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# Rapid diagnostic tests to inform clinical decision-making for antifungal stewardship in the ICU: a qualitative study with NHS staff, patients, and their legal representatives

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## Abstract

**Background:** Invasive candidiasis is a fungal infection of the blood or organs that is associated with high morbidity and mortality in critically ill patients. Current diagnosis is based on blood culture, which typically takes 2 days to confirm the presence of *Candida*, and longer for differentiating the species and sensitivities to antifungal drugs. Administration of antifungal treatment is time-critical, hence critically ill patients considered 'at-risk' of *Candida* infection are often started on antifungal treatment pending test results. However, many of these patients may not have empirical treatment stopped when test results become available because of concerns about the sensitivity of blood culture. The Antifungal STewardship Opportunities study is a multisite national diagnostic test accuracy study investigating the use of rapid tests in the intensive care unit that have the potential to influence decision-making.

**Objective(s), study design, settings and participants:** Our aim is to understand patient and physician risk preferences for using the Antifungal STewardship Opportunities testing strategy to discontinue empirical antifungal therapy using semi-structured interviews. An a priori sample size of 30 National Health Service staff and 10 patient interviews was selected to elicit information relating to the aims. Interview schedules were developed, and all interviews were conducted via video or teleconferencing between December 2021 and December 2022 and lasted between 10 and 60 minutes. Interviews were recorded, transcribed and subjected to thematic analysis.

**Findings:** Semi-structured interviews were conducted with 21 National Health Service clinicians and seven patients and legal representatives. National Health Service staff were risk-averse to stopping empirical antifungal therapy, especially if the patient was improving, while patients were risk-neutral. Although there is a clear unmet need for new rapid testing strategy, clinical confidence in its accuracy, clinical utility, cost-effectiveness and usability were strong factors for its consideration for use in decision-making and adoption. Patients did not exhibit strong feelings towards stopping empirical antifungal treatment as they expressed reliance on clinical judgement.

**Limitations:** There was a potential for selection bias as interview participants being from participating sites. The target recruitment numbers of patients and their legal representatives was not achieved due to low retention rates.

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**Conclusions:** If found to have high accuracy and cost-effectiveness, the potential of the Antifungal STewardship Opportunities diagnostic strategy to aid decision-making on antifungal prescribing could change intensive care unit clinicians practice, as they are risk-averse to stopping empirical antifungal treatment. However, consideration of the resources needed including staff, and lab facilities, adequate training as well as established guidelines to facilitate its adoption is required.
**Future work:** Our next aim is to use Antifungal STewardship Opportunities results to inform the update of National Institute for Health and Care Excellence guidelines and explore schemes such as the Accelerated Access Collaborative and MedTech funding mandate to propel the adoption of this testing strategy.
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## Background

Invasive candidiasis (IC) is a septic condition where the blood or other organs are infected with *Candida* species, a fungus,[1] and is considered an opportunistic infection in patients with disrupted host defences.[2] IC consists of candidaemia and disseminated candidiasis.[3] It is the most common fungal infection in the intensive care unit (ICU), and, although it may occur in as few as 0.59% of critically ill adult patients,[4,5] it is associated with longer lengths of hospital stay and mortality often exceeding 30%.[1,5,6] Starting antifungal treatment is time-critical; consequently, suspicion of IC is often sufficient to prompt antifungal prescribing in the ICU.

At present, the diagnosis of IC infection relies on blood cultures which have reported sensitivity between 50% and 80%.[1,2] Blood cultures typically take 2 days for a positive result to become available and longer for speciation and susceptibility to treatment to be determined.[1,7] A definitive negative result takes up to 5 days to be confirmed. This results in increased systemic antifungal prescribing as clinicians try to mitigate the risk of delayed treatment.

Management of IC is expensive due to the high costs associated with hospitalisation and antifungal drug treatment.[8] Empirical antifungal treatment has been found to be inadequate in 47% of patients[9] and may also be rendered ineffective by resistant *Candida* species, namely *Candida glabrata* and *Candida krusei* (now known as *Pichia kudriavzevii*).[4,10] In addition, the Fungal Infection Risk Evaluation (FIRE) Study found that unnecessary systemic antifungals were prescribed in 95% of ICU admissions.[4] Thus, rapid identification of the causative pathogen to prevent indiscriminate antifungal prescribing and the resulting costs and increased resistance is necessary to improve patient outcomes and reduce the length of ICU and overall hospital stay.[4,11] Proposed solutions that have been developed to guide antifungal prescribing include the use of a colonisation index, more complex clinical prediction rules and non-culture-based tests.[12]

New, non-culture based, testing strategies have been developed that could reduce the time to results.[12,13] The Antifungal STewardship Opportunities (A-STOP) study aims to determine the diagnostic accuracy and cost-effectiveness of two such testing techniques: detection of a fungal cell wall component, (1,3)-beta-D-glucan (BDG) and multiplex polymerase chain reaction (PCR) assays for *Candida* spp.[14] BDG is an insoluble component of the cell wall in some fungi, whose levels can be detected as it dissolves in blood and other body fluids.[15] The BDG assay is an FDA-approved adjunct for the diagnosis of invasive fungal disease.[2] It has been proposed as a rule-out test for invasive fungal disease due to its high negative predictive value in some patient groups.[15] The PCR-based tests can detect the most common *Candida* species: *Candida albicans*, *C. glabrata*, *C. krusei*, *Candida parapsilosis*, *Candida tropicalis* and *Candida dubliniensis*.[10] Previous PCR studies using blood samples have shown good sensitivity and specificity for the diagnosis of IC, which offers an attractive method for early diagnosis of specific *Candida*.[13] The T2 Magnetic Resonance Assay identifies Candida species based on clinical relevance – *C. albicans/tropicalis*, *C. glabrata/krusei* and *C. parapsilosis*,[16] while the Bruker Fungiplex Candida detects *Candida* spp. (*C. albicans*, *C. parapsilosis*, *C. dubliniensis*, *C. tropicalis*), *C. glabrata* and *C. krusei*.[17] These results can be obtained directly from whole blood samples in approximately 2–5 hours.[16,17] The PCR-based index tests produce categorical results, while the BDG test produces a quantitative result. Interpretation of BDG results is based on pre-specified cut-off values from the established manufacturer guidelines.[15]

The A-STOP trial is a prospective, multicentre diagnostic accuracy study. The objective of the study is to assess the diagnostic accuracy of the proposed testing strategy. Its secondary objective is to develop the test-based protocol to guide antifungal drug prescribing in the ICUs. As part of the A-STOP study, the Newcastle MedTech and in vitro diagnostics co-operative (MIC), (now the HealthTech Research Centre in Diagnostic and Technology Evaluation) conducted a care pathway analysis for IC. This paper reports on this work.

