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Clinical audits/service improvements

# Antifungal stewardship in critical care: Implementing a diagnostics-driven care pathway in the management of invasive candidiasis

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## SUMMARY

**Background:** Invasive candidiasis (IC) is the most common invasive fungal disease in patients admitted to critical care and is associated with high mortality rates. Diagnosis can be delayed by the poor sensitivity of culture-based methods, leading to unnecessary use of empirical antifungal therapy (EAFT). The fungal biomarker (1–3)- $\beta$ -d-glucan (BDG) has been shown to aid in the diagnosis of IC in critical care and has been incorporated into antifungal stewardship (AFS) programmes.

**Aim:** To describe our experience using a diagnostics-driven AFS programme incorporating the fungal biomarker BDG, analyse its impact on antifungal therapy (AFT), and gain an improved understanding of the epidemiology of IC in our critical care unit (CrCU).

**Methods:** An AFS care pathway incorporating BDG was introduced in the CrCU in St James's Hospital, Dublin. Following an educational programme, compliance with the pathway was prospectively audited between December 1st, 2017 and July 31<sup>st</sup>, 2018.

**Results and Conclusion:** One hundred and nine AFT episodes were included, of which 95 (87%) had a BDG sent. Of those with BDG results available at the time of decision-making, 38 (63%) were managed in accordance with the care pathway. In compliant episodes without IC, median EAFT duration was 5.5 days [IQR 4–7] and no increase in mortality or subsequent IC was observed. Although adopting a diagnostics-driven approach was found to be useful in the cohort of patients with BDG results available, the use of once-weekly BDG testing did not result in an observed reduction in the consumption of anidulafungin, highlighting an important limitation of this approach.

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## Introduction

### Problem description

Invasive candidiasis (IC) is the most common invasive fungal disease complicating critical care and is recognised as an increasingly common cause of sepsis in this population [1]. Overall crude mortality rates have been estimated at 40–60%, [2–5] which are associated with delayed institution of antifungal therapy (AFT) [6]. Furthermore, the diagnosis of IC is challenging due to the poor sensitivity of culture-based techniques [7]. This situation of an infection associated with a high mortality, coupled with poor diagnostic tests, inevitably leads to the overuse of antifungal agents in vulnerable populations; exposing patients to potential drug toxicity and contributing to the growing problem of antifungal drug resistance [8].

### Available knowledge

The fungal biomarker (1–3)- $\beta$ -d-glucan (BDG) has been shown to aid in the management of IC in critical care due to its high negative predictive value [9–11] and has been incorporated into biomarker-based antifungal stewardship (AFS) strategies in many centres [11–13]. In a randomised controlled trial of 109 patients Rouz e *et al.* [12] showed that the use of a biomarker-based strategy which included BDG led to early discontinuation of empiric antifungal therapy (EAFT) and did not negatively impact on patient outcomes. Similarly, Rautemaa-Richardson *et al.* [13] showed that safe cessation of EAFT in at-risk intensive-care unit (ICU) patients can be guided by BDG, as part of a diagnostics-driven antifungal stewardship programme and did not impact negatively on patient outcome or the incidence of candidaemia. A prospective study carried out in our critical care unit (CrCU) in 2015 demonstrated that BDG distinguished patients with probable and proven IC from those who did not have IC, and indicated that access to on-site BDG testing may be of use to guide AFT [14]. This approach is supported by evidence-based guidelines [15].

### Rationale

Antimicrobial stewardship (AMS) is a systematic approach to optimising antimicrobial therapy through a variety of structures and interventions, and effective AMS programmes have been shown to improve patient outcomes [16]. Guidelines published by the National Institute for Health and Care Excellence (NICE) [17] and by the Centre for Disease Control and Prevention (CDC) [18] recommend that hospital AMS programmes should involve a number of important components; including regular monitoring of antimicrobial prescribing, the integration of clinical audit into quality improvement strategies, and the provision of education and feedback to healthcare practitioners and prescribers. Based on these principles, we devised a multi-faceted antifungal stewardship initiative to optimise and guide antifungal use in our CrCU.

### Specific aims and objectives

The primary objective of this study was to demonstrate the impact and safety of a multi-faceted diagnostic-driven AFS

care pathway incorporating BDG on duration of EAFT and antifungal consumption in patients with suspected IC in CrCU. Secondly we describe the epidemiology of IC in CrCU during the same period.

