Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Synthesis
Number 01 March 2019

Pre-emptive antifungal strategies incorporating galactomannan (GM) testing and/or polymerase chain reaction (PCR) assays compared with empirical antifungal strategies for invasive *Aspergillus* infection in patients with haematological malignancies

What were we asked to look at?

The Scottish Antimicrobial Prescribing Group (SAPG) asked us to look at pre-emptive strategies incorporating galactomannan (GM) testing and/or polymerase chain reaction (PCR) assays compared with empirical antifungal treatment strategies for invasive *Aspergillus* infection in patients with haematological malignancies.

Why is this important?

Patients receiving treatments for haematological malignancies often experience severe and prolonged neutropenia which puts them at risk of life-threatening invasive fungal infections including *Aspergillus* infection. Since current diagnostic methods have poor sensitivity and can be slow, overuse of empirical antifungal therapies in this clinical setting is a significant problem which exposes patients to potential harms of treatment from which they derive no benefit. Resistance to antifungal medications is emerging as a serious threat. Our review assesses whether pre-emptive antifungal strategies incorporating novel biomarker tests could potentially address these issues.

What was our approach?

We produced an evidence synthesis; examining evidence published up to 31 October 2018 on the clinical effectiveness, cost effectiveness and safety of pre-emptive antifungal strategies. Information on our evidence synthesis product is here.

What next?

SAPG will use the findings of this work to inform the development of good practice recommendations for suspected fungal infection in haemato-oncology patients as part of their antifungal stewardship programme.

Key findings

- Six randomised controlled trials (RCTs) were identified, of which two were of good methodological quality. Two systematic reviews, incorporating four of these RCTs alongside comparative and non-comparative observational studies, were also identified.
- Pre-emptive strategies are not standardised and the contribution of test findings to prescribing decisions varies. Protocols vary widely across the published literature, as does the use of prophylactic antifungal agents. Trials employ a wide range of patient inclusion criteria meaning that invasive fungal infection risk varies across studies. There is also heterogeneity across empirical strategies, measures of antifungal use and means of classifying invasive fungal infections.
- Whilst it is not possible to reach robust conclusions from this heterogeneous evidence base, trials suggest that the use of pre-emptive strategies incorporating test findings may result in improved rates of identification of invasive fungal infection and reduced use of empirical antifungal medications.
- There is no strong evidence that these potential benefits can be attained without adverse effects on mortality, meaning that there is substantial uncertainty surrounding the safety of pre-emptive strategies.
- Cost-effectiveness evidence is subject to similar issues of heterogeneity, and the applicability of some economic analyses to the UK context may be limited.
- One Australian economic study reported a non-significant difference in costs between a pre-emptive diagnostic-driven strategy and an empirical approach. Another study found a small difference in costs between the strategies, but was undermined by a lack of clarity around reporting and transcription. There was heterogeneity in the strategies analysed and the applicability of these findings may be limited by the local approach to empirical/pre-emptive antifungal treatment and cost setting. A UK economic study reported a large cost saving associated with the diagnostic-driven strategy, but methodological weaknesses relating to model design and data inputs were identified, and the reporting was unclear.
- Uncertainty may be resolved on publication of a large (n=556) multicentre European trial comparing an empirical therapy strategy with a strictly defined diagnostic driven strategy. The primary outcome is mortality at 42 days and the investigators anticipate reporting their findings in 2019. NCT01288378

Contents

Literature search

Systematic searches were carried out in an iterative fashion due to the complexity of identifying relevant studies. Terms used in the three searches included: galactomannan, PCR, anti-fungal, *Aspergillus*, *Candida* and allergic bronchopulmonary aspergillosis. A full list of resources searched and terms used are available on request.

An initial systematic search of the primary and secondary literature was carried out between 7-12 September 2017 to identify systematic reviews, health technology assessments, guidelines, other evidence based reports and randomised controlled trials (RCTs) and observational studies. Medline and Embase databases were searched for reviews and RCTs. Results were limited to dates between 2006 and September 2017 and limited to English language. Filters used were the McMaster reviews filter and the Cochrane RCT filter in Medline and the SIGN RCT filter in Embase.

Medline and Embase were searched on 12 July 2018 using the terms Aspergillus and biomarkers, galactomannan and PCR and terms for haemato-oncology. No filters on date or study type were used. Studies in English language only were included.

