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
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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
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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.
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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**

- **Identification**
  - Records identified through database searching (n = 1259)
  - Additional records identified through other sources (n = 1)

- **Screening**
  - Records after duplicates removed (n = 1103)

- **Eligibility**
  - Records screened (n = 1104)
  - Records excluded (n = 951)
    1. Studies were not in humans (14)
    2. Reviews (41)
    3. Conference abstracts/editorials (14)
    4. Studies did not include children (18)
    5. Related to ELP but non-English (27)
    6. Not related to ELP (837)

- **Included**
  - Full-text articles excluded with reasons (n = 110)
    1. Not specific to ELP (57)
    2. Participants details also published among included studies (10)
    3. Accidental/iatrogenic ELP (40)
    4. Insufficient information to describe as ELP (3)

Studies included in narrative synthesis (n = 43)

1. Suspected ELP without histological assessment (11/43)
2. Possible ELP with suggestive histological assessment but no mention of lipid staining (4/43)
3. Probable ELP with lipid staining on histology/cytology but no mention of extracellular lipid on BAL/frozen section lung biopsy (14/43)
4. Confirmed ELP with lipid staining on histology/cytology plus mention of extracellular lipid on BAL/frozen section lung biopsy (12/43)
5. Confirmed ELP with lipid staining on histology/cytology plus mention of extracellular lipid on BAL/frozen section lung biopsy and additional fat analysis (2/43)
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
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.

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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*

*Book with authors*

*Book with editors*

*Chapter from a book*

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](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.

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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
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References


CHAPTER 2: PUBLICATION-READY MANUSCRIPT
Exogenous lipoid pneumonia: an important cause of interstitial lung disease in African infants

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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® 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® 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 abscessus 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, 71 days), 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 \textit{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 \textit{M. abscessus} co-infection has not previously been reported in children with ELP. Other NTMs described in children with ELP include \textit{M. fortuitum}, \textit{M. chelonei} and \textit{M. smegmatis}\(^{(11, 20, 22-24)}\). \textit{M. abscessus complex} has been previously described in adult patients with ELP\(^{(25-27)}\). In a Japanese study in which \textit{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.

Acknowledgements
Diana Marangu is a recipient of the African Paediatric Fellowship Program and the Margaret McNamara Education Grant for Africa 2017. Aneesa Vanker holds a Medical Research Council of South Africa Clinician Researcher Scholarship.


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.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender</th>
<th>Age (months)</th>
<th>Type of oil</th>
<th>Duration; onset; amount and frequency oil administered</th>
<th>Underlying comorbidity and risks for aspiration</th>
<th>Clinical presentation</th>
<th>Duration of symptoms (weeks)</th>
<th>Co-infections on NPA and/or BAL†</th>
</tr>
</thead>
<tbody>
<tr>
<td>01β</td>
<td>Male</td>
<td>6.1</td>
<td>Sunflower oil</td>
<td>12 months; from day 2 of life; 2.5ml orally twice daily</td>
<td>GORγ, no aspirationε</td>
<td>Cough, tachypnea, hypoxia</td>
<td>0.9</td>
<td>Parainfluenza</td>
</tr>
<tr>
<td>02σ</td>
<td>Female</td>
<td>9.8</td>
<td>Not available</td>
<td>Not available</td>
<td>Noneγ</td>
<td>Cough, fever, tachypnea, hypoxia</td>
<td>12.0</td>
<td>None</td>
</tr>
<tr>
<td>03ββ</td>
<td>Male</td>
<td>7.5</td>
<td>Olive oil</td>
<td>14 days; from the age of 6 months; 2.5ml orally once daily</td>
<td>Noneγ</td>
<td>Tachypnea, hypoxia</td>
<td>4.0</td>
<td>Enterovirus†, Human Rhinovirus</td>
</tr>
<tr>
<td>04αα</td>
<td>Male</td>
<td>1.4</td>
<td>Mother denied giving oil</td>
<td>Not known</td>
<td>Resolved renal diseaseε</td>
<td>Cough, tachypnea, hypoxia</td>
<td>0.3</td>
<td>Klebsiella pneumoniae†, Human Rhinovirus</td>
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<tr>
<td>Date</td>
<td>Gender</td>
<td>Age</td>
<td>Type of Oil</td>
<td>Duration of Oil Reception</td>
<td>Description of Refusal</td>
<td>Symptoms</td>
<td>Virus Detection</td>
<td></td>
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</tr>
<tr>
<td>05&lt;sup&gt;o&lt;/sup&gt; Male 6.2</td>
<td>Male</td>
<td>6.2</td>
<td>Plant-based ‘cooking’ oil&lt;sup&gt;**&lt;/sup&gt;</td>
<td>5 months; from day 1 of life; 5ml orally twice daily</td>
<td>*Refused to drink oil</td>
<td>Cough, wheeze, crepitations, 2 prior LRTI hospitalisations</td>
<td>Adenovirus&lt;sup&gt;†&lt;/sup&gt;, RSV-B&lt;sup&gt;†&lt;/sup&gt;, Enterovirus&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>06&lt;sup&gt;o&lt;/sup&gt; Male 1.9</td>
<td>Male</td>
<td>1.9</td>
<td>Sunflower oil changed to liquid paraffin</td>
<td>1.6 months; from week 1 of life; 5ml orally thrice daily</td>
<td>No GOR&lt;sup&gt;0&lt;/sup&gt; No aspiration&lt;sup&gt;5&lt;/sup&gt; *Coughed and choked after getting oil</td>
<td>Cough, tachypnea, hypoxia, digital clubbing, air trapping</td>
<td>Human Metapneumovirus</td>
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<tr>
<td></td>
<td>Male</td>
<td>Age</td>
<td>Oil</td>
<td>Duration/start age</td>
<td>Feeding/Health</td>
<td>Presenting Symptoms</td>
<td>Pathogens</td>
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<tr>
<td>07&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>Male</td>
<td>10.8</td>
<td>Olive oil</td>
<td>14 days; from age of 6 months; 2.5ml orally twice daily</td>
<td>Failure to thrive; No GOR&lt;sup&gt;θ&lt;/sup&gt;; *Coughed and choked after getting oil; fed oil while lying flat</td>
<td>Cough, tachypnea, hypoxia, digital clubbing</td>
<td>Parainfluenza 2 and 4†, Streptococcus pneumoniae†, Moraxella catarrhalis†, Adenovirus, Human Bocavirus, Enterovirus, RSV-B</td>
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</tr>
<tr>
<td>08&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>Male</td>
<td>4.3</td>
<td>Plant-based 'fish' oil***</td>
<td>Exact details not known; Child under the care of grandmother</td>
<td>None&lt;sup&gt;γ&lt;/sup&gt;; No aspiration&lt;sup&gt;ε&lt;/sup&gt;</td>
<td>Cough, tachypnea, hypoxia, crepitations</td>
<td>Proteus mirabilis†, Human Rhinovirus†, RSV-B†, PCP oocysts†, Human Bocavirus, Coronavirus NL63</td>
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<tr>
<td>09&lt;sup&gt;ia&lt;/sup&gt;</td>
<td>Male</td>
<td>3.7</td>
<td>Sunflower oil</td>
<td>3 months; from age 2 months; 2.5ml orally thrice daily</td>
<td>GOR&lt;sup&gt;θ&lt;/sup&gt;, silent aspiration&lt;sup&gt;δ&lt;/sup&gt;, renal disease&lt;sup&gt;φ&lt;/sup&gt;, bronchial breath sounds,</td>
<td>Cough, fever, tachypnea, crepitations, bronchial breath sounds,</td>
<td>M. abscessus†, Klebsiella pneumoniae†, Acinetobacter baumannii†, Human</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Age</td>
<td>Gender</td>
<td>Type of Oil</td>
<td>Age Information</td>
<td>Clinical Details</td>
<td>Duration of Hospitalization</td>
<td>Microbiology</td>
<td></td>
</tr>
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</tr>
<tr>
<td>10&lt;sup&gt;π&lt;/sup&gt;</td>
<td>Male</td>
<td>2.1</td>
<td>Sunflower oil</td>
<td>2 months; from day 6 of life; 5ml orally twice daily</td>
<td>GOR&lt;sup&gt;θ&lt;/sup&gt;, silent aspiration&lt;sup&gt;δ&lt;/sup&gt;</td>
<td>1 prior LRTI hospitalization</td>
<td>Rhinovirus, Human Bocavirus</td>
<td></td>
</tr>
<tr>
<td>11&lt;sup&gt;π&lt;/sup&gt;</td>
<td>Male</td>
<td>2.6</td>
<td>Olive oil</td>
<td>1.6 months; from age of 4 weeks; 2.5ml orally once daily</td>
<td>No GOR&lt;sup&gt;θ&lt;/sup&gt;, no aspiration&lt;sup&gt;δ&lt;/sup&gt; *Coughed and cried after getting oil</td>
<td>1 prior LRTI hospitalization</td>
<td>M. abscessus&lt;sup&gt;†&lt;/sup&gt;, Pseudomonas aeruginosa&lt;sup&gt;†&lt;/sup&gt;, Candida species&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>12&lt;sup&gt;π&lt;/sup&gt;</td>
<td>Male</td>
<td>3.1</td>
<td>Plant-based ‘cooking’ oil&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.1 months; from age</td>
<td>None&lt;sup&gt;ι&lt;/sup&gt; *Coughed and cried</td>
<td>1 prior LRTI hospitalization</td>
<td>RSV-A&lt;sup&gt;†&lt;/sup&gt;, Klebsiella pneumoniae&lt;sup&gt;†&lt;/sup&gt;, Bordetella Pertussis</td>
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<td>After getting oil</td>
<td>1 prior LRTI hospitalization</td>
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</tr>
</tbody>
</table>

