EXOGENOUS LIPOID PNEUMONIA IN CHILDREN: A SYSTEMATIC REVIEW AND CASE SERIES FROM SOUTH AFRICA

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A dissertation submitted in part fulfillment of the requirements of the University of Cape Town award of the degree of Master of Philosophy in Paediatric Pulmonology

DECLARATION

I, ***Diana Marangu***, hereby declare that the work on which this dissertation 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.

Signature: Signed by candidate

Date: **04/09/2018**

ACKNOWLEDGEMENTS

Diana Marangu conceived and designed the study; and substantially contributed to data acquisition, analysis and interpretation; drafting the dissertation and final approval of the version submitted. Komala Pillay substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Ebrahim Banderker substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Diane Gray substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Aneesa Vanker substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Marco Zampoli substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted.

This dissertation has been presented with the full approval of supervisors: 1) Marco Zampoli; 2) Diane Gray; 3) Aneesa Vanker.

TABLE OF CONTENTS

LISTS OF FIGURES AND ABBREVIATIONS

List of Figures

Abbreviations

ALD - adrenoleukodystrophy

BAL – bronchoalveolar lavage

CT – computed tomography

ELP – exogenous lipoid pneumonia

GOR – gastro-oesophageal reflux

MRI - magnetic resonance imaging

NTM - non-tuberculous mycobacteria

PAS – periodic acid schiff

ABSTRACT

Exogenous lipoid pneumonia: an important cause of interstitial lung disease in African infants

Background and objective: To describe the clinical-radiological-pathological characteristics and treatment outcomes of childhood exogenous lipoid pneumonia (ELP) and elucidate oil administration practices.

Methods: A retrospective study of children with histologically-confirmed ELP at Red Cross Children's Hospital, South Africa. Caregivers were interviewed to understand oil administration practices.

Results: Twelve children of Zimbabwean heritage aged 2.1-10.8 months were identified between 2012 and 2017. Repeated oral administration of plant-based oil for cultural reasons was reported by 10/11 caregivers. Cough (12/12), tachypnea (11/12), hypoxia (9/12) and diffuse alveolar infiltrates on chest radiography (12/12) were common at presentation. Chest computed tomography revealed ground glass opacification with lower zone predominance (9/9) and interlobular septal thickening (8/9). All bronchoalveolar lavage specimens appeared cloudy/milky, with abundant lipid laden macrophages and extracellular lipid on Oil-Red-O staining and documented polymicrobial (6/12) and *Mycobacterium abscessus* (2/12) co-infection. Antibiotics, systemic corticosteroids and therapeutic partial lung lavage were interventions in all, 8 and 5 patients respectively. Median time to clinical resolution was 1.1 months IQR (0.5-8.0) with radiological resolution only in 2/12 cases.

Conclusions: Paediatric ELP resembles pulmonary alveolar proteinosis. Health workers should explicitly probe for a history of oil administration in children with non-resolving pneumonia and consider the diagnosis of ELP in settings where this is a common practice.

CHAPTER 1: INTRODUCTION

1.1 Context

Exogenous lipoid pneumonia (ELP) is a disorder caused by inhalation or aspiration of mineral, plant-based or animal-based oils that is generally considered uncommon[1, 2]. Lipoid pneumonia related to the use of nonvolatile oils in children has been reported in the literature in several parts of the world. One of the earliest articles published on this condition was based on autopsy findings in Canadian children who developed pneumonia following nasopharyngeal injections of oil in hospital[3]. Subsequently, literature on lipoid pneumonia related to medical use of oil-based products in children as well as the use of various folk remedies involving nasal or oral administration of these oils in children and related cultural practices have also been documented[1, 4, 5].

In addition to a history of oil ingestion or aspiration, children with ELP have been reported to present with non-specific clinical and radiologic findings and variable treatment outcomes[1, 2]. Expert reviews provide a consensus approach of discontinuing oil, treating infections and identifying underlying risk factors[1] however to the best of our knowledge, no formal systematic reviews and meta-analyses have been conducted. Systematically reporting on the global context of non-accidental ELP in children with regard to clinical-radiological-pathological characteristics and treatment outcomes may provide a holistic perspective with a robust evidence base for management of these children.

1.1.1 Methodological aspects

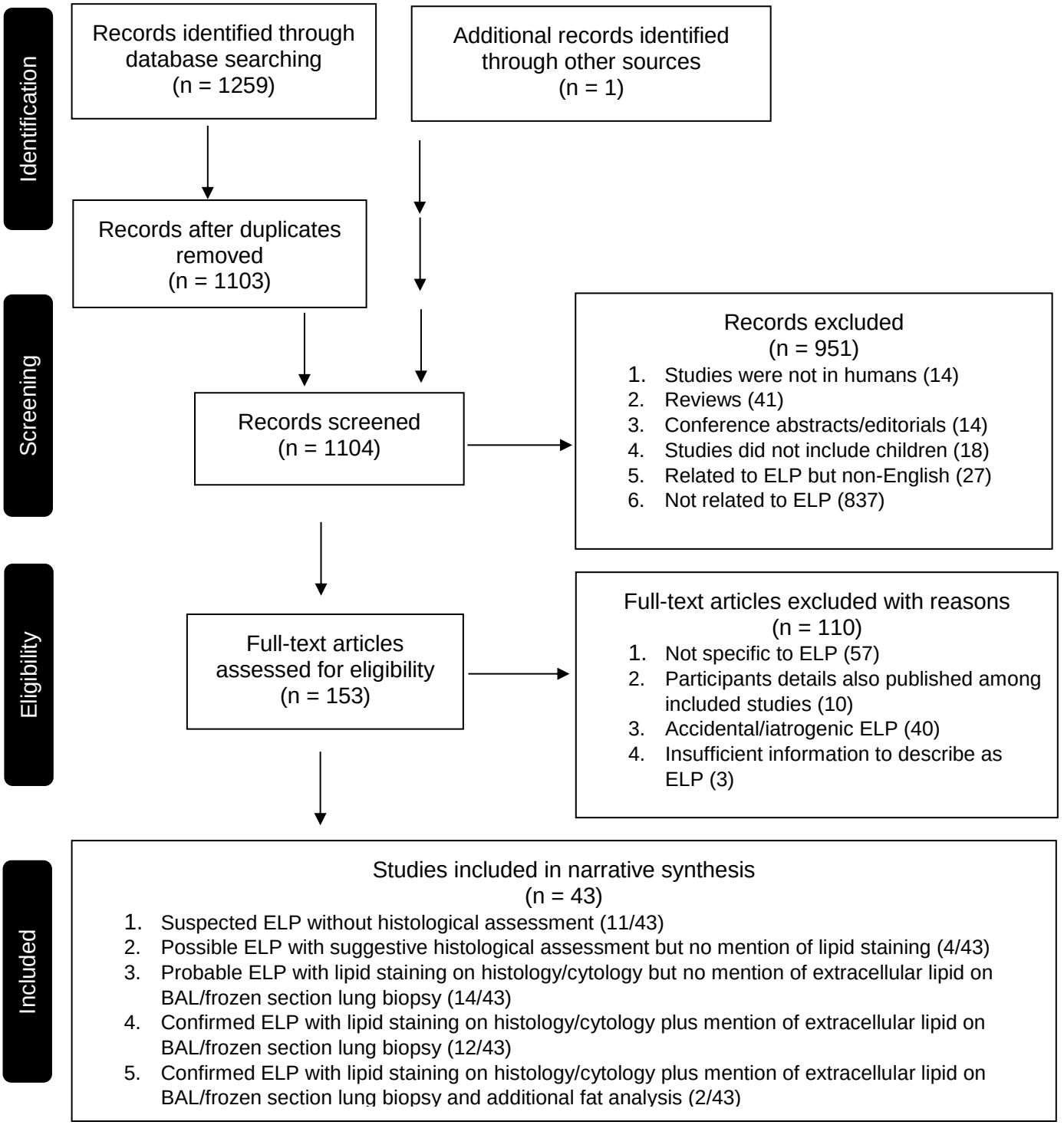
This study was registered on PROSPERO, an international prospective register for systematic reviews as CRD42017068313 and detailed methodology published online. We included studies conducted in any context globally involving children less than 18 years old suspected to have

ELP, suspected under the following conditions:1) history of oil administration related to time of presentation/diagnosis, 2) clinical presentation of persistent or recurrent unexplained pneumonia associated with hypoxia or tachypnea, 3) radiological evidence of persistent diffuse alveolar infiltrates on chest radiograph or computed tomography (CT) chest, and/or 4) histological/cytological findings on bronchoalveolar lavage (BAL) or lung biopsy that were consistent with exogenous lipid content. Studies that had adults along with children were included if the data on adults could be separated and excluded. Letters, editorials, commentaries, conference abstracts, all types of reviews, meta-analyses, non-human studies and non-English studies were excluded.

We employed a multi-concept Boolean search strategy based on the Population, Intervention, Control, Outcome, Timing and Setting (PICOTS) framework[(6)]. This search strategy used keywords related to ELP in children and was restricted to English publications published within the last 50 years. This period was arbitrarily deemed to represent data that was currently relevant. The first author systematically searched Pubmed, EMBASE, Web of Science, SCOPUS, CINAHL and the Cochrane Library to identify studies describing ELP in children published from 1967 to December 2017. The Pubmed search strategy used was: ("child"[MeSH Terms] OR Child[tw]) OR ("infant"[MeSH Terms] OR infant[tw]) AND ("pneumonia, lipid"[MeSH Terms] OR ("pneumonia"[All Fields] AND "lipid"[All Fields]) OR "lipid pneumonia"[All Fields] OR ("exogenous"[All Fields] AND "lipoid"[All Fields] AND "pneumonia"[All Fields]) OR "exogenous lipoid pneumonia"[All Fields]) AND (1967:2017[dp]) AND "English"[la]. The primary reviewer screened abstracts for eligibility, retrieved full texts to confirm eligibility and extracted data for quantitative synthesis. Using a standardized tool, the first author independently extracted data from eligible articles and consulted senior reviewers during this process whenever required. Specific information recorded from each study included and details on study quality assessment are provided as supplementary material. (Technical Appendix)

We identified 1,259 articles through the electronic database search and one additional record through hand search of references in the current literature. Duplicates were excluded and of the remaining 1,104 titles and abstracts, 153 were eligible for full text assessment. Of these, 43 studies were included for qualitative synthesis as depicted in the PRISMA flow chart (Figure 1).

Figure 1: PRISMA Flow Chart



A narrative summary for the studies eligible for this systematic review is provided classified restricted to non-accidental etiologies. Majority of the studies included were case series and case reports, thus summary measures could not be pooled together nor could quantitative data be consolidated in a metanalysis.

1.1.2 Summary

In the past half-century, paediatric ELP resulting from non-accidental etiologies, predominantly cultural practices, continued to be documented in Asia, the Americas and Europe. However published data from Africa and Australia are lacking. Furthermore, the trend in reporting studies of paediatric ELP has been decreasing over the last five decades, with the highest peak of published articles noted between 1987 and 2006. Increased awareness of the complications of these oil practices may explain this decline over time. Notably, the medical use of Lorenzo's oil and ketogenic diets in children with severe neurological conditions should be recognized as a possible albeit rare cause of ELP [7-9].

Figure 2: Global map depicting the number of studies conducted on non-accidental paediatric exogenous lipoid pneumonia in the English literature

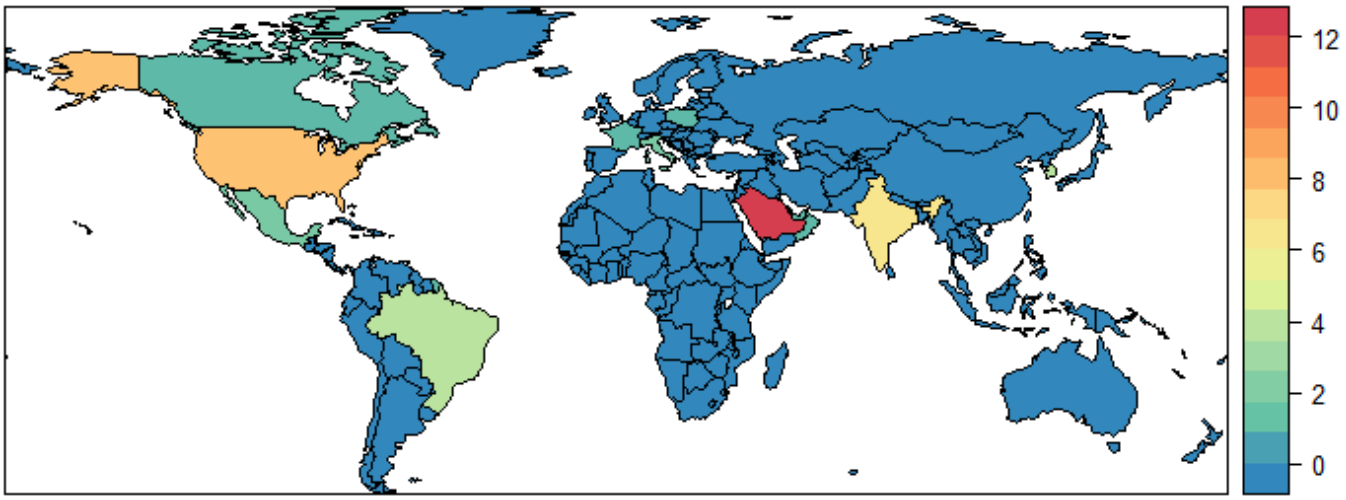
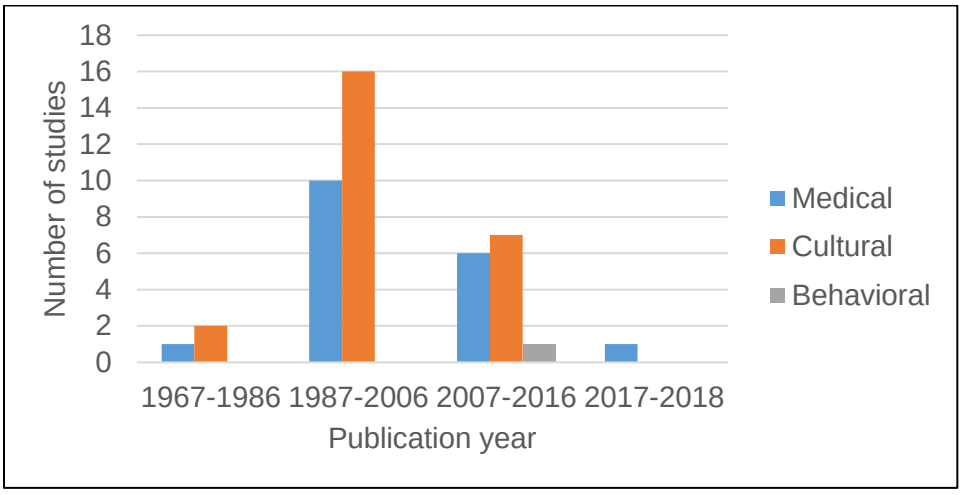


Figure 3: Graph depicting the number of studies conducted on non-accidental paediatric exogenous lipoid pneumonia in the English literature by publication year and aetiology



The type, amount, frequency and duration of oil use documented in the selected studies varied widely; and may partly explain the heterogeneous clinical-radiological pattern of paediatric ELP that makes it indistinguishable from other causes of persistent pneumonia. Five studies in this review reported on NTM infections in children with ELP that resulted in significant morbidity, a finding consistent with previous experimental studies [10] and literature in adults[11, 12]. Supportive management particularly antibiotic treatment is the most common treatment offered to children with ELP. Although qualitative findings from this systematic review seem to suggest that steroids and lavage may improve time to clinical resolution, surgery could be associated with many complications including death, and radiologic resolution may be delayed in comparison to clinical resolution, prospective studies to assess the efficacy of treatment interventions in paediatric ELP are needed.

Furthermore, the definitions of paediatric ELP are too heterogenous to make comparisons across studies. We therefore propose a scale of diagnostic certainty comprising five levels: suspected, probable, possible, confirmed on histocytological assessment, and confirmed on both histological/cytological assessment and fat analysis. This scale is envisaged to provide

standardized case definitions for patient eligibility in future ELP studies. Diagnostic certainty levels have been proposed for randomized control trials in other conditions in children such as wheezing, where standardized definitions are lacking [13]. Additionally, standardized reporting could be adapted from international registries such as the international management platform for ChILD[14] or any other global registry. Preferably data collection should be prospective to prevent pitfalls of bias and missing data.

The main limitations of this systematic review were the studies included comprised case reports, case series and few cross-sectional studies making it difficult to pool data; exclusion of non-English articles; and a single reviewer. Studies reviewed were highly biased with respect to patient selection due to the nature of their design. Notwithstanding these limitations, we believe that our study provides a current and robust perspective on ELP in children resulting from non-accidental aetiologies. This review highlights that paediatric ELP resulting from cultural/medical practices continues to be described in Asia, the Americas and Europe. Although clinical-radiological patterns vary widely making them non-specific to diagnosing paediatric ELP, health-workers should not forget that this is an important cause of ILD in children with persistent pneumonia. Standardized reporting, treatment efficacy studies and data from other global regions are lacking.

1.2 Ethical Considerations

We obtained consent from the University of Cape Town Human Research and Ethics Committee (548/2017) to conduct the case series. Additionally, we sought permission from the Red Cross War Memorial Children's Hospital administration for retrospective review of patient records. Researchers and interpreters signed a study confidentiality agreement to mitigate against the risk disclosure of caregivers' contact details occurring, accidentally or otherwise. Data captured electronically was anonymized, encrypted and stored in databases and devices that were password protected to ensure data privacy. The lead researcher, trained in qualitative research employed an empathetic approach during the conduct of all interviews and was cognizant of not attributing any blame to the caregivers of study participants. To maintain confidentiality, telephonic interviews were conducted in a private room with an interpreter if needed, and without audio recording participant names. Data were stored in password-protected files with access restricted to researchers, and audio-recorded files will be destroyed 6 months after transcription.

1.3 Author guidelines for Pediatric Pulmonology

Original Research Articles

Original Research Articles should follow the standard structure of abstract, introduction, methods, results, discussion, and references, and may include up to six tables and/or images when appropriate. Original Research Articles should be limited to 3,500 words (not including the abstract or references). The abstract should not exceed 250 words, and references should be limited to forty (40).

Main Document

All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

Title page: The title should be brief (no more than 100 characters in length including spaces) and useful for indexing. All authors' names with highest academic degree, affiliation of each, but no position or rank, should be listed. For cooperative studies, the institution where research was primarily done should be indicated. In a separate paragraph, specify grants, other financial support received, and the granting institutions (grant number(s) and contact name(s) should be indicated on the title page). If support from manufacturers of products used is listed, assurances about the absence of bias by the sponsor and principal author must be given. Identify meetings, if any, at which the paper was presented. The name, complete mailing address, telephone number, fax number, and e-mail address of the person to whom correspondence and reprint requests are to be sent must be included. Keywords should also be noted on the title page. For usage as a running head, provide an abbreviated title (maximum 50 characters) on the bottom of the title page.

Summary/Abstract: In accordance with the structure of the article, with or without separate headings, outline the objectives, working hypothesis, study design, patient-subject selection, methodology, results (including numerical findings) and conclusions. The Summary should not exceed the word counts outlined above. If abbreviations are used several times, spell out the words followed by the abbreviations in parentheses.

Acknowledgements: Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under “Acknowledgements.”

Informed Consent: Informed consent statements, if applicable, should be included in the Methods section.

References/citations: References may be included at the end of your text, or uploaded as a separate file. Ensure your references are up to date, and include a critical selection from the world literature. References should be prepared according to CSE (Council of Science Editors) citation-sequence style. Refer to the *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers*, 8th edition (University of Chicago Press). Start the listing on a new page, double-spaced throughout.

Number the references in the sequence in which they first appear in the text, listing each only once even though it may be cited repeatedly.

When citing a reference in the text, the style advocated by CSE suggests numbers appear in superscript and appear before punctuation marks (commas or periods). In the citation-sequence system, sources are numbered by order of reference so that the first reference cited in the paper is [1], the second [2], and so on. If the numbers are not in a continuous sequence, use commas (with

no spaces) between numbers. If you have more than two numbers in a continuous sequence, use the first and last number of the sequence joined by a hyphen, for example [2,4,6-10].

In the references, list the first ten authors of the cited paper. If there are more than ten authors, list the first 10 authors followed by 'et al'.

Journals' names should be shown by their abbreviated title in *Index Medicus*.

Manuscripts in preparation or submitted for publication are not acceptable references. If a manuscript "in press" is used as a reference, a copy of it must be provided with your submission.

Sample references:

Standard journal article

Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.

Book with authors

Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.

Book with editors

Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.

Chapter from a book

Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.

For a book reference only include the page numbers that have direct bearing on the work described.

Keywords: On the title page, supply a minimum of 3 to 5 keywords, exclusive of words in the title of the manuscript. A guide to medical subject heading terms used by PubMed is available at http://www.nlm.nih.gov/mesh/MBrowser.html

Abbreviations: Define abbreviations when they first occur in the manuscript and from there on use only the abbreviation. Whenever standardized abbreviations are available use those. Use standard symbols with subscripts and superscripts in their proper place.

Drug names: Use generic names. If identification of a brand name is required, insert it in parentheses together with the manufacturer's name and address after the first mention of the generic name.

Eponyms: Eponyms (diseases or biologic entities named for persons) should not be used when standard descriptive terminology is available. Examples include club cells (formerly known as Clara cells); and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). It is permissible to use the eponym in parenthesis at the first mention of the term in cases in which the eponym is still in common use.

Formatting Specific to Original Research Articles: Divide article into: Title Page, Summary/Abstract, Introduction, Materials and Methods, Results, Discussion, and References, starting each section on a new page. All methodology and description of experimental subjects should be under Materials and Methods; results should not be included in the Introduction. Please ensure the following appears in the appropriate section of your manuscript:

- a concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- a succinct description of the working hypothesis;

- a detailed explanation of assumptions and choices made regarding study design and methodology;
- a description of the reasons for choosing the type and number of experimental subjects (patients, animals, controls) and individual measurements; if applicable, information about how and why the numbers may differ from an ideal design (e.g., the number required for achieving 90% confidence in eliminating Type II error);
- specifics about statistical principles, techniques and calculations employed and, if applicable, methods for rejecting the null hypothesis;
- a concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- a brief summary of the limitations of the scientific methods and results; and
- a brief discussion of the implications of the findings for the field and for future studies.

Tables

Tables should not be included in the Main Document but submitted as a separate DOC or RTF file. Number tables with Arabic numbers consecutively and in order of appearance. Type each table double-spaced on a separate page, captions typed above the tabular material. Symbols for units should be used only in column headings. Do not use internal horizontal or vertical lines; place horizontal lines between table caption and column heading, under column headings, and at the bottom of the table (above the footnotes if any). Use footnote letters (a, b, c, etc.) in consistent order in each table. All tables should be referred to in the text. Do not submit tables as photographs and do not separate legends from tables.

Images

Image files must be submitted in TIF or EPS (with preview) formats. Do not embed images in the Main Document. Number images with Arabic numbers and refer to each image in the text. The

preferred form is 5 X 7 inches (12.5 X 17.5 cm). Print reproduction requires files for full color images to be in a CMYK color space.

Please note authors are encouraged to supply color images regardless of whether or not they are amenable to paying the color reproduction fees. Color images will be published online, while greyscale versions will appear in print at no charge to the author. See Author Charges below.

Journal quality reproduction requires grey scale and color files at resolutions yielding approximately 300 ppi. Bitmapped line art should be submitted at resolutions yielding 600-1200 ppi. These resolutions refer to the output size of the file; if you anticipate that your images will be enlarged or reduced, resolutions should be adjusted accordingly.

Lettering on images should be of a size and weight appropriate to the content and the clarity of printing must allow for legibility after reduction to final size. Labeling and arrows on images must be done professionally. Spelling, abbreviations, and symbols should precisely correspond to those used in the text. Indicate the stain and magnification of each photomicrograph. Photographs of recognizable subjects must be accompanied by signed consent of the subject of publication. Images previously published must be accompanied by the author's and publisher's permission. Image legends should be brief and included as a separate DOC file under the heading: "Image Legends." When borrowed material is used, the source of the image should be shown in parentheses after its legend, either by a reference number or in full if not listed under References.

Online Supporting Information

Additional non-essential material such as text, appendices, tables, images, video, and soundtrack files may be submitted for posting as supporting information to an article. The scientific value of such material should be evident. The material should be submitted simultaneously with the

manuscript so that it may undergo peer review. In naming these files, please note the file names should be preceded by the letter “E.” For example “E-table 1,“E-image 1,” “E-text,” etc.

Note that supporting online material is not typeset, nor proofread following the review process, so please ensure the material is accurate and free of typographical errors. Supporting material should be prepared in the same manner as the print material.

While supporting information does not appear in the print version, a notation is made that supporting material is available online.

References

1. Hadda V, Khilnani GC. Lipoid pneumonia: an overview. Expert Rev Respir Med. 2010;4(6):799-807.

2. Betancourt SL, Martinez-Jimenez S, Rossi SE, Truong MT, Carrillo J, Erasmus JJ. Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol. 2010;194(1):103-9.

3. Laughlen GF. Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil. Am J Pathol. 1925;1(4):407-14.1.

4. Pinkerton H. Oils and fats: Their entrance into and fate in the lungs of infants and children: a clinical and pathologic report. Am J Dis Child. 1927;33(2):259-85.

5. Ikeda K. Oil aspiration pneumonia (lipoid pneumonia): clinical, pathologic and experimental consideration. Am J Dis Child. 1935;49(4):985-1006.

