Evidence Note
Number 89 January 2019

In response to an enquiry from The Scottish Antimicrobial Prescribing Group (SAPG)

Clinical and cost effectiveness of diagnostic strategies incorporating Beta-D-glucan (BDG) tests to reduce unnecessary use of empirical antifungal therapies for invasive *Candida* infection in the critical care setting

What is an evidence note?

Evidence notes are rapid reviews of clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) have developed an Advice Statement to accompany this evidence review.

Key points

There is insufficient published evidence on the use of Beta-D-glucan (BDG) tests to guide the withholding or discontinuation of empirical antifungal therapy in the critical care setting. Ongoing studies were identified.

All identified studies were conducted in adult populations and used the Fungitell® assay.

One randomised controlled trial (RCT) was identified (n=110). In this study a biomarker based strategy combining serum BDG in conjunction with mannan and anti-mannan testing led to a significantly higher rate of discontinuation of empirical antifungal therapy before day 7 when compared with no biomarker testing. The study was not sufficiently powered to investigate the

safety of the strategy with respect to patient outcomes such as subsequent infection rate or mortality.

One prospective and three retrospective exploratory non-comparative observational studies concluded that the use of strategies incorporating the Fungitell® assay have the potential to facilitate early discontinuation of empirical antifungal therapy. All four studies were conducted outside of the UK.

No relevant cost-effectiveness analyses were identified.

A Healthcare Improvement Scotland (HIS) de-novo economic evaluation demonstrated that a clinically-driven testing strategy with BDG (Fungitell®), to inform withholding of empirical antifungal therapy in critical care patients presenting with signs and symptoms of infection, is associated with a small cost increase, lower toxicity and a reduction in unnecessary prescriptions of antifungals compared with an empirical strategy alone. Indirect benefits relating to antimicrobial stewardship and potential impact on resource use, as well as improvements in patient quality of life by avoiding antifungal treatments and antifungal-related complications, were not included in the economic model.

The high negative predictive value of the test and the low infection prevalence in the population treated ensures the new strategy correctly rules out infection in a high number of patients. The imperfect sensitivity of the test however, misidentifies a small percentage of people as false negatives. The economic model showed this risk could be partially mitigated by using a lower BDG cut-off value which increases the test's sensitivity, albeit at the expense of lower specificity and a higher rate of unnecessary treatment in false positives.

Further sensitivity analysis showed the incremental cost of the BDG strategy to be minimal and potentially cost saving in units with 'less stringent' empirical strategy (where a high proportion of admissions are treated empirically and there is a low prevalence of infection in the population treated). In units with a more strict empirical strategy, the BDG strategy is associated with high incremental cost and can also produce a high number of false negative cases. The choice of antifungal medicines used in practice is also important, the BDG strategy being particularly cost-saving when only micafungin or amphotericin B are used and associated with a larger incremental cost in relation to agents from the cheaper triazole class.

Furthermore, the testing throughput, determined by the annual number of admissions, has important implications for service organisation owing to its impact on the variable cost of testing (higher throughput increases the number of patients that can be tested per testing plate). The model predicts the BDG strategy to be cost saving in excess of 9,448 admissions, assuming 10% of admissions are treated empirically and the infection prevalence among those treated is 7%. Any service reorganisation should consider same day turnover of testing results to mitigate the risk associated to treatment delays.

An alternative testing strategy assessed within the economic evaluation was using BDG results to inform discontinuation of empirical treatment at various points after initiation. Whilst this strategy may mitigate the risks of withholding therapy in patients with false negative results, it

was also associated with an increasing incremental cost (£155 and £236 with discontinuation at days three and seven respectively) and risked exposing the entire target population to avoidable antifungal treatments and associated toxicity.

Definitions

Critical care – in Scotland, critical care settings include intensive care units (ICU) and high dependency units (HDU).

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease.

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease.

Negative predictive value: The proportion of negative results that are true negative results.

Positive likelihood ratio: the probability that a positive test result will occur in a person with the target condition divided by the probability of a positive test result occurring in a person without the disease, that is the sensitivity divided by 1-specificity.

Negative likelihood ratio: the probability that a negative test result will occur in a person with the target condition divided by the probability of a negative test result occurring in a person without the disease, that is the 1-sensitivity divided by specificity.

Receiver operating characteristic (ROC) curve: a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values. Area under the ROC curve (AUROC) can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.

Literature search

A systematic search of Medline and Embase was carried out on 12 July 2018 to identify studies of any type relating to the topic. No filters were used and no restrictions in dates. English studies only were selected.

Concepts used in all searches included: *Candida*, beta-D-glucan and critical care. A full list of terms used is available on request.

Introduction

Invasive *Candidiasis* in critical care settings

Candida species are part of the human microbiota, colonising the skin and the gastrointestinal and genitourinary tracts. Invasive *Candidiasis* (IC) is associated with mortality rates of up to 70% in patients receiving critical care[1] and delays in initiating antifungal therapy are associated with increased mortality.[2] *Candidaemia* is the most commonly diagnosed form of IC. In a UK study across 96 ICUs, the main infection sites were blood (55%), peritoneal fluid (25%) and pleural fluid (10%).[3]

Risk factors for invasive *Candida* include; surgery, mechanical ventilation, immunosuppression, parenteral nutrition, central venous catheter, pancreatitis and use of broad spectrum antibiotics.[1]

The gold standard for diagnosis of IC is microbial culture and pathogen identification from samples of body fluids or tissues. This allows antifungal sensitivity to be measured and guides appropriate therapy. However, the sensitivity of blood cultures is only around 50%. Clinical risk scoring algorithms are also used to support diagnosis, as are radiological investigations where applicable.[1]

There are three categories of invasive fungal IC disease; possible, probable and proven. These definitions were developed to apply within cancer treatment and may not be applicable to ICU patients.[4]

The turnaround time for microbial culture, which can be up to 4 weeks, and the level of diagnostic uncertainty is likely to lead to overuse of antifungal medications in critically ill patients.[5]

The systemic antifungals used to treat fungal infections in acute hospitals are triazoles (fluconazole, itraconazole, voriconazole, posaconazole and isavacoconazole); echinocandins (caspofungin, micafungin and anidulafungin); and amphotericin B.[6] Antifungal exposure is likely to have an impact on susceptibility of *Candida* species to antifungal agents and development of resistance.[7]

As well as the optimal targeted use of antifungal therapies for confirmed infections with known and susceptible organisms, the following overlapping strategies for antifungal therapy use may be employed (see also figure 1):[8]

Empirical treatment – where patients have symptoms/signs suggestive of invasive fungal infection but where neither organism nor susceptibility is confirmed. Current practice in Scotland is to instigate antifungal therapy based on:

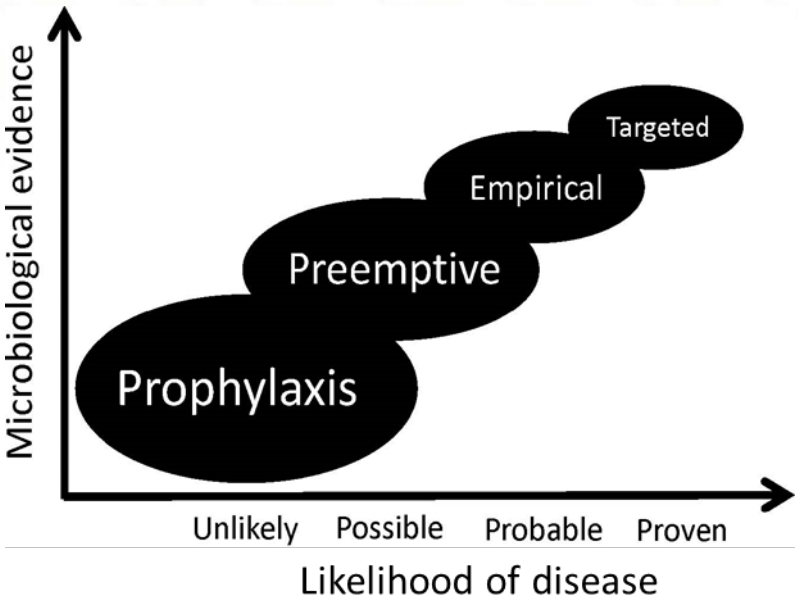
- failure to respond to broad spectrum antibiotics
- clinical assessment
- microbiological investigations
- radiological testing

(B Jones, Consultant Medical Microbiologist, Glasgow Royal Infirmary. Personal Communication, 9 May 2018)

Pre-emptive treatment – where patients have no clinical symptoms but some form of screening suggests infection.

Prophylactic treatment – where patients are deemed at high risk of developing invasive fungal infection but where there is no evidence of infection.