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

- Milk scan performed
- Contrast swallow performed
- Swallowing assessed by speech therapist
- 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
- Unable to reach patient on phone or in the community
- Child was left under the care of the grandmother
- Retrospective diagnosis of ELP, child given oil for an additional 6 months
- Siblings within the case series
- Has sibling/s who also received oil but did not experience respiratory-related complications
- Has sibling/s who also received oil and experienced respiratory-related complications
- Sibling death during infancy related to a similar respiratory illness
- Has no siblings
Posterior urethral valves (PUVs) ablated and bladder neck surgically excised

Dysplastic right kidney with cysts, enlarged left kidney with hydroureter, no PUVs, normal renal function
**Table 2: Treatment and outcomes**

<table>
<thead>
<tr>
<th>ID</th>
<th>Oxygen (days)</th>
<th>NIV/ MV (days)</th>
<th>Antibiotics (days)</th>
<th>Steroid use (days)</th>
<th>Therapeutic lavage (number) [number of days post-admission]</th>
<th>Total days hospitalised in the diagnostic BAL admission</th>
<th>Time to clinical resolution (months)</th>
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<tbody>
<tr>
<td>01</td>
<td>23</td>
<td>CPAP (2)</td>
<td>Yes (7)</td>
<td>Prednisone at 2mg/kg/day (7)</td>
<td>Yes (1) [21]</td>
<td>24</td>
<td>8.0</td>
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<td>7</td>
<td>None</td>
<td>Yes (11)</td>
<td>None</td>
<td>None</td>
<td>13</td>
<td>0.3</td>
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<tr>
<td>03</td>
<td>16</td>
<td>None</td>
<td>Yes (15)</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>0.5</td>
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<tr>
<td>04</td>
<td>23</td>
<td>CPAP (6)</td>
<td>Yes (14)</td>
<td>Prednisone at 1mg/kg/day (14)</td>
<td>None</td>
<td>25</td>
<td>12.0</td>
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<tr>
<td>05</td>
<td>0</td>
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<td>No</td>
<td>None</td>
<td>None</td>
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<td>14.0</td>
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<td>06</td>
<td>15</td>
<td>IPPV (1)</td>
<td>Yes (14)</td>
<td>Methylprednisone at 10mg/kg/day (3)</td>
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<td>22</td>
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<td>Yes (7)</td>
<td>Prednisone at 1mg/kg/day (5)</td>
<td>None</td>
<td>6</td>
<td>1.2</td>
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<td></td>
<td></td>
<td>CPAP</td>
<td></td>
<td></td>
<td>Dexamethasone stat; Prednisone at 2mg/kg/day</td>
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<tr>
<td>08</td>
<td>27</td>
<td>CPAP (23)</td>
<td>Yes (26)</td>
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<td>Yes (1) [19]</td>
<td>30</td>
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<tr>
<td>09</td>
<td>71</td>
<td>CPAP (27) HFNC (8)</td>
<td>Yes (ongoing) M. abscessus treatment</td>
<td>Prednisone commenced at 2mg/kg/day (94)</td>
<td>Yes (3) [38; 56; 86]</td>
<td>98</td>
<td>3.2</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>CPAP (2)</td>
<td>Yes (5)</td>
<td>Prednisone at 2mg/kg/day (7)</td>
<td>Yes (1) [22]</td>
<td>23</td>
<td>0.8</td>
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<td>11</td>
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<td>CPAP (16) HFNC (7)</td>
<td>Yes (ongoing) M. abscessus treatment</td>
<td>Prednisone commenced at 2mg/kg/day, tapered (ongoing)</td>
<td>Yes (1) [52]</td>
<td>117</td>
<td>3.9</td>
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<td>12</td>
<td>12</td>
<td>CPAP (3) HFNC (3)</td>
<td>Yes (5)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>23</td>
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</tbody>
</table>

NIV, non-invasive ventilation; MV, mechanical ventilation; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannulae; IPPV, intermittent positive pressure ventilation

