The Short *versus* Long Antibiotic Course for Pleural Infection Management (SLIM) randomised controlled open-label trial

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Abstract

Introduction Based on expert opinion, the length of antibiotic treatment for pleural infection in adults is typically recommended to be a minimum of 4 weeks. This clinical trial aimed to assess whether shorter antibiotic courses lead to more treatment failures than standard longer courses.

Methods In an open-label randomised controlled trial, adult patients with pleural infection who were medically treated and stabilised within 14 days of admission were randomised to either a short antibiotic course (total course 14–21 days) or a long antibiotic course (total course 28–42 days). Patients were excluded if their baseline RAPID score was >4 (high-risk category). The primary outcome was the incidence of treatment failure by 6 weeks post-admission. Secondary outcomes were total length of antibiotic treatment, proportion of patients who resumed normal activity levels within 6 weeks post-admission, time from discharge to resuming normal activity levels and incidence of antibiotic-related adverse reactions.

Results Between September 2020 and October 2021, 50 patients (mean±SD age 46±13.7 years; 35 (70%) males) were recruited to the trial and randomly assigned to the short course group (n=25) or the long course group (n=25), with outcome data available for 24 patients in each study group. Treatment failure occurred in four (16.7%) patients in the short course group and three (12.5%) patients in the long course group. In the intention-to-treat analysis the OR for treatment failure in the long course group was 0.714 (95% CI 0.142–3.600; p=0.683). The median (interquartile range) duration of antibiotic treatment in the short course group was 20.5 (18–22.5) days compared with 34.5 (32–38) days in the long course group (p<0.001). There were no statistically significant differences in the other outcomes.

Conclusions In medically treated adult patients with pleural infection a long course of antimicrobial therapy did not lead to fewer treatment failures compared with a shorter course. These findings need to be confirmed in a larger multicentre trial.

Introduction

Infection of the pleural space is a serious condition associated with substantial morbidity and mortality [1]. The core management involves drainage of the infected fluid and antimicrobial therapy [2]. Based on expert opinion, a minimum of 4 weeks of antibiotics is used to treat pleural infection, although frequently this is extended to up to 6 weeks in routine clinical practice [1, 3–5].

A key principle of antimicrobial stewardship is administering the minimum effective duration of an antibiotic course that aims to reduce the risk of antimicrobial resistance and drug toxicity, both associated with unnecessarily long courses [6, 7]. In lower respiratory tract infections, randomised controlled trial studies have shown that short courses of antibiotics lead to good clinical outcomes [8, 9]. However, in pleural infection there is a paucity of good quality evidence to inform on the optimal duration of antibiotic

therapy in adults. A retrospective study of 91 patients with pleural infection reported that antibiotics were prescribed for an average of 4 weeks but were extended to longer durations in some patients [5]. The authors of that study concluded that 3 weeks of antibiotics was sufficient to treat empyema. The only clinical trial studying the optimum length of antibiotic therapy in pleural infection found that short and long antibiotic regimens had similar risks of treatment failure [10]. However, due to the exclusion criteria for participation in that trial (which led to the exclusion of two-thirds of screened patients) the results are not applicable to a substantial proportion of adult patients with pleural infection.

The RAPID score (comprising renal function, age, purulence of pleural fluid, infection source and dietary factors) has been validated as a robust tool to predict 3-month mortality in adult patients with pleural infection [11]. The score is stratified into three tiers, with a predicted 3-month mortality of 3%, 9% and 30% in the low-, intermediate- and high-risk categories, respectively [12]. The clinical utility of this score is yet to be determined. However, a robust tool for predicting outcomes is appealing to help identify patients who may be safely treated with shorter antibiotic courses.

This pilot study aimed to investigate whether prescribing shorter courses of antibiotics (2–3 weeks) *versus* standard longer courses (4–6 weeks) would lead to a difference in rates of treatment failure (defined as the requirement for further management) in adult patients with pleural infection at low-to-intermediate risk of mortality (RAPID score 0–4) who can be safely discharged home within 14 days of hospitalisation.

Methods

Study design

The Short *versus* Long antibiotic course for pleural Infection Management (SLIM) trial was a pilot open-label pragmatic randomised controlled clinical trial that recruited adult participants admitted with pleural infection to a university hospital (Alexandria University, Alexandria, Egypt). The protocol of the study was approved by the Alexandria University Faculty of Medicine Ethics Committee (0304785) and was registered at ClinicalTrials.gov with identifier number NCT04615286. A copy of the protocol is included in the supplementary material.

