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Rapid diagnostic tests and treatment opportunities for fungal infection in critically ill patients

Submission date
04/10/2017

Recruitment status
No longer recruiting

Registration date
09/10/2017

Overall study status
Completed

Last Edited
05/08/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Treatment with ‘antifungal’ drugs is started when patients are thought to be at risk of fungal infection, even though the large majority turn out not to have this infection. This leads to the clinical problem that is over-prescription of drugs used to treat Candida fungal infection in adults and children in intensive care units (ICU). The majority of ICU patients who are treated with an antifungal drug receive treatment on an empirical basis. Typically, 7% of patients in ICU receive treatment for fungal infection and the majority of patients are started on a presumptive, basis. Of these, only 1 in 20 have fungal infection confirmed. Up to 11000 patients receive potentially unnecessary antifungal treatment each year, at a cost of up to £12 million to the NHS. Most patients treated fail to benefit and are disadvantaged by the risk of side effects. Over-treatment can also lead to resistance to these drugs in the wider population. This study evaluates how accurately three different rapid tests can diagnose fungal infection in adults and children, started presumptively on antifungal treatment. Blood samples from patients who are being started on antifungal treatment are collected and the results of the tests will not be made available to their doctors in this study and their treatment will not be affected by participating. The clinical and economic impact of implementing these rapid tests, based on how accurately they diagnose fungal infection is determined. The main aim of this study is to establish the ability of these tests, to rule out fungal infection in this patient group. We will use these results to develop a guideline that could be used by ICU staff to reduce unnecessary antifungal drug use.

Who can participate?
Adults and children over the age of 4 weeks old who are admitted to the ICU and are started or been prescribed systemic antifungal therapy.

What does the study involve?
A blood sample is taken from each participant and tested with three new diagnostic tests. If there is any blood sample left after completing these tests the study team would like to store this, with permission, for potential use in future ethically approved research studies. In addition, adult participants are asked to complete a short questionnaire about health-related quality of life approximately one month after entry into the study.

What are the possible benefits and risks of participating?
Participants in this research will not benefit as the results obtained from the new tests will not be used to guide doctors or alter current patient care. The main benefit of this study will be to help future patients with fungal infection by reducing unnecessary treatment which may result in fewer side effects and drug resistance. Patients taking part in this research may experience discomfort from the blood sampling required.

Where is the study run from?
This study is being run by The Queen's University of Belfast (UK) and takes place in UK hospitals.

When is the study starting and how long is it expected to run for?
April 2017 to May 2023

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mary Guiney, ASTOP@nictu.hscni.net

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
B17/23

Study information

Scientific Title
Antifungal stewardship opportunities with rapid tests for fungal infection in critically ill patients

Acronym
A-STOP

Study objectives
The rapid tests under study have high diagnostic accuracy for ruling out Candida infection in critically ill adults and children.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/01/2018, South Central - Hampshire A Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; 0207 104 8049), ref: 17/SC/0613

Primary study design
Observational

Study design
A multi-centre prospective diagnostic test accuracy study

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Critically ill patients with suspected fungal infection or proven fungal infection

Interventions
The A-STOP Study is a multi-centre, prospective, diagnostic test accuracy study. The purpose of this project is to assess the performance of three rapid tests for fungal infection. The accuracy of these tests are compared and the optimal test (or combination) identified. The emphasis is on their ability to rule-out infection so that a test-based protocol for early discontinuation of antifungal therapy can be developed.

This test-based protocol is modelled for clinical and cost effectiveness, accounting for expected beneficial and adverse outcomes. This modelling, together with a value of information analysis, will inform the design of a future clinical & cost effectiveness RCT.

In order to see if these new tests could be used to make decisions in the future, it is necessary to see how they compare to conventional tests currently used in the NHS. Blood samples for Candida infection are tested with three new tests (beta-D-glucan and two PCR-based tests) and the results are compared with those obtained from cultures that have been sent to the laboratory as part of the patient's normal care. This is to work out how accurate and useful the

new tests might be. An exploratory sub-analysis of the main diagnostic accuracy analysis is undertaken to evaluate variation in accuracy measures in the following sub-groups; children; patients with end organ dysfunction, assessed using SOFA and PELOD score (for adults and children respectively); prior antifungal exposure; patients with infection due to different Candida species; and patients with candidaemia.

At least 35 paediatric and adult intensive care units (ICUs) across the UK participate. Adult and paediatric patients admitted to the ICU who are started on presumptive antifungal treatment will be screened for inclusion into the study.