9 Nebulized Amikacin (underlying renal disease), Intravenous Imipinem, Linezolid and Ciprofloxacin) and oral Azithromycin for 1 month. Then discharged on oral Linezolid, Ciprofloxacin and Azithromycin. 1-month follow-up BAL was negative on mycobacterial culture.
Intravenous Imipenem and Amikacin and oral Linezolid, Levofloxacin and Azithromycin for 1 month. 1-month follow-up BAL including mycobacterial culture still positive.
**E-table 1: Radiological and pathological findings**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Chest radiograph</th>
<th>CT chest</th>
<th>BAL macroscopic appearance</th>
<th>BAL/Biopsy microscopic appearance</th>
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</thead>
<tbody>
<tr>
<td>01</td>
<td>Bilateral ground glass opacification, predominantly on the right. Lobar distribution more confluent in the RUL, RLL, LLL and lingula with air bronchograms. Air trapping.</td>
<td>Not done</td>
<td>Milky</td>
<td>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.</td>
</tr>
<tr>
<td>02</td>
<td>Diffuse ground glass opacification confluent in the RUL. Bilateral patchy consolidation in all lobes predominantly on the right with peripheral sparing.</td>
<td>Not done</td>
<td>Cloudy</td>
<td>Numerous macrophages, scattered lymphocytes and neutrophils. &gt;50% lipid laden macrophages with abundant extracellular lipid. Negative PAS.</td>
</tr>
<tr>
<td>03</td>
<td>Diffuse airspace opacification, parahilar and non-segmental RUL, LUL, RML and lingula.</td>
<td>Homogenous ground glass opacification. Airspace consolidation in a perihilar distribution. Interlobular septal</td>
<td>Cloudy</td>
<td>Numerous macrophages, scattered lymphocytes and neutrophils. Abundant lipid laden macrophages and extracellular lipid.</td>
</tr>
<tr>
<td>04</td>
<td>Diffuse airspace opacification predominantly of the right lung.</td>
<td>Thickening with characteristic crazy paving pattern.</td>
<td>[Cell count: neutrophils 66%, lymphocytes 16%, monocytes 14%, eosinophils 4%]</td>
<td></td>
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<td>---</td>
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<td></td>
</tr>
<tr>
<td>05</td>
<td>Diffuse ground glass opacification more confluent in the RUL, RML, left parahilar segmental LUL and lingula, and patchy in the lower lobes bilaterally.</td>
<td>Diffuse ground glass opacification and airspace consolidation of both lower lobes particularly RLL. Interlobular septal thickening and crazy paving. Increased perihilar and mediastinal soft tissue.</td>
<td>Numerous macrophages, scattered lymphocytes and neutrophils with 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%]</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Diffuse ground glass opacification with a right sided predominance and confluent in the right upper lobe.</td>
<td>Diffuse ground glass opacification with a lower zone predominance. Mild interlobular septal thickening.</td>
<td>Cloudy</td>
<td>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.</td>
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<tr>
<td>07</td>
<td>Diffuse homogenous ground glass opacification in both right and left lung fields with dense airspace opacification.</td>
<td>Predominant central, basal and posterior involvement, distinct sparing of the peripheral lung zones with geographical pattern</td>
<td>Purulent (“thick yellow”) BAL fluid</td>
<td>Numerous vacuolated macrophages and neutrophils, scattered lymphocytes. Abundant lipid laden macrophages and extracellular lipid. PAS negative. Scattered bacterial cocci.</td>
</tr>
<tr>
<td>Date</td>
<td>Description</td>
<td>Radiological Findings</td>
<td>Microscopic Findings</td>
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<tr>
<td>08</td>
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<tr>
<td>Diffuse homogenous ground glass opacification predominantly on the right, slightly sparing part of the left lower lobe. Bilateral air bronchograms.</td>
<td>Diffuse involvement (interlobular septal thickening and crazy paving). 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.</td>
<td>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 88%, lymphocytes 3%, monocytes 9%]</td>
<td></td>
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</tr>
<tr>
<td>09</td>
<td>Confluent airspace opacification of the RUL, RML and LLL.</td>
<td>Mass like opacification within the posterior segment of the RUL that demonstrates mild</td>
<td>Milky BAL. Abundant macrophages, scattered lymphocytes and no neutrophils. Abundant</td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>Description</td>
<td>Findings</td>
<td>Diagnosis</td>
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<tr>
<td>11</td>
<td>Lobulated density occupies entire right hemithorax sparing the right costophrenic angle, a confluent expansile consolidation. Patchy airspace opacification.</td>
<td>Bilateral pneumonia (airspace opacification) with significant expansile component of the right. Multiple nodules. RML. Cloudy and clear BALs.</td>
<td>Abundant lipid laden macrophages &gt;50%. Candida and numerous acid-fast bacilli. 20% lipid laden macrophages and extracellular lipid present in second sample.</td>
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<tr>
<td>#</td>
<td>Observation</td>
<td>Description</td>
<td>BAL Findings</td>
<td>Cell Count</td>
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<tr>
<td>12</td>
<td>Diffuse ground glass opacification bilaterally predominantly RUL and RML.</td>
<td>None</td>
<td>Milky BAL</td>
<td>Neutrophils 33%, Lymphocytes 17%, Monocytes 50%, Eosinophils 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cell count: neutrophils 24%, lymphocytes 8%, monocytes 70%, eosinophils 0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Date of Interview</th>
<th>Participant Enrollment ID</th>
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</thead>
<tbody>
<tr>
<td>dd</td>
<td>mmm</td>
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</tbody>
</table>

**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)
- **Frequency?** [ ] Hourly

- **Total Amount Daily?** [ ] ML
### 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]

<table>
<thead>
<tr>
<th>Co-morbidities:</th>
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<tbody>
<tr>
<td>Any underlying swallowing problem? □ No □ Yes (specify)____________</td>
</tr>
<tr>
<td>□ Other (specify) _____________________________________________</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>□ Yes (why)____________ □ No</th>
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<tbody>
<tr>
<td>When did you stop?</td>
</tr>
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</table>

| dd | mmm | yyyy |

<table>
<thead>
<tr>
<th>Why did you stop?</th>
</tr>
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<tbody>
<tr>
<td>□ The doctor told me □ It was making my child sick</td>
</tr>
<tr>
<td>□ Other (specify) _____________________________________</td>
</tr>
</tbody>
</table>

### 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, |
**Section 5:** How many times have they shown (frequency, duration, reason)? [Only use as probes, allow for detailed caregiver description]

<table>
<thead>
<tr>
<th></th>
<th>□ No</th>
<th>□ Yes (How many?)</th>
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<tr>
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</table>

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) ________

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**Section 6: Do you know other people who use oils? Who? How? Why?**

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

<table>
<thead>
<tr>
<th></th>
<th>□ Family members (specify e.g. mother, sister, aunty, cousin, niece etc.)</th>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>□ Community members (specify e.g. friends, neighbors, religious circles, general etc.)</th>
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</table>

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 gonna get the wrong one then baby gonna pass away. You don’t know this is the right one or this 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 gonna 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 gonna 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.”
Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist


<table>
<thead>
<tr>
<th>No.</th>
<th>Item</th>
<th>Guide questions/description</th>
<th>Reported on Page #</th>
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<tbody>
<tr>
<td></td>
<td><strong>Domain 1: Research team and reflexivity</strong></td>
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<tr>
<td></td>
<td><strong>Personal Characteristics</strong></td>
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</tr>
<tr>
<td>1.</td>
<td>Interviewer/facilitator</td>
<td>Which author/s conducted the interview or focus group?</td>
<td>E-text</td>
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<tr>
<td>2.</td>
<td>Credentials</td>
<td>What were the researcher’s credentials? E.g. PhD, MD</td>
<td>E-text</td>
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<td>3.</td>
<td>Occupation</td>
<td>What was their occupation at the time of the study?</td>
<td>E-text</td>
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<td>4.</td>
<td>Gender</td>
<td>Was the researcher male or female?</td>
<td>N/A</td>
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<tr>
<td>5.</td>
<td>Experience and training</td>
<td>What experience or training did the researcher have?</td>
<td>E-text</td>
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<td><strong>Relationship with participants</strong></td>
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<td>6.</td>
<td>Relationship established</td>
<td>Was a relationship established prior to study commencement?</td>
<td>E-text</td>
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<td>7.</td>
<td>Participant knowledge of the interviewer</td>
<td>What did the participants know about the researcher? e.g. personal goals, reasons for doing the research</td>
<td>E-text</td>
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<td>8.</td>
<td>Interviewer characteristics</td>
<td>What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic</td>
<td>E-text</td>
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<td><strong>Domain 2: study design</strong></td>
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<td><strong>Theoretical framework</strong></td>
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<td>9.</td>
<td>Methodological orientation</td>
<td>What methodological orientation was stated to</td>
<td>E-text</td>
</tr>
<tr>
<td>and Theory</td>
<td>underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis</td>
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<tr>
<td><strong>Participant selection</strong></td>
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<tr>
<td>10. Sampling</td>
<td>How were participants selected? e.g. purposive, convenience, consecutive, snowball</td>
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<tr>
<td>11. Method of approach</td>
<td>How were participants approached? e.g. face-to-face, telephone, mail, email</td>
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<tr>
<td>12. Sample size</td>
<td>How many participants were in the study?</td>
<td></td>
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<tr>
<td>13. Non-participation</td>
<td>How many people refused to participate or dropped out? Reasons?</td>
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<tr>
<td><strong>Setting</strong></td>
<td></td>
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<tr>
<td>14. Setting of data collection</td>
<td>Where was the data collected? e.g. home, clinic, workplace</td>
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<tr>
<td>15. Presence of non-participants</td>
<td>Was anyone else present besides the participants and researchers?</td>
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<tr>
<td>16. Description of sample</td>
<td>What are the important characteristics of the sample? e.g. demographic data, date</td>
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<tr>
<td><strong>Data collection</strong></td>
<td></td>
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<tr>
<td>17. Interview guide</td>
<td>Were questions, prompts, guides provided by the authors? Was it pilot tested?</td>
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</tr>
<tr>
<td>18. Repeat interviews</td>
<td>Were repeat interviews carried out? If yes, how many?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Audio/visual recording</td>
<td>Did the research use audio or visual recording to collect the data?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Field notes</td>
<td>Were field notes made during and/or after the interview or focus group?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Duration</td>
<td>What was the duration of the interviews or focus group?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Data saturation</td>
<td>Was data saturation discussed?</td>
<td>E-text</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>23. Transcripts returned</td>
<td>Were transcripts returned to participants for comment and/or correction?</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**Domain 3: analysis and findings**

