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A randomised controlled trial of the feasibility of early administration of clot-busting medication through a chest tube versus early surgery in pleural infection

Submission date
29/07/2019

Recruitment status
No longer recruiting

Registration date
30/07/2019

Overall study status
Completed

Last Edited
12/10/2023

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Pleural infection is a serious complication of pneumonia where infected fluid collects around the lung in a large abscess. It can affect anyone, and occurs in 40 patients every day in the UK. Treatment requires antibiotics and drainage of fluid using a chest tube inserted with local anaesthetic between the ribs, and admission to hospital for 2 weeks.
When these treatments fail, patients either die (about 20% of cases) or are referred for major surgery (a further 20%). Surgery is important when initial treatment fails, but has several side effects and is not an option for elderly and sick patients, where the death rate is 40%. In this study, we will consult with patients to understand what factors are important to them when treating pleural infection. This will help us to understand what should be measured in a study to best improve care. We will randomise patients to usual treatment (chest tube and antibiotics), early VATS or early IET. We will measure whether it is acceptable to patients to be randomised in this way and whether a larger study in the future is important and possible.

Who can participate?
Patients with pleural infection aged 18 years or older that meet the inclusion/exclusion criteria

What does the study involve?
A chest tube will be inserted into the patient's chest to drain the infected fluid and they will receive antibiotics in the usual way. Once the patient is in the study, they will receive one of the following treatments in addition to standard antibiotics; to continue with the chest drain (current standard of care), or receive two drugs through the chest tube, or patient will be considered for a surgical procedure. This will be randomly selected by a computer within the first 24 hours following diagnosis. All patients will be admitted to hospital to treat the infection with antibiotics which is normal care, for a period of up to one week. This period may vary depending on the progress of their condition. Patients in the group receiving the drugs through the tube (IET), will have these injected into the chest tube and left for one hour to mix with the infected chest fluid. This will be twice a day for 3 days. In the surgical group, a surgeon who

specialises in chest surgery will be asked to assess the patient's fitness and suitability for an operation to be carried out safely and discuss the planned procedure. The surgical procedure itself is well established and not "experimental" in any way.

Patients whose chest tube drains successfully and where the clinical team feels they have made a good response within the first 24 hours will not be eligible to be randomised so their inpatient treatment will continue as per standard care. A member of the trial team will contact them by telephone two weeks after discharge to see how they recovered and ask about their experience during your stay. This will be followed up by one further telephone call at approximately 3 months after discharge.

In all randomised cases, during the first week of the study patients will have routine daily blood tests to assess how well your infection is responding to the treatment. These tests are normal care for this type of infection (standard care). Patients will also have chest x-rays and sometimes chest scans throughout their treatment as normal care. One chest x-ray will be done before entering the study and patients may have already had one done as part of diagnosis. During their stay in hospital, patients will also be asked to complete some questionnaires if they are well enough. These questionnaires will be about health, mobility, activities and pain.

For patients who have received the study treatment (standard treatment or medication through the chest tube), their doctors will decide whether the infected fluid has drained successfully. If it has not, they will advise whether the patient needs an operation, to help remove any remaining infected fluid. This will be at the discretion of the hospital doctors and is not decided by the organisers of the study. For patients who underwent the surgical treatment, normal surgical care after the operation will be conducted.

Patients will visit the out-patient clinic within two to three weeks of discharge. This will be followed by further appointments at two and six months which is routine care. The study team will also perform a check of patients' medical notes at 12 months.

During these appointments patients will have basic breathing tests, a blood test and a chest x-ray and a doctor will assess their progress. At the six month clinic appointment there will be a final chest x-ray. Patients may also be asked to complete the same set of questionnaire they may have completed whilst in hospital.

What are the possible benefits and risks of participating?
The main risk of taking part would be any unexpected side effects from one of the drugs (IET) or a surgical complication. These are explained in detail in the PIS.
Patients may also experience some side effects following the collection of blood samples including bruising and/or fainting. There is a very small risk of infection but blood sampling will be carried out in a manner that strict infection control procedures are followed.

Where is the study run from?
The study is co-ordinated by the Oxford Respiratory Trials Unit (University of Oxford)

When is the study starting and how long is it expected to run for?
September 2019 to December 2021 (updated 02/03/2021, previously: March 2021)

Who is funding the study?
National Institute for Health Research (NIHR), UK as part of their Research for Patient Benefit Programme

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
255746

Central Portfolio Management System (CPMS)
41580

Protocol serial number
14006

Study information

Scientific Title
The third Multi-Centre Intra-Pleural Sepsis Trial (MIST-3): Early Video Assisted Thoracoscopic Surgery (VATS) or Intrapleural Enzyme Therapy (IET) in Pleural infection - a feasibility, randomised trial

Acronym
MIST-3

Study objectives
Would it be feasible and acceptable to both clinicians and patients to intervene with surgery or intrapleural enzyme treatment earlier on in the course of pleural infection?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Current ethics approval as of 19/11/2019:
Approved 28/07/2019, East of England - Cambridge East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; +44(0)207 104 8101; NRESCommittee.EastofEngland-CambridgeEast@nhs.net), ref: 19/EE/0174

Previous ethics approval:
Approval pending, East of England - Cambridge East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; NRESCommittee.EastofEngland-CambridgeEast@nhs.net; +44(0)207 104 8101), ref: 19/EE/0174

Study design
Randomized; Interventional; Design type: Treatment, Drug, Surgery

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute respiratory infection, pleural infection

Interventions
Participants will be approached initially by the clinical team as in-patients, who are suspected of having pleural infection. The aim is to enrol all participants with pleural infection and then assess who would be willing to undergo randomisation (random selection by a computer) to the trial interventions. It will be explained to participants that, if pleural infection is confirmed, they will be randomised to receive either referral to standard care, referral for intrapleural enzyme therapy (IET), which are 2 drugs given in combination through the tube or referral for surgery (this would either take the form of an actual operation or inserting a 'surgical' chest tube, depending on the local surgeon’s clinical view, taking into account patient suitability, general anaesthetic risk etc) via the agreed pathways.