Medline and Embase were searched on 31 October 2018 specifically to update a 2015 systematic review[1]. Search terms included: anti-fungals, fungal infections and terms for haemato-oncology. Results from 2015 to October 2018 in English only were collected. No study filters were used.

Introduction

Invasive *Aspergillus* infection (invasive aspergillosis) (IA) is associated with significant mortality in patients receiving treatment for haematological malignancies[2, 3]. In these patients, prolonged severe neutropenia is the most important risk factor for the development of invasive *Aspergillus*[4, 5]. To avoid delayed diagnosis, and owing to the poor sensitivity of microbial culture and histological methods, standard care to reduce morbidity and mortality in this patient group is empirical treatment with antifungal agents during fever refractory to broad spectrum antibacterial medications[4].

A wide range of diagnosis and treatment strategies have been proposed as alternatives to empiric treatment in order to reduce unnecessary antifungal therapy[1-3]. These include the use of pre-emptive strategies which, in addition to clinical indicators, employ imaging tools such as high resolution computed tomography (HRCT) scans, biomarkers such as galactommannan (GM) and molecular diagnostics such as polymerase chain reactions (PCR) to identify *Aspergillus* DNA. The aim of pre-emptive strategies is to detect infection which can then be treated before overt disease develops.

GM is a cell wall polysaccharide found in most *Aspergillus* species and may be detected in serum, bronchoalveolar lavage fluid (BAL) and other body fluids during active infection[2]. Detection of GM forms part of the criteria for probable invasive aspergillosis set out by the

European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).[6]

PCR assays target specific genetic sequences for detection of *Aspergillus* in blood or BAL.

This Evidence Synthesis compares the use of pre-emptive strategies incorporating galactomannan (GM) and/or polymerase chain reaction (PCR) assays, with empirical strategies; examining outcomes related to treatment of invasive *Aspergillus* disease and the potential to address the emerging problem of antifungal resistance.

Outcomes of interest include rates of use and duration of use of antifungal therapies, cost/cost-effectiveness, 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

The Platelia™ Aspergillus GM antigen enzyme immunoassay (EIA) (BioRad, Marnes-la-Cocquette, France) has been validated for detection of GM in serum and BAL fluid. The presence or absence of GM antigen in the test sample is determined by calculation of an optical density index (ODI) for each patient specimen. The manufacturer states that serum or BAL fluid samples with an ODI ≥ 0.50 are considered to be positive for galactomannan antigen[7]. When using an ODI of 0.50 as a cut-off value, a Cochrane review reported that the sensitivity of the test was 78% (95% CI 70% to 85%) and the specificity was 85% (95% Confidence Interval (CI) 78% to 91%) for identifying proven or probable aspergillosis in immunocompromised patients[8]. European guidelines for diagnosis and management of *Aspergillus* diseases notes that GM detection in fluids is more sensitive than culture for diagnosis of IA in haematological patients in the absence of mould-active prophylaxis. The guidelines recommend that serial GM screening should not be used in patients on mould-active prophylaxis[4]. GM testing does not identify non-*Aspergillus* moulds such as those belonging to the order *Mucorales*[3].

PCR assays allow pathogen DNA detection and identification to the species level in a variety of clinical samples. A wide variety of in-house and commercial PCR assays are available to detect *Aspergillus* species. Commercial platforms include:[9]

- AsperGenius® (PathoNostics, Maastricht, Netherlands)
- MycAssay *Aspergillus*® (Myconostica Ltd., Cambridge, United Kingdom)
- MycoReal *Aspergillus*® (Ingenetix GmbH, Austria)
- RenDX Fungiplex® (Renishaw Diagnostics Ltd., Glasgow, United Kingdom)
- MycoGenie® (Ademtech, Pessac, France)
- LightCycler SeptiFast® (Roche Molecular Diagnostics, Penzberg, Germany)

- GeneProof *Aspergillus* PCR® (Brno, Czechia)
- *Aspergillus* spp. Alert Kit® (Nanogen, now ELITechGroup, Turin, Italy)
- *Aspergillus* Real-time PCR Panel® (Viracor Eurofins, Framingham, MA, United States)
- *A. fumigatus*® Bio-Evolution (Bio-Evolution, Bry-sur-Marne, France)
- Fungiplex *Aspergillus*® (Bruker Daltonik GmbH, Bremen, Germany)

In a meta-analysis of 18 studies of the diagnostic accuracy of PCR for detection of invasive *Aspergillus* (IA) in a population of patients at risk of IA, the sensitivity and specificity of PCR blood assays for the diagnosis of IA varied according to the interpretative criteria used to define a test as positive. The mean sensitivity and specificity were 80.5% (95% CI 73.0% to 86.3%) and 78.5% (95% CI 67.8% to 86.4%) for a single positive test result, and 58.0% (95% CI 36.5% to 76.8%) and 96.2% (95% CI 89.6% to 98.6%) where two consecutive positive test results were required to characterise a positive finding[10]. Subgroup analysis indicated that antifungal prophylaxis may impair test performance.