6. Samson D, Schoelles KM. AHRQ Methods for Effective Health Care Developing the Topic and Structuring Systematic Reviews of Medical Tests: Utility of PICOTS, Analytic Frameworks, Decision Trees, and Other Frameworks. In: Chang SM, Matchar DB, Smetana GW, Umscheid CA, editors. Methods Guide for Medical Test Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.

7. Cheon KR, Cho HJ, Kim SS, Woo YJ. Lipoid pneumonia following aspiration of lorenzo's oil in a child with x-linked adrenoleukodystrophy. HK J Paediatr. 2017;22(4):225-8.

8. Buda P, Wieteska-Klimczak A, Wlasienko A, Mazur A, Ziolkowski J, Jaworska J, et al. Lipoid pneumonia--a case of refractory pneumonia in a child treated with ketogenic diet. Adv Respir Med. 2013;81(5):448-52.

9. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45(9):1116-23.

10. Kudoh S. [The virulence of saprophytic acid-fast bacteria coated with oil or fat, with special reference to an observation on the so-called atypical acid-fast bacteria. 1. Experiments with guinea-pigs on intrapulmonal and subcutaneous inoculation of saprophytic bacteria coated with liquid paraffin]. Nihon Saikingaku Zasshi. 1962;17:154-61.

11. Hutchins GM, Boitnott JK. Atypical mycobacterial infection complicating mineral oil pneumonia. JAMA. 1978;240(6):539-41.

12. Okamori S, Asakura T, Nishimura T, Tamizu E, Ishii M, Yoshida M, et al. Natural history of Mycobacterium fortuitum pulmonary infection presenting with migratory infiltrates: a case report with microbiological analysis. BMC Infect Dis. 2018;18(1):1.

13. Marangu D, Kovacs S, Walson J, Bonhoeffer J, Ortiz JR, John-Stewart G, et al. Wheeze as an adverse event in pediatric vaccine and drug randomized controlled trials: A systematic review. Vaccine. 2015;33(41):5333-41.

14. Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, et al. International management platform for children's interstitial lung disease (chILD-EU). Thorax. 2018;73(3):231-9.

CHAPTER 2: PUBLICATION-READY MANUSCRIPT

Exogenous lipoid pneumonia: an important cause of interstitial lung disease in African infants

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Keywords: Children's interstitial lung disease (chILD), Oil, *Mycobacterium abscessus*

Abstract

Background and objective: To describe the clinical-radiological-pathological characteristics and treatment outcomes of childhood exogenous lipoid pneumonia (ELP) and elucidate oil administration practices.

Methods: A retrospective study of children with histologically-confirmed ELP at Red Cross Children's Hospital, South Africa. Caregivers were interviewed to understand oil administration practices.

Results: Twelve children of Zimbabwean heritage aged 2.1-10.8 months were identified between 2012 and 2017. Repeated oral administration of plant-based oil for cultural reasons was reported by 10/11 caregivers. Cough (12/12), tachypnea (11/12), hypoxia (9/12) and diffuse alveolar infiltrates on chest radiography (12/12) were common at presentation. Chest computed tomography revealed ground glass opacification with lower zone predominance (9/9) and interlobular septal thickening (8/9). All bronchoalveolar lavage specimens appeared cloudy/milky, with abundant lipid laden macrophages and extracellular lipid on Oil-Red-O staining and documented polymicrobial (6/12) and *Mycobacterium abscessus* (2/12) co-infection. Antibiotics, systemic corticosteroids and therapeutic partial lung lavage were interventions in all, 8 and 5 patients respectively. Median time to clinical resolution was 1.1 months IQR (0.5-8.0) with radiological resolution only in 2/12 cases.

Conclusions: Paediatric ELP resembles pulmonary alveolar proteinosis. Health workers should explicitly probe for a history of oil administration in children with non-resolving pneumonia and consider the diagnosis of ELP in settings where this is a common practice.

Introduction

Exogenous lipoid pneumonia (ELP) is considered a rare disorder caused by inhalation or aspiration of mineral, plant-based or animal oils[1, 2]. It results from a foreign body type of inflammatory reaction due to the presence of lipid material in the lung parenchyma initiating cellular and humoral defense mechanisms[3, 4]. Populations at risk include the elderly, children, and those with an underlying swallowing dysfunction or neurological/neuromuscular disorder resulting in an unprotected airway. Additionally, forced ingestion in the recumbent position in infants and young children who actively refuse oil may result in gagging and aspiration of the oil[5, 6]. Common ailments for which oil has been used for both medical and cultural practices include constipation, colic, and nasal stuffiness[7].

Paediatric ELP resulting from non-accidental etiologies, mainly cultural practices, has continued to be documented in Asia, the Americas and Europe in the past half-century. There is a dearth of published data from Africa. Moreover, there has been a downward trend in reporting studies of ELP in children during this time period. Oil administration may be a common practice that is not recognised to be potentially dangerous by caregivers or medical professionals. A history of this practice may not be forthcoming from caregivers unless health workers probe for it explicitly, leading to misdiagnosis, treatment delay and a missed opportunity to prevent ongoing oil aspiration[8]. The aim of this study was to describe the clinical-radiological-pathological pattern of ELP in children in the South African context and explore related oil administration practices.

Methods

Following ethical approval from the University of Cape Town Human Research Ethics Committee (*548/2017),* we conducted a retrospective case series and investigated oil administration practices in study participants at Red Cross War Memorial Children's Hospital, a tertiary referral hospital serving the Western Cape province of South Africa.

Participant selection

We consecutively selected children aged < 18 years with cytohistologically confirmed ELP defined under the following conditions: 1) clinical presentation of persistent or recurrent unexplained pneumonia associated with tachypnea or hypoxia; 2) radiological evidence of persistent diffuse alveolar infiltrates on chest radiography or computed tomography (CT) chest; 3) extracellular lipid and lipid laden macrophages in bronchoalveolar lavage (BAL) and/or frozen section lung biopsy and/or a; 4) history of oil administration related to time of presentation/diagnosis. There were no exclusion criteria for the retrospective aspect of the study which was descriptive reporting based on standard of care.

Study procedures

Permission to search patient records including medical folders and contact information was obtained from the hospital management. We sought a waiver of consent for these patients as their data was anonymised in this phase of the study. The lead researcher

reviewed medical records of eligible patients and extracted relevant clinical data which included socio-demographic characteristics, clinical findings, laboratory results and data relating to treatment and outcomes. Data were captured electronically, anonymised and recorded in a standard case report form.

The study radiologist and pathologist independently reviewed and entered data related to chest radiography, CT findings, bronchoalveolar lavage (BAL) and lung biopsy findings respectively. Children with suspected interstitial lung disease (ILD) routinely underwent high resolution CT utilising a paediatric friendly radiation dosing protocol with controlled ventilation if under the age of six years. Flexible bronchoscopy (Olympus^{R} 2.8 mm) and BAL was performed in all children under general anesthesia through a laryngeal mask. Sites for BAL were informed by prior radiology findings. Histocytological assessment of BAL and lung biopsy specimens routinely include Oil Red O stain for lipids, Periodic acid Schiff stain for glycoprotein exudates, Perls' Prussian Blue stain for iron, Grocott's methanamine silver stain for fungi and Ziehl-Neelsen stain for acid fast bacilli. Processing and examination of BAL and lung tissue were conducted according to the European Management Platform for Childhood Interstitial Lung Disease protocols[(9)].

Partial therapeutic lung lavage (using 2.8 mm Olympus^{R} flexible bronchoscope) with 200-300 ml 0.9% warmed saline, targeting the worst affected regions of the lung, was performed in selected cases where clinically significant hypoxemia and/or symptoms did not resolve spontaneously with medical management and cessation of oil administration in hospital. Given the limited evidence available for this therapeutic modality, treatment

was individualized, and sub-optimal response judged clinically by the pulmonologist. Repeated therapeutic lavages were also performed, if the patient's symptoms and signs persisted despite a prior lavage.

The lead researcher contacted caregivers of identified participants and conducted interviews telephonically or in person to elucidate oil administration practice information. Verbal or written informed consent was obtained from caregivers who agreed to participate in this component of the study. Detailed qualitative methods, emergent themes and selected quotes are available. (E-text)

Analyses

Quantitative data around clinical-radiological-pathological characteristics and treatment outcomes of children suspected with ELP were analyzed using STATA version 15.1. Continuous variables were described using medians and interquartile ranges. Categorical variables were described using proportions. Qualitative data around oil practices related to ELP in children from in-depth analysis of narratives powered for information[10] were transcribed, manually coded, synthesized into themes and managed using ATLAS.ti software.

Results

Clinical characteristics

Between October 2012 and December 2017, we identified twelve children with ELP as per our study case definition. All children were of Zimbabwean heritage, presenting in

infancy (median age 4.0 months, range 2.1-10.8). Cough was the main presenting symptom in all children with a duration varying from 1 day to 3 months. Common symptoms at presentation of these infants included: tachypnea (11/12), hypoxia in room air (9/12), fever (4/12), air trapping (2/12) and digital clubbing (2/12). Six out of 12 children were hospitalised for pneumonia on at least one other occasion besides the episode in which the diagnostic BAL done provided histocytological evidence of ELP. Underlying risk factors that were documented included gastro-oesophageal reflux (GOR) confirmed on scintigraphy (3/6), and in combination with silent aspiration confirmed on contrast swallow (2/4). (Table 1)

Details of oil administration

A history of oil administration was obtained from caregivers prospectively in seven out of 12 patients once the clinical pattern was recognised. In the remaining 5, the history of oil administration was confirmed retrospectively. Ten of the 11 mothers interviewed confirmed the administration of oil to their children. This emerged to be a nearly universal cultural practice by Zimbabweans, even in the Cape Town diaspora.

One of the 11 mothers interviewed denied a history of oil administration. She however acknowledged that she had heard of this practice from other Zimbabwean caregivers while in the hospital. Notably her child was left under the care of the child's paternal grandmother while she was at work and suspected she may have given oil.

Two children in this case series were siblings [ID-03 and ID-07]. All caregivers with more than one child also confirmed giving oil to their other children (7/10). The younger sibling to child [ID-01] was hospitalised for pneumonia at the age of 6 weeks. His mother stopped oil administration at the age of 2 months following our team's advice during the preliminary phase of this study. On a follow-up telephone call, the infant was reported to be asymptomatic at the age of 6 months, and BAL was not done. It was noted that the elder sibling to child [ID-08] also received oil and developed respiratory symptoms like his brother but died at the age of 3 months with a respiratory illness. (E-text)

Radiological characteristics

Plain chest radiographs were performed on all children. The initial radiographs taken at the hospitalisation in which a diagnostic BAL was performed showed diffuse ground glass opacification in all 12 cases. Expansile consolidation predominantly in the right upper lobe was noted in 2/12. Nine out of 12 children underwent HRCT chest and four distinct patterns were evident: 1) ground glass opacification with lower zone predominance (9/9); 2) smooth interlobular septal thickening (8/9)/ crazy-paving appearance (5/9); 3) expansile right upper lobe consolidation (2/9) and 4) fat attenuation within the areas of airspace consolidation (1/9). These patterns were present in various combinations. (Figures 1-3)

Pathological and microbiological characteristics

Twelve BAL samples and one frozen section lung biopsy [ID-6] were assessed. On gross inspection, all BAL specimens were cloudy, 11/12 being predominantly milky in nature (Figure 4). Cytohistological assessment of most specimens revealed an abundance of fat laden macrophages and large extracellular droplets on Oil Red O staining. Eight children had BAL samples with neutrophil predominant type inflammation (median neutrophil 33%, range 12-88% in those who had cytopsin done). Lung biopsy done in one patient showed evidence of chronic lymphocytic interstitial inflammation in addition to large extracellular lipid droplets on the Oil Red O stain of the frozen section. All BAL and biopsy specimens stained periodic acid Schiff negative, excluding other diagnoses such as pulmonary alveolar proteinosis. (E-table 1)

Microbiological evaluation of BAL specimens included bacterial, fungal, mycobacterial and viral studies. Only 3/12 children had negative BAL specimens on microbiology assessment; 6/9 were polymicrobial. In two children with normal immunological work up, *Mycobacterium absessus complex* was cultured from BAL, both with evidence of pulmonary disease. The first child [ID-9] presented with persistent right upper lobe consolidation and pleural effusion. This child had significant underlying comorbidity including severe GOR and silent aspiration necessitating Nissen fundoplication and gastrostomy. The second child [ID-11] presented with an expansile pneumonia of the right upper and middle lobe. In addition to BAL from multiple lobes, *M. abscessus boletti* was isolated from blood culture after 108 hours.

Treatment and outcomes

Supportive treatment provided comprised: educating caregivers to stop administering oil to their children (7/12); oxygen supplementation (11/12) (duration range 5, 71days), non-invasive ventilation including continuous positive airway pressure (8/12) (duration range 1, 27 days) and high flow nasal cannula oxygen (5/12) (duration range 3, 8 days), mechanical ventilation (1/12); antibiotics (12/12) and systemic corticosteroids (8/12). Varying corticosteroid regimens including a three-day pulse of intravenous methylprednisolone in one child, and oral prednisone in seven children administered at 1-2 mg/kg/day for 5-14 days, or longer in the cases on treatment for *M.abscessus*. All children on prolonged courses of corticosteroids also received prophylactic cotrimoxazole. Five patients underwent partial therapeutic lung lavage. Four children needed only one procedure to obtain satisfactory clinical response and one needed 3 sequential lavages over 11 weeks before achieving satisfactory clinical improvement. (Table 2)

The median hospital stay duration was 23 (IQR 6-30, range 2-117) days. Clinical resolution was documented in 10/12, with a median time to clinical resolution from presentation of 1.1 (IQR 0.6-8.0, range 0.3-14) months. To date, radiological resolution on plain radiography from presentation is only documented in two, at 19.4 months and 27.0 months respectively. In the remaining ten children, radiological resolution has not been documented at 0.8–4.4 months of follow-up. No mortalities were reported and the children continue to be followed-up in our service.

Discussion

Exogenous lipoid pneumonia in children has been widely described in the Middle East, particularly Saudi Arabia, India and South Korea, as well as Central and South America, specifically Mexico and Brazil[11-15]. To the best of our knowledge, this is the first study from Africa describing histologically confirmed ELP. Although ELP has been described in the literature to be uncommon[1, 2], our study reveals that this diagnosis may go unrecognised if a history of oil administration is not obtained in children presenting with recurrent/persistent pneumonia or ILD. Furthermore, our study highlights significant morbidity associated with ELP as reflected by severe disease observed in most cases, likely from prolonged and repeated oil aspiration.

All but one of the caregivers interviewed reported that oil administration was a universal cultural practice among Zimbabweans. Oil was administered to alleviate colic and constipation, similar to cultural and medical reasons provided from other regions[5, 6, 11, 16]. Only one caregiver denied a history of oil administration. Gupta *et al* reported that up to 18% of caregivers of children with ELP denied administration of oil to their children[17]. ELP should therefore not be immediately excluded if caregivers deny oil administration at initial presentation. Although all the children in this series were of Zimbabwean heritage, our qualitative research findings suggest that oil administration to children occurs among various local South African cultures, and we could have missed out on these children.

From a clinical perspective, distinct CT and BAL patterns were identified that are similar to pulmonary alveolar proteinosis (PAP). The macroscopic milky appearance of BAL and

finding of extracellular alveolar lipid is key to the diagnosis of ELP. Similar to previous literature, diffuse ground glass opacification predominantly in the posterior segments, and interlobular thickening were common patterns on chest CT in children with ELP. Fatty attenuation within consolidation has also been described in children with ELP, however we only observed this pattern in one child in our series[15, 18, 19]. Interestingly, a unique pattern of a dense expansile right upper lobe consolidation was noted in two children with confirmed *M. abscessus* disease. This radiological presentation has not been typically described in children with ELP or comorbid nontuberculous mycobacteria (NTM) infection[13, 20]. We postulate that this expansile pattern possibly reflects a severe form of a lung oleoma/paraffinoma described as a localized lipoid pneumonia due to exogenous lipid in the alveoli, characteristically seen in adults[18, 21]

To the best of our knowledge *M. abscessus* co-infection has not previously been reported in children with ELP. Other NTMs described in children with ELP include *M. fortuitum, M. chelonei* and *M. smegmatis*[11, 20, 22-24]. *M. abscessus complex* has been previously described in adult patients with ELP[25-27]. In a Japanese study in which *M. abscessus* was identified in the sputum sample of an adult with ELP, the NTM was additionally identified in the mineral oil the patient was ingesting[26]. Several authors have postulated that oil increases the pathogenicity of mycobacteria possibly by hindering macrophage function and phagocytosis[3, 28]. In an animal experiment, Kudoh et al. demonstrated that there was increased virulence of NTM when inoculated in oil in comparison to aqueous solutions[29]. Similarly, the lipid environment in the lung may be responsible for other secondary infections detected in BAL cultures among children with ELP[7, 30], also seen

in this series. Our study suggests that NTM infections in children with ELP are not uncommon in our context. Health workers should be vigilant for NTM co-infection in children with ELP and conversely, consider ELP in children presenting with NTM infections.

Discontinuing oil, treating infections, identifying underlying risk factors and overall supportive care in line with consensus reviews, [1, 2, 15, 18] was instituted for children in this study. Furthermore, we report success in utilising corticosteroids and partial therapeutic lung lavage as additional treatment strategies for ELP. Therapeutic lung lavage is frequently employed in the treatment of PAP with the aim of reducing alveolar deposits, a mechanism of action that would be comparable in ELP and is therefore biologically plausible. Similar to previously reported studies of ELP in children in Brazil[15, 31], all children who underwent partial therapeutic lavage in our study showed clinical improvement, however radiological resolution was delayed. Data to establish the effectiveness of corticosteroids and therapeutic lavage for ELP are limited[1, 2].

We set out to describe a case series of children with histologically confirmed ELP, with no intention of proving association or determining causation. Incomplete data and recall bias are potential limitations inherent to our study design. Although aspiration risk was identified in two cases, it remains unclear why not all children exposed to repeated oil ingestion develop ELP. Notwithstanding these limitations, we believe the strengths of this study lie in the multi-method approach to highlighting and understanding the clinical-

radiological-pathological characteristics and oil administration practices associated with ELP in our context.

In conclusion, our case series highlights that ELP masquerading as persistent pneumonia or PAP, is an uncommon but serious condition in our context and may occur anywhere in the world where similar cultural practices are common. Obtaining a history of oil administration from caregivers, chest radiography and cytological analysis of BAL are sufficient to make the diagnosis of ELP. NTM co-infection should be excluded in children with suspected ELP. Health education messages to highlight the risks associated with the cultural practice of oil administration are needed.

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References

1. Hadda V, Khilnani GC. Lipoid pneumonia: an overview. Expert Rev Respir Med. 2010;4(6):799-807.

2. Salgado IA, Santos CC, Salgado JV, Ferraz PC, Haidar DM, Pereira HA. Exogenous lipoid pneumonia in children: a disease to be reminded of. Rev Assoc Med Bras (1992). 2012;58(2):135-7.

3. Laughlen GF. Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil. Am J Pathol. 1925;1(4):407-14.1.

4. Mirghani Z, Zein T, Annoble S, Winter J, Mostafa R. Analysis of fatty acids in ghee and olive oil and their probable causal effect in lipoid pneumonia. J Med Biochem. 2011;30(2):141-7.

5. Bandla HP, Davis SH, Hopkins NE. Lipoid pneumonia: a silent complication of mineral oil aspiration. Pediatrics. 1999;103(2):E19.

6. Zanetti G, Marchiori E, Gasparetto TD, Escuissato DL, Soares Souza A, Jr. Lipoid pneumonia in children following aspiration of mineral oil used in the treatment of constipation: high-resolution CT findings in 17 patients. Pediatr Radiol. 2007;37(11):1135-9.

7. Hoffman LR, Yen EH, Kanne JP, Effmann EL, Gibson RL, Van Niel CW. Lipoid pneumonia due to Mexican folk remedies: cultural barriers to diagnosis. Arch Pediatr Adolesc Med. 2005;159(11):1043-8.

8. Sias SMA, Ferreira AS, Daltro PA, Caetano RL, Moreira JS, Quirico-Santos T. Evolution of exogenous lipoid pneumonia in children: Clinical aspects, radiological aspects and the role of bronchoalveolar lavage. J Bras Pneumol. 2009;35(9):839-45.

9. Griese M, Seidl E, Hengst M, et al. 2018. International management platform for children's interstitial lung disease (chILD-EU). Thorax 73(3):231–239.

10. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2015; 26(13):1753-60.

11. Annobil SH, Benjamin B, Kameswaran M, Khan AR. Lipoid pneumonia in children following aspiration of animal fat (ghee). Ann Trop Paediatr. 1991;11(1):87-94.

12. Balakrishnan S. Lipoid pneumonia in infants and children in South India. BMJ. 1973;4(5888):329-31.

13. Lee JY, Lee KS, Kim TS, Yoon HK, Han BK, Han J, et al. Squalene-induced extrinsic lipoid pneumonia: serial radiologic findings in nine patients. J Comput Assist Tomogr. 1999;23(5):730-5.

14. Furuya ME, Martinez I, Zuniga-Vasquez G, Hernandez-Contreras I. Lipoid pneumonia in children: clinical and imagenological manifestations. Arch Med Res. 2000;31(1):42-7.

15. Sias SM, Daltro PA, Marchiori E, Ferreira AS, Caetano RL, Silva CS, et al. Clinic and radiological improvement of lipoid pneumonia with multiple bronchoalveolar lavages. Pediatr Pulmonol. 2009;44(4):309-15.

16. Midulla F, Strappini PM, Ascoli V, Villa MP, Indinnimeo L, Falasca C, et al. Bronchoalveolar lavage cell analysis in a child with chronic lipid pneumonia. Eur Respir J. 1998;11(1):239-42.

17. Gupta M, Chowdhury MSA. A common practice of traditional medication with oil and/or ghee, as folk medicine in children of Southern Saudi Arabia. Saudi Med J. 1992;13(2):106-8.

18. Marchiori E, Zanetti G, Mano CM, Irion KL, Daltro PA, Hochhegger B. Lipoid pneumonia in 53 patients after aspiration of mineral oil: comparison of high-resolution computed tomography findings in adults and children. J Comput Assist Tomogr. 2010;34(1):9-12.

19. Betancourt SL, Martinez-Jimenez S, Rossi SE, Truong MT, Carrillo J, Erasmus JJ. Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol. 2010;194(1):103-9.

20. Ridaura-Sanz C, Lopez-Corella E, Salazar-Flores M. Exogenous lipoid pneumonia superinfected with acid-fast bacilli in infants: a report of nine cases. Fetal Pediatr Pathol. 2006;25(2):107-17.

21. Borrie J, Gwynne JF. Paraffinoma of lung: lipoid pneumonia. Report of two cases. Thorax. 1973;28(2):214-21.

22. Verghese S, Ramesh S, Pararmasivan CN, Kubendiran G, Vijayasekaran D. Mycobacterium fortuitum infection complicating lipoid pneumonia. Indian J Prac Pediatr. 2007;9(4):326-8.

23. Sharma D, Hilinski JA. Refractory pneumonia in a Mexican American infant. Clin Pediatr. 2010;49(7):710-2.

24. Cox EG, Heil SA, Kleiman MB. Lipoid pneumonia and Mycobacterium smegmatis. Pediatr Infect Dis J. 1994;13(5):414-5.

25. Kobayashi T, Tsuyuguchi K, Yoshida S, Kurahara Y, Tsuji T, Nakao K, et al. A case of Mycobacterium abscessus subsp. massiliense lung disease complicated by lipoid pneumonia. Int J Tuberc Lung Dis. 2017;21(1):124-6.

26. Matsunaga S, Kurashima A, Nagai H, Akagawa S, Machida K, Yotsumoto H, et al. [A Mycobacterium abscessus infection complicated with lipoid pneumonia]. Nihon Saikingaku Zasshi. 2003;41(1):14-8.

27. Tranovich VL, Buesching WJ, Becker WJ. Pathologic quiz case. Chronic pneumonia after gastrectomy. Pathologic diagnosis: chronic aspiration lipoid pneumonia with Mycobacterium abscessus. Arch Pathol Lab Med. 2001;125(7):976-8.

28. Hutchins GM, Boitnott JK. Atypical mycobacterial infection complicating mineral oil pneumonia. JAMA. 1978;240(6):539-41.

29. Kudoh S. [The virulence of saprophytic acid-fast bacteria coated with oil or fat, with special reference to an observation on the so-called atypical acid-fast bacteria. 1. Experiments with guinea-pigs on intrapulmonal and subcutaneous inoculation of saprophytic bacteria coated with liquid paraffin]. Nihon Saikingaku Zasshi. 1962;17:154-61.

30. Lu G, Xie Y, Huang L, Tong Z, Xie Z, Yu J, et al. Study of Acute Exogenous Lipoid Pneumonia. Indian J Pediatr. 2016;83(8):787-91.

31. Azevedo Sias S, Oliveira Caetano R, Dutra Comarella J, de Oliveira E, Santos Ferreira A, Quirico-Santos T. Successful treatment of lipoid pneumonia associated with bowel obstruction by Ascaris lumbricoides. J Trop Pediatr. 2011;57(4):269-73.