## Aim and objectives

The aim of our study was to assess patient and physician (described as NHS staff from here on) risk preferences for using the A-STOP testing strategy to discontinue presumptive antifungal therapy. We conducted interviews with healthcare professionals involved in the management of ICU patients as well as patients' post-recovery and their legal representatives enrolled in the A-STOP clinical trial. From NHS staff perspectives, secondary objectives were to: (1) determine the care pathway for suspected IC infection diagnosis and treatment in the ICU, (2) identify the clinical requirements for diagnostic tests for suspected IC and (3) explore the potential value of the diagnostic strategy underway in the A-STOP study. From patient interviews, we sought to understand their experiences in the ICU.

## Methods

A-STOP is a multicentre, prospective, diagnostic accuracy study with a qualitative component involving 44 adult and paediatric ICUs across the UK. Patients enrolled in the clinical trial were screened for eligibility based on inclusion/exclusion criteria described elsewhere (https://doi.org/10.1186/ISRCTN43895480). The clinical study is funded by the NIHR Health Technology Assessment (HTA) programme for the period of 48 months between 1 April 2017 and 31 March 2021 but was extended due to the pandemic until 31 December 2023.

### *Recruitment and sampling*

An a priori sample size of 30 NHS staff and 10 patient interviews was selected to elicit information relating to the aims. NHS staff were purposefully identified by the study principal investigators (PIs) based on their expertise and location, while patients were identified by their clinical research team. Healthcare professionals and patients meeting the inclusion criteria, as specified in *Table 1*, and willing to participate were then contacted by a Newcastle MIC team member via e-mail and provided with the participant information sheet (PIS). Some PIs were also invited to take part. Interviews were conducted with consenting staff and patients.

### *Interview structure*

Separate interview schedules were developed for NHS staff, patients and legal representatives. The interview schedule for NHS staff was divided into three sections, with questions covering the demographics, the current practice of diagnosing IC in an ICU setting and the potential value of the proposed A-STOP diagnostic strategy. Pilot interviews were conducted with a couple of consultant microbiologists to refine the schedule. An interim analysis of the schedule was conducted after 10 interviews, and the schedule was revised. The final schedule is included in *Appendix 1*. Semistructured interviews were conducted between January 2021 and May 2022 and lasted between 45 and 60 minutes.

The interview schedules for patients and/or legal representatives was divided into two sections, with questions covering their ICU experience and their proclivity for risk regarding antifungal treatment under uncertain diagnostic circumstances. The final schedules are included in *Appendix 2*. Interviews were conducted between April 2022 and December 2022 and lasted between 10 and 30 minutes.

### *Patient and public involvement and engagement*

At Newcastle University and Newcastle upon Tyne Hospitals, we have several readily formed patient and public involvement and engagement (PPIE) groups with different aim and scope. Some groups are formed by patients with lived experience; others are focused on a target clinical area or operate on a broader scale to capture the diverse perspectives of the general public. We actively engage with these individuals to bring a range of perspectives to conduct research that is scientifically rigorous, ethically sound, culturally sensitive and reflective of the diverse needs of the populations we serve. As researchers, we engage with PPIE leads relevant to our studies and bring our research to their group meetings. For this study, two such groups were consulted.

**TABLE 1** Inclusion/exclusion criteria

| | NHS staff | Patients | Legal representatives |
|---|---|---|---|
| Inclusion criteria | 1. Relevant expertise and experience of the management and/or diagnosis of invasive fungal infection in the ICU<br>2. Or insight into possible route to adoption for diagnostic devices | 1. Discharged adult ICU patients with suspected or confirmed fungal infection as part of the A-STOP trial | 1. Legal representative of child ICU patient (> 4 weeks old) with suspected or confirmed fungal infection as part of the A-STOP trial |
| Exclusion criteria | None | 1. Patients too unwell to participate in interview | 1. Legal representatives that lost their child |

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The NIHR Newcastle Clinical Research Facility patient and public involvement (PPI) group was consulted in July 2021, where the research proposal was presented to them. They helped in shaping the study design, provided an overview of the research agenda and asked for feedback on their comments. They reviewed the participant-facing material, such as PISs, consent forms as well as topic guides and interview schedules for the semistructured interviews for both clinicians and patients/legal representatives. The NIHR Newcastle MIC PPI Insight Panel was approached in December 2022. On this occasion, findings from the interviews with clinicians were presented. The PPIE supported the decision to interview patients and felt that they would be more informed of the impact and outcomes than lay members. They also provided feedback on the development of the patient and/legal representative interview schedule and contributed to the recruitment strategy. Their suggestions helped finalise the documents. In the final stage, the findings were presented to the groups, and they were asked to provide feedback on the lay summary.

Every quarter, PPIE members were sent an update, which included a project progress update, any arising issue, next steps and a summary how their contribution helped the study so far.

### *Data collection*

The interviews were conducted via video call or phone. All participant information was anonymised (Chikomborero Cynthia Mutepfa/Jana Suklan), with each participant assigned a unique identifier prior to analysis – for example, ID01, ID02, and so forth, for clinicians; or P01, P02, and so forth, for patients/legal representatives. All data collection was carried out by Chikomborero Cynthia Mutepfa and Jana Suklan. Chikomborero Cynthia Mutepfa and Jana Suklan had a combined experience of 9 years in qualitative research and were independent evaluators with no existing relationship with clinical team during the interviews.

### *Analysis*

Transcripts were generated using *Otter.ai* and checked for accuracy by the researchers (Chikomborero Cynthia Mutepfa/Jana Suklan). Interview recordings and transcripts were stored on the secure network server. The data from the interviews were subjected to thematic analysis following Braun and Clarke's[18] guidelines. This was our method of choice due to its pragmatism, flexibility and reliance on the inductive approach to data analysis. This allowed us to derive themes and patterns directly from the data without imposing a pre-existing theoretical framework. Coding was conducted using NVivo 1.2 (QSR International, Warrington, UK). A codebook was drafted based on main themes identified from the interview schedule; emerging themes were added during the analysis and refined as the analysis progressed. All interviews were coded by two methodologists independently (Chikomborero Cynthia Mutepfa and Jana Suklan), and discrepancies were resolved through discussion. We constructed a mind map using LucidSpark (Lucid Software Inc., South Jordan, UT, USA) software to summarise the relationships between the themes identified during analysis in relation to our aim.[19] In order to ensure internal reliability, a third coauthor, William Jones, was given insight into coding work, and codes were discussed among coauthors. Issues were resolved until consensus was reached. In addition, Ronan McMullan evaluated the results that were presented by the primary coauthor following the analyses, to increase the validity of results.

### *Reporting*

We checked our manuscript against the Standards for Reporting Qualitative Research: a synthesis of recommendations checklist (see *Appendix 3*).

### *Ethics*

This part/work package of the study obtained Health Research Authority and Health Care Research Wales Approval from the Hampshire Research Ethics Committee in August 2021, Integrated Research Application System identification (ID) 234779.

## Findings

### *National Health Service staff characteristics*

We interviewed a broad range of clinicians, 21 in total (*Table 2*). This report excludes results from the pilot interviews. Data saturation was reached at around 20 interviews.[20]

### *Patient and legal representatives characteristics*

Out of 19 eligible patients and legal representatives, 7 agreed to be interviewed, including 6 patients and 1 legal representative. Attrition was due to a lack of response (42%, 5/12), inability to participate (33%, 4/12) and a lack of interest (25%, 3/12). The characteristics of the participants are shown in *Table 3*.