European guidelines for diagnosis and management of *Aspergillus* diseases states that prospective screening of high-risk haematological patients by combining GM and PCR improves diagnostic accuracy and is associated with an earlier diagnosis[4].

Epidemiology

Invasive mould infections (proven or probable) - most commonly invasive pulmonary aspergillosis, are identified in an estimated 11-18% of patients with acute myeloid leukaemia, in 5-10% of patients who are allogeneic haematopoietic stem cell transplant (HSCT) recipients, and in up to 10% of patients with acute or heavily treated chronic lymphoid leukaemia[11]. A total of 2,455 haematological cancers were registered in Scotland in 2016. Table 1 notes the number of registrations of selected haematological cancers in that year.

In 2016 there were 42 adults who had HSCT for a haematological cancer (D Clark, Information Analyst, ISD Scotland. Personal Communication, 11 Jan 2019).

Table 1: number of registrations of selected haematological cancers in Scotland in 2016[12]

Diagnosis	Registrations 2016 Males (all ages)	Registrations 2016 Females (all ages)	Registrations 2016 Total
Acute lymphoblastic leukaemia (ALL)	50	24	74
Acute myeloblastic leukaemia (AML)	85	84	169
Chronic lymphocytic leukaemia (B-cell)	105	49	154
Chronic myeloid leukaemia	31	26	57
Multiple myeloma and plasma cell neoplasms	255	198	453
Non-Hodgkin lymphoma	573	449	1,022
Hodgkin lymphoma	82	68	150

Clinical effectiveness

Systematic reviews and guidelines

A systematic review with meta-analysis compared empirical strategies with pre-emptive antifungal strategies in patients with haematological cancers who had high risk febrile neutropenia [1]. The authors included five randomised controlled trials (RCTs) and four non-randomised studies identified up to June 2015. Although methodological quality of included studies was assessed, this was not used in the meta-analysis of clinical outcomes. The analysis reported that pre-emptive approaches may decrease antifungal use (RR=0.48, 95% CI 0.27 to 0.85) and increase detection of invasive fungal disease (RR= 1.47, 95% CI 0.55 to 3.96). We identified at least one data transcription error in the mortality analysis so findings for this outcome have been disregarded here.

Australian consensus guidelines systematically searched for studies from 2007 to 2014 identifying 5 RCTs and 7 observational studies.[2] Based on these, a narrative synthesis concluded that, compared with empirical treatment strategies, pre-emptive strategies have

the potential to reduce use of and costs of antifungal therapy, improve the ability to diagnose invasive aspergillosis and enable earlier diagnosis than culture and histology and, at a minimum, have no adverse effect on survival. The guideline recommended that pre-emptive strategies can be used in clinical practice but the choice of diagnostic tools and type of strategy should be adapted to local resources and type of antifungal prophylaxis used. The guidelines suggest that the development of pre-emptive strategies requires involvement of stakeholders including haematologists, infectious diseases specialists, microbiologists, respiratory physicians, histopathologists and pharmacists due to the impact on service infrastructure and the need for rapid turnaround of laboratory and imaging investigations.

Randomised controlled trials

Six RCTs were identified. Four of these were incorporated into the systematic review and the consensus guideline outlined above. Two were published more recently. The RCTs are described here to explore the variation in interventions, patient groups and outcomes. Trials compared the effectiveness of empirical strategies with either surveillance-driven (also referred to as diagnostic driven) pre-emptive strategies or clinically-driven pre-emptive strategies. In the surveillance-driven approach, laboratory markers of infection are used at regular intervals throughout the period of risk of invasive fungal disease (IFD) whilst, for the clinically-driven approach, markers of infection are used only in the presence of persistent fever or other stated clinical features[2].