**Data analysis**

<table>
<thead>
<tr>
<th>24. Number of data coders</th>
<th>How many data coders coded the data?</th>
<th>E-text</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Description of the coding tree</td>
<td>Did authors provide a description of the coding tree?</td>
<td>N/A</td>
</tr>
<tr>
<td>26. Derivation of themes</td>
<td>Were themes identified in advance or derived from the data?</td>
<td>E-text</td>
</tr>
<tr>
<td>27. Software</td>
<td>What software, if applicable, was used to manage the data?</td>
<td>E-text</td>
</tr>
<tr>
<td>28. Participant checking</td>
<td>Did participants provide feedback on the findings?</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Reporting**

<table>
<thead>
<tr>
<th>29. Quotations presented</th>
<th>Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number</th>
<th>Results and E-text</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Data and findings consistent</td>
<td>Was there consistency between the data presented and the findings?</td>
<td>Results and E-text</td>
</tr>
<tr>
<td>31. Clarity of major themes</td>
<td>Were major themes clearly presented in the findings?</td>
<td>Results and E-text</td>
</tr>
<tr>
<td>32. Clarity of minor themes</td>
<td>Is there a description of diverse cases or discussion of minor themes?</td>
<td>Results and E-text</td>
</tr>
</tbody>
</table>
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 lipid 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 lipid pneumonia diagnosis *

Mark only one oval per row.

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

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. **Other management (details)**  

132. **Other management (details)**  

133. **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 Immunofluorescence**

*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
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.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td></td>
</tr>
<tr>
<td>Right lower lobe</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td></td>
</tr>
<tr>
<td>Right lower lobe</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*  

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td></td>
</tr>
<tr>
<td>Right lower lobe</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*  

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td></td>
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<tr>
<td>Right lower lobe</td>
<td></td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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
   - [x] Yes

23. **Distribution CXR-5**
   *Mark only one oval per row.*
   
<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
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<tr>
<td>Right middle lobe</td>
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<td>Right lower lobe</td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*
   
<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
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<td>Right middle lobe</td>
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<td>Right lower lobe</td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>
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.*

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td></td>
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<td>Right middle lobe</td>
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<td>Right lower lobe</td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
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<td>Right middle lobe</td>
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<td>Right lower lobe</td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
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<td>Right middle lobe</td>
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<td>Right lower lobe</td>
<td></td>
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<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.*

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
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<td>Right upper lobe</td>
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<td>Right middle lobe</td>
<td></td>
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<tr>
<td>Right lower lobe</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td>☐</td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>☐</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>☐</td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>☐</td>
</tr>
<tr>
<td>Lingula</td>
<td>☐</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>☐</td>
</tr>
</tbody>
</table>

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 lipid 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
   - 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
   - [ ] Positive - 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.*

<table>
<thead>
<tr>
<th></th>
<th>Not requested</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 biopsy**

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/documentated
- No
- Yes - minimal
- Yes - moderate
- Yes - abundant
- Yes - not quantified

29. **Periodic acid schiff stain on biopsy**  
*Mark only one oval.*
- Not requested/documentated
- 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.*

<table>
<thead>
<tr>
<th></th>
<th>Not requested</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
38. Specify additional histology details of biopsy
**Interview Guide**

Date of Interview: 

<table>
<thead>
<tr>
<th>dd</th>
<th>mmm</th>
<th>yyyy</th>
</tr>
</thead>
</table>

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*

<table>
<thead>
<tr>
<th>Co-morbidities: Any underlying swallowing problem?</th>
<th>□ No □ Yes (specify) □ Other (specify)</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>□ Yes (why) □ No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>When did you stop?</th>
</tr>
</thead>
<tbody>
<tr>
<td>dd mmm yyyy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Why did you stop?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ The doctor told me □ It was making my child sick □ Other (specify)</td>
</tr>
</tbody>
</table>

### 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*

<table>
<thead>
<tr>
<th>□ No □ Yes (How many?)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>How old? Any respiratory problems? Did you give them oil?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. □ No □ Yes (specify) ; □ No □ Yes (specify)</td>
</tr>
<tr>
<td>2. □ No □ Yes (specify) ; □ No □ Yes (specify)</td>
</tr>
<tr>
<td>3. □ No □ Yes (specify) ; □ No □ Yes (specify)</td>
</tr>
<tr>
<td>4. □ No □ Yes (specify) ; □ No □ Yes (specify)</td>
</tr>
<tr>
<td>5. □ No □ Yes (specify) ; □ No □ Yes (specify)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>□ Family members (specify e.g. mother, sister, aunty, cousin, niece etc.)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>□ Community members (specify e.g. friends, neighbors, religious circles, general etc.)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>How? Why?</th>
</tr>
</thead>
</table>
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, but will require further information or more time to make a decision

☐ 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.
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: nnwasha@y.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 Marangu¹,²
Komala Pillay²
Ebrahim Banderker²
Diane Gray²
Aneesa Vanker²
Marco Zampoli²

¹University of Nairobi, Kenya
²University 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:**

30th May 2017
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 lipid 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.

30\(^{th}\) May 2017
Context:
Research conducted in any context globally.

Outcome(s):

Primary outcome(s)
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.

30th May 2017
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.

30th May 2017
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 meta-analysis. 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

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<th>Started</th>
<th>Completed</th>
</tr>
</thead>
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<td>Preliminary searches</td>
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<td>No</td>
</tr>
<tr>
<td>Piloting of the study selection process</td>
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<td>No</td>
</tr>
<tr>
<td>Formal screening of search results against eligibility criteria</td>
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<td>No</td>
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<tr>
<td>Data extraction</td>
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<td>No</td>
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<tr>
<td>Risk of bias (quality) assessment</td>
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<td>No</td>
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<td>Data analysis</td>
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## Appendix 1: PICOTS Framework

<table>
<thead>
<tr>
<th>Components</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **P** | **Population** Children with suspected exogenous lipoid pneumonia.  
Population characteristics:  
- 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] |
| 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

<table>
<thead>
<tr>
<th>Framework</th>
<th>Search terms</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>Intervention</td>
<td>-</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Control</td>
<td>-</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Outcome</td>
<td>AND (Exogenous lipoid pneumonia)</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td>Timing</td>
<td>Publication date ≥ 1967 AND (1967:2017[dp])</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>Setting</td>
<td>English language articles AND (&quot;English&quot;[la])</td>
</tr>
</tbody>
</table>

## Appendix 3: Data Extraction Tool

### DATA EXTRACTION FORM

#### SCREENING

- 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)
- **No** .... END HERE (exclude from final analysis n)

**Reason For Exclusion**

---

#### FULL DATA ANALYSIS

- **Note:** ND - not documented

**Study Details:**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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<td>First author: _______</td>
<td>Publication Year:</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Study start: Month</td>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Study end: Month</td>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Study design:</td>
<td>Case report</td>
<td>Case series</td>
</tr>
</tbody>
</table>

- Cohort | Experimental | Qualitative | Mixed methods

---

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

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### Neurological risk factors:
- Number: ___
- Proportion: ___%
- Not documented: ___

### Not documented:
- Number: ___
- Proportion: ___%

### Other:
- Number: ___
- Proportion: ___%

### Co-infection:
- Bacterial: Number: ___
- Proportion: ___%
- Not documented: ___

### Viral:
- Number: ___
- Proportion: ___%
- Not documented: ___

### Mycobacterial:
- Number: ___
- Proportion: ___%
- Not documented: ___

### Fungal:
- Number: ___
- Proportion: ___%
- Not documented: ___

### Other:
- Number: ___
- Proportion: ___%

### Section 3: Symptom description

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Number</th>
<th>Proportion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cough?</td>
<td>Number</td>
<td>Proportion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hotness of body?</td>
<td>Number</td>
<td>Proportion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fast breathing?</td>
<td>Number</td>
<td>Proportion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (specify)</td>
<td>Number</td>
<td>Proportion</td>
<td></td>
</tr>
</tbody>
</table>

|2. | Positive history of oil usage? | Number | Proportion |   |
|   | Type of oil?           |        |            |   |

---

30th May 2017
- 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. Treatment modalities
   Offending agent identified and discontinued?
      Number □□□□□ Proportion □□□□□% □ND
   Supportive [O2, respiratory Rx, control risk factors]?
      Number □□□□□ Proportion □□□□□% □ND

30th May 2017
<table>
<thead>
<tr>
<th>Steroids?</th>
<th>Number</th>
<th>Proportion</th>
<th>□ ND</th>
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<tbody>
<tr>
<td>Therapeutic Lavage?</td>
<td>Number</td>
<td>Proportion</td>
<td>□ ND</td>
</tr>
<tr>
<td>Other?</td>
<td>Number</td>
<td>Proportion</td>
<td>□ ND</td>
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2. Treatment outcomes

Clinical resolution?

