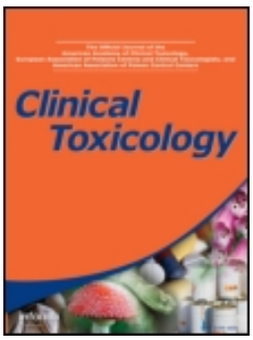

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CRITICAL CARE

The efficacy of prophylactic antibiotics in the management of children with kerosene-associated pneumonitis: a double-blind randomised controlled trial

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Context. Hydrocarbons, especially kerosene (paraffin), are the most common agents causing childhood poisoning in low and middle income countries (LMICs). Aspiration of kerosene causes an inflammatory sterile chemical pneumonitis, which may increase susceptibility to secondary lower respiratory tract bacterial infection. This study aimed to assess the efficacy of prophylactic antibiotics in the management of kerosene-associated pneumonitis in children and to identify risk factors associated with severity or outcome. *Methods.* A double-blind placebo-controlled trial of prophylactic antibiotics in the management of kerosene-associated pneumonitis of children presenting to a referral hospital was performed from July 2010 to September 2011. Sequential children with a history of kerosene ingestion and mild respiratory illness were randomised to receive placebo or amoxicillin. Each child was followed-up at Day 3 and Day 5 post-ingestion. The primary outcome measure was the number of treatment failures in each group, defined as any child who deteriorated within this time, necessitating a change in treatment regimen. Secondary outcome measures were length of hospital stay and symptoms and signs at follow-up. *Results.* Seventy-four patients were enrolled. Thirty-five (47%) received placebo and 39 (53%) active treatment. There was no significant difference in treatment failures between placebo (3/35, 9%; 95% CI, 3–22) and active (2/39, 5%; 95% CI, 1–17) groups (relative risk, 0.60; 95% CI, 0.11–3.37). The median length of hospital stay was identical (placebo 0.5 days; IQR, 0–1.0 and active 0.5 days; IQR, 0.5–1.0). Symptoms and signs at Days 3 and 5 post-ingestion were similar. The only significant risk factor for treatment failure was residence in formal housing. Clinical severity at presentation was similar for treatment successes and failures. *Conclusion.* Prophylactic antibiotics do not improve the outcome in children with mild respiratory illness after kerosene ingestion.

Keywords Kerosene; poisoning; Paraffin poisoning; Chemical pneumonitis; Childhood poisoning

Introduction

Ingestion of kerosene (paraffin) is a common cause of childhood poisoning in low- and middle-income countries or LMICs.[1–6] In 2006, it was estimated that there were 40 000 to 60 000 cases per annum in South Africa.[7] At Red Cross War Memorial Children's Hospital (RCH) in Cape Town, for each of the six years (2003–2008), kerosene ingestion presentations were on average 100 patients per annum and constituted over 20% of all poisoning cases seen.[4] The large number of kerosene ingestions in children in South Africa indicates the ongoing high use of kerosene for heating and cooking in low socioeconomic groups and the failure of education and primary prevention around safety.[8–10]

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Kerosene ingestion may result in aspiration, however the majority of kerosene ingestions do not result in poisoning.[11] Where poisoning does ensue in children, a sterile inflammatory chemical pneumonitis is the predominant clinical presentation.[12] Of those patients requiring hospital admission, the majority are discharged within a few days.[11–16] Concerns over the lung's subsequent potential susceptibility to bacterial superinfection raise the issue of early antibiotic use in treatment. A South African study in 111 children concluded that secondary infection is rare, as all but one recovered spontaneously without antibiotics.[17] Despite this limited data, routine treatment of kerosene pneumonitis in South Africa usually includes prophylactic antibiotics.[13] The use of early antibiotic treatment may partly be due to difficulty in clinically distinguishing sterile pneumonitis from lower respiratory tract infection.

There has only been one study on the effect of antibiotics on outcome in children with kerosene-associated pneumonitis,[18] which reported a decrease in morbidity when broad-spectrum prophylactic antibiotics were used. Given

the frequency of kerosene poisoning and the paucity of evidence, we aimed to investigate the efficacy of prophylactic antibiotics in children with mild pneumonitis following accidental kerosene ingestion.

