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Aspergillosis in patients with severe influenza or coronavirus infection

Submission date
02/12/2019

Recruitment status
No longer recruiting

Registration date
06/12/2019

Overall study status
Completed

Last Edited
13/02/2024

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Some patients with seasonal Influenza ('flu') develop severe infections requiring admission to the Intensive Care Unit (ICU) to support their breathing. Recent research has suggested that when patients have such severe influenza they may be susceptible to a second infection with a mould (a type of fungus) called Aspergillus. The mortality for patients infected with both severe 'flu and Invasive pulmonary Aspergillus (IPA) is high but life-saving antifungal treatments exist and
thus it is important that a diagnosis of IA in patients with severe influenza is not missed. Unfortunately, IPA can be difficult and lengthy to diagnose in the laboratory and until recently it was only thought to occur in patients whose immune systems were severely impaired. This means that IPA in patients with severe influenza may be under-diagnosed currently and the main aim of this study is to establish how common this condition is in UK patients.

In 2020 a new coronavirus was identified as the cause of an outbreak of unexplained pneumonia in China. This coronavirus was later named 'SARS-CoV-2', and the disease it causes 'COVID-19'. It is not yet known whether patients with severe COVID-19 infection are also at risk of IPA. This study offers an excellent opportunity to understand the risk of developing IPA in COVID-19 and find out whether fungal infection is contributing to the high death rate of COVID-19 patients in the ITU. An increased risk of IPA may not just apply to these two severe viral infections of the lung- it may also be that a heightened risk of secondary Aspergillus infection applies to any patient on the ICU with severe lung infection. In order to best understand this, we also plan to enrol patients on ICU with bacterial lung infection (pneumonia)as a control group so that we can compare the rates of IPA between patients with influenza, COVID19 and bacterial infections on the ICU infection.

This study will take place across seven hospital trusts during the 2019/2020, 2020/2021, and 2021/2022 and 2022/2023 influenza seasons. It will enrol adults admitted to Intensive Care with either severe influenza or COVID-19 as well a control group with bacterial lung infection (pneumonia). The proportion thathave evidence of IPA using routine diagnostic samples sent to the laboratory will be analysed. Clinical information will be recorded and analysed to identify any factors that increase the IPA.

Ventilated patients with severe lung infection often have a procedure called a bronchoscopy where a small camera is used to look inside the lungs and flush through a small volume of fluid (bronchoalveolar lavage, BAL) to send to the local Microbiology laboratory to diagnose the cause of the infection.

Following informed consent, this study will store surplus BAL samples from patients, and later use them to evaluate lateral flow tests for Aspergillus. These tests are very quick and have the potential, if found to be useful, to be incorporated into clinical guidelines to make the diagnosis of IPA in ICU much easier. As well as left-over BAL samples, blood samples from patients will also be stored for later immune and immunogenetic studies, to help us understand why certain patients with influenza or COVID-19 might be at greater risk of developing IPA.

Who can participate?
Ventilated adults admitted to intensive care with severe influenza or COVID-19 ('coronavirus') or bacterial pneumonia

What does the study involve?
This is an observational study which means that the care and treatments patients receive will not be any different whether they decide to take part or not. A set of research blood tests will be taken once patients are enrolled into the study and once more 5-10 days later if the patient is still on ICU. If the clinical team feel a bronchoscopy is indicated as part of routine clinical care the study group will take a sample of surplus bronchoalveolar lavage fluid and/or store any leftover samples. A bronchoscopy will not be performed or delayed for the purpose of this study. After the flu season is over these stored blood and BAL samples will be tested using both galactomannan and the AspLFD to compare how well both tests perform in diagnosing invasive aspergillosis. Since this will occur after the flu season the results of this testing will not influence the treatment of those enrolled. In addition to the samples that will be taken and stored, the researchers will collect clinical information from the participants' medical notes until their discharge from hospital or 90 days, whichever is the latest.