## Methods

### Context

St James’s Hospital (SJH) is the largest tertiary referral centre in Ireland and has a multi-speciality 27-bed CrCU comprising an 18 bed multi-speciality ICU, a 6-bed cardiothoracic ICU and a 3-bed high dependency unit (HDU). Our centre is also the site of the National Stem Cell Transplantation Unit and the National Burns Unit. Local surveillance records have shown that *Candida* spp. caused 9% of significant bloodstream infections in our CrCU in 2018, and an audit carried out in 2016 demonstrated that the average duration of EAFT in our CrCU was 8 and 10 days in a cohort of patients who had no evidence of IC and *Candida* colonisation respectively [19]. Although diagnostics-driven AFS programmes that include BDG determination have been used elsewhere [11–13], no other hospitals in Ireland have had access to on-site BDG testing to help guide the management of IC prior to this initiative.

### Interventions

A multi-faceted AFS initiative was developed to guide the management of suspected IC in CrCU. This consisted of a diagnostics-driven pathway (Figure 1) that incorporates BDG testing which was implemented and prospectively audited, in addition to close monitoring of antifungal prescribing and an educational programme delivered to stakeholders with regular feedback sessions.

Our care pathway was designed to identify patients started on EAFT for suspected IC who had negative sterile site cultures at 48–72hrs and a negative serum BDG result, with a view to safely discontinuing EAFT. This was based on an algorithm devised by Rautemaa-Richardson *et al.* [13], which we adapted to our institution. Results were discussed when available during daily multi-disciplinary AMS rounds between CM and CrCU physicians. However, the decision to initiate or discontinue AFT was ultimately made by the CrCU physician responsible for the patient’s care.

Our educational programme consisted of a series of formal and informal lectures and posters detailing the principles of AFS and the design of our proposed care pathway. These lectures were delivered to both medical and nursing CrCU staff prior to the initiation of the project, and to the clinical and laboratory staff in clinical microbiology (CM). Feedback was delivered to CrCU on a weekly basis and at a formal multi-disciplinary meeting, as well as updates being delivered at CM departmental meetings.

Microbiology laboratory staff training and technical validation of the BDG assay were performed along with a pilot analysis of clinical samples in November 2017, with roll-out in CrCU in December 2017. Serum BDG testing was then performed once weekly and results made available to clinicians as soon as available to aid in clinical decision-making.