Consecutive patients admitted with pleural infection were invited to take part in an observational study (Pleural Infection Cohort Study (PICS)) and consenting to the SLIM trial occurred at the same time (using the "trials within cohorts" study design [13]). All patients provided written informed consent for the observational study and the trial, but were only assigned a trial number at the point of discharge (see the Randomisation section).

Participants

The trial included adult participants (⩾18 years old) admitted to hospital for treatment of non-tuberculous pleural infection (both parapneumonic and primary pleural infections included). Pleural infection was defined by the presence of at least one of the following: presence of pus in the pleural space, positive pleural fluid Gram stain or culture, or pleural fluid pH <7.2 or pleural fluid glucose <40 mg·dL^{-1} in the setting of acute respiratory infection. Included participants had to have a low-to-intermediate RAPID score (0–4) at admission and to be fit for discharge within 14 days of admission. Participants were excluded if they needed referral for surgery during admission, if their admission was due to a recurrent ipsilateral pleural infection within the last 3 months, or the infected pleural collection was not amenable to drainage at time of diagnosis or a large residual collection persisted despite drainage and therefore a prolonged antibiotic course was deemed necessary by the treating clinician.

Randomisation

Eligible participants were recruited to the trial immediately before discharge and randomised in a 1:1 ratio to either the short course group or the long course group. Randomisation *via* permuted blocks with variable sizes was used and was unstratified. The sequence was generated using the online platform Sealed Envelope (www.sealedenvelop.com). At the point of randomisation, a member of the study team logged into the website to obtain the treatment allocation after confirmation of eligibility criteria. The allocation was unblinded to participants and team members performing study assessments.

Procedures

The study intervention was the modification of the length of the antibiotic course at the point of discharge from hospital. All other aspects of management were carried out according to standards of care.

Baseline data including patient demographics, admission blood and pleural fluid results, thoracic ultrasound (TUS) and computed tomography (CT) findings, and treatments received were recorded on a

case report form (supplementary material). The initial choice of the antibiotic regimen was based on international guidelines for treating pleural infection [4, 14, 15], local patterns of microbiology and known participants' drug allergies. The regimen was subsequently modified according to results of microbiological studies where necessary.

At discharge, repeat blood tests and TUS were performed. In the intervention arm (short course antibiotic group), participants were discharged with a minimum of 7 days oral antibiotics and a maximum period of 21 days (total number of antibiotic days 14–21 days, including the intravenous course). In the control arm (long course antibiotic group), participants were prescribed an oral antibiotic course for a minimum of 14 days and up to a maximum period of 42 days (total number of antibiotic days 28–42 days).

Follow-up occurred at two visits: 2 weeks post-discharge and 6 weeks post-admission. While these were encouraged to be face to face, for participants unable to attend both appointments, the first or the second follow-up was *via* telephone. At each visit participants underwent a clinical review for symptom recurrence, treatment adherence was confirmed and adverse antibiotic reactions were recorded. In addition, during each physical visit, TUS with/without chest radiography was performed, and blood samples were sent for white cell count and C-reactive protein (CRP). The size of residual collection on TUS was quantified using the maximum effusion depth (in cm) and the height in rib spaces.

Outcomes

The primary outcome was the incidence of treatment failure defined by the requirement for further management (additional antibiotics and/or drainage procedure and/or surgical intervention) within 6 weeks post-index admission. Treatment failure was determined by 1) clinical deterioration (*i.e.* worsening or recurrence of symptoms) plus either 2) biochemical parameters (worsening of white cell count (by 2000 mm^{-3}) or CRP (by >20%) from discharge values) or 3) radiological parameters (chest radiography and/or TUS evidence of increasing or new pleural collection).

Secondary outcomes included the total length of antibiotic treatment, proportion of participants who returned to normal activity levels within 6 weeks post-admission, time from discharge to resuming normal activity levels and incidence of antibiotic-related adverse reactions in the study groups. The following outcomes were explored *post hoc*: number of participants with residual pleural collection on thoracic imaging at 6 weeks post-admission and number of participants with persistent respiratory symptoms 6 weeks post-admission.