Figure 1: antifungal treatment strategies[8]



US guidelines on empiric treatment for suspected invasive candidiasis in non-neutropenic patients in the ICU recommend that empirical treatment should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. This should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from non-sterile sites.[9] European guidelines however suggest that in the ICU setting this approach is only marginally supported in the absence of microbiological evidence.[10]

This evidence note examines the potential for diagnostic strategies incorporating beta-D-glucan (BDG) - a non-culture based test - to safely reduce unnecessary empirical treatment by ruling out invasive *Candida* disease. Outcomes of interest include rates and duration of use of antifungal therapies and cost/cost-effectiveness, as well as clinical outcomes such as mortality and process outcomes such as length of stay. Morbidity relating to toxicity of antifungal medications and drug interactions is also of interest.

Health technology description

A NICE Medtech Innovation Briefing (MIB) described the BDG technology which was the test used in all identified studies.[5] The description of the technology as below is taken from the MIB.

The Fungitell® assay (Associates of Cape Cod) is an in-vitro diagnostic test for the detection of (1–3)-beta-D-Glucan (BDG) in serum. BDG is a major cell-wall component of most pathogenic fungi and tiny quantities are released into circulation during infection. Fungitell® is a kinetic colourimetric assay that works with computer software. If BDG is present in a serum sample, the Fungitell® reagent reacts with the BDG and turns yellow. The rate of this colour change is measured against a standard curve of BDG concentrations to produce estimates of concentration in the sample. The results range from non-detectable (less than 31 pg/ml) to over 500 pg/ml. Fungitell® can detect the presence of many pathogenic fungal infections including candidiasis, aspergillosis and fusariosis, but cannot differentiate these by type. Fungitell® cannot identify fungal infections caused by certain fungal species such as Cryptococcus, the yeast phase of Blastomyces dermatitidis or Mucorales such as Absidia, Mucor and Rhizopus.

The Fungitell® assay provides results within 2 hours.

Fungitell® was CE marked as an in vitro diagnostic device in June 2008.

Several alternative technologies are available including:

Dynamiker Fungus (1-3)--β-D-glucan Assay (Dynamiker) CE marked

Goldstream Fungus (1-3)--β-D-glucan Test (by Era Biology) CE marked

Endosafe-PTS glucan (Charles River Laboratories (U.S.)

Fungitec G-Test MK (Seikagaku)

β-Glucan Test Wako (Wako Pure Chemical Industries)

MB-80Set microbial dynamic detection system (Beijing Gold Mountainriver Tech)

B-G Star kit (Maruha)

Epidemiology

Complexity around the diagnosis of invasive fungal disease (IFD) limits the precision of epidemiological data. A study of 60,778 admissions, conducted across 96 critical care units in the UK between 2009 and 2011 identified that 383 patients (0.6%) were admitted with, or developed, IFD.[3] The incidence of IFD identified in-unit was 4.7 cases per 1,000 admissions, and of unit-acquired IFD (based on samples taken more than 48 hours after admission) was 3.2 cases per 1,000 admissions.

The IFD definitions were selected to best capture invasive *Candida*. Around 7.4% of patients received systemic antifungal therapies. Of systemic antifungal therapy commenced during (rather than prior

to) admission (n=3,413), 93% of instances were for patients who were not subsequently diagnosed with invasive *Candida* infection.

The Scottish Intensive Care Society Audit Group (SICSAG): Audit of Critical Care in Scotland recorded information on 46,931 admissions in 2017.[11] Some specialty HDUs, e.g. renal and most obstetric HDUs, are not included in the audit data (SICSAG, Personal Communication, 13 September 2018). In 2016, the use of systemic antifungals in acute hospitals in NHSScotland was 128.9 defined daily doses per 1,000 admissions.[6] No data specifically on the critical care setting are available.

Clinical effectiveness

Patients receiving critical care are inevitably a heterogeneous population. In examining the clinical effectiveness literature, comparability between studies is likely to be influenced by the risk profiles of the study populations. All identified studies focused on adult populations.

Guidelines

UK Best Practice Guidelines for the diagnosis of serious fungal diseases recommend that BDG screening of serum from patients at high risk of invasive fungal disease should be considered, noting that a negative result has a high negative predictive value, enabling invasive fungal disease to be excluded.[12]

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) published guidelines on the diagnosis and management of *Candida* diseases in non-neutropenic adult patients in 2012.[10] Based on the evidence available at that time, it was stated that glucan tests cannot reliably confirm invasive candidiasis, although there may be a role for the test as part of a set of diagnostic tools and patient characteristics. A recommendation, based on uncontrolled studies, marginally supported the use of a positive BDG test to identify ICU patients requiring antifungal therapy. The guideline stated that, in some studies identified, a negative glucan test practically rules out invasive candidiasis.

Another guideline from the ESCMID in 2012 focused on diagnostic procedures in *Candida* diseases more broadly.[13] The guideline panel considered the BDG test (Fungitell® only so far) as recommended for Candidaemia detection in adults being also very useful for ruling out infection. There were also recommendations for the use of BDG in detecting invasive candidiasis and chronic disseminated candidiasis.

Randomised controlled trial

One randomised controlled trial (RCT) was identified.[7] This non-blinded study (n=110 adults aged >18 years) compared a biomarker-based rule-out strategy to support early discontinuation of empirical antifungal treatment with routine empirical treatment in a single ICU centre in France. In addition to the BDG test, measures of mannan antigen and anti-mannan antibody were assessed. As well as clinical suspicion, study inclusion criteria required at least one major risk factor; systemic antibiotic therapy and/or central venous catheter and at least two minor risk factors from;

parenteral nutrition, dialysis, major surgery, pancreatitis and use of corticosteroids. Patients who were neutropenic or on immunosuppressive therapy were excluded. Only 5.5% of the study participants (9% in intervention group and 2% in control group) had proven invasive *Candida* infection based on samples taken at randomisation. This may indicate a low risk population. The biomarker-based strategy involved testing serum BDG (Fungitell®) and mannan (Platelia™ Candidia Ag plus) and anti-mannan (Platelia™ Candidia Ab Plus) levels at day 0 (commencement of antifungal therapy) and at day 4 of empirical treatment. Laboratory recommendations were issued to the treating physicians on the basis of the test results. Findings are outlined in Table 1. Use of the combination of fungal biomarkers increased the rate of early discontinuation of empirical antifungal therapy. The discontinuation rate in the routine care arm of the study was only 2% compared with 54% in the biomarker strategy arm. The difference between the results was statistically significant. Study authors commented that that the rate of discontinuation in the routine care group was lower than expected. The comparison with routine care meant that the effect of the new multidisciplinary protocol, with formal reconsideration of continuation of treatment, in the intervention arm could not be excluded as an effective component of the intervention independent of the biomarker tests. In addition, this small study was unlikely to have sufficient statistical power to compare the two strategies in terms of secondary outcomes, meaning that no robust conclusions can be made on the safety of biomarker-led discontinuation of empirical antifungal therapy.

Table 1: Findings of RCT comparing biomarker strategy with routing empirical treatment [7]

Outcome	Biomarker Strategy n=54	Routine Empirical Treatment n=55	p value
Primary outcome			
Early discontinuation of empirical antifungal treatment before day 7	29 (54%)	1 (2%)	<0.0001
Secondary outcomes			
Total duration of antifungal therapy	6 (IQR 4-13)	13 (IQR 12-14)	<0.0001
Subsequent proven invasive Candida infection	2 (4%)	1 (2%)	0.547
Subsequent probable invasive Candida infection	2 (4%)	0 (0%)	0.243
Median length of ICU stay	26 (IQR 16-32)	25 (IQR 14-33)	0.654
Died prior to day 7	3 (6%)	4 (7%)	>0.99
28 day mortality	15 (28%)	15 (27%)	0.953
IQR=interquartile range			

Non-comparative observational studies

Four non-comparative observational studies were identified and are summarised in Table 2. None of the studies were from the UK and only one was prospective. All the studies used Fungitell® although the strategies for use either varied or were unclear with respect to clinical context (pre-emptive or empirical) and number of sequential tests applied in the strategy. These descriptive studies indicate that use of BDG testing has the potential to reduce duration of antifungal therapy in patients at risk of IC but, as most have small patient numbers and are retrospective, they do not provide methodologically robust evidence for the safety of BDG guided discontinuation of empirical antifungal therapy.

