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Should serum biomarker monitoring replace primary antifungal chemoprophylaxis in patients with acute leukaemia receiving systemic anti-cancer therapy? A PRO/CON debate

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Fungal infection exacts a severe burden on patients with acute leukaemia. Azole prophylaxis attempts to mitigate this impact but is associated with toxicity and cost as well as the potential to select for resistance. The development of biomarkers including galactomannan and β-1,3-D-glucan may improve detection of early disease and thus reduce the need for prophylaxis, though these assays also have their limitations. In this debate, Howard *et al*. argue in favour of continuing chemoprophylaxis in patients with acute leukaemia receiving systemic chemotherapy, citing the multiple randomized control trials and meta-analyses that demonstrate its efficacy. Taynton *et al*. argue that fungal biomarker surveillance in the absence of primary antifungal chemoprophylaxis is a safe alternative that could reduce antifungal use and the development of resistance.

Prolonged use of antimicrobials in patients who do not currently have infection is an anathema to infection doctors in most circumstances due to the associated cost, toxicity and potential driving of resistance. Compelling evidence of benefit over alternative management strategies is therefore required to justify such an approach and the required threshold for this evidence, both generally and in the specific patient, remains unresolved in most contexts, including urinary tract infection prophylaxis and selective digestive decontamination.

Fungal infection exacts a severe burden on patients with acute leukaemia. Invasive aspergillosis has an incidence of 6.1% in this population, candidaemia 3.5%, and a variety of less common organisms are also encountered. The mortality rates are high, with an attributable mortality rate of 38.5% and 33%, respectively.[1] These figures mean clinicians are keen to minimize this risk to patients, particularly during cycles of chemotherapy when patients are at most risk.

Randomized controlled trials performed across the 1990s established fluconazole as an effective means of reducing invasive fungal infection (IFI) in neutropenic haematology patients, with a reduction in mortality demonstrated in stem cell transplant patients and those with prolonged neutropenia but not in other groups.[2] A paradigm shift occurred in many centres in 2007 following the demonstration of superior efficacy and increased overall survival with the mould-active posaconazole compared with fluconazole or itraconazole by Cornely *et al.*[3] This has led several guidelines to recommend primary antifungal chemoprophylaxis (PAC) in the haematology setting including IDSA[4] and ESCMID.[5] The use of posaconazole was modelled as being cost-effective strategy by a French group due to reduced incidence of IFI.[6]

Over a similar period, fungal biomarkers (FBs) were introduced and their role in the diagnosis of IFI evaluated. These assays have a number of advantages over conventional culture and microscopy.[7] Galactomannan (GM) is an *Aspergillus* cell wall polysaccharide and can be present in various body fluids, including serum. It can be detected via ELISA and performs particularly well in neutropenic patients with leukaemia though its sensitivity is adversely affected by mould-active prophylaxis. β-1,3-D-glucan (BDG) is a fungal cell wall polysaccharide present in a range of relevant species (Table 1) and detected most commonly via the Limulus lysate assay. These assays were approved by the FDA in 2003 and 2004 respectively, and so were still in development during the early trials of PAC.

There is significant motivation to reduce the use of systemic antifungals: the NHS currently spends ~£150 million each year on antifungal drugs[8] and it is recognized that the emergence of drug-resistant strains such as azole-resistant *Aspergillus fumigatus* and *Candida auris* may compromise antifungal therapy and patient outcomes in the future. This has led to a national Commissioning for Quality and Innovation (CQUIN) incentive aiming to reduce consumption of these drugs.[9]