FIGURES

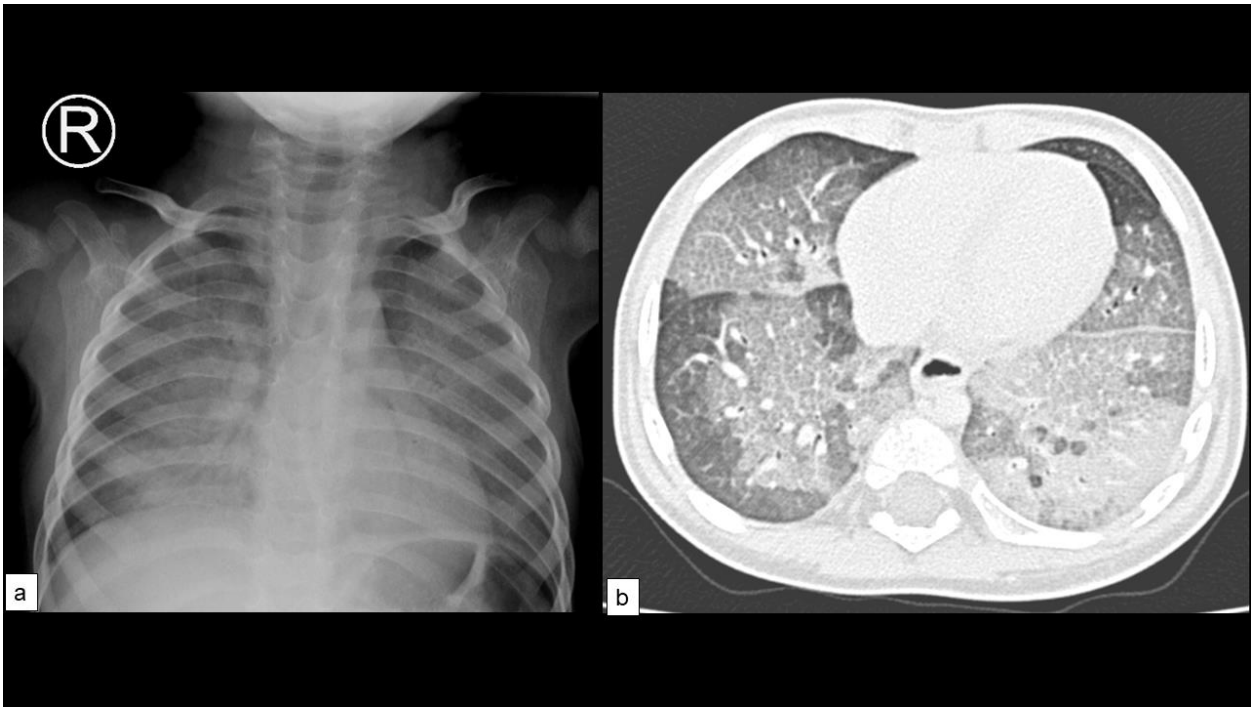

Figure 1 (a): Frontal Chest Radiograph: Widespread bilateral ground-glass attenuation with more confluent right middle and right lower lobe consolidation. Note the apico-basal distribution of airspace disease and the prominent right basal air-bronchograms.

Figure 1 (b): High Resolution CT Chest: Widespread areas of ground-glass opacification demonstrate smooth interlobular septal thickening resulting in the so called appearance of “crazy paving”. Note the predominant posterior and basal predilection with areas of geographic sparing.

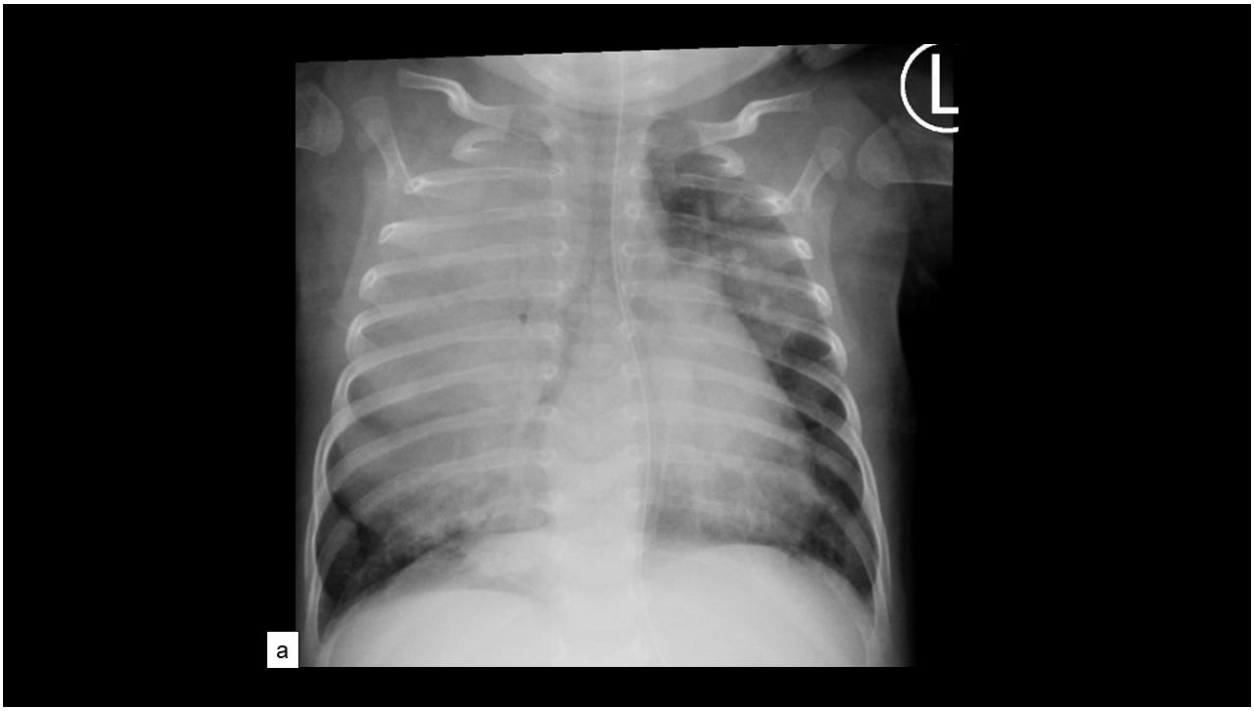

Figure 2 (a): Frontal Chest Radiograph: Confluent expansile consolidation of the right upper and right mid zone with further patchy left upper lobe airspace disease. Note the background air trapping without any large airway attenuation.

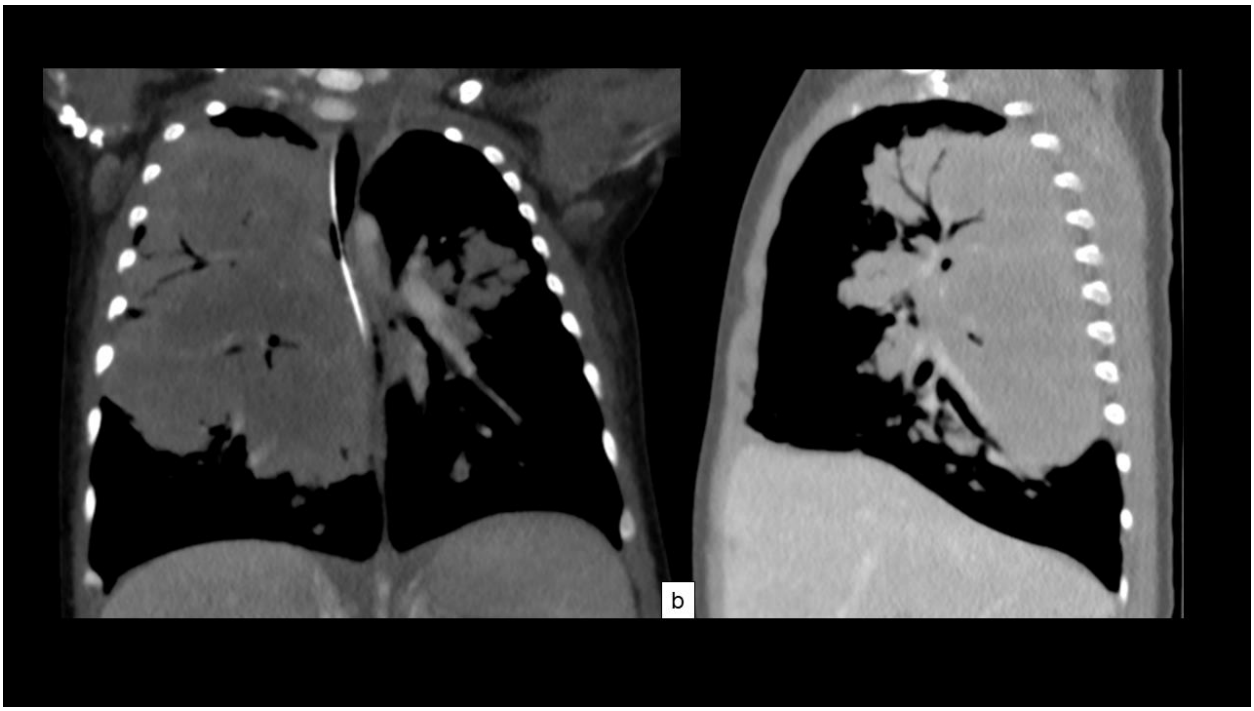

Figure 2 (b): CT Chest (mediastinal settings): Expansile consolidation involving the posterior segment of the right upper lobe and the superior segment of the right lower lobe. Note the areas of low attenuation within the areas of consolidation that signify parenchymal liquefaction. This patient had *M. abscessus* cultured from BAL and blood.

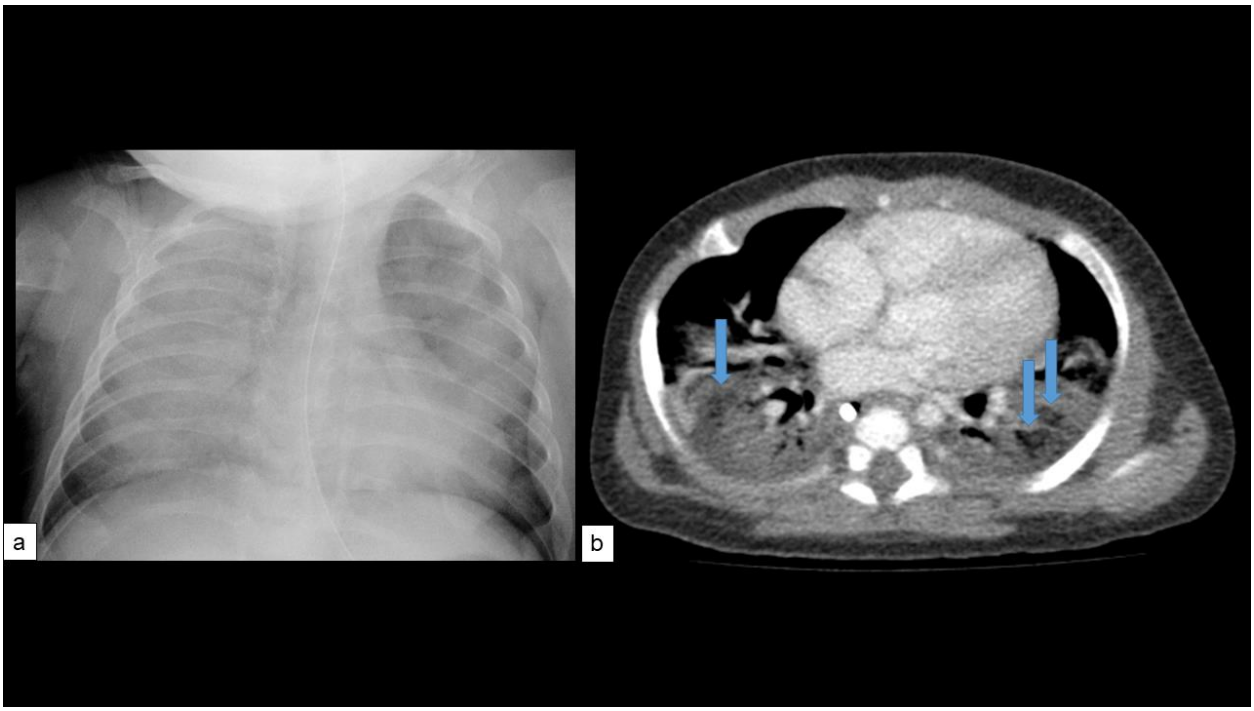

Figure 3(a): Frontal Chest Radiograph: Extensive, bilateral ground-glass opacification with relative sparing of the peripheries and lung bases.

Figure 3(b): High Resolution CT Chest (mediastinal settings): Posterior airspace opacification with interspersed areas of low attenuation that registers Hounsfield values consistent with that of fat (blue arrows).

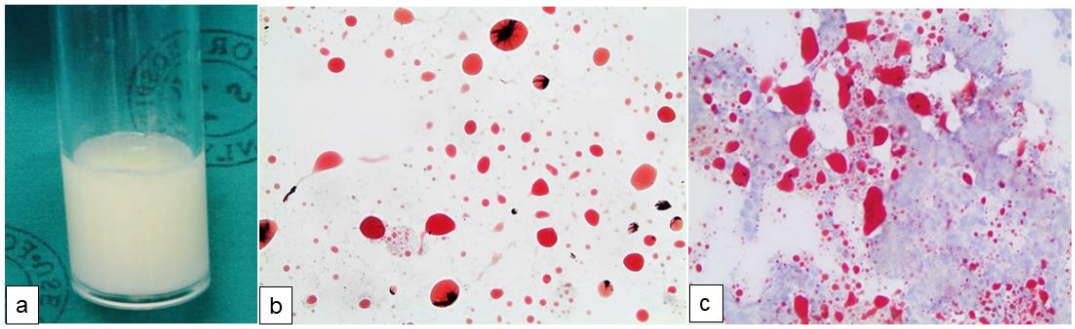

Figure 4 (a): Bronchoalveolar specimen macroscopic appearance: Milky-oily.

Figure 4 (b): Bronchoalveolar specimen microscopy: Oil Red O staining showing mainly large extracellular lipid droplets with isolated macrophages.

Figure 4 (c): Frozen section lung biopsy microscopy: Oil Red O staining showing large lipid droplets within the alveolar space.

480 **Table 1: Demographic, clinical and oil exposure characteristics**

Patient ID	Gender	Age diagnosis (months)	Type of oil	Duration; onset; amount and frequency oil administered	Underlying comorbidity and risks for aspiration	Clinical presentation	Duration of symptoms (weeks)	Co-infections on NPA and/or BAL[†]
01[β]	Male	6.1	Sunflower oil	12 months; from day 2 of life; 2.5ml orally twice daily	GOR[θ], no aspiration[ϵ]	Cough, tachypnea, hypoxia	0.9	Parainfluenza
02[μ]	Female	9.8	Not available	Not available	None[γ]	Cough, fever, tachypnea, hypoxia	12.0	None
03[§β]	Male	7.5	Olive oil	14 days; from the age of 6 months; 2.5ml orally once daily	None[γ]	Tachypnea, hypoxia	4.0	Enterovirus[†], Human Rhinovirus
04[πσ]	Male	1.4	Mother denied giving oil	Not known	Resolved renal disease[¥]	Cough, tachypnea, hypoxia,	0.3	Klebsiella pneumoniae[†], Human Rhinovirus

				Child under the care of grandmother Unconfirmed suspicion that grandmother gave oil	None[ɣ]	3 prior LRTI hospitalisations		
05[α]	Male	6.2	Plant-based 'cooking' oil[**]	5 months; from day 1 of life; 5ml orally twice daily	*Refused to drink oil	Cough, wheeze, crepitations, 2 prior LRTI hospitalisations	0.4	Adenovirus[†], RSV-B[†], Enterovirus[†]
06[α]	Male	1.9	Sunflower oil changed to liquid paraffin	1.6 months; from week 1 of life; 5ml orally thrice daily	No GOR[θ] No aspiration[δ] *Coughed and choked after getting oil	Cough, tachypnea, hypoxia, digital clubbing, air trapping	4.3	Human Metapneumovirus

07[§β]	Male	10.8	Olive oil	14 days; from age of 6 months; 2.5ml orally twice daily	Failure to thrive No GOR[θ] *Coughed and choked after getting oil, fed oil while lying flat	Cough, tachypnea, hypoxia, digital clubbing	1.0	Parainfluenza 2 and 4[†], Streptococcus pneumoniae[†], Moraxella catarrhalis[†], Adenovirus, Human Bocavirus, Enterovirus, RSV-B
08[πσ]	Male	4.3	Plant-based 'fish' oil[***]	Exact details not known Child under the care of grandmother	None[γ] No aspiration[ϵ]	Cough, tachypnea, hypoxia, crepitations	0.7	Proteus mirabilis[†], Human Rhinovirus[†], RSV-B[†], PCP oocysts[†], Human Bocavirus, Coronavirus NL63
09[βλ]	Male	3.7	Sunflower oil	3 months; from age 2 months; 2.5ml orally thrice daily	GOR[θ], silent aspiration[δ], renal disease[φ],	Cough, fever, tachypnea, crepitations, bronchial breath sounds,	0.6	M. abscessus[†], Klebsiella pneumoniae[†], Acinetobacter baumannii[†], Human

					haemo-dynamically insignificant 3mm ASD	1 prior LRTI hospitalization		Rhinovirus, Human Bocavirus
10[α]	Male	2.1	Sunflower oil	2 months; from day 6 of life; 5ml orally twice daily	GOR[θ], silent aspiration[δ]	Cough, tachypnea, hypoxia, 1 prior LRTI hospitalization	0.1	None
11[π]	Male	2.6	Olive oil	1.6 months; from age of 4 weeks; 2.5ml orally once daily	No GOR[θ], no aspiration[δ] *Coughed and cried after getting oil	Cough, fever, tachypnea, hypoxia, reduced air entry on the right	1.4	M.abscessus[†], Pseudomonas aeruginosa[†], Candida species[†]
12 [π]	Male	3.1	Plant-based 'cooking' oil[**]	2.1 months; from age	None[γ] *Coughed and cried	Cough, fever, tachypnea, air trapping, crepitations,	0.4	RSV-A[†], Klebsiella pneumoniae[†], Bordetella Pertussis

					after getting oil	1 prior LRTI hospitalization		

BAL, bronchoalveolar lavage; GOR, gastroesophageal reflux; LRTI, lower respiratory tract infection

[θ]Milk scan performed

[δ]Contrast swallow performed

[ϵ]Swallowing assessed by speech therapist

[γ]Only clinical history at BAL diagnosis

[*]Risk factor history from caregiver qualitative interview

[**]Plant-based oil including blends of soya bean oil, sunflower oil, canola oil, or unspecified

[***]'Fish' oil is not oil from fish but rather a plant-based oil used for frying fish among other foods

[†]Infection present in the BAL

[μ]Unable to reach patient on phone or in the community

[σ]Child was left under the care of the grandmother

[ρ]Retrospective diagnosis of ELP, child given oil for an additional 6 months

[§]Siblings within the case series

[α]Has sibling/s who also received oil but did not experience respiratory-related complications

[β]Has sibling/s who also received oil and experienced respiratory-related complications

[λ]Sibling death during infancy related to a similar respiratory illness

[π]Has no siblings

¥Posterior urethral valves (PUVs) ablated and bladder neck surgically excised

φDysplastic right kidney with cysts, enlarged left kidney with hydronephrosis, no PUVs, normal renal function

518 **Table 2: Treatment and outcomes**

ID	Oxygen (days)	NIV/ MV (days)	Antibiotics (days)	Steroid use (days)	Therapeutic lavage (number) [number of days post-admission]	Total days hospitalised in the diagnostic BAL admission	Time to clinical resolution (months)
01	23	CPAP (2)	Yes (7)	Prednisone at 2mg/kg/day (7)	Yes (1) [21]	24	8.0
02	7	None	Yes (11)	None	None	13	0.3
03	16	None	Yes (15)	None	None	2	0.5
04	23	CPAP (6) HFNC (4)	Yes (14)	Prednisone at 1mg/kg/day (14)	None	25	12.0
05	0	None	No	None	None	2	14.0
06	15	IPPV (1) CPAP (1) HFNC (8)	Yes (14)	Methylprednisone at 10mg/kg/day (3)	None	22	0.6
07	5	None	Yes (7)	Prednisone at 1mg/kg/day (5)	None	6	1.2

08	27	CPAP (23)	Yes (26)	Dexamethasone stat; Prednisone at 2mg/kg/day (21)	Yes (1) [19]	30	1.0
09	71	CPAP (27) HFNC (8)	Yes (ongoing) M.abscessus treatment [§]	Prednisone commenced at 2mg/kg/day (94)	Yes (3) [38; 56; 86]	98	3.2
10	16	CPAP (2)	Yes (5)	Prednisone at 2mg/kg/day (7)	Yes (1) [22]	23	0.8
11	52	CPAP (16) HFNC (7)	Yes (ongoing) M.abscessus treatment[¥]	Prednisone commenced at 2mg/kg/day, tapered (ongoing)	Yes (1) [52]	117	3.9
12	12	CPAP (3) HFNC (3)	Yes (5)	None	None	23	0.8

519 NIV, non-invasive ventilation; MV, mechanical ventilation; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannulae; IPPV, intermittent
520 positive pressure ventilation
521 [§]Nebulized Amikacin (underlying renal disease), Intravenous Imipinem, Linezolid and Ciprofloxacin) and oral Azithromycin for 1 month. Then discharged on oral
522 Linezolid, Ciprofloxacin and Azithromycin. 1-month follow-up BAL was negative on mycobacterial culture.

¥Intravenous Imipinem and Amikacin and oral Linezolid, Levofloxacin and Azithromycin for 1 month. 1-month follow-up BAL including mycobacterial culture still positive.

543 **E-table 1: Radiological and pathological findings**

Patient ID	Chest radiograph	CT chest	BAL macroscopic appearance	BAL/Biopsy microscopic
01	Bilateral ground glass opacification, predominantly on the right. Lobar distribution more confluent in the RUL, RLL, LLL and lingula with air bronchograms. Air trapping.	Not done	Milky	Numerous macrophages, scattered lymphocytes and neutrophils. 70% lipid laden macrophages with abundant extracellular lipid. No free lying PAS material. Surfactant A and B present on immunohistochemistry. Possible lipid like material present on electron microscopy.
02	Diffuse ground glass opacification confluent in the RUL. Bilateral patchy consolidation in all lobes predominantly on the right with peripheral sparing.	Not done	Cloudy	Numerous macrophages, scattered lymphocytes and neutrophils. >50% lipid laden macrophages with abundant extracellular lipid. Negative PAS.
03	Diffuse airspace opacification, parahilar and non-segmental RUL, LUL, RML and lingula.	Homogenous ground glass opacification. Airspace consolidation in a perihilar distribution. Interlobular septal	Cloudy	Numerous macrophages, scattered lymphocytes and neutrophils. Abundant lipid laden macrophages and extracellular lipid.

		thickening with characteristic crazy paving pattern.		[Cell count: neutrophils 66%, lymphocytes 16%, monocytes 14%, eosinophils 4%]
04	Diffuse airspace opacification predominantly of the right lung.	Ground glass opacification. Confluent consolidation involving RUL with sparing of the posterobasal and anterior segment of the RLL. Characteristic crazy paving pattern secondary to interlobular septal thickening in both lower lobes.	Cloudy	Numerous macrophages, scattered lymphocytes and neutrophils. Abundant lipid laden macrophages and extracellular lipid. PAS negative. Normal lamella bodies and focal lipid droplets on electron microscopy. Squamous metaplasia suggestive of viral infection. [Cell count: neutrophils 31%, lymphocytes 18%, monocytes 48%, eosinophils 1%, mesothelial cells 2%]
05	Diffuse ground glass opacification more confluent in the RUL, RML, left parahilar segmental LUL and lingula, and patchy in the lower lobes bilaterally.	Diffuse ground glass opacification and airspace consolidation of both lower lobes particularly RLL. Interlobular septal thickening and crazy paving. Increased perihilar and mediastinal soft	Milky	Numerous macrophages, scattered lymphocytes and neutrophils with abundant lipid laden macrophages and extracellular lipid. PAS negative.

		tissue suggestive of lymphadenopathy.		
06	Diffuse ground glass opacification with a right sided predominance and confluent in the right upper lobe.	Diffuse ground glass opacification with a lower zone predominance. Mild interlobular septal thickening.	Cloudy Frozen tissue biopsies taken of the RML and RLL.	Numerous macrophages, scattered lymphocytes and neutrophils. 50% lipid laden macrophages with abundant extracellular lipid. Negative PAS. Abundant lipid laden macrophages and extracellular lipid. Negative PAS. Absent iron laden macrophages. Mild lymphocytic interstitial inflammation. No fibrosis. Normal lamellar bodies and lipid droplets present on electron microscopy.
07	Diffuse homogenous ground glass opacification in both right and left lung fields with dense airspace opacification.	Predominant central, basal and posterior involvement, distinct sparing of the peripheral lung zones with geographical pattern	Purulent (“thick yellow”) BAL fluid	Numerous vacuolated macrophages and neutrophils, scattered lymphocytes. Abundant lipid laden macrophages and extracellular lipid. PAS negative. Scattered bacterial cocci.

		involvement (interlobular septal thickening and crazy paving).		[Cell count: neutrophils 88%, lymphocytes 3%, monocytes 9%]
08	Diffuse homogenous ground glass opacification predominantly on the right, slightly sparing part of the left lower lobe. Bilateral air bronchograms.	Dense consolidation with air bronchograms in the posterior segments of the upper and lower lobes bilaterally with some sparing of the anterior segments both basally and upper lobes. Areas of ground glass opacification in non-consolidated areas of the lung. Focal areas measuring fat density (-7 to 20HU) within the consolidated lung. Minimal interlobular septal thickening.	Milky BAL.	Moderate macrophages and neutrophils, scattered lymphocytes. Abundant lipid laden macrophages and extracellular lipid. PAS negative. Scattered fungal spores and pseudohyphae compatible with candida. [Cell count: neutrophils 50%, lymphocytes 36%, monocytes 14%]
09	Confluent airspace opacification of the RUL, RML and LLL.	Mass like opacification within the posterior segment of the RUL that demonstrates mild	Milky BAL	Abundant macrophages, scattered lymphocytes and no neutrophils. Abundant

		satellite nodularity. Homogenous ground glass opacification predominantly in the posterior segments. Mild smooth interlobular septal thickening.		lipid laden macrophages and extracellular lipid. Numerous acid-fast bacilli. Candida. [Cell count: neutrophils 12%, lymphocytes 31%, monocytes 57%]
10	Diffuse ground glass opacification, predominantly of the right lung - confluent and dense. Patchy lingula airspace opacification.	Diffuse bilateral ground glass opacification with lower zone predominance. More pronounced on the right, with confluent right posterior subpleural airspace consolidation. Interlobular septal thickening and crazy paving pattern.	Milky BAL	Abundant macrophages, admixed lymphocytes and neutrophils. Abundant foamy lipid laden macrophages and diffuse extracellular lipid. Mixed commensal bacteria. [Cell count: neutrophils 33%, lymphocytes 17%, monocytes 50%, eosinophils 0%]
11	Lobulated density occupies entire right hemithorax sparing the right costophrenic angle, a confluent expansile consolidation. Patchy	Bilateral pneumonia (airspace opacification) with significant expansile component of the right. Multiple nodules. RML	Cloudy and clear BALs	Abundant lipid laden macrophages >50%. Candida and numerous acid-fast bacilli. 20% lipid laden macrophages and extracellular lipid present in second sample.

	airspace opacification of the LUL and lingula. Hyperinflated lungs.	atelectasis. No air trapping. Small sub-centimeter enhancing paratracheal, precarinal, subcarinal and bilateral axillary lymphadenopathy.		[Cell count: neutrophils 24%, lymphocytes 8%, monocytes 70%, eosinophils 0%]
12	Diffuse ground glass opacification bilaterally predominantly RUL and RML.	None	Milky BAL	Abundant foamy macrophages and scattered lymphocytes. Absent neutrophils and eosinophils. Diffuse lipid laden macrophages and abundant extracellular lipid. PAS negative. Mixed commensal bacteria. [Cell count: neutrophils 33%, lymphocytes 17%, monocytes 50%, eosinophils 0%]

544

545 RUL – right upper lobe; RML – right middle lobe; RLL – right lower lobe; LUL – left upper lobe; LLL – left lower lobe

546
547

E-text: Additional information on qualitative methodology and results

Research team and reflexivity

The lead researcher, a Kenyan paediatrician with formal training and experience in qualitative research, currently training as a pulmonology fellow, may or may not have established a relationship with participants prior to commencement of the qualitative phase of the case series. The research team also comprised senior researchers with extensive experience in the fields of paediatric pulmonology, radiology and pathology.