Table 2: Non comparative observational studies[2, 14-16]

Study/location / study type/technology	Patient group	Strategy	Outcomes	Findings
Nucci 2016[15] Brazil Prospective multicentre observational study – single arm Fungitell® (positive cut-off ≥80pg/ml)	ICU patients screened as high risk of developing Candidaemia and with indirect markers of infection (n=85, adults >18 years) All patients started on anidulafungin. Candidaemia prevalence 8.2%	Blood cultures and BDG testing on days 1-3. All patients with negative blood cultures plus 3 consecutive negative BDG tests (n=21) discontinued anidulafungin therapy on day 4 of study.	Safety of discontinuation of empirical antifungal therapy according to negative blood cultures + 3 consecutive negative BDG tests. Median duration of antifungal therapy.	No case of recurrent Candidaemia was observed in this group during 30 days of follow up. 3/21 patients received another antifungal agent between days 4 and 30. BDG negative cohort: 3 days (IQR 2-12) BDG positive cohort: 10 days (IQR 1-20) P<0.001
Bansal 2018[14] India	Critically ill patients where single BDG assay had been	Retrospective study - strategy unclear	Change in prescription.	Use of BDG assay associated with discontinuation of antifungal

Retrospective single centre observational study – single arm Fungitell®(positive cut-off >80pg/ml)	requested (n=154, adults ≥18 years) Prevalence of proven or probable Candidaemia/invasive Candidiasis 60%		Duration of antifungal therapy.	therapy in 10 of 12 patients who had negative BDG.
Posteraro 2016[2] Italy Retrospective observational study – single arm Fungitell®(positive cut-off >80pg/ml)	Patients with sepsis and *Candida* score ≥3 who had at least one BDG assay conducted (n=198, adults ≥18 years) Prevalence of Candidaemia 24%	BDG used to guide early diagnosis and treatment	Median duration of antifungal therapy	BDG negative cohort (n=135) 5 days (IQR 3-10) BDG positive cohort (n=63) 10 days (IQR 3-17) p=0.04 Therapy was discontinued for 14 of 25 patients with delayed (negative) BDG results who had started empirical therapy.
Prattes 2014[16] Austria Retrospective single centre	Patients with clinical suspicion of invasive fungal infection (n=66, adults > 18 years)	BDG implemented following decision making consultation	Impact of BDG testing on initial clinical decisions	BDG results led to discontinuation of systemic antifungal therapy in 13

observational study – single arm Fungitell®(positive cut-off <60pg/ml)	Prevalence of suspected/probable or proven IFD 20% *(Candida* and *Aspergillus)*	between ICU and infectious disease physicians Single test but repeated if intermediate (60-120pg/ml)		patients, none of whom went on to develop invasive fungal infection during intensive care unit stay. BDG led to initiation of antifungal therapy in 7 patients.

Service evaluation

A retrospective evaluation of a multi-faceted antifungal stewardship intervention in a UK ICU setting (n=68) described how a reduction in inappropriate initiation of empirical antifungals (where clinical symptoms and host risk factors were absent) was achieved through implementation of local guidelines. Educational activities and ongoing input from an infectious disease team and a local ICU champion were components of the intervention. Within the guideline, serum BDG testing at the time of initiation of empirical therapy and twice weekly if required, was recommended to exclude Candidaemia where sterile site cultures were also negative. This facilitated early discontinuation of empirical therapy and contributed to reductions in antifungal consumption associated with the overall intervention. Consumption was reduced by 49% between audit periods in 2014 and 2016.[17]

Ongoing trials

Three ongoing RCTs were identified:

NCT03090334 Examines the effectiveness of de-escalation of antifungal therapy according to BDG testing in patients with a severe abdominal condition developing severe sepsis or septic shock. Outcomes include antifungal consumption, length of stay and mortality. It is being conducted in Italy, aims to randomise 180 patients and study end date is December 2018.

NCT02734550[18] Compares the effect of BDG-driven antifungal therapy with targeted antifungal therapy on the rate of death from any cause by 28 days after inclusion. The study is being conducted at 19 intensive care units in Germany and aims to randomise 348 patients by September 2019.

NCT03538912 Compares antifungal use and mortality between empirical antifungal durations determined by biomarkers (including BDG) and according to routine strategy. It is being conducted in France and study end date is May 2021.

A UK diagnostic accuracy study is ongoing (ISRCTN43895480). This will, in addition to the primary outcome of negative predictive value, report on rates of unnecessary antifungal therapy and the expected cost-effectiveness of a protocol based on BDG testing in patients started on empirical antifungal therapy. The study will be conducted in 35 paediatric and adult ICUs across the UK, target n=1,720. Study end date is March 2021.

Safety

No safety issues related to conducting the BDG test were identified in the literature examined for this evidence note.

Patient and social aspects

Most patients who have systemic antifungal therapy in the critical care setting do not have IFD and so receive no benefit. Interventions to reduce the duration of antifungal therapy may reduce the negative effects of overtreatment including potential toxicity, drug interactions, the risk of an increase in drug resistant organisms and also unnecessary costs.[7] Resistance to antifungal medications is emerging as a serious threat.[6]

No further investiagtion of patient and social aspects has been included in this Evidence Note owing to the nature of the technology (diagnostic test).

Cost effectiveness

No relevant economic studies were identified in the published literature that looked at biomarker-based testing strategies in the population of interest or at the relevant time point in the clinical care pathway.

An economic evaluation was undertaken by HIS which is detailed in Appendix 1 of this Evidence Note. The focus of the economic evaluation was the Fungitell® assay, as data on its cost were readily available and it appeared to be the most widely used test. One Fungitell® test kit costs £737.05 and includes all necessary reagents for duplicate tests on 42 individual patient serum samples (21 duplicate samples on 2 sequential plates)[5]. This means that when using the test at full capacity the cost of the test per patient is £17.55. However, in practice the cost per patient will vary depending on the number of patient samples run per plate. If fewer than 42 patients will be tested a whole plate must still be used and so the cost per patient would increase. Additional consumables costs include laboratory consumables such as pipette tips, glass dilution and storage tubes. It is important for the consumables used to be certified glucan-free in order to ensure reliability of the test. An incubating plate reader machine is also needed which is serviced and calibrated as part of an annual agreement. Other costs associated with the test may include staff costs, maintenance contracts and additional quality assurance requirements. According to the NICE MIB118 on Fungitell®, the

company provides onsite training including equipment installation, analyst training and data interpretation at no extra cost.

The results of the analysis (Table 3) found that a clinically-driven testing strategy with BDG (Fungitell®) to inform withholding of empirical antifungal therapy in critical care patients presenting with signs and symptoms of infection (that would otherwise be initiated on empirical treatment under the standard of care) would be associated with an incremental cost of £93.71 per patient. The strategy also leads to considerably lower toxicity and reduced unnecessary antifungal treatment (in 70.68% of the target population) compared with the standard of care empirical strategy.

The economic model assumed a hypothetical scenario with in-house testing and same-day turnover of results within a critical care unit with 2,000 admissions distributed uniformly across one year. Under current practice, the unit treats 10% of these admissions empirically with an estimated disease prevalence of 7% amongst those treated. The assumed utilisation of antifungal agents used in this model was based on usage data from a single unit: 60% fluconazole, 32% caspofungin, 3% micafungin, 3% anidulafungin, and 2% liposomal amphotericin B. Further details regarding the assumptions and parameters used in this economic evaluation can be found in Appendix 1. Indirect benefits relating to antimicrobial stewardship and impact on resource use and patient quality of life due to reduced overprescribing and antifungal-related complications have not been accounted for in the economic model.

Table 3: Base case results of BDG testing strategy vs empirical strategy

	Empirical therapy	**BDG testing**
Distribution of patients into health states		
infected & treated	7.00%	5.25%
NOT infected & treated	93.00%	22.32%
infected & NOT treated	0.00%	1.75%
NOT infected & NOT treated	0.00%	70.68%
Cost-effectiveness results (per patient)		
Testing throughput (patients tested per kit)	-	2

Total cost	£407.10	£500.81
AF cost per patient	£407.10	£112.24
Cost of Fungitell® kit per patient	-	£368.53
Cost of testing consumables per patient	-	£0.35
Fixed cost element per patient	-	£12.58
AEs rate	18.48%	5.42%
Incremental cost	-	£93.71
Incremental AEs rate	-	-13.06%
Cost per AE averted	-	£717.66
AE – adverse event; ICER – incremental cost-effectiveness ratio		

Owing to the high negative predictive value of BDG and the low infection prevalence in the empirically treated population, infection is ruled-out in a high proportion of patients which considerably reduces over-treatment with costly antifungal agents. However, the imperfect sensitivity of the test means that a small percentage of patients would be misidentified as false negatives. Expert opinion suggests the clinical risk associated to these patients is minimal as standard clinical protocols should pick up their rapidly deteriorating symptoms. The economic model showed this risk could be partially mitigated by using a lower BDG cut-off value which boosts the test sensitivity, albeit at the expense of lower specificity and a higher rate of unnecessary treatment in false positives.

Further sensitivity analysis (Table 4) showed the incremental cost of BDG strategy is likely to be minimal or potentially cost saving in units with a 'less stringent ' empirical strategy, which treats a high proportion of admissions empirically and with a low infection prevalence among those treated. On the other hand, units employing a 'strict' empirical strategy, with low proportion of admissions treated empirically and high probability of identifying infected patients (high infection prevalence), the BDG strategy is associated with higher incremental cost. In such units, the introduction of BDG strategy may not be justifiable from the cost perspective and may also result in a relatively high number of false negative cases.

