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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
[X] 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

Contact name
Dr Ronan McMullan

Contact details
Kelvin Laboratory Building
The Royal Hospitals
Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Type(s)
Public

Contact name
Ms Mary Guiney

Contact details
7 Lennoxvale
Belfast
United Kingdom
BT9 5BY
+44 (0)28 961 51447
ASTOP@nictu.hscni.net

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
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Birmingham Heartlands Hospital
Birmingham
United Kingdom
B9 5SS

Study participating centre
Royal Cornwall Hospital
Truro
United Kingdom
TR1 3LJ

Study participating centre
Royal Derby Hospital
Derby
United Kingdom
DE22 3NE

Study participating centre
James Cook University Hospital
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Liverpool University Hospital
Liverpool
United Kingdom
L7 8XP

Study participating centre
Arrowe Park Hospital
Wirral
United Kingdom
CH49 5PE

Study participating centre
Antrim Area Hospital
Antrim
United Kingdom
BT41 2RL

Study participating centre
Altnagelvin Hospital
Londonderry
United Kingdom
BT47 6SB

Study participating centre

East Surrey Hospital
Redhill
United Kingdom
RH1 5RH

Study participating centre
Ulster Hospital
Belfast
United Kingdom
BT16 1RH

Study participating centre
Milton Keynes University Hospital
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
Queen Elizabeth Hospital
Birmingham
United Kingdom
B15 2GW

Study participating centre
Craigavon Area Hospital
Portadown
United Kingdom
BT63 5QQ

Study participating centre
Royal Bolton Hospital
Bolton
United Kingdom
BL4 0JR

Study participating centre

John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DU

Study participating centre
Birmingham Chidren's Hospital
Birmingham
United Kingdom
B4 6NH

Study participating centre
Royal Berkshire Hospital
Reading
United Kingdom
RG1 5AN

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

Study participating centre
Southmead Hospital
Bristol
United Kingdom
BS10 5NB

Study participating centre
King’s College Hospital
London
United Kingdom
SE5 9RS

Study participating centre

King’s Mill Hospital
Sutton-In-Ashfield
United Kingdom
NG17 4JL

Study participating centre
Freeman’s Hospital
Newcastle
United Kingdom
NE1 4LP

Study participating centre
Morriston Hospital
Swansea
United Kingdom
SA6 6NL

Study participating centre
Norfolk and Norwich
Norwich
United Kingdom
NR4 7UY

Study participating centre
North Tees
Stockton-on-Tees
United Kingdom
TS19 8PE

Study participating centre
Rotherham
Rotherham
United Kingdom
S60 2UD

Study participating centre

Royal Devon and Exeter
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Glamorgan
Llantrisant
United Kingdom
CF72 8XR

Study participating centre
United Hospital Bath
Bath
United Kingdom
BA1 2NG

Study participating centre
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
Torbay Hospital
Torquay
United Kingdom
TQ2 7AA

Study participating centre
Worcestershire Hospital
Worcester
United Kingdom
WR5 1HN

Study participating centre

Worcestershire Royal Hospital
Worcester
United Kingdom
WR5 1DD

Study participating centre
Medway Maritime Hospital
Gillingham
United Kingdom
ME7 5NY

Study participating centre
Northwick Park Hospital
Harrow
United Kingdom
HA1 3UJ

Study participating centre
St James's University Hospital
Leeds
United Kingdom
LS9 7TF

Study participating centre
University Hospital of North Durham
Durham
United Kingdom
DH1 5TW

Study participating centre
University Hospital of Wales
Cardiff
United Kingdom
CF14 4XW

Study participating centre

Barnsley Hospital
Barnsley
United Kingdom
S75 2EP

Study participating centre
Northumbria Specialist Emergency Hospital
North Shields
United Kingdom
NE29 8NH

Study participating centre
The Royal Oldham Hospital
Oldham
United Kingdom
OL1 2JH

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