Within pre-emptive strategies, laboratory tests are not used in isolation from imaging and clinical indications of invasive fungal infection (IFI). Commonly incorporated features from protocols in the literature include:

- Characteristic abnormalities on HRCT
- Pneumonia or acute sinusitis
- Positive histopathology or culture from any sterile site
- Mucositis
- Septic shock
- Skin lesion suggesting IFI
- Unexplained central nervous system symptoms
- Peri-orbital inflammation
- Hepatic abscess
- Severe diarrhoea

Surveillance-driven strategies compared with empirical treatment

Table 2 outlines the parameters of three RCTs comparing surveillance-driven pre-emptive strategies with empirical strategies.

In an open label RCT conducted in Australia, Morrissey et al used GM (Platelia Aspergillus Ag Kit BioRad) and PCR (in house nested qualitative real time PCR format incorporating an *Aspergillus* specific TaqMan probe) in combination within their pre-emptive strategy[13]. The comparator was a standard diagnostic strategy where suspicion of invasive fungal disease due to persistent fever triggered empirical antifungal therapy and investigations including culture, histology and high resolution chest CT. Therapy was continued, changed or de-escalated according to test results.

The primary outcome was the proportion of patients receiving at least one course of empirical antifungal treatment, i.e. treating without any proven/probable/possible invasive fungal disease (IFD), within 26 weeks of randomisation in both groups. Treatment based solely on a single positive galactomannan or PCR result in the biomarker based strategy group was classified as empirical. In the empirical strategy group 32% (39/122) of patients received treatment in the absence of proven/probable/possible IFD whilst in the pre-emptive strategy group only 15% (18/118) of patients received such treatment, a between group difference of 17% (95% CI 4% to 26%), RR 0.48 (95% CI 0.29 to 0.79), p=0.002. When combining proven, probable and possible cases there were more cases of invasive aspergillosis diagnosed in the pre-emptive strategy group (23/118) than in the empirical strategy group (1/122). For patients in the biomarker group, 55% of cases of invasive aspergillosis were diagnosed in the absence of persistent fever. Unmasking of biomarker findings for the empirical strategy group, which were not available to clinicians, identified that the standard diagnosis group (empirical) had a similar incidence of invasive aspergillosis. This suggests that invasive aspergillosis was underdiagnosed by the standard strategy.

There was no statistically significant difference in mortality between the study groups although the study was not powered for this outcome.

The proportions of patients with nephrotoxic effects or hepatotoxic effects did not differ significantly between study groups.

Subgroup analysis examined the effect of mould-active prophylaxis and suggested that intensive biomarker screening is most useful in the context of no prophylaxis or where patients are receiving fluconazole or itraconazole. These findings indicate that biomarker screening may be considered as an alternative to voriconazole or posaconazole prophylaxis in specific high-risk groups.

Tan compared empirical treatment with a pre-emptive strategy focused on twice weekly GM testing in patients aged 12 and over undergoing treatments for haematological

malignancies (n=47)[14]. All patients were receiving itraconazole for *Candida* prophylaxis. The primary outcome was the use of broad spectrum antifungal agents. The study found that 33% (9/27) of patients in the pre-emptive arm were started on antifungals whilst for the empirical therapy group the figure was 44% (11/25). The difference was not statistically significant. Findings are compromised in this trial through issues around compliance with study protocol. The trial was stopped early because the distinction between study arms was lost when the GM test became freely available for clinicians to request.

Hebart compared empirical therapy with a pre-emptive strategy based on PCR testing (twice weekly till day 30 then once weekly) for *Aspergillus* or *Candida* DNA in patients undergoing allogeneic stem-cell transplantation[15]. Patients in the PCR arm had either empirical therapy based on fever or with the aim of instigating earlier treatment, based on a single positive PCR result. The primary outcome was incidence of invasive fungal infection at 100 days after transplantation (proven and probable). For both groups this was 8.2%. The trial was stopped early due to a lower than anticipated rate of invasive fungal infection in the empirical therapy group being noted at an interim analysis making the study underpowered. In addition, adherence to PCR testing was poor. At five weeks post-transplant only 24% of participants had blood samples analysed twice weekly.

