The Short versus Long antibiotic course for pleural Infection Management (SLIM) randomised controlled open label trial

Supplementary Material

Contents

1- Trial Protocol

Title: Short versus Long antibiotic course for pleural Infection Management (SLIM trial): protocol of a randomized controlled open label trial

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Sponsor:

Alexandria University Faculty of Medicine and Alexandria University Hospitals

Champlion Street, Azarita, Alexandria, Egypt

Study personnel:

Principal investigator

Dr Maged Hassan

Lecturer of Chest Diseases

Alexandria University Faculty of Medicine

Study co-investigator

Dr Ahmed S Sadaka

Lecturer of Chest Diseases

Alexandria University Faculty of Medicine

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Introduction

Infection of the pleural space is serious condition that requires hospitalization, invasive interventions and long courses of antibiotics[1]. Treatment of pleural infection requires long hospital admission with a median of 19 days[2] and medical treatments fails requiring surgical intervention in up to 30% of cases[3]. The mortality from pleural infection is around 10% at 3 months[4].

Besides drainage of the infected fluid, antibiotics are a core component of management of pleural infection[5] and are typically given intravenously in the first few days of treatment until the condition is stabilized at which stage patients are shifted to oral antibiotics of equivalent spectrum. In almost half of the cases of pleural infection, the choice of antibiotics is entirely empirical due to low yield of microbiological tests on pleural fluid in these cases[6]. International guidelines cite a minimum length of antibiotic course of pleural infection of four weeks[5,7] with antibiotic courses typically lasting six weeks[8]. However, these recommendations are based on expert opinion with no robust evidence to support such durations. A recent trial compared a two-week versus a three-week antibiotic course for parapneumonic pleural infections. The trial that concluded prematurely due to inability to recruit to target sample size and found that the two regimens were equivalent in terms of risk of failure of medical treatment[9]. Besides being an underpowered study, the results are only applicable to parapneumonic effusions but not primary pleural infections.

The RAPID score has recently been validated as a robust tool to predict 3-month mortality of patients with pleural infection based on demographic and laboratory data (table 1)[4]. A low score (0-2) is associated with 2-3% mortality, medium score (3-4) 9% mortality and high score (5-7) 30% mortality at three months[10]. The utility for this score in clinical management is yet to be determined and this study will attempt using this score to stratify lengths of antibiotic treatment based on proposed risk of adverse outcomes as stipulated by the RAPID score. A shorter antibiotic course that is as effective as the standard long course is desirable given the common occurrence of side effects with antibiotic treatment. The presence of a robust predictive score of outcome seems as an attractive tool to help stratify patients who can be safely treated with shorter antibiotic courses.

The aim of this study is to investigate the feasibility and safety of prescribing shorter courses of antibiotics (2-3 weeks) versus the standard longer courses (4-6 weeks) in medically-treated patients with pleural infection at lower risk of mortality (RAPID score 0–4) who can be safely discharged home within 14 days of hospitalization and how this impacts success of medical treatment.

Table 1: Components of the RAPID score[4]

Parameter	Value	Score
Renal function (blood urea nitrogen)	<14 mg/dL 14-23 mg/dL >23 mg/dL	0 1 2
Age	< 50 years 50 – 70 years > 70 years	0 1 2
Purulence of pleural fluid	Purulent Non-purulent	0 1
Infection Source	Community-acquired Hospital-acquired	0 1
Dietary factors (serum albumin)	≥2.7 g/dL <2.7 g/dL	0 1

Methods

This protocol is written in accordance with the guidance of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[11].

Trial design and study setting

SLIM is an open label randomized controlled clinical trial that will recruit patients admitted with pleural infection to a University Hospital. Consecutive patients admitted with pleural infection will be invited to take part in an observational study (the Pleural Infection Cohort Study) and consenting to SLIM will occur at the same time of consenting to the cohort study. This design is termed trials within cohorts.[12]

Inclusion of other hospitals as recruiting sites is not planned but will be considered if recruitment is deemed slow.

Eligibility criteria

Inclusion

- Adult patients (≥18 years old)
- Willing to provide informed consent
- Admitted to hospital for treatment of pleural infection (both parapneumonic and primary pleural infections included). Pleural infection will be defined by the presence of one of the following:
  a) the presence of pus in the pleural space;
  b) positive pleural fluid gram stain or culture; or
  c) pleural fluid pH < 7.2 or pleural fluid glucose < 40 mg/dL in the setting of acute respiratory infection.
- RAPID low or intermediate score (0-4)
- Fit for discharge within 14th day of admission

Exclusion:

- Failure of medical treatment within 14 days of admission and need for surgical referral
- Need for hospital admission beyond 14 days due to medical reasons
- Admission to recurrent ipsilateral pleural infection within the last three months
- RAPID high score (5 or more)
- Pleural infection not amenable to drainage at time of diagnosis and therefore upfront decision to treat with prolonged antibiotics
- Residual pleural collection (despite attempted drainage) that the managing clinician indicated is for prolonged oral suppressive therapy (i.e. six weeks of oral antibiotics).

