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Biomarker-based exclusion of ventilator-associated pneumonia for improved antibiotic stewardship

Submission date 22/08/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 22/08/2013	**Overall study status** Completed	
Last Edited 09/12/2019	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Critically ill patients whose lungs are supported by breathing machines (ventilators) commonly develop a new lung infection, called ventilator-associated pneumonia (VAP). Because VAP is often fatal, antibiotics are administered whenever it is suspected. However, VAP is hard to distinguish from several non-infective lung conditions and most patients with suspected VAP do not have pneumonia. Therefore, many patients receive unnecessary antibiotics for several days, promoting the emergence of 'superbugs'. Laboratory test results for diagnosing VAP typically only reach the doctors after 3 days. A simple test rapidly and confidently excluding VAP should improve patient care, reduce unnecessary antibiotic use and decrease costs. We recently showed that low levels of specific proteins in fluid from the lungs of patients with suspected VAP effectively excluded VAP, using a test that may yield results within 6 hours. The test used is an extension of existing technology produced by our commercial partner Becton Dickinson (BD) Biosciences. Our previous findings were derived from a single hospital's intensive care unit. We have recently confirmed this finding across many intensive care units, which will help show that the test can be used in 'real life'. The aim of this study is to take the new test to the next step and determine whether it can improve the care of patients by reducing the amount of unnecessary antibiotics prescribed.

Who can participate?
Patients with suspected VAP, aged 18 or over.

What does the study involve?
All participants will have a lung sample taken. They will then be randomly allocated to receive either 'usual care' for suspected VAP, or to have the new test performed on their lung fluid. If the new test suggests no lung infection, the doctors will be asked to consider not giving antibiotics. We shall test how much antibiotic is given to each group. Patients are followed up for a maximum of 56 days.

What are the possible benefits and risks of participating?
There are no direct benefits to patients. However, being part of the study probably gives us a

better chance of making an accurate diagnosis of infection - we believe that the bronchoscopy test is by far the best way of diagnosing infection. The bronchoscopy is a common procedure on the intensive care unit and is safe.

Where is the study run from?
The study is run from the University of Newcastle Upon Tyne, and patients will be recruited from 23 hospitals in the UK.

When is the study starting and how long is it expected to run for?
November 2013 to December 2015

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Jennie Parker
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Study website
http://www.ncl.ac.uk/icm/research/project/5004

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01972425

Secondary identifying numbers
14666

Study information

Scientific Title
A randomised controlled trial of biomarker-based exclusion of ventilator-associated pneumonia to improve antibiotic stewardship

Study objectives
Critically ill patients whose lungs are supported by breathing machines (ventilators) commonly develop a new lung infection, called ventilator-associated pneumonia (VAP). Because VAP is often fatal, antibiotics are administered whenever it is suspected. However VAP is hard to distinguish from several non-infective lung conditions and most patients with suspected VAP do not have pneumonia. Therefore many patients receive unnecessary antibiotics for several days, promoting emergence of 'superbugs'. Laboratory test results for diagnosing VAP typically only reach the doctors after 3 days.

A simple test rapidly and confidently excluding VAP should improve patient care, reduce unnecessary antibiotics and decrease costs. We recently showed that low levels of specific proteins in fluid from the lungs of patients with suspected VAP effectively excluded VAP, using a test that may yield results within 6 hours. The test used is an extension of existing technology produced by our commercial partner Becton Dickinson (BD) Biosciences.

Our previous findings were derived from a single hospital's intensive care unit. We are carrying out a study to see if we can show this finding across many intensive care units, which will help show that the test can be used in 'real life'. The aim of this study is to take the new test to the next step and determine whether it can improve the care of patients by reducing the amount of unnecessary antibiotics prescribed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/LO/0651; First MREC approval date 28/06/2013

Study design
Randomised; Interventional; Design type: Prevention

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Topic: Respiratory, Generic Health Relevance and Cross Cutting Themes; Subtopic: Respiratory (all Subtopics), Generic Health Relevance (all Subtopics); Disease: Respiratory, Critical Care

Interventions
We shall identify patients with suspected VAP, all of whom will have a lung sample - half of the patients will receive 'usual care' for suspected VAP, the other half will have the new biomarker-based diagnostic test performed on their lung fluid. If the new test suggests no lung infection, the doctors will be asked to consider not giving antibiotics. We shall test how much antibiotic is given to each group.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Antibiotic-free days (AFD); Timepoint(s): The frequency distribution of antibiotic-free days (AFD) in the 7 days following BAL