Data collection process

Caregivers listed were called using phone numbers provided in their hospital records and invited to the qualitative phase of the study that was conducted telephonically or in person based on patient preference. Verbal or written informed consent was obtained from caregivers who agreed to participate in the study. Caregivers whose phone numbers were unreachable were tracked in the community by a social worker using their contact address and details provided in hospital records. Caregivers who declined telephonic invitation, or did not provide verbal informed consent, were excluded from the qualitative phase of the study and we only included their documented retrospective data. Employing qualitative interviewing skills using open ended questions outlined in the interview guide, D.M. obtained recall data of practices including oil use if any, type(s), age(s) at onset of use, route of administration, frequency, duration, reasons for oil use, underlying illnesses/concerns, and the current health status of eligible study participants from their caregivers. (I: Interview Guide)

In this study we sought to gain an in-depth understanding of oil administration practices from the perspective of individual caregiver level and thus our choice of individual interviews. Methodologically, this approach is powered for information as the topic is of a narrow scope, it is backed by an established theoretical background, the participants held characteristics that are highly specific for the study aim, we designed our interview guide to enable a focused interview dialogue, and our chosen analytic strategy was heading for an in-depth analysis of narratives [10]. All possible caregivers of children with an ascertained outcome who could be reached and provided informed telephonic consent were interviewed and provided sufficient variations. An empathetic approach was employed during the conduct of all interviews being cognisant of not attributing any blame to the caregivers of study participants. A log of socio-demographic characteristics of non- participants was kept to determine how they differed from participants. Data obtained from participants in the qualitative phase of the study were audio recorded and the researcher concurrently took notes. All interviews were conducted in a private room, without taking names of the caregivers to maintain privacy and confidentiality. For non-English speaking/non-English fluent caregivers, the services of a trained interpreter were enlisted to ensure potential participants understood the interview.

Analyses

Qualitative data around oil practices associated with ELP in children were manually coded solely by D.M. following transcription of the audio-recorded interviews. These data were reduced and analyzed into summaries that were reconstructed and synthesized into themes and managed using ATLAS.ti software.

I: Interview Guide

Date of Interview	Participant Enrollment ID
dd mmm yyyy	

Section 1: ***How is your child doing today?***

[Only use as probes, allow for detailed caregiver description]

Cough? □ No □ Yes …. Duration _____ (days)

Hotness of body? □ No □ Yes …. Duration _____ (days)

Fast breathing? □ No □ Yes …. Duration _____ (days)

Other (specify) _____

Section 2: ***Tell me, have you ever used any oil for your child?***

[Only use as probes, allow for detailed caregiver description]

□ No □ Yes (specify) _____

Type(s) of oil? □ No □ Yes *(tick all that apply)*

Mineral □ No □ Yes (specify) _____

Vegetable □ No □ Yes (specify) _____

Animal □ No □ Yes (specify) _____

Age at onset of use? ___ **Years** ___ **Months**

Route of administration? □ Nose □ Mouth □ Topical □ Other

_____

Amount? ___ **Milliliters (Ml)** and Frequency? ___ **Hourly**

Total Amount Daily? ___ **Ml**

Duration? |__|__| **Days** |__|__| **Months** |__|__| **Years**

WHY? Reasons for oil use/Past illnesses/concerns at the time of oil use:

□ Constipation (specify) _____ □ Colic (specify)

_____

□ Nasal stuffiness (specify) _____ □ Religion (specify) _____

□ Culture (specify) _____ □ Other (specify)_____

Section 3: ***Does your child have any problems swallowing? Does your child have any other condition/problems?***

[Only use as probes, allow for detailed caregiver description]

Co-morbidities:

Any underlying swallowing problem? □ No □ Yes (specify)_____

□ Other (specify) _____

Section 4: ***Tell me, are you using any oil for your child at the moment?***

[Only use as probes, allow for detailed caregiver description]

□ Yes (why)_____ □ No

When did you stop? |__|__| |__|__|__| |__|__|__|__|

dd mmm yyyy

Why did you stop?

□ The doctor told me □ It was making my child sick

□ Other (specify) _____

Section 5: ***Do you have other children? How old are they now? Did they have any respiratory problems (at what age, what problem, any hospital admissions)? Did you ever give them oil (age of onset, route, type, amount,***

frequency, duration, reason)? *[Only use as probes, allow for detailed caregiver description]*	
	□ No □ Yes (How many?) ☐☐ How old? Any respiratory problems? Did you give them oil? 1. ☐☐ □ No □ Yes (specify) _____ ; □ No □ Yes (specify) _____ 2. ☐☐ □ No □ Yes (specify) _____ ; □ No □ Yes (specify) _____ 3. ☐☐ □ No □ Yes (specify) _____ ; □ No □ Yes (specify) _____ 4. ☐☐ □ No □ Yes (specify) _____ ; □ No □ Yes (specify) _____ 5. ☐☐ □ No □ Yes (specify) _____ ; □ No □ Yes (specify) _____
Section 6: ***Do you know other people who use oils? Who? How? Why?*** *[Only use as probes, allow for detailed caregiver description]*	
	□ Family members (specify e.g. mother, sister, aunty, cousin, niece etc.) _____ □ Community members (specify e.g. friends, neighbors, religious circles, general etc.) _____ How? _____ Why? _____

II: Emergent themes and selected quotes

A. Oil administration is a nearly universal cultural practice

ID-11: “Almost every single Zimbabwean (uses oil). Every Zimbabwean, because that is what they say. Even when he was coughing and I decided to bring him to hospital and they were like, ‘No, just keep giving him the oil’ for the wind. In Cape Town, Johannesburg, everywhere (Zimbabweans everywhere use oil). Noo… (I wouldn’t say it is religious). I don’t know (why one child will get a teaspoon and another a tablespoon). (They told me) Teaspoon, yes. Once a day. Sometimes three times but I preferred once a day. Because I thought he would get a lot of fat. People just use any oil, but I decided to use olive oil. I don’t know, because it is natural I think.”

ID-12: “All the Zimbabweans use oil. If you don’t use mti, you will use oil. (Mti) that cultural herbs. Yea, so if you don’t use that cultural herbs then you use cooking oil. You must use only one because if you use herbs then it is fine. The only problem when you use herbs, if you meet, another baby with herbs they fight. Those herbs fight each other. That is why we don’t want to use herbs because if yours get weak then he gonna pass or something is gonna happen. (They get mti) even from sangoma or like our grandfather and grandmother or they know where to get those mti because it is just roots or leaves of the trees. (I chose to give oil) because where I am going to church they don’t use mti. Yes but sometimes you can buy…, like here there is colic oil, there is different, lots of…, but me I just try one from ‘Pharmacy X’ then I stop it because when I use that one the baby doesn’t sleep. It is not a type of oil, it is like water. In Zimbabwe it is like culture that if you don’t use mti, you use oil but most of the people are using oil. They (People from Zimbabwe) are also religious but some of them are scared to use mti. Like me I am also scared to use mti. You gonnna get the wrong one then baby gonna pass away. You don’t know this is the right one or this is the… When I get out of the hospital (after delivery). Yes (I started giving oil). The oil is like for the wind and for the head for the…. *‘Nava’* (anterior fontanelle). They said if you give cooking oil like my baby’s.. it was too big.. so they said you must give cooking oil and it is gonna come back to normal and for the wind. Even if you give him that, number two is gonna come out nicely.”

ID-10: “Yea, it is true we used to do that because our elders they teach me, they teach us already so I believe in them because they did years ago, you see. So now we are calling it our tradition for everyone. Yea, they use oil. Even now they are going to force me at home; you can use it. If I am complaining to them my child is struggling to push *‘kaka’* (stool) they say, ‘You must give the child oil.’. But from now, no I cannot. It is not a force, but if I complain to them, they are going to say, ‘How is the boy? I am going to tell them, ‘He is struggling to do this and do this.’ Already they will say, ‘You must give the boy oil’. I cannot do that again. You know I love my boy. I am going to lie to them I am giving him to shut them out, that is all.

ID-03: “Yes (I have ever used oil). Olive oil. We started at six months. One teaspoon for each day for two weeks. Then I stopped. Because in our culture every newborn child we used to give cooking oil to clean the stomach… when the baby has a problem with the stomach we would give oil to help…. She was suffering from constipation, yea. If she wants to make a pupu, she can make a hard pupu, so suffering to have a pupu, so they say we can help like that. We just gave it for two weeks then I stopped. (I stopped because) She was okay. So everyone in my culture they give children oil. they just…, I don’t know how they give it but maybe a teaspoon maybe two times a day, I don’t know but they give oil. If you get a child you have to give the child oil. It will help in cleaning the stomach. We just boil it and then make it warm and then you give the child. Other people they would just add a little bit of salt, others just give plain like that.”

B. One caregiver reports no history of oil administration

ID-04: “No, for us no, we don’t use oil at all… I do see some of them (other Zimbabweans) but I don’t know what it is for. I saw them in Red Cross but I don’t know, if you are mixed up more than from your country. So I don’t know when, the age and in which form, I don’t know.”

C. Force feeding as a possible risk factor

ID-05: Yes (I have ever used oil). Cooking oil. The one we use to cook. (I started) the day I gave birth. The following day when I was at home after I was discharged from hospital when I went home I started to give him. I put the oil in a pot dish then I put little salt then I boil. I put it on the stove then it boils, then I put somewhere it gets cold then I sometimes give him three teaspoons or two teaspoons, the small one. Sometimes I give him two times, sometimes once. (I gave him oil) because of the stomach. Sometimes he feels painful, he cannot even pupu so if I give oil it was like it was helping him for his stomach. (I stopped) long time now. Like three to six months. I cannot remember. (I stopped) because he refused to drink it. Sometimes he holds the spoon and throws it away. And also at that time, he was not struggling to pupu or so,so I check the pupu was fine and there was no struggling so I decided to stop giving him.

ID-12: "Yes (I have ever used oil for my child)… for the baby you give teaspoon in the morning and one teaspoon in the evening… Sometimes he coughs because he doesn't want it, but we don't have choice because even when I go to Zimbabwe they say you must force him to drink you cannot say the baby doesn't want because he is still young."

D. Some siblings given oil developed overt respiratory problems and complications

ID-08 [Interpreted]: Yes (I have used oil for my child). Cooking oil. Sun flower oil. (I started using it when he was) two months. (I would give) morning teaspoon, afternoon teaspoon, evening teaspoon. (I used it for) three months. (I would give it to) his mouth. When the child was born, the anterior fontanelle was pulsating a lot. So I asked my mum for advice and she said if I don't want the fontanelle to pulsate, I give him oil. (I would give it for) one year (so that the anterior fontanelle does not pulsate). At home in Zimbabwe there is some black substance we they put on the anterior fontanelle which can be given to stop the pulsating… No (I do not have other children), I had one child who passed away… When I left 'YYY' which is in Zimbabwe, he was coughing. The child was coughing and when I came with the child here (Cape Town, South Africa) the coughing continued and it was actually worse. Then I went to the clinic with the child, and the child passed away that same day. (He was)

two months (when he started coughing). Yes (I know other people who use oil). (My) older brother's wife used oil and the child's anterior fontanelle never pulsated afterwards… There are people that I stay with who also use oil. (They are from) Zimbabwe as well. No, I have not seen people from this country using it… Yes, I used oil for my first baby. (I would give) a teaspoon in the morning, teaspoon in the afternoon, teaspoon in the evening…

E. Some siblings given oil did not develop overt respiratory problems

ID-05: Yes (I have other children). The other one is six years. A boy. Yes, I gave oil also. Yes, but that one my mother was staying with him until he was one year six months then he came to me. I don't know how many teaspoons. It is my mother who was giving him. The six years old didn't have any problem, I don't want to lie. That one was fine. Even me as I was growing up they (my sisters) gave me oil. I was also drinking oil. Yes. If my stomach is painful, my mother wanted to boil oil but I refused because you know oil is not sweet to drink. And sometimes if I feel stomach pain I always put it with salt and then I try to go to the toilet and my stomach is clean. But now I just think about oil and how…, I cannot drink it. I am big, it cannot help."

F. Oil is also given to adults

ID-12: "Yes (I have ever used oil for my child), even for me. I was using it when I was pregnant because it is our culture. So when I was pregnant I was also drinking oil from three months but when I gave birth…, I noticed it today, that when I gave birth I was also admitted at Facility X (the secondary level health facility that referred her child to our unit) with a lung problem. Yea, I was in High Care, that thing came in today when I was in theatre (waiting for her son undergoing the bronchoscopy). I didn't think about it. I was drinking just once. One tablespoon. Once a day. That cooking oil."" You cook it but when you drink it you must make it warm then you drink… because they say…, our elders say if you drink cooking oil it is gonnna make a way for the baby to come out. Me I was drinking one

tablespoon but for the baby you give teaspoon in the morning and one teaspoon in the evening… Sometimes he coughs because he doesn't want it, but we don't have choice because even when I go to Zimbabwe they say you must force him to drink you cannot say the baby doesn't want because he is still young. You cook it but when you drink it you must make it warm then you drink… because they say…, our elders say if you drink cooking oil it is gonnna make a way for the baby to come out. Me I was drinking one tablespoon but for the baby you give teaspoon in the morning and one teaspoon in the evening… Sometimes he coughs because he doesn't want it, but we don't have choice because even when I go to Zimbabwe they say you must force him to drink you cannot say the baby doesn't want because he is still young."

G. Oil is also administered to children of local South African descent

ID-10: "Yea (there are others not from Zimbabwe who use oil). I was in hospital…, the time I was in (Hospital Y, a secondary referral hospital in the province), there was a coloured woman next to me. Her boy was like my boy, pneumonia, fever, what what. So, she said to me, 'Even me I used to give my boy cooking oil, but I used to give him in the [then points to the ears], yes and in the nose.' She said, 'If my boy is coughing too much, I used to give him in the mouth to make his chest soft.' She said so to me. Even the sisters, mhh, what can I say, Venda sisters at [Hospital Y] they say so. They say, 'In our cultures…' they say, 'We used to do that.' I think Vendas…, other Vendas, they are in Zimbabwe. Some of them, they say, 'We used to do this to our children'. (They would give the oil through the) nose, mouth, the ears. Yea, for the same reason (to help with the stool), because I asked them… (they use) sunflower oil. Yes, they say so to me. Another woman who was next, after that one…. she showed me a sweet oil and she told me, 'You must buy a sweet oil in the pharmacy. Yea, sweet oil not sunflower'. No (she was not from Zimbabwe), coloured again. She said, 'You guys you must stop using sunflower. Let me show you my sweet oil that I was using to give my boy'. She said, 'You go and buy in the pharmacy. It is small sweet oil.'"

606 **Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist**

607 Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research

608 (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health*

609 *Care*. 2007. Volume 19, Number 6: pp. 349 – 357

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	E-text
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	E-text
3. Occupation	What was their occupation at the time of the study?	E-text
4. Gender	Was the researcher male or female?	N/A
5. Experience and training	What experience or training did the researcher have?	E-text
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	E-text
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	E-text
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	E-text
Domain 2: study design		
Theoretical framework		
9. Methodological orientation	What methodological orientation was stated to	E-text

and Theory	underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	E-text
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	E-text
12. Sample size	How many participants were in the study?	Results and E-text
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Results and E-text
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	E-text
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	E-text
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Results and E-text
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	E-text
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	E-text
20. Field notes	Were field notes made during and/or after the interview or focus group?	E-text
21. Duration	What was the duration of the interviews or focus group?	N/A

22. Data saturation	Was data saturation discussed?	E-text
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	E-text
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	E-text
27. Software	What software, if applicable, was used to manage the data?	E-text
28. Participant checking	Did participants provide feedback on the findings?	N/A
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results and E-text
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Results and E-text
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results and E-text
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results and E-text

610
611

APPENDICES

Appendix 1: Data Capture Instruments

Case Report Forms 2A, 2B, 2C

Interview Guide

CRF 2A - Clinical: Exogenous Lipoid Pneumonia Retrospective Case Series

Case report form for clinical description of children with histologically confirmed exogenous lipoid pneumonia case at Red Cross Children's Hospital

* Required

1. **Date of Form Completion** *

   Example: December 15, 2012

2. **Enrollment ID** *

3. **Histologically confirmed exogenous lipoid pneumonia diagnosis** *
   Mark only one oval per row.

	No	Yes
1) Histological findings on bronchoalveolar lavage (BAL) and/or lung biopsy that is consistent with exogenous lipid content AND	◯	◯
2) Clinical presentation of persistent or recurrent unexplained pneumonia associated with prolonged hypoxia or tachypnea, AND	◯	◯
3) Radiological evidence of persistent diffuse alveolar infiltrates on chest radiograph or computed tomography (CT) chest, AND/OR	◯	◯
4) History of oil administration related to time of presentation/diagnosis.	◯	◯

Demographic characteristics

4. **Date of Birth** *

   Example: December 15, 2012

5. **Sex** *
   Mark only one oval.

   ◯ Male
   ◯ Female

6. **Nationality/heritage** *
   Check all that apply.

   - [ ] South African
   - [ ] Zimbabwean
   - [ ] Malawian
   - [ ] Other: _____

7. **Caregiver phone number 1** *

   _____

8. **Caregiver phone number 2** *

   _____

FIRST presentation with clinical/radiological features of a lower respiratory tract condition

FIRST DOCUMENTED presentation with respiratory related symptoms/signs/imaging

9. **Date of first presentation** *

   _____
   Example: December 15, 2012

10. **Cough** *
    Mark only one oval.

    - ◯ Not documented
    - ◯ No
    - ◯ Yes

11. **Specify duration of cough (days)**

    _____

12. **Hotness of body** *
    Mark only one oval.

    - ◯ Not documented
    - ◯ No
    - ◯ Yes

13. **Specify duration of hotness of body (days)**

    _____

14. **Fast breathing** *
Mark only one oval.

- ◯ Not documented
- ◯ No
- ◯ Yes

15. **Specify duration of fast breathing (days)**

_____

16. **Feeding difficulties/symptoms of aspiration** *
Mark only one oval.

- ◯ No
- ◯ Yes

17. **Specify duration of feeding difficulties/symptoms of aspiration (days)**

_____

18. **Documented risk factors/comorbidities** *
Check all that apply.

- ☐ None
- ☐ Risk factor without objective assessment e.g. known neurological disorder like cerebral palsy
- ☐ Documented swallowing disorder e.g. confirmed aspiration on contrast study
- ☐ Other: _____

19. **Weight (kg)** *
Mark only one oval.

- ◯ Not documented
- ◯ Documented

20. **Specify weight (kg)**

_____

21. **Height (cm)** *
Mark only one oval.

- ◯ Not documented
- ◯ Documented

22. **Specify height (cm)**

_____

23. **Pallor** *
Mark only one oval.

- ◯ Not documented
- ◯ None
- ◯ Yes - mild
- ◯ Yes - moderate
- ◯ Yes - severe
- ◯ Yes - not graded

24. **Oedema** *
Mark only one oval.

- ◯ Not documented
- ◯ No
- ◯ Yes

25. **Clubbing** *
Mark only one oval.

- ◯ Not documented
- ◯ None
- ◯ Yes - Grade 1 - Fluctuation of the nail bed
- ◯ Yes - Grade 2 - Loss of Shamroth's Window
- ◯ Yes - Grade 3 - Drumstick appearance
- ◯ Yes - Grade 4 - Hypertrophic osteoarthropathy
- ◯ Yes - not graded

26. **Temperature (degrees Celsius)** *
Mark only one oval.

- ◯ Not documented
- ◯ Documented - no fever
- ◯ Documented - fever

27. **Specify temperature (degrees Celsius)**

_____

28. **Respiratory rate (/min)** *
Mark only one oval.

- ◯ Not documented
- ◯ Documented - no tachypnea
- ◯ Documented - tachypnea

29. **Specify respiratory rate (/min)**

30. **SPO2 in room air (%)** *
Mark only one oval.

- Not documented
- Documented - no hypoxia (>=92%)
- Documented - hypoxia (<92%)

31. **Specify SPO2 in room air (%)**

32. **Hyperinflation** *
Mark only one oval.

- Not documented
- Absent
- Present

33. **Air Entry** *
Mark only one oval.

- Not documented
- Good bilaterally
- Reduced - Mainly left
- Reduced - Mainly right
- Reduced - Both sides
- Reduced - Not defined

34. **Wheeze** *
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not defined

35. **Crepitations** *
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not defined

36. **Bronchial breathe sounds** *
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not Defined

37. **White cell count (*10^9/L)** *
Mark only one oval.

- Not documented
- Leukopenia
- Normal
- Leukocytosis

38. **Specify white cell count (*10^9/L)**

39. **White cell predominance**
Mark only one oval.

- None
- Neutrophil
- Lymphocyte
- Monocyte
- Eosinophil

40. **Specify neutrophil %**

41. **Specify lymphocyte %**

42. **Specify monocyte %**

43. **Specify eosinophil %**

44. **C-Reactive Protein** *
Mark only one oval.

- Not documented
- Normal
- High (=>10)

45. **Specify CRP level**

46. **Respiratory viral panel** *
Mark only one oval.

- Not documented
- Negative
- Positive

47. **Specify respiratory viruses**
Check all that apply.

- Human Rhinovirus
- Human Bocavirus
- Adenovirus
- Influenza
- Para-influenza
- Other:

48. **Blood culture** *
Mark only one oval.

- Not documented
- Negative
- Positive

49. **Specify organism if culture positive**

50. **Imaging done e.g. CXR, CT, other ?** *

Mark only one oval.

- ◯ No
- ◯ Yes

51. **BAL or/and Lung Biopsy done?** *

Mark only one oval.

- ◯ No *After the last question in this section, skip to question 72.*
- ◯ Yes *After the last question in this section, skip to question 136.*

52. **Other investigations, provide details?**

_____

_____

_____

_____

_____

53. **Offending agent identified and discontinued?** *

Mark only one oval.

- ◯ No
- ◯ Yes

54. **Oxygen therapy?** *

Mark only one oval.

- ◯ No
- ◯ Yes

55. **Specify total number of days on oxygen**

_____

56. **CPAP/IPPV?** *

Mark only one oval.

- ◯ No
- ◯ Yes - CPAP
- ◯ Yes - IPPV

57. **Specify total number of days on CPAP/IPPV**

_____

58. **Antibiotics?** *

Mark only one oval.

- No
- Yes

59. **Specify total number of days of antibiotics**

60. **Specify antibiotics used (details)**

61. **Steroids?** *

Mark only one oval.

- No
- Yes

62. **Specify total number of days of steroids**

63. **Specify steroid used (details)**

64. **Therapeutic lavage?** *

Mark only one oval.

- No
- Yes

65. **Specify total number of lavages**

66. **Other management (details)**

67. **Total number of days hospitalized in this admission** *

68. **Clinical resolution in this admission** *

Mark only one oval.

- Not documented
- No
- Yes

69. **Date of clinical resolution in this admission**

Example: December 15, 2012

70. **Death?** *

Mark only one oval.