What are the possible benefits and risks of participating?
As an observational study, the only way participants will be directly affected by this research study is the extra blood and BAL samples taken. It is therefore not expected that any patients will come to harm. Patients are also unlikely to directly benefit from taking part in this research either. It is important to realize that any extra testing performed on samples (such as with the AspLFD) will be done at a much later date in the Spring/Summer.

Where is the study run from?
St George's University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
July 2019 to August 2023

Who is funding the study?
Gilead Sciences (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
271269

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 43440, IRAS 271269

Study information

Scientific Title
Incidence and pathogenesis of invasive aspergillosis in intensive care patients with severe influenza or COVID-19 (AspiFlu)

Acronym
AspiFlu

Study objectives
The main objective of the study is to assess what proportion of critically ill patients with severe influenza develop invasive aspergillosis (IA), and what factors increase the risk of this happening. The study will also look at whether those that do develop IA are more likely to have a prolonged ICU admission or die.

Hypothesis: Evidence of invasive aspergillosis (IA) will be found in a significant proportion of ICU patients with severe influenza - comparable to the 20% found in recent retrospective studies.

Added 26/03/2020:
The incidence of IA will also be evaluated in a comparison group of critically ill patients with COVID-19. This may illuminate whether IA is an influenza-specific phenomenon, or should be considered in any critically unwell patient with viral pneumonia.

Hypothesis: The incidence of IA in ICU patients with COVID-19 will be lower.

Added 13/01/2022:
The incidence of IA will also be evaluated in an additional group of critically ill patients with bacterial pneumonia. This will serve as a control group to which the incidence of invasive Aspergillosis in patients with COVID-19 or influenza can be compared against. This will illustrate whether secondary aspergillosis is more likely to occur as a direct result of severe viral infection or is equally likely to occur in any unwell ICU patient with a respiratory infection

Hypothesis: The incidence of IA in ICU patients with COVID-19 will be lower, and the incidence of IA will be lower still in those with bacterial pneumonia

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 04/11/2019, Wales Research Ethics Committee 5 Bangor (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; Tel: +44 (0)7970 422139; Email: Wales.REC5@wales.nhs.uk), REC ref: 19/WA/0310
2. Significant amendment approved 18/03/2020 and 13/01/2022 (details as above)

Study design
Observational; Design type: Cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Aspergillosis

Interventions
Current intervention as of 24/08/2020:
After consent and enrolment patients will undergo a baseline set of blood tests including serum (5 ml) and Paxgene DNA (2.5 ml). At the London study sites, peripheral blood mononuclear cells (32 ml) will also be taken. A second serum sample (5 ml) will be taken 5-10 days later if the patient remains on ICU. BAL will only be performed at the discretion of the treating team as per standard clinical care. Surplus BAL samples from participants will be stored for analysis after the influenza season. Leftover serum will also be stored.

Data Collection
Clinical data will be collected from the electronic hospital records at baseline, during the patient' s ICU stay, and after ICU discharge - up to 90 days or hospital discharge (whichever is longer).

Data Analysis
The researchers will use the collected clinical and microbiological data and BAL/blood galactomannan results to determine the primary and secondary outcome measures, with input from the study statistician for the multivariable analyses.

Retrospective Diagnostic Evaluation
Once the prospective study is complete, stored BAL/blood samples will be tested retrospectively in parallel by two tests: galactomannan EIA (the current 'gold standard' biomarker test for IA) and by the AspLFD (the new test we wish to validate). This will be done after the influenza season so results will have no implications for participants. The BAL/blood AspLFD results will be compared against the IA status of the patient to evaluate test performance against the AspICU definition.

Planned Sub-studies
These will be subject to further funding and are laboratory studies to help us understand why certain patients with influenza might be at greater risk of developing IA. This will involve measuring levels of immune system cells and immune parameters known as cytokines to look at how influenza affects the immune. The researchers will also use stored DNA to look at specific immune genes that might play a role.