Secondary outcome measures
Current secondary outcome measures as of 27/11/2013:
1. Antibiotic associated infections; Timepoint(s): upto day 56 post-BAL follow up
2. Antibiotic days in the 28 days following BAL; Timepoint(s): number of days on antibiotics compared with both interventions on both randomised groups
3. Antibiotic resistant pathogens; Timepoint(s): collected up to day 56 post-BAL follow up
4. Antibiotics days in 28 days following BAL; Timepoint(s): Comparison of AFD in 28 days between both randomised arms
5. Duration of ICU and hospital stay; Timepoint(s): up to 56 day post-BAL follow up
6. Length of ICU sty and level 3 or level 2 patient; Timepoint(s): up to day 56 post-BAL follow up
7. Mortality; Timepoint(s): 28 day mortality and ICU mortality
8. Sequential organ failure (SOFA) score; Timepoint(s): SOFA score at day 3, day 7, day 14 after enrollment on the study
9. Ventilator Free days; Timepoint(s): Total number of ventilator free days up to day 28 post-BAL follow-up

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6. Length of ICU sty and level 3 or level 2 patient; Timepoint(s): up to day 56 post-BAL follow up
7. Mortality; Timepoint(s): 28 day mortality and ICU mortality
8. Sequential organ failure (SOFA) score; Timepoint(s): SOFA score at day 3, day 7, day 28 after

enrollment on the study
9. Ventilator Free days; Timepoint(s): Total number of ventilator free days up to day 56 post-BAL follow-up

Overall study start date
01/09/2013

Completion date
25/11/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/11/2013:
1. Age 18 years or over
2. Mechanically ventilated for 48hrs
3. New or worsening changes on chest x-ray or CT scan of the lungs
4. Two or more from:
4.1. Temperature <35°C or >38°C
4.2. Blood white cell count <4x10*9/L or >11x10*9/L
4.3. Purulent tracheal secretions
5. The patient is considered suitable for early discontinuation of antibiotics
Target Gender: Male & Female ; Lower Age Limit 18 years

Previous inclusion criteria:
1. Age 18 years or over
2. Intubated and mechanically ventilated for 48 hrs
3. New or worsening changes on chest x-ray or CT scan of the lungs
4. Two or more from:
4.1. Temperature <35°C or >38°C
4.2. Blood white cell count <4x10*9/L or >11x10*9/L
4.3. Purulent tracheal secretions
Target Gender: Male & Female ; Lower Age Limit 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 210; UK Sample Size: 210

Total final enrolment

159

Key exclusion criteria
1. PaO2 <8kPa on FiO2 >0.7
2. Positive end-expiratory pressure >15 cmH2O
3. Peak airway pressure >35 cmH2O
4. Heart rate >140 bpm
5. Mean arterial pressure <65 mmHg
6. Bleeding diathesis (including platelet count <20x10*9 per litre of blood or international normalised ratio (INR) >3)
7. Poorly controlled intracranial pressure (>20 mmHg)
8. ICU consultant deems procedure not to be safe
9. Previous BAL as part of this study
10. Consent declined

* Patients who are enrolled in observational studies will be eligible for co-enrolment. Co-enrolment with interventional studies will be possible following consideration of any scientific or statistical interaction, in accordance with current UK Critical Care Research Forum (UKCCRF) recommendations (see appendix). Until coenrolment
is considered appropriate for a particular study, patients enrolled in an interventional trial will not be included.

Date of first enrolment
01/09/2013

Date of final enrolment
30/09/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle University
Newcastle Upon Tyne
United Kingdom
NE2 4HH

Study participating centre
23 hospitals
United Kingdom
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Sponsor information

Organisation
Newcastle Upon Tyne Hospitals NHS Trust and University of Newcastle Upon Tyne (UK)

Sponsor details
School of Medical SciencesMedical School
Framlington Place
Newcastle Upon Tyne
England
United Kingdom
NE2 4HH

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust; Grant Codes: WT094949

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	16/07/2016		Yes	No
Results article	results	01/11/2017		Yes	No
Results article	results	01/02/2020	09/12/2019	Yes	No
HRA research summary			28/06/2023	No	No