Table 4: Variability of incremental cost per patient with varying rates admissions treated and infection prevalence

	Infection prevalence							
% treated	1%	5%	15%	30%	45%	60%	75%	90%
2.5%	£113	£125	£156	£203	£249	£295	£342	£388
5%	£88	£100	£131	£177	£224	£270	£317	£363
7.5%	£79	£92	£123	£169	£215	£262	£308	£355
10%	£75	£88	£118	£165	£211	£258	£304	£351
20%	£69	£81	£112	£159	£205	£251	£298	£344
30%	£67	£79	£110	£156	£203	£249	£296	£342
40%	£33	£46	£77	£123	£170	£216	£262	£309
50%	-£34	-£22	£9	£55	£102	£148	£195	£241
75%	-£125	-£113	-£82	-£35	£11	£58	£104	£150
100%	-£170	-£158	-£127	-£80	-£34	£12	£59	£105

Another important factor is the utilisation of antifungal agents in practice. The scenario analysis against each antifungal agent individually showed the incremental cost of the BDG strategy to vary substantially depending on the AF agent used in practice. The BDG strategy was cost-saving if only micafungin (-£1,643) or amphotericin B (-£5,311) are used, yet the BDG strategy was associated with a larger incremental cost where antifungal agents from the less expensive triazole class (£258 to £372) were used.

The testing throughput, determined by the annual number of admissions, has important implications for service organisation due to its impact on the variable cost of testing. For example, a higher throughput increases the number of patients that can be run per testing plate (21 samples per plate, two plates per kit). The model predicts the BDG strategy to be cost saving assuming in excess of 9,448 admissions, 10% of admissions are treated empirically, and the infection prevalence among those treated is 7%. Any service reorganisation should consider same day turnover of testing results to mitigate the risk associated to treatment delays.

An alternative testing strategy considered the use of BDG results to inform discontinuation of empirical treatment at certain points after initiation. Whilst this strategy may mitigate the risks of withholding therapy in patients with false negative results, it was also associated with an increased incremental cost (£155 and £236 with discontinuation at days three and seven respectively) while still exposing the entire target population to antifungal treatment and associated toxicity.

Conclusion

There is insufficient published evidence to reach conclusions on the effectiveness of diagnostic strategies incorporating BDG testing in critical care patients with respect to safe reduction of empirical antifungal use.

A de-novo economic evaluation suggested that a clinically-driven testing strategy with BDG (Fungitell®) to inform initiation of antifungal therapy in critical care patients presenting with signs and symptoms of infection has the potential to be be cost saving and also results in a lower rate of adverse events per patient compared to the standard of care empirical treatment.

This result was mainly driven by the high negative predictive value of the test and the low prevalence of infection in the empirical population, and was generally applicable to larger units with a high test throughput and a less stringent approach to empirical antifungal prescribing. In smaller units with a stricter empirical strategy, the BDG strategy is associated with an overall cost increase and can also result in a high number of false negative patients, but lower toxicity overall.

Identified research gaps

More studies are needed to assess the benefits of biomarker-based strategies with a particular focus on the safety outcomes of withholding or discontinuing antifungal use. Further research may also be needed into the rates of toxicity and adverse events associated with antifungal use and their impact on patient morbidity/mortality, quality of life and healthcare resource utilisation. Several upcoming studies are mentioned in this evidence note that aim to address such issues which may support a more comprehensive cost-effectiveness analysis.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Appendix 1: Economic evaluation of the use of clinically-driven (1-3)-beta-D-Glucan strategy to guide antifungal therapy in critical care patients with suspected invasive fungal infection

BACKGROUND

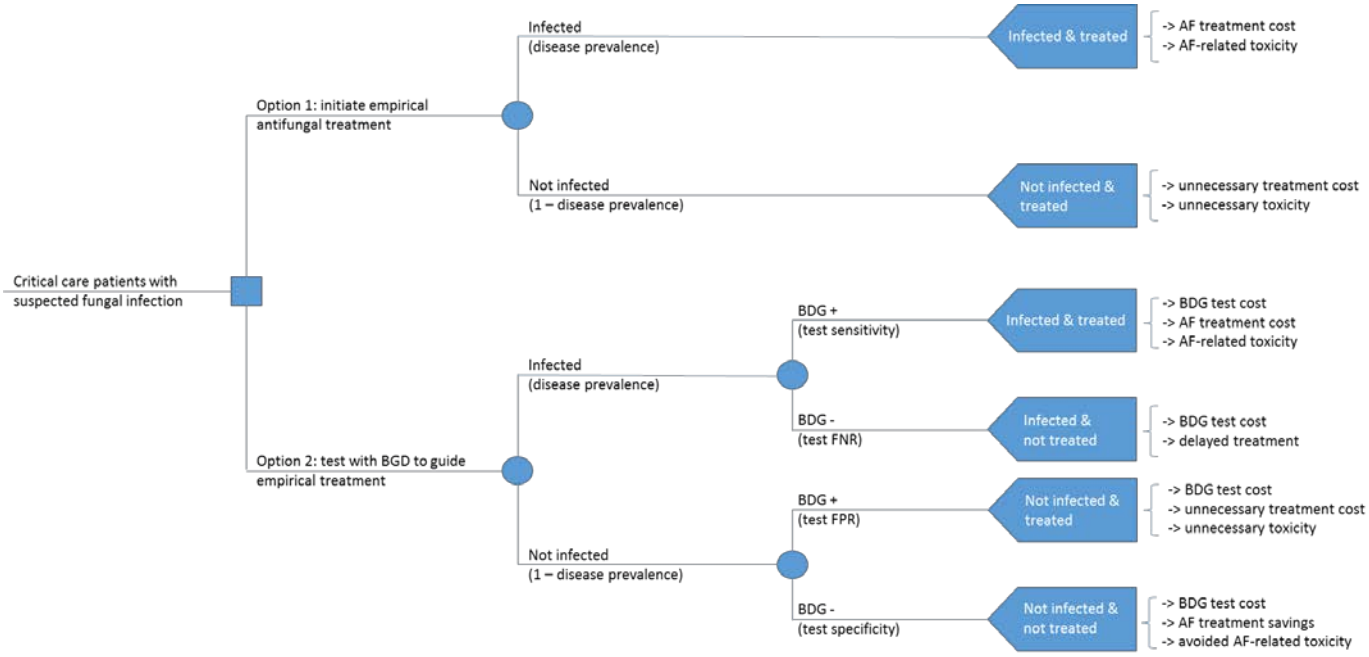
A Healthcare Improvement Scotland (HIS) economic model has been developed which evaluates the use of (1-3)-beta-D-Glucan (BDG) in the critical care population to guide the withholding/discontinuation of empirical antifungal (AF) treatment for patients with suspected invasive *Candida* infection.

METHODS

Model structure

The modelling framework underpinning this analysis is structured as a decision-tree which compares the BDG strategy with the standard empirical treatment strategy by considering the difference in testing costs, antifungal treatment costs and difference in toxicities associated with antifungal use. The analysis is hence structured as a cost-consequence analysis.

Figure 1: Economic model framework on the use of BDG to guide empirical antifungal treatment



Population

The population analysed in the framework is that of critical care patients having been identified with signs and symptoms of invasive *Candida* infection such as persisting fever. This population would normally be initiated on empirical antifungal treatment under standard practice, i.e. it is assumed that the test is used at the point at which the clinician would have otherwise started empirical therapy.

Despite many presenting with similar signs and symptoms of infection, the actual prevalence of disease in this population is low and hence a considerable proportion of non-infected patients are initiated on empirical treatment, thus leading to overprescribing of AF agents and an increase in cost and toxicity associated with their use.

Intervention

The intervention assessed is a clinically-driven, biomarker-based, diagnostic strategy which tests with BDG the target population suspected of infection in order to inform the withholding or initiation of empirical AF treatment. The baseline approach to the intervention is to test once with BDG and initiate AF treatment based on a positive result, or not treat based on a negative result.

This intervention is compared with an empirical approach in which the full target population is initiated on AF agents based on signs and symptoms of infection. The aim of the intervention is to reduce overtreatment with antifungals, thus saving costs and avoiding toxicities, benefits which need to be balanced against the increased cost of testing.

Health states

The prevalence of disease in the target population, coupled with the accuracy of the BDG tests and the clinical decisions informed by the test result, determines the distribution of patients across the following four health states:

- Infected & treated
- Infected & not treated
- Not infected & treated
- Not infected & not treated

Under the current practice of empirically treating all suspected patients with signs and symptoms, the full population in the analysis would receive AF agents and hence patients will be distributed solely across the 'infected & treated' and 'not infected & treated' health states. This distribution is determined by the prevalence of the disease in the target population i.e. the proportion of critical care patients with suspected fungal infection that are actually infected.

Under the new intervention, the population is distributed across all four states, with the clinical accuracy of the BDG test also playing a role in the distribution. A strong negative predictive value (NPV) of the BDG test should ensure that a considerable share of patients that are not infected but would otherwise receive treatment based on the empirical strategy, would be correctly identified as negative by the BDG test and therefore not receive AF agents. This reduces overtreatment and the associated toxicity.