- No
- Yes

71. **Date of Death**

Example: December 15, 2012

BAL/BIOPSY not previously done - presentation at which histology is suggestive

72. **Date of presentation at diagnosis**

Example: December 15, 2012

73. **Cough**

Mark only one oval.

- Not documented
- No
- Yes

74. **Specify duration of cough (days)**

75. **Hotness of body**

Mark only one oval.

- Not documented
- No
- Yes

76. **Specify duration of hotness of body (days)**

77. **Fast breathing**
Mark only one oval.

- ◯ Not documented
- ◯ No
- ◯ Yes

78. **Specify duration of fast breathing (days)**

79. **Feeding difficulties/symptoms of aspiration**
Mark only one oval.

- ◯ No
- ◯ Yes

80. **Specify duration of feeding difficulties/symptoms of aspiration (days)**

81. **Risk factors/comorbidities**
Check all that apply.

- ☐ None
- ☐ Comorbidity associated with impaired swallowing e.g. cerebral palsy, but not formally assessed
- ☐ Documented swallowing disorder e.g aspiration on contrast swallow
- ☐ Other:

82. **Weight (kg)**
Mark only one oval.

- ◯ Not documented
- ◯ Documented

83. **Specify weight (kg)**

84. **Height (cm)**
Mark only one oval.

- ◯ Not documented
- ◯ Documented

85. **Specify height (cm)**

86. **Pallor**

Mark only one oval.

- Not documented
- None
- Yes - mild
- Yes - moderate
- Yes - severe
- Yes - not graded

87. **Oedema**

Mark only one oval.

- Not documented
- No
- Yes

88. **Clubbing**

Mark only one oval.

- Not documented
- None
- Yes - Grade 1 - Fluctuation of the nail bed
- Yes - Grade 2 - Loss of Shamroth's Window
- Yes - Grade 3 - Drumstick appearance
- Yes - Grade 4 - Hypertrophic osteoarthropathy
- Yes - not graded

89. **Temperature (degrees Celsius)**

Mark only one oval.

- Not documented
- Documented - no fever
- Documented - fever

90. **Specify temperature (degrees Celsius)**

91. **Respiratory rate (/min)**
Mark only one oval.

- Not documented
- Documented - no tachypnea
- Documented - tachypnea

92. **Specify respiratory rate (/min)**

93. **SPO2 in room air (%)**
Mark only one oval.

- Not documented
- Documented - no hypoxia (>=92%)
- Documented - hypoxia (<92%)

94. **Specify SPO2 in room air (%)**

95. **Hyperinflation**
Mark only one oval.

- Not documented
- Absent
- Present

96. **Air Entry**
Mark only one oval.

- Not documented
- Good bilaterally
- Reduced - Mainly left
- Reduced - Mainly right
- Reduced - Both sides
- Reduced - Not defined

97. **Wheeze**
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not defined

98. **Crepitations**
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not defined

99. **Bronchial breathe sounds**
Mark only one oval.

- Not documented
- None
- Present - Mainly right
- Present - Mainly left
- Present - Both sides
- Present - Not Defined

100. **White cell count (*10^9/L)**
Mark only one oval.

- Not documented
- Leukopenia
- Normal
- Leukocytosis

101. **Specify white cell count (*10^9/L)**

_____

102. **White cell predominance**
Mark only one oval.

- None
- Neutrophil
- Lymphocyte
- Monocyte
- Eosinophil

103. **Specify neutrophil %**

_____

104. **Specify lymphocyte %**

_____

105. **Specify monocyte %**

_____

106. **Specify eosinophil %**

_____

107. **C-Reactive Protein**
Mark only one oval.

- ◯ Not documented
- ◯ Normal
- ◯ High (=>10)

108. **Specify CRP level**

_____

109. **Respiratory viral panel**
Mark only one oval.

- ◯ Not documented
- ◯ Negative
- ◯ Positive

110. **Specify respiratory viruses**
Check all that apply.

- ☐ Human Rhinovirus
- ☐ Human Bocavirus
- ☐ Adenovirus
- ☐ Influenza
- ☐ Para-influenza
- ☐ Other: _____

111. **Blood culture**
Mark only one oval.

- ◯ Not documented
- ◯ Negative
- ◯ Positive

112. **Specify organism if culture positive**

_____

113. **Imaging done e.g. CXR, CT, other ?**
Mark only one oval.

- No
- Yes

114. **BAL or/and Lung Biopsy done?**
Mark only one oval.

- No
- Yes

115. **Other investigations? (provide details)**

116. **Offending agent identified and discontinued?**
Mark only one oval.

- No
- Yes

117. **Oxygen therapy?**
Mark only one oval.

- No
- Yes

118. **Specify total number of days on oxygen**

119. **CPAP/IPPV?**
Mark only one oval.

- No
- Yes - CPAP
- Yes - IPPV

120. **Specify total number of days on CPAP**

121. **Specify total number of days on IPPV**

122. **Antibiotics?**
Mark only one oval.

- No
- Yes

123. **Specify total number of days of antibiotics**

124. **Specify antibiotics used (details)**

125. **Steroids?**
Mark only one oval.

- No
- Yes

126. **Specify total number of days of steroids**

127. **Specify steroid used (details)**

128. **Therapeutic lavage?**
Mark only one oval.

- No
- Yes

129. **Specify total number of lavages**

130. **Other management (details)**

131. **Total number of days hospitalized in this admission**

132. **Clinical resolution in this admission**
Mark only one oval.

- Not documented
- No
- Yes

133. **Date of clinical resolution in this admission**

Example: December 15, 2012

134. **Death?**
Mark only one oval.

- No
- Yes

135. **Date of Death**

Example: December 15, 2012

Other admissions for similar condition

136. **Other admissions for lower respiratory tract illness** *
Mark only one oval.

- No
- Yes

137. **Specify total number of hospitalizations for a lower respiratory tract illness** *

138. **Date - 2nd admission (enter if applicable)**

Example: December 15, 2012

139. **Date - 3rd admission (enter if applicable)**

Example: December 15, 2012

140. **Date - 4th admission (enter if applicable)**

Example: December 15, 2012

141. **Date - 5th admission (enter if applicable)**

Example: December 15, 2012

142. **Specify details of admissions**

143. **Clinical resolution?**
Mark only one oval.

- Not documented
- No
- Yes

144. **Date of clinical resolution**

Example: December 15, 2012

145. **Death?**
Mark only one oval.

- No
- Yes

146. **Date of death**

Example: December 15, 2012

BAL/Lung Biopsy Microbiology/Virology

Bronchoalveolar lavage and/or Lung Biopsy Results

147. **Bronchoalveolar lavage (BAL) done?** *
Mark only one oval.

- No
- Yes

148. **Date BAL done** *

Example: December 15, 2012

149. **Site of BAL specimen sample** *
Check all that apply.

- [ ] Not documented
- [ ] RUL
- [ ] RML
- [ ] RLL
- [ ] LUL
- [ ] Lingula
- [ ] LLL
- [ ] Other: _____

150. **Cell type proportion indicated in BAL?** *
Mark only one oval.

- ◯ No
- ◯ Yes

151. **Specify lymphocyte %**

_____

152. **Specify neutrophil %**

_____

153. **Specify eosinophil %**

_____

154. **Microbiology on BAL - Bacterial cultures** *
Mark only one oval.

- ◯ Not requested
- ◯ Negative
- ◯ Positive

155. **Specify Bacterial culture on BAL**

_____

156. **Microbiology on BAL - TB cultures** *
Mark only one oval.

- ◯ Not requested
- ◯ Negative
- ◯ Positive

157. **Specify Mycobacterial culture on BAL**

158. **Microbiology on BAL - Fungal cultures** *
Mark only one oval.

- Not requested
- Negative
- Positive

159. **Specify Fungal culture on BAL**

160. **Microbiology on BAL - Respiratory viral panel** *
Mark only one oval.

- Not requested
- Negative
- Positive

161. **Specify Respiratory viruses on BAL**

162. **Microbiology on BAL - PCP PCR or Immunoflourescence** *
Mark only one oval.

- Not requested
- Negative
- Positive

163. **Specify PCP test on BAL**

164. **Microbiology on BAL - CMV PCR** *
Mark only one oval.

- Not requested
- Negative
- Positive

165. **Specify CMV Viral Load on BAL**

166. **Specify other microbiological test done on BAL**

167. **LUNG BIOPSY done?** *
Mark only one oval.

- No
- Yes

168. **Date Lung Biopsy done**

Example: December 15, 2012

169. **Site of lung biopsy specimen sample**
Check all that apply.

- Not documented
- RUL
- RML
- RLL
- LUL
- Lingula
- LLL
- Other:

170. **Microbiology on Biopsy - Bacterial cultures**
Mark only one oval.

- Not requested
- Negative
- Positive

171. **Specify Bacterial culture on Biopsy**

172. **Microbiology on Biopsy - TB cultures**
Mark only one oval.

- Not requested
- Negative
- Positive

173. **Specify Mycobacterial culture on Biopsy**

174. **Microbiology on Biopsy - Fungal cultures**
Mark only one oval.

- Not requested
- Negative
- Positive

175. **Specify Fungal culture on Biopsy**

176. **Microbiology on Biopsy - Respiratory viral panel**
Mark only one oval.

- Not requested
- Negative
- Positive

177. **Specify Respiratory viruses on Biopsy**

178. **Microbiology on Biopsy - PCP PCR or Immunoflourescence**
Mark only one oval.

- Not requested
- Negative
- Positive

179. **Specify PCP test on Biopsy**

180. **Microbiology on Biopsy - CMV PCR**
Mark only one oval.

- Not requested
- Negative
- Positive

181. **Specify CMV Viral Load on Biopsy**

182. **Specify other microbiological test done on Biopsy**

CRF 2B - Radiology: Exogenous Lipoid Pneumonia Retrospective Case Series

Case report form for the description of the radiological characteristics of children with histologically confirmed exogenous lipoid pneumonia case at Red Cross Children's Hospital

* Required

1. **Date of Form Completion** *

   Example: December 15, 2012

2. **Enrollment ID** *

3. **Chest X-Ray(s) done?** *
   Mark only one oval.

   - ◯ No
   - ◯ Yes

4. **Specify total number of CXRs done to date**

5. **First Presentation Chest X-Ray Date** *

   Example: December 15, 2012

6. **Ground glass opacification present [CXR1]?** *
   Mark only one oval.

   - ◯ No
   - ◯ Yes

7. **Distribution on first presentation CXR** *
   Mark only one oval per row.

	Normal	Abnormal
Right upper lobe	◯	◯
Righ middle lobe	◯	◯
Right lower lobe	◯	◯
Left upper lobe	◯	◯
Lingula	◯	◯
Left lower lobe	◯	◯

8. **Specify details of first presentation CXR abnormality**

9. **Chest X-Ray-2 Date** *

Example: December 15, 2012

10. **Ground glass opacification present [CXR2]?** *

Mark only one oval.

- No
- Yes

11. **Distribution CXR-2** *

Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

12. **Progress CXR-2** *

Mark only one oval.

- Not done
- Better
- Similar
- Worse

13. **Chest X-Ray-3 Date (enter if applicable)**

Example: December 15, 2012

14. **Ground glass opacification present [CXR3]?**

Mark only one oval.

- No
- Yes

15. **Distribution CXR-3**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe	◯	◯
Righ middle lobe	◯	◯
Right lower lobe	◯	◯
Left upper lobe	◯	◯
Lingula	◯	◯
Left lower lobe	◯	◯

16. **Progress CXR-3**
Mark only one oval.

- ◯ Not done
- ◯ Better
- ◯ Similar
- ◯ Worse

17. **Chest X-Ray-4 Date (enter if applicable)**

_____
Example: December 15, 2012

18. **Ground glass opacification present [CXR4]?**
Mark only one oval.

- ◯ No
- ◯ Yes

19. **Distribution CXR-4**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe	◯	◯
Righ middle lobe	◯	◯
Right lower lobe	◯	◯
Left upper lobe	◯	◯
Lingula	◯	◯
Left lower lobe	◯	◯

20. **Progress CXR-4**
Mark only one oval.

- ◯ Not done
- ◯ Better
- ◯ Similar
- ◯ Worse

21. **Chest X-Ray-5 Date (enter if applicable)**

_____
Example: December 15, 2012

22. **Ground glass opacification present [CXR5]?**
Mark only one oval.

- No
- Yes

23. **Distribution CXR-5**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

24. **Progress CXR-5**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

25. **Chest X-Ray-6 Date (enter if applicable)**

Example: December 15, 2012

26. **Ground glass opacification present [CXR6]?**
Mark only one oval.

- No
- Yes

27. **Distribution CXR-6**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

28. **Progress CXR-6**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

29. **Chest X-Ray-7 Date (enter if applicable)**

Example: December 15, 2012

30. **Ground glass opacification present [CXR7]?**
Mark only one oval.

- No
- Yes

31. **Distribution CXR-7**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

32. **Progress CXR-7**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

33. **Chest X-Ray-8 Date (enter if applicable)**

Example: December 15, 2012

34. **Ground glass opacification present [CXR8]?**
Mark only one oval.

- No
- Yes

35. **Distribution CXR-8**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

36. **Progress CXR-8**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

37. **Chest X-Ray-9 Date (enter if applicable)**

Example: December 15, 2012

38. **Ground glass opacification present [CXR9]?**
Mark only one oval.

- No
- Yes

39. **Distribution CXR-9**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

40. **Progress CXR-9**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

41. **Chest X-Ray-10 Date (enter if applicable)**

Example: December 15, 2012

42. **Ground glass opacification present [CXR10]?**
Mark only one oval.

- No
- Yes

43. **Distribution CXR-10**
Mark only one oval per row.

	Normal	Abnormal
Right upper lobe		
Righ middle lobe		
Right lower lobe		
Left upper lobe		
Lingula		
Left lower lobe		

44. **Progress CXR-10**
Mark only one oval.

- Not done
- Better
- Similar
- Worse

45. **Summary CXR progression and other details**

46. **Radiological resolution on CXR?** *
Mark only one oval.

- No
- Yes

47. **Date of radiological resolution on CXR**

Example: December 15, 2012

48. **CT Scan Chest done** *
Mark only one oval.

- No
- Yes

49. **Date of CT Chest**

Example: December 15, 2012

50. **Pattern - CT Chest**

Check all that apply.

- [ ] Ground glass opacities
- [ ] Airspace consolidation
- [ ] Fatty attenuation inside airspace opacification
- [ ] Crazy paving
- [ ] Nodules
- [ ] Interlobular septal thickening
- [ ] Subpleural cysts
- [ ] Other cysts

51. **Distribution - CT Chest**

Mark only one oval per row.

	Normal	Abnormal
Right upper lobe	◯	◯
Righ middle lobe	◯	◯
Right lower lobe	◯	◯
Left upper lobe	◯	◯
Lingula	◯	◯
Left lower lobe	◯	◯

52. **Predominance - CT Chest**

Mark only one oval.

- ◯ None
- ◯ Upper zones
- ◯ Lower zones

53. **Specify other CT Chest details**

54. **Other imaging done (not CXR or CT Chest)?** *

Mark only one oval.

- ◯ No
- ◯ Yes

55. **Specify details of other imaging done**

CRF 2C - Histology: Exogenous Lipoid Pneumonia Retrospective Case Series

Case report form for the description of the histological characteristics of children with histologically confirmed exogenous lipoid pneumonia case at Red Cross Children's Hospital

* Required

1. **Date of Form Completion** *

   Example: December 15, 2012

2. **Enrollment ID** *

3. **Bronchoalveolar lavage (BAL) done?** *

   Mark only one oval.

   - ◯ No
   - ◯ Yes

4. **Date BAL done** *

   Example: December 15, 2012

5. **Site of BAL specimen sample** *

   Check all that apply.

   - ☐ Not documented
   - ☐ RUL
   - ☐ RML
   - ☐ RLL
   - ☐ LUL
   - ☐ Lingula
   - ☐ LLL
   - ☐ Other:

6. **Macroscopic appearance of BAL?** *
Mark only one oval.

- ◯ Not documented
- ◯ Clear
- ◯ Turbid
- ◯ Milky
- ◯ Bloody
- ◯ Oily
- ◯ Cloudy
- ◯ Other: _____

7. **Specify BAL macrophages - qualitative description**
Mark only one oval.

- ◯ Not documented
- ◯ Absent
- ◯ Moderate
- ◯ Abundant

8. **Specify BAL lymphocytes - qualitative description**
Mark only one oval.

- ◯ Not documented
- ◯ Absent
- ◯ Moderate
- ◯ Abundant

9. **Specify BAL neutrophils - qualitative description**
Mark only one oval.

- ◯ Not documented
- ◯ Absent
- ◯ Moderate
- ◯ Abundant

10. **Specify BAL eosinophils - qualitative description**
Mark only one oval.

- ◯ Not documented
- ◯ Absent
- ◯ Moderate
- ◯ Abundant

11. **Specify BAL lipid laden macrophages - qualitative description** *
Mark only one oval.

- ◯ Not documented
- ◯ Absent
- ◯ Moderate
- ◯ Abundant

12. **Specify lipid laden macrophage %**

_____

13. **Lipid stain used in BAL** *
Mark only one oval.

- ◯ Oil Red O
- ◯ Sudan III
- ◯ Sudan IV
- ◯ Other: _____

14. **Extracellular free lipid in BAL** *
Mark only one oval.

- ◯ Not documented
- ◯ No
- ◯ Yes - minimal
- ◯ Yes - moderate
- ◯ Yes - abundant
- ◯ Yes - not quantified

15. **Periodic acid schiff stain of BAL** *
Mark only one oval.

- ◯ Not requested
- ◯ Negative
- ◯ Positive - weak
- ◯ Positive - moderate
- ◯ Positive - strong
- ◯ Postive - not quantified

16. **Iron laden macrophages in BAL**
Mark only one oval.

- ◯ No
- ◯ Yes - few
- ◯ Yes - moderate
- ◯ Yes - abundant
- ◯ Yes - not quantified

17. **Specify iron laden macrophage % in BAL**

_____

18. **Electron microscopy of BAL?**
Mark only one oval.

- ◯ Not requested
- ◯ Not assessed (poor quality)
- ◯ Normal
- ◯ Abnormal
- ◯ Results pending

19. **Specify EM details of BAL**

_____

_____

_____

_____

_____

20. **Infection stains done on BAL histology?** *
Mark only one oval per row.

	Not requested	Negative	Positive
AFBs	◯	◯	◯
PCP	◯	◯	◯
Fungi	◯	◯	◯

21. **Specify additional histology details of BAL**

_____

_____

_____

_____

_____

22. **LUNG BIOPSY done?** *

Mark only one oval.

- ◯ No
- ◯ Yes

23. **Date Lung Biopsy done**

_____

Example: December 15, 2012

24. **Site of lung biopsy specimen sample**

Check all that apply.

- ☐ Not documented
- ☐ RUL
- ☐ RML
- ☐ RLL
- ☐ LUL
- ☐ Lingula
- ☐ LLL
- ☐ Other: _____

25. **Lipid laden macrophages present on biopsy**

Mark only one oval.

- ◯ Not documented
- ◯ No
- ◯ Yes

26. **Specify lipid laden macrophage % on biospy**

_____

27. **Lipid stain used on biopsy**

Mark only one oval.

- ◯ Oil Red O
- ◯ Sudan III
- ◯ Sudan IV
- ◯ Other: _____

28. **Extracellular free lipid on biopsy**
Mark only one oval.

- Not requested/documented
- No
- Yes - minimal
- Yes - moderate
- Yes - abundant
- Yes - not quantified

29. **Periodic acid schiff stain on biospsy**
Mark only one oval.

- Not requested/documented
- Negative
- Positive - weak
- Positive - moderate
- Positive - strong
- Positive - not quantified

30. **Iron laden macrophages on biopsy**
Mark only one oval.

- Absent
- Present - few
- Present - moderate
- Present - abundant
- Present - not quantified

31. **Specify iron laden macrophages % on biopsy**

_____

32. **Interstitial inflammation on biopsy**
Mark only one oval.

- Not documented
- No
- Yes - mild
- Yes - moderate
- Yes - marked
- Yes - not quantified

33. **Pneumatocyte changes on biopsy**
Mark only one oval.

- Not documented
- No
- Yes - mild
- Yes - moderate
- Yes - marked
- Yes - not quantified

34. **Fibrosis on biopsy**
Mark only one oval.

- Not documented
- No
- Yes - mild
- Yes - moderate
- Yes - marked
- Yes - not quantified

35. **Electron microscopy on lung biopsy?**
Mark only one oval.

- Not requested
- Not assessed (poor quality)
- Normal
- Abnormal
- Results pending

36. **Specify EM details on lung biopsy**

37. **Infection stains on biopsy histology?**
Mark only one oval per row.

	Not requested	Negative	Positive
AFBs			
PCP			
Fungi			

38. **Specify additional histology details of biopsy**

Interview Guide

Date of Interview ☐☐ ☐☐☐ ☐☐☐☐ (dd mmm yyyy)

Participant Enrollment ID ☐☐☐☐

Section 1: *How is your child doing today?*
[Only use as probes, allow for detailed caregiver description]

Cough? ☐ No ☐ Yes …. Duration _____ (days)

Hotness of body? ☐ No ☐ Yes …. Duration _____ (days)

Fast breathing? ☐ No ☐ Yes …. Duration _____ (days)

Other (specify) _____

Section 2: *Tell me, have you ever used any oil for your child?*
[Only use as probes, allow for detailed caregiver description]

☐ No ☐ Yes (specify) _____

Type(s) of oil? ☐ No ☐ Yes *(tick all that apply)* Mineral ☐ No ☐ Yes (specify) _____

Vegetable ☐ No ☐ Yes (specify) _____

Animal ☐ No ☐ Yes (specify) _____

Age at onset of use? ☐☐ **Years** ☐☐ **Months**

Route of administration? ☐ Nose ☐ Mouth ☐ Topical ☐ other _____

Amount? ☐☐ **Milliliters (Ml)** and Frequency? ☐☐ **Hourly**

Total Amount Daily? ☐☐ **Ml**

Duration? ☐☐ **Days** ☐☐ **Months** ☐☐ **Years**

WHY? Reasons for oil use/Past illnesses/concerns at the time of oil use:

☐ Constipation (specify) _____ ☐ Colic (specify) _____ ☐ Nasal stuffiness (specify) _____

☐ Religion (specify) _____ ☐ Culture (specify) _____ ☐ Other (specify)_____

Section 3: ***Does your child have any problems swallowing? Does your child have any other condition/problems?***
[Only use as probes, allow for detailed caregiver description]

Co-morbidities: Any underlying swallowing problem? ☐ No ☐ Yes (specify) _____

☐ Other (specify) _____

Section 4: ***Tell me, are you using any oil for your child at the moment?***
[Only use as probes, allow for detailed caregiver description]

☐ Yes (why)_____ ☐ No

When did you stop? |__|__| |__|__|__| |__|__|__|__|
dd mmm yyyy

Why did you stop?

☐ The doctor told me ☐ It was making my child sick ☐ Other (specify) _____

Section 5: ***Do you have other children? How old are they now? Did they have any respiratory problems (at what age, what problem, any hospital admissions)? Did you ever give them oil (age of onset, route, type, amount, frequency, duration, reason)?***
[Only use as probes, allow for detailed caregiver description]

☐ No ☐ Yes (How many?) |__|__|

How old? Any respiratory problems? Did you give them oil?

1. |__|__| ☐ No ☐ Yes (specify) _____ ; ☐ No ☐ Yes (specify) _____
2. |__|__| ☐ No ☐ Yes (specify) _____ ; ☐ No ☐ Yes (specify) _____
3. |__|__| ☐ No ☐ Yes (specify) _____ ; ☐ No ☐ Yes (specify) _____
4. |__|__| ☐ No ☐ Yes (specify) _____ ; ☐ No ☐ Yes (specify) _____
5. |__|__| ☐ No ☐ Yes (specify) _____ ; ☐ No ☐ Yes (specify) _____

Section 6: ***Do you know other people who use oils? Who? How? Why?***
[Only use as probes, allow for detailed caregiver description]

☐ Family members (specify e.g. mother, sister, aunty, cousin, niece etc.) _____

☐ Community members (specify e.g. friends, neighbors, religious circles, general etc.) _____
How? _____ Why? _____

Appendix 2: Consent and Confidentiality Agreements

Consent

Confidentiality agreements

Telephone Invitation Protocol

Good Morning/Afternoon _____,

My name is Dr. Diana Marangu. I am part of a team that is conducting a study at Red Cross Children's Hospital to understand a lung condition in children associated with swallowed oil called lipoid pneumonia. We would like to invite you to participate in this study because your child may have had this condition. Your participation is completely voluntary. If you agree to give consent to participate in this study, we will ask you some questions on the telephone. This will take approximately 15-20 minutes of your time. All this information is private and confidential and we will only use it for the purposes of this study.

Do you have any questions? What are your thoughts? [*give time for response – note response*]

- ☐ Willing to participate in the study – Proceed to Verbal Consent
- ☐ Not willing to participate in the study at the moment, <u>but will require further information or more time to make a decision</u>
  - ☐ Information required: _____
  - ☐ Timelines to be contacted: _____
  - ☐ Telephone number willing to be contacted on: _____
- ☐ Not willing to participate in the study, child deceased
- ☐ Not willing to participate in the study

Thank you very much for your time. Please do not hesitate to contact me in the future if you have any (other) questions or require further clarification on Tel: 0733-396219. Have a good day/morning/afternoon.

Appendix 2B: Verbal Consent

Clinical, radiological and pathological characteristics and treatment outcomes of children with exogenous lipoid pneumonia: a case series from South Africa

Introduction: You are being asked to participate in this research study by Dr. Diana Marangu from the University of Cape Town and Red Cross Children's Hospital as part of her Masters in Philosophy degree training in Paediatric Pulmonology.