Previous intervention:
After consent and enrolment patients in the influenza cohort will undergo a single-draw set of baseline blood tests. This will include peripheral blood mononuclear cells and Paxgene DNA. Approximately 30-40 ml of blood will be taken. BAL will only be performed at the discretion of the treating team as per standard clinical care. Surplus BAL samples from participants will be stored for analysis after the influenza season. Leftover serum will also be stored.

Data Collection
Clinical data will be collected from the electronic hospital records at baseline, during the patient' s ICU stay, and after ICU discharge - up to 90 days or hospital discharge (whichever is longer).

Data Analysis
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Planned Sub-studies
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Intervention Type
Other

Primary outcome measure
1. Incidence and risk factors for invasive aspergillosis (IA) in the study cohort (as per modified AspICU criteria):
1.1. Diagnostic classification of Influenza-associated aspergillosis (IAA) during ICU admission as per modified AspICU criteria, determined at the end of ICU stay
1.2. Risk factors to be elicited from baseline clinical data points collected at enrolment (within three days of ICU admission) and ICU therapeutics/interventions collected at the end of ICU stay

Secondary outcome measures
Current secondary outcome measures as of 26/03/2020:
1. The incidence of IA in critically ill patients with influenza and a comparison group with COVID-19:
1.1. Diagnostic classification of COVID-19-associated aspergillosis during ICU admission using modified AspICU criteria as per patients with influenza
2. Morbidity and mortality associated with both influenza-associated IA and COVID-19-

associated IA, measured by:
2.1. Duration (days) of mechanical ventilation at end of ICU stay
2.2. Duration (days) of ICU stay at end of ICU stay
2.3. Duration (days) of hospital stay at end of hospital stay
2.4. ICU all-cause mortality at end of ICU stay
2.5. Inpatient all-cause mortality at end of hospital stay
2.6. 90-day all-cause mortality at 90 days from study ICU admission
2.7. Survival analysis: time to death (all-cause mortality) for all patients at 90-days from study ICU admission
3. Utility of AspLFD device for diagnosis of IAA: sensitivity and specificity/negative and positive predictive values measured by diagnostic evaluation of results using stored samples against AspICU criteria. Performed retrospectively at a subsequent time after the influenza season

Previous secondary outcome measures:
1. Morbidity and mortality of IAA, measured by:
1.1. Duration (days) of mechanical ventilation at end of ICU stay
1.2. Duration (days) of ICU stay at end of ICU stay
1.3. Duration (days) of hospital stay at end of hospital stay
1.4. ICU all-cause mortality at end of ICU stay
1.5. Inpatient all-cause mortality at end of hospital stay
1.6. 90-day all-cause mortality at 90 days from study ICU admission
1.7. Survival analysis: time to death (all-cause mortality) for all patients at 90-days from study ICU admission
2. Utility of AspLFD device for diagnosis of IAA: sensitivity and specificity/negative and positive predictive values measured by diagnostic evaluation of results using stored samples against AspICU criteria. Performed retrospectively at a subsequent time after the influenza season

Overall study start date
06/07/2019

Completion date
15/08/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 13/01/2022:
1. Adults > 18 years
2. Admitted to ICU for respiratory support requiring intubation and ventilation for >24h
AND EITHER:
3. Positive influenza or SARS-CoV-2 PCR from nasal, throat swab, BAL or other respiratory specimen taken either < 7 days pre, or < 3 days post, admission to ICU
OR
4. Influenza or SARS-CoV-2 suspected but PCR results awaited – under these circumstances the patient can be provisionally enrolled, but later excluded if no specimens taken within either < 7 days pre, or < 3 days post admission to ICU positive as above
OR
5. Clinically suspected bacterial lower respiratory tract infection with associated radiological changes (pneumonia) encompassing both community and hospital-acquired pneumonia diagnosed ≤72hrs prior to ICU admission or ≤48 hours after admission. These patients must not have tested positive for influenza or SARS-CoV-2 PCR during their hospital admission