On the other hand, the imperfect nature of the test also carries the risk of miss-identifying a patient that is actually infected i.e. a false negative result on the test. Hence some patients may end up in the 'infected & not treated' state and can be subject to additional clinical risks if treatment is delayed or not initiated. According to clinical expert opinion, the proportion of these patients is very low due to the low prevalence of the disease and, in practice, these patients would be picked up eventually by the clinical algorithms in place as clinical signs and symptoms become increasingly more apparent. Thus, in practice, it is unlikely the treatment delay will be important and therefore the potential dis-benefit of late treatment initiation associated to this health state has been assumed to be negligible and is excluded for the purpose of this analysis. Since these patient would be eventually treated, the cost of antifungal treatment also applies to this health state.

The clinical outcomes (AF-related toxicity) and direct costs (testing and AF treatment) associated with each state are quantified and compared between the two interventions.

Model inputs

All parameters used in the economic framework are summarised in Table A1. These have been validated by a panel of clinical experts.

Table A1: Clinical and cost inputs for the economic framework

PARAMETER	ESTIMATE (95% CI)	SOURCE
Demographics		
% male among critical care admissions	56%	SICSAG audit[11]
Mean age of patients admitted to critical care	60	SICSAG audit[11]
Average life-expectancy Scotland (male)	77.1	NRS
Average life-expectancy Scotland (female)	81.2	NRS
Clinical accuracy		
BDG pooled accuracy		
Sensitivity	0.78 (0.75 – 0.81)	He *et al.* (2015)[20]
Specificity	0.81 (0.80 – 0.83)	He *et al.* (2015)[20]
Fungitell® specific accuracy		
Sensitivity	0.75 (0.71 – 0.79)	He *et al.* (2015)[20]
Specificity	0.76 (0.74 – 0.78)	He *et al.* (2015)[20]
Epidemiology		
Annual number of critical care admissions in Scotland	46,931	SICSAG audit[11]
No. of admissions in hypothetical single centre	2,000	Assumption
% admissions treated empirically	10%	Expert opinion
Infection prevalence in empirical population	7%	Harrison *et al.* (2013)[3]
AF agents usage		
Fluconazole	60%	GRI data

Itraconazole	0%	GRI data
Voriconazole	0%	GRI data
Caspofungin	32%	GRI data
Micafungin	3%	GRI data
Anidulafungin	3%	GRI data
Liposomal amphotericin B	2%	GRI data
Antifungal-related toxicity (AE rates)		
Fluconazole	13.0% 26.4%	Winston *et al.* (2000)[21] Reboli *et al.* (2007)[22]
Itraconazole	5.0%	Boogaerts *et al.* (2001)[23]
Voriconazole	13.4%	Herbrecht *et al.* (2002)[24]
Caspofungin	12.2%	Maertens *et al.* (2004)[25]
Micafungin	31.9%	Denning *et al.* (2006)[26]
Anidulafungin	24.4%	Reboli *et al.* (2007)[22]
Liposomal amphotericin B	54.0% 81.0% 24.3%	Boogaerts *et al.* (2001)[23] Winston *et al.* (2000)[21] Reboli *et al.* (2007)[22]
Costs		
Testing costs		
Fungitell® (per kit – 42 patients max)	£737.05	NICE MIB118[5]
Certified BDG pipette tips (768 tips of 1,000 microlitre)	£85.50	NICE MIB118[5]
Certified BDG glass dilution tubes (50 tubes per pack)	£11.75	NICE MIB118[5]
Biotek ELx808iu plate reader instrument	$8,699.06 (£6,580.84)	www.fishersci.com
Annual service and calibration agreement for the plate reader	£1,200.00	NICE MIB118[5]
AF treatment costs (for 14 days course)		

Fluconazole	[redacted]*	National contract (CIC)
Itraconazole	£13.03	BNF
Voriconazole	[redacted]	National contract (CIC)
Caspofungin	[redacted]	National contract (CIC)
Micafungin	[redacted]	National contract (CIC)
Anidulafungin	[redacted]	National contract (CIC)
Liposomal amphotericin B	[redacted]	National contract (CIC)
***Blanked out figures are CIC**		

Test accuracy

The accuracy of the BDG test was derived in a meta-analysis of 28 studies comprising a total of 4,214 subjects. Among the reference standards included were the EORTC/MSG criteria, histopathologic examination and microbiological culture. At present, there are several CE marked BDG detection assays available. Fungitell® is used as the base case test for the purpose of this analysis as data on its cost were readily available, although the pooled accuracy of all the tests synthesised in the meta-analysis is also tested in a scenario analysis. Subgroup analyses as part of this meta-analysis indicated that in cohort studies, the cut-off value of BDG at 80 pg/mL had the best diagnostic accuracy, whereas in case–control studies the cut-off value of 20 pg/mL had the best diagnostic accuracy. The 60 pg/mL cut-off value has the best diagnostic accuracy with the Fungitell® assay.

Target population size

The annual size of the population initiated on empirical treatment is important as it determines the cost per patient associated with the fixed expenditure of BDG testing, namely the initial capital investment in the plate reader machine (expressed as capital amortisation over lifetime of the machine) and the annual service and calibration agreement for this machine. The capital cost for the plate reader machine is attributed assuming a 5-year functioning lifetime. The size of the population also drives the running variable costs associated with testing. A single BDG testing kit can be used to test between 2 and 42 patients before being discarded and hence the variable cost of testing depends on the throughput of patients tested.

The Scottish Intensive Care Society Audit Group (SICSAG): Audit of Critical Care in Scotland recorded information on 46,931 admissions in 2017[11]. In 2016, the use of systemic antifungals in acute hospitals in NHSScotland was 128.9 defined daily doses per 1,000 admissions, but this looked at wider use than critical care setting. Expert opinion suggests roughly 10% of critical care admissions are treated empirically, whereas data from specific centres (suggested by clinical experts) indicate a percentage as low as 2.25%. Hence the size of the empirical population eligible for testing with BDG under the new strategy is likely to be centre-specific. A baseline rate of 10% of critical care admissions was used to derive the size of the empirical population in the framework, with a range of figures being tested in the sensitivity analysis and in centre-specific sub-analyses.

[a] Calculated based on a mean weight of an adult ICU patient of 76.5 kg and a 1:1 male-female ratio

Infection prevalence

The prevalence of infection in the population treated empirically is a key driver in the economic framework as the clinical utility of the test is diminished with a high prevalence i.e. if a high proportion of the patients treated empirically are infected then the empirical strategy alone may be the preferred approach. The prevalence is likely to be centre-specific and will depend on the clinical protocols and criteria used in practice for initiating empirical treatment. Some centres might have a more relaxed clinical decision criteria for initiating empirical antifungal treatment and hence a lower prevalence, while other centres may have a stricter policy and thus a higher prevalence. Therefore, a range of various disease prevalence rates is tested in the parameter sensitivity analysis.

Estimates from the published literature indicate that in 93% of instances where systemic antifungal treatment was initiated during admission the patients were not subsequently diagnosed with invasive candidiasis infection in a study of 60,778 admissions conducted across 96 critical care units in the UK between 2009 and 2011. This estimate can be uncertain in this setting as it does not relate specifically to empirical treatment, hence a range of various disease prevalence rates was tested in the parameter sensitivity analysis.

AF agents usage

The antifungal agents available for use within the critical care units can be categorised into the following three main classes: triazole, echinocandin, polyene. The agents most used in the triazole class according to expert input are fluconazole, itraconazole and voriconazole. In the echinocandin class the licensed agents used are caspofungin, micafungin and anidulafungin. Finally, liposomal amphotericin B is the agent from the polyene class licensed for use.

The distribution of the antifungal used within a given unit is important as different antifungals have different costs and are associated with different rates of toxicities. The baseline distribution represents the antifungal use within a single unit provided by expert input. Other distributions are also tested in the analysis and results against individual AF agents are also reported.

Antifungal-related toxicity

Toxicity rates were derived from published literature where available. Where several estimates of toxicity rates were available for a given agent, a mean estimate was calculated and used in the analysis.

In an RCT of itraconazole versus amphotericin B as empirical antifungal therapy for persistent fever in 384 neutropenic patients with cancer across 10 centres[23], significantly fewer drug-related adverse events occurred in the itraconazole group (5%) compared to the amphotericin B group (54%). In another multicentre RCT which compared fluconazole with amphotericin B for empiric antifungal therapy in 317 febrile neutropenic patients with cancer[21], adverse events related to study drug (especially fever, chills, renal insufficiency, electrolyte disturbances, and respiratory distress) occurred more often in patients treated with amphotericin B (81%) than patients treated with fluconazole (13%, p = 0.001). Fewer severe adverse events that were potentially related to the study drug occurred in the voriconazole group (26 patients [13.4 percent]) than in the amphotericin B group (45 patients [24.3 percent], P=0.008) for primary therapy of invasive aspergillosis in another RCT[24].