Statistics

This was a pilot study and therefore no formal power calculation was made. A sample size of 50 participants (25 per group) was chosen by the study team to simulate sizes chosen by trials examining outcomes in pleural infection in adult and paediatric populations [3, 16].

Continuous variables were summarised using mean and standard deviation or median and interquartile range (IQR) according to whether data were normally distributed. Categorical variables were summarised using frequencies and percentages.

The primary outcome was analysed both in the intention-to-treat population (including all participants with known outcome) and the per-protocol population using the Chi-squared test and Fisher's exact test. The per-protocol population excluded participants who received antibiotic durations that were discordant with the prespecified durations for their allocated group. An analysis of the primary outcome adjusted for the RAPID score (low *versus* intermediate score), infection source (community- *versus* hospital-acquired), presence of sonographic septations and whether the split pleura sign was seen on CT scan was carried out using a binary logistic regression model. The adjusted odds ratio (aOR) with 95% confidence interval for treatment failure in the long course group was calculated from the regression model.

For secondary outcomes, continuous variables were compared between the study groups using the Mann–Whitney U-test. Categorical variables were compared using the Chi-squared test or Fisher's exact test as appropriate. A significance level of p<0.05 was used throughout the analyses.

Results

Between 28 September 2020 and 30 October 2021, 80 participants were recruited to the observational study. Of these, 50 participants were recruited to the SLIM trial: 25 participants randomised to the short antibiotic course group and 25 participants randomised to the long antibiotic course group. Exclusions are

summarised in figure 1. The final SLIM study visit was conducted on 9 December 2021, after which the dataset was locked.

Baseline and discharge data are summarised in table 1. The median (IQR) age of participants in the short course group was 43 (34–49) years and in the long course group was 52 (39–59) years (p=0.153). 72% of the short course group participants and 68% of the long course group participants were males. More participants in the short course group (68%) were in the low RAPID score category than in the long course group (40%). In addition, sonographic evidence of septations was more common in the long course group (77.7%) than in the short course group (28.6%). Participants in the long course group received more days of intravenous antibiotics (mean difference 2 (95% CI 0.3–3.8) days).

One participant in the long course group was lost to follow-up and one participant from the short course group died from a malignancy-related pulmonary embolism before attending the first follow-up visit. Therefore, outcome data were available for 24 participants for each study group. There were four instances of protocol deviation, all in the short course group, where participants received antibiotic courses ranging between 24 and 30 days.

Outcomes

All participants attended physically for the first follow-up visit. The second follow-up visit was attended physically by 93% of the participants and the remaining undertook the visit *via* telephone. The primary outcome, *i.e.* treatment failure, occurred in four (16.7%) participants in the short course group and three (12.5%) participants in the long course group (table 2). In the intention-to-treat population, the OR for treatment failure in the long course group was 0.714 (95% CI 0.142–3.600; p=0.683). After adjusting for other covariates, the aOR was 0.542 (95% CI 0.070–4.227; p=0.559). The difference in treatment failure was not statistically significant in the analysis of the per-protocol population (table 2).

