Title Page

Can Beta-D-Glucan testing as part of the diagnostic pathway for Invasive Fungal Infection reduce anti-fungal treatment costs?

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Can Beta-D-Glucan testing as part of the diagnostic pathway for Invasive Fungal Infection reduce anti-fungal treatment costs?

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ABSTRACT

We performed a cost comparison of the current diagnostic and treatment pathway for invasive fungal infection (IFI) versus a proposed pathway that incorporates Beta-D-Glucan (BDG) testing from the NHS perspective. A fungal pathogen was identified in 58/107 (54.2%) patients treated with systemic anti-fungals in the Critical Care Department. Mean therapy duration was 23 days (standard deviation [SD]=22 days), and cost was £5,590 (SD=£7,410) per patient. Implementation of BDG tests in the diagnostic and treatment pathway of patients with suspected IFI could result in a mean saving of £1,643 per patient should a result be returned within two days.

LAY SUMMARY

Invasive fungal infection increases the risk of death in very sick people. So, treatment is started before test results are known. Beta-D-Glucan (BDG) test is faster than standard blood culture tests. We estimate that using BDG tests in how patients are diagnosed could save about £1,643 per patient.

Invasive fungal infection (IFI) is a common cause of mortality and morbidity in critically ill adults [1], with an inpatient mortality of 40-50%.[1-3] Complications include endocarditis, chorioretinitis or haematogenous dissemination.[1,4,5] Around 0.6% of all critically ill patients are diagnosed with IFI during their admission.[2] Risk factors include prolonged intensive care unit (ICU) admission, treatment with broad-spectrum antibiotics, abdominal surgery, central venous catheter insertion, total parenteral nutrition, renal replacement therapy, immunosuppression and colonisation with *candida* species.[1,2,6]

Healthcare costs related to anti-fungal treatment are significant.[1,6-8] Implementation of anti-fungal stewardship programmes have the potential to reduce healthcare costs and increase patient safety.[8,9] It is therefore important to be able to exclude IFI and stop treatment. The Beta-D-glucan (BDG) assay has an excellent negative predictive value and has been used to exclude IFI and guide anti-fungal treatment.[5,7,8,10-12] A number of studies have shown that using BDG testing to cease anti-fungal therapy is effective and safe.[8,12,13] Using BDG to de-escalate treatment has also been shown to be cost-effective.[13,14] We evaluated whether the implementation of routine BDG testing in the diagnostic and treatment pathway of patients with suspected IFI could result in cost savings through a reduction in the use of anti-fungal therapy.

A detailed description of Methods can be found in the Supplementary Material. Case notes and electronic records of all patients treated with systemic anti-fungals whilst in Critical Care from 01 December 2018 to 01 December 2019 were retrospectively screened. Health outcome data and resource utilisation were retrieved from patient records who had anti-fungal treatment initiated for possible IFI. Sample microscopy and culture for fungal species, galactomannan antigen testing and BDG were used

to establish a diagnosis of IFI. Negative test results indicated absence of IFI, while positive results were regarded as diagnostic for the presence of a fungal pathogen in the fluid or tissue sample assessed.

The resource use items collected as part of the study were directly associated with testing and treatment of IFI. Accordingly, in line with established cost analysis methodology,[15,16] only two categories of costs were extracted from the case notes, i) treatment costs and ii) testing costs. The anti-fungal medication and treatment duration were extracted from patients' case notes. The treatment cost for each drug for a specific treatment course was obtained by multiplying the drug quantity for that treatment course by the unit cost of that drug. The unit cost of the sample microscopy and culture for fungi was obtained from the 2019 NHS schedule of reference cost while the unit cost of galactomannan and BDG were obtained from the local laboratory at the Liverpool University Hospital.

The overall costs per patient were calculated as the combined treatment and testing costs. The current diagnostic and treatment pathway for a patient with presumed IFI is presented in Figure 1a. The potential cost savings that could have been achieved from using BDG test was based on the assumptions that (1) all BDG tests would be conducted on the day that empirical anti-fungal treatment starts, (2) the specificity and sensitivity of BDG is 100%, (3) the mean waiting time for BDG test result is 2 days, and (4) clinicians would stop empirical anti-fungal treatment immediately after receiving a negative BDG test (Figure 1b). These assumptions imply that only the cost of anti-fungal treatment for the first two days should be considered in patients without a fungal pathogen in their culture. Thus, any further treatment duration in these patients are excess treatment days on which costs could have been saved and

side-effects averted. Scenario analyses were conducted and are presented in Supplementary Material.