Table 2: randomised controlled trials comparing surveillance driven pre-emptive strategies with empirical strategies

Study / Location/N	Patient group	Empirical strategy	Pre-emptive strategy
Morrissey 2013[13] Australia Multicentre n=240	Adults (≥18) undergoing allogeneic stem-cell transplantation or intensive combination induction-consolidation chemotherapy for acute myeloid or lymphoblastic leukaemia. 79% of participants on fluconazole or itraconazole prophylaxis, 17% on voriconazole or	Antifungal medications started after persistent fever on 3-5 consecutive days - and revised in light of standard investigations including high resolution chest CT.	GM (optical density index cut off ≥0.5) and PCR testing once (outpatients) or twice (inpatients) per week with single positive result, or serially negative results in persisting neutropenic fever, prompting high resolution chest CT - with antifungal treatment if radiology criteria met.

	posaconazole prophylaxis.		
Tan 2011[14] Singapore Single centre n=47	Age ≥12 with acute leukaemia or high risk myelodysplastic syndrome, on consolidation regimens or HSCT recipients (allogeneic or autologous). Itraconazole prophylaxis.	Antifungal therapy in accordance with established guidelines.	All patients screened twice weekly with GM Antifungal therapy if two positive GM (Optical density index cut off ≥1.5) or positive chest CT after positive GM.
Hebart 2009[15] Germany Multicentre n= 403	Patients receiving allogeneic stem-cell transplant. Fluconazole and/or amphotericin B suspension prophylaxis.	Antifungal medications started after 5 days of febrile neutropenia not responding to broad spectrum antibacterial therapy.	PCR detection of clinically relevant *Aspergillus* and *Candida* species twice weekly to day 30 followed by once weekly from day 30 to day 90. Antifungal medication started after one positive PCR result or after 5 days of febrile neutropenia not responding to broad spectrum antibacterial therapy.

Clinically-driven strategies compared with empirical treatment

Table 3 outlines the parameters of 3 RCTs comparing clinically driven pre-emptive strategies with empirical strategies.

In a well conducted non-inferiority trial (n=293) conducted in 13 centres across France, Cordonnier compared empirical treatment with a pre-emptive strategy incorporating clinical parameters, imaging and twice weekly GM screening[16]. A high ODI cut-off of ≥1.5 was used in this study. The primary outcome was the proportion of patients alive at 14 days after recovery from neutropenia. Overall survival, for patients receiving consolidation or induction therapy or transplant was not lower with pre-emptive treatment (95.1%) than with empirical treatment (97.3%), difference -2.2% (95% CI -5.95% to 1.4%) p=0.31. In exploratory subgroup analyses the 8% pre-specified non-inferiority margin was included in the 95% confidence interval for the difference in survival in the subgroup of patients receiving induction therapy (n=151) so inferiority of the pre-emptive strategy in this group could not be ruled out.

Incidence of invasive fungal infection (including *Aspergillus* and *Candida*) was significantly higher in the pre-emptive strategy arm RR=3.41 (95% CI 1.14 to 10.21) p<0.02, and rate of antifungal use was significantly lower in the pre-emptive treatment arm RR=0.64 (95% CI 0.50 to 0.81) p<0.001.

Antifungal prophylaxis was at the discretion of the study centre and 42% of participants in the empirical strategy arm received prophylaxis, the most frequently used being amphotericin. In the pre-emptive strategy arm amphotericin was also the most frequently used agent and 48% of participants had some form of prophylaxis.

A study conducted in Chile focused on children (n=149) with cancer (mainly leukaemia or lymphoma) and high risk febrile neutropenia[17]. The trial compared empirical antifungal treatment starting on day 4 of fever with a clinically driven pre-emptive strategy incorporating a number of clinical, laboratory and imaging parameters indicative of invasive fungal disease, one of which was GM testing. Antifungal therapy could be initiated based on a single positive GM test. The monitoring frequency with which the parameters were investigated is not clear from the study report. The primary (non-inferiority) endpoint was overall mortality at day 30. Non-inferiority margins were not stated. There was no significant difference between study groups RR 0.64 (95% CI 0.19 to 2.18) p=0.47. As a secondary outcome, it was noted that 58% of children in the pre-emptive strategy group did not require initiation of antifungals. The median number of days of antifungal therapy was 11 in the empirical arm and six in the pre-emptive arm (p<0.001). Nine children in each study arm were diagnosed with proven or probable invasive fungal disease. No significant difference between study arms was identified for this outcome RR= 0.96 (95% CI 0.40 to 2.28) p=0.92; *Candida* and *Aspergillus* were the most frequently identified organisms.