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<th>Number</th>
<th>Proportion</th>
<th>□ ND</th>
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Median time to clinical resolution? □□□□ Years □□□ Months □□ Days

Radiological resolution?

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<tr>
<th>Number</th>
<th>Proportion</th>
<th>□ ND</th>
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</table>

Median time to radiological resolution? □□□□ Years □□□ Months □□ Days

Mortality?

<table>
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<tr>
<th>Number</th>
<th>Proportion</th>
<th>□ ND</th>
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</table>

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.

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<th>SELECTION BIAS</th>
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<td>ATTRITION BIAS</td>
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<td>---</td>
<td>----------------------------------------------------</td>
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<tr>
<td></td>
<td>INCOMPLETE DATA</td>
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**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

<table>
<thead>
<tr>
<th>□ Applicable</th>
<th>□ Not applicable</th>
</tr>
</thead>
</table>

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)**

<table>
<thead>
<tr>
<th>Selection: (Maximum 5 stars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Representativeness of the sample:</td>
</tr>
<tr>
<td>a) Truly representative of the average in the target population. * (all subjects or random sampling)</td>
</tr>
<tr>
<td>b) Somewhat representative of the average in the target population. * (non-random sampling)</td>
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<tr>
<td>c) Selected group of users.</td>
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<tr>
<td>d) No description of the sampling strategy.</td>
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<tr>
<td>2) Sample size:</td>
</tr>
<tr>
<td>a) Justified and satisfactory. *</td>
</tr>
<tr>
<td>b) Not justified.</td>
</tr>
<tr>
<td>3) Non-respondents:</td>
</tr>
<tr>
<td>a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *</td>
</tr>
<tr>
<td>b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.</td>
</tr>
<tr>
<td>c) No description of the response rate or the characteristics of the responders and the non-responders.</td>
</tr>
<tr>
<td>4) Ascertainment of the exposure (risk factor):</td>
</tr>
<tr>
<td>a) Validated measurement tool. **</td>
</tr>
<tr>
<td>b) Non-validated measurement tool, but the tool is available or described.*</td>
</tr>
<tr>
<td>c) No description of the measurement tool.</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Study objective</th>
<th>Yes</th>
<th>Partial</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>1. Was the hypothesis/aim/objective of the study clearly stated?</td>
<td></td>
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<tr>
<td>2. Was the study conducted prospectively?</td>
<td>Yes</td>
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<tr>
<td>3. Were the cases collected in more than one centre?</td>
<td>Yes</td>
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<tr>
<td>4. Were patients recruited consecutively?</td>
<td>Yes</td>
<td></td>
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<tr>
<td>5. Were the characteristics of the patients included in the study described?</td>
<td>Yes</td>
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<td>6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?</td>
<td>Yes</td>
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<tr>
<td>7. Did patients enter the study at a similar point in the disease?</td>
<td>Yes</td>
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* 30th May 2017
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<th>Intervention and co-intervention</th>
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<td>9.</td>
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<th>Outcome measure</th>
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<th>Results and conclusions</th>
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<td>18.</td>
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</tbody>
</table>
19. Were the conclusions of the study supported by results?

