a few times and providing suggestions to improve the language and the flow of reading. As referencing software we used RefWorks 2.0 Web Based Referencing Manager Software.

References

- Alvin, J. 2003. Cough and gastro-oesophageal reflux. In *Cough: Causes, Mechanisms and Therapy*. K.F. Chung, J.G. Widdicombe & H.A. Boushey, Eds. Edition 1 ed. Oxford: Wiley-Blackwell. 97-106.
- Beattie, R.M. 2001. Diagnosis and management of gastro-oesophageal reflux. *Current Paediatrics*. (11):269.
- Davies, F. & Gupta, R. 2002. Apparent life threatening events in infants presenting to an emergency department. *Emergency Medicine Journal : EMJ*. 19(1):11-16.
- Indrio, F., Riezzo, G., Raimondi, F., Cavallo, L. & Francavilla, R. 2009. Regurgitation in healthy and non healthy infants. *Italian Journal of Pediatrics*. 35(1):39-7288-35-39. DOI:10.1186/1824-7288-35-39; 10.1186/1824-7288-35-39.
- Jacobs, F., Thierens, H., Piepsz, A., Bacher, K., Van de Wiele, C., Ham, H., Dierckx, R.A. & European Association of Nuclear Medicine 2005. Optimised tracer-dependent dosage cards to obtain weight-independent effective doses. *European Journal of Nuclear Medicine and Molecular Imaging*. 32(5):581-588. DOI:10.1007/s00259-004-1708-5.
- Jeffery, H.E., Rahilly, P. & Read, D.J. 1983. Multiple causes of asphyxia in infants at high risk for sudden infant death. *Archives of Disease in Childhood*. 58(2):92-100.
- Jones, A.B. 2001. Gastroesophageal reflux in infants and children. When to reassure and when to go further. *Canadian Family Physician Medecin De Famille Canadien*. 47:2045-50, 2053.
- Mann, M.D. & Wynchank, S. 1994. Chapter 55 - Esophageal function (transport and motility). In *Nuclear medicine in clinical diagnosis and*

treatment. I.P.C.(.P.C. Murray & P.J. Ell, Eds. 2nd ed. Edinburgh:
Edinburgh : Livingstone. 377.

Moraes-Filho, J.P., Navarro-Rodriguez, T., Barbuti, R., Eisig, J., Chinzon, D.,
Bernardo, W. & Brazilian Gerd Consensus Group 2010. Guidelines for
the diagnosis and management of gastroesophageal reflux disease: an
evidence-based consensus. *Arquivos De Gastroenterologia*. 47(1):99-
115.

Papadopoulou, A., Koletzko, S., Heuschkel, R., Dias, J.A., Allen, K.J., Murch,
S.H., Chong, S., Gottrand, F. et al. 2014. Management guidelines of
eosinophilic esophagitis in childhood. *Journal of Pediatric
Gastroenterology and Nutrition*. 58(1):107-118.

DOI:10.1097/MPG.0b013e3182a80be1;
10.1097/MPG.0b013e3182a80be1.

Rudolph, C.D., Mazur, L.J., Liptak, G.S., Baker, R.D., Boyle, J.T., Colletti,
R.B., Gerson, W.T., Werlin, S.L. et al. 2001. Guidelines for evaluation
and treatment of gastroesophageal reflux in infants and children:
recommendations of the North American Society for Pediatric
Gastroenterology and Nutrition. *Journal of Pediatric Gastroenterology
and Nutrition*. 32 Suppl 2:S1-31.

*Standard Treatment Guidelines and Essential Drug List for South Africa -
Hospital Level Paediatrics*. 2006. 2nd Edition ed. Pretoria, South Africa:
The National Department of Health.

Vaezi, M.F. 2005. Atypical manifestations of gastroesophageal reflux
disease. *MedGenMed : Medscape General Medicine*. 7(4):25.

Vandenplas, Y., Rudolph, C.D., Di Lorenzo, C., Hassall, E., Liptak, G.,
Mazur, L., Sondheimer, J., Staiano, A. et al. 2009. Pediatric
gastroesophageal reflux clinical practice guidelines: joint
recommendations of the North American Society for Pediatric
Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the
European Society for Pediatric Gastroenterology, Hepatology, and
Nutrition (ESPGHAN). *Journal of Pediatric Gastroenterology and
Nutrition*. 49(4):498-547. DOI:10.1097/MPG.0b013e3181b7f563;
10.1097/MPG.0b013e3181b7f563.

