Healthcare Improvement Scotland | SHTG Advice on health technologies

Advice Statement 02-19
January 2019

Advice Statement

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

Advice for NHSScotland

Overuse of empirical antifungal therapies in the critical care setting is a significant problem which exposes patients to potential harms of treatment from which they derive no benefit. Also, resistance to antifungal medications is emerging as a serious threat.

Preliminary clinical evidence and economic modelling suggests there is potential for the Fungitell® Beta-D glucan (BDG) test to reduce empirical antifungal overuse with minimal direct cost impact, however, caution should be exercised in relation to the imperfect nature of the test and the potential risk involved in withholding or discontinuing empirical treatment in false negative cases.

Evidence from a small number of published studies indicates that BDG tests can be used as part of strategies to increase the rate of early discontinuation of empirical antifungal therapies in the adult critical care setting, although studies were not large enough to inform the safety of this approach. No evidence was identified on the use of BDG testing to withhold empirical antifungal therapy in this setting. Several relevant trials are in progress.

Economic modelling was conducted to inform the antifungal stewardship work of the Scottish Antimicrobial Prescribing Group. Diagnostic accuracy data were applied to clinical parameter estimates. Key findings were:

- A rapid turnaround Fungitell® testing strategy to inform withholding of empirical therapy results in a large reduction in unnecessary antifungal use due to the test's high negative predictive value (NPV);
- The strategy is associated with an incremental cost resulting from the additional cost of testing which is not fully offset by the savings realised from the reduction in antifungal use;

- The strategy is associated with a minimal incremental cost or is potentially cost-saving, in settings with higher testing throughputs (maximising test kit utilisation) and where there is low infection prevalence and high empirical use, and where micafungin or amphotericin B are the most commonly used agents;
- In units where use of empirical therapy is less common costs may be significantly increased;
- There is a potential clinical risk linked to delaying treatment initiation in infected patients in whom empirical therapy is withheld based on false negative results, but this could not be properly quantified due to a lack of robust evidence;
- Indirect benefits such as reduced rates of serious adverse events and associated resource use and impact on quality of life, or the impact on antimicrobial resistance were not properly quantified due to a lack of robust data.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

Why is SHTG looking at this topic?

A topic referral was received from the Scottish Antimicrobial Prescribing Group (SAPG) in relation to its work in developing a national approach to antifungal stewardship. Examining the potential of diagnostics to minimise unnecessary use of antifungals and reduce development of resistance is a key strand in the SAPG strategy.

Evidence Note 89 was produced by Healthcare Improvement Scotland in response to this request.

Background

The majority (>90%) of invasive fungal infections in the critical care setting are due to *Candida* species. Invasive *Candida* infection (ICI) is associated with high mortality rates. Culture-based diagnostic methods are unable to provide timely and sufficiently sensitive results. In the critical care setting in Scotland empirical antifungal (AF) therapy may be instigated where there is suspicion of ICI based on clinical assessment. This leads to unnecessary use of systemic AF agents in a population where the incidence of invasive fungal infection is low. Patients are exposed to harms associated with treatment and medication interactions. There are also significant resource use issues and potential impact on development of treatment resistant organisms.

In Scotland, critical care settings include intensive care unit (ICU), intensive therapy unit (ITU) and high dependency unit (HDU).The Scottish Intensive Care Society Audit Group (SICSAG) captured information on 46,931 admissions in 2017. It may be estimated that around 3,500 of these patients will receive systemic AF medications, based on a large epidemiological study (FIRE study). Over 90% of patients treated with empirical AFs will not have invasive fungal infection and so will not receive benefit from these medications.

Beta-D-Glucan (BDG) is a constituent of fungal cell walls. A number of non-culture-based laboratory assays are available to measure BDG levels in serum or other fluids as an indicator of invasive fungal disease (IFD). The high negative predictive value of these tests

has potential to rule out IFD meaning that empirical therapy can be avoided or discontinued. The imperfect nature of the test however means that, for a small proportion of patients, risks of delayed treatment associated with false negative results remain.