Methods

A double-blind placebo-controlled trial of prophylactic antibiotics in the management of kerosene-associated pneumonitis following ingestion was performed. Sequential children older than 3 months presenting to the Medical Emergency Department at RCH, from July 2010 to September 2011, with a history of kerosene ingestion and meeting the inclusion criteria (Table 1), were randomised to receive either placebo or amoxicillin, 20–30 mg/kg orally per dose 8 hourly for 5 days. Amoxicillin is recommended as first-line antibiotic therapy for community-acquired pneumonia (CAP)[19] and therefore would provide adequate coverage for the pathogens likely to cause secondary lower respiratory tract bacterial infection.[12,20–22] It also provides good coverage against mouth flora from aspiration, is cheap and readily available, and is therefore the antibiotic of choice.

The study drug was an oral preparation prepared by the RCH pharmacy; placebo was manufactured to look identical to amoxicillin. Study drug was prepared in batches of 6–10 at a time; in each there was an equal number of active and placebo study drug, randomly assigned by the RCH pharmacy. All investigators, except the pharmacist, were blinded to treatment allocation.

RCH in Cape Town, South Africa is a 288-bed public referral hospital, serving children under the age of 13 years. It has a 24-hour emergency unit with inpatient beds.

Table 1. Inclusion and exclusion criteria for study participation.

INCLUSION CRITERIA

- Kerosene ingestion within the preceding 24 hours
- Older than 3 months
- Respiratory symptoms (history of cough or difficulty in breathing) AND/OR respiratory signs (age-specific tachypnoea*, chest indrawing, stridor, wheeze)
- Informed consent obtained from parent or legal guardian
- Resident in the RCH† drainage area and able to come for two follow-up visits

*Age-specific tachypnoea regarded as:
Respiratory rate > 50 breaths per minute (3 to 12 months) or
Respiratory rate > 40 breaths per minute (12 months to 5 years)
†Red Cross War Memorial Children's Hospital

EXCLUSION CRITERIA

- Asymptomatic and no clinical signs
- Too ill to be excluded from receiving an antibiotic as judged by
  - Requiring more than 2 L/min nasal prong oxygen
  - Requiring continuous or intermittent positive airway pressure ventilation
  - Fever > 40˚C
- Needing an antibiotic for another reason, e.g. otitis media, tonsillitis
- Current antibiotic use, prior to kerosene ingestion
- Allergic to amoxicillin

Kerosene poisoning referrals were from clinics and day hospitals in the City of Cape Town.

Children were observed as ambulatory patients for a minimum of 6–8 h post-ingestion[11] and thereafter considered for discharge or admission. A detailed record of respiratory symptoms and signs was taken including cough, respiratory rate, oxygen saturation, recession, grunting, flaring, wheezing and crepitations. Temperature and alteration in mental status were also recorded. A chest X-ray or CXR was done for each study participant.

Children were followed up at Day 3 and Day 5 post-ingestion, and ongoing symptoms and signs were recorded. Symptoms were cough, shortness of breath, wheezing and fever; they were either absent or reported according to their change since previous assessment (resolved, improving, static or deteriorating). Signs were a review of those recorded at presentation. Study drug adherence was confirmed at each visit; caregivers were questioned on the dose administered and this was checked against the dose prescribed and amount left in the bottle. Where patients did not return for their scheduled appointments, caregivers were contacted by telephone and a standardised questionnaire of only symptoms was conducted.

Participants were enrolled by the on-duty doctor and one of two study investigators (KB and DS), all of whom had prior training in the assessment of common paediatric respiratory illnesses and making decisions regarding the need for admission or home care. Follow-ups were performed by the two study investigators only.

The study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (FHS HREC 095/2010). Informed consent was provided by a caregiver. The study was registered with clinical trials registries after enrolment of the first patient (ClinicalTrials.gov NCT01253980 and Pan African Clinical Trials Registry PACTR201201000259370).

The primary outcome measure was treatment failure, defined as deterioration necessitating a change to the treatment regimen. Once a treatment failure was identified, children who had been receiving placebo were started on amoxicillin, and those already on amoxicillin were switched to another broad-spectrum antibiotic. Treatment failures were included in the analysis up to the point of alteration of treatment. Secondary outcome measures were the length of hospital stay, expressed in days, and symptoms and signs at follow-up.