Purpose of the study: This study aims to understand a lung condition in children associated with giving babies or children oil called lipoid pneumonia. Your child was selected as a possible participant in this study because s/he may have had this condition.

Procedures: If you agree to give consent for your child to participate in this study, we will ask you some questions that will take approximately 15-20 minutes of your time. We will audio record this conversation so that we do not miss out on important details that you tell us.

Risks of participation: The risks from your participation are minimal. You may find some of the questions and responses to be tiresome. Disclosure (accidental or otherwise) of personal information is very unlikely but may occur. To reduce this risk, all research staff will be sworn to confidentiality.

Anticipated Benefits: Benefits of your child's participation are aimed at understanding practices related to this condition to prevent avoidable illness and recognize and treat this condition in other children early.

Confidentiality: We will respect your privacy. Data will be stored in a secure web-based database. Results published or presented in public will not have information that would allow people to identify you.

Voluntariness: Participation in this study is out of your own free will. You may choose not to participate with no consequences whatsoever.

Who do I contact if I have questions or problems? For any enquiries or further clarification about the study, or should you experience any harm by participating in this study, contact the Principal Investigator Dr. Diana Marangu: +27-733- 396219. For questions about your rights as a research participant, you should contact Professor Marc Blockman, the Chair of the Human Ethics Research Committee, Office situated at the Old Main Building of Groote Schuur Hospital, Floor E53, Room 46, Observatory, 7925.

Do you have any questions? What are your thoughts?

☐ Willing to participate in the study ☐ Not willing to participate in the study

Investigator initials: _____ Date: _____

Thank you very much for your time. Please do not hesitate to contact me in the future if you have any (other) questions or require further clarification. Have a good day/morning/afternoon.

"CLINICAL-RADIOLOGICAL-PATHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EXOGENOUS LIPOID PNEUMONIA: A CASE SERIES AND SYSTEMATIC REVIEW" STUDY

CONFIDENTIALITY AGREEMENT – PRINCIPAL INVESTIGATOR/RESEARCHERS

Confidentiality

Researchers shall treat all contact information i.e. telephone numbers and contact addresses of study participants, learned from the Red Cross Children's Hospital medical folders and contact information software 'Clinicom' during the study, as confidential. Researchers shall not use this information to further their own personal interests or the interests of a friend, relative or business associate.

Violations

Researchers shall withdraw immediately from encounters that they perceive to be in violation of this Confidentiality Agreement. In the event of a breach by the researchers of this Confidentiality Agreement, Red Cross Children's Hospital in any dispute shall be entitled to seek the remedies of injunction, specific performance or other equitable relief, for any threatened or actual breach of this Confidentiality Agreement by the researcher. Further, Red Cross Children's Hospital shall be entitled to recover from the researcher costs incurred in such dispute including without limitation its reasonable legal fees.

By signing this document, I am verifying that I have read, understand and agree to all the provisions listed in the above Confidentiality Agreement.

Name (printed): DR. DIANA MWENDWA MARANGU

Researcher

E-mail address: dmarangu@uonbi.ac.ke

Date: 21st June 2017

Phone: 0733-39219

Signature

Appendix 5C

"CLINICAL-RADIOLOGICAL-PATHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EXOGENOUS LIPOID PNEUMONIA: A CASE SERIES AND SYSTEMATIC REVIEW" STUDY

CONFIDENTIALITY AGREEMENT & INTERPRETER CODE OF ETHICS

Confidentiality

Interpreters shall treat all information learned during the interpretation as confidential. Interpreters shall not use confidential information acquired in the course of official duties, or request or gain access to confidential information maintained by Principle Investigator in order to further his or her own personal interests or the interests of a friend, relative or business associate.

Accuracy: Conveying the content and spirit of what is said

Interpreters shall transmit the message in a thorough and faithful manner, giving consideration to linguistic variation in both languages and conveying the tone and spirit of the original message. A word-for-word interpretation may not convey the intended idea. The interpreter shall determine the relevant concept and say it in language that is readily understandable and culturally appropriate to the Principle Investigator. In addition, the interpreter will make every effort to assure that the patient has understood questions, instructions and other information transmitted by the Principle Investigator.

Completeness: Conveying everything that is said

Interpreters shall interpret everything that is said by all people in the interaction where necessary, without omitting, adding, condensing or changing anything. If the content to be interpreted might be perceived as offensive, insensitive or otherwise harmful to the dignity and well-being of the patient, the interpreter should advise the Principle Investigator of this before interpreting. If the interpreter is taking notes to aid in ensuring the complete message is relayed, notes will be destroyed immediately following the session or otherwise treat such notes as may be instructed by the Principle Investigator.

Conveying cultural frameworks

Interpreters shall explain cultural differences or practices to the Principle Investigator and patients when appropriate.

Non-judgmental attitude about the content to be interpreted

An interpreter's function is to facilitate communication. Interpreters are not responsible for what is said by anyone for whom they are interpreting. Even if the interpreter disagrees with what is said, thinks it is wrong, an untruth, or even immoral, the interpreter shall suspend judgment, make no comment, and interpret everything accurately.

Patient self-determination

The interpreter may be asked by the patient's caregiver for his or her opinion. When this happens, the interpreter may provide or restate information that will assist the caregiver in making his or her own decision. The interpreter will not influence the opinion of the patient's caregiver by telling him/her what action to take.

Attitude toward patient

The interpreter should strive to develop a relationship of trust and respect at all times with the caregiver by adopting a caring, attentive, yet discreet and impartial attitude toward the caregiver, toward his or her questions, concerns and needs. The interpreter shall treat each caregiver equally with dignity and respect regardless of race, color, gender, religion, nationality, political persuasion or life-style choice.

Acceptance of Assignments

If level of competency or personal sentiments make it difficult to abide by any of the above conditions, the interpreter shall decline or withdraw from the assignment. Interpreters should disclose any real or perceived conflict of interest that could affect their objectivity. For example, interpreters should refrain from providing services to family members or close personal friends. In personal relationships, it is difficult to remain unbiased or non-judgmental.

Self-evaluation

Interpreters shall represent their certification(s), training and experience accurately and completely.

Ethical violations

Interpreters shall withdraw immediately from encounters that they perceive to be in violation of the Confidentiality Agreement & Interpreter Code of Ethics. In the event of a breach by the interpreters of this Confidentiality Agreement & Interpreter Code of Ethics, the Principle Investigator in any dispute shall be entitled to seek the remedies of injunction, specific performance or other equitable relief, for any threatened or actual breach of this Confidentiality Agreement & Interpreter Code of Ethics by the interpreter. Further such Principle Investigator shall be entitled to recover from the interpreter her costs incurred in such dispute including without limitation its reasonable legal fees.

By signing this document, I am verifying that I have read, understand and agree to all the provisions listed in the above Confidentiality Agreement & Interpreter Code of Ethics.

Name (printed): Norbertta Washaya

Interpreter

E-mail address: nnwashaya@gmail.com

Date: 7/09/2017

Phone: 072 345 7560

Signature

Appendix 3: Technical Appendix

Systematic review protocol

Systematic review - Table 1

Systematic review - Table 2

Clinical-radiological-pathological characteristics and treatment outcomes of children with suspected exogenous lipoid pneumonia: a systematic review.

Date: 30th May 2017

Authors & Affiliations:

Diana Marangu[1,2]

Komala Pillay[2]

Ebrahim Banderker[2]

Diane Gray[2]

Aneesa Vanker[2]

Marco Zampoli[2]

[1]University of Nairobi, Kenya

[2]University of Cape Town, South Africa

Review question(s):

1. What are the clinical-radiologic-pathological characteristics of children with suspected exogenous lipoid pneumonia?
2. What are the treatment outcomes of children with suspected exogenous lipoid pneumonia?
3. What is the efficacy of treatment modalities (therapeutic lavage, steroids, discontinuation of oil) for suspected exogenous lipoid pneumonia in children?

Searches:

We will consider studies in indexed and peer reviewed sources, and employ a multi-concept boolean search strategy based on the Population, Intervention, Control, Outcome, Timing and Setting (PICOTS) framework(1). (Appendix 1) This search strategy will use keywords related to exogenous lipoid pneumonia in children and will be restricted to English publications published within the last 50 years. This period was arbitrarily deemed to represent data that will be currently relevant.The electronic databases that we will use for searching will include Pubmed, EMBASE, Web of Science, SCOPUS, CINAHL and the Cochrane Library. For example, we will use the following search strategy in Pubmed: ("child"[MeSH Terms] OR Child[tw]) OR ("infant"[MeSH Terms] OR infant[tw]) AND ("pneumonia, lipid"[MeSH Terms] OR ("pneumonia"[All Fields] AND "lipid"[All Fields]) OR "lipid pneumonia"[All Fields] OR ("exogenous"[All Fields] AND "lipoid"[All Fields] AND "pneumonia"[All Fields]) OR "exogenous lipoid pneumonia"[All Fields]) AND (1967:2017[dp]) AND "English"[la] (Appendix 2).

Types of studies to be included:

Inclusion: Studies in which children <18 years old are suspected to have exogenous lipoid pneumonia. Exogenous lipoid pneumonia will be suspected under the following conditions:1) History of oil administration related to time of presentation/diagnosis, 2) Clinical presentation of persistent or recurrent unexplained pneumonia associated with hypoxia or tachypnea, 3) Radiological evidence of persistent diffuse alveolar infiltrates on chest radiograph or computed tomography (CT) chest, and/or 4) Histological findings on bronchoalveolar lavage (BAL) or lung biopsy that are consistent with exogenous lipid content. Two levels of case definitions will be applied in this systematic review: a) Suspected exogenous lipoid pneumonia, for cases in which a histological diagnosis is not available/documented; and b) Confirmed exogenous lipoid pneumonia, for cases that

include histological findings. Eligible study designs include retrospective or prospective: (a) analytic studies (cross sectional, case-control, cohort or intervention studies), (b) descriptive studies (case reports, case series, cross sectional studies), and (c) qualitative studies. We will include studies that include adults along with children if the data for adults can be separated and excluded.

Exclusion: Letters, editorials, commentaries, all types of reviews, meta-analyses and non-human studies will be excluded.

Condition or domain being studied:

Suspected exogenous lipoid pneumonia in children.

Participants/population:

Studies done in children (age <18 years) globally.

Intervention(s), exposure(s):

For interventional studies, the intervention may be a treatment modality e.g. therapeutic lavage, steroid use, discontinuation of oil.

Comparator(s)/ controls:

For interventional studies, the control will be the group without the intervention e.g. no therapeutic lavage. For case control studies, controls are children without exposure to the risk factors e.g. no history of exposure to oil. For cohort studies, the comparator will be the group unexposed to risk factors. For case series and case reports, there will be no control group.

Context:

Research conducted in any context globally.

Outcome(s):

Primary outcome(s)

1. Clinical-radiologic-pathological characteristics of children with suspected exogenous lipoid pneumonia, specifically caregiver reason/s for oil usage and the predominant pattern of clinical and radiological presentation.
2. Treatment outcomes of children with suspected exogenous lipoid pneumonia, specifically proportion of children with clinical resolution, proportion of children with radiological resolution, median time to clinical resolution, median time to radiological resolution, and proportion of children who do not survive (mortality).
3. Efficacy of treatment modalities (therapeutic lavage, steroids, other) for suspected exogenous lipoid pneumonia in children, specifically odds ratio/risk ratio.

Secondary outcome(s)

1. Factors associated with exogenous lipoid pneumonia in children.

Data extraction, selection and coding:

Studies will be reviewed based on the inclusion and exclusion criteria by as follows:

Stage 1: The primary reviewer (D.M) will screen titles of all citations that meet study eligibility in the initial screen. Studies which are approved by this author will move to the second stage of appraisal.

Stage 2: Abstracts of studies selected in stage one will be obtained and evaluated for eligibility into the systematic review by the primary reviewer.

Stage 3: In the third screen, full texts of any studies selected in the second screen will be reviewed to determine eligibility into the final analysis. To account for any differences in inferences made, the primary reviewer will keep a log of all studies excluded and reasons for exclusion after the 1st, 2nd and 3rd screen.

A standardized pre-tested data extraction form will be used. (Appendix 3) Senior reviewers will be consulted during this process whenever required. Broad characteristics under which data will be extracted will include: clinical-radiological characteristics and treatment outcomes in children with suspected exogenous lipoid pneumonia. Specific information that the primary reviewer will record from each study will include: citation details (first author, year of publication, journal); country where the study was conducted including the World Bank economy classification and continent; study design; total number of study participants; median, interquartile range and age range of study participants; race; age of onset of oil use; type of oil use; route of administration; amount and frequency of oil used per day; duration of oil use; reason for oil use; pattern of clinical presentation e.g. hypoxia, tachypnea, mixed, other; comorbidity status - underlying swallowing dysfunction (clinical aspiration/ neurological deficit/ other); co-infection e.g. bacterial, viral, mycobacterial, fungal, other; radiological pattern e.g. fatty attenuation inside airspace opacification, predominant lower/posterior zone, crazy paving, ground glass opacities or nodules; treatment modality/modalities employed e.g. discontinuation of oil, steroids, therapeutic lavage, multiple approaches; proportion of children with resolution including time to clinical resolution and time to radiological resolution; mortality.

We will contact authors of the respective studies in an attempt to obtain required details in case there is missing information or lack of clarity with regard to methodology/outcomes.

Risk of bias (quality) assessment:

The primary reviewer (D.M) will assess the quality of studies included using the Institute of Health Economics (IHE) criteria for case series; the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies; the adapted NOS for cross-sectional studies; and the Cochrane Collaboration Tool for Clinical Trials for observational studies and clinical trials respectively. These will be embedded in the standardized pre-tested data extraction form. (Appendix 3)

Strategy for data synthesis:

We will provide a narrative summary for included studies, particularly studies for which a meta-analysis is not possible. Quantitative data will be consolidated in a metanalysis. We will summarize continuous data using median of differences and categorical data using measures such as odds ratio (OR) and risk ratio (RR) for risk estimation. Summary measures will be pooled together according to the study design and use a random-effects model as it is assumed that studies may be heterogeneous. Pooled effect estimates will be stated with 95% confidence intervals. We will conduct a metaregression analysis to determine independent factors associated with exogenous lipoid pneumonia from analytic studies. We will to assess publication bias and provide a sensitivity analyses based on study quality.

Analysis of subgroups or subsets:

Where data are available, we will conduct a subgroup analysis, to compare clinical-radiologic characteristics and treatment outcomes according to, but not limited to: (a) type of oil (e.g. mineral, animal, vegetable or mixed), (b) age of oil use onset (e.g. neonate, infant, under 5 years or over 5 years old), and (c) reason for oil use (e.g. cultural or medical use). While subgroup analyses may be undertaken, it is not possible to specify all the groups in advance and additional groups may be require to be analyzed posthoc.

Contact details for further information:

Diana Marangu

dmarangu@uonbi.ac.ke

Organizational affiliation of the review:

Department of Paediatrics and Child Health, University of Cape Town, South Africa

Review team:

Dr. Diana Marangu, Division of Pulmonology, Department of Paediatrics and Child Health, University of Nairobi, Kenya, and University of Cape Town, South Africa

Dr. Diane Gray, Division of Pulmonology, Department of Paediatrics and Child Health, University of Cape Town, South Africa

Dr. Aneesa Vanker, Division of Pulmonology, Department of Paediatrics and Child Health, University of Cape Town, South Africa

Dr. Marco Zampoli, Division of Pulmonology, Department of Paediatrics and Child Health, University of Cape Town, South Africa

30th May 2017

Collaborator(s):

Dr. Komala Pillay, Division of Pathology, Department of Paediatrics and Child Health, University of Cape Town, South Africa

Dr. Ebrahim Banderker, Division of Radiology, Department of Paediatrics and Child Health, University of Cape Town, South Africa

Anticipated or actual start date:

June 2017

Anticipated completion date:

December 2017

Funding sources or sponsors:

D.M is a recipient of the African Paediatric Fellowship Programme (APFP) scholarship and the Margaret McNamara Education Grant (MMEG) 2017 for Africa. However, the views expressed through this project do not necessarily represent the views of APFP or MMEG.

Conflict of interest:

None known

Language:

English

Country:

South Africa

30th May 2017

Subject index term status:

Subject indexing assigned by CRD

Subject index terms:

Humans; Child; Neonate; Infant; Exogenous Lipoid Pneumonia; Clinical; Radiological; Treatment outcomes

Stage of review:

Began preliminary searches.

Date of registration in PROSPERO: 30/05/2017

Stage of review at time of this submission	**Started**	**Completed**
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Appendix 1: PICOTS Framework

	Components	Characteristics
P	**Population**	Children with suspected exogenous lipoid pneumonia. <u>Population characteristics:</u> • Age: ≤ 18 years (< 1month; <12months; < 5years; ≥ 5years) • Sex • Region: country; World Bank classification of economies; continent • Setting: rural, urban; public, private • Comorbidity status: underlying swallowing dysfunction, other
I	**Intervention/ Exposure**	No restriction on the intervention, if any. • Type of oil – mineral, animal, vegetable, mixed • Age of onset of oil use • Amount of oil • Frequency of oil given • Duration of oil use
C	**Control**	No restriction on the control, if any. • Treatment option – stopping oil usage; therapeutic lavage; steroids; other
O	**Outcomes**	• Clinical characteristics – predominant clinical pattern [hypoxia/ tachypnea/mixed; acute/chronic presentation]; caregiver reason for oil usage [cultural/medical; specific indication/rationale] • Radiological characteristics – CT pattern [fatty attenuation inside airspace opacification, predominant lower/posterior zone, crazy paving, ground glass opacities or nodules]

		• Treatment outcome – proportion with clinical resolution; proportion with radiological resolution; time to clinical resolution; time to radiological resolution; mortality.
T	**Timing**	Articles will be restricted to those published between 1987 to date. This 50 year period was arbitrarily deemed to represent data that will be currently relevant.
S	**Setting**	No restriction on the setting. However, articles not published in English, systematic reviews, letters and commentaries will be excluded.

Appendix 2: PubMed Search Strategy - 30/05/2017 2200hrs SAST

	Framework	Search terms	Number of articles
P	**Population**	(Child[mh] OR Child[tw]) OR (Infant[mh] OR infant[tw])	P: **2,367,222**
I	**Intervention**	-	-
C	**Control**	-	-
O	**Outcome**	AND (Exogenous lipoid pneumonia)	P+O: **194**
T	**Timing** Publication date ≥ 1967	AND (1967:2017[dp])	P+O+T: **181**
S	**Setting** English language articles	AND ("English"[la])	P+O+T+S: **126**

("child"[MeSH Terms] OR Child[tw]) OR ("infant"[MeSH Terms] OR infant[tw]) AND ("pneumonia, lipid"[MeSH Terms] OR ("pneumonia"[All Fields] AND "lipid"[All Fields]) OR "lipid pneumonia"[All Fields] OR ("exogenous"[All Fields] AND "lipoid"[All Fields] AND "pneumonia"[All Fields]) OR "exogenous lipoid pneumonia"[All Fields]) AND (1967:2017[dp]) AND "English"[la]

Appendix 3: Data Extraction Tool

DATA EXTRACTION FORM

SCREENING Study ID

A ____

☐ Related to exogenous lipoid pneumonia **e.g.A001**

☐ Includes children aged < 18 years

☐ Not a letter to the editor, editorial, review article, systematic review/metanalysis

☐ Full text in English

Study Eligible?

☐Yes *Proceed to* ***(final analysis n_i)***

☐No …… *END HERE* ***(exclude from final analysis n_e)***

Reason For Exclusion _____

FULL DATA ANALYSIS Study ID

B ____

Note: ND - not documented **e.g.B001**

Study Details:

1	First author: _____ Publication Year: ____ Journal: _____
2	Study start: Month ____ Year____ ☐Not documented
3	Study end: Month ____ Year____ ☐Not documented
4	Study design: ☐ Case report ☐ Case series ☐ Cross-sectional ☐ Case control ☐ Cohort ☐ Experimental ☐ Qualitative ☐ Mixed methods

4	Intervention: _____ ☐Not documented ☐Not applicable
5	Control: _____ ☐Not documented ☐Not applicable
Study Population:	
1	Country/Countries: _____; _____; _____
2	Country World Bank Economy Classification in study year: ☐Low income country (LIC) ☐Lower middle income country (LMIC) ☐Higher middle income country (HMIC) ☐High income country (HIC)
3	Region: ☐Africa ☐Asia ☐Australia ☐Asia ☐Europe ☐North America ☐South America
4	Sector: ☐Private ☐Public ☐Both ☐Not documented
5	Setting: ☐Rural ☐Urban ☐Not documented
5	Age (years): Lowest _____ Highest _____ Median _____ IQR _____
6	Sex: Number male ___ Proportion ___% ☐ND
7	Comorbidity status: Swallowing abnormality - Number ___ Proportion ___% ☐ND - Clinical aspiration: Number ___ Proportion ___% ☐ND - Fluoroscopy confirmed: Number ___ Proportion ___% ☐ND

	- Neurological risk factors: Number ___ Proportion ___% ☐ND - Not documented: Number ___ Proportion ___% ☐ND - Other: Number ___ Proportion ___% ☐ND
8	Co-infection: - Bacterial: Number ___ Proportion ___% ☐ND - Viral: Number ___ Proportion ___% ☐ND - Mycobacterial: Number ___ Proportion ___% ☐ND - Fungal: Number ___ Proportion ___% ☐ND - Not documented: : Number ___ Proportion ___% ☐ND - Other: Number ___ Proportion ___% ☐ND
Section 3: Symptom description	
1.	Cough? Number ___ Proportion ___% ☐ND Hotness of body? Number ___ Proportion ___% ☐ND Fast breathing? Number ___ Proportion ___% ☐ND Other (specify) Number ___ Proportion ___% ☐ND
2.	Positive history of oil usage? Number ___ Proportion ___% ☐ND Type of oil?

- Mineral: Number ___ Proportion ___% ☐ND
- Vegetable: Number ___ Proportion ___% ☐ND
- Animal: Number ___ Proportion ___% ☐ND

Median Age at onset of use? ___ **Years** ___ **Months**

Route of administration?

- Nose: Number ___ Proportion ___% ☐ND
- Mouth: Number ___ Proportion ___% ☐ND
- Topical: Number ___ Proportion ___% ☐ND
- Other: Number ___ Proportion ___% ☐ND

Median Total Amount of Oil used Daily? ___ **Millilitres**

Median Duration of Oil usage? ___ **Days** ___ **Months** ___ **Years**

Reasons for oil use/Past illnesses/concerns at the time of oil use?

- Constipation: Number ___ Proportion ___% ☐ND
- Colic: Number ___ Proportion ___% ☐ND
- Nasal stuffiness: Number ___ Proportion ___% ☐ND
- Religion: Number ___ Proportion ___% ☐ND
- Culture: Number ___ Proportion ___% ☐ND
- Other: Number ___ Proportion ___% ☐ND

Section 3: Examination at diagnosis

1.	Tachypnea? Number ___ Proportion ___% ☐ND
2.	Hypoxia? Number ___ Proportion ___% ☐ND
3.	Hyperinflation? Number ___ Proportion ___% ☐ND
4.	Clubbing? Number ___ Proportion ___% ☐ND
5.	Wasting? Number ___ Proportion ___% ☐ND

Section 4: Imaging

1.	CXR done? Number ___ Proportion ___% ☐ND Diffuse alveolar infiltrates: Proportion ___% ☐ND
2.	CT scan done?: Number ___ Proportion ___% ☐ND Fatty attenuation inside airspace opacification: Proportion ___% ☐ND Predominant lower/posterior zone: Proportion ___% ☐ND Crazy paving: Proportion ___% ☐ND Ground glass opacities: Proportion ___% ☐ND Nodules: Proportion ___% ☐ND Other: Proportion ___% ☐ND

Section 5: Treatment

1.	<u>Treatment modalities</u> Offending agent identified and discontinued? Number ___ Proportion ___% ☐ND Supportive [O2, respiratory Rx, control risk factors]? Number ___ Proportion ___% ☐ND

	Steroids? Number ___ Proportion ___% ☐ND Therapeutic Lavage? Number ___ Proportion ___% ☐ND Other? Number ___ Proportion ___% ☐ND
2.	<u>Treatment outcomes</u> Clinical resolution? Number ___ Proportion ___% ☐ND Median time to clinical resolution? ___ **Years** ___ **Months** ___ **Days** Radiological resolution? Number ___ Proportion ___% ☐ND Median time to radiological resolution? ___ **Years** ___ **Months** ___ **Days** Mortality? Number ___ Proportion ___% ☐ND
Section 6: Treatment Efficacy	
1.	Steroids vs other? Odds Ratio/Risk Ratio ___ . ___ ☐Not applicable
2.	Therapeutic lavage vs other? Odds Ratio/Risk Ratio ___ . ___ ☐Not applicable

3.	Supportive treatment [O2, respiratory Rx, control risk factors] vs other? Odds Ratio/Risk Ratio ___ . ___ ☐Not applicable
4.	Oil discontinuation vs other? Odds Ratio/Risk Ratio ___ . ___ ☐Not applicable

Trial Study Quality: The Cochrane Collaboration's tool for assessing risk of bias.