Warrington, J.C. & Charron, M. 2007. Pediatric gastrointestinal nuclear medicine. *Seminars in Nuclear Medicine*. 37(4):269-285.
DOI:10.1053/j.semnuclmed.2007.02.005.

Tables and Graphs

Table 1
Severity criteria for 30 minutes milk scans (as used by RCWMCH)

Degree of severity	Number of GOR episodes	Refluxed content volume (in %)	Duration (in seconds)	Level of GOR
--------------------	------------------------	--------------------------------	-----------------------	--------------

Term until < 3 months of age:

Normal*	≤4	<1	≤5	any
Mild	<8	<4	Half of GOR episodes ≤10	≤3 episodes up to cervical or higher
Moderate	8 - 14	4 - 8	Between mild and severe	Between mild and severe
Severe	≥15	8 - 11	≥30 <u>or</u> 3 episodes ≥ 15	>8 episodes up to cervical or higher
Gross	innumerable	>11	≥60	

3 months until 12 months of age:

Normal*	≤3	<1	≤5	Low to mid thoracic
Mild	4 - 5	<4	¼ of GOR episodes ≤10	≤3 episodes up to cervical or higher
Moderate	6 - 11	4 - 8	Between mild and severe	Between mild and severe
Severe	≥12	8 - 11	≥30 <u>or</u> 3 episodes ≥ 15	>4 episodes up to cervical or higher
Gross	innumerable	>11	≥60	

> 12 months of age:

Normal*	≤2	<1	≤5	Low to mid thoracic
Mild	3 - 5	<4	¼ of GOR episodes ≤10	Low to mid thoracic
Moderate	6 - 9	4 - 8	Between mild and severe	Between mild and severe
Severe	≥10	8 - 11	≥30 <u>or</u> 3 episodes ≥ 15	Cervical or higher
Gross	Innumerable	>11	≥60	

* For normal reflux all four criteria need to be fulfilled simultaneously, for any other category of reflux only one criterion needs to be fulfilled. The highest ranking criterion determines the reflux category.

Table 2
Excluded patients overview (Indications other than GOR)

Indication for procedure performed other than GOR	Number of cases excluded
Suspected volvulus (9) or malrotation (5)	14
Post-surgical complications	13
tracheo-oesophageal fistula repaired (4)*	
presumed gastro-enteric fistula (2)	
repositioning of PEG (2)	
persistent vomiting post choledochal cyst removal (1)	
persistent vomiting post Nissen's (1)	
persistent vomiting post gastroschisis repair (1)	
review of bowel lengthening procedure (1)	
recurrence of hiatus hernia (1)	
Suspected isolated aspiration (5) or performed modified contrast study (3)	8
Presumed or followed-up oesophageal strictures	7
Presumed tracheo-oesophageal fistula*	5
Other	10
Oesophageal foreign body for perforation review (3)	
Extended workup for bronchial compression (2)	
Follow through for gastric outlet obstruction (1) or short bowel (1)	
Contrast enema for Hirschsprung's disease (1)	
chronic constipation and abdominal pain (1)	
cleft lip and palate (1)	
Total excluded	57

* One patient had an initial confirmatory scan for trachea-oesophageal fistula and a repeat scan post surgical repair

Table 3
Excluded studies per patient with more than one investigation in four months study period

Patient	Presentation*	Reason for exclusion*	Study excluded [†]	Study remained*
1	Infant with metabolic encephalopathy for PEG workup	Deciding criterion for addition of Nissen's depends on evidence of GOR as appropriately assessed by milk scan	Initial & repeated CS after presumed aspiration episode (2 studies)	MS
2	Pulmonary tuberculosis with bronchial compression, possible aspiration, requested by pulmonology	Repeated scan after new LRTI episode, both scans showed identical result	Second MS	Initial MS
3-5	Presumed GOR (3 patients)	GOR appropriately assessed by MS	CS	MS
6-11	Vomiting and cyanosis / apnoea after feeds (5 patients)	GOR as appropriately assessed by MS	CS	MS
12	Presumed GOR confirmed on MS, hold-up at GOJ [‡] required CS follow-up	GOR as appropriately assessed by MS	CS	MS
13	Uncontrolled asthma, possible GOR?	GOR as appropriately assessed by MS	CS	MS
14	Heartburn unsuccessful on treatment	GOR as appropriately assessed by MS	CS	MS
15	PEG workup for known GORD without improvement on treatment	GOR as appropriately assessed by MS	CS	MS
16	PEG workup for cerebral palsy patient on long-term naso-gastric tube feeds	Deciding criterion for addition of Nissen's depends on evidence of GOR as appropriately assessed by milk scan	CS	MS
17	Toddler with FTT, food allergy and food refusal	GOR as appropriately assessed by MS	CS	MS
18	ENT referral for glottic oedema	GOR as appropriately assessed by MS	CS	MS