Secondary study objectives were to identify risk factors associated with outcome or the severity of pneumonitis. Possible risk factors to be investigated included post-ingestion vomiting, age, household smoking contacts, HIV exposure or infection, malnutrition (defined by WHO Child Growth Standards),[23] prior respiratory illness and socioeconomic status. Housing served as a crude proxy for socioeconomic status and was defined as formal or informal. Formal housing was a brick house or hostel which was more likely to contain running water, basic sanitation and electricity, whereas informal housing included temporary dwellings made of wood or iron sheeting with no water, sanitation or electricity.

Possible confounding conditions were active *Mycobacterium tuberculosis* infection (TB) and upper respiratory tract infection (URTI). URTI was defined as the presence of rhinitis, otitis media, tonsillitis or pharyngitis; a preceding URTI was one within the week prior to kerosene ingestion and a new-onset URTI was one diagnosed at follow-up.

Statistical analysis

The sample size was calculated from an average of 100 children with kerosene ingestion per annum attending RCH[4] giving a possible sample of 200 children over a two-year period, with 100 patients in each group. The estimated secondary infection rate for the placebo group was calculated from published literature. In one study, the number with suspected infection decreased from 54/111 (49%) on Day 1 to 17 (15%) on Day 4, without antibiotic intervention.[17] One further study's control group had 45% (9 of 20) with suspected secondary infection after 48 h.[18] Using a combined suspected secondary infection rate of 15–50% at 48–96 h for patients not receiving an antibiotic, we took a midway point of 25% as the estimate for treatment failure rate in the placebo group. With no information available on the treatment failure rate in the active group, we estimated failure rates of 10% and 5%. At a level of $\alpha = 0.05$ and 25% and 5% treatment failure rates for placebo and active groups, respectively, a sample size of 100 per group gives a power of 0.98 and failure rates of 25% and 10% gives a power of 0.80. After an interim analysis at 14 months, the study was stopped early due to a lower than anticipated number of treatment failures.

Data were entered into Microsoft Excel 2007. Statistical analysis was done using IBM SPSS Version 20 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as numbers and continuous variables as median with interquartile range (IQR). A p value of ≤ 0.05 was considered significant for all situations. For categorical variables, Fischer's exact test was used for small samples or less frequent occurrences. Chi-square testing was applied for larger samples or more frequent occurrences. Mann–Whitney or Kruskal–Wallis tests were used for ordinal and continuous variables. Continuous variables were categorised for clinical relevance and logistic regression testing.

Results

During the 14-month study period, 126 patients attended the emergency department for kerosene ingestion of which 74 (59%) were enrolled (Fig. 1). Twenty-three patients could not be enrolled as study staff were unavailable. Twenty-nine patients were excluded as per study criteria (Table 1): 10 were too sick and needed intravenous antibiotics, six needed an antibiotic for another reason, two were on an antibiotic prior to kerosene ingestion, three presented more than 24 h after ingestion and eight had no symptoms or signs (Fig. 1). Sixty-eight (92%) of the study participants were referred by primary health care centres; the remaining six patients presented directly to RCH. Of the 74 study participants, there were 21 (28%) ambulatory patients and 53 (72%) admissions. All participants, except one, had an oxygen saturation in room air of above 94% at presentation and follow-up. The one patient with oxygen saturation of 92% at presentation required nasal prong oxygen during overnight admission.

Baseline characteristics

Thirty-five patients (47%) were assigned to placebo and 39 (53%) to active treatment. The groups were similar with regards to demographics, ingestion event and the presence of possible risk factors and confounding conditions for treatment outcome (Table 2). No infants were enrolled in the study; the majority (58/74, 78%) were under 24 months old. Most children (63/74, 85%) came from five large peri-urban suburbs (placebo $n = 29/35$, 83%; active $n = 34/39$, 87%), with most patients residing in informal housing (placebo $n = 20/35$, 57%; active $n = 26/39$, 67%). The placebo and active groups had similar pneumonitis severity at presentation (Table 3).