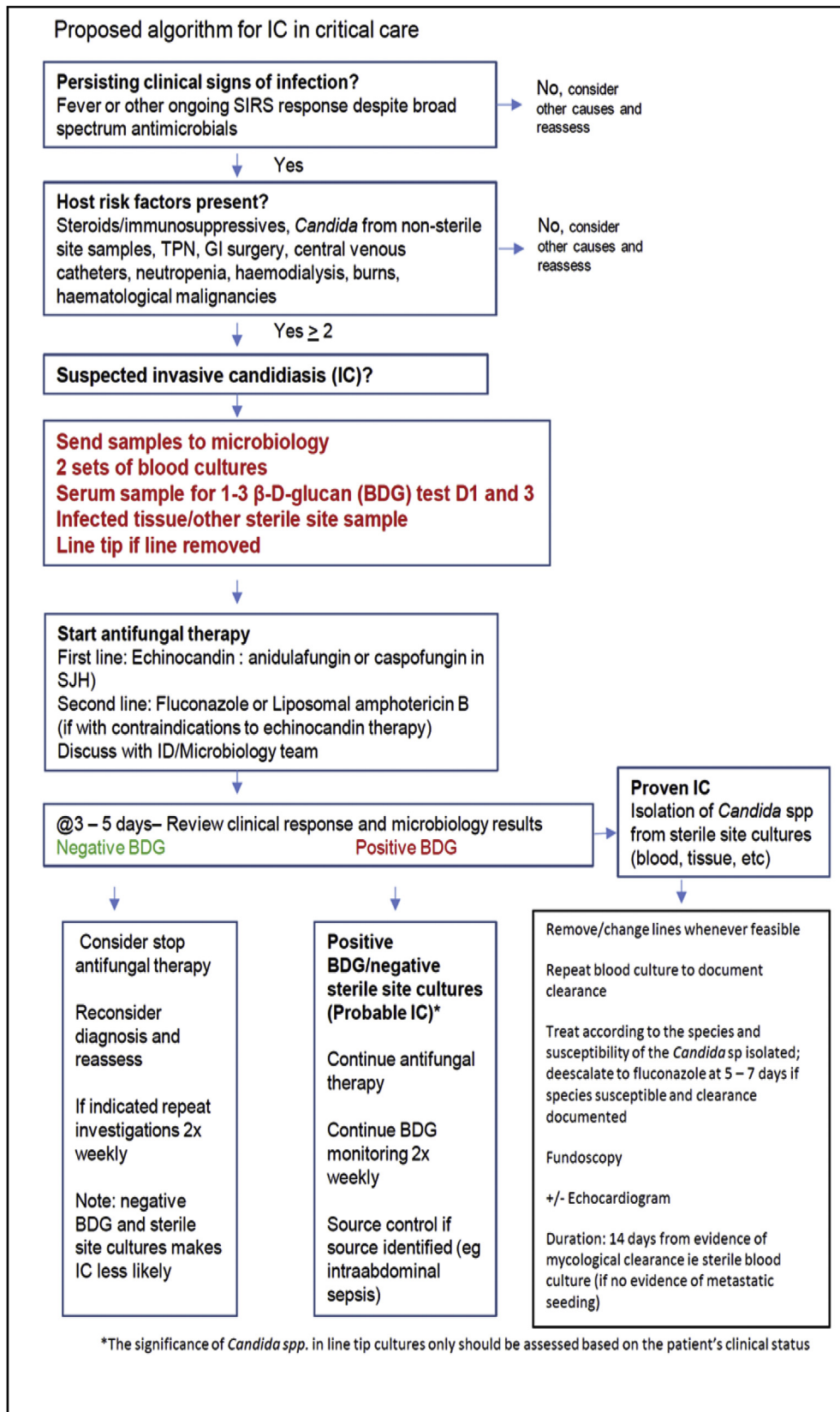


Figure 1. Diagnostics-driven care pathway.

## Audit of compliance to the pathway

A prospective audit of compliance with the care pathway was performed in two four-monthly cycles, firstly between 1st December 2017 and 31<sup>st</sup> March 2018. After this, an intervention was put in place to improve adherence which consisted of a prompt embedded into the CrCU electronic drug chart to remind prescribers to send BDG samples on initiation of AFT, as well as a formal feedback session delivered to CM and CrCU staff. Re-audit then took place between 1<sup>st</sup> April 2018 and 31<sup>st</sup> July 2018.

## Data collected

Using the electronic patient records and the laboratory information systems, the following data were collected for all episodes whereby AFT was commenced for suspected IC in CrCU: demographic data including gender and age, risk factors for IC, the indication for starting AFT, BDG results, and culture results from both sterile and non-sterile sites. The diagnostic category of IC in each treatment episode once serum BDG results became available was documented-i.e. proven, probable, colonised or no evidence of IC. Compliance with the care pathway, the duration of each AFT episode, and the monthly antifungal consumption expressed as Defined Daily Dose for 100 Bed Day Used (DDD/100BDU) for anidulafungin (the first line EAFT recommended for suspected IC in our institution) were also recorded.

## Definitions

Compliance with the clinical pathway was documented and measured in two ways. Firstly, by the number of episodes with BDG samples appropriately sent on initiation of AFT, and secondly by the proportion of episodes managed in accordance with the care pathway once BDG and culture results became available - i.e. those whereby AFT was stopped when classified as having no evidence of IC or continued in episodes with probable or proven IC.

AFT episodes in which  $\geq 1$  dose of a systemic antifungal agent was administered for suspected IC in CrCU, having not been on AFT in the previous 24 hours, were included. Patients on AFT prior to admission to ICU and for indications other than suspected IC were excluded from the final analysis. EAFT was that given to patients with risk factors for IC and persistent or recurrent fever despite broad spectrum antibacterial therapy, but without microbiological or histological evidence of IC at the time of initiation (Figure 1).