[†] CS = contrast swallow, MS = milk scan

[‡] GOJ = gastro-oesophageal junction

Continuation:

Study	Presentation	Reason for exclusion	Study excluded	Study remained
19-20	Recurrent or persistent right upper lobe pneumonia/collapse (2 patients)	Suspicious of vascular ring or aspiration, appropriately assessed by CS	MS	CS
21-23	Presumed aspiration (3 patients)	Aspiration as appropriately assessed by CS	MS	CS
24	Hypoplastic supraglottis with feeding difficulties for PEG insertion	In this case the review of the abnormal anatomy was considered more important than the finding of GOR	MS	CS
25	Complex cardiac lesion after augmentation of coarctation with aspiration risk as assessed by speech therapy	Aspiration as appropriately assessed by CS	MS	CS
26	Newly diagnosed HIV [§] positive infant with severe pneumonia and 40% LLM on BAL on NJT feeds	Aspiration as appropriately assessed by CS	MS	CS

[§] HIV = human immunodeficiency virus

Table 4
Table of main results

		Appropriate study request*				Appropriate timing*			Appropriate modality*			Appropriate modality* (after removal of inappropriate study requests)			Trial of antacids†		
		No	Yes	Exc. ‡	Total	No	Yes	Total	No	Yes	Total	No	Yes	Total	No	Yes	Total
Milk scan	frequency	11	94	5	110	7	100	107	5	106	111	5	95	100	82	16	98
	percent	57.9	59.5	50.0	58.8	70	57.8	58.5	13.5	70.2	59	15.6	69.3	59.2	62.6	66.7	63.2
Contrast swallow	frequency	8	64	5	77	3	73	76	32	45	77	27	42	69	49	8	57
	percent	42.1	40.5	50.0	41.0	30	42.2	41.5	86.5	29.8	41	84.4	30.7	40.8	37.4	33.3	36.8
Total	frequency	19	158	10	187	10	173	183	37	151	188	32	137	169	131	24	155
	percent	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Analysis§		Chi ² =0.36 (2); p=0.84				Fisher p=0.53			Chi ² =39.49 (1); p<0.001			Chi ² =30.98 (1); p<0.001			Chi ² =0.14 (1); p=0.70		

* analysis done on number of studies performed

† analysis done on number of patients for studies performed

‡ Exc. = exception

§ Analysis using Chi-square (degrees of freedom) or Fisher's exact test where appropriate

Table 5
GOR severity found by study type per studies performed

		No GOR	Severity of GOR					Total	
			Normal	Mild	Moderate	Severe	Gross		
Study type	Milk scan	frequency	17	22	22	25	24	1	111
		percentage	32.1	84.6	78.6	69.4	61.5	33.3	60.0
	Contrast swallow	frequency	36	4	6	11	15	2	74
		percentage	67.9	15.4	21.4	30.6	38.5	66.7	40.0
	Total	frequency	53	26	28	36	39	3	185
		percentage	100	100	100	100	100	100	100

Table 6
Comparison of GOR found per modality in subgroup with both examinations

Milk scan found GOR	Contrast swallow found GOR	Number of patients	Details / comment
Yes*	No	9	Two of the contrast swallows did not assess for GOR, one of these found an aberrant subclavian artery
No	Yes†	1	Contrast swallow noted very irritable child during test, a month later this patient proved to have eosinophilic oesophagitis on gastroscopy with biopsy
No	No	2	No GOR
Normal	Normal	1	Both normal range GOR
Mild	Moderate	1	
Mild	Severe	2	First patient: multiple vomits on milk scan, contrast swallow demonstrated nasopharyngeal backflow; second patient: swallowed very little milk on milk scan, contrast swallow demonstrated nasopharyngeal backflow
Moderate	Moderate	1	Both moderate GOR
Moderate	Severe	2	First patient: balanced translocation 3p/8q, drinking reluctantly on contrast swallow, application of contrast via NGT; second patient: contrast swallow demonstrated nasopharyngeal backflow
Severe	Minimal	1	
Severe	Moderate	1	
Severe	Severe	4	Both severe

* Severe (4), mild (3) and normal reflux (2)

† Moderate

Table 7
Structural abnormalities with background information and contrast swallow result