Participants may be consented prior to confirmation of pleural infection, as the diagnostic procedure required to do this is often conducted at the same time as the chest drain is inserted, as drainage of infected fluid . Actual randomisation will only occur once pathological/radiological confirmation has been obtained, and will occur within 24 hours of confirmation of diagnosis to allow a 'fair' comparison of all three treatments, which means participants would continue on their current 'standard' treatment or be switched to one of the other two interventions.

All participants will initially receive a small bore (size <15F) chest tube and antibiotics once diagnosis is confirmed (as is standard care according to current national guidelines) and after initial drain insertion, it is permitted, according to local investigator preference, to wait for an initial drainage period before offering entry to the trial (which includes up to 24 hours as above). Those participants in whom drainage occurs successfully will not be randomised (and not counted towards the denominator for this feasibility study), but outcomes kept with their consent.

The first week will involve routine daily blood tests to monitor treatment response, which are a normal part of routine care for this condition. Chest x-rays and ultrasound assessments may be

carried out in addition to the ones done initially to diagnose the condition but this is all part of routine care.

Intervention Type
Other

Primary outcome(s)
The feasibility of randomising 75 participants with pleural infection to standard care, early VATS or early IET, assessed using:
1. Recruitment rate
2. Retention rate and the proportion of participants screened
3. Who consented to be randomised
4. Who consented to be interviewed

Key secondary outcome(s))
1. The risks/benefits from a participant/carer perspective of a referral to standard care, VATS or IET treatment strategy as well as which outcomes of pleural infection are most important to the participants assessed by performing structured qualitative interviews with a selection of participants who have had pleural infection and their carers (carer interviews at Oxford recruiting site only)
2. The acceptability of randomisation in a surgery versus non-surgery trial assessed by proportion of participants who accepted/did not accept to be randomised. Conduct structured interviews with all groups of participants to collect information about their concerns and reasons for accepting/not accepting randomisation
3. Feasibility of collecting accurate long-term outcomes assessed by completeness of data collected over 6 months from randomisation, regarding mortality, length of hospital stay (time from starting intervention until discharge), number of hospital readmissions, completion of lung function tests (FEV1/FVC), proportion of participants requiring further surgery. Assess the number of qualitative assessments completed such as functional assessments, questionnaires and visual analogue scores. Collect data on quality of life
4. Feasibility of trial interventions assessed by recording type of surgery (VATS, thoracotomy) and time surgery (from randomisation to surgery point of surgical intervention) in the surgical arm and details of compliance (proportion initiating treatment/completing treatment/requiring dose reductions/missed doses) in each interventional arm along with the reasons for non-completion
5. Costs of surgery will be assessed using a micro-costing study evaluating staff time, theatre time and consumables. Other healthcare resource use will be obtained from participants' trial records; hospital records; and participant self-report through questionnaires. Resource use will be costed using appropriate unit costs
6. Outcomes of pleural infection that are most important to the participants assessed by performing structured qualitative interviews with all participants who have had pleural infection to collect information on their priorities of care
7. Proportion of adverse events for the intervention arms

Completion date
31/12/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/03/2021:

1. A clinical presentation compatible with pleural infection AND
2. A pleural collection with a chest drain in situ
3. Has pleural fluid requiring drainage which is either:
3.1 Purulent or
3.2 Gram stain positive or
3.3 Culture positive or
3.4 Acidic with a pH < 7.2 or
3.5 Low pleural fluid glucose (< 2mmol / L) in the absence of accurate pH measurement or
4. Residual collection/ongoing sepsis after 24h standard care
5. Willing and able to give written informed consent

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Previous inclusion criteria:

1. A clinical presentation compatible with pleural infection AND
2. Has pleural fluid requiring drainage which is either:
2.1 Purulent or
2.2 Gram stain positive or
2.3 Culture positive or
2.4 Acidic with a pH < 7.2 or
2.5 Low pleural fluid glucose (< 2mmol / L) in the absence of accurate pH measurement or
2.6 Septated pleural fluid on ultrasound which is likely secondary to pleural infection (on the basis of local investigator view).
3. Able to give written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
Current exclusion criteria as of 02/03/2021:

1. Age < 18 years
2. Pleural collection not ameanable to chest tube drainage
3. Chest tube already in place for >= 72 hours
4. Has previously received intra-pleural fibrinolytics and /or DNase for this empyema
5. Has a known sensitivity to DNase or tissue plasminogen activator
6. Has had a previous pneumonectomy on the side of infection
7. Pregnant or lactating
8. Estimated survival less than three months from a different pathology to this empyema, (e.g. metastatic lung carcinoma)

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4. Previous pneumonectomy on the side of infection
5. Pregnant or lactating
6. Estimated survival less than three months from a different pathology to this empyema, (e.g. metastatic lung carcinoma)

Date of first enrolment
12/11/2019

Date of final enrolment
31/07/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Guy's Hospital
Guy's & St Thomas' NHS Foundation Trust
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Southmead Hospital
North Bristol NHS Trust
Southmead Road
Westbury-on-Trym

Bristol
United Kingdom
BS10 5NB

Study participating centre
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffield
South Yorkshire
Sheffield
United Kingdom
S5 7AU

Study participating centre
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
GX12 0XH

Study participating centre
Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Sponsor information

Organisation

University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-0416-20020

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		11/10/2023	12/10/2023	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 10.0	14/04/2021	27/09/2022	No	No