With respect to the diagnostic categories of each treatment episode, proven IC involved isolation of a *Candida* spp. from a normally sterile site (including blood, CSF, synovial fluid, tissue culture or surgical biopsies and samples from surgical drains in situ  $\leq 24$  hours) regardless of BDG result. Episodes classified as probable IC were those in which sterile site cultures were negative but BDG results were positive, and episodes classified as colonised were those whereby *Candida* spp. were isolated from non-sterile sites (including broncho-alveolar lavage samples) only, with negative BDG results (Figure 1.) Of note, routine screening for *Candida* spp. colonisation is not performed in our CrCU, with swabs of non-sterile sites sent only when deemed clinically appropriate.

## Safety

To assess the safety of using our AFS care pathway, patients diagnosed with proven IC within 7 days of discontinuing AFT based on our algorithm were recorded, as was the all-cause mortality at 30 days from initiation of therapy. In order to minimise missing data, efforts were made by the AMS service to capture all patient outcomes and data regarding AFT duration by clinical assessment of patients discharged from CrCU.

## Analysis

Serum BDG values were determined using the Fungitell assay™ (Associates of Cape Cod, USA) following manufacturer's instructions. A negative result was defined as  $< 60$ pg/ml, positive was  $> 80$ pg/ml, and 60–80pg/ml was classified as indeterminate.

Quarterly antifungal consumption data were recorded, and in order to minimise for the impact of seasonal variation, AFT consumption data were compared to the same period in previous years. Binary categorical variables were compared through  $\chi^2$  analysis. Median durations of AFT were expressed with interquartile ranges [25<sup>th</sup>- 75<sup>th</sup>] and non-normally distributed continuous variables were compared using the Mann-Whitney U test. IBM SSPS Statistics v.26 was used, and a (two-tailed) value of  $P \leq 0.05$  was considered significant.

## Ethical considerations

This was an observational study whereby compliance to an evidence-based care pathway was prospectively audited. Thus, consent of individual patients was not required. Approval by the institutional Research and Ethics Committee was obtained prior to initialisation. (Reference: 2017-02 Chairman's Action (3)).

## Results

A total of 161 AFT episodes in CrCU over 8 months were screened for eligibility for inclusion. Fifty-two episodes were excluded as AFT was initiated prior to admission to CrCU or was started for a reason other than suspected IC. This left 109 treatment episodes eligible for inclusion. Of these, 95 (87%) had a BDG sample sent. (Figure 2).

The mean age at initiation of AFT was 59 years (range 23–85 years) and 66 episodes (66%) were in male patients. Anidulafungin was the agent of choice in 78 (72%) of episodes. Five episodes (5%) were commenced on targeted therapy at initiation, with the remaining 104 (95%) receiving EAFT. Following our definitions, there were 11 (12%) diagnosed with proven IC, 26 (27%) with probable IC, 44 (46%) were colonised and 14 episodes (15%) had no clinical or microbiological evidence of IC. Median turnaround time (TAT) to obtaining a BDG result was 4 days [IQR 2–6]. These data are summarised in Table 1, along with a description of the source and distribution of the *Candida* spp. isolated.

In total, sixty (63%) of the AFT episodes in which a BDG was sent had a result available when the continuing indication was being reviewed. Of these, 38 (63%) were managed in accordance with our pathway (Figure 2). In audit cycle 1, 76% ( $n = 44$ ) had samples sent for BDG testing on initiation of AFT. Of these,