Follow-up

All 74 study participants were available, by attendance or telephone, for at least one follow-up. At Day 3 post-ingestion, 59 (80%) patients attended, 10 (13%) were telephone interviewed and five (7%) were unable to be contacted (Fig. 1). Of the patients who did not attend follow-up at Day 3 post-ingestion ($n = 15$), seven telephone interviewees attended their appointment at Day 5 post-ingestion and were improving, three telephone interviewees were again available by telephone only and asymptomatic, one untraceable patient attended second follow-up and was improving and four further untraceable patients were available via telephone only at Day 5 post-ingestion and improving. At Day 5 post-ingestion, 55 patients (80%) attended, 13 (19%) were telephone interviewed and one (1%) patient was unable to be contacted.

There was consistency between the caregiver's reported symptoms and clinical findings at examination in the 114 follow-ups where patients attended. In 89 follow-ups, caregivers reported improving or absent symptoms and only one was clinically worse and regarded as a treatment failure. In 12 reviews, caregivers reported ongoing static symptoms, of which 2 were regarded as treatment failures. In another 12 follow-ups, caregivers reported deteriorating symptoms, of which 7 were clinically stable, three required a bronchodilator for lower airway obstruction and thereafter remained well, and four were clinically worse and regarded as treatment failures. In one further patient, a record of symptoms could not be found, but clinical examination revealed a healthy child.

Antibiotic efficacy

There were five treatment failures (Table 4). There was no significant difference between placebo and active groups in the number of treatment failures (Table 5), relative risk: 0.60 (95% confidence interval or CI, 0.11–3.37). All five

