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A study to minimise the risks of emergence of drug-resistant bacteria in patients with Intensive Care Unit pulmonary infection by determining the optimal approach to administer existing antimicrobial treatments

Submission date
17/08/2021

Recruitment status
Stopped

Registration date
26/04/2022

Overall study status
Stopped

Last Edited
27/09/2022

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Resistance to antimicrobial drugs (antibiotics) has been identified in the UK, European Union and many other countries as an important problem which, if not addressed, will have a major effect on how patients will be looked after in the future. Combination antimicrobial therapy is used clinically to prevent emergence of resistance in mycobacterial or HIV disease and it has been suggested that combination antibacterial therapy may reduce the risks of emergence of resistance for infections in critically ill patients.

The study has been designed to establish the feasibility of conducting a larger scale randomised controlled trial to determine whether a combination of both antibiotic dose individualization and combination antimicrobial therapy are clinically effective in reducing the risks of bacterial resistance and improving clinical outcomes. This study will be using tazobactam-piperacillin (Tazocin) and cidomicin (Gentamicin) as the investigational medicinal products.

Who can participate?
The study will recruit patients who have been admitted to the ICU and have been on a ventilator for five or more days, with suspected pulmonary infection. The study excludes patients under the age of 18, patients with specific co-morbidities, pregnant women and prisoners.

What does the study involve?
This is a Phase II, four arm unblinded feasibility study. Patients in ICU with proven Gram-negative pulmonary infection as indicated by a bronchoalveolar lavage culture will be recruited to the study and randomised onto one of four arms. All patients will have additional tests (above standard of care) as part of the study. Patients on two of the study arms will have additional blood draws for analysis for personalised drug-dosing using a dose personalisation algorithm.

Antimicrobial resistance will be established using standard methodologies and strains will be typed and the mechanism of resistance established.

What are the possible benefits and risks of participating?
Benefits: This research will benefit patients by offering a route to potentially stop emergence of resistant bacteria in patients with ICU pulmonary infection by determining the optimal approach to administer existing antimicrobials to reduce the risk of resistance. The potential impact of these approaches are enormous. The findings from this study have implications for other clinical scenarios where the emergence of drug resistance is problematic – for example, treatment of neutropenic sepsis or the management of blood stream infection.

The work will likely have impact on local policy making – potentially increasing use of combination chemotherapy as well as the wider application of therapeutic drug monitoring – such changes, once shown to be effective, will lead to improvements in service delivery.

Risks: There are minimal additional risks associated with the study. Drug related reactions are a possible occurrence for patients. There are a number of known reactions to both penicillin-class antibiotics and for aminoglycoside-class antibiotics. As these drugs are being administered in a clinical setting there is a low risk to patients. Risk from drug interactions between piperacillin-tazobactam and gentamicin are minimal. Bronchoscopy is a safe procedure which is perform frequently in critically ill patients with a low incidence of complication.

Where is the study run from?
This is a multi-centre study which is being conducted by North Bristol NHS Trust and Manchester University NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2019 to March 2024

Who is funding the study?
The study is funded by the National Institute of Health Research (NIHR) Research for Patient Benefit (RfPB) programme (UK)

Who is the main contact?
Professor Alasdair MacGowan, Alasdair.Macgowan@nbt.nhs.uk

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Clinical Trials Information System (CTIS)
2019-003166-40

Integrated Research Application System (IRAS)
259350

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 42609, IRAS 259350

Study information

Scientific Title
Minimising the risks of emergence of antibiotic resistance during therapy by precise regimen individualisation and use of combination therapy

Acronym
MINIRES

Study objectives
The overall aim of this study is to investigate the feasibility of conducting a randomised controlled trial to determine whether a combination of both antibiotic dose individualisation and combination antimicrobial therapy are clinically effective in reducing the risks of bacterial resistance and improving clinical outcomes. This hypothesis will be tested with intubated critically ill patients undergoing critical care who develop Gram-negative pulmonary infection requiring antibiotics.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/01/2021, North West – Greater Manchester (GM) South Multi-centre Research Ethics Committee (MREC) (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 161 625 7820; Elaine.hutchings@northwest.nhs.uk), ref: 20/NW/0041