Treatment failure was diagnosed at the first follow-up visit in all four participants in the short course group. In the long course group, treatment failure was diagnosed at the first follow-up visit in one participant, while the two other treatment failures were diagnosed at the second follow-up visit. Of those with treatment failure, two participants from the short course group required another chest tube insertion, while two participants of the short course group and all those in long course group with treatment failure were referred to surgery.
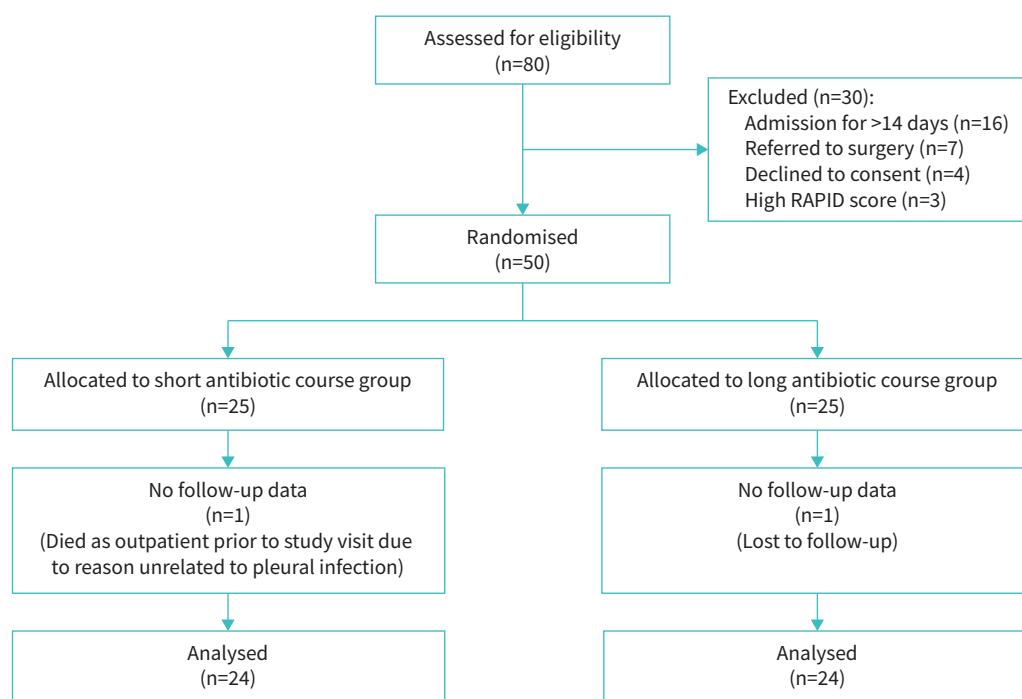

FIGURE 1 Flow of participants through the trial.

TABLE 1 Admission and in-hospital data of study participants

	Short antibiotic course (n=25)		Long antibiotic course (n=25)	
	Participants with available data	Result	Participants with available data	Result
Age, years	25	43 (34–49)	25	52 (39–59)
Male	25	18 (72)	25	17 (68)
Symptom duration before admission, days	24	17 (9.25–39)	24	16.5 (10–27.5)
Any comorbidity or risk factor[#]	25	23	25	24
Poor dentition		13		11
Intravenous drug user		6		5
Cardiovascular disease		4		4
Diabetes		5		7
Respiratory disease		4		3
Septations on ultrasound	14	4 (28.6)	18	14 (77.7)
CT signs				
Split pleura sign	22	18 (81.1)	24	17 (70.8)
Volume loss	22	3 (13.6)	24	2 (8.3)
Multiloculated	25	10 (40)	24	10 (41.7)
Infection source	25		25	
Community-acquired		20 (80)		22 (88)
Hospital-acquired		5 (20)		3 (12)
Infection type	23		25	
Primary pleural		19 (82.6)		18 (72)
Parapneumonic		4 (17.4)		7 (28)
Purulent pleural fluid	25	20 (80)	25	16 (64)
RAPID category	25		25	
Low		17 (68)		10 (40)
Intermediate		8 (32)		15 (60)
Admission blood tests				
Albumin, mg·dL^{-1}	25	3.01±0.58	25	2.71±0.61
WCC, ×10^9 L^{-1}	24	12.3 (8.77–17.23)	25	12.8 (10.2–18.85)
Haemoglobin, g·dL^{-1}	24	11.19±1.99	25	10.66±2.15
Platelets, mm^{-3}	24	328.5 (213.25–444)	25	376 (312–484)
CRP, mg·L^{-1}	20	158.68±94.95	15	163.60±92.64
Drain size	20		21	
<18 Fr		9 (45)		12 (57)
⩾18 Fr		11 (55)		9 (43)
Duration of drainage, days	18	9 (6–12)	18	7 (4–11)
Discharge blood tests				
WCC, ×10^9 L^{-1}	24	9.09±3.44	25	9.68±3.93
Platelets, mm^{-3}	24	362 (276–486.25)	25	508 (287–596)
CRP, mg·L^{-1}	23	32 (15.9–44.7)	24	21.9 (16.5–32.7)
Length of intravenous antibiotic course, days	25	9.12±3.56	25	11.20±2.51
Length of stay, days	25	10.52±3.28	25	11.63±2.58
Status at discharge	25		25	
No residual collection		11 (44)		11 (44)
Residual collection		14 (56)		13 (52)
Outpatient drainage		0 (0)		1 (4)
Inpatient antibiotics	25		25	
Ampicillin-sulbactam/metronidazole		15 (60)		14 (56)
Cephalosporin/metronidazole		3 (12)		3 (12)
Other		7 (28)		8 (32)
Outpatient antibiotics	25		25	
Co-amoxiclav/metronidazole		6 (24)		10 (40)
Moxifloxacin		6 (24)		6 (24)
Moxifloxacin/metronidazole		7 (28)		0 (0)
Co-amoxiclav		0 (0)		4 (24)

Data are presented as n, median (interquartile range), n (%) or mean±SD, unless otherwise stated. CT: computed tomography; WCC: white cell count; CRP: C-reactive protein. [#]: some participants had more than one comorbidity or risk factor.