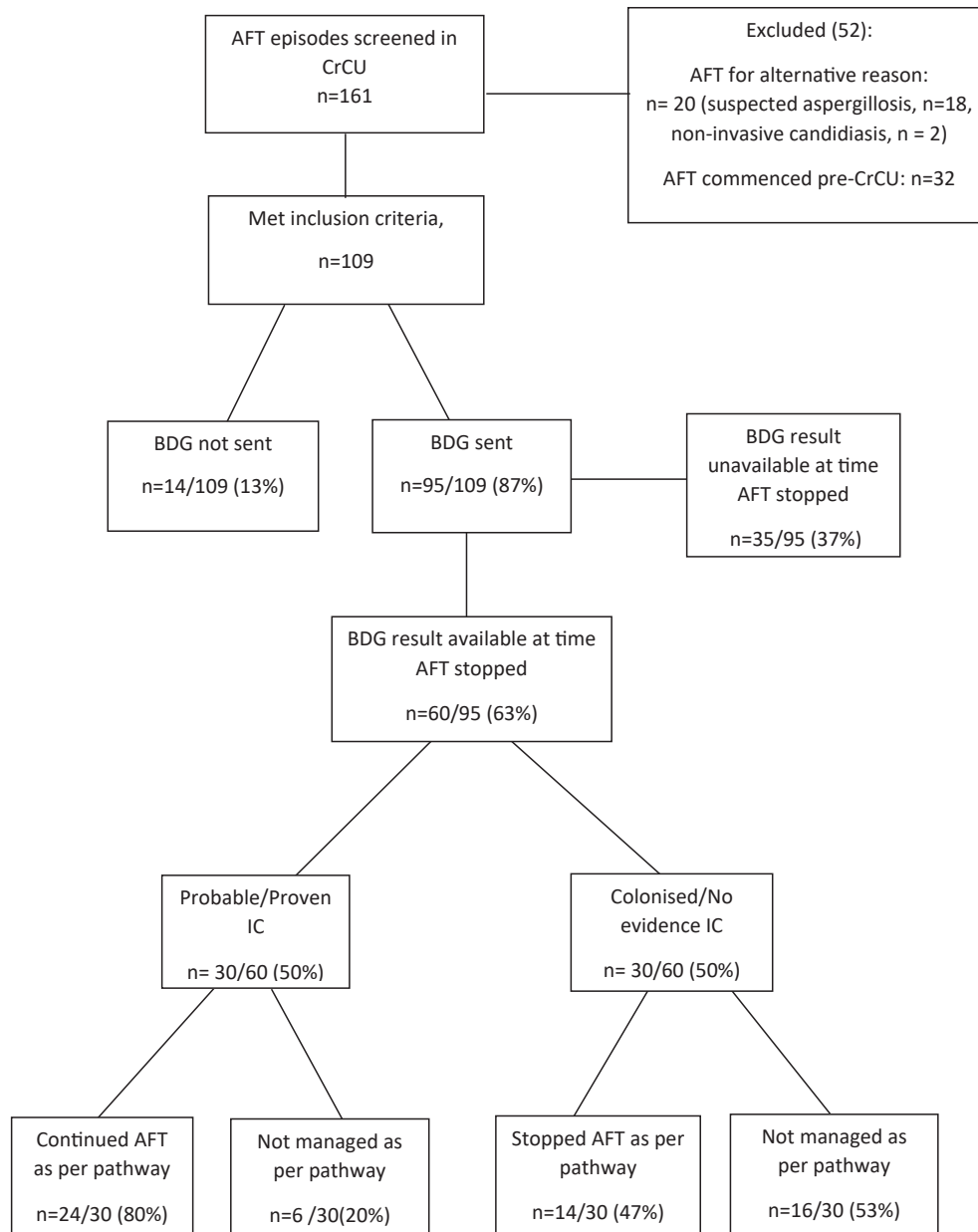


Figure 2. Flow diagram of the study.

57% (n=16) were subsequently managed in accordance with the pathway. In cycle 2, compliance with sending BDG improved after the introduction of the electronic prompt, with BDG sent appropriately in 100% (n=42,  $P<0.001$ ) of episodes. Sixty-nine per cent (n=22) of episodes were subsequently managed as per the algorithm, although this rise relative to cycle 1 did not meet statistical significance ( $P=0.43$ ) (Table 2).

Table 3 details the outcomes of EAFT episodes whereby BDG results were available. In compliant episodes with no evidence of IC, median duration of EAFT was 5.5 days [IQR 4–7] compared with a duration of 14.5 days [IQR 9–23] in non-compliant episodes ( $P<0.001$ ). Antifungal consumption of anidulafungin, however, was static over the period analysed (Figure 3). All-cause mortality was similar in episodes without IC that were compliant with the algorithm compared with those that were non-compliant, with just 1 patient having died in each group at

30 days from initiation of EAFT (neither from IC). Of the episodes whereby EAFT was continued despite a negative BDG, none were diagnosed with proven IC. Furthermore, just one episode of proven IC was recorded within 7 days of stopping EAFT in accordance with the pathway, involving a patient who had *Candida albicans* isolated from a knee aspirate 3 days after a negative BDG result.