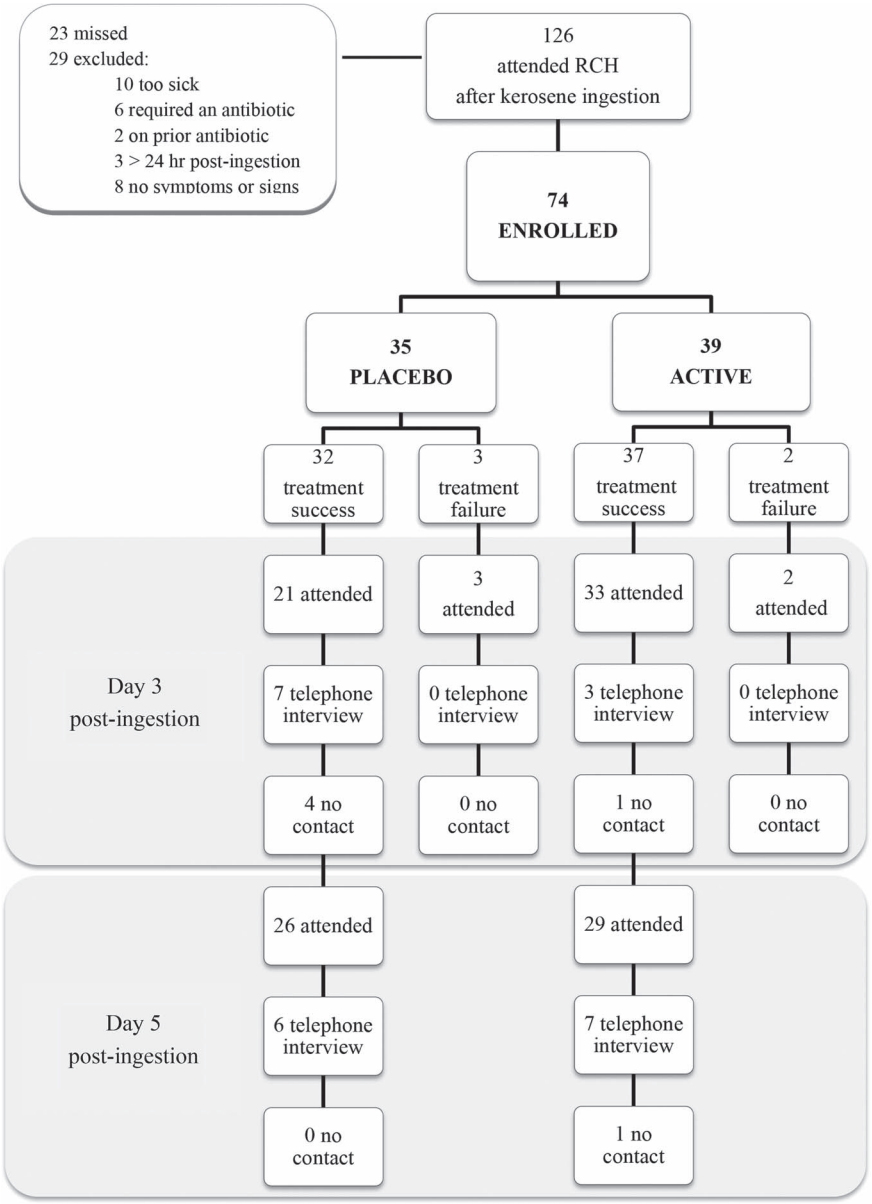

Fig. 1. The flow of study participants through enrolment and follow-up.

presented as a treatment failure at follow-up, one (P2) was identified 48 h post-ingestion and four at Day 3 post-ingestion. The treatment failures who developed new-onset flaring and grunting at Day 3 post-ingestion were the only patients to do so (Table 4). All other patients with grunting at presentation settled within 24 h of ingestion before discharge, and were treatment successes. Despite patient A2 (Table 4) having less clear signs of deterioration, additional findings of irritability, lethargy and reported static symptoms warranted his management as a treatment failure. He had a subsequent delayed recovery; the only patient to do so.

The median length of hospital stay was identical in both placebo and active groups (Table 5). There were no differences between treatment groups in resolution of symptoms and signs on Day 3 post-ingestion (Table 5). At Day 5 post-ingestion, the number of children with an ongoing cough was greater in the placebo group ($p = 0.002$)(Table 5). However, the clinical relevance of this is unclear as most were improving ($p = 0.01$): in the placebo group, 13/32 (41%) were improving, 3/32 (9%) were static and 3/32 (9%) were deteriorating, and in the active group, 5/36 (14%) were improving, 0/36 (0%) were static and 3/36 (8%) were deteriorating.

Identification of risk factors for treatment outcome

As there was no evidence of treatment differences, the placebo and active groups were combined and analysed by treatment success or failure to identify possible risk factors for treatment failure. There were no differences in presenting clinical parameters (Table 6), and the length of stay in hospital was similar (treatment success median, 0.5 days: IQR, 0–1.0; treatment failure median, 0 days: IQR, 0–0.5; $p = 0.054$). Linear regression modelling of factors for

Table 2. Baseline characteristics, ingestion event details and possible risk factors and confounding conditions for outcome in placebo and active groups.

	PLACEBO $n = 35$	ACTIVE $n = 39$
PATIENT MEASUREMENTS		
Male:female, *n* (%)	21:14 (60:40)	24:15 (62:38)
Age (months)*	19 (15–21)	20 (16–24)
Weight (kg)*	11.8 (10.0–12.4)	11.3 (10.1–12.9)
INGESTION EVENT, *n* (%)		
Hours post-ingestion at enrolment*	6.0 (3.5–11.0)	6.0 (4.0–8.0)
Season		
Spring	8 (23)	10 (26)
Summer	10 (29)	11 (28)
Autumn	5 (14)	6 (15)
Winter	12 (34)	12 (31)
Witnessed	13 (37)	11 (28)
Occurred at home	19 (54)	27 (69)
Container		
Paraffin bottle	8 (23)	12 (31)
Juice bottle	20 (57)	22 (56)
Given milk and/or water at place of ingestion	24 (69)	28 (72)
POSSIBLE RISK FACTORS, *n* (%)		
Vomiting post-ingestion	19 (54)	22 (56)
Age categories (months)		
12–23	29 (83)	29 (74)
24–35	5 (14)	8 (21)
>36	1 (3)	2 (5)
Smoking contact	14 (40)	12 (31)
HIV exposure or infection	13 (37)	7 (18)
Prior respiratory illness†	7 (20)	10 (26)
Formal housing‡	13 (37)	10 (26)
POSSIBLE CONFOUNDING CONDITIONS, *n* (%)		
Upper respiratory tract infection (URTI)		
Preceding	9 (26)	8 (21)
New-onset	15 (43)	16 (41)
Active TB disease¶	2 (6)	1 (3)

