The Pleural Infection Cohort Study (PICS) – study protocol

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1.0 Background

Pleural infection is a condition that requires hospitalization for management and is associated with significant in-hospital morbidity and mortality[1]. Predictors of poor outcome include advancing age, poor nutrition, hospital-acquired infection and impaired renal function.[2] Medical management is centred on appropriate antibiotic treatment and fluid drainage usually by the means of an intercostal tube. Up to 30% of patients fail medical treatment and referred for surgery.[3] A recent systematic review of adults patient with pleural infection has shown that the demographics of patients with pleural infection are different in patients from high-income vs lower income countries; the latter being of younger age and lower comorbidity burden.[4] However, the results of the review did not show significant differences in patient outcomes. The same systematic review pointed to the need for more data from patients residing in lower income countries given that the majority of data is contributed by studies from higher income countries.[4]

This study aims to prospectively investigate the incidence of pleural infection in a large tertiary centre gathering demographic and clinical data about patients recruited. In addition, the study will examine the different treatment offered and how this related to in-hospital outcomes (length of hospital stay, rate of referral to surgery and mortality).

2.0 Methods

PICS STUDY

2.1.1Setting

The Pleural Infection Cohort Study (PICS) will aim to recruit consecutive patients admitted to Alexandria University Hospitals with pleural infection during a one-year period from the starting date of the study.

2.1.2 Design

The study will be designed as a modified trial within cohort (TwiC) study.[5] PICS will primarily aim to recruit patients prospectively to gather clinical and demographic data on patients admitted with pleural infection in addition to clinical data on tests performed and treatments received as part of the standard care. The in-patient outcomes will be recorded at the time of discharge data or death, whichever is earlier. Within the TWIC design, PICS will be a platform for recruiting patients to interventional trials for eligible patients within the cohort (see 'consenting' section)

2.1.3 Eligibility

All adult patients admitted with pleural infection who are willing to sign an informed consent will be recruited. 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.

2.1.4 Consenting and co-enrollment

In the TwiC design patients are consented to take part in the cohort study with the possibility of being randomized in the future into trials without being specifically told if a given eligible participant is randomized into a control arm of a trial[5].

The consenting process for PICS will involve obtaining consent for the core observational part of the study. There will be a separate clause asking for permission to enroll a participant into an interventional trial if the participant meets the eligibility criteria. Participants will have the opportunity to accept taking part in PICS and reject taking part in interventional trials. The consent form will be modified to include clauses for any new trial anchored to the PICS platform. Participants will be given clear written information about PICS and any additional trials and will be given enough time consider taking part.

All consenting eligible participants for an interventional trial will be informed in case they are randomized to a given trial regardless of the arm they are randomized to. In all cases, a single participant will not be enrolled into more than one interventional trial at the same time.

2.1.5 Study assessments

PICS is a strictly observational study and all data gathered will be related to the patient's clinical care. The following data will be collected:

- Average age and gender proportion of patients admitted (from screening log)
- Comorbidities
- RAPID score
- Baseline blood tests and follow up inpatient tests (minimum urea and electrolytes, full blood count, C-reactive protein, and serum albumin)
- Pleural fluid results
- Microbiological results (pleural fluid and blood)
- Ultrasound findings
- CT findings if available
- Baseline and follow up CXRs
- Treatments received for pleural infection
- Length of hospital stay (LOS)
- Outcome at discharge (medical, surgical, dead)

Medical treatment will include: thoracentesis, chest drain, fibrinolytic, medical thoracoscopy

2.1.6 Outcomes

- Examining the incidence of pleural infection admissions locally, the demographics of this cohort and range of medical treatments offered.
- Correlating inpatient outcomes with baseline clinical, biochemical, microbiological and radiological parameters

- Percent of eligible patients randomized to interventional trials

'Antiseptic irrigation for patients with pleural infection' sub-study

2.2.1 Rationale and design

The antiseptic povidone-iodine can safely be instilled into the pleural for the purpose of pleurodesis[6]. Pleural irrigation with antiseptics is used in adults with open drainage for chronic empyema[7] and has been described in the acute management of paediatric pleural infection[8].

This sub-study will investigate the safety and usefulness of povione-iodine pleural irrigation in 15 eligible patients recruited to PICS. A matched control group will be used and will be composed of 15 patients previously recruited to PICS without receiving povione-iodine pleural irrigation.

2.2.2 Additional eligibility criteria

- Inclusion criteria:

  - Unilocular pleural collection

- Exclusion criteria:

  - Known or suspected thyroid disease

  - Allergy to iodine

  - Persistent large collection on follow up imaging 24-48 of post tube insertion that is deemed to require another drainage procedure

2.2.3 Specific assessments

- Two applications of 100-250 ml solution of 2% povidone-iodine will be irrigated into the pleural space of eligible patients 12 hours apart. The tube will be clamped for 15 minutes after irrigation and the patient will be asked to change position frequently during this period. The first dose will be applied 24-72 hours after tube insertion.

2.2.4 Outcomes

- Safety: incidence of adverse events (new chest pain, fever, dyspnoea or desaturtion) within 24 hours from the first irrigation

- Efficacy

  - Time to defervescence

  - Time to chest tube removal

  - Length of hospital stay

  - Need for additional aspiration/tubes

_ Failure of medical treatment

3.0 Data management

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 potential participants approached for the study. Separate study numbers for PICS and the interventional trial(s) will be assigned and in case of non-enrolment to either, reasons will be recorded.

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.

4.0 Statistics

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.

5.0 References

1. Davies HE, Davies RJO, Davies CWH, on behalf of the BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. Thorax 2010;65(Suppl 2):ii41–53.

2. Corcoran JP, Psallidas I, Gerry S, Piccolo F, Koegelenberg CF, Saba T, et al. Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. Eur Respir J 2020;

3. Maskell NA, Davies CWH, Nunn AJ, Hedley EL, Gleeson FV, Miller R, et al. U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection. New England Journal of Medicine 2005;352(9):865–74.

4. Cargill TN, Hassan M, Corcoran JP, Harriss E, Asciak R, Mercer RM, et al. A systematic review of comorbidities and outcomes of adult patients with pleural infection. Eur Respir J 2019;

5. Kim SY, Flory J, Relton C. Ethics and practice of Trials within Cohorts: An emerging pragmatic trial design. Clinical Trials 2018;15(1):9–16.

6. Agarwal R, Khan A, Aggarwal AN, Gupta D. Efficacy & safety of iodopovidone pleurodesis: a systematic review & meta-analysis. Indian J Med Res 2012;135:297–304.

7. Light RW. Parapneumonic effusions and empyema. Proc Am Thorac Soc 2006;3(1):75–80.

8. Togo S, Ouattara MA, Sangaré I, Saye J, Touré CAS, Maiga IB, et al. Management for Pediatric Pleural Empyema in Resource-Poor Country: Is Chest Tube Drainage with Antiseptic Lavage-Irrigation Better than Tube Thoracostomy Alone? SS 2015;06(12):541–8.