### *Thematic analysis*

Four major themes were found in our analysis, including current practice in managing IC, the evidence requirements for adoption of a diagnostic test for IC, and barriers and facilitators to adoption and implementation from the NHS

**TABLE 2** Demographic profile of NHS staff

| ID | Job role | Years of experience | Type of hospital | Location (country, England – North/East/South/West) | Perceived hospital prevalence of IC (low, medium, high) | Clinical population (adults, paediatric) |
|---|---|---|---|---|---|---|
| 03 | Consultant in intensive care | 25–29 | Tertiary | England – South | – | Adults |
| 04 | Consultant in critical care | 15–19 | Secondary | England – South | – | Adults |
| 05 | Consultant in intensive care medicine and anaesthesia | 15–19 | Secondary, District General Hospital (DGH) | England – North | Very low | Adults |
| 06 | Consultant in intensive care medicine | 15–19 | Secondary DGH, teaching hospital | England – North | – | Adults |
| 07 | Consultant in intensive care medicine and anaesthesia | 25–29 | Tertiary, teaching hospital | England – Midlands and East of England | Low | Adults |
| 08 | Consultant in intensive care | 20–24 | Tertiary, teaching hospital | England – South | Low | Adults |
| 09 | Pharmacist in critical care | 5–9 | Secondary DGH, teaching hospital | Northern Ireland | – | Adults |
| 11 | Intensive care consultant | 5–9 | Secondary DGH, teaching hospital | England – South | Very low | Adults and children (in transit to tertiary hospital) |
| 12 | Consultant in intensive care | 25–29 | Tertiary, teaching hospital | England – North | High | Adults |
| 13 | Consultant in critical care and acute medicine | 0–4 | Tertiary, teaching hospital | England – North | Low | Adults |
| 15 | Consultant in intensive care | 25–29 | Tertiary, teaching hospital | England – North | Medium | Adults |
| 16 | Consultant microbiologist | 20–24 | Tertiary, teaching hospital | England – North | High | Adults |
| 18 | Specialist registrar in infectious diseases and microbiology | 0–4 | Tertiary, teaching hospital | Northern Ireland | Low to medium | Adults and children (process samples) |
| 20 | Critical Care Research nurse | 20–24 | Tertiary, teaching hospital | England – Midlands and East of England | High | Adults |
| 21 | Critical Care Research nurse | - | Tertiary, teaching hospital | England – Midlands and East of England | High | Adults |
| 22 | Consultant in anaesthetics and intensive care | 5–9 | Secondary DGH, teaching hospital | England – North | Low | Adults |
| 23 | Specialty doctor | 0–4 | Tertiary, teaching hospital | England – North | – | Adults |
| 24 | Anaesthetist, speciality doctor specialist grade | 5–9 | Tertiary, teaching hospital | England – North | Medium | Adults |
| 25 | Consultant in paediatric intensive care | 25–29 | Tertiary, teaching hospital | England – Midlands and East of England | Very low | Children |
| 26 | Consultant microbiologist | 25–29 | Tertiary, teaching hospital | England –Midlands and East of England | Very low | Adults and children |
| 28 | Trainee consultant, clinical scientist in microbiology | 5–9 | Secondary DGH, teaching hospital (mycology reference laboratory) | England – North | Low | Adults and children (process samples) |

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**TABLE 3** Demographic profile of patients and legal representatives

| ID | Gender | Age group | Hospital region | Type of hospital | Admitting condition | ICU length of stay |
|---|---|---|---|---|---|---|
| P01 | Female | 35–65 | South | Secondary | Acute pancreatitis | 9 days |
| P02 | Female | 35–65 | North | Tertiary, teaching hospital | Ruptured bowel | 21 days |
| P03 | Male | 18–34 | Midlands | Tertiary, teaching hospital | Gastric bypass | 17 days |
| P04 | Male | 35–65 | South | Tertiary | Sepsis/pneumonia | 14 days |
| P06 | Male | Over 65 | North | Secondary, teaching hospital | Bowel cancer | 30 days |
| P07 | Female | Over 65 | North | N/A | N/A | N/A |
| P12 | Female | 35–65 | South | Tertiary, teaching hospital | Sepsis | 49 days |

N/A, not applicable.

staff perspective and the patient perspective on their experience in the ICU.

In the following sections, direct quotes from the interviews are highlighted in *italics*.

## Current practice for diagnosis and management of invasive candidiasis

The diagnosis and management of IC were found to be similar across trusts and are in line with international guidelines.[5,21–24] The treatment protocols from the interviews have been collated, and the derived care pathway is shown in *Figure 1*.

Clinicians stated that the prevalence of IC varied due to differences in case mix and interventions (11), but it was generally described as being low across the UK ICUs included in the study.

When there is a clinical suspicion of IC (unresolving fever or/and relevant patient history), samples are collected and sent for culture to identify the presence of a causative pathogen and its sensitivity to antifungals, particularly fluconazole. They also listed other tests, such as BDG, mannan, anti-mannan and *Aspergillus* PCR that were also requested, to establish differential diagnoses. However, there is a high variability in availability and accessibility among trusts across the NHS for these. BDG testing is becoming increasingly available, and its results are used as a guide for the presence of invasive fungal infection or as an add-on test to rule in candidaemia. Nevertheless, most clinicians believed that BDG has a high false-positive rate, so were not relied on solely if positive.[15]

Empirical treatment is commenced as soon as there is clinical suspicion of disease and before any test results for invasive fungal disease are available. The gravity of the condition of ICU patients makes it imperative for treatment to be given as soon as possible to avoid further morbidity and mortality. The decision to treat empirically is based on the risk factors and relatively non-specific clinical features of a fungal infection and whether the benefits outweigh the harms (further renal or liver dysfunction) of introducing potentially toxic antifungals. The choice of drug prescribed is based on the patient's medical history and is guided by the microbiology team and prescribing guidelines.[22,25] The patient's condition and other prescribed medications are also considered.