Study design
Randomized; Interventional; Design type: Treatment, Process of Care, Drug, Complex Intervention

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pulmonary infection

Interventions
80 patients over two sites will be recruited onto study. Patients shall be randomised on a 1:1:1:1 basis throughout the study and allocated using pre-generated lists produced by a statistician at the Liverpool Cancer Trials Unit (LCTU). Lists shall be produced using permuted blocks algorithm with random block sizes of 4 and 8. Stratification factors used in the study are randomising centre and age. The patients will be randomised onto one of four arms:
Arm A: Standard care piperacillin-tazobactam
Arm B: Standard care piperacillin-tazobactam & gentamicin
Arm C: Drug personalised piperacillin-tazobactam
Arm D: Drug personalised piperacillin-tazobactam & gentamicin

All patients will receive a course of IV antibiotics over 5-7 days as per the randomisation.

All patients will have blood draws through a central line conducted on a daily basis as part of standard of care in ICU. Patients on Arm C & Arm D will have additional blood draws on up to 3 day days of study treatment. These bloods will be analysed and a personalised dose calculated.

Patient's will receive a bronchoscopy and bronchoalveolar lavage on days 1 and 7. If the patient has regained consciousness prior to day 7 a sample from the extubation procedure will be used instead.

Patients will have a rectal swab on days 1 and 7. If the patient has regained consciousness prior to day 7 a stool sample will be taken instead.

Adverse events will be monitored up to day 28 or discharge from the ICU, whichever is first.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Piperacillin, tazobactam, gentamicin

Primary outcome(s)
1. Clinical cure measured using resolution of temperature, reduction of CRP, change of antibiotics from trial medications by 7 days
2. Emergence of resistance measured using culture of respiratory secretions and rectal swabs taken at day 0 and at 7 days
3. Ventilator free days measured using clinical recording of ventilation status at 28 days

4. Mortality measured using recorded death on relevant healthcare data bases at 28 days
5. Mortality measured using recorded death on NHS record at 3 months
6. Proportion of patients with gentamicin and/or piperacillin related toxicity measured monitoring of adverse reactions and events throughout the study with focus on adverse reactions listed on both drugs Summary of Product Characteristics(SmPC) at the end of the study
7. Duration of ICU stay measured using relevant hospital IT systems at ICU discharge
8. Duration of hospitalisation measured using ..relevant hospital IT systems. at hospital discharge
9. Proportion of patients achieving pre-determined pharmacodynamics targets for piperacillin-tazobactam and gentamicin measured using pathogen specific MIC values and drug determination on days 1 to 5.
10. Clinical efficacy, defined as the suppression of emergence of antimicrobial resistance after 7 days antimicrobial therapy, measured using pathogen isolation and susceptibility testing from respiratory secretions and rectal swabs taken on day 0 and at 7 days

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/03/2024

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
1. Intubated patients with clinician suspected Gram-negative pulmonary infection requiring antibacterial therapy
2. Adults aged 18 years upwards
3. Patient admitted to ICU for at least 5 days
4. Patient ventilated for at least 48 hours

Inclusion criteria for analysis:
Infection with a piperacillin-tazobactam and gentamicin susceptible Gram-negative organism.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Patients for whom informed consent cannot be obtained
2. Allergies or intolerance to piperacillin-tazobactam or gentamicin
3. Neutropaenic sepsis
4. Past medical history of cystic fibrosis
5. Other underlying infections pulmonary process unlikely to respond to piperacillin/tazobactam with or without gentamicin (i.e. tuberculosis, fungal pneumonia)
6. Subject unlikely to survive longer than 24 hours
7. Prisoners
8. Pregnant women
9. Non-NHS patients

Date of first enrolment
01/09/2022

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
United Kingdom

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Study participating centre
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Sponsor information

Organisation

North Bristol NHS Trust

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-1013-32031

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request to Alasdair.Macgowan@nbt.nhs.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No