## Discussion

### Summary

Our results indicate that adopting a diagnostics-driven approach can be useful in reducing EAFT duration in CrCU, particularly in a cohort of patients with BDG results available at

**Table I**  
Summary of results

	n (%)
Total AFT episodes, n=109	
Male	66/109 (60)
Mean age, years (range)	59 (23–85)
Episodes with BDG sent	95/109 (87)
Median turnaround time to first BDG result, days [IQR]	4 [2–6]
<b>Indication on initiation of AFT:</b>	
Targeted AFT	5/109 (5)
Empirical AFT	104/109 (95)
<b>Choice of AFT on initiation:</b>	
Anidulafungin	78/109 (72)
Fluconazole	29/109 (27)
Amphotericin B	1/109 (<1)
Caspofungin	1/109 (<1)
<b>Diagnosis (BDG sent, n=95):</b>	
Proven IC	11/95 (12)
Probable IC	26/95 (27)
Colonised	44/95 (46)
No evidence IC	14/95 (15)
<b>Proven IC, n=11</b>	
Candida species:	
<i>C. albicans</i>	7/11 (64)
<i>C. parapsilosis</i>	1/11 (9)
<i>C. glabrata</i>	1/11 (9)
<i>C. dubliniensis</i>	1/11 (9)
Mixed – <i>C. glabrata</i> & <i>C. albicans</i>	1/11 (9)
Anatomical site:	
Bloodstream	1/11 (9)
Pleural fluid/Lung tissue	2/11 (18)
Intra-abdominal/pelvic collection	5/11 (45)
Bone	1/11 (9)
Joint fluid	1/11 (9)
Other	1/11 (9)

the time of clinical decision-making. However, the use of once-weekly BDG testing resulted in a slow TAT and did not result in an observed reduction in antifungal consumption over the period analysed, highlighting an important limitation of this approach.

### Interpretation

The results of this AFS initiative were encouraging as the median duration of EAFT (5.5 days [IQR 4–7]) was reduced in

**Table II**  
Audit cycles - compliance with pathway

	Audit Cycle 1 n (%)	Audit Cycle 2 n (%)	P-value
AFT episodes	58	51	-
BDG sent	44/58 (76)	51/51 (100)	<0.001
Episodes with BDG available when AFT decision made	28/58 (48)	32/51 (63)	0.18
Managed as per pathway	16/28 (57)	22/32 (69)	0.43

**Table III**  
Outcomes: Episodes managed as per care pathway

	Episodes with BDG available, n=60	Compliant, n (%)	Not Compliant n (%)	P-value
<b>Proven/probable IC, n=30</b>				
Episodes	24/30 (80)	6/30 (20)	-	
Median ICU LOS, days [IQR]	18 [10–31]	18 [10–28]	-	
Median duration of EAFT, days [IQR]	29 [15–45]	7 [5–8]	0.02	
All-cause mortality at 30 days	6/25 (24)	3/6 (50)	0.32	
<b>Colonised/No IC, n=30</b>				
Episodes	14/30 (47)	16/30 (53)	-	
Median ICU LOS, days [IQR]	10 [6–32]	23 [15–60]	0.19	
Median duration of EAFT, days [IQR]	5.5 [4–7]	14.5 [9–23]	<0.001	
All-cause mortality at 30 days	1/14 (7)	1/16 (6)	-	
Proven IC within 7 days of stopping AFT	1/14 (7)	0	-	

the episodes whereby a negative BDG was available and the algorithm was followed appropriately. Compliance with sending BDG on initiation of AFT was also good in that 87% of episodes had appropriate samples sent. Importantly, the pathway appeared to be safe for use given that only one compliant AFT episode was classified as 'proven IC' within 7 days of stopping EAFT and no difference was observed in relation to mortality between compliant and non-compliant episodes. Despite a programme of education and regular feedback to prescribers, compliance with discontinuation of EAFT in accordance with the algorithm proved to be more difficult, highlighting the challenges associated with stopping AFT in complex, critically unwell patients. Furthermore, in contrast to the findings of Rautemaa-Richardson *et al.* [13] a sustained reduction in overall antifungal consumption was not observed. This was likely impacted by the limitations of once-weekly batch-testing of the BDG assay, meaning that results were often not available to clinicians at the time of decision-making and due to the relatively short duration of the study. Ongoing analysis over a longer time-period is needed to fully appreciate the impact on this parameter. Of note, a single test BDG assay has recently been launched in Europe which has the potential to shorten TAT, which could provide real-time BDG results to clinicians and impact on duration of EAFT [20].