There is a risk of toxicity posed by the broader spectrum of antifungals due to the increased risk of drug interactions and higher pharmacokinetic activity.[1,26] Drug toxicity in patients who are already critically ill could lead to renal or hepatic failure.[1]

> *One of the main concerns that we have is under-dosing the patient … that means the infection continues and carries on. Whereas if the patient achieves toxic doses of an antibiotic, we know for sure we'll have to deal with the side effects of this, but then which of the two is worse? This is why we're in that constant conundrum of measuring levels and trying to get it right.*
>
> *ID07*

Decisions on stopping continuing or tailoring treatment are based on the advice from the microbiology team. Clinicians are reluctant to stop antifungal therapy if patients are improving, even when test results are negative. The results obtained from blood cultures do not necessarily influence the decision to stop the use of empirical antifungals. The patients' condition seems to weigh more heavily in determining further actions. The time required to obtain a negative result often leaves room for a patient to improve from other causes (or respond to the antifungals if it is a false negative), thus confounding decision-making. For

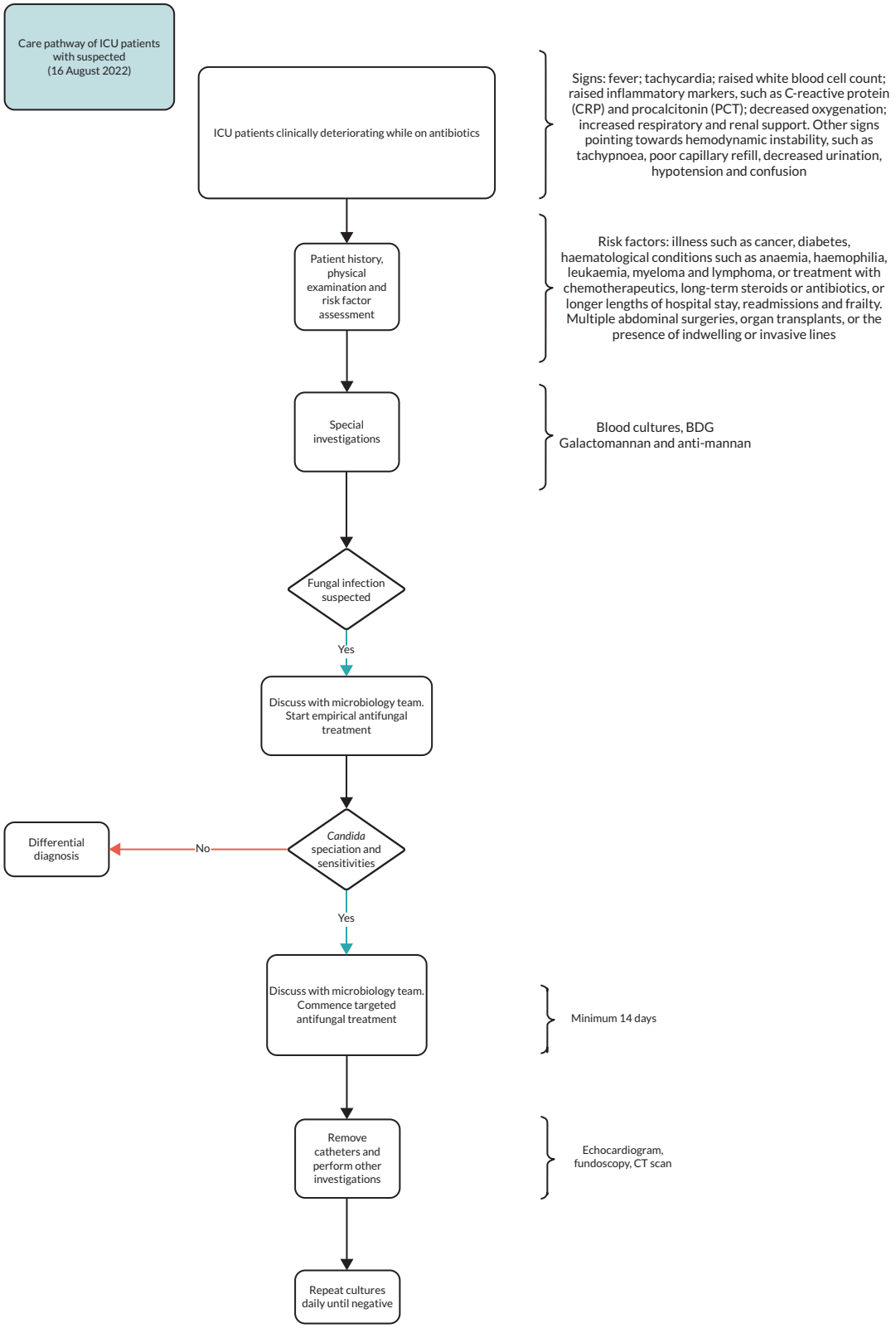


**FIGURE 1** Care pathway of patients with suspected IC.

positive blood cultures, only the choice of drug used is reviewed, when the sensitivities are available. Sometimes positive cultures from samples other than blood may not be acted upon, as they are treated as colonisation, whereby the *Candida* spp. proliferate in an area but cause no inflammation or harm.[12] Consequently, these positive results are treated based on clinical judgement or local trust protocols.

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### Diagnostic test and evidence requirements for invasive candidiasis

Clinicians expressed a need for a rapid diagnostic test with high accuracy, clinical utility, cost-effectiveness and usability. A prospective randomised clinical study comparing the A-STOP diagnostic strategy to the reference standard blood culture was suggested to generate robust evidence of these.

It was specified that a rapid test would need turnaround times to be either < 4 hours to forgo empirical treatment and commence targeted treatment, or within 12–24 hours to inform the decision to stop or continue empirical antifungal treatment. Longer lengths of turnaround time would allow for the empirical treatment to be given and for the drug to start effecting change.[27] In addition, patients also expressed the need for quicker diagnostic tests as they experienced multiple testing and long waiting times for the results during their ICU stay.

> *[Neutropenic patients] are likely to have multi organ failure if they're in intensive care. So, their renal failure, or their liver failure, may be worsened by giving antifungals. We've got to be careful about the choice of antifungal we use and the dose that we use in those patients. It would be very helpful to be able to [quickly] rule out a fungal infection, so we didn't have to give them the drugs that may contribute to their multi-organ failure.*
>
> *ID11*

High accuracy and the ability to speciate are the desired specifications of an ideal diagnostic test to give clinicians confidence in their decision-making. Both high sensitivity and specificity around 90% would be best, but a higher sensitivity to rule out IC is preferred.

Some clinicians ($n$ = 9) were in favour of having the A-STOP testing strategy available as a point-of-care test (POCT) as they viewed it as the ultimate ideal test. Others ($n$ = 7) felt that POCTs were unnecessary, and a rapid and accurate test done in a laboratory was sufficient. They were worried about trade-off with POCTs providing less accurate results, and the risk of declining/inappropriate/ineffectual quality control measures.

Clinical utility showing outcomes such as length of stay or reduced organ support or reduced mortality would facilitate the adoption of the test. Patient safety concerns were also raised. It was felt that diagnostic uncertainty might be increased if the test were used in populations that were not assessed during development and may provide positive results in patients with low pre-test probability.

For the A-STOP diagnostic strategy to be considered, it needs to be shown that cost savings from stopping unnecessary antifungal prescribing (thus avoiding side effects and related complications) is worth the additional cost of adopting this strategy. Another consideration is that the test (including machinery and disposables) does not cost more than the course of treatment, given the constraints on NHS resources. Outcomes such as shorter hospital stay, less laboratory activity or reduction in the number of days on ventilation were also suggested. HTA produced by National Institute for Health and Care Excellence (NICE) would provide convincing evidence. This strategy could also prove to be cost-effective for other regions of the world.

A few clinicians remarked upon requirements unique to their situations. For example, clinicians ($n$ = 2) involved with the diagnosis or treatment of children noted that diagnosing IC in children is more challenging due to the immaturity of their immune system and that challenges also arise from a limited volume of blood sample. Thus, the potential test needs to be able to process using very little sample volume to provide rapid and accurate results.