*Values are median (interquartile range)
†Prior respiratory illness = perinatal oxygen or ventilation, prior peripheral airway obstruction and/or use of beta-2-agonist, exercise- or URTI-associated wheezing, history of pneumonia or bronchiolitis
‡Formal housing = brick house or hostel likely to contain running water, basic sanitation and electricity
¶TB, *Mycobacterium tuberculosis*

treatment failure showed only formal housing as significant (Table 7).

Discussion

The absence of a difference in treatment failures between groups shows that antibiotic prophylaxis in children with mild pneumonitis following kerosene ingestion is not effective. In addition, the small number of treatment failures suggests that secondary infection is rare or is self-limited and therefore routine antibiotics are not necessary. Moreover, the persistence or worsening of symptoms and signs at follow-up may not even be due to secondary bacterial infection. The pathological process described in animals of an acute alveolitis which peaks at 3 days post-ingestion and resolves by 10 days and a concurrent chronic process of alveolar proliferation and thickening peaking at 10 days and resolving by 2 weeks[12,20,25] is one alternative explanation. Confounding conditions such as URTI and active TB disease are others, but these occurred similarly in both groups. This clinical study adds to results from previous animal studies, which investigated both bacterial superinfection and antibiotic use. In one paper, histological samples from baboons showed no visible organisms or positive lung cultures in either the experimental group with kerosene pneumonitis or controls, highlighting that secondary bacterial infection is rare.[21] Earlier studies in dogs and guinea pigs showed no increased frequency of lower respiratory tract bacterial isolates and no benefit from the use of prophylactic antibiotics.[20,22]

The severity of pneumonitis at presentation may be a guide to those at risk of deterioration. However, there were no clinical findings at presentation that predicted outcome. This has implications for the triage and subsequent management of patients. The updated 2011 British Thoracic Society (BTS) guidelines on the management of CAP[24] suggest certain clinical severity indicators for infants and older children to determine which patients should receive hospital-based care, but also state that the ultimate decision is based on a number of clinical and social findings. Similar principles may apply to decisions on children with mild kerosene-associated

Table 3. Clinical findings in placebo and active groups at presentation.

	PLACEBO $n = 35$	ACTIVE $n = 39$
INCLUSION CRITERIA, *n* (%)		
Cough only	6 (17)	7 (18)
Clinical signs only	2 (6)	1 (3)
Cough and clinical signs	27 (77)	31 (79)
CLINICAL EXAMINATION, *n* (%)		
Respiratory rate (bpm)*	48 (40–56)	44 (33–58)
Respiratory rate severity[†]		
Mild to moderate (41–50 bpm)	11 (31)	10 (26)
Severe (>50 bpm)	10 (29)	12 (31)
Recessions[‡]		
Mild	8 (23)	8 (21)
Moderate	1 (3)	3 (8)
Flaring	11 (31)	13 (33)
Grunting	6 (17)	6 (15)
Wheezing	2 (6)	5 (13)
Crepitations	10 (29)	11 (28)
Temperature severity		
Mild to moderate (37.5–38.5˚C)	8 (23)	9 (23)
Severe (>38.5˚C)	6 (17)	7 (18)
Altered mental status[¶]	8 (23)	11 (28)

*Values are median (interquartile range)
bpm, breaths per minute
[†]As there were no infants in the study, the respiratory rate severity values are for children aged 1–5years[24]
[‡]Recessions: Mild = intercostal retractions only; Moderate = intercostal and subcostal retractions
[¶]Altered mental status = drowsiness, lethargy, irritability or restlessness

pneumonitis, as although some study patients fulfilled severe category criteria according to the BTS guidelines, they were successfully managed as outpatients.

The only risk factor for treatment failure was residence in formal housing. This is surprising as the suburbs where most kerosene cases occurred are a mixture of low-cost housing and informal shacks reflecting peri-urban communities with low socioeconomic status, a known risk factor for kerosene ingestion. Possible explanations for the finding of formal housing as a risk factor for treatment failure include an unreliable definition of formal housing, caregivers with better social circumstances and higher education seeking medical attention earlier for potential deterioration and random error.