Patients will only be randomised to one of the study arms of SLIM if found eligible, and for ineligible patients, their data collection will follow the protocol of the cohort study with no change in their care.

Interventions

The study intervention is the modification of the length of the antibiotic course at the point of discharge from hospital. All other aspects of care will be carried out according to recognised clinical standards. The choice of the antibiotics will rely on results of microbiological studies, and if non-informative will follow international guidelines for treating pleural infection and local patterns of microbiology[1,6]. A separate document will be prepared to provide guidance for outpatient antibiotics in the absence of culture results.

In the active arm, patients who are ready for discharge will be prescribed an oral antibiotic course for a minimum period of 7 days and a maximum period that makes the overall length of antibiotic administration 21 days (total number of antibiotic days 14-21 days). In the control arm, at the point of discharge, patients will be prescribed an oral antibiotic course for a minimum of 14 days and a maximum period that makes the overall length of antibiotic administration 42 days (total number of antibiotic days 28-42 days). Treatment duration allocation will be open label.

Baseline data

Besides patient demographics and infection source, the following data will be collected at the points of admission and discharge as appropriate:

- Date of diagnosis confirmation

- Vital signs

-Blood investigations (minimum: urea and electrolytes, full blood count, C-reactive protein, and serum albumin)

- Pleural fluid parameters (macroscopic appearance, biochemistry, cultures (blood and pleural fluid), pH)

- Chest X-ray at baseline and at discharge

- Thoracic ultrasound (TUS) images at baseline (effusion size and extent of septations)

- Chest computed tomography images at baseline (presence of pleural split sign, lung consolidation or microbubbles)

- Treatments received as inpatient (chest tube size and time till removal, volume of effusion drained, intravenous and oral antibiotics given)

- Total length of hospital admission

Participant timeline:

Participants admitted to hospital for treatment of pleural infection will be approached to take part in both the observational and interventional studies. For patients who sign an informed consent to both, and upon confirmation of their eligibility to the trial, they will be randomised to a study arm once a decision is made about fitness for discharge from hospital which is within 14 days from admission.

Upon discharge, two face-to-face follow up visits will be planned to coincide with clinical practice of following up patients post admission for pleural infection.

a- Two weeks post discharge (+/- 7 days)

A clinical review to ascertain adherence to treatment and ensure no symptoms of recurrence are present (fever, night sweats, haemoptysis or purulent expectoration, chest pain). Any adverse events related to antibiotic treatment will be recorded. During this visit thoracic US (TUS) +/- chest X-ray will be performed. If a participant is not willing or able to attend in person, a remote review will be performed (via telephone).

b- Six weeks from initial admission (+/- 7 days)

During this visit the following will be performed:

Clinical review of symptoms (relating to infection recurrence or adverse events due to antibiotic treatment)

Check adherence to study treatment. Participants will be asked to bring back the used empty antibiotic packs.

Blood to be sent for white cell count and C-reactive protein

Chest X-ray

c- Unscheduled Visits - Besides the two planned visits, participants will be allowed to contact the study team between the time points if they develop any of the symptoms of recurrence mentioned above. A study clinician will determine whether a clinical review is required and will arrange accordingly

Outcomes

Primary outcome:

Incidence of failure of treatment as judged by trial clinician requiring further antibiotics and/or tube drainage and/or surgical intervention by six weeks post initial admission. Failure will be determined based on the one or more of the following parameter: clinical (recurrence of symptoms), biochemical (worsening of WCC [by 2000/mm^3] or CRP [by $\geq$ 20%] from discharge values) and radiological (chest X-ray +/- TUS evidence of increasing or new pleural collection).

Secondary outcomes:

- Total length of antibiotic treatment (in days) in the study arms
- Number of participants with worsening in the 6-week chest X-ray as compared to discharge chest X-ray in the study arms. Chest X-ray pairs (discharge vs 6-week) will be read by a respiratory physician blinded to treatment allocation who will judge whether there is worsening (versus stability or improvement)
- Time (in days) to return to normal daily activities in participants of the study arms

- Readmission within 30 days from discharge

Sample Size:

A sample size of 50 participants (25 per arm) was chosen by the study team simulating sizes chosen by trials examining outcomes in pleural infection in adult[8] and paediatric[13] populations.

Randomisation and treatment allocation

Patients will be randomised 1:1 to the active or the control arm. Randomisation using permuted blocks with variables sizes will be used and the sequence will be generated using the online platform Sealedenvelop.com. At the point of randomisation, a member of the study team will log into the website and obtain the treatment allocation after confirmation of eligibility criteria. Being an open label study, allocation will be known to the patient and the study team performing assessments of study visits.

Data management

Data will be collected directly into paper case report forms that will bear the study number of the participants but no other identifiable information. No data sources (e.g. lab results, etc.) will be stored within the trial files to maintain confidentiality of patients' medical data.

A screening log will be kept electronically on a spreadsheet that is password protected on a secure computer. This log will have the name and demographics of patients approached for the study as well as study number and treatment allocation for randomised patients.