> *[T]here's difficulties with using beta-D-glucan in children less than six months old, because you can't interpret what that data means. It is slightly more challenging to diagnose paediatric IC infections. Just because, partly, your blood cultures are going to be even less sensitive because you can't get the same volume of blood that you would be getting from an adult. And in addition, you can't rely on beta-D-glucan in paediatrics, it can give false positives.*
>
> *ID28*

Similarly, consideration of the provision of appropriate and adequate resources for wider implementation is needed. Sufficient staff capacity and capability to support rapid turnaround times as interviewees revealed that there are currently various work patterns and opening hours of activity in laboratories across the UK. Finally, a testing algorithm that is developed by a team of microbiologists was also mentioned as a requirement.

### Barriers to adoption and implementation of A-STOP testing strategy

Several economic issues were brought up that pose a threat to the adoption of the testing strategy. Firstly, the NHS has a finite budget for all resources, so expenditure needs to benefit the most patients within that budget. Thus, an inexpensive test relative to the added advantage of speed and accuracy achieved by its use is needed. Secondly, accounting for the direct costs, such as the cost of

equipment, and staff needed to run the tests, plus indirect costs caused by the implementation of a novel technology in the system, is essential. The cost of implementation may be a barrier to adoption at an individual trust level. However, taking into consideration the costs of treatment associated with the seriousness of their side effects, a test which can facilitate cost-effective prescribing is likely to overcome this barrier. Furthermore, there was concern about who incurred the cost of procuring the new test, as departments within hospitals have separate budgets. Although ICUs have relatively high budgets compared to other departments (due to their nature in caring for critically ill patients), costs still need to be conservative. The feedback seemed to indicate that the testing strategy is most useful in a high disease prevalence setting, due to cost efficiencies. A protocol would be needed to determine which patients are at greater risk of contracting an invasive fungal disease to avoid unnecessary costs from accruing through testing all ICU patients.

> *Making testing affordable so that some of the smaller centres can bring them in-house, it would make quite a big impact on antifungal stewardship generally in the hospital.*
>
> *ID28*

> *[I]f the prevalence is higher, they're going to benefit because there's obviously going to be a cost implication in terms of these diagnostics. So, you know, maybe for our unit, the prevalence is very low compared to other units, but there's clearly going to be a cost implication because the actual equipment and the reusables and stuff on these tests are going to have an impact to whether certain units can afford to bring them in. And I guess you'd have to have a cost benefit analysis to say, we are we having enough invasive fungal infections to justify this expense? So, for us, it might be nice to have these tests available. But, if the frequency that we use them in is low, then it wouldn't be necessarily viable and maybe best using our resources elsewhere.*
>
> *ID13*

Clinicians also remarked that equitable access for patients to the technologies is extremely important to ensure maximum patient benefit. We established that there is high variability in accessibility to diagnostics technologies across hospitals. Some have easily accessible in-house laboratories, while other hospitals need to send their samples away for testing. Sending samples away may result in missing samples, delays in sending samples, wasted time in chasing reports or wasted time in waiting for batch sampling before running the analysis. Additionally, working patterns may be unfavourable for adoption, as there are variable working patterns and hours of lab activity. For instance, many hospital laboratories do not provide overnight or weekend services, leaving clinical decision-making in the ICU unsupported. All these factors cause delays in obtaining results, which impedes timely clinical decision-making. Furthermore, we found that clinical knowledge and awareness about fungal infections is lacking. This can be seen in the lack of key performance indicators or regulatory measures for hospitals or laboratories, which could incentivise the use of fungal diagnostics. Training in these areas is needed to initiate timely investigations and to prevent indiscriminate use of tests and the subsequent unnecessary expenditure. A NICE recommendation would be needed for hospitals to adopt A-STOP testing strategy.

> *Fungal infections have always been like the kind of sidekick to all other infectious diseases, and I think that there's a lot less attention paid to fungal diagnostics … So that's always difficult when you're trying to pose a business case for a new fungal diagnostic.*
>
> *ID28*

Navigating bureaucratic procurement processes is also a big barrier to test adoption.

### Patients' experience

Most patients ($n$ = 5) were satisfied with the care they received and were grateful to the staff. Mixed responses were received on their involvement in shared decision-making regarding their care, with some being included in their care ($n$ = 4) and others feeling like their input was overlooked. This perception was particularly influenced by their state of consciousness. Some ($n$ = 3) did recall the trial-and-error approach to their management as various medications were not relieving symptoms. Patients felt that under the uncertainty of diagnostic test results, medical teams should use their knowledge and experience to make clinical decisions for their patients' benefit. They found empirical treatment in patients with suspected IC before test results were available reasonable – in critical situations, quicker actions are preferred to delay.

> *Medical staff … do the test, and they go by the results of the test, it is nothing to do with the patient as such because the patient's not going to know what they are doing. They're not educated enough to know what these tests mean. Or what the results mean. Or whether they're 100% perfect or not 100% perfect; But you don't do a test if you don't think it's going to work.*
>
> *P07*

> *And it comes back and it's negative. But there's other indicators that are going on. That is down to*

*professionalism and clinical decision. I do think it should still be those tests should still be run.*

*P12*

Patients were divided on whether to stop antifungal treatment based on a negative test result. Some felt that the full course of antifungals is needed, while others felt that the test results should be acted upon; otherwise, ignoring the results would make testing futile.

### Thematic map

We visualised the gathered themes in a thematic map and framed them together based on the participant's potential acceptance of stopping empirical antimicrobials based on the A-STOP testing strategy for IC (*Figure 2*). Each theme is displayed in a different colour.

## Discussion

### *Lessons learnt*

We interviewed 21 clinicians with various roles in the ICU across the UK on the current clinical requirements for diagnosing in IC, alongside six patients and one representative of a patient. Our findings demonstrated the risk preferences to stopping empirical antifungals and the clinical need for the A-STOP strategy. Clinicians were risk averse and patient had no preference to stopping empirical antifungal drugs. An effort was also made to document the care pathway for the diagnosis and management of IC in the UK. We found that although the UK has no published recommended guidelines, there is consensus on the diagnosis and management of IC based on the clinical interviews presented in this report. The experience and training of clinicians, clinician's knowledge of the local population, microbiological support and availability of other guidelines has likely contributed to this uniformity.[2,23]

In our interviews with clinical experts in the ICU, we found that clinicians were risk-averse to stopping empirical antifungal treatment for IC, even if the patient tested negative. The clinical condition of the patient was primarily considered in this decision-making. A rapid test for quicker diagnosis may be useful for stopping empirical treatment or start targeted treatment. However, further evidence is required to convince clinicians to adopt this change, including the test sensitivity and specificity, clinical utility and cost-effectiveness. We also highlighted several barriers to adoption that add weight to physician's risk aversion. These are mainly around the potential for behavioural change, economic barriers, including costs of the test and treatment, regulatory hurdles and the availability of infrastructure and resources.