Table 1. Fungal biomarkers

	Ideal biomarker	BDG	GM
Sensitivity	100%	80%[21]	78% (cut-off 0.5)[22]
Specificity	100%	63%[21]	85% (cut-off 0.5)[22]
TAT	Hours or point of care	Assay TAT is hours, but clinical TAT depends on frequency of runs. Few hospital laboratories will receive sufficient samples to make daily runs viable and most currently operate a send-away service with clinical TAT of several days	
Cost	Cheap	£61.32	£54.82
Organisms detected most relevant to UK acute leukaemia population	All relevant species that would result in specific intervention or treatment	*Pneumocystis jirovecii*, *Aspergillus* spp., *Fusarium* spp., *Candida* spp.	*Aspergillus* spp., *Fusarium* spp.
Other organisms detected		*Histoplasma capsulatum*, *Acremonium* spp., *Trichosporon* spp., *Sporothrix schenckii*, *Saccharomyces cerevisiae*, *Coccidioides immitis*, *Prototheca*[7]	*Paecilomyces* spp., *Acremonium* spp., *Penicillium* spp., *Alternaria* spp., *H. capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Emmonsia* spp., *Exophiala dermatitidis*, *Prototheca*, *Myceliophthora*, *Geotrichum capitatum*, *Chaetomium globosum*

TAT, turnaround time.

FBs have since been used in combination for patients with febrile neutropenia to identify those less likely to have IFI and so prevent the use of empirical antifungal therapy.[10] Several trials have shown the benefit of FB-guided therapy over empirical treatment of suspected IFI, including earlier diagnosis and reduced use of antifungal drugs, with no increase in mortality. There are arguments that a strategy of regular combined FBs for the early detection of IFI could be a viable alternative to PAC in efforts to reduce antifungal use. However, neither of the existing most commonly used biomarkers is perfect (Table 1), and they have not currently been evaluated in the outpatient setting in place of PAC, and their role thus remains uncertain.[11,12] Aside from challenges related to test sensitivity and interpretation, significant challenges exist with respect to turnaround time for FBs in many UK laboratories. Few centres have sufficient testing volumes to introduce the assays in house in their current format and most therefore rely on send-away testing in reference laboratories. In our large teaching hospital this results in a median turnaround time of 7 days. Such a delay is inappropriate in the context of an assay used to initiate pre-emptive antifungal therapy in a high-risk patient group.

Local incidence and epidemiology of fungal disease is important in guiding decisions about cost and clinical effectiveness of PAC or an FB-driven approach.[13] Some centres are no longer using posaconazole as PAC. Centres in the Netherlands have used a national rate of invasive pulmonary aspergillosis below 10% to justify the prophylactic use of fluconazole alongside serial GM monitoring.[14] A centre in Korea reported concerns about resistance and drug interactions of PAC as motivation for trialling a pause in fluconazole prophylaxis in its haematology patients.[15]

An interesting parallel can be drawn with the use of fluoroquinolone (FQ) prophylaxis in the haematology setting, which has also been shown to reduce bloodstream infections but with conflicting evidence for mortality benefit.[16] There has been a large rise in FQ resistance since the original studies were performed, which now brings in to question the continuing benefit of its use. Along with concerns about side effects, this has led several centres in the UK to discontinue FQ prophylaxis.[17] A similar narrative could be constructed for azole PAC, especially given the relative paucity of currently licensed alternative treatment agents. In view of the evidence for PAC benefit, this would have to be justified by improvements in prevention, risk stratification or early diagnosis of IFI.

In this issue of *JAC-Antimicrobial Resistance*, Howard *et al.*[18] argue in favour of continuing PAC in patients with acute leukaemia receiving systemic chemotherapy, citing the multiple randomized control trials and meta-analyses that demonstrate its efficacy. Taynton *et al.*[19] argue that FB surveillance for IFI in the absence of PAC is a safe alternative that could reduce antifungal use and the development of resistance. It will become clear that there is no direct head-to-head comparison of these interventions, which highlights the importance of future research in this area. We welcome the news that the multicentre randomized controlled trial BioDriveAFS,[20] which starts recruitment in the UK in 2022, has been funded and hope that it will help to resolve the controversy in this area.

Transparency declarations

Thomas Harrison has none to declare. David Partridge was local PI for a Pfizer-sponsored study within the last 3 years.

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