In testing a hypothetical cohort of 1,000 patients with estimated invasive fungal infection prevalence of 7%, testing using the BDG (0.75 sensitivity and 0.76 specificity) assay:

- 52 will test positive and have invasive fungal infection and empirical treatment will be appropriately commenced
- 223 will test positive and not have invasive fungal infection, thus will be exposed to unnecessary AF treatment
- 707 will test negative and correctly avoid AF therapy
- 18 will test negative but will have invasive fungal infection so will be exposed to consequences of treatment delay.

Outcomes of interest include rates and duration of use of AF therapies, cost/cost-effectiveness, clinical outcomes such as mortality and morbidity and process outcomes such as length of stay.

Clinical effectiveness

All identified studies were of the Fungitell® assay (Associates of Cape Cod Inc). All were conducted in adult populations. All of the studies examined the use of BDG testing in strategies for discontinuation of empirical therapy. No studies were identified where the aim was to withhold empirical therapy.

- One randomised controlled trial (RCT) was identified. This was conducted in France (n=110). A strategy incorporating BDG testing and mannan/antimannan testing improved the rates of discontinuation of empirical AF therapy at 7 days (54% vs 2%, $p<0.0001$). Although no negative impacts were identified, this small study was not sufficiently powered to investigate the safety of the strategy in terms of subsequent infection or mortality.
- One small prospective single-arm observational study conducted in Brazil (n=85) reported no cases of recurrent *Candidaemia* at 30 days follow up in 21 patients for whom empirical anidulafungin treatment was discontinued based on negative blood cultures plus three consecutive negative BDG tests.
- Three retrospective single arm observational studies were identified; from India (n=154), Italy (n=198) and Austria (n=66). Each provided preliminary indication that use of BDG testing may reduce the use of empirical AF therapy. These studies are at high risk of bias in patient selection.

Safety

- Balancing the potential harms of toxicity and medication interactions with the implications of delaying or discontinuing AF treatment constitute important patient safety issues. Further evidence is required to inform this. Additionally, the impact of withholding or early discontinuation of empirical AF treatment on antimicrobial resistance is unclear.

Cost effectiveness

- No relevant published cost-effectiveness analyses were identified.
- An economic evaluation was undertaken by HIS (Appendix 2 in the Evidence Note accompanying this Advice Statement).
- The Fungitell® assay considered in the analysis costs £737.05 and includes all necessary reagents for duplicate tests on 42 individual patient serum samples (21 duplicate samples on 2 sequential plates). However, in practice the cost per patient will vary depending on the number of patient samples run per plate.
- The analysis suggested that a clinically-driven testing strategy with BDG (Fungitell®), to inform withholding of empirical therapy in critical care patients presenting with signs and symptoms of infection, is associated with a small cost increase, a large reduction in unnecessary prescribing of AFs and lower toxicity (expressed as rate of AEs) compared with an empirical strategy. Indirect benefits such as associated resource use linked to reduced toxicity and impact on quality of life, or the impact on antimicrobial resistance have not been quantified. A rapid turnaround of test results was assumed so that no clinically significant delays in treatment initiation occur compared with the empirical approach in true positive cases, hence the logistical feasibility of this should be considered.

*Table 1: Base case results of introducing BDG strategy in a single unit**

	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%
ICER (£/AE)	**-**	£717.66
AE – adverse event; ICER – incremental cost-effectiveness ratio		
***Assuming** 2,000 admissions distributed uniformly across one year, 10% of these treated empirically, 7% infection prevalence, and using a distribution of 60% fluconazole, 32% caspofungin, 3% micafungin, 3% anidulafungin, and 2% liposomal amphotericin B		

- The high negative predictive value of the test and the low infection prevalence in the population treated ensures the new strategy rules out infection in a large proportion of patients. The imperfect sensitivity of the test however, misidentifies a small percentage of people as false negatives. There appears to be a clinical risk associated with these patients which could not be properly quantified due to a lack of robust data. Within the economic model, this risk could be partially mitigated by using a lower BDG cut-off value which boosts the test's sensitivity, albeit at the expense of lower specificity and a higher rate of unnecessary treatment in false positives, but this might fall outwith the manufacturer recommended cut-off.
- Further sensitivity analysis showed the incremental cost of the BDG strategy to be minimal or the strategy to be potentially cost saving in units with a 'loose' empirical strategy (i.e. high proportion of admissions treated empirically and low prevalence of infection in the population treated). In units with a stricter empirical

strategy, the BDG strategy is associated with high incremental cost and can produce a high number of false negative cases. The market utilisation of AFs used in practice is also important, the BDG strategy being particularly cost-saving if only micafungin (-£1,643) or amphotericin B (-£5,311) are used for empirical treatment, while associated with a larger incremental cost if agents from the triazole class are used (£258 to £372).