We also considered the views of patients and the public on stopping and starting antimicrobial treatment when diagnostic accuracy is uncertain. The responses highlighted

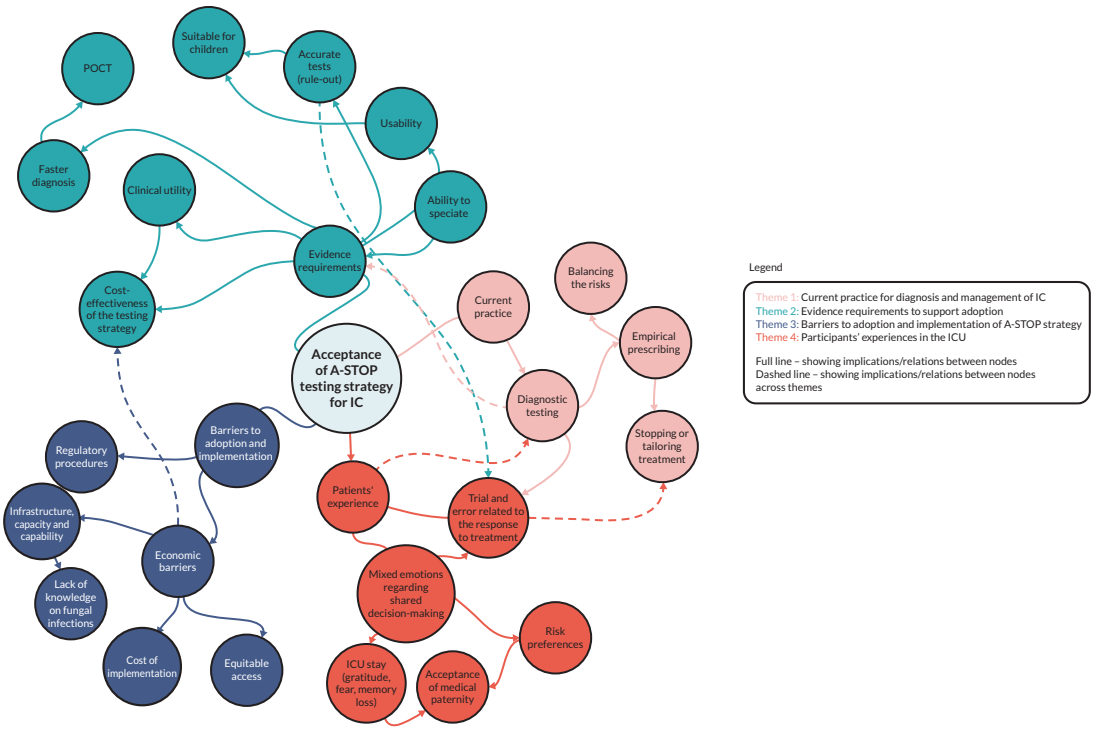


**FIGURE 2** Thematic map – acceptance of A-STOP testing strategy for IC.

a high degree of trust from patients and the public in the decision-making of medical professionals, especially in critical and time-sensitive situations.[28]

Besides a faster turnaround time compared to culture, the A-STOP strategy has the added advantage of providing quicker speciation that can guide antifungal prescribing, in turn combatting the growing resistance of *C. glabrata* and *C. krusei* to fluconazole and voriconazole.[10] However, changing clinical behaviour from a conservative approach, where antimicrobial treatment is continued if the patient is improving, to an approach where clinical decision-making is based on test results might need time to adopt.[12]

Confidence in the accuracy of the results is needed for more appropriate antifungal prescribing. Currently, the diagnostic accuracy of the A-STOP testing strategy is still under evaluation in the UK ICU setting, but sensitivities of 44% and 80%, and specificities of 87% and 90% for the PCR tests and BDG, respectively, were attained in a feasibility study.[29] While the BDG accuracy was similar to that found in previous studies, the low sensitivity of the PCR-based tests differed from previous studies and was attributed to the small sample size and retrospective testing.[13,29] Nevertheless, when the PCR and BDG results were combined by treating positive results from either test as a positive diagnosis, the sensitivity improved to 90% and the specificity was 80%.[29] As the specificity is not as high as our clinicians prefer, this indicates that any test-based protocol arising from A-STOP should focus on high-sensitivity tests for ruling out infection and the need for ongoing treatment.

There was concern about the high false-positive results of BDG especially in ICU patients due to the treatments utilised and nature of the patients. Firstly, some drugs used in ICU patients contain glucans that may produce false-positive test results.[15] Secondly, colonisation may occur, where there is harmless proliferation of microorganisms. Colonisation is a controversial issue in infection diagnostics as it is difficult to differentiate between this harmless proliferation or a pathologic invasion that must be treated. Clinical decision-making is then confounded, as studies have shown that only 5–30% of patients with colonisation develop IC.[12]

There was a misconception among some clinicians that hospitals with higher disease prevalence would benefit the most from the testing strategy; however, we could argue that it may be most impactful when IC is very unlikely. Here, testing would allow a lot of unnecessary treatment to be stopped, and thus curb costs.

The results of the A-STOP trial could be far-reaching. For instance, the current practice guidelines of the European Society of Intensive Care Medicine and the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESICM/ESCMID) do not strongly recommend the use of BDG and PCR in the diagnosis of IC due to poor evidence.[30] A robust study of these could alter their recommendations. Clinicians also call for a NICE recommendation so that hospitals can confidently adopt A-STOP testing strategy.

The A-STOP diagnostic strategy is anticipated for deployment to UK NHS hospitals, subject to rigorous evaluation, due to its potential to aid decision-making within a day, which could impact antifungal prescribing and improve patient costs and outcomes. Notwithstanding this, it needs to be bolstered by appropriate and adequate resources for wider implementation and supported by a testing algorithm that is developed by microbiologists.

### *Equality, diversity and inclusion*

All our documents are drafted within the NIHR equality, diversity and inclusion strategy. Our PPIE panel reviewed all participant-facing documents and commented on the language in use. We updated our PISs and consent forms to ensure that language was respectful, culturally inclusive and free from bias. We ensured that our language could be easily understood by individuals with varying levels of health literacy and provided the use of interpretative services and accommodating diverse communication preferences.

We based our research on results of FIRE Study, where disease burden, variations in disease presentation and outcomes across different demographic groups were explored.

We targeted participants that were already in the A-STOP study or linked with it. Participants were either clinical experts in critical care or patients in critical care that had a suspected fungal infection. At the time of recruitment, there were almost no paediatric patients available across sites. Hence, perspectives from legal guardians and representatives of children are missing in this analysis. Although almost double the number of our targeted recruitment participants were eligible and approached to take part, less than half consented and took part in the interviews. Despite appealing to social motivators and removing barriers and cognitive burdens as described by Wong and colleagues[31] through building the legitimacy of, or trust in, the research team; appealing to participants' sense of altruism; highlighting the benefits of taking part; offering telephone or video interviews, interpreting

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services, target recruitment numbers could not be reached and further recruitment was ceased, as the main A-STOP study had reached its target. It may be possible that financial or material incentives could have improved recruitment and retention.[31] In two cases, participants withdrew from the study due to rehospitalisation.