No	History	Finding	Expected
1*	Fetal alcohol syndrome with congenital cytomegalovirus (CMV) disease and oesophageal strictures, recurrent dilatations	Smooth short segment stricture in distal oesophagus and small hiatus hernia	known
2	Oesophageal atresia with trachea-oesophageal fistula repaired in infancy	Small focal irregularity at anastomosis site, no hold-up demonstrated	known
3	Previous Nissen's fundoplication with loss of appetite and weight and retrosternal pain	Para-oesophageal hernia	suspected
4	VACTERL syndrome, previous redo-Nissen's fundoplication, persistent vomiting	Several stenoses	suspected
5*	Hoarseness & glottic oedema on flexible endoscopy	Swollen glottis	suspected
6*	Oesophageal candidiasis (HIV Stage 4) with dysphagia	Dilated distal oesophagus	suspected
7*	Dysphagia & coughing on liquids with hold-up on Milk scan (later diagnosed as Cornelia-de-Lange syndrome)	Aberrant subclavian artery not causing mass effect on oesophagus, small sliding hiatus hernia	suspected
8	Three months old with one month history of vomiting, no other complaints	Aberrant right subclavian artery with minimal pressure effect	incidental

* Patients with both investigation modalities in research interval (refer to subgroup analysis)

Table 8
Comparison of indication and results by number of patients

		No GOR	Severity of GOR					Total
			Normal	Mild	Moderate	Severe	Gross	
Indication as per request form	GORD*	30	11	15	15	14	1	86
	Aspiration [†]	2	2	1	1	3	1	10
	GORD plus aspiration	2	3	1	4	3	0	13
	Apnoea	1	4	3	4	5	0	17
	For PEG/Nissen's	2	1	0	1	3	1	8
	Other functional [‡]	2	2	2	1	2	0	9
	Other anatomical [§]	7	1	3	3	2	0	16
	Total	46	24	25	29	32	3	159

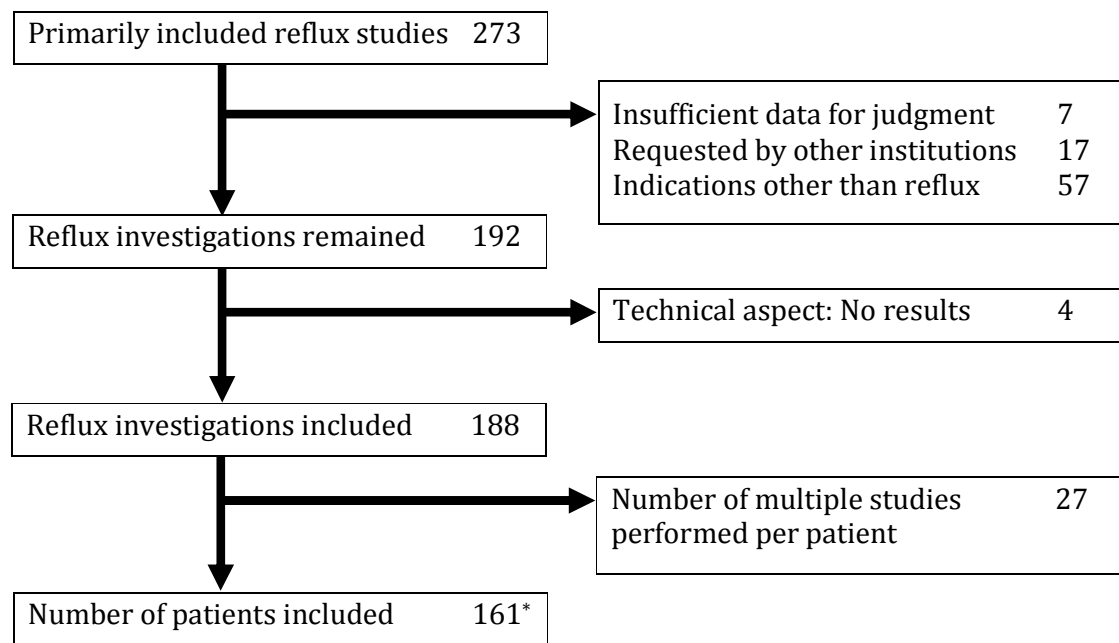
* Split-up: previously diagnosed GORD (16), previously diagnosed GORD with presumed persistence (8) and presumed GORD (62)

[†] Split-up: previously diagnosed aspiration (1) and presumed aspiration (9), on folder review these studies qualified as reflux investigation, but request was for aspiration

[‡] Split-up: reflux versus asthma (4), Sandifer syndrome (3) and abdominal pain with vomiting (2)