At completion of study assessments for the last recruited patients, data will be transferred from paper CRFs to electronic form (spreadsheets) to allow statistical analysis. These spreadsheets will be stored securely after trial conclusion with the principal investigator and will be accessible to other members of the study team. Request to access study data by other teams will be expected via email and access will be granted by the principal investigator if the request is deemed reasonable.

Statistics

A per protocol analysis will be carried out for all outcomes. Given that this is a feasibility study, no replacement for participants lost to follow up will be attempted. Continuous variables will be compared between the study arms using t-test or Mann Whitney test according to the normality of the study data. Categorical variables (including primary outcome measure) will be compared using the Chi squared test or Fisher exact test as appropriate. A binary logistic regression model will be used to predict treatment failure (dependent variable) adjusting for RAPID score and whether infection was primary or parapneumonic (independent variables).

Safety monitoring reporting

The study intervention (shorter antibiotic course) is envisaged to cause less adverse events due to less exposure to antibiotics. All treatment-related adverse events will be collected routinely as part of the study. As a safety measure, an interim analysis will be planned when half the recruitment target is reached to ensure that the study intervention does not impose unacceptable risks to subjects randomised to this arm.

Ethics and dissemination

Approval will be sought from the Ethics Committee of Alexandria Faculty of Medicine and the protocol will be registered in an open-access trials database before the recruitment of the first patient. All participants will be required to sign an informed consent form prior to enrolment in the study. A scientific report with the results of the study will be prepared once the recruitment finishes.

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2- Trial Case Report Forms

3- Age		Date of admission	dd/mm/yy
Gender		Date of consent	dd/mm/yy
Symptoms at admission (circle all that applies)	Cough Fever Sputum Night sweats Chest Pain Weight Loss Dyspnoea	Duration of symptoms before admission	days
		Pre-admission antibiotics	Y / N
Risk factors / comorbidities (circle all that applies)	Poor dentition IVDU Cardiovascular Diseases DM Liver Disease	Renal Disease Neurological disease Active cancer Immune suppression Other (specify):	Respiratory Smoker: PYI:
Radiology			
Ultrasound	Depth: cm	Height: spaces	Echogenic Septated Complex septated
CXR	Loculated: y / n	Consolidation: y / n	
CT	Split sign: y / n Consolidation: y / n	Microbubbles: y / n Volume loss: y / n	Air-fluid level: y / n
Community Acquired		Y / N	
Vital signs on admission: BP:		Temp:	
Pleural Fluid			
Physical	Pus/turbid/straw	pH	
LDH		Glucose	
Protein		ADA	
Neutrophils		Lymphocytes	
C&S		AFB	
Blood culture		Other microbiology	
Blood tests on admission			
BUN:	Creatinine:	Na:	K:
Albumin:	Hb:	Platelets:	WBC:
Neutrophils:	Lymphocytes:	CRP:	
RAPID Score*	Low (0-1)	Intermediate (2-4)	High (5-7)
Initial treatments			
Chest tube	Size: F Date inserted:	Volume drained initial 24 hours	ml
Antibiotics			
Anticoagulation			

*RAPID score: BUN: <14, 14-23, >23; Age: <50, 50-70, >70 year; Purulence: purulent, non-purulent; Infection source: community, hospital-acquired; Albumin: $\geq$2.7 gm, <2.7 gm

Date of discharge	dd/mm/yy
LOS	days
Status at discharge (tick what applies)	No tube, suppressive antibiotics Tube out, good drainage, oral antibiotics Tube out, residual collection, oral antibiotics Tube out, full antibiotic course completed inpatient Ongoing outpatient drainage, oral antibiotics Referred to surgery Other (specify)
RAPID score	
Eligible for SLIM	Y / N
Randomisation group	
Antibiotics	
Date of IV to oral shift	
N0. of days of IVs	
No. of days of oral antibiotics prescribed	
Vitals	
Temp	
Bloods	
Creatinine	
CRP	
WBC	
Neutrophils	
Platelets	
Discharge antibiotics Duration prescribed	
Radiology	
US (residual effusion)	Height: Depth:
CXR	
Date tube out	
No. of days tube in situ	
SLIM Follow-up visit 1 date	
SLIM Follow-up visit 2 date	

Visit number	FU 1 / FU 2 / unscheduled	
Visit format	Face-to-face / telephone	
Date	dd/mm/yy	
Time since admission	Days	
Time since discharge	Days	
Respiratory symptoms (tick all that applies)	Chest pain Fever Cough Night sweats Sputum Dyspnoea	
Duration of symptoms		
Study arm	Short course - Long course	
Antibiotics		
No. of days of oral completed		
Adherence confirmed	Y / n	
Remaining days of oral antibiotic		
Time from discharge to return to work/normal activity	Days	
Bloods/radiology		
WBC		
CRP		
Platelets		
US Residual effusion	Depth: Height	
Lung consoildation	Y / n	
Pleural thickening	mm	
CXR evidence of new/worsened collection	Y / n	
Treatment Failure (tick if any applies)	Hospital re-admission Further antibiotics Insertion of chest drain Referral to surgery	Date IV/Oral Date Date Date
Details		

3- CONSORT checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	7-9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.