TABLE 2 Primary and secondary outcomes for the study groups

	Short antibiotic course (n=24)		Long antibiotic course (n=24)		p-value
	Participants with available data	Result	Participant with available data	Result	
Treatment failure					
ITT population	24	4 (16.7)	24	3 (12.5)	χ^2=0.167 (p=0.683), Fisher's exact p=1
PP population	20	4 (20)	24	3 (12.5)	χ^2=0.459 (p=0.498), Fisher's exact p=0.684
Total antibiotic duration, days	24	20.5 (18–22.5)	24	34.5 (32–38)	<0.001
Returned to ADL	20	11 (55)	21	9 (42.9)	0.436
Time to return to ADL from admission, days	11	10 (4.5–18)	9	13 (6–18)	0.970
Antibiotic-related adverse events	21	0 (0)	24	2 (8.3)	Fisher's exact p=0.488
Residual pleural collection	20	4 (20)	21	2 (9.5)	Fisher exact p=0.409
Persistent symptoms at 6 weeks post-admission	20	9 (45)	21	11 (52.4)	χ^2=0.382 (p=0.537)

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. ADL: activities of daily living; ITT: intention-to-treat; PP: per-protocol.

Table 2 summarises the results of the secondary outcomes. The median (IQR) duration of antibiotic treatment in the short course group was 20.5 (18–22.5) days compared with 34.5 (32–38) days in the long course group (p<0.001) (figure 2). There were no statistically significant differences in the other outcomes. Notably, in the 41 participants with treatment success at 6 weeks post-admission, 20 (48.8%) participants had at least one persistent respiratory symptom: nine (45%) participants from the short course group and 11 (52.4%) participants from the long course group.

Discussion

The results of this pilot randomised trial confirm the feasibility of randomising adult patients with low-to-intermediate risk pleural infection to shorter courses of antibiotic. There was no statistically significant difference in short-term outcomes between short and long courses of antibiotics, but a larger study power is needed to definitively rule out the superiority of longer antibiotic courses. Despite an
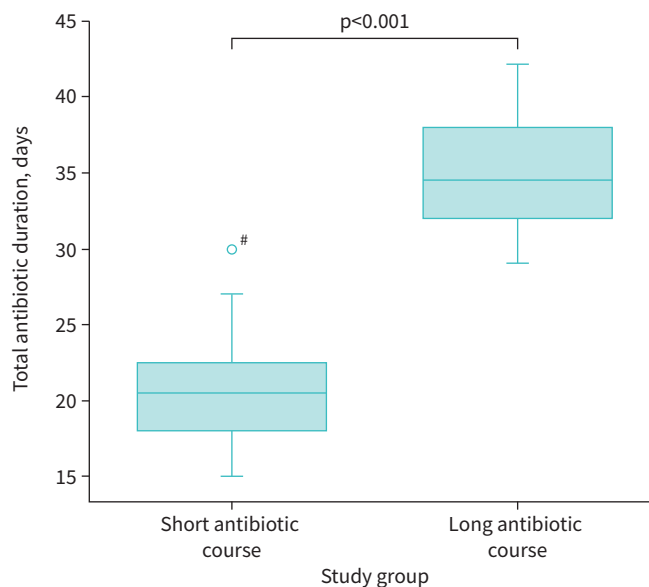

FIGURE 2 Difference of antibiotic duration between the study groups. [#]: the data point above the left box plot refers to trial participant number 10 who was randomised to the short course group but received 30 days of antibiotic therapy (a trial deviation).

antibiotic course that was on average reduced by 14 days, there were no significant differences in time taken by patients to return to their normal levels of activity or the rate of persistent respiratory symptoms by 6 weeks from diagnosis.

