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CandiRes - Understanding how receiving antifungal medications can lead to Candida yeast drug resistance among patients treated in intensive care

Submission date
24/11/2021

Recruitment status
Recruiting

Registration date
29/11/2021

Overall study status
Ongoing

Last Edited
04/09/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Candida is a commensal yeast (a type of fungus) that normally lives on the skin and in the gut, without causing any harm. If it grows out of control, Candida can cause infections such as thrush. If it enters the bloodstream or some internal organs, Candida can cause serious infections. The risk of serious infection with Candida is higher for people admitted to the ICU and those with a suppressed immune system. Around 1 in 20 people admitted to the ICU will develop a bloodstream infection from Candida. Candida infections are treated with antifungal medications. Some types of Candida can become resistant to antifungal drugs, making treatment more difficult. Just like with antibiotics, the overuse of antifungal medications is one of the drivers of higher resistance to these drugs. We do not have much information about how Candida develops resistance in the ICU, and about the impact of antifungal drugs on this development. It is hope that the results of this study will help to improve tools to identify drug resistance, identify whether a treatment for Candida is working in a given patient, and establish a way to assess whether treatment for a Candida bloodstream infection is working. This could allow researchers to better study antifungal drugs within clinical trials.

Who can participate?
Patients aged 18 years and over who have been admitted to the ICU and who are more likely to receive antifungal treatment, for example because they are receiving antibiotics.

What does the study involve?
Participants' medical care will not change. The following information will be collected from the participants' medical records: demographic information on age and gender, clinical information regarding length of ICU and hospital stay, illness severity, use of antifungal drugs, risk factors for Candida infection. A blood sample will be collected on the day of study enrolment. Twice weekly, swabs from the mouth and the skin around the anus will be taken and tested for Candida. For

participants who develop a serious Candida infection during the study, extra samples will be taken (from the blood or from any drain that might have been inserted for clinical reasons), and a stool sample.

What are the possible benefits and risks of participating?
There are no direct benefits to the participants from participating. Taking swabs of the mouth and skin do not pose any risk. Blood sampling will be very limited in volume and will be performed from a central or arterial line whenever possible, to avoid any discomfort.

Where is the study run from?
St George's, University of London (UK)

When is the study starting and how long is it expected to run for?
November 2021 to March 2027

Who is funding the study?
1. Pfizer (UK)
2. Medical Research Foundation UK

Who is the main contact?
Dr Tihana Bicanic, tbicanic@sgul.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
305864

Protocol serial number
IRAS 305864, CPMS 51121

Study information

Scientific Title
Relationship of antifungal exposure to emergence of Candida resistance in Intensive Care patients: a multi-site cohort study

Acronym
CandiRes

Study objectives
Current study objectives as of 10/07/2025:
1. To assess the Candida resistance ecology of ICU patients, and its relationship with antifungal exposure
2. To evaluate mycological clearance as a treatment response biomarker and its relationship with resistance evolution and antifungal exposure in patients with candidaemia
3. To describe the use of antifungal drugs and the epidemiology of invasive candidiasis in the ICU
4. Compare species distribution and resistance profile (MIC, genetic testing) of Candida colonising flora in ICU patients exposed or not exposed to an antifungal
5. Evaluate treatment response biomarkers in IC and the relationship with antifungal drug exposure
6. Elucidate the mechanism of resistance evolution in serial clinical isolates and the relationship with drug exposure
7. Evaluate the association between faecal mycobiome and candidaemia

Previous study objectives:
1. Antifungal use impacts local fungal ecology, and acts a driver for the micro-evolution of resistance.
2. Patients develop invasive candidiasis in critical care with their colonising flora.
3. Serial quantitative measurements (Candida CFU/ml, time to culture positivity, beta-D-glucan [BDG]) are a feasible marker of microbiological treatment response.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/11/2021, HRA and Health and Care Research Wales (HCRW, Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 2920 230457; HCRW.approvals@wales.nhs.uk) ref: 21/WA/0370

Study design
Multi-centre prospective observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Antifungal resistance in Candida among ICU patients

Interventions
Current interventions as of 08/05/2025:

Participants will undergo:
- twice weekly oral/perianal skin swab for Candida spp.
- 7 blood draws from CVC at 0 h, 6 h, 12 h, 24 h, 36 h, 48 h, 72 h, and D7 for serial culture, BDG /Candida PCR, PK (total volume: 65-139 ml above standard of care); BDG/ BDG/Candida PCR D14 and D21 (total volume: 6ml above standard of care)
- urine sampling at 0 h, 24 h,72 h and D7 for fungal culture, If drain in situ: drain fluid sampling (10 ml) at 0 h, 6 h, 12 h, 24 h, 72 h and D7, then every 72 h for fungal culture and PK until drain removed

Participants with confirmed candidaemia will have additional:
- Stool sampling for faecal mycobiome analysis

For each participant, the end of the study is defined as the date of ICU discharge or D30 from study enrolment (whichever is later).

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Current interventions as of 25/08/2023:

Participants will undergo:
- a baseline blood sample (for beta-D-glucan)
- twice weekly oral and perianal skin swab for Candida spp.

Participants who develop suspected or confirmed invasive candidiasis will have additional serial sampling:
- Serial blood sampling for participants with candidaemia (for BDG, culture, Candida quantification, drug level)
- Serial drain fluid sample for participants with deep-seated candidiasis and a drain inserted for clinical reasons.
- Serial urine samples for participants with deep-seated candidiasis and a urinary catheter for clinical reasons.