| Yes | ☐ |
| Unclear | ☐ |
| No | ☐ |

**Competing interests and sources of support**

| Yes | ☐ |
| Partial | ☐ |
| No | ☐ |

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

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**References:**


# Systematic Review - Table 1: Study characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year, first author</th>
<th>Country, city/area</th>
<th>Study design</th>
<th>Study subjects</th>
<th>Age range in days</th>
<th>% Male</th>
<th>Type of oil (amount, frequency)</th>
<th>Age range at onset in days, nature [duration]</th>
<th>Rationale (risk factors/comorbidities)</th>
<th>Diagnostic certainty level of ELP</th>
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</thead>
<tbody>
<tr>
<td>01</td>
<td>Bakshi [15]</td>
<td>India, Chandigarh</td>
<td>Case report</td>
<td>1</td>
<td>90</td>
<td>0</td>
<td>Animal-based (5ml daily melted ghee)</td>
<td>30 Chronic [14]</td>
<td>Culture - force feeding (infancy)</td>
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<td>02</td>
<td>Balakrishnan [16]</td>
<td>India, Pondicherry</td>
<td>Case series</td>
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<td>23-1095</td>
<td>58</td>
<td>Plant-based (2.5ml daily sesame gingili)</td>
<td>5-540 Chronic [5-540]</td>
<td>Culture - oil baths, mouth cleaning (infancy)</td>
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<td>03</td>
<td>de Oliviera [17]</td>
<td>Brazil, Rio de Janeiro</td>
<td>Case series</td>
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<td>570-630</td>
<td>25</td>
<td>Mineral-based (20ml hourly repeated until abdominal mass disappears)</td>
<td>ND Acute* ND</td>
<td>Medical - treatment for ascariasis partial intestinal obstruction (ND)</td>
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<td>04</td>
<td>Rabah [18]</td>
<td>USA, Pittsburgh</td>
<td>Case report</td>
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<td>0</td>
<td>Mineral-based (multiple mineral oil enemas and irrigations)</td>
<td>ND Chronic* ND</td>
<td>Medical - treatment for impacted stools (Hirschsprungs)</td>
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<td>60-240</td>
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<td>Animal and plant-based (7/8 ghee; 1/8 olive oil)</td>
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<td>Culture - force feeding ghee, olive oil nasal cleansing agent (ND)</td>
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<tr>
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<td>1991</td>
<td>Saudi Arabia, Abha</td>
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<td>Culture - force feeding ghee, instilled nasally for regular bowels, ease coughs/colds, and general well-being (ND)</td>
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<td>Culture - butter fat as a nutritional supplement; olive oil instilled nasally (Failure to thrive)</td>
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<td>24</td>
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<td>Culture - force feeding ghee in 21/24 patients (3/24 had severe cerebral palsy and feeding problems)</td>
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<td>Medical - treatment of constipation (&quot;vigorous objection of oil with gagging&quot;)</td>
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<td>6205</td>
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<td>Type</td>
<td>Authors</td>
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<td>18</td>
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<td>(anoxic encephalopathy; swallowing disorder with probable aspiration)</td>
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<td>Khamis Mushayt</td>
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<td>Culture - for normal bowel habits, treat coughs and cold and general good health (ND)</td>
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<td>Medical - given orally for constipation (Neuro-developmental delay with seizure disorder; Swallowing disorder and aspiration on MBS)</td>
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<td>Culture - given orally: only olive oil 9/16; olive oil plus almond oil 1/16;</td>
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<td>1188</td>
<td>Medical - treating constipation (Spastic quadriplegic CP)</td>
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<td>Epileptic syndromes Chronic Neurological disorders</td>
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<td>27</td>
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<td>Case series</td>
<td>8</td>
<td>90-2190</td>
<td>50</td>
<td>Animal-based</td>
<td>Chronic ND</td>
<td>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)</td>
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<td>60-120</td>
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<td>Plant-based</td>
<td>1-30 Chronic 21-90</td>
<td>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</td>
<td>3</td>
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<td>swallow and poor growth; Both no G0R</td>
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<td>17</td>
<td>60-3285</td>
<td>53</td>
<td>Mineral-based</td>
<td>ND</td>
<td>Chronic</td>
<td>ND</td>
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<td></td>
<td>Cultural – oil instillation (2/9 – perinatal brain damage; 4/9 – G0R; 9/9 malnutrition)</td>
<td></td>
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<tr>
<td>31</td>
<td>2007</td>
<td>India, Chennai</td>
<td>Case report</td>
<td>1</td>
<td>4745</td>
<td>0</td>
<td>Plant-based</td>
<td>4745</td>
<td>Acute [1]</td>
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<td></td>
<td>Culture - force feeding of sesame oil (choked)</td>
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<tr>
<td>32</td>
<td>2007</td>
<td>Oman, Muscat</td>
<td>Case report</td>
<td>1</td>
<td>45</td>
<td>0</td>
<td>Animal-based</td>
<td>ND</td>
<td>Acute [7]</td>
<td></td>
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<td></td>
<td>Culture - fed ghee to ensure well-being (ND)</td>
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<tr>
<td>33</td>
<td>2008</td>
<td>Brazil, Rio de Janeiro</td>
<td>Case series</td>
<td>28</td>
<td>30-3240</td>
<td>46</td>
<td>Mineral-based</td>
<td>ND</td>
<td>Acute</td>
<td>ND</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Medical - treatment of constipation 23/28 and complicated ascariasis 5/28 (infancy 22/28; G0R 5/28; swallowing disorder 5/28)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>34</td>
<td>2009</td>
<td>South Korea, Seoul</td>
<td>Case report</td>
<td>1</td>
<td>180</td>
<td>100</td>
<td>Mineral-based</td>
<td>180</td>
<td>Chronic</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medical - 5ml daily as a laxative</td>
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<tr>
<td>Study No.</td>
<td>Year</td>
<td>Location</td>
<td>Study Design</td>
<td>Patient Count</td>
<td>Patient Age &amp; Gender</td>
<td>Treatment</td>
<td>Control</td>
<td>Procedure Details</td>
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<tr>
<td>35</td>
<td>2009</td>
<td>India, Pondicherry</td>
<td>Cross-sectional</td>
<td>69/774</td>
<td>15-330</td>
<td>55</td>
<td>Animal and plant-based</td>
<td>ND</td>
<td>ND</td>
<td>Culture - sesame oil 45/69; Coconut oil 20/69; Neem 4/69 (ND)</td>
</tr>
<tr>
<td>36</td>
<td>2009</td>
<td>India, Pondicherry</td>
<td>Cross-sectional study</td>
<td>9/41</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Chronic ND</td>
<td>Culture – oil instillation</td>
</tr>
<tr>
<td>37</td>
<td>2010</td>
<td>UAE, Sharjah</td>
<td>Case series</td>
<td>8</td>
<td>379-2920</td>
<td>ND</td>
<td>Animal and plant-based</td>
<td>ND</td>
<td>ND</td>
<td>Culture - fed ghee or olive oil (given in the recumbent position)</td>
</tr>
<tr>
<td>38</td>
<td>2010</td>
<td>USA, Atlanta</td>
<td>Case report</td>
<td>1</td>
<td>90</td>
<td>100</td>
<td>Mineral-based</td>
<td>ND</td>
<td>Chronic [76]</td>
<td>Medical - for constipation (aspiration syndrome)</td>
</tr>
<tr>
<td>39</td>
<td>2010</td>
<td>Brazil, Sao Luis</td>
<td>Case report</td>
<td>1</td>
<td>120</td>
<td>100</td>
<td>Mineral-based</td>
<td>ND</td>
<td>Chronic [110]</td>
<td>Medical - for constipation in a child with meconium ileus</td>
</tr>
<tr>
<td>40</td>
<td>2012</td>
<td>Poland, Warsaw</td>
<td>Case report</td>
<td>1</td>
<td>1095</td>
<td>0</td>
<td>Animal and plant-based</td>
<td>ND</td>
<td>Chronic [365]</td>
<td>Medical - ketogenic diet consisting of lipid oil mixtures for seizure control (intractable epilepsy due to organic disease)</td>
</tr>
<tr>
<td>ID</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>Case Number</td>
<td>Treatment</td>
<td>Disease</td>
<td>Description</td>
<td></td>
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<tr>
<td>41</td>
<td>2013</td>
<td>France, Lille</td>
<td>Case report</td>
<td>1</td>
<td>Plant-based</td>
<td>Chronic ND</td>
<td>Behavioral - drank large amounts of olive oil when frustrated (Behavioral disorder)</td>
<td></td>
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<tr>
<td>42</td>
<td>2015</td>
<td>India, Pondicherry</td>
<td>Case report</td>
<td>1</td>
<td>Plant-based</td>
<td>Chronic ND</td>
<td>Culture - orally administered castor oil for constipation (choked after given oil)</td>
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<tr>
<td>43</td>
<td>2015</td>
<td>South Korea, Gwangju</td>
<td>Case report</td>
<td>1</td>
<td>Plant-based (20ml twice daily of Lorenzo's oil)</td>
<td>Chronic [90]</td>
<td>Medical - treatment for X-linked adrenoleukodystrophy (neurological impairment with associated swallowing difficulty and oromotor dysfunction)</td>
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</tr>
</tbody>
</table>

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

Diagnostic accuracy of exogenous lipid 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.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year, first author, study type (participants)</th>
<th>Co-infection</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Reference time</th>
<th>Outcome (radiological/clinical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>1971 Bakshi[19] Case report</td>
<td>ND</td>
<td>CXR (dense opacity in the RUL and RML); CT (mass in posterior mediastinum); Lung biopsy; Autopsy</td>
<td>Surgical resection (right pneumonectomy)</td>
<td>None</td>
<td>No radiological resolution Death (postsurgical complication)</td>
</tr>
<tr>
<td>02</td>
<td>1973 Balakrishnan[16] Case series (12)</td>
<td>ND</td>
<td>CXR in 12/12 (diffuse pattern more common in the RUL and RML); No CT; 1/12 BAL; 2/12 lung biopsies</td>
<td>Supportive treatment; Steroids in 1/12 (details not specified)</td>
<td>None</td>
<td>ND No deaths</td>
</tr>
<tr>
<td>03</td>
<td>1985 de Oliveira[17] Case series (4)</td>
<td>Recurrent infections in 1 child (microbiology ND)</td>
<td>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</td>
<td>4/4 supportive treatment; 4/4 steroids (details not specified); 4/4 antibiotics; 4/4 therapeutic lavage</td>
<td>Post aspiration; post supportive treatment; post discharge</td>
<td>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</td>
</tr>
<tr>
<td>04</td>
<td>1987 Rabah[18] Case report</td>
<td>Peritoneal exudate - Enterococcus, E.coli, Klebsiella, Coagulase</td>
<td>CXR (bilateral alveolar and interstitial infiltrates); no CT;</td>
<td>Supportive treatment – antibiotics; Colonostomy</td>
<td>post admission day; post colonostomy day</td>
<td>Died at age 5 months - 1 month after colonostomy</td>
</tr>
<tr>
<td>Year</td>
<td>Reference</td>
<td>Study Type</td>
<td>Findings</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
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</tr>
<tr>
<td>1990</td>
<td>Riff(19)</td>
<td>Case report</td>
<td>Positive: Staphylococcus and Clostridium</td>
<td>Autopsy: Gas chromatography of the oil - matched the mineral oil</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Annobil(20)</td>
<td>Case series (10)</td>
<td>M. fortuitum on open lung biopsy specimen; drug susceptibility details ND</td>
<td>CXR (diffuse bilateral infiltrates); no CT</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Hugosson(21)</td>
<td>Case series (9)</td>
<td>Negative (bacterial, fungal and AFBs tested)</td>
<td>Supportive treatment (10/10) – antibiotics and antifungals; Steroids (10/10) – Prednisone at 2mg/kg/day for 2 weeks to 14 months; Surgical resection (2/10) - lobectomies</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Kameswaran(22)</td>
<td>Case series (24)</td>
<td>Negative (bacterial, fungal and AFBs tested)</td>
<td>Supportive treatment (24/24); Steroids (24/24) – not specified; Therapeutic lavage (24/24)</td>
<td>Post-bronchoscopy</td>
<td></td>
</tr>
</tbody>
</table>