- Testing throughput, expressed as patients tested per Fungitell® kit and determined by the annual number of admissions and percentage of admissions treated empirically, has important cost implications and may inform service organisation. Threshold analysis predicts the BDG strategy becomes cost-saving for throughputs of three patients ran per test and higher. A conservative example of such a throughput would be a local testing laboratory that can service around 1,000 tests distributed uniformly across a year (this is the equivalent of 10,000 admissions with an empirical treatment rate of 10%). Any service organisation should consider feasibility of rapid turnover of testing results to mitigate the risk associated with treatment delays.
- An alternative strategy has been explored, that uses BDG to inform discontinuation of empirical therapy at a given time point after initiation. This may provide an alternative where rapid turnaround of results is not possible. It also mitigates the risks of withholding empirical therapy in infected patients based on false negative results under the previous strategy. However, a risk of discontinuing therapy in false negative cases arises. Compared with the previous strategy it is associated with a higher incremental cost (£155 and £236 with discontinuation at days three and seven respectively), while exposing the entire target population to AF treatment and toxicity. Impact on antimicrobial resistance is also questionable.

Patient and social aspects

- See safety section

Context (includes organisational issues)

- This advice will inform national consensus guidance to optimise use of antifungals in NHSScotland being developed by the antifungal steering group of SAPG. www.sapg.scot/
- NICE published a medication innovation briefing on the Fungitell® assay in 2017 www.nice.org.uk/advice/mib118
- The effectiveness of diagnostic strategies will depend on adherence to protocols for use and the multidisciplinary clinical liaison context (eg daily microbiology ward rounds) within which they are implemented.

Further research

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 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=1720. Study end date is March 2021.

Advice context

No part of this advice may be used without the whole of the advice being quoted in full. This advice represents the view of the SHTG at the date noted.

It is provided to inform NHS boards in Scotland when determining the place of health technologies for local use. The content of this Advice Statement was based upon the evidence and factors available at the time of publication. An international evidence base is reviewed and thus its generalisability to NHSScotland should be considered by those using this advice to plan services. It is acknowledged that the evidence constitutes only one of the sources needed for decision making and planning in NHSScotland. Readers are asked to consider that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

SHTG Advice Statements will be considered for review if new evidence becomes available which is likely to materially change the advice. Stakeholders may submit a request, highlighting new evidence to shtg.hcis@nhs.net

Acknowledgements

SHTG would like to thank the following individuals and organisations who provided comments on the draft Advice Statement:

- Dr Malcolm G Booth, Consultant in Anaesthesia and Intensive care, Royal Infirmary Glasgow
- Dr Sanjiv Chohan, Consultant ICU and Anaesthetics, Clinical Lead Monklands Intensive Care Unit, Deputy Clinical Director Surgery, Anaesthesia and Critical Care, Scottish Quality and Safety Fellow
- Dr Laura Cottom, Consultant Microbiologist, Glasgow Royal Infirmary
- Dr Mark Dunn, Consultant in Critical Care, Royal Infirmary of Edinburgh
- Prof Brian Jones, Consultant Medical Microbiologist, Glasgow Royal Infirmary, Head of Service, Microbiology & Virology, and Professor of Clinical Microbiology & Infection, Institute of Infection, Immunity & Inflammation, University of Glasgow
- Dr Jacqueline Sneddon, Project Lead for Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland
- Alan Timmins, Lead Clinical Pharmacist- Acute, NHS Fife

Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by the SHTG's Evidence Review Committee. However, reviewers had no role in authorship or editorial control and the views expressed are those of SHTG. Details of SHTG membership are available on the Healthcare Improvement Scotland *website*.

Chair
Scottish Health Technologies Group