For each participant, the end of the study is defined as date of ICU discharge or D30 from study enrolment (whichever is later).

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Previous interventions:

Participants will undergo:
- a baseline blood sample (for beta-D-glucan)
- twice weekly oral and perianal skin swab for Candida spp.

Participants who develop invasive candidiasis will have additional serial sampling:
- Serial blood sampling for participants with candidaemia (for BDG, culture, Candida

quantification, drug level)
- Serial drain fluid sample for participants with deep-seated candidiasis and a drain inserted for clinical reasons.

Added 07/11/2022: - Serial urine samples for participants with deep-seated candidiasis and a urinary catheter for clinical reasons.

For each participant, the end of the study is defined as date of ICU discharge or D30 from study enrolment (whichever is later).

Intervention Type
Other

Primary outcome(s)
Current primary outcome measure as of 10/07/2025:
Incidence rate of colonisation and invasive infection with azole or echinocandin-resistant Candida spp. in those exposed or not exposed to an antifungal during their ICU stay. Change in isolate MIC and supra-MIC growth (tolerance).

Previous primary outcome measure:
Colonisation and invasive infection with azole or echinocandin-resistant Candida spp. (e.g. C. glabrata; C. parapsilosis; C. auris) measured using MALDI-ToF mass spectrometry and resistance profiling at the end of follow-up

Key secondary outcome(s))
Measured at end of follow-up unless otherwise noted:
1. Invasive candidiasis, rationale and duration of antifungal therapy, measured using EORTC diagnostic classification at the end of follow-up
2. Isolate antifungal tolerance, measured using change in isolate MIC and supra-MIC growth measured according to CLSI standards at end of follow-up
3. Emergence of genetic mutations associated with antifungal resistance, measured using genetic analysis at end of follow-up
4. Mycological clearance in candidaemic patients treated with antifungals, measured using rate of decline in CFU/BDG/time-to-culture-positivity at 12 h, 24 h, 36 h, 48 h, 72 h and D7 from diagnosis of candidaemia.
5. Exploratory: relationship between Candida resistance phenotype and genotype, PK and PD in candidaemia, measured using MIC, tolerance, antifungal drug levels and mycological clearance at 12 h, 24 h, 36 h, 48 h, 72 h and D7 from diagnosis of candidaemia
6. In-hospital mortality measured using patient records at end of follow-up

Added 10/07/2025:
7. Stool sample for faecal mycobiome analysis on days 1, 7 and 14

Completion date
31/03/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 10/07/2025:

1. Age ≥18 years
2. Suspected or confirmed invasive candidiasis

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Previous inclusion criteria as of 12/11/2024:

1. Age ≥18 years
2. Currently receiving intravenous antibiotics
3. One or more of the following Candida risk factors:
3.1. Abdominal surgery in the last 4 weeks
3.2. Upper gastrointestinal/mediastinal perforation or surgery in the last 4 weeks
3.3. Liver failure
3.4. Haematological malignancy
3.5. Previous bone marrow or solid organ transplant
3.6. Neutropenia (neutrophils < 0.5*10e9/l)
3.7. Receipt of an immunosuppressive drug (including corticosteroids, chemotherapy, immune-modulators)
3.8. Total parenteral nutrition (TPN)
3.9. Renal replacement therapy
3.10. Extracorporeal membrane oxygenation (ECMO)
4. Suspected or confirmed invasive candidiasis

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Previous inclusion criteria:

1. Age ≥18 years
2. Currently receiving intravenous antibiotics
3. One or more of the following Candida risk factors:
3.1. Abdominal surgery in the last 4 weeks
3.2. Upper gastrointestinal/mediastinal perforation or surgery in the last 4 weeks
3.3. Liver failure
3.4. Haematological malignancy
3.5. Previous bone marrow or solid organ transplant
3.6. Neutropenia (neutrophils < 0.5*10e9/l)
3.7. Receipt of an immunosuppressive drug (including corticosteroids, chemotherapy, immune-modulators)
3.8. Total parenteral nutrition (TPN)
3.9. Renal replacement therapy
3.10. Extracorporeal membrane oxygenation (ECMO)
4. Suspected invasive candidiasis (added 25/08/2023)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Expected ICU length of stay <48 h

Date of first enrolment
06/12/2021

Date of final enrolment
31/07/2027

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Guy’s and St Thomas’ NHS Foundation Trust
Westminster Bridge Road
London
United Kingdom
SE1 9RT

Study participating centre
St George's Hospital NHS Foundation Trust
Cranmer Terrace
London
United Kingdom
SW17 0RE

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

Study participating centre
Aintree University Hospital
University Hospital Aintree
Fazakerley Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

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

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
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United Kingdom
NW3 2QG

Study participating centre
London North West University Healthcare NHS Trust
Northwick Park Hospital
Watford Road
Harrow
United Kingdom
HA1 3UJ

Sponsor information

Organisation
St George's University Hospitals NHS Foundation Trust

ROR
https://ror.org/039zedc16

Funder(s)

Funder type
Industry

Funder Name
Pfizer

Alternative Name(s)
Pfizer Inc., Pfizer Consumer Healthcare, Davis, Charles Pfizer & Company, Warner-Lambert, King Pharmaceuticals, Wyeth Pharmaceuticals, Seagen, Pfizer Inc

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Medical Research Foundation UK

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

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