CXR (diffuse bilateral infiltrates); no CT
Supportive treatment (9/9) – antibiotics (9/9), anti-TBs (1/9); Steroids (9/9) – details not specified; Surgical resection (4/9) – affected parts
Radiological resolution (1/9) – 1 year after presentation
Clinical resolution (7/10); Radiological resolution (7/10)
Death (1/10) – extensive M. fortuitum infection
Clinical resolution (24/24); No radiological resolution - CXR infiltrates still present
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Authors</th>
<th>Methodology</th>
<th>Findings</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Gupta</td>
<td>(23)</td>
<td>Cross-sectional study among medical pediatric admissions between April 1989-1990 of a hx of oil instillation (800/1090=73.4%)</td>
<td>multilobar consolidation (2/24); No CT; BAL (22/24); Lung biopsy (2/24)</td>
<td>Supportive treatment – oxygen, antibiotics</td>
<td>1-month post bronchoscopy</td>
<td>No deaths</td>
</tr>
<tr>
<td>1994</td>
<td>Fan</td>
<td>(24)</td>
<td>Case report</td>
<td>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</td>
<td>Supportive treatment – oxygen, antibiotics</td>
<td>ND</td>
<td>Followed up to age 5 years</td>
</tr>
<tr>
<td>1994</td>
<td>McDonald</td>
<td>(25)</td>
<td>Case report</td>
<td>Negative (bacterial and fungal cultures) CXR – bilateral infiltrates; No CT; Autopsy</td>
<td>Supportive treatment – oxygen, conventional ventilation</td>
<td>Post admission</td>
<td>Clinical resolution (4.7 years); No radiological resolution (mild residual bilateral interstitial opacities on CXR); No deaths</td>
</tr>
<tr>
<td>1994</td>
<td>Cox</td>
<td>(26)</td>
<td>Case report</td>
<td>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</td>
<td>Supportive treatment – antibiotics [amikacin stopped after 15/7 due to renal toxicity; doxycycline</td>
<td>Post admission**</td>
<td>After starting steroids - prompt fever resolution and mild tachypnea at discharge 14/7 later</td>
</tr>
<tr>
<td>Year</td>
<td>1994</td>
<td>Annobil(27)</td>
<td>Case series (4)</td>
<td>Negative (ZN and silver stain)</td>
<td>CXR (4/4) – 3/4 bilateral consolidation; 1/4 LLL collapse consolidation &amp; bronchiectasis; No CTs; Lung biopsy 1/4</td>
<td>Supportive treatment (4/4) – antibiotics; Surgical resection (3/4) - lobectomies</td>
<td>Lost to follow-up</td>
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<tr>
<td>13</td>
<td>1995</td>
<td>Hugosson(28)</td>
<td>Case report</td>
<td>Negative (no AFBs)</td>
<td>CXR - bibasal chronic lung changes; No CTs; Lung biopsy</td>
<td>Educated caregivers to stop giving oil</td>
<td>Post-stopping oil</td>
</tr>
</tbody>
</table>

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 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

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
<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Author(s)</th>
<th>Country</th>
<th>Study Type</th>
<th>Findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1995</td>
<td>Haddad</td>
<td>ND</td>
<td>Case report</td>
<td>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</td>
<td>Supportive treatment (antibiotics); Steroids – not specified; Chest physiotherapy</td>
<td>Post-treatment Clinical resolution 3 months post treatment</td>
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<td></td>
<td>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</td>
</tr>
<tr>
<td>16</td>
<td>1996</td>
<td>Al-Orainy</td>
<td>Negative (No AFBs)</td>
<td>Case series (2)</td>
<td>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)</td>
<td>Supportive treatment (2/2) - antibiotics; Steroids (1/2)</td>
<td>Post-admission No deaths; Follow-up details ND *Concerns about duplication data from Saudi Arabia</td>
</tr>
<tr>
<td>17</td>
<td>1996</td>
<td>Ciravegna</td>
<td>ND</td>
<td>Case report</td>
<td>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</td>
<td>Supportive treatment – oxygen; Educated caregivers to stop oil; Therapeutic lavage – whole lung lavage 30</td>
<td>Post-admission; Post-therapeutic lavage Clinical resolution – 10 days post therapeutic lavage (oxygen saturations normalized 3 weeks post admission)</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Case Type</td>
<td>Negative (Bacterial, Fungal and AFBs tested)</td>
<td>CXR (5/5) - Diffuse perihilar infiltrates; No CT</td>
<td>Supportive therapy (5/5) – antibiotics; Steroids (5/5) - Prednisolone at 2mg/kg/day; Educated caregivers to stop oil; physiotherapy twice daily</td>
<td>Duration post therapy day</td>
<td>Radiological resolution - almost clearing 40 days post therapeutic lavage</td>
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<tr>
<td>18</td>
<td>1997</td>
<td>Annobil[32]</td>
<td>Negative</td>
<td>CXR (5/5)</td>
<td>Supportive therapy (5/5) – antibiotics; Steroids (5/5) - Prednisolone at 2mg/kg/day; Educated caregivers to stop oil; physiotherapy twice daily</td>
<td>Duration post therapy day</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series (5)</td>
<td>(5)</td>
<td></td>
<td></td>
<td></td>
<td>* Steroid use in treatment seems to improve clinical outcome (1/2 with late improvement, suffered from unresolved pneumonia despite antibiotics until steroids started)</td>
</tr>
</tbody>
</table>