### *Limitations*

There was a potential for bias in the selection of interview participants. All interviewees were from participating sites (but not necessarily personally involved in the study), so they were aware of the clinical study and may have subconscious bias towards it. This was mitigated by objective questioning in the interviews.

However, as our patient participants were reluctant to accept a role in shared decision-making about the use of antibiotics, with the prevailing view being that the 'Dr knows best', we presume that participant selection from a wider pool of patients at risk of IC, instead of with/recovered from IC, may have given varied responses, including the risk of litigation from concerns around the validity of the diagnostic tests in most likely false-negative cases.

The A-STOP study is exploring a very complex issue, where they have yet to demonstrate the accuracy and effectiveness of the diagnostic tests. Therefore, the ability to change clinical practice without the evidence will be limited.

### Ethical issues

Although we considered the ethical challenges of undertaking research in what could be considered a vulnerable group as part of the ethical approval process, we did not fully explore this in our analysis. Enhanced consent and additional resources to reduce distress that could be caused by recalling their stay in ICU were included in our methodology. In addition to mitigate risks, all patients that participated were recruited several weeks after hospitalisation and were required to be well enough to participate as per inclusion criteria.

## Conclusions

Our research confirmed that there is a difference in opinion on the risks that clinicians and patients would be willing to take when considering the discontinuation of empirical antifungal therapy based on the A-STOP testing strategy. NHS staff were more reluctant to stop empirical therapy for IC in the ICU due to many factors, but, in particular, the vulnerability of the patient population, high morbidity and mortality were most persuasive in decision-making. The A-STOP testing strategy would need to be very accurate, have clinical utility and produce results within 4 hours of ICU admission for clinicians to adopting it.

On the other hand, patients/legal representative were found to be risk-neutral making decision about their treatment while in critical life or death situations and thus were willing to trust clinicians' judgements about their treatment needs while acknowledging the uncertainty of testing.

### *Future research*

Based on analysis of the interviews, future work could include:

- Evaluating the clinical utility, including the impact on prescribing and patient outcomes, of the A-STOP test-based protocol in a randomised trial. This would provide the level of evidence that clinician feedback indicated is necessary to enable practice change.
- Sharing with NICE the findings from modelling the A-STOP test-based protocol for clinical and cost-effectiveness.[14]
- Consideration of strategies that would make provision for the difference in perspectives between healthcare professionals and patients as there is limited overlap between the two groups in their acceptance of.
- Assessing accuracy of the A-STOP strategy in neutropenic patients, as most clinicians placed these patients foremost in their risk factors group.
- There is limited overlap on the views of both groups. This would suggest that strategies to enact a change/acceptance of change in both these groups would be starkly different going a point that needs greater consideration for future research suggested.
- Consideration of the accessibility of testing facilities and other practicalities is necessary for the deployment of the A-STOP strategy in a real-world setting, including aligning with government schemes for adoption into the NHS. Therefore, exploration of schemes, such as the Accelerated Access Collaborative and MedTech funding mandate which offer incentive schemes for trusts adopting new technologies, is recommended.[32]

## Additional information

### *CRediT contribution statement*

**Chikomborero Cynthia Mutepfa (https://orcid.org/0000-0002-1308-0594)**: Data curation, Formal analysis (equal), Investigation, Methodology, Project administration, Software,

Validation, Visualisation (lead), Writing – original draft (lead), Writing – editing and reviewing.

**Jana Suklan** (https://orcid.org/0000-0001-8665-6593): Conceptualisation, Data curation, Formal analysis (equal), Investigation, Methodology, Project administration, Software, Validation (lead), Visualisation, Writing – original draft, Writing – editing and reviewing.

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**William Jones** (https://orcid.org/0000-0001-9352-3916): Conceptualisation, Investigation (lead), Methodology (lead), Supervision, Writing – original draft.

**John Simpson** (https://orcid.org/0000-0003-4731-7294): Conceptualisation, Funding acquisition, Writing – original draft.

**Ronan McMullan** (https://orcid.org/0000-0001-6760-6072): Conceptualisation, Funding acquisition, Validation, Writing – original draft, Writing – editing and reviewing.

## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

## Ethics statement

This study was granted ethical approval on the 2 August 2021 by the South-Central Hampshire A Research Ethics Committee (17/SC/0613). No changes were made to it conduct during the study period.

## Information governance statement

The NIHR Newcastle In Vitro Diagnostics Co-operative is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation NIHR Newcastle In Vitro Diagnostics Co-operative is the Data Processor; Belfast Health and Social Care Trust is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for Belfast Health and Social Care Trust's Data Protection Officer here: https://belfasttrust.hscni.net/about/access-to-information/data-protection/.

## Disclosure of interests

***Full disclosure of interests:*** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJRM3321.

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This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

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## About this article

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constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.



## List of abbreviations

| | |
|---|---|
| A-STOP | Antifungal STewardship Opportunities |
| BDG | beta-D-glucan |
| FIRE | Fungal Infection Risk Evaluation |
| HTA | Health Technology Assessment |
| IC | invasive candidiasis |
| ICU | intensive care unit |
| MIC | MedTech and in vitro diagnostics co-operative |
| NICE | National Institute for Health and Care Excellence |
| PCR | polymerase chain reaction |
| PI | principal investigator |
| PIS | participant information sheet |
| PPI | patient and public involvement |
| PPIE | patient and public involvement and engagement |

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## Appendix 1 National Health Service staff interview schedule

1. Demographics

What is your job role?
- Where in the UK? Which trust?
- How many years have you worked in intensive care?
- What sort of hospital do you work in? (teaching/research, community specialist centre or smaller practice)

2. Current practice

- What are the initial clinical signs that would make you suspect an IC?
  - Why are these specific to IC?
  - Are there patient populations more likely to develop an IC?
  - Approximately, what is the prevalence of invasive fungal infection in your ICU?

- What diagnostic tests do you perform to reduce your uncertainty in diagnosing an IC?
  - Type of sample(s) required, invasiveness of test(s), turnaround times, type of information received.
  - What form the current results come in: quantitative, semi-quant, qualitative? Do they get current practice results pieces at a time or all at once?
  - Are there any contraindications for certain diagnostics?
  - If a patient tests negative for *Candida* infection, do you test for other fungi?
  - What happens to the value of the test as the prevalence changes?

- What treatments do you use on suspected *Candida* infection?
  - At what point in the patient pathway do you start treatment?
  - If empirical, presumptive: how do you balance the risk of giving empirical, presumptive treatment in situations of diagnostic uncertainty?
  - Are there patient populations where you are more or less risk-averse prescribing antifungals?
  - Are there clinical scenarios where you would hold off from giving treatment?
  - When do you revise the decision for the use of empirical treatment that is continuing or stopping empirical treatment?

- What is the clinical need in IC diagnostics?
  - Differences between adults and children?