This research collects 1720 blood samples (one per person) over a 36-month period, with the result of each being compared to its paired culture result to estimate conventional diagnostic metrics (sensitivity, specificity, positive/negative predictive values (at specified prevalence), and positive/negative likelihood ratios) in the main analysis. The standard care blood samples are taken in the usual manner, for the participating study site. At the time a blood culture is taken, a 'research' sample of blood are also collected for testing. For adults, this is approximately 12mL and for children approximately 4mL.

Health related quality of life (for adults only) is measured using the EQ-5D-5L questionnaire at day 28 (up to day 35 if required). Patient survival after discharge from hospital will be determined either from hospital information systems, using the Health and Social Care Information Centre (if available) or by contacting their GP.

There is no change to standard care treatment of recruited patients.

Intervention Type
Other

Primary outcome(s)
Accuracy is measured using the negative predictive value for each index test

Key secondary outcome(s)
1. Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for proven invasive fungal disease, applied for Candida infection. These will comprise sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios.
2. Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for proven and probable invasive fungal disease, applied for Candida infection.
3. Estimated proportion of patients receiving systemic antifungal therapy in this cohort for whom treatment is unnecessary, derived from the reference standards used. Estimated number of days' avoidable antifungal treatment if negative index test results were used to stop treatment.
4. Development of a test-based protocol using the index tests (alone or in combination), as a strategy for early cessation of empirical antifungal treatment, with assessment of its expected cost-effectiveness modelled on test accuracy, disease prevalence and clinical/economic outcomes in this patient group.

Completion date
15/05/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 11/04/2019:
1. Adults and children >4 weeks old
2. Admitted to a UK ICU (level 2 or 3)
3. Prescribed systemic antifungal therapy, for suspected or confirmed Candida infection, during the preceding 24 hours

Previous participant inclusion criteria:
1. Adults and children >4 weeks old
2. Admitted to a UK ICU (level 2 or 3)
3. Started systemic antifungal therapy, for presumed Candida infection, during the preceding 24 hours

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
4 Weeks

Sex
All

Total final enrolment
1251

Key exclusion criteria
1. More than 24 hours systemic antifungal therapy in the preceding 7-days
2. Treatment with antifungal therapy for proven or suspected mould infection (eg.e.g. aspergillosis)
3. Neutropenia (absolute neutrophil count <0.5x109/L) during preceding 28 days
4. Acute leukaemia or within 12 months of bone-marrow transplantation
5. Hospitalised prisoners
6. Previously enrolled in this study

Added 26/10/2021:
7. Proven or suspected active infection with COVID-19

Date of first enrolment
01/01/2018

Date of final enrolment
01/01/2022

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Wales

Study participating centre
Belfast Trust
Belfast
United Kingdom
BT12 6BA

Study participating centre
Basildon University Hospital
Basildon
United Kingdom
SS16 5NL

Study participating centre
Pinderfields Hospital
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WF1 4DG

Study participating centre
Birmingham Heartlands Hospital
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Study participating centre
Royal Cornwall Hospital
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TR1 3LJ

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Study participating centre
Antrim Area Hospital
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Study participating centre
Altnagelvin Hospital
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BT47 6SB

Study participating centre

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RH1 5RH

Study participating centre
Ulster Hospital
Belfast
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Study participating centre
Milton Keynes University Hospital
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MK6 5LD

Study participating centre
Queen Elizabeth Hospital
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Study participating centre
Craigavon Area Hospital
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BT63 5QQ

Study participating centre
Royal Bolton Hospital
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BL4 0JR

Study participating centre

John Radcliffe Hospital
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OX3 9DU

Study participating centre
Birmingham Chidren's Hospital
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B4 6NH

Study participating centre
Royal Berkshire Hospital
Reading
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RG1 5AN

Study participating centre
University Hospital of South Manchester
Manchester
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M23 9LT

Study participating centre
Southmead Hospital
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BS10 5NB

Study participating centre
King’s College Hospital
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SE5 9RS

Study participating centre

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Study participating centre
Freeman’s Hospital
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Study participating centre
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NR4 7UY

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Stockton-on-Tees
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TS19 8PE

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S60 2UD

Study participating centre

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Study participating centre
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CF72 8XR

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TQ2 7AA

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WR5 1HN

Study participating centre

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HA1 3UJ

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LS9 7TF

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Study participating centre

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Study participating centre
The Royal Oldham Hospital
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Sponsor information

Organisation
The Queen's University of Belfast

ROR
https://ror.org/00hswnk62

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 7.0	25/03/2021	28/09/2021	No	No
Protocol file	version 8.0	27/05/2021	07/12/2021	No	No