As with all studies, there are some limitations. Firstly, the overall small sample size meant that any potential differences in treatment outcome may not have been found and possible confounding conditions and risk factors could not be adequately analysed. Secondly, the study was terminated early. As patient recruitment was slower than expected, and the small number of outcome events and lack of treatment differences made the possibility of any significant differences in treatment failure with the proposed sample size very unlikely, a truncated study was justified on the grounds of 'futility'.[26] Thirdly, the study specifically selected for milder cases of kerosene pneumonitis, as it was considered unethical to withhold antibiotic therapy in children with severe respiratory illness. As most children present with mild illness, this is the group of patients in which antibiotics may potentially be overused and could even risk inducing antibiotic resistance. Lastly, a few patients did not attend their follow-up appointment and could only be assessed by telephonic interview. This allowed for limited evaluation of symptoms only, through administration of a standardised questionnaire.

Conclusions

Children with mild kerosene-associated pneumonitis do not require routine prophylactic antibiotics. Despite the small sample size, the small number of treatment failures supports the view that secondary infection following kerosene-associated pneumonitis in children is rare. Antibiotic prophylaxis does not improve outcome or hasten clinical resolution in children with mild pneumonitis. However, as there are no predictive risk factors for deterioration, the omission of antibiotics in the management of these patients does not obviate the need for routine reassessment by a medical practitioner, preferably at Day 3 post-ingestion.

Several areas require further study. A better way of investigating risk factors for deterioration would be to recruit all patients with a history of kerosene ingestion, irrespective of severity of illness, allowing for an increased sample size and

Table 4. Clinical findings for treatment failures at presentation (a) and when treatment failure was identified (b).

		RR	Recessions*	Flaring	Grunting	Wheezing	Creps	Sats	Temp
a	P1	40	Mild	Present	Absent	Absent	Absent	97	37.2
b		56	Resolved	Present	Present	Absent	Localised	99	37.1
a	P2	28	Absent	Absent	Absent	Absent	Absent	nr	37.0
b		42	Absent	Present	Present	Absent	Localised	96	37.3
a	A1	48	Moderate	Present	Absent	Present	Diffuse	98	39.1
b		60	Mild	Present	Present	Resolved	Diffuse	96	38.9
a	P3	40	Absent	Absent	Absent	Absent	Absent	97	38.0
b		57	Absent	Present	Absent	Absent	Absent	97	38.0
a	A2	46	Absent	Present	Absent	Absent	Absent	99	36.9
b		36	Absent	Present	Absent	Absent	Localised	99	36.7

P, placebo, A, active, RR, respiratory rate in breaths per minute, Creps, crepitations, Sats, pulse oximetry %, nr, not recorded, Temp, temperature in degrees Celsius
*Recessions: Mild = intercostal retractions only; Moderate = intercostal and subcostal retractions

Table 5. Summary of outcome measures for placebo and active groups.

OUTCOME	PLACEBO		ACTIVE		*p* value
PRIMARY, *n* (%) (95% CI)	*n* = 35		*n* = 39		0.662
Treatment success	32 (91) (78–97)		37 (95) (83–99)		
Treatment failure	3 (9) (3–22)		2 (5) (1–17)		
SECONDARY					
A) Stay in hospital (days)*	0.5 (0–1.0)		0.5 (0.5–1.0)		0.514
B) Clinical features	DAY 3	DAY 5	DAY 3	DAY 5	
SYMPTOMS, *n* (%)†	*n* = 31	*n* = 32	*n* = 38	*n* = 36¶	
Cough					
Asymptomatic	17 (55)	13 (41)§	21 (55)	27 (75)§	
Symptomatic	13 (42)	19 (59)§	17 (45)	8 (22)§	
Wheezing					
Asymptomatic	26 (84)	27 (84)	32 (84)	34 (94)	
Symptomatic	4 (13)	5 (16)	6 (16)	1 (3)	
Shortness of breath					
Asymptomatic	23 (74)	28 (88)	31 (82)	34 (94)	
Symptomatic	7 (23)	4 (12)	7 (18)	1 (3)	
Fever					
Asymptomatic	19 (61)	23 (72)	23 (61)	29 (81)	
Symptomatic	11 (35)	9 (28)	15 (39)	6 (17)	
SIGNS, *n* (%)†	*n* = 24	*n* = 26	*n* = 35	*n* = 29	
Respiratory rate (bpm)*	37 (33–44)	37 (32–42)	38 (32–43)	35 (31–40)	
Respiratory rate severity‡					
Mild to moderate (41–50 bpm)	5 (21)	7 (27)	8 (23)	6 (21)	
Severe (> 50 bpm)	4 (17)	0 (0)	5 (14)	0 (0)	
Recessions (mild)	1 (4)	1 (4)	1 (3)	0 (0)	
Flaring	3 (13)	0 (0)	5 (14)	1 (3)	
Grunting	2 (8)	0 (0)	1 (3)	0 (0)	
Wheezing	3 (13)	1 (4)	2 (6)	0 (0)	
Crepitations	4 (17)	1 (4)	11 (31)	3 (10)	