A poorly reported study compared empirical therapy with pre-emptive therapy in adults with haematological malignancy who were undergoing chemotherapy and had severe neutropenia of 10 days or more duration[18]. Randomisation procedures were not described and, from the study report, the differences between procedures used in the two study arms were unclear. The description of per-protocol and intention to treat population was not well delineated. The primary outcome was survival rate of patients who recovered from neutropenia by day 14. There was no significant difference between the treatment arms, RR= -2.5 (95% CI -5.9 to 1.4), p=0.305. The overall survival rate was 94.6% for pre-emptive group, 97.1% in the empirical group. No information was provided on whether the study was sufficiently powered for this outcome.

Table 3: randomised controlled trials comparing clinically driven pre-emptive strategies with empirical strategies

Study / Location/N	Patient group	Empirical strategy	Pre-emptive strategy
Cordonnier 2009[16] France Multicentre n=293	Adults with haematological malignancies undergoing for chemotherapy or autologous stem cell transplantation expected to cause neutropenia for at least 10 days. 45% of study population had antifungal prophylaxis as per centre protocol	Initiation of antifungal therapy after persistent or recurrent fever (≥4 days).	Antifungal therapy if positive GM (Optical density index cut off ≥1.5) and/or clinical indications or imaging suggestive of invasive fungal infection after 4 days of fever and antibacterial treatment. All patients screened twice weekly with GM.
Santolaya 2018[17] Chile Mulitcentre	Children (≤18) with cancer (>80% had leukaemia or lymphoma) and high risk febrile neutropenia. Those having HSCT or on antifungal	Initiation of antifungal therapy on day 4 of neutropenic fever despite antimicrobial treatment.	Antifungal therapy only initiated if clinical indications or imaging findings suggestive of invasive fungal infection or if there was a single positive

n=149	prophylaxis were excluded.		GM or positive mycological finding.
Yuan 2016[18] China Single centre n=268	Adults with haematological malignancy undergoing chemotherapy and severe neutropenia of ≥10 days. 83% of study population had antifungal prophylaxis.	Antifungal therapy started within 4 days of start of persistent fever and antibacterial treatment.	Antifungal therapy only initiated if clinical indications or imaging findings suggestive of invasive fungal infection or biomarkers test positive (beta-D-glucan test or galactomannan test).

Ongoing studies

The Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC) is currently conducting a trial comparing an empirical therapy strategy with a strictly defined diagnostic driven strategy in patients at high risk of invasive fungal infection. Patients will be stratified according to institution, prior allogeneic stem cell transplantation, and type of air flow (laminar air flow vs high-efficiency particulate air). The primary outcome is survival at six weeks following randomisation. The study enrolled 556 participants and it is anticipated that findings will be available during 2019. NCT01288378

Safety

No safety issues related to conducting GM or PCR assays were identified in the literature examined for this Evidence Synthesis.

Patient and social aspects

Pre-emptive strategies for antifungal use may help patients receiving treatment for haematological malignancies to avoid harms associated with unnecessary use of antifungal medications. 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. Resistance to antifungal

medications is emerging as a serious threat which could lead to untreatable infections and make routine surgery or chemotherapy much more hazardous [19, 20].

Cost effectiveness

Three potentially relevant studies were excluded from this review owing to irrelevant clinical context or lack of appropriate comparisons[18, 21, 22].

Three economic evaluations were identified that compared various forms of pre-emptive diagnostic-driven antifungal treatment strategies with an empirical treatment strategy[1, 23, 24]. Two utilised decision analytic models to estimate the relative cost/cost-effectiveness of the strategies based on clinical parameters derived from the literature[1, 23] while one used a 'real-world evidence' approach by prospectively comparing the relative cost-effectiveness on the back of a pragmatic RCT[24].

Barnes et al. (2015)[23] developed an economic model comparing an empirical strategy with conventional amphotericin B (in 3.51% of patients), liposomal amphotericin B (57.86%), or caspofungin (38.63%), versus a diagnostic-driven (DD) (surveillance-driven) strategy - initiated based on positive results for GM and/or PCR - using conventional amphotericin B (2.33%), liposomal amphotericin B (52.75%), or voriconazole (44.92%)[23]. Additionally, all patients in the DD strategy group received prophylaxis with fluconazole. Patients in the model were adults with haematologic malignancies, undergoing chemotherapy or autologous/allogeneic hematopoietic stem cell transplantation, and were expected to be severely neutropenic for ≥10 days. Incidence of IFD (10.9%), overall mortality (10.7%), and IFD-related mortality (28.6%) in this population were obtained from epidemiological studies in a German tertiary care centre. The targeted use of antifungal therapy (AF) with caspofungin and voriconazole improved survival by a hazard ratio of 0.59 compared with the amphotericin-based agents in the model. The GM and PCR tests were assumed to have a sensitivity of 67.7% and the empirical strategy was assumed to identify 30% of IFD cases. Adverse events in the model were those that occurred in ≥10% of patients in the empirical trials for the AF agents used and were limited to nephrotoxicity, tachycardia, and hypertension. The model was developed from a UK health service perspective over a time horizon of 5 months and costs were estimated in 2012 British pounds sterling by using standard UK costing sources.