In a study investigating the efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy[25], only 11 patients out of the 90 enrolled (12.2%) had a clinical AE event that was related to caspofungin therapy. In a non-comparative study of the use of micafungin for the treatment of acute invasive aspergillosis[26], adverse events considered by the investigator to be possibly or probably related to the study drug were reported for 104/326 patients (31.9%). In an RCT comparing anidulafungin with fluconazole for invasive candidiasis, the number of treatment-related

adverse events was similar in the two groups (anidulafungin group, 59 events in 32 patients [24.4%]; fluconazole group, 64 events in 33 patients [26.4%])[22].

A limitation of these studies is that some were conducted in an oncology population with invasive aspergillosis and hence the applicability to the intensive care population is questionable. However, xxpert opinion was generally in agreement that the same AE rates are likely to be seen in the intensive care population and additional rates were explored in the sensitivity analysis to explore this uncertainty.

Costs

One Fungitell® test kit includes all necessary reagents for duplicate tests on 42 individual patient serum samples (21 duplicate samples on 2 sequential plates)[5]. This means that if the test is used at its full capacity the cost of the test per patient is £17.55. This represents the minimum boundary in the framework for the running variable cost associated with the testing kit. However, in practice the cost per patient will vary depending on the number of patient samples run per plate. If fewer than 42 patients will be tested a whole plate must still be used and so the cost per patient would increase. Hence the cost of the test per patient will depend on the throughput of critical care patients presenting with signs and symptoms in a given unit. The number of patients run per test also depends on the interval of time that is allowed from when the signs and symptoms that would call the initiation of empirical strategy becomes apparent and when the test is actually performed. For the purpose of this analysis it has been assumed that a test is performed on the same day. If a test kit would be used weekly for example, this will allow more patients to be used per kit but with the increased risk of delaying treatment.

Additional consumables costs include laboratory consumables such as pipette tips, glass dilution and storage tubes. It is important the consumables used to be certified glucan-free in order to ensure the reliability of the test. An incubating plate reader machine is also needed which is serviced and calibrated as part of an annual agreement. The cost attributed to each test of this fixed annual cost depends on the annual size of the tested population. Other costs associated with the test may include staff costs, maintenance contracts and additional quality assurance requirements. These have not been specifically factored in the analysis as no information as readily available. According to the NICE MIB118 on Fungitell®, the company provides onsite training including equipment installation, analyst training and data interpretation at no extra cost.

NHSScotland prices for the main licensed antifungal agents used in practice have been provided by National Procurement and are summarised in Table A2. Where no national contracts were in place, BNF indicative prices, or drug tariff prices if available, were used with preference given to generic/lower-cost brand. Dosages have been derived based on US and European guidelines and apply to a population of non-neutropenic patients for a treatment duration of 14 days.[9, 10]

Table A2: Antifungal agents commercial prices

Antifungal agent	Formulation	Pack size	Price	Dosage
Triazole class				
Fluconazole	Fluconazole 400mg/200ml infusion bags	5 x bag (POM)	[redacted]	800-mg loading dose, then 400-mg daily

Itraconazole	Itraconazole 100mg capsules (A A H Pharmaceuticals Ltd)	15 x capsule (POM)	£3.49	200-mg twice daily
Voriconazole	Voriconazole 200mg powder for solution for infusion vials	1 x vial (POM)	[redacted]	400-mg twice loading dose, then 200-mg twice daily
Echinocandin class				
Caspofungin	Caspofungin 70mg powder for concentrate for solution for infusion vials Caspofungin 50mg powder for concentrate for solution for infusion vials	1 x vial (POM) 1 x vial (POM)	[redacted]	70-mg loading dose, then 50-mg daily
Micafungin	Mycamine 100mg powder for solution for infusion vials	1 x vial (POM)	[redacted]	100-mg daily
Anidulafungin	Anidulafungin 100mg powder for concentrate for infusion vials	1 x vial (POM)	[redacted]	200-mg loading dose, then 100-mg daily
Polyene class				
Amphotericin	AmBisome 50mg powder for solution for infusion vials	10 x vial (POM)	[redacted]	3-5 mg/kg daily

RESULTS

Base case analysis

The base case results are estimated for a hypothetical critical care centre with 2,000 admissions annually, uniformly distributed across time[b], and assuming the test is being conducted in-house with rapid turnover of results (typically within one hour, according to the manufacturer). The proportion of admissions treated empirically and prevalence used are as per Table A1. Results of this base case are presented in Table A3.

As expected, the clinically-driven testing strategy with BDG reduces over-treatment compared to the empirical strategy largely due to its high NPV and low infection prevalence in the target population - preventing unnecessary use of AF agents in 70.68% patients. It should also be pointed out that under the new approach 1.75% of patients would be incorrectly ruled-out as negative by the BDG test when in fact they have invasive fungal disease[c].

The BDG strategy results in an incremental cost of £93.71 per patient compared to the empirical strategy and a decreased rate of adverse events due to the reduced toxicity associated with antifungal use. Assuming a 13.06% decrease in adverse events due to AF-related toxicities, the new strategy would cost £717.66 per adverse event avoided on average. It should be noted that the potential cost savings realized from reduced toxicities and rates of adverse events have not been included in the framework and may offset to some extent the incremental cost of the BDG strategy. Likewise, no benefits relating to meeting antimicrobial stewardship aims through reducing antifungal prescribing have been quantified and accounted for in the framework.

Table A3: Base case results

	Empirical therapy	**BDG testing**
Distribution of patients into health states		
infected & treated	7.00%	5.25%
NOT infected & treated	93.00%	22.32%
infected & NOT treated	0.00%	1.75%
NOT infected & NOT treated	0.00%	70.68%
Cost-effectiveness results (per patient)		

[b] In real-world the number of patients tested in a day can vary greatly and hence the variable cost. In the event that the annual target population is small enough so that the daily average of patients tested is less than one, it is assumed that only two patients per testing kit will be tested separately, hence incurring the maximum cost

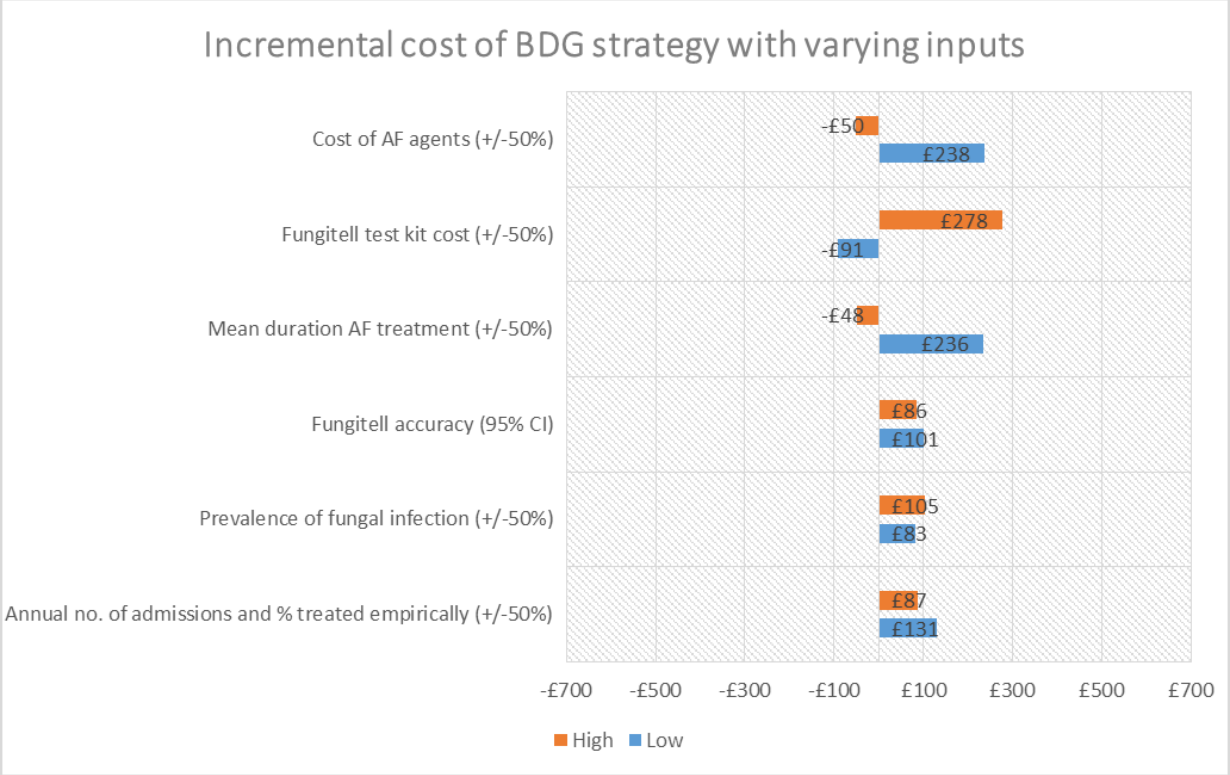
[c] No dis-benefit/penalty was incorporated into the framework for these patients. Instead, it was assumed any clinical dis-benefits would be negligible as the patient would still be picked-up by the surveillance team and get initiated on antifungals. The framework can be easily adapted to incorporate a dis-benefit for these patients.