☐Applicable ☐Not applicable

1 SELECTION BIAS

	Description	Bias Judgment (Yes/No)
RANDOM SEQUENCE GENERATION		
ALLOCATION CONCEALMENT		

2 PERFOMANCE BIAS

	Description	Bias Judgment (Yes/No)
BLINDING OF PARTICIPANTS AND PERSONNEL		

3 DETECTION BIAS

	Description	Bias Judgment (Yes/No)
BLINDING OF OUTCOME ASSESSMENT		

4	ATTRITION BIAS			
		Description	Bias Judgment (Yes/No)	
	INCOMPLETE DATA			

Cohort Study Quality: The Newcastle-Ottawa Scale for Cohort Studies

☐Applicable ☐Not applicable

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community Ø
b) somewhat representative of the average _____ in the community Ø
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort Ø
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (eg surgical records) Ø
b) structured interview Ø
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes Ø
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis a) study controls for _____ (select the most important factor) Ø

b) study controls for any additional factor Ø (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
a) independent blind assessment Ø
b) record linkage Ø
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) Ø
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for Ø
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) Ø c) follow up rate < ____% (select an adequate %) and no description of those lost d) no statement

Case Control Study Quality: The Newcastle-Ottawa Scale for Case Control Studies

☐Applicable ☐Not applicable

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation Ø
b) yes, eg record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases Ø
b) potential for selection biases or not stated
3) Selection of Controls
a) community controls Ø
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint) Ø
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) Ø

b) study controls for any additional factor Ø (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) Ø
b) structured interview where blind to case/control status Ø
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes Ø
b) no
3) Non-Response rate
a) same rate for both groups Ø
b) non respondents described
c) rate different and no designation NEWCASTLE - OTTAWA QUALITY

Cross-sectional Study Quality: The Newcastle-Ottawa Scale (Customized)

☐Applicable ☐Not applicable

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. * (all subjects or random sampling)
   b) Somewhat representative of the average in the target population. * (non-random sampling)
   c) Selected group of users.
   d) No description of the sampling strategy.
2) Sample size:
   a) Justified and satisfactory. *
   b) Not justified.
3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):
   a) Validated measurement tool. **
   b) Non-validated measurement tool, but the tool is available or described.*
   c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (select one). *
   b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)
1) Assessment of the outcome:
a) Independent blind assessment. **
b) Record linkage. **
c) Self report. *
d) No description.
2) Statistical test:
a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
b) The statistical test is not appropriate, not described or incomplete.

Case Series Study Quality: The Institute of Health Economics

☐Applicable ☐Not applicable

Study objective		
1.	**Was the hypothesis/aim/objective of the study clearly stated?**	Yes ☐ Partial ☐ No ☐
Study design		
2.	**Was the study conducted prospectively?**	Yes ☐ Unclear ☐ No ☐
3.	**Were the cases collected in more than one centre?**	Yes ☐ Unclear ☐ No ☐
4.	**Were patients recruited consecutively?**	Yes ☐ Unclear ☐ No ☐
Study population		
5.	**Were the characteristics of the patients included in the study described?**	Yes ☐ Partial ☐ No ☐
6.	**Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?**	Yes ☐ Partial ☐ No ☐
7.	**Did patients enter the study at a similar point in the disease?**	Yes ☐ Unclear ☐ No ☐

Intervention and co-intervention		
8.	**Was the intervention of interest clearly described?**	Yes ☐ Partial ☐ No ☐
9.	**Were additional interventions (co-interventions) clearly described?**	Yes ☐ Partial ☐ No ☐
Outcome measure		
10.	**Were relevant outcome measures established a priori?**	Yes ☐ Partial ☐ No ☐
11.	**Were outcome assessors blinded to the intervention that patients received?**	Yes ☐ Unclear ☐ No ☐
12.	**Were the relevant outcomes measured using appropriate objective/subjective methods?**	Yes ☐ Partial ☐ No ☐
13.	**Were the relevant outcome measures made before and after the intervention?**	Yes ☐ Unclear ☐ No ☐
Statistical analysis		
14.	**Were the statistical tests used to assess the relevant outcomes appropriate?**	Yes ☐ Unclear ☐ No ☐
Results and conclusions		
15.	**Was follow-up long enough for important events and outcomes to occur?**	Yes ☐ Unclear ☐ No ☐
16.	**Were losses to follow-up reported?**	Yes ☐ Unclear ☐ No ☐
17.	**Did the study provided estimates of random variability in the data analysis of relevant outcomes?**	Yes ☐ Partial ☐ No ☐
18.	**Were the adverse events reported?**	Yes ☐ Partial ☐ No ☐

19.	**Were the conclusions of the study supported by results?**	Yes Unclear No	☐ ☐ ☐
Competing interests and sources of support			
20.	**Were both competing interests and sources of support for the study reported?**	Yes Partial No	☐ ☐ ☐

*Note: Assessor(s) may decide to remove from the checklist the items that are not applicable to their project.

References:

1. Samson D, Schoelles KM. Agency for healthcare research and quality (AHRQ) methods for effective health care. Developing the topic and structuring systematic reviews of medical tests: utility of PICOTS, analytic frameworks, decision trees, and other frameworks. In: Chang SM, Matchar DB, Smetana GW, Umscheid CA, editors. Methods guide for medical test reviews. Rockville (MD): Agency for healthcare research and quality (US); 2012.
2. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

Systematic Review - Table 1: Study characteristics

Study ID	Year, first author	Country, city/area	Study design	Study subjects	Age range in days	% Male	Type of oil (amount, frequency)	Age range at onset in days, nature [duration]	Rationale (risk factors/ comorbidities)	Diagnostic certainty level of ELP
01	1971 Bakshi[15]	India, Chandigarh	Case report	1	90	0	Animal-based (5ml daily melted ghee)	30 Chronic [14]	Culture - force feeding (infancy)	4
02	1973 Balakrishnan[16]	India, Pondicherry	Case series	12	23-1095	58	Plant-based (2.5ml daily sesame gingili)	5-540 Chronic [5-540]	Culture - oil baths, mouth cleaning (infancy)	2
03	1985 de Oliviera[17]	Brazil, Rio de Janeiro	Case series	4	570-630	25	Mineral-based (20ml hourly repeated until abdominal mass disappears)	ND Acute* ND	Medical - treatment for ascariasis partial intestinal obstruction (ND)	3
04	1987 Rabah[18]	USA, Pittsburgh	Case report	1	120	0	Mineral-based (multiple mineral oil enemas and irrigations)	ND Chronic* ND	Medical - treatment for impacted stools (Hirschsprungs)	5
05	1990 Riff[19]	Saudia Arabia, Riyadh	Case series	8	60-240	63	Animal and plant-based (7/8 ghee; 1/8 olive oil)	30 Chronic ND	Culture - force feeding ghee, olive oil nasal cleansing agent (ND)	3

06	1991 Annobil[20]	Saudi Arabia, Abha	Case series	10	60-2555	40	Animal-based	30-370 Chronic 30-2505	Culture - force feeding ghee, instilled nasally for regular bowels, ease coughs/colds, and general well-being (ND)	3
07	1991 Hugosson[21]	Saudia Arabia, Riyadh	Case series	9	3-240	67	Animal and plant-based	1-60 Chronic 3-60	Culture - butter fat as a nutritional supplement; olive oil instilled nasally (Failure to thrive)	3
08	1992 Kameswaran[22]	Saudi Arabia, Abha	Case series	24	3-132	50	Animal-based	ND Chronic ND	Culture - force feeding ghee in 21/24 patients (3/24 had severe cerebral palsy and feeding problems)	3
09	1992 Gupta[23]	Saudi Arabia, Abha	Cross sectional study	176/1090	3-ND	ND	Animal and plant-based	ND Chronic ND	Culture (ND)	1
10	1994 Fan[24]	USA, Denver	Case report	1	120	0	Mineral-based (given orally)	14 Acute [10]	Medical - treatment of constipation ("vigorous objection of oil with gagging")	3
11	1994 McDonald[25]	USA, Durham	Case report	1	3-1825	100	Mineral-based (given nasally)	ND Chronic ND	Medical - treatment of constipation	4

									(Bilateral Porencephaly; Endogenous lipoid pneumonia; Aspiration; GOR)	
12	1994 Cox[26]	USA, Indianapolis	Case report	1	6205	100	Mineral-based (given orally)	ND Chronic ND	Medical - treatment of constipation (developmental delayed, dysfunctional swallowing)	3
13	1994 Annobil[27]	Saudi Arabia, Abha	Case series	4	4-2190	50	Animal-based	1-180 Chronic 75-2008	Culture - force feeding or nasal instillation of ghee (infancy)	4
14	1995 Hugosson[28]	Saudi Arabia, Riyadh	Case report	1	4-1825	100	Animal-based	ND Chronic ND	Culture - force feeding of ghee (stunting; delayed milestones)	3
15	1995 Haddad[29]	Saudi Arabia, Riyadh	Case report	1	90	0	Animal-based (10ml daily)	1 Chronic [90]	Culture - feeding of ghee (infancy)	2
16	1996 Al-Orainy[30]	Saudi Arabia, Riyadh	Case series	2	17-180	50	Plant-based (5ml twice daily sesame oil)	10-ND Chronic 7-ND	Culture - feeding and nasal instillation (ND)	3
17	1996 Ciravegna[31]	Italy, Genoa	Case report	1	2920	100	Mineral-based (daily)	ND Chronic [60]	Medical - Vaseline oil for constipation	4

									(anoxic encephalopathy; swallowing disorder with probable aspiration)	
18	1997 Annobil[32]	Saudi Arabia, Abha	Case series	5	120-2160	100	Plant-based	1-120 Chronic 120-1440	Culture - nasal instillation of olive oil (recumbent position)	4
19	1997 Czechowski[33]	Saudi Arabia, Khamis Mushayt	Case report	1	150	100	Animal-based	ND Chronic ND	Culture - for normal bowel habits, treat coughs and cold and general good health (ND)	1
20	1997 Midulla[34]	Italy, Rome	Case report	1	1460	100	Mineral-based	730 Chronic 730	Medical - given as a laxative (refusal of the oil)	3
21	1998 Bandla[35]	USA, New Orleans	Case report	1	2190	100	Mineral-based	ND Chronic ND	Medical - given orally for constipation (Neuro-developmental delay with seizure disorder; Swallowing disorder and aspiration on MBS)	4
22	1999 Furuya[36]	Mexico, Mexico City	Case series	16	30-570	63	Animal and plant-based in 12/16	ND Chronic ND	Culture - given orally: only olive oil 9/16; olive oil plus almond oil 1/16;	3

									olive oil plus turtle oil 1/16; castor oil 1/16 (8/16: neuroblastoma, diaphragmatic eventration, congenital cardiomyopathy, congenital myopathy, CP, vascular ring, Down Syndrome, Down Syndrome + congenital cardiomyopathy; 8/16 - GOR or swallowing disorder)	
23	2000 Requena-Karssajian[37]	USA, Boston	Case report	1	42	0	Plant-based	35 Acute [7]	Culture - 5ml olive oil for constipation (GOR and poor esophageal motlity confirmed on upper GI study)	1
24	2001 Weinstein[38]	Canada, Toronto	Case report	1	1278	0	Mineral-based (given orally 3-4 times weekly)	1188 Acute [90]	Medical -treating constipation (Spastic quadriplegic CP)	1

25	2001 Banjar[39]	Saudi Arabia, Riyadh	Case series	25	180-720	44	ND	120-300 Chronic [60-420]	Culture - 20/25 positive history; 15/25 given orally (GOR 12/25)	2
26	2004 Kang[9]	South Korea, Seoul	Cohort	10/129	157-3478	53	Ketogenic diet (John Hopkin protocol)	Epileptic syndromes Chronic Neurological disorders	Medical	1
27	2005 Lee[40]	South Korea, Seoul	Case series	8	90-2190	50	Animal-based	ND Chronic ND	Culture - shark liver oil given orally (all involuntarily ingested the oil; 2/8 post encephalitis, 1/8 Lennox Gestaut; 1/8 GOR; 1/8 ingest oil while sleeping)	1
28	2005 Hoffman[41]	USA, Seattle	Case series	2	60-120	100	Plant-based	1-30 Chronic 21-90	Culture - given 200ml daily of olive oil for fussiness; for nasal congestion (Child 1: silent aspiration with thin liquids on contrast swallow; Child 2 - discoordinated swallow on contrast	3

									swallow and poor growth; Both no GOR)	
29	2005 Ridaura-Sanz[42]	Mexico, Mexico City	Case series	9	120-270	56	NA	ND ND ND	Cultural – oil instillation (2/9 -perinatal brain damage; 4/9 – GOR; 9/9 malnutrition)	1
30	2006 Zanetti[43]	Brazil, Rio de Janeiro	Case series	17	60-3285	53	Mineral-based	ND Chronic ND	Medical - treatment for chronic constipation (Cerebral Palsy 9/17; GOR 2/17)	3
31	2007 Verghese[44]	India, Chennai	Case report	1	4745	0	Plant-based	4745 Acute [1]	Culture - force feeding of sesame oil (choked)	1
32	2007 Al-Kindi[45]	Oman, Muscat	Case report	1	45	0	Animal-based	ND Acute [7]	Culture - fed ghee to ensure well-being (ND)	4
33	2008 Sias[46]	Brazil, Rio de Janeiro	Case series	28	30-3240	46	Mineral-based	ND Acute ND	Medical - treatment of constipation 23/28 and complicated ascariasis 5/28 (infancy 22/28; GOR 5/28; swallowing disorder 5/28)	4
34	2009 Kim[47]	South Korea, Seoul	Case report	1	180	100	Mineral-based	180 Chronic	Medical - 5ml daily as a laxative	4

							(10 peeled off squalene capsules daily, each capsule 0.5ml)	[90]	(forceful oil adminstration in the supine position)	
35	2009 Chetan[48]	India, Pondicherry	Cross sectional	69/774	15-330	55	Animal and plant-based	ND Acute ND	Culture - sesame oil 45/69; Coconut oil 20/69; Neem 4/69 (ND)	1
36	2009 Kumar[49]	India, Pondicherry	Cross-sectional study	9/41	ND	ND	ND	ND Chronic ND	Culture – oil instillation	1
37	2010 Mirghani[50]	UAE, Sharjah	Case series	8	379-2920	ND	Animal and plant-based	ND Chronic ND	Culture - fed ghee or olive oil (given in the recumbent position)	5
38	2010 Sharma[51]	USA, Atlanta	Case report	1	90	100	Mineral-based	14 Chronic [76]	Medical - for constipation (aspiration syndrome)	2
39	2010 Salgado[52]	Brazil, Sao Luis	Case report	1	120	100	Mineral-based	10 Chronic [110]	Medical - for constipation in a child with meconium ileus	4
40	2012 Buda[8]	Poland, Warsaw	Case report	1	1095	0	Animal and plant-based	730 Chronic [365]	Medical - ketogenic diet consisting of lipid oil mixtures for seizure control (intractable epilepsy due to	4

									congenital CMV; no cough/ swallowing reflex, feeding in the horizontal position)	
41	2013 Hochart[53]	France, Lille	Case report	1	3285	100	Plant-based	ND Chronic ND	Behavioral - drank large amounts of olive oil when frustrated (Behavioral disorder)	4
42	2015 Ramdass[54]	India, Pondicherry	Case report	1	300	0	Plant-based	ND Chronic ND	Culture - orally administered castor oil for constipation (choked after given oil)	1
43	2015 Cheon[7]	South Korea, Gwangju	Case report	1	2190	100	Plant-based (20ml twice daily of Lorenzo's oil)	2100 Chronic [90]	Medical - treatment for X-linked adreno-leukodystrophy (neurological impairment with associated swallowing difficulty and oromotor dysfunction)	4

ND – not documented; GOR – gastro-esophageal reflux.

Diagnostic accuracy of exogenous lipoid pneumonia: 1 – (Suspected) suggestive clinical history without histological assessment; 2 – (Possible) suggestive clinical history with non specific histological findings e.g. foamy macrophages/granulomas on BAL or lung biopsy but no mention of lipid staining; 3 – (Probable) suggestive clinical history with positive intracellular lipid staining of macrophages e.g. Oil Red O positive on BAL or lung biopsy but no mention of extracellular lipid; 4 – (Confirmed) suggestive clinical history with positive intracellular lipid staining macrophages in addition to being macroscopically oily or the presence of extracellular lipid in BAL or frozen section of lung biopsy; 5 – Confirmed+) suggestive clinical history with positive staining of both intracellular and extracellular lipid in BAL/frozen section lung biopsy plus additional BAL lipid analysis e.g. gas chromatography/mass spectrometry

Systematic Review - Table 2: Diagnostic profile and treatment outcomes reported in studies

Study ID	Year, first author, study type (participants)	Co-infection	Diagnostics	Treatment	Reference time	Outcome (radiological/ clinical)
01	1971 Bakshi[15] Case report	ND	CXR (dense opacity in the RUL and RML); CT (mass in posterior mediastinum); Lung biopsy; Autopsy)	Surgical resection (right pneumonectomy)	None	No radiological resolution Death (post-surgical complication)
02	1973 Balakrishnan[16] Case series (12)	ND	CXR in 12/12 (diffuse pattern more common in the RUL and RML); No CT; 1/12 BAL; 2/12 lung biopsies	Supportive treatment; Steroids in 1/12 (details not specified)	None	ND No deaths
03	1985 de Oliviera[17] Case series (4)	Recurrent infections in 1 child (microbiology ND)	CXR in 4/4 (diffuse bilateral infiltrates); CT in 2/4 (predominant posterior basal densities, negative HU); 4/4 BAL; 1/4 lung biopsies; 2 autopsies	4/4 supportive treatment; 4/4 steroids (details not specified); 4/4 antibiotics; 4/4 therapeutic lavage	Post aspiration; post supportive treatment; post discharge	2/4 clinical resolution 2/4 deaths - 30 days post discharge, and 3 months post discharge due to recurrent LRTIs respectively No radiological resolution at 4 and 6 months post discharge - CT densities present although CXR improved
04	1987 Rabah[18] Case report	Peritoneal exudate - Enterococcus, E.coli, Klebsiella, Coagulase	CXR (bilateral alveolar and interstitial infiltrates); no CT;	Supportive treatment – antibiotics; Colonostomy	post admission day; post colonostomy day	Died at age 5 months - 1 month after colonostomy

		positive Staphylococcus and Clostridium	Autopsy; Gas chromatography of the oil - matched the mineral oil			
05	1990 Riff[19] Case report	ND	CXR (diffuse bilateral infiltrates); no CT	ND	ND	ND
06	1991 Annobil[20] Case series (10)	M. fortuitum on open lung biopsy specimen; drug susceptibility details ND	CXR (perihilar infiltration; RUL and RML consolidation; bilateral extensive consolidation involving multiple lobes of both lungs); 3/10 CT (no fatty attenuation); BAL 8/10; Lung biopsy 2/10; 1 autopsy.	Supportive treatment (10/10) – antibiotics and antifungals; Steroids (10/10) - Prednisone at 2mg/kg/day for 2weeks to 14 months; Surgical resection (2/10) - lobectomies	ND	Clinical resolution (7/10); Radiological resolution (7/10) Death (1/10) – extensive M. fortuitum infection
07	1991 Hugosson[21] Case series (9)	TB treatment had been started for one child prior to clinical presentation	CXR (9/9) - diffuse bilateral consolidation medial posterior areas and perihilar distribution; CT (8/9) - areas of consolidation involving specific segments; Lung biopsy (4/9); FNA biopsy (6/9)	Supportive treatment (9/9) – antibiotics (9/9), anti-TBs (1/9); Steroids (9/9) – details not specified; Surgical resection (4/9) – affected parts	ND	Radiological resolution (1/9) – 1 year after presentation
08	1992 Kameswaran[22] Case series (24)	Negative (bacterial, fungal and AFBs tested)	CXR (2/24) - bilateral multilobar consolidation (12/24), bilateral peri-hilar infiltrates (5/24), right perihilar infiltrates (5/24), unilateral right	Supportive treatment (24/24); Steroids (24/24) – not specified; Therapeutic lavage (24/24)	Post-bronchoscopy	Clinical resolution (24/24); No radiological resolution - CXR infiltrates still present

			multilobar consolidation (2/24); No CT; BAL (22/24); Lung biopsy (2/24)			1-month post bronchoscopy; No deaths
09	1992 Gupta[23] Cross-sectional study among medical pediatric admissions between April 1989-1990 of a hx of oil instillation (800/1090=73.4%)	ND	CXR - 176 patients had positive CXRs i.e. 176/800=22% and had a positive hx of oil ingestion: RUL opacities -40%, RML opacities - 44%, generalized bilateral patchy opacities - 30%, bilateral midzone involvement - 52%; No CTs	ND	ND	ND
10	1994 Fan[24] Case report	Negative	CXR - Diffuse bilateral perihilar and RUL airspace opacification; No CT	Supportive treatment – oxygen, antibiotics	ND	Followed up to age 5 years Clinical resolution (4.7 years); No radiological resolution (mild residual bilateral interstitial opacities on CXR); No deaths
11	1994 McDonald[25] Case report	Negative (bacterial and fungal cultures)	CXR – bilateral infiltrates; No CT; Autopsy	Supportive treatment – oxygen, conventional ventilation	Post admission	No clinical or radiological resolution Death at 4 weeks post-admission
12	1994 Cox[26] Case report	M. smegmatis on open lung biopsy specimen susceptible to imipenem, tetracycline,	CXR - dense opacification lower lobes, RML and lingula; No CT; gastric and bronchial washings; open lung biopsy	Supportive treatment – antibiotics [amikacin stopped after 15/7 due to renal toxicity; doxycycline	Post admission**	After starting steroids - prompt fever resolution and mild tachypnea at discharge 14/7 later

		kanamycin, tobramycin, amikacin, sulfisoxazole, ciprofloxacin and doxycycline		3/12; ciprofloxacin 1 year]; Prednisone 60mg daily for 14/7 then tapered		Lost to follow-up Clinical resolution at 1-year post-admission (well and had regained baseline developmental function) No radiological resolution on CXR at 1-year post admission
13	1994 Annobil[27] Case series (4)	Negative (ZN and silver stain)	CXR (4/4) – 3/4 bilateral consolidation; 1/4 LLL collapse consolidation & bronchiectasis; No CTs; Lung biopsy 1/4	Supportive treatment (4/4) – antibiotics; Surgical resection (3/4) - lobectomies	Post-surgery	Clinical resolution (2/4) Radiological resolution (2/4) Bronchiectasis in 2 patients as sequelae - one of whom died Deaths (2/4) - died 11th post op day, and year 2 post lobectomy from severe chest infection
14	1995 Hugosson[28] Case report	Negative (no AFBs)	CXR - bibasal chronic lung changes; No CTs; Lung biopsy	Educated caregivers to stop giving oil	Post-stopping oil	Clinical resolution after 1 year after stopping oil Radiological resolution ND

15	1995 Haddad[29] Case report	ND	CXR – hyperinflation, bilateral infiltrates in a batwing distribution more prominent in the mid and lower lung fields; CT - bilateral consolidations with air bronchograms in the mid and lower lung fields more prominent on the left side; FNA biopsy	Supportive treatment (antibiotics); Steroids – not specified; Chest physiotherapy	Post-treatment	Clinical resolution 3 months post treatment No radiological resolution - CXR at 20 months showed incomplete clearing of infiltrates in the posterior segment of the LLL Alive at 4 months and 20 months post treatment
16	1996 Al-Orainy[30] Case series (2)	Negative (No AFBs)	CXR (2/2) - RUL expansile pneumonia and patchy perihilar consolidation; homogenous consolidation right lung, perihilar and midzones of the left with air bronchograms; CT (1/2) - Bilateral consolidations with air bronchograms in the mid and lower lung fields, no cavitations, no fat densities; FNA biopsy (1/2)	Supportive treatment (2/2) - antibiotics; Steroids (1/2)	Post-admission	No deaths; Follow-up details ND *Concerns about duplication data from Saudi Arabia
17	1996 Ciravegna[31] Case report	ND	CXR - Homogenous alveolar consolidation of the right lung; CT - consolidation contained low fat densities (-30 to -150 HU) mixed with soft tissue densities in the R	Supportive treatment – oxygen; Educated caregivers to stop oil; Therapeutic lavage – whole lung lavage 30	Post-admission; Post-therapeutic lavage	Clinical resolution – 10 days post therapeutic lavage (oxygen saturations normalized 3 weeks post admission)

			and non-specific acinar infiltrates in the posterior segment of the LLL; BAL	aliquots of 20ml sterile saline		Radiological resolution - almost clearing 40 days post therapeutic lavage Alive 40 days post lavage, no other follow-up documented
18	1997 Annobil[32] Case series (5)	Negative (Bacterial, Fungal and AFBs tested)	CXR (5/5) - Diffuse perihilar infiltrates; No CT	Supportive therapy (5/5) – antibiotics; Steroids (5/5) - Prednisolone at 2mg/kg/day; Educated caregivers to stop oil; physiotherapy twice daily	Duration post therapy day	Clinical resolution (5/5) – varied: 2/5 – completely recovered after 1 month; 1/5 – recovered after 2 months 2/5 – recovered after 5 months of therapy; Radiological resolution ND * Steroid use in treatment seems to improve clinical outcome (1/2 with late improvement, suffered from unresolved pneumonia despite antibiotics until steroids started)
19	1997 Czechowski[33] Case report	ND	CXR - Expansile RUL pneumonia; CT - Homogenous (tumor like) opacification in the RUL: 30 - 40 HU.	Supportive treatment – antibiotics; Steroids - Prednisolone (2 mglkg per	Time at starting steroids	Followed for 2 months after steroids, antibiotics and other supportive