Previous inclusion criteria as of 26/03/2020 - 13/01/2022:
1. Adults aged >18 years
2. Admitted to ICU for respiratory support requiring intubation and ventilation for >24 hours
AND EITHER:
3. Positive influenza or SARS-CoV-2 PCR from nasal, throat swab, BAL or other respiratory specimen taken either < 7 days pre, or < 3 days post, admission to ICU
OR
4. Influenza or SARS-CoV-2 suspected but PCR results awaited – under these circumstances the patient can be provisionally enrolled, but later excluded if no specimens taken within either < 7 days pre, or < 3 days post admission to ICU positive as above

Previous inclusion criteria:
1. Adults > 18 years
2. Admitted to intensive care for respiratory support requiring intubation and ventilation for > 24 hours
AND EITHER:
3. Positive influenza PCR from nasal, throat swab, BAL or other respiratory specimen taken within 48 hours (of admission to ICU – pre or post
OR
4. Influenza suspected but influenza PCR results awaited – under these circumstances the patient can be provisionally enrolled, but later excluded if no specimens taken within 48 hours pre/post admission to ICU is positive as above

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: Influenza (n=60-80), COVID-19 (n=265-295), controls (n=50-70)

Total final enrolment
357

Key exclusion criteria
1. Respiratory failure not the primary reason for ICU admission
2. History of proven/ probable invasive pulmonary aspergillosis

Date of first enrolment
13/12/2019

Date of final enrolment
30/04/2023

Locations

Countries of recruitment
England

United Kingdom

Wales

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

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
St George's University Hospitals NHS Foundation Trust
St George's Hospital
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Manchester University NHS Foundation Trust
Wythenshawe Hospital and Manchester Royal Infirmary
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
University Hospital of Wales
Cardiff and Vale University Health Board
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Glenfield Hospital
University Hospitals of Leicester NHS Trust
Leicester
United Kingdom
LE3 9QP

Study participating centre
Royal Papworth Hospital NHS Foundation Trust
Papworth Road
Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0AY

Study participating centre
Birmingham Heartlands (facilities)
Birmingham Heartlands Hospital
51 Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5SS

Study participating centre
Royal Brompton Hospital
Sydney Street
London
United Kingdom
SW3 6NP

Sponsor information

Organisation
St George’s University Hospitals NHS Foundation Trust

Sponsor details
Joint Research and Enterprise Services (JRES)
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United Kingdom
SW17 0RE
+44 (0)2087254986
researchgovernance@sgul.ac.uk

Sponsor type
Hospital/treatment centre

Website
https://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=29686

ROR
https://ror.org/039zedc16

Funder(s)

Funder type
Industry

Funder Name
Gilead Sciences

Alternative Name(s)
Gilead, Gilead Sciences, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Presented at a stakeholder forum for ICU clinicians across the three sites
4. Main findings may also be presented at patient and public engagement events

Intention to publish date
05/08/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository:
St George's University of London (SGUL) research data repository (http://sgul.figshare.com). The anonymised Redcap database will be deposited. This contains no patient-identifiable information. Data will be available after an embargo period of 1 year to allow publication of the initial AspiFlu findings. Relevant summary data will be shared as part of the publication process. The data will be shared at the discretion of the Chief Investigator with bona fide researchers wishing to use the data for purposes that lie within the scope consented to in the AspiFlu study. Applications for data held on the SGUL research data repository are administered and processed by the SGUL Research Data Management Service following an independent and transparent process. Consent forms include the use of anonymised data and/or results being used for future research
comments on data anonymisation. The database does not contain any patient-identifiable information. External users of the data will be bound by a data-sharing agreement which will set out the user(s)' main responsibilities when re-using the data.

IPD sharing plan summary
Available on request, Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1.2	31/10/2019	06/12/2019	No	Yes
Protocol file	version v2.0	26/11/2019	06/12/2019	No	No
Participant information sheet	version V2.0	17/03/2020	26/03/2020	No	Yes
HRA research summary			28/06/2023	No	No
Results article		15/12/2023	13/02/2024	Yes	No