

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	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 29/11/2021	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 12/11/2024	Condition category Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English Summary

Background and study aims

Candida is a 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 like 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 hoped 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).

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

Dr Tihana Bicanic

ORCID ID

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Contact details

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

305864

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

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 hypothesis

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

Prospective observational cohort study

Primary study design

Observational

Secondary study design

Cohort study

Study setting(s)

Hospital

Study type(s)

Other

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Condition

Antifungal resistance in Candida among ICU patients

Interventions

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).

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 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

Secondary outcome measures

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

Overall study start date

01/11/2021

Overall study end date

31/03/2027

Eligibility

Participant inclusion criteria

Current 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 $< 0.5 \times 10^9/\text{l}$)
 - 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

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
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 - 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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

520

Participant exclusion criteria

Expected ICU length of stay <48 h

Recruitment start date

06/12/2021

Recruitment end date

31/07/2027

Locations

Countries of recruitment

England

United Kingdom

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

Sponsor information

Organisation

St George's University Hospitals NHS Foundation Trust

Sponsor details

Joint Research and Enterprise Services (JRES)
Ground Floor Jenner Wing
St George's, University of London
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England
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SW17 0RE
+44 (0)2087254986
researchgovernance@sgul.ac.uk

Sponsor type

University/education

Website

<https://www.sgul.ac.uk/>

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

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

Publication and dissemination plan

The study findings will be presented at national and relevant international meetings with abstract publication, and published in high impact peer-reviewed journals, with media coverage where applicable, so that findings and their implications quickly reach all of relevant UK clinical

communities and can be translated into policy. This will be facilitated by our investigator group which includes key individuals linked to Infection, Mycology and Intensive Care societies, laboratory networks, professional bodies, NHS England antifungal CQUIN committee and patient /relative groups across a wide range of responsibilities relevant to the management of fungal infection and intensive care in the NHS.

Intention to publish date

31/08/2027

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