Testing throughput (patients tested per kit)	-	2
Total cost	£407.10	£500.81
AF cost per patient	£407.10	£112.24
Cost of Fungitell® kit per patient	-	£368.53
Cost of testing consumables per patient	-	£0.35
Fixed cost element per patient	-	£12.58
AEs rate	18.48%	5.42%
Incremental cost	-	£93.71
Incremental AEs rate	-	-13.06%
Cost per AE averted	-	£717.66
AE – adverse event; ICER – incremental cost-effectiveness ratio		

Deterministic sensitivity analysis

Figure 2 shows how the incremental cost of the new strategy varies when key model inputs are being varied.

Figure 2: One-way sensitivity analysis on key model inputs



The cost of AF agents and duration of AF treatment appear to be important drivers within the model. This is intuitive as a lower treatment course or lower AF agents costs would result in fewer savings being realised from reducing the overprescribing of antifungals. The cost of the Fungitell® test kit itself is also important and the model shows that when its cost is halved , the new strategy becomes cost saving. This issue could be explored further as part of national contract discussions.

The accuracy of Fungitell® was derived in a meta-analyses of studies which used several different tests/criteria as the reference standard which are not perfect. As such, the accuracy of the test is likely to be subject to uncertainty and, as shown in Table A4, the specificity of the test is also a key driver in the model.

Table A4: Effect of test specificity on incremental cost of BDG strategy

Specificity	Incremental cost (per patient)
0.5	£192
0.6	£154
0.7	£116
0.8	£79
0.9	£41
1.0	£3

The size of the target population, given by the annual number of admissions and proportion of admissions treated empirically, does not seem to be a key driver on its own, but its interplay with the prevalence of fungal infection can make a difference and this is illustrated in Table A5.

Table A5: Two-way sensitivity analysis of incremental cost against infection prevalence and % of admissions treated empirically

	Infection prevalence							
% treated	1%	5%	15%	30%	45%	60%	75%	90%
2.5%	£113	£125	£156	£203	£249	£295	£342	£388
5%	£88	£100	£131	£177	£224	£270	£317	£363
7.5%	£79	£92	£123	£169	£215	£262	£308	£355
10%	£75	£88	£118	£165	£211	£258	£304	£351
20%	£69	£81	£112	£159	£205	£251	£298	£344
30%	£67	£79	£110	£156	£203	£249	£296	£342
40%	£33	£46	£77	£123	£170	£216	£262	£309
50%	-£34	-£22	£9	£55	£102	£148	£195	£241
75%	-£125	-£113	-£82	-£35	£11	£58	£104	£150
100%	-£170	-£158	-£127	-£80	-£34	£12	£59	£105

Scenario analyses

Other scenarios were tested and reported in Table A6. Further implications are discussed in the next section.

Table A6: Scenario analyses results

Scenario	**Parameters changed from base case**	**Incremental cost**
Service organisation		
Low-throughput single ICU with in-house testing	1,200 admissions 2.25% (27 patients) treated empirically 7% infection prevalence	£174.32

High-throughput centralised testing (national)	46,931 admissions 10% treated empirically 7% infection prevalence	-£229.53
Moderate-throughput centralised testing (local)	10,000 admissions 10% treated empirically 7% infection prevalence	-£15.85
Individual AF agents		
Fluconazole	100% fluconazole usage	£362.39
Itraconazole	100% itraconazole usage	£372.24
Voriconazole	100% voriconazole usage	£258.26
Caspofungin	100% caspofungin usage	£93.43
Micafungin	100% micafungin usage	-£1,643.11
Anidulafungin	100% anidulafungin usage	£63.39
Liposomal amphotericin B	100% amphotericin usage	-£5,311.35
Other scenarios		
Using pooled sensitivity of multiple BDG tests	Sensitivity - 0.78 Specificity - 0.81	£74.78
Fungitell® with 60 pg/mL cutoff	Sensitivity - 0.81 Specificity - 0.67	£127.79
Fungitell® with 80 pg/mL cutoff	Sensitivity - 0.73 Specificity - 0.81	£74.78

DISCUSSION

Implications of variations in empirical strategy

The two-way analysis in Table A5 likely captures a wide spectrum of critical care units with varying proportions of admissions treated empirically and different prevalence of infection amongst the treated populations. The BDG strategy is likely to be cost-saving in units that currently treat a high proportion of their admissions with a low prevalence of infection e.g. treating the full population at risk preventively (prophylaxis).

On the other hand, the BDG strategy is associated with an increased overall cost in units which have a stricter empirical strategy i.e. treating only a small proportion of admissions and having a high rate of success at picking up patients that are actually infected. In such units, the introduction of BDG strategy may not be justifiable from the cost perspective and can also result in a high number of false negative patients. The benefits of reduced toxicity and achieving antimicrobial stewardship goals are still likely to hold however.

Another important factor is the market utilisation of antifungal use in practice. The scenario analysis against each AF agent individually showed the incremental cost of the BDG strategy to vary a lot depending on the AF agent used in practice, being particularly cost-saving in settings where micafungin and amphotericin B are used, and associated with a larger cost increase in settings where agents from the less expensive triazole class are used.

Implications for service organisation

The one-way sensitivity analysis showed the price of Fungitell® test kit is a key driver of results as it directly impacts the variable cost of testing per patient. Since the test is designed for batch-testing, the throughput of patients tested also plays key role in estimating the variable cost because higher throughput, up to 42 maximum test kit capacity, translates into lower cost per patient. The throughput can be increased either by running the test in-house at more infrequent set time intervals, e.g. once a week, or by pooling together patient samples from multiple intensive care units for testing at a remote facility[d]. However, the first option would undermine the clinical utility of the test though, as results are generally needed on the same day for effective antifungal initiation. Therefore, it is worth exploring further the second option and discussing further an in-house versus a centralised approach to testing.

As a case study for an in-house based approach, data from a single ICU show roughly 1,200 admissions per year, out of which 27 are treated empirically. The low throughput means that this centre would incur the highest possible variable cost of testing per patient, with only two patients tested per Fungitell® kit and assuming the 27 patients are distributed across the year uniformly such that no two patients are being tested in the same day[e]. In such a low-throughput centre, testing in-house is associated with an even higher incremental cost of £174.32 per patient.

To illustrate the effect of scaling up the testing throughput, a fictional scenario assuming national centralised BDG testing for all critical care unit in Scotland (i.e. target population set at 10% of 46,931 critical care admissions reported in Scotland in 2017) points to cost savings of £229.53 per patient. The cost saving is maintained in a more realistic localised testing scenario (i.e. covering 10,000 critical care admissions). Furthermore, the threshold analysis shows that for centralised testing facilities that can cover anything higher than 9,448 critical care admissions (i.e. the equivalent of five medium-sized units as per the baseline) and assuming that 10% of these admissions are treated empirically under current practice, the new BDG strategy

[d] A third way in which empirical AF treatment is first initiated and then discontinued based on a future test result may act as decreasing testing costs, but may also increase unnecessary AF treatment costs. It is difficult to state which effect would outbalance the other without further modelling.

[e] The uniform distribution in this case is the most conservative assumption; in reality 2 or 3 out of the 27 patients could be referred for testing within the same day, hence reducing the variable cost of testing.

starts to be cost saving in addition to reducing toxicities (and indirect resource use) and improving antimicrobial prescribing.

There are of course other implications and issues around centralisation of testing which would have to be considered, such as the geographical distribution of critical care units adjusted for utilisation, or the logistical feasibility of collecting samples and facilitating the timely communication of results electronically for the test to maintain its clinical utility. Hence, a one-central-laboratory-fits-all approach may not be feasible. That said, the model still shows that the BDG strategy starts to be cost saving even for lower, more localised, levels of throughput. This result is important as centralisation at local level among closely located centres may be more feasible.

Other implications

Using Fungitell® with an 80 pg/mL cut-off reduces the overall incremental cost of the strategy due to the higher specificity, but this means sacrificing sensitivity and increasing the risk of withholding treatment in false negative cases. The economic model showed the risk of withholding therapy in false negative cases (1.75% of patients in the baseline) could be partially mitigated by using a lower BDG cut-off value which boosts the test's sensitivity, albeit then at the expense of lower specificity and a higher rate of unnecessary treatment in those people with a false positive result.