Total cost per patient was 32% lower with the DD strategy (£1,561.29) versus the empirical strategy (£2,301.93), mainly driven by a 41% decrease in the use of AF agents in the DD strategy group. The costs relating to GM and PCR testing were an incremental cost of £27.46 per patient. The probability of survival at 5 months was similar in the DD strategy group (90.8%) compared with the empirical strategy group (89.8%). In the one-way sensitivity analysis, results were most sensitive to test sensitivity, the relative increase in the number of patients treated in empirical versus DD approach (1.70 baseline), IFD incidence (which varies between centres and populations), and duration of treatment with liposomal amphotericin B. In the probabilistic sensitivity analysis the DD strategy was found to be less

costly, while also more effective in 90.16% of instances (preventing deaths). The study authors report multiple conflicts of interest.

The following key uncertainties and limitations were identified with respect to this study:

- Proportion of patients treated in the DD group: The impact of false negative and false positive results linked to the imperfect nature of the diagnostic tests is not explicitly modelled. The likely impact of this structural limitation in the model is an underestimation of costs and mortality in the DD group.

- Proportion of patients treated in the empirical group: It is assumed 70% more cases are treated in the empirical group compared with the DD group but there appears to be no justification or reference for this assumption. It also appears the empirical strategy is not missing any IFD patients within the model, which is unlikely since this assumption would only hold if all patients with IFD present with neutropenic fever and signs of infection, and hence are treated according to the empirical protocol.

- Resource use: The distribution of AF agents used differs between the DD group and the empirical group. Caspofungin is used in the empirical group which is more costly compared to the voriconazole used in the DD group which may inflate the saving estimated but the effect is not likely to be very large.

- Screening algorithm: The DD strategy included four diagnostic tools (patients began AF therapy when they were suspected of having IFD based on: characteristic lesions on CT scan; *Aspergillus* species colonization; and/or positive ELISA results for GM; and/or positive results on the PCR assay) but it is not clear whether a suite of tests/tools was used or not and how this relates to the clinical accuracy data used in the model.

- IFD mortality: A much higher IFD-related mortality rate for amphotericin B (40.4%) compared with caspofungin/voriconazole (16.6%) was derived based on an unbalanced sample from a German epidemiological study. In this study, a relatively smaller sample of 15/84 patients received caspofungin/voriconazole, while the rest were assumed to receive amphotericin B for the purpose of deriving mortality for the model in Barnes (2015). However, only 57/84 actually received amphotericin B in the epidemiological study, while 4/84 received no AF treatment which could have inflated the mortality derived for amphotericin B in Barnes (2015).

- Probabilistic sensitivity analysis: The parameters used for the distributions spread are not detailed and hence it was not possible to comment on their appropriateness.

Fung *et al.* (2016) conducted a cost analysis comparing an empirical (fever-directed) strategy, in which patients febrile after four days of broad-spectrum antibiotics start empirical antifungals, with a pre-emptive (diagnostic test-based) strategy, in which patients start pre-emptive antifungal therapy if they have a positive GM test and pneumonia on

chest imaging[1]. However, both groups were assigned the same diagnostic testing strategy consisting of two GM tests per week and one high resolution CT scan, therefore it is not clear how the screening protocols in the two groups differed. The clinical data were derived from a systematic review and meta-analysis summarised in the clinical effectiveness section of this review. Within the comparative costing model, patients in both groups receive antifungals pre-IFD diagnosis at different rates (RR 0.48, 95% CI 0.29-0.79, for pre-emptive group, p<0.01) and different durations (7 days empirical group vs 4.5 days pre-emptive group, p<0.01). Patients in both groups received subsequent AF treatment for another 84 days if they developed incident proven or probable IFD, informed by a relative risk of IFD detection (RR 1.47 for pre-emptive group, p=0.01). Direct costs of drugs and diagnostic testing are derived from US sources and are expressed in 2014 US dollars. Healthcare utilisation and health outcomes for the two groups, beyond specified differences in the antifungal therapeutic strategy and measured clinical outcomes, were assumed to be similar.