			*follow up CT chest – more infiltrates…	day) for 2 months thereafter continued for several months (duration not specified)		treatment - thoracic consult recommended to continue treatment for several more months
20	1997 Midulla[34] Case report	ND	CXR - Diffuse infiltrates; CT - expanded appearance; BAL including quantifying the number of activated T lymphocytes and alveolar macrophages: CD3CD8 predominance	Supportive therapy; Steroids NOT used because noted declining levels of BAL lymphocytes; Educated caregivers to stop oil; Therapeutic lavage - 4 lavages in total: admission, 6 months, 12 months and 18 months	Post-diagnosis day	Clinical resolution No radiological resolution - CXR – 1yr after: reduced lung consolidation Perfusion scan – 1 yr after: unchanged (perfusion defects LLL and RUL)
21	1998 Bandla[35] Case report	Negative	CXR – RUL anterior and posterior segment dense alveolar infiltrate; CT - dense infiltrate RUL anterior + posterior segments; BAL; and BAL mass spectrometry identical to oil patient used	Supportive therapy – antibiotics; Educated caregivers to stop oil	Post-stopping oil day	Clinical resolution No radiological resolution - CXR 1 and 3 month after stopping oil – no change; CT chest – RUL anterior and posterior segments at 1month after stopping oil
22	1999 Furuya[36] Case series (16)	ND	CXR (16/16) - Right lung always involved; CT (8/16) - Perihilar and posterior dependent lung portions [nonspecific], 2/8 CTs fatty	Supportive therapy (16/16) – antibiotics 11/16, bronchodilators 10/16;		Clinical resolution (14/16) – during the hospitalization

			attenuation; BAL (15/16); Lung biopsy (1/16)	Steroids (6/16); Surgical resection - lobectomy		Clinically unchanged during hospitalization (1/16) Death (1/16) – autopsy done Radiological resolution ND *Although predominantly olive oil, two were mixed - almond and the second with turtle oil
23	2000 Requena-Karssajian[37] Case report	Negative (Chlamydia and respiratory viral panel negative)	CXR - Diffuse consolidation RUL, RLL and LLL; No CT	Supportive therapy – oxygen, antibiotics	Post-admission day	Clinical resolution – 7 days post admission Radiological resolution ND Follow-up duration not documented
24	2001 Weinstein[38] Case report	Negative (Blood cultures, viral NPAs – negative)	CXR - Bilateral airspace disease with relative sparing of the upper lobes; CT - suggested lipid within airspace opacification	Supportive therapy – oxygen (20 months), antibiotics;	Post admission day	Clinical resolution – 600 days post admission Radiological resolution ND No deaths
25	2001 Banjar[39] Case series (25)	ND	CXR (25/25) - Consolidation 23/25, atelectasis 18/25. Predominant lobe involved = RLL 20/25; No CTs	Supportive therapy (8/25) – antibiotics; Educate caregivers to stop oil	None	Clinical resolution ND Radiological resolution ND Period of follow up was 42 ± 56 month Complications: Bronchiectasis 6/25

26	2002 Lee[55] Case series (8)	ND	CXR (8/8) - Bilateral, parahilar predominantly right lung; CTs (7/8) - Dense consolidation surrounded by GGOs with geographic lobular distribution-7/7 1/7-fatty attenuation; crazy paving 3/7; 7/7 central posterior zones affected.	Supportive therapy (8/8) – antibiotics; Educate caregivers to stop oil (8/8)	Post-admission day	Clinical resolution ND No radiological resolution - improvement on follow up CXR mean 5.4 months (1.1-8.4 months)
27	2004 Kang[9] Cohort (10/129)	ND specifically for children with lipoid pneumonia	ND	ND	Post-administration of the ketogenic diet	Followed up for 12 months 3/10 diagnosed with ELP within first 4 weeks 6/10 diagnosed with ELP after 4 weeks 1/10 diagnosed both before and after 4 weeks 1/10 death within 2 months of the ketogenic diet
28	2005 Hoffman[41] Case series (2)	Positive Branhamella catarrhalis positive on BAL of child 1, fungi and viruses negative; Child 2: negative AFBs	CXRs (2/2) – Child 1 bilateral perihilar infiltrates with mild hyperinflation and RUL atelectasis; Child 2: RUL, RLL and LUL consolidation; CTs (1/2) – Child 1: Bilateral consolidation, fatty attenuation, crazy paving; BAL (1/2)	Supportive therapy (2/2) – antibiotics (2/2), oxygen (1/2), CPAP (1/2); Educated caregivers to stop giving oil (2/2)	Post-discharge day	Clinical resolution 7 months post discharge for child one, and at discharge for child two. No radiological resolution for child two, ND for child one.
29	2005 Ridaura-Sanz[42]	M.fortuitum/	CXR/CT ND; Lung biopsy (5/9); Autopsy (4/9)	Surgical resection (4/9) – RUL resection	None	Clinical resolution (3/9) Radiological resolution ND

	Case series (9)	chelonei in 1/5 BAL cultures				Deaths (5/9) Loss to follow-up (1/9)
30	2006 Zanetti[43] Case series (17)	Negative	CXR (17/17) - bronchitis/peribronchitis and patchy infiltrates in the middle; CT (17/17) - Air space consolidation (17); fatty attenuation (12) [-21 to -90 HU]; ground glass attenuation (10) – 4/10 focal, 3/10 crazy paving pattern; predominant posterior/lower regions of the lung; 1/17 – confluent airspace nodules in the periphery of a consolidation; NO pleural effusion, LN enlargement or other chest abnormality; 8/17 – central, 9/17 both central and peripheral; Lower lobes abnormal in ALL (17/17); Severe dx – RLL 15/17 , RUL 14/17 and LLL 13/17; 14/17 – predominant air space consolidation; 3/17 predominant crazy paving pattern; 17/17 – bilateral abnormality on CT, predominant right 10/17,	Supportive therapy (17/17) – antibiotics 17/17, conventional ventilation 2/17	ND	Follow-up data available for 12/17 1/17 - deteriorated on mechanical ventilation for respiratory insufficiency

			predominant left 1/17, both 6/17; BAL (15/17); Lung biopsy (2/17)			
31	2007 Verghese[44] Case report	M.fortuitum	CXR – both lower lobes; CT - Cavitating consolidation of all segments of the LLL and inferior segment of the lingual, RML and RLL; sputum;	Supportive therapy – antibiotics. M.fortuitum regimen total 12 months of treatment: RHE for 2/12 then Clarithromycin + Amikacin thrice weekly – Amikacin stopped after 2/12; the rest continued for another 10 months	Post-discharge day	Clinical resolution 6 months post discharge (asymptomatic and gained weight) No radiological resolution - CXR near complete clearance of infiltrates 6 months post discharge
32	2007 Al-Kindi[45] Case report	Negative (Blood cultures; BAL-ZN, gram, fungal, bacterial cultures)	CXR - Extensive bilateral consolidation RUL, RML, lower lobes; CT - Extensive bilateral consolidation RUL, RML, lower lobes; BAL; Lung biopsy	Supportive therapy – oxygen, CPAP and antibiotics; Steroids - Prednisolone at 2mg/kg/day for 3 weeks tapered over 9 weeks; inhaled beclomethasone 250mcg q12h for 6 months	Post-admission day	Clinical resolution 6 months post admission Radiological resolution not complete - radiological improvement on CXR at 6 months almost normal
33	2008 Sias[46] Case series (28)	ND	CXR (27/28) - Consolidation 23/28, perihilar infiltrates 13/28; CT (28/28) - Consolidation and bronchograms 24/28, decreased	Supportive therapy (28/28) – antibiotics; Steroids (2/28) – details not specified; Therapeutic	Post-admission day; post therapeutic lavage	Clinical resolution (20/28) - 20/22 that had therapeutic BALs were

			attenuation in areas of consolidation 16/28, GGOs 3/28, crazy paving 1/28; 28 BAL	lung-lavages (22/28) – multiple mean 9.6 Therapeutic lavage done in 22 (of these 2 had add on steroids) - Lavage – clearance of mineral oil from lungs AND prevention of fibrosis >>>> reducing morbidity		asymptomatic after treatment Radiological resolution - 18/20 that were asymptomatic after therapeutic lavage had CTs normalized Follow-up period of 24 months: 22/28 – therapeutic BAL (20 of the 22, asymptomatic after treatment; 18 of 20 CTs normalized); 2/28 – steroids (and multiple BALs); 6/28 – abandoned treatment
34	2009 Kim[47] Case report	ND	CXR - Diffuse consolidation bilaterally; CT - Extensive bilateral consolidation; heterogenous attenuation including fat-like densities within consolidations; BAL; Lung biopsy	Supportive therapy – oxygen and antibiotics; Steroids – Dexamethasone IV 0.3mg/kg for 2/52, tapered with oral prednisolone;	Post-admission day	No clinical resolution No radiological resolution Persistent clinical and radiological features 3 months of discharge - 2-week follow-up partial CXR and respiratory

				Educated caregivers to stop giving oil		improvement; Discharged from hospital after 3 months; Received intermittent oxygen at home.
35	2009 Chetan[48] Cross-sectional study among children with pneumonia (69/774=8.9%)	ND	CXRs (69/69) - Radiographic features suggestive of oil aspiration (persistent collapse consolidation, RUZ collapse consolidation in infants, perihilar dense infiltrates etc.; No CTs	Supportive therapy (69/69) - 7/69 ventilation, 69/69 antibiotics	Duration between aspiration and presentation (grouped into 3 categories) <24hrs (25/69), 2-7 days (23/69); >7 days (21/69)	Clinical resolution ND Radiological resolution ND Deaths: 3/7 who needed mechanical ventilation died No follow-up info provided
36	2009 Kumar[49] Cross-sectional study among children with persistent pneumonia (9/41=21%)	Pseudomonas, Acinetobacter, Klebsiella, Mixed flora (7/41 BAL cultures done) - cannot separate findings for patients with lipoid pneumonia	CXRs (41) and CTs (23) – cannot separate findings for patients with lipoid pneumonia;	Supportive therapy (9/9) – antibiotics.	ND	Clinical resolution/ improvement: 6 No clinical change: 1 Death: 2
37	2010 Mirghani[50] Case series (8)	ND	CXR/CT – ND; BAL (8/8) – gas chromatography done and mass spectrometry compared to home-made ghee and olive oil given to the children	ND	ND	ND

38	2010 Sharma[51] Case report	M. fortuitum on gastric aspirates, central venous catheter blood culture and 2 endotracheal cultures; Candida glabrata on 1st BAL not considered a true pathogen (AFBs and bacterial culture negative)	CXR - Bilateral consolidations; CT - Consolidations in the RUL, RLL and LLL with possible necrosis; BAL	Supportive therapy – oxygen, HFOV for 2/52 then conventional ventilation, antibiotics including M.fortuitum regimen: 6/12 Ciprofloxacin and Amikacin; Imipinem Nebulizer treatment, Chest Physiotherapy	Post-admission day	Clinical resolution – after 42 days (6/52) hospitalization Radiological resolution ND
39	2010 Salgado[52] Case report	ND	CXR - Bilateral apical infiltrates; CT - Extensive consolidation and geographical GGOs bilaterally; BAL	Supportive treatment – oxygen, antibiotics. Steroids - Prednisone at 1mg/kg/day for 30 days.	Post-admission day	Clinical resolution – 30 days post admission No radiological resolution - partial decrease in parenchymal lesion No death by follow-up at 30 days post-admission
40	2012 Buda[8] Case report	Negative (blood culture; viral and atypical organism serology; TB excluded; BAL negative for bacteria and fungi)	CXR and CT - Diffuse parenchymal infiltration of the right lung, atelectasis left dorsal basal lung segment, enlarged pretracheal and hilar LN; BAL	Supportive therapy – oxygen, antibiotics. Steroids - at 1-2mg/kg/day initially parenterally, then orally. Immunoglobulins. Stopped ketogenic diet. Inhalational treatment.	Time after starting steroids	Clinical resolution – 42 days after starting steroids No radiological resolution - CXR showed significant improvement in the lungs 6 weeks after steroids

41	2013 Hochart[53] Case report	Chlamydia serology (both IgM and Ig G) positive. Started on Clarithromycin Negative Mycoplasma, Toxocaria and Ascariasis. TST negative.	CXR - RUL + RLL infiltrates; CT - Airspace consolidation posterior segment RUL and apical segment RLL characterized by very low density similar to fat tissue; BAL	Supportive therapy – antibiotics. Therapeutic whole lung lavage.	Post total lung eviction.	Clinical resolution 30 days post therapeutic lung lavage. Radiological resolution 60 days post therapeutic lung lavage. lavage led to clinical and radiological resolution
42	2015 Ramdass[54] Case report	ND	CXR - Bilateral fluffy infiltrates upper and mid zones; No CT; No BAL	Supportive therapy – oxygen, antibiotics, IV fluids. Steroids - Dexamethasone IV (no dose provided)	Post admission day	Clinical resolution – 7 days post admission. Radiological resolution ND.
43	2015 Cheon[7] Case report	Negative (bacteria, fungal, mycobacteria BAL analyses)	CXR - Bilateral multifocal increased opacities; CT - Diffuse bilateral GGOs, smooth interstitial thickening, bilateral crazy paving pattern predominantly posterior and lower zones; BAL	Supportive therapy. Educated caregivers to stop giving oil.	Post admission day	Clinical resolution – 7 days post admission. Radiological resolution ND. Length of follow-up implied in the text was 10 hospital days.

AFB – acid fast bacilli; BAL – bronchoalveolar lavage; CT – chest computed tomograph; CXR – plain chest radiograph; FNA – final needle aspirate; GGO – ground glass opacification; Ig – immunoglobulin; IV – intravenous; ND – not documented; RUL – right upper lobe; RML - right middle lobe; RLL – right lower lobe; LLL – left lower lobe; TB – tuberculosis

References

1. Hadda V, Khilnani GC. Lipoid pneumonia: an overview. Expert review of respiratory medicine. 2010;4(6):799-807.
2. Betancourt SL, Martinez-Jimenez S, Rossi SE, Truong MT, Carrillo J, Erasmus JJ. Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR American journal of roentgenology. 2010;194(1):103-9.
3. Laughlen GF. Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil. The American journal of pathology. 1925;1(4):407-14.1.
4. Pinkerton H. Oils and fats: Their entrance into and fate in the lungs of infants and children: a clinical and pathologic report. American Journal of Diseases of Children. 1927;33(2):259-85.
5. Ikeda K. Oil aspiration pneumonia (lipoid pneumonia): clinical, pathologic and experimental consideration. American Journal of Diseases of Children. 1935;49(4):985-1006.
6. Samson D, Schoelles KM. AHRQ Methods for Effective Health Care Developing the Topic and Structuring Systematic Reviews of Medical Tests: Utility of PICOTS, Analytic Frameworks, Decision Trees, and Other Frameworks. In: Chang SM, Matchar DB, Smetana GW, Umscheid CA, editors. Methods Guide for Medical Test Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
7. Cheon KR, Cho HJ, Kim SS, Woo YJ. Lipoid pneumonia following aspiration of lorenzo's oil in a child with x-linked adrenoleukodystrophy. Hong Kong Journal of Paediatrics. 2017;22(4):225-8.
8. Buda P, Wieteska-Klimczak A, Wlasienko A, Mazur A, Ziolkowski J, Jaworska J, et al. Lipoid pneumonia--a case of refractory pneumonia in a child treated with ketogenic diet. Pneumonologia i alergologia polska. 2013;81(5):448-52.
9. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45(9):1116-23.
10. Kudoh S. [The virulence of saprophytic acid-fast bacteria coated with oil or fat, with special reference to an observation on the so-called atypical acid-fast bacteria. 1. Experiments with guinea-pigs on intrapulmonal and subcutaneous inoculation of saprophytic bacteria coated with liquid paraffin]. Nihon saikingaku zasshi Japanese journal of bacteriology. 1962;17:154-61.
11. Hutchins GM, Boitnott JK. Atypical mycobacterial infection complicating mineral oil pneumonia. Jama. 1978;240(6):539-41.
12. Okamori S, Asakura T, Nishimura T, Tamizu E, Ishii M, Yoshida M, et al. Natural history of Mycobacterium fortuitum pulmonary infection presenting with migratory infiltrates: a case report with microbiological analysis. BMC infectious diseases. 2018;18(1):1.
13. Marangu D, Kovacs S, Walson J, Bonhoeffer J, Ortiz JR, John-Stewart G, et al. Wheeze as an adverse event in pediatric vaccine and drug randomized controlled trials: A systematic review. Vaccine. 2015;33(41):5333-41.
14. Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, et al. International management platform for children's interstitial lung disease (chILD-EU). Thorax. 2018;73(3):231-9.
15. Bakshi S, Bhakoo ON, Singh S, Bannerjee AK. Lipoid pneumonia. (A case report). Indian pediatrics. 1971;8(11):793-5.
16. Balakrishnan S. Lipoid pneumonia in infants and children in South India. British medical journal. 1973;4(5888):329-31.
17. de Oliveira GA, Del Caro SR, Bender Lamego CM, Mercon de Vargas PR, Vervloet VE. Radiographic plain film and CT findings in lipoid pneumonia in infants following aspiration of mineral oil used in the treatment of partial small bowel obstruction by Ascaris lumbricoides. Pediatric radiology. 1985;15(3):157-60.
18. Rabah R, Evans RW, Yunis EJ. Mineral oil embolization and lipid pneumonia in an infant treated for hirschsprung's disease. Fetal and pediatric pathology. 1987;7(4):447-55.
19. Riff EJ, Moore C, Tufenkeji H, Harfi H. Infantile lipoid pneumonia. Annals of Saudi Medicine. 1990;10(4):378-82.
20. Annobil SH, Benjamin B, Kameswaran M, Khan AR. Lipoid pneumonia in children following aspiration of animal fat (ghee). Annals of tropical paediatrics. 1991;11(1):87-94.
21. Hugosson CO, Riff EJ, Moore CCM, Akhtar M, Tufenkeji HT. Lipoid pneumonia in infants: a radiological-pathological study. Pediatric radiology. 1991;21(3):193-7.
22. Kameswaran M, Annobil SH, Benjamin B, Salim M. Bronchoscopy in lipoid pneumonia. Archives of disease in childhood. 1992;67(11):1376-7.
23. Gupta M, Chowdhury MSA. A common practice of traditional medication with oil and/or ghee, as folk medicine in children of Southern Saudi Arabia. Saudi Medical Journal. 1992;13(2):106-8.
24. Fan LL, Graham LM. Radiological cases of the month. Lipoid pneumonia from mineral oil aspiration. Archives of pediatrics & adolescent medicine. 1994;148(2):205-6.
25. McDonald JW, Roggli VL, Bradford WD. Coexisting endogenous and exogenous lipoid pneumonia and pulmonary alveolar proteinosis in a patient with neurodevelopmental disease. Pediatric pathology. 1994;14(3):505-11.
26. Cox EG, Heil SA, Kleiman MB. Lipoid pneumonia and Mycobacterium smegmatis. The Pediatric infectious disease journal. 1994;13(5):414-5.
27. Annobil SH, Morad NA, Khurana P, Kameswaran M, Ogunbiyi O, al-Malki T. Reaction of human lungs to aspirated animal fat (ghee): a clinicopathological study. Virchows Archiv : an international journal of pathology. 1995;426(3):301-5.
28. Hugosson C, Bahabri S, Rifai A, al-Dalaan A. Hypertrophic osteoarthropathy caused by lipoid pneumonia. Pediatric radiology. 1995;25(6):482-3.
29. Haddad MC, Fehaid MA. Exogenous infantile lipoid pneumonia. Saudi Medical Journal. 1996;17(4):524-7.
30. Al-Orainy IA, Ahmed MF, Patel PJ. The radiological manifestations of childhood lipoid pneumonia in saudi arabia: Literature review and report of two new cases. Journal of the Bahrain Medical Society. 1996;8(2):120-3.
31. Ciravegna B, Sacco O, Moroni C, Silvestri M, Pallecchi A, Loy A, et al. Mineral oil lipoid pneumonia in a child with anoxic encephalopathy: treatment by whole lung lavage. Pediatric pulmonology. 1997;23(3):233-7.
32. Annobil SH, el Tahir M, Kameswaran M, Morad N. Olive oil aspiration pneumonia (lipoid) in children. Tropical medicine & international health : TM & IH. 1997;2(4):383-8.
33. Czechowski J. Childhood lipoid pneumonia due to animal fat aspiration diagnosed by MRI. Saudi Medical Journal. 1997;18(3):318-20.
34. Midulla F, Strappini PM, Ascoli V, Villa MP, Indinnimeo L, Falasca C, et al. Bronchoalveolar lavage cell analysis in a child with chronic lipid pneumonia. The European respiratory journal. 1998;11(1):239-42.

35. Bandla HP, Davis SH, Hopkins NE. Lipoid pneumonia: a silent complication of mineral oil aspiration. Pediatrics. 1999;103(2):E19.
36. Furuya ME, Martinez I, Zuniga-Vasquez G, Hernandez-Contreras I. Lipoid pneumonia in children: clinical and imagenological manifestations. Archives of medical research. 2000;31(1):42-7.
37. Requena-Kassarjian Y, Flores G. An infant with respiratory distress. Clinical pediatrics. 2001;40(9):507-9.
38. Weinstein M. First do no harm: The dangers of mineral oil. Paediatrics and Child Health. 2001;6(3):129-31.
39. Banjar H. Lipid pneumonia in the pediatric age group: Experience in a tertiary care center in Saudi Arabia. Current Pediatric Research. 2002;6(1):35-8.
40. Lee KH, Kim WS, Cheon JE, Seo JB, Kim IO, Yeon KM. Squalene aspiration pneumonia in children: radiographic and CT findings as the first clue to diagnosis. Pediatric radiology. 2005;35(6):619-23.
41. Hoffman LR, Yen EH, Kanne JP, Effmann EL, Gibson RL, Van Niel CW. Lipoid pneumonia due to Mexican folk remedies: cultural barriers to diagnosis. Archives of pediatrics & adolescent medicine. 2005;159(11):1043-8.
42. Ridaura-Sanz C, Lopez-Corella E, Salazar-Flores M. Exogenous lipoid pneumonia superinfected with acid-fast bacilli in infants: a report of nine cases. Fetal and pediatric pathology. 2006;25(2):107-17.
43. Zanetti G, Marchiori E, Gasparetto TD, Escuissato DL, Soares Souza A, Jr. Lipoid pneumonia in children following aspiration of mineral oil used in the treatment of constipation: high-resolution CT findings in 17 patients. Pediatric radiology. 2007;37(11):1135-9.
44. Verghese S, Ramesh S, Pararmasivan CN, Kubendiran G, Vijayasekaran D. Mycobacterium fortuitum infection complicating lipoid pneumonia. Indian Journal of Practical Pediatrics. 2007;9(4):326-8.
45. Al-Kindi H, Abdoani R, El-Iraqi M, Praseeda I. Lipoid Pneumonia Following Aspiration of Ghee (animal fat) in an Omani Infant. Oman medical journal. 2008;23(2):108-11.
46. Sias SM, Daltro PA, Marchiori E, Ferreira AS, Caetano RL, Silva CS, et al. Clinic and radiological improvement of lipoid pneumonia with multiple bronchoalveolar lavages. Pediatric pulmonology. 2009;44(4):309-15.
47. Kim ES, Kim KW, Song TW, Cho SH, Kim M, Kim K, et al. Squalene-induced exogenous lipoid pneumonia in an infant. Pediatrics International. 2009;51(5):751-3.
48. Chetan G, Ramar RS, Narayanan P, Vishnu Bhat B, Srinivasan S. Oil instillation pneumonia - A social evil. Current Pediatric Research. 2009;13(1-2):39-42.
49. Kumar M, Biswal N, Bhuvaneswari V, Srinivasan S. Persistent pneumonia: Underlying cause and outcome. Indian Journal of Pediatrics. 2009;76(12):1223-6.
50. Mirghani Z, Zein T, Annoble S, Winter J, Mostafa R. Analysis of fatty acids in Ghee and olive oil and their probable causal effect in lipoid pneumonia. Medical Journal of Indonesia. 2010;19(4):252-7.
51. Sharma D, Hilinski JA. Refractory pneumonia in a Mexican American infant. Clinical pediatrics. 2010;49(7):710-2.
52. Salgado IA, Santos CC, Salgado JV, Ferraz PC, Haidar DM, Pereira HA. Exogenous lipoid pneumonia in children: a disease to be reminded of. Revista da Associacao Medica Brasileira (1992). 2012;58(2):135-7.
53. Hochart A, Thumerelle C, Petyt L, Mordacq C, Deschildre A. Chronic Lipoid Pneumonia in a 9-Year-Old Child Revealed by Recurrent Chest Pain. Case reports in pediatrics. 2015;2015:402926.
54. Ramdass K, Soma V, Venkatesh C, Gunasekaran D, Srinivasan S. Lipoid pneumonia in a 10 month old infant. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015;6(4):1333-5.
55. Lee JY, Lee KS, Kim TS, Yoon HK, Han BK, Han J, et al. Squalene-induced extrinsic lipoid pneumonia: serial radiologic findings in nine patients. Journal of computer assisted tomography. 1999;23(5):730-5.

Appendix 4: Ethical Approval and Permissions

Ethical Approval

Hospital Permission

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 August 2017

HREC REF: 548/2017

Dr Marco Zampoli
Paediatric Pulmonology
Red Cross War Memorial Children's Hospital

Dear Dr Zampoli

PROJECT TITLE: CLINICAL- RADIOLOGICAL PATHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EXOGENOUS LIPOID PNEUMONIA: A CASE SERIES AND SYSTEMATIC REVIEW - (Masters candidate Dr D Marangu)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student Dr Diana Marangu will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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Dr Diana Marangu
Red Cross War Memorial Children's Hospital

Dear Dr Diana Marangu

APPROVAL OF RESEARCH

PROJECT TITLE: CLINICAL-RADIOLOGICAL-PATHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EXOGENOUS LIPOID PNEUMONIA: A CASE SERIES AND SYSTEMATIC REVIEW

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

MMS

Dr J Kawadza
Manager: Medical Services
Date: 16.08.17