There has been a paucity of evidence for the optimum length for antimicrobial therapy for adult pleural infection to inform guidelines, which is highlighted in the recent European Respiratory Society/European Society of Thoracic Surgeons statement on pleural infection [17]. This study is an attempt to tackle this gap in evidence and the results support the feasibility of prescribing a 3-week treatment course. It is noteworthy that the study excluded patients who required hospital admission for a duration of >14 days (20% of screened patients). Therefore, the results of the study are not applicable to those with longer periods of hospitalisation.

Shorter durations of antimicrobials are associated with lower future risk of infection by antibiotic-resistant organisms, a problem that was responsible for 1.27 million deaths globally in 2019 [18]. Avoiding longer durations of antimicrobial therapy has been shown to improve mortality in severe community-acquired pneumonia [19]. Another implication of a shorter antibiotic course in treating pleural infection is to prevent the delay in declaring failure of medical treatment and referral for definitive management. In two of the three participants who failed medical therapy in the long course group in this study, the decision to refer to surgery was delayed until they completed >4 weeks of antibiotics.

This study utilised the RAPID score to stratify participants according to the severity of infection, to exclude participants at high risk of mortality, who may be more vulnerable to complications with a shorter antimicrobial treatment course. Unlike predictive scores in community-acquired pneumonia, such as CURB-65 which is used to inform the site of care [20] and the choice of empirical antibiotic therapy [21], the RAPID score has not been studied as a tool to guide management. To the best of our knowledge, this is the first study to suggest a clinically meaningful use for the RAPID score, where patients with low-to-intermediate scores can be given shorter outpatient antimicrobial courses. Future studies looking into other clinical/biochemical factors to guide the intensity and length of antimicrobial therapy in pleural infection would be useful. Indeed, in other respiratory infections, guidance by sputum bacterial load [22] or serum biomarkers [23] has been successfully used to guide antimicrobial therapy with improved outcomes.

The results of this trial are in agreement with the only published randomised trial studying antibiotic duration in adult pleural infection. The trial included 55 participants with community-acquired parapneumonic pleural infection and no excess treatment failure with a 3- *versus* 2-week antibiotic course was observed [10]. However, in that trial all patients were treated with co-amoxiclav and therefore patients who were penicillin-allergic were excluded. In our trial, the choice of any suitable antibiotic regimen was modifiable according to microbiological results and informed by patients' drug intolerances, to make the study more pragmatic and the results more generalisable. Additionally, and unlike the aforementioned trial, our study included patients with both community- and hospital-acquired pleural infections, and both parapneumonic and primary pleural infections. Our results also agree with a retrospective study of predominantly surgically treated patients [5], where it was found that 3 weeks of antibiotics was sufficient to treat empyema.

Despite randomisation in this trial, between study groups there were baseline differences in the number of participants in each RAPID score category and in the proportion of participants with sonographic septations. However, these imbalances were subsequently adjusted for in the analysis of the primary outcome. Furthermore, it remains unclear whether higher RAPID scores or the presence of septations on ultrasound are predictors of treatment failure [11, 24]. The median age of the subjects included was relatively younger than commonly reported in pleural infection. However, this partially reflects different patient demographics where the trial recruited and inclusion of a lower risk tier of the RAPID score spectrum. It is worth noting that imaging findings suggestive of evolving fibrosis (split pleura sign, multiloculation and volume loss) were not different between study groups.

Important limitations of this study are that the study was conducted in a single centre and the sample size was relatively small. This small size may have not provided enough study power to detect significant change in the primary outcome between the study groups. The findings will need to be replicated in a larger multicentre study. Another limitation of the study was the open-label design; however, ensuring generalisability with a pragmatic flexible choice of antibiotic regimens did not make blinding possible. The short course group had a number of protocol deviations in terms of antibiotic course length. Finally, the study did not collect long-term data, such as 1-year mortality, which is another limitation of the study.

Conclusions

This single-centre pilot randomised controlled trial showed that there was no statistically significant difference between long and short courses of antimicrobial therapy in terms of incidence of treatment failure in medically treated adult patients with pleural infection who are stabilised within 14 days of admission and who have a low-to-intermediate risk of mortality per the RAPID score. Due to the pilot nature of this trial, a larger multicentre study is needed to confirm these findings. Further studies are needed to identify clinical and/or biochemical factors to help triage suitable patients to ambulatory or less invasive management with shorter antimicrobial courses.

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