<p>| 19   | 1997   | Czechowski[33] | ND                                        | CXR - Expansile RUL pneumonia; CT - Homogenous (tumor like) opacification in the RUL: 30 - 40 HU. | Supportive treatment – antibiotics; Steroids - Prednisolone (2 mg/kg per day) | Time at starting steroids | Followed for 2 months after steroids, antibiotics and other supportive |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Year</th>
<th>Name</th>
<th>Method</th>
<th>Case Type</th>
<th>Description</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1997</td>
<td>Midulla(26)</td>
<td>ND</td>
<td>Case report</td>
<td><em>follow up CT chest – more infiltrates…</em></td>
<td>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</td>
<td>Post-diagnosis day</td>
<td>Clinical resolution</td>
</tr>
<tr>
<td>21</td>
<td>1998</td>
<td>Bandla(35)</td>
<td>Negative</td>
<td>Case report</td>
<td>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</td>
<td>Supportive therapy – antibiotics; Educated caregivers to stop oil</td>
<td>Post-stopping oil day</td>
<td>Clinical resolution</td>
</tr>
<tr>
<td>22</td>
<td>1999</td>
<td>Furuya(36)</td>
<td>ND</td>
<td>Case series (16)</td>
<td>CXR (16/16) - Right lung always involved; CT (8/16) - Perihilar and posterior dependent lung portions [nonspecific]. 2/8 CTs fatty</td>
<td>Supportive therapy (16/16) – antibiotics 11/16, bronchodilators 10/16;</td>
<td>Clinical resolution (14/16) – during the hospitalization</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Publication</td>
<td>Case Type</td>
<td>Diagnosis</td>
<td>Initial Therapy</td>
<td>Follow-up</td>
<td>Outcome</td>
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<tr>
<td>23</td>
<td>2000 Requena-Karssajian(37)</td>
<td>Case report</td>
<td>Negative (Chlamydia and respiratory viral panel negative)</td>
<td>CXR - Diffuse consolidation RUL, RLL and LLL; No CT</td>
<td>Supportive therapy – oxygen, antibiotics</td>
<td>Post-admission day</td>
<td>Clinical resolution – 7 days post admission</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Radiological resolution ND Follow-up duration not documented</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2001 Weinstein(38)</td>
<td>Case report</td>
<td>Negative (Blood cultures, viral NPAs – negative)</td>
<td>CXR - Bilateral airspace disease with relative sparing of the upper lobes; CT - suggested lipid within airspace opacification</td>
<td>Supportive therapy – oxygen (20 months), antibiotics;</td>
<td>Post admission day</td>
<td>Clinical resolution – 600 days post admission</td>
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<td></td>
<td></td>
<td>Radiological resolution ND No deaths</td>
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<tr>
<td>25</td>
<td>2001 Banjar(39)</td>
<td>Case series (25)</td>
<td>ND</td>
<td>CXR (25/25) - Consolidation 23/25, atelectasis 18/25. Predominant lobe involved = RLL 20/25; No CTs</td>
<td>Supportive therapy (8/25) – antibiotics; Educate caregivers to stop oil</td>
<td>None</td>
<td>Clinical resolution ND Radiological resolution ND Period of follow up was 42 ± 56 month Complications: Bronchiectasis 6/25</td>
<td></td>
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<tr>
<td>#</td>
<td>Year</td>
<td>Author(s)</td>
<td>Methodology</td>
<td>Findings</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Outcome</td>
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<tr>
<td>26</td>
<td>2002</td>
<td>Lee</td>
<td>Case series (8)</td>
<td>ND</td>
<td>CXR (8/8) - Bilateral, parahilar predominantly right lung; CTs (7/8) - Dense consolidation surrounded by GGOs with geographic lobular distribution 1/7 fatty attenuation; crazy paving 3/7; 7/7 central posterior zones affected.</td>
<td>Supportive therapy (8/8) – antibiotics; Educate caregivers to stop oil (8/8)</td>
<td>Post-admission day</td>
<td>Clinical resolution ND No radiological resolution - improvement on follow up CXR mean 5.4 months (1.1-8.4 months)</td>
</tr>
<tr>
<td>27</td>
<td>2004</td>
<td>Kang</td>
<td>Cohort (10/129)</td>
<td>ND specifically for children with lipoid pneumonia</td>
<td>ND</td>
<td>ND</td>
<td>Post-administration of the ketogenic diet</td>
<td>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</td>
</tr>
<tr>
<td>28</td>
<td>2005</td>
<td>Hoffman</td>
<td>Case series (2)</td>
<td>Positive Branhamella catarrhalis positive on BAL of child 1, fungi and viruses negative; Child 2: negative AFBs</td>
<td>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)</td>
<td>Supportive therapy (2/2) – antibiotics (2/2), oxygen (1/2), CPAP (1/2); Educated caregivers to stop giving oil (2/2)</td>
<td>Post-discharge day</td>
<td>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.</td>
</tr>
<tr>
<td>29</td>
<td>2005</td>
<td>Ridaura-Sanz</td>
<td>M.fortuitum/</td>
<td>CXR/CT ND; Lung biopsy (5/9); Autopsy (4/9)</td>
<td>Surgical resection (4/9) – RUL resection</td>
<td>None</td>
<td>Clinical resolution (3/9) Radiological resolution ND</td>
<td></td>
</tr>
<tr>
<td>Case series (9)</td>
<td>chelonei in 1/5 BAL cultures</td>
<td>Deaths (5/9)</td>
<td>Loss to follow-up (1/9)</td>
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<td>2006 Zanetti[43]</td>
<td>Negative</td>
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<tr>
<td>Case series (17)</td>
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<tr>
<td>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;</td>
<td>Supportive therapy (17/17) – antibiotics 17/17, conventional ventilation 2/17</td>
<td>ND</td>
<td>Follow-up data available for 12/17</td>
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<td></td>
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<td>1/17 - deteriorated on mechanical ventilation for respiratory insufficiency</td>
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<tr>
<td>31</td>
<td>2007</td>
<td>Verghese[44]</td>
<td>Case report</td>
<td>M.fortuitum</td>
<td>CXR – both lower lobes; CT - Cavitating consolidation of all segments of the LLL and inferior segment of the lingual, RML and RLL; sputum;</td>
<td>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</td>
<td>Post-discharge day</td>
<td>Clinical resolution 6 months post discharge (asymptomatic and gained weight)</td>
</tr>
<tr>
<td>01</td>
<td>2007</td>
<td>Al-Kindi[45]</td>
<td>Case report</td>
<td>Negative (Blood cultures; BAL-ZN, gram, fungal, bacterial cultures)</td>
<td>CXR - Extensive bilateral consolidation RUL, RML, lower lobes; CT - Extensive bilateral consolidation RUL, RML, lower lobes; BAL; Lung biopsy</td>
<td>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</td>
<td>Post-admission day</td>
<td>Clinical resolution 6 months post admission</td>
</tr>
<tr>
<td>32</td>
<td>2008</td>
<td>Sias[46]</td>
<td>Case series (28)</td>
<td>ND</td>
<td>CXR (27/28) - Consolidation 23/28, perihilar infiltrates 13/28; CT (28/28) - Consolidation and bronchograms 24/28, decreased</td>
<td>Supportive therapy (28/28) – antibiotics; Steroids (2/28) – details not specified; Therapeutic post therapeutic lavage</td>
<td>Post-admission day; post therapeutic lavage</td>
<td>Clinical resolution (20/28) - 20/22 that had therapeutic BALs were</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Study Type</td>
<td>Imaging Findings</td>
<td>Therapeutic Measures</td>
<td>Outcome</td>
<td>Follow-up Period</td>
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<tr>
<td>2009</td>
<td>Kim(47)</td>
<td>Case report</td>
<td>CXR - Diffuse consolidation bilaterally; CT - Extensive bilateral consolidation; heterogeneous attenuation including fat-like densities within consolidations; BAL; Lung biopsy</td>
<td>Supportive therapy – oxygen and antibiotics; Steroids – Dexamethasone IV 0.3mg/kg for 2/52, tapered with oral prednisolone;</td>
<td>No clinical resolution</td>
<td>No radiological resolution</td>
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<td></td>
<td></td>
<td></td>
<td>Persistent clinical and radiological features 3 months of discharge</td>
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<td>2-week follow-up partial CXR and respiratory</td>
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</tbody>
</table>

Attenuation in areas of consolidation 16/28, GGOs 3/28, crazy paving 1/28; 28 BAL

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

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
<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Study Type</th>
<th>Findings</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Chetan (48)</td>
<td>Cross-sectional study</td>
<td>CXRs (69/69) - Radiographic features suggestive of oil aspiration (persistent collapse consolidation, RUZ collapse consolidation in infants, perihilar dense infiltrates etc.; No CTs)</td>
<td>Supportive therapy (69/69) - 7/69 ventilation, 69/69 antibiotics</td>
<td>Duration between aspiration and presentation (grouped into 3 categories) &lt;24hrs (25/69), 2-7 days (23/69); &gt;7 days (21/69) Clinical resolution ND Radiological resolution ND Deaths: 3/7 who needed mechanical ventilation died No follow-up info provided</td>
</tr>
<tr>
<td>2009</td>
<td>Kumar (49)</td>
<td>Cross-sectional study</td>
<td>Pseudomonas, Acinetobacter, Klebsiella, Mixed flora (7/41 BAL cultures done) - cannot separate findings for patients with lipoid pneumonia;</td>
<td>Supportive therapy (9/9) – antibiotics.</td>
<td>ND Clinical resolution/ improvement: 6 No clinical change: 1 Death: 2</td>
</tr>
<tr>
<td>2010</td>
<td>Mirghani (50)</td>
<td>Case series</td>
<td>CXR/CT – ND; BAL (8/8) – gas chromatography done and mass spectrometry compared to home-made ghee and olive oil given to the children</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>38</td>
<td>2010</td>
<td>Sharma(^{51})</td>
<td>Case report</td>
<td>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)</td>
<td>CXR - Bilateral consolidations; CT - Consolidations in the RUL, RLL and LLL with possible necrosis; BAL</td>
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<tr>
<td>39</td>
<td>2010</td>
<td>Salgado(^{52})</td>
<td>Case report</td>
<td>ND</td>
<td>CXR - Bilateral apical infiltrates; CT - Extensive consolidation and geographical GGOs bilaterally; BAL</td>
</tr>
<tr>
<td>40</td>
<td>2012</td>
<td>Buda(^{8})</td>
<td>Case report</td>
<td>Negative (blood culture; viral and atypical organism serology; TB excluded; BAL negative for bacteria and fungi)</td>
<td>CXR and CT - Diffuse parenchymal infiltration of the right lung, atelectasis left dorsal basal lung segment, enlarged pretracheal and hilar LN; BAL</td>
</tr>
</tbody>
</table>
| 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

Appendix 4: Ethical Approval and Permissions

Ethical Approval

Hospital Permission
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- RADIOLICAL PATHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EXOGENOUS LITPOID 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: PWA00001637.
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

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
Dr 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,

Dr J Kawadza  
Manager: Medical Services  
Date: 16.08.17