3. Questions on the A-STOP diagnostic tests

- Are there clinical scenarios where these diagnostic tests would be useful?
  - How would they alter clinical decision-making? Could you mind just elaborating a bit more on how it would change clinical decision-making compared to current practice?
  - What are the advantages of using these tests?
  - Would you consider a positive biomarker test or negative biomarker test more clinically useful? (*Rule in, rule out?*)
  - Could this reduce unnecessary antifungal prescribing?
  - In what form would you like to see the results (quantitative, semi-quant, qualitative, pieces at a time or all at once)?

- What type of patients would benefit most from these tests?
- What hospitals would benefit the most from these tests?
- Do you see any potential disadvantages to these diagnostic tests?
  - Are there any risks of using the tests?
  - What patients wouldn't you use these tests on?

5. Barriers and facilitators to adoption

- What are the perceived barriers and facilitators for adoption of these tests in the ICU?
  - Are there ways to overcome these barriers?
  - Do you have any experience in getting a diagnostic test adopted in the ICU?

6. Evidence requirements

- What evidence would you want to see in these diagnostic tests in order to feel confident in using them?
  - Accuracy (compared to the reference standard or the test you are currently using)? How many false negatives out of 1000 patients with an invasive fungal infection would be acceptable? *(Se)*

- Speed (turnaround time) (ICU or for lab scientist)?
- Would you like to see any sort of cost-effectiveness studies? How important is that?
- Usability
- Safety (for lab scientist)?
- Usability (for lab scientist)?

## Appendix 2 Patient/legal representatives interview schedule

1. General ICU experience

- Could you tell us what can you remember about your experience in the ICU?
  - Which hospital where you in?
  - What was the reason for being in the ICU (background to their illness)?
  - How long was your stay in ICU? When (approximately) was you discharged?

---

- What is your relationship to the dependant?
- Could you tell us about the recent experience when your dependant was in the ICU?
  - Which hospital were they in?
  - What was the reason for them being in the ICU (background to their illness)?
  - How long was their stay in ICU? When (approximately) were they discharged?

2. Shared decision-making

- During your stay in the ICU, how were you kept informed of any clinical changes, tests or decisions that were being made?
  - What did you understand about your treatment at the time of your stay in the ICU?

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- During their stay in the *hospital, how involved were you in the decision-making around their care?*
  - What did you understand about their treatment at the time of their stay in the ICU?

- Were you kept informed of any clinical changes, tests or decisions that were being made?

7. Further comments

Is there anything else you feel is important to tell us about the IC that we haven't touched upon in this interview?

- Do you have any feedback on questions from the interview?

3. Risk preferences

*When an ICU doctor suspects that a patient may have a fungal infection in their blood, they may start treatment before they get the test results from the laboratory. They start the treatment before getting the results because the results can take days to come back and they are worried that if the patient does have a fungal infection and they don't start treatment, then the patient might deteriorate. Often, though, the results from the laboratory say that the patient hasn't got an infection. Inappropriate treatment can lead to serious side effects for the patient and is costly to the NHS.*

- Would you like us to explain any of that in more detail?
- What are your initial feelings about the approach just described?

*No diagnostic test is 100% accurate, which means some patients who have a disease will receive an incorrect negative test result and some patients who don't have a disease will receive an incorrect positive test.*

- Given this, how do you find the idea of stopping treatment for IC based on negative test results?

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*When an ICU doctor suspects that a patient may have a fungal infection in their blood, they may start treatment before they get the test results from the laboratory. They start the treatment before getting the results because the results can take days to come back and they are worried that if the patient does have a fungal infection and they don't start treatment, then the patient might die. Often, though, the results from the laboratory say that the patient hasn't got an infection. Inappropriate treatment can lead to serious side effects for the patient and is costly to the NHS.*

- Would you like us to explain any of that in more detail?
- What are your initial feelings about the approach just described?

*No diagnostic test is 100% accurate, which means some patients who have a disease will receive an incorrect negative test result and some patients who don't have a disease will receive an incorrect positive test.*

- Given this, do you find the idea of stopping treatment for CI based on negative test results acceptable?

4. Further comments
- Is there anything about the A-STOP trial specifically that you would like to tell us?
- Do you have any further comments?
- Is there anything about the A-STOP trial specifically that you would like to tell us?
- Do you *have any further comments*?

## Appendix 3 Standards for reporting qualitative research: a synthesis of recommendations (SRQR)

We used the SRQR reporting guidelines by O'Brien and colleagues.

| | | Reporting item | Page number |
|---|---|---|---|
| Title | #1 | Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended | Pg. 2 |
| Abstract | #2 | Summary of the key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions | Pg. 2 |
| Problem formulation | #3 | Description and significance of the problem/phenomenon studied: review of relevant theory and empirical work; problem statement | Pg. 5–6 |
| Purpose or research question | #4 | Purpose of the study and specific objectives or questions | Pg. 6 |
| Qualitative approach and research paradigm | #5 | Qualitative approach and guiding theory if appropriate; identifying the research paradigm is also recommended; rationale. The rationale should briefly discuss the justification for choosing that theory, approach, method or technique rather than other options available; the assumptions and limitations implicit in those choices and how those choices influence study conclusions and transferability. As appropriate the rationale for several items might be discussed together. | Pg. 6 |
| Researcher characteristics and reflexivity | #6 | Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results and/or transferability | Pg. 7 |
| Context | #7 | Setting/site and salient contextual factors; rationale | Pg. 4 |
| Sampling strategy | #8 | How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g. sampling saturation); rationale | Pg. |
| Ethical issues pertaining to human subjects | #9 | Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues | Pg. 8 |
| Data collection methods | #10 | Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale | Pg. 7 |
| Data collection instruments and technologies | #11 | Description of instruments (e.g. interview guides, questionnaires) and devices (e.g. audio recorders) used for data collection; if/how the instruments(s) changed over the course of the study | Pg. 6–7 |

| | | Reporting item | Page number |
|---|---|---|---|
| Units of study | #12 | Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results) | Pg. 8–9 |
| Data processing | #13 | Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymisation/deidentification of excerpts | Pg. |
| Data analysis | #14 | Process by which inferences, themes, etc. were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale | Pg. 7 |
| Techniques to enhance trustworthiness | #15 | Techniques to enhance trustworthiness and credibility of data analysis (e.g. member checking, audit trail, triangulation); rationale | Pg. 7–8 |
| Syntheses and interpretation | #16 | Main findings (e.g. interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory | Pg. 8–16 |
| Links to empirical data | #17 | Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings | Pg. 6–11 |
| Intergration with prior work, implications, transferability and contribution(s) to the field | #18 | Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contributions(s) to scholarship in a discipline or field | Pg. 16–19 |
| Limitations | #19 | Trustworthiness and limitations of findings | Pg. 18 |
| Conflicts of interest | #20 | Potential sources of influence of perceived influence on study conduct and conclusions; how these were managed | Pg. 30 |
| Funding | #21 | Sources of funding and other support; role of funders in data collection, interpretation and reporting – no funding | Pg. 2 |

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;**89**:1245–51.