*Values are median (interquartile range)
bpm, breaths per minute
†The values for symptoms include telephone interviewees and patients who attended follow-up, whereas the values for signs includes patients who attended only
‡As there were no infants in the study, the respiratory rate severity values are for children aged 1–5years[24]
¶Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number
§$p < 0.05$

Table 6. Clinical findings for treatment success and failure at presentation.

	TREATMENT SUCCESS *n* = 69	TREATMENT FAILURE *n* = 5	*p* value‡
INCLUSION CRITERIA, *n* (%)			0.371
Cough only	11 (16)	2 (40)	
Clinical signs only	3 (4)	0 (0)	
Cough and clinical signs	55 (80)	3 (60)	
CLINICAL EXAMINATION, *n* (%)			
Respiratory rate (bpm)*	46 (36–58)	40 (34–47)	0.281
Respiratory rate severity†			0.273
Mild to moderate (41–50 bpm)	19 (28)	2 (40)	
Severe (> 50 bpm)	22 (32)	0 (0)	
Recessions			0.334
Mild	15 (22)	1 (20)	
Moderate	3 (4)	1 (20)	
Flaring	21 (30)	3 (60)	0.323
Grunting	12 (17)	0 (0)	0.583
Wheezing	6 (9)	1 (20)	0.410
Crepitations	20 (29)	1 (20)	0.680
Temperature severity			1.000
Mild to moderate (37.5–38.5˚C)	14 (20)	1 (20)	
Severe (> 38.5˚C)	14 (20)	1 (20)	
Altered mental status	18 (26)	1 (20)	1.000

*Values are median (interquartile range)
bpm, breaths per minute
†As there were no infants in the study, the respiratory rate severity values are for children aged 1–5years[24]
‡For categorical variables, Fischer's exact test was used for small samples or less frequent occurrences. Chi-square testing was applied for larger samples or more frequent occurrences. Mann–Whitney or Kruskal–Wallis tests were used for continuous variables.

Table 7. Linear regression analysis of possible confounding conditions and risk factors for treatment failure.

RISK FACTOR	Wald Chi-square	Degrees of freedom	*p* value
Vomiting	0.031	1	0.860
Smoking contact	0.077	1	0.781
URTI*	0.249	2	0.883
Prior respiratory illness†	0.345	1	0.557
Active TB disease‡	2.055	1	0.152
Season	1.766	3	0.622
Formal housing¶	3.998	1	0.046§

*URTI, Upper respiratory tract infection
†Prior respiratory illness = perinatal oxygen or ventilation, prior peripheral airway obstruction and/or use of beta-2-agonist, exercise- or URTI-associated wheezing, history of pneumonia or bronchiolitis
‡TB, *Mycobacterium tuberculosis*
¶Formal housing = brick house or hostel likely to contain running water, basic sanitation and electricity
§$p < 0.05$

an assessment of the importance of possible risk factors such as vomiting. Another future area for study is the need for antibiotics in severely ill patients and establishing if patients with HIV infection or malnutrition are at higher risk for progression to secondary bacterial infection.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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