Over the study period, 1,480 patients were admitted to Critical Care (858 ICU admissions, 622 HDU admissions). One-hundred-and-seven (7.2% of admissions) patients fulfilled inclusion criteria. Patient characteristics and additional results are presented in the Supplementary Material. The mean treatment cost for the entire anti-fungal treatment that each patient received was £5,590 (Table 1). The large proportion of the mean treatment cost per patient (82.8%, £4,631/£5,590) was incurred from the first course of anti-fungal treatments that patients received. Including treatment costs and testing costs, the mean cost per patient was £5,605 (SD=£7,412). The aggregated cost incurred by all the patients in the current diagnostic and treatment pathway was £599,692 (SE=£76,674).

If patients with suspected IFI were tested for BDG and anti-fungal treatments were discontinued after two days in those with a negative test result, patients would have received fewer drug doses leading to a cost reduction (Table 1). The estimated saving was £1,643 as the actual average drug cost per case would have been reduced to £3,947 with the optimised testing protocol. The potential per patient cost savings would have accumulated to £175,840 for the 107 cases included study.

Strategies to exclude IFI are needed in critical care to reduce healthcare costs and promote anti-fungal stewardship.[1,6-8] Due to its excellent negative predictive value, if measured in conjunction with scoring systems or clinical context, serial BDGs can exclude IFI and guide anti-fungal treatment,[5-8,10-12] thereby saving on healthcare costs with no increase in mortality from under-treated fungal infection.[6,8] Our results are in agreement with previously published reports[8] which observed a reduction in the number of patients initiated on anti-fungal therapy inappropriately following implementation of BDG testing. Furthermore, our cost analysis supports the potential for cost savings by routine use of BDG testing in critically ill adults suspected of IFI.[13,14]

Costs have to be considered alongside the benefits and side effects of anti-fungal therapy for IFI. Anti-fungal medications are expensive and its use in patients without proven IFI does not confer a mortality benefit.[8,9] However, when IFI is suspected, anti-fungal therapy should be initiated as soon as possible due to the incremental increase in mortality risk associated with treatment delays.[3,17,18] Potential drug toxicity and development of resistance are compelling arguments to cease anti-fungal administration once a negative test result is provided. It has been demonstrated that advice to de-escalate or stop anti-fungal treatment in patients with no evidence of IFI does not compromise microbiological or clinical outcomes.[9,19] However, despite the excellent negative predictive value of BDG, the safety of discontinuing empiric anti-fungals based on only one negative BDG result, as opposed to serial negative results, needs confirming in prospective randomised controlled trials.[1]

Our study demonstrates that cost savings and drug use could be made by routine use of BDG testing in critically ill adults suspected of IFI. It highlights the importance of timely routine BDG testing in critical care patients receiving empirical treatment as an adjunct to anti-fungal stewardship. BDG testing is not routinely used in the NHS with a recent survey finding only 57% of trusts had access to rapid diagnostic testing.[20] In the UK, a multi-centre prospective study (Anti-fungal stewardship opportunities with rapid tests for fungal infection in critically ill patients, ISRCTN43895480), is investigating the diagnostic accuracy of BDG and two PCR-based tests for *Candida* infection and is expected to provide further guidance on anti-fungal prescription and its cost effectiveness in the critical care setting. The limitations of this study are presented in the Supplementary materials.

In summary, our model estimates that appropriate BDG testing in a tertiary critical care unit may reduce anti-fungal costs by £1,643 per patient and suggests that access to testing should increase across the NHS.