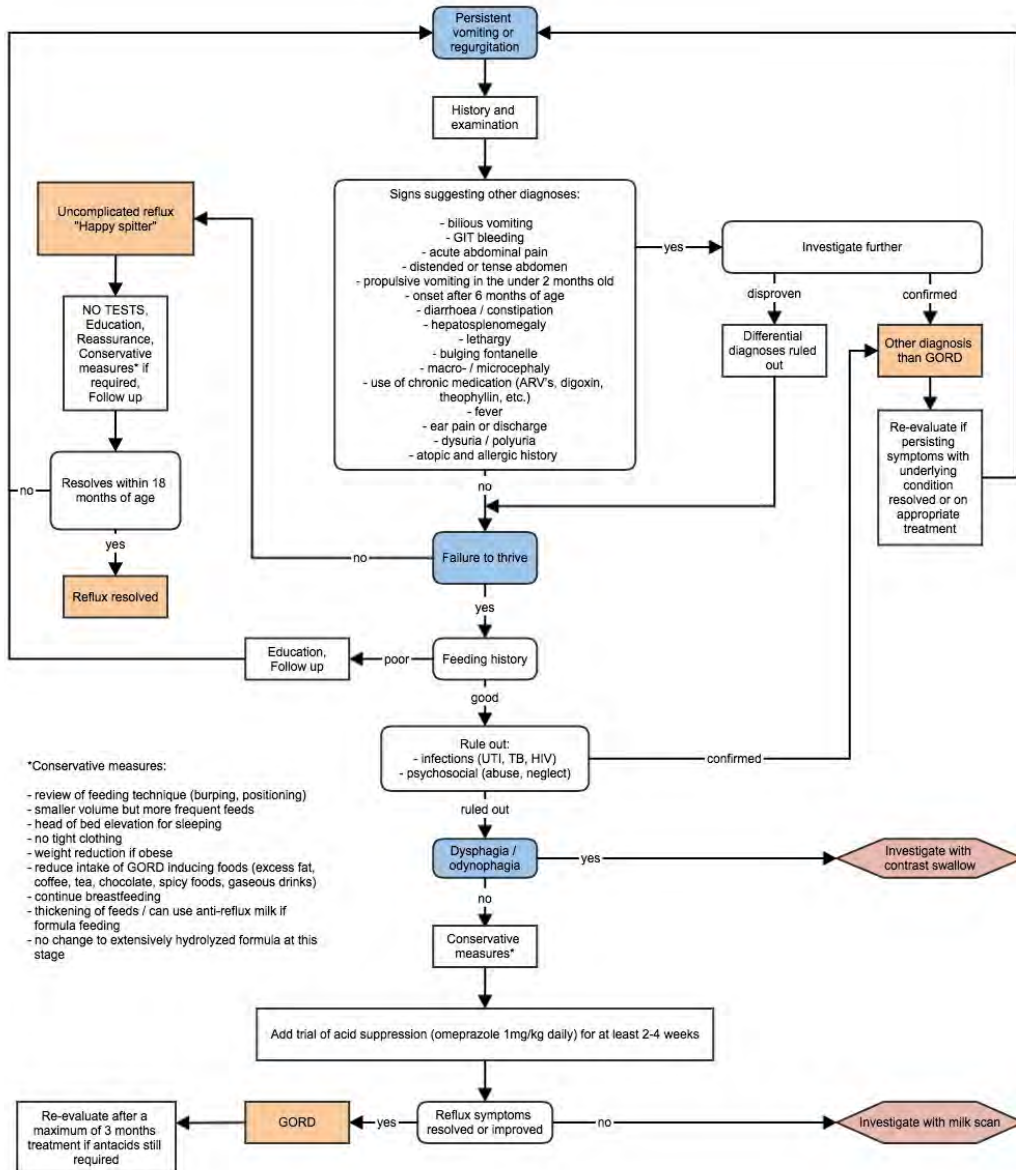
[§] Split-up: known stricture (1), presumed stricture (2), presumed tracheo-oesophageal fistula (1), presumed vascular ring (1), presumed hiatus hernia (1), bronchiectasis or chronic lung disease workup (4) and dysphagia or odynophagia (6)

Graph 1
Excluded patients diagram



* For analysis purposes by number of patients the investigation with the most weight regarding the raised question was retained and the other(s) were removed. (Table 3) The remaining study commonly was the milk scan as the symptoms described and question asked were mostly related to investigating for presumed GORD.

Graph 2
Suggested flow diagram for the investigation of GORD
(persistent vomiting)



Graph 3
Suggested flow diagram for the investigation of GORD
(chronic cough and chest infections)