There are additional issues that may be of importance for decision making and which have not been incorporated in the analysis:

- Indirect benefits linked to antimicrobial stewardship aims: Potential reduction in development of AF resistance resulting from reducing overprescribing.
- Indirect benefits linked to reduced AF-related toxicity: Impact of antifungal-related adverse events on resource use and quality of life has not been factored in the analysis.
- Risk of delaying AF initiation in false negatives: Potential increased mortality and morbidity risk associated with a delay in initiating treatment in false negatives has not been considered.
- Using a suite of microbiology tests: Implications of using a sequence of tests and/or using BDG as part of a suite of other tests/clinical criteria has not been considered; in order for these options to be incorporated in such a framework, clinical decision rules should be formulated in relation to each possible combination of test(s) outcomes; the likely effect is increased testing cost but increased accuracy of overall result.

A summary of the main assumptions used in the framework is provided as follows:

- The potential harm associated with false negative BDG test results has been assumed to be negligible. It is assumed that patients which are ruled out with the BDG test will still be monitored for signs and symptoms of infection as per the standard empirical strategy protocol. A resource saving linked to the staff time and protocols involved in this form of monitoring has not been factored in the analysis as it would be equally applicable to both interventions.
- For the purpose of this analysis it has been assumed BDG testing is performed on the same day in which empirical treatment would otherwise commence and the turnover of test result is fast enough so that no clinically significant treatment would occur in AF initiation compared to the standard empirical approach.
- BDG testing costs were derived based on the Fungitell® assay
- AF agent costs were derived from National Procurement figures and BNF list prices with preference given to generic/cheaper options

- No discontinuation of empirical treatment before the conclusion of a full AF course was assumed in the standard of care arm

ADDITIONAL SCENARIOS EXPLORED

Incorporating higher risk of mortality in the analysis associated to treatment delay in false negatives

In an alternative analysis, in addition to all-cause mortality, the mortality risks summarised in Table A7 were incorporated in the framework. This scenario assumes false negatives would be treated with a delay of 24-72h and having a as opposed to 0-2h for true positives.

Table A7: Additional mortality risk

Mortality	Risk	Source
30-day mortality post-ICU	19.3%	Appendix A, SICSAG 2018 report
Survival if infected		
AF administered within 0-2h	82%	Fungitell® website, Kumar, A et al. Poster 2174 ICAAC 2007
AF administered within 2-6h	65%	Fungitell® website, Kumar, A et al. Poster 2174 ICAAC 2007
AF administered within 6-12h	17%	Fungitell® website, Kumar, A et al. Poster 2174 ICAAC 2007
AF administered within 12-24h	9%	Fungitell® website, Kumar, A et al. Poster 2174 ICAAC 2007
AF administered within 24-72h	8%	Fungitell® website, Kumar, A et al. Poster 2174 ICAAC 2007

The base case results for this scenario are summarised in Table A8. The BDG strategy is associated with a higher risk of death due to the treatment delay, resulting in an increased cost and fewer expected life years (LYs) per patient. However, this scenario does not take into account any potential increase in mortality associated to the toxicity of the AF treatment. When a hypothetical additional mortality risk of 2% is included in the framework for patients treated with antifungals (i.e. 1 in 50 patients dies due to AF agents-related complications), the BDG strategy provides more life years per patient, at an additional cost of £3,948 per life year gained, as illustrated in Table A9.

Table A8: Base case results of alternative scenario which includes mortality risk associated to treatment delay

	Empirical therapy	BDG testing
Distribution of patients into health states		
infected & treated	4.63%	3.47%
NOT infected & treated	75.05%	18.01%
infected & NOT treated	0.00%	0.11%
NOT infected & NOT treated	0.00%	57.04%
dead	20.32%	21.36%
Cost-effectiveness results (per patient)		
Total cost	£407.10	£494.15
AEs rate	14.72%	3.99%
LYs	15.06	14.87
Incremental cost	-	£87.05
Incremental AEs rate	-	-10.73%
Incremental LYs	-	-0.20
ICER (£/AE)	-	£811.19
ICER (£/LY)	-	Dominated

Table A9: Alternative scenario which includes mortality risk associated to both treatment delay and AF use

	Empirical therapy	BDG testing
Distribution of patients into health states		
infected & treated	4.54%	3.40%
NOT infected & treated	73.55%	17.65%
infected & NOT treated	0.00%	0.11%
NOT infected & NOT treated	0.00%	57.04%
dead	21.91%	21.79%
Cost-effectiveness results (per patient)		
Total cost	£407.10	£494.14
AEs rate	14.43%	3.91%
LYs	14.76	14.78
Incremental cost	-	£87.04
Incremental AEs rate	-	-10.52%
Incremental LYs	-	0.02
ICER (£/AE)	-	£827.66
ICER (£/LY)	-	£3,948.42

Using BDG to inform discontinuation of empirical treatment

This scenario assumes empirical initiation of AF treatment in the entire population presenting with signs and symptoms of infection as per the standard approach. BDG testing result is used to guide discontinuation of empirical treatment at a later stage following initiation. Such an approach might be considered in situations where fast turnaround of the test is not possible or to mitigate the increased mortality risk associated to treatment delay in false negative[f]. The incremental cost of this BDG strategy for a range of discontinuation

[f] Note however that this scenario creates a potential risk of discontinuation based on false negative BDG result

time points is given in Table A10. Under this approach however, the savings associated with reducing AF use are realised by reducing the length of the full treatment course in patients discontinued rather than preventing AF use altogether - the entire target population would still be exposed to potential unnecessary prescribing of antifungals and antifungal-related toxicity, with its indirect resource use and impact on quality of life, while the benefit of antimicrobial stewardship becomes questionable.

Table A10: Incremental cost of BDG strategy to inform discontinuation of empirical strategy at various time points

Discontinue after	Incremental cost (per patient)
0 days of initiation (base case strategy)	£93.71
1 days	£114.03
3 days	£154.66
5 days	£195.29
7 days	£235.92
9 days	£276.55
11 days	£317.18
13 days	£357.82

CONCLUDING REMARKS

This analysis has demonstrated that a clinically-driven testing strategy with BDG (Fungitell®), to inform initiation of antifungal therapy in critical care patients presenting with signs and symptoms of infection that would otherwise be initiated on empirical treatment under the standard of care, is associated with a low incremental cost per patient and results in considerable lower toxicity and overprescribing of antifungal agents compared to the standard of care empirical treatment. Indirect benefits relating to antimicrobial stewardship, and impact on resource use and patient quality of life due to reduced overprescribing and antifungal-related complications, have not been incorporated within the analysis..

The high negative predictive value of BDG and the overall low infection prevalence in the empirically treated population, infection is ruled-out in a high proportion of patients which considerably reduces over-treatment with costly antifungal agents. However, owing to the imperfect sensitivity of the test, a small percentage of patients would be misidentified as false negatives. Expert opinion suggests the clinical risk associated to these patients is minimal because standard clinical protocols should pick up their rapidly deteriorating symptoms.

Sensitivity analyses showed the incremental cost of BDG strategy is likely to be minimal or potentially cost saving in units with a 'less stringent' empirical strategy, i.e. treating a high proportion of admissions empirically and therefore a low infection prevalence among those treated. On the other hand, units employing a 'strict' empirical strategy, i.e. low proportion of admissions treated empirically and high probability of identifying infected patients (high infection prevalence), the BDG strategy is associated with higher incremental cost. In such units, the introduction of BDG strategy may not be justifiable from the cost perspective and can also result in a high number of false negative cases.

Another important factor is the market utilisation of antifungal use in practice. The scenario analyses using individual antifungal agents showed the incremental cost of the BDG strategy to vary a lot depending on the

AF agent used in practice, being particularly cost-saving when only micafungin or amphotericin B and associated with a larger cost increase where agents from the less expensive triazole class are used.

The testing throughput, as determined by the annual number of admissions, has important implications for service organisation due to its impact on the variable cost of testing, i.e. higher throughput increases the number of patients that can be run per testing plate (two plates per kit). It has been shown that for anything above 9,448 admissions, the BDG strategy starts to be associated with cost savings, assuming 10% are treated empirically and the infection prevalence among those treated is 7%. Any service organisation should consider same day turnover of testing results to mitigate the risk associated to treatment delays.

The baseline analysis assumed no additional clinical risk linked to false negative cases. When considering a 24-72h treatment delay in false negative cases linked to an increased mortality risk, the BDG strategy is associated with a higher cost per patient and results in fewer life-years gained overall. Adding mortality associated to antifungal-related complications may reverse this negative effect on life-years gained.

An alternative testing strategy also considered is using BDG results to inform discontinuation of empirical treatment at certain points after initiation. This may mitigate the risks of withholding therapy in patients with false negative results, but it has been shown to be associated with an increasing incremental cost while exposing the entire target population to antifungals overprescribing and toxicity.

More studies are needed to assess the benefits of biomarker-based strategies with a particular focus on the safety outcomes of withholding or discontinuing antifungal use. Further research may also be needed focussing on the rates of toxicity and adverse events related to antifungal use and their impact on patient morbidity/mortality, quality of life and healthcare resource utilisation. Several upcoming studies are mentioned in this evidence note that aim to address such issues; the data from which may improve the robustness of inputs to the economic analysis.