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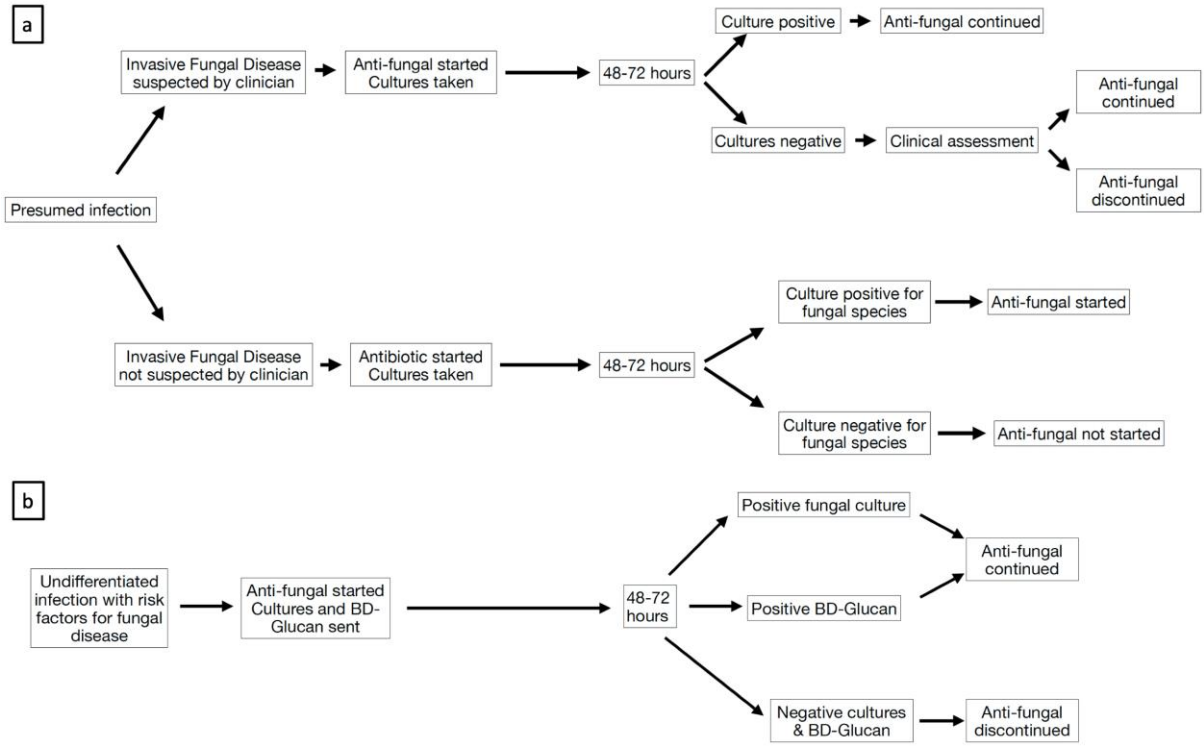

Figure 1 Current diagnostic and treatment pathway for management of invasive fungal infection (a) and diagnostic and treatment pathway for management of invasive fungal infection incorporating a Beta-D-Glucan test (b)

Table 1 Mean treatment cost per patient, by treatment and course for the current pathway and optimised pathway incorporating a Beta-D-Glucan test

Current diagnostic and treatment pathway	First course, mean (SD)	Second course, mean (SD)	Third course, mean (SD)
Ambisome	£7808 (£8223)	£5342 (£0)	£0 (£0)
Anidulafungin	£5000 (£3501)	£3000 (£1200)	£3750 (£3182)
Caspofungin	£7710 (£10785)	£13762 (£0)	£0 (£0)
Fluconazole	£107 (£82)	£125 (£111)	£506 (£0)
Flucytosine	£0 (£0)	£849 (£901)	£0 (£0)
Micafungin	£5637 (£7051)	£5286 (£4029)	£0 (£0)
Voriconazole	£14579 (£16146)	£4396 (£0)	£0 (£0)
Treated patients	**£4631 (£7068)**	**£2869 (£3727)**	**£2668 (£2927)**
Study population†	**£4631 (£7068)**	**£885 (£2442)**	**£74 (£598)**
Total: study population (n=107) †			**£5590 (£7410)**
Diagnostic and treatment pathway incorporating a Beta-D-Glucan test	**First course, mean (SD)**	**Second course, mean (SD)**	**Third course, mean (SD)**
Ambisome	£3493 (£3170)	£822 (£0)	£0 (£0)
Anidulafungin	£3814 (£3858)	£2640 (£1649)	£3450 (£3606)
Caspofungin	£4293 (£11097)	£983 (£0)	£0 (£0)
Fluconazole	£56 (£71)	£126 (£111)	£506 (£0)
Flucytosine	£0 (£0)	£849 (£901)	£0 (£0)
Micafungin	£4209 (£7190)	£4365 (£4142)	£0 (£0)
Voriconazole	£13345 (£17891)	£4397 (£0)	£0 (£0)
Treated patients	**£3258 (£6748)**	**£2021 (£2962)**	**£2468 (£3064)**
Study population†	**£3258 (£6748)**	**£620 (£1876)**	**£69 (£587)**
Total: study population (n=107) †			**£3947 (£7162)**

†=drug cost was assumed to be zero for treatments that patients did not receive; SD=standard deviation
Optimised regimen is based on a 2-day waiting time for Beta-D-Glucan test result