### Limitations and challenges

This prospective audit had several limitations and challenges. Firstly, our sample size was small, and the audit was conducted over a short period which made it difficult to assess the true impact on antifungal consumption, particularly given the high degree of baseline variation of anidulafungin use in our institution in recent years. Resource restrictions meant that BDG testing was performed once-weekly which had implications on TAT and often meant that results were unavailable when decisions regarding AFT were being made. Thus, the

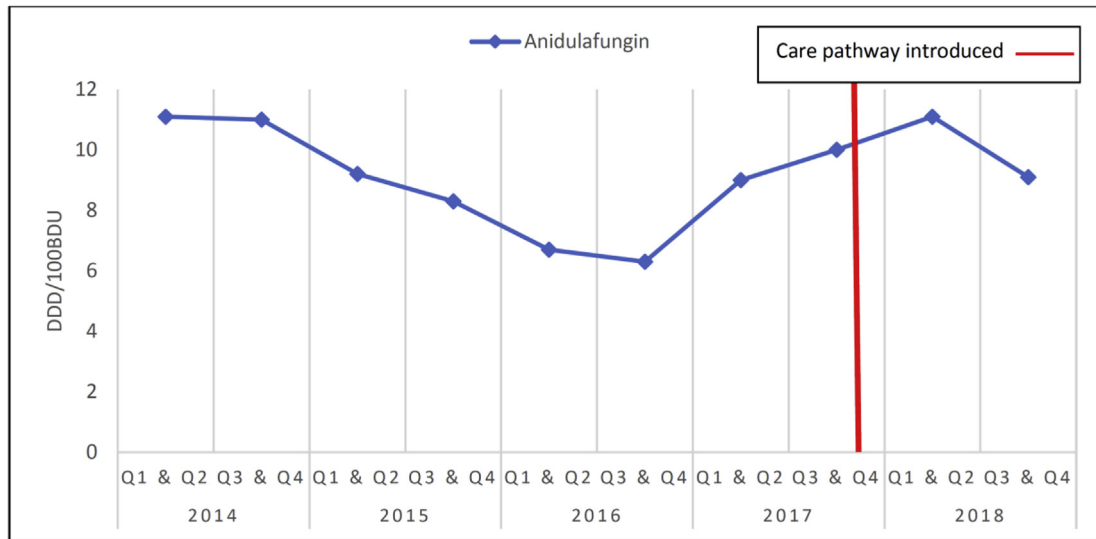


Figure 3. Antifungal consumption of Anidulafungin in CrCU, 2014–2018.

precise impact of having BDG determination available was difficult to quantify. Efforts were made to adjust for this by assessing the impact of compliance with the algorithm on median AFT duration in episodes whereby BDG results were available to clinicians.

## Conclusion

This is the first study in Ireland where on-site BDG determination has been incorporated into an IC care pathway, in the setting of a large tertiary referral centre with a multi-speciality CrCU. Despite the absence of an observed impact on antifungal consumption, these findings remain useful as they have the potential to guide others considering the introduction of non-culture-based fungal diagnostics such as BDG in this setting - particularly the limitations of once-weekly testing. Further research is needed to establish the precise contribution of BDG to the management of IC and other IFD both in critical care and other at-risk patient cohorts.

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## CRedit statement

**D Hare:** Conceptualisation, Methodology, Investigation, Project Administration, Data Curation, Writing – Original draft preparation, Visualisation, Formal analysis; **C Coates:** Investigation; **M Kelly:** Resources; **E Cottrell:** Resources; **E Connolly:** Supervision; **EG Muldoon:** Writing – Review and Editing; **B O'Connell:** Writing – Review and Editing, Supervision; **TR Rogers:** Writing – Review and Editing, Supervision; **AF Talento:** Conceptualisation, Methodology, Project Administration; Validation, Funding acquisition, Supervision, Writing – Review and Editing, Resources.

## Declaration of Competing Interest

None declared.

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