During the pre-IFD diagnosis period, the pre-emptive approach costs $594 [UK £461] less than empirical approach ($1,209 [UK £938] pre-emptive vs $1,803 [UK £1,399] empirical) per febrile neutropenic episode, due to a greater rate and duration of antifungal drug exposure using the empirical strategy. Overall, the pre-emptive approach cost $325 [UK £252] less than the empirical approach ($2,054 [UK £1,593] pre-emptive vs $2,378 [UK £1,843] empirical) per febrile neutropenic episode, the difference being partly offset by the higher IFD detection and proportion of patients treated subsequently. Probabilistic sensitivity analysis was conducted to derive 95% credible intervals which showed no significant difference in costs, although the intervals reported did not contain the mean estimates for reasons that are unclear.

Macesic et al. (2017)[24] evaluated the cost effectiveness of a biomarkers-based diagnostic strategy (BDS) compared with a standard diagnostic strategy (SDS) across four hematology and transplant tertiary centers in Australia, using specific costing data from patients enrolled in a pragmatic RCT with 180 days follow-up (Morrisey 2013[13]). Under the SDS strategy empirical treatment was given to patients in whom IFD was suspected, while patients underwent standard investigations including high resolution CT chest scan. The empirical treatment could be continued, de-escalated, or changed depending on whether definite, probable, or possible IA was diagnosed as per the EORTC/MSG criteria. The BDS strategy consisted of GM and PCR testing twice weekly on blood for inpatients and once weekly for outpatients for 26 weeks (or until death), with a single positive GM or PCR, or serially negative results for both tests in patients with persistent neutropenic fevers, prompting high resolution CT scan of chest. IFD was defined according to a modified EORTC/MSG criteria. AF treatment was recommended when the criteria for probable or possible IA or other IFD were met.

The median total costs at 180 days, expressed in 2015 US dollars, between the SDS ($78,774 [UK £61,112]) and BDS ($80,439 [UK £62,404]) arms were not statistically significantly different (p=0.49). Length of stay was also similar between the two groups (median 47 days

vs 52 days, p=0.75). The median cost of GM and PCR testing in the BDS arm was $1,069 [UK £829], based on per sample costs of $14.80 [UK £11.48] and $23.80 [UK £18.46] respectively. When survival was taken into account, the costs per life-year saved were $325,448 [UK £252,480] at 180 days, $81,966 [UK £63,589] at one year, and $3,670 [UK £2,848] at five years respectively, but these results are subject to a high level of uncertainty.

The study only included 137/240 of the patients enrolled in the original RCT for which complete costing data was available. The groups appeared fairly balanced in terms of patient characteristics. Mortality was determined at 180 days based on the RCT data and was extrapolated to five years by fitting the Gompertz survival model. In the underlying RCT there was no statistically significant difference in mortality between the groups and the study was not sufficiently powered to detect such a difference. Likewise, there was no significant difference in all-cause mortality at 180 days between the subsample of patients selected for the cost-effectiveness analysis (14.7% [10/68] for SDS and 10.1% [7/69] for BDS, p=0.573). Despite this, the long-term survival was modelled and extrapolated based on no difference in mortality estimates, and hence the results of the cost-effectiveness analysis are subject to considerable uncertainty. No probabilistic sensitivity analysis was attempted to quantify the uncertainty in model inputs. The data used in the study pertain to the period 2005-2009, hence limiting generalisability to current practice. Also, the costs may not be applicable to the UK setting.

Conclusion

It is not possible to develop robust conclusions since the evidence base is limited by substantial heterogeneity in patient groups, intervention characteristics and outcome measures.
When compared with empirical antifungal treatment strategies, trials suggest that use of pre-emptive strategies incorporating biomarkers may result in improved rates of identification of invasive fungal infection and reduced consumption of empirical antifungal medications. However, there is no strong evidence on which to be certain that these benefits can be attained without adverse effects on mortality for patient groups receiving treatment for haematological malignancies.

The randomised controlled trial of the EORTC (NCT01288378) may provide more certainty to the evidence base.

Two non-UK economic studies reported a small or not significant difference in costs between a pre-emptive diagnostic-driven strategy and an empirical approach. One UK economic study reported a large cost saving associated with a diagnostic-driven strategy, but methodological and reporting problems were identified.

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 syntheses 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

Acknowledgements

The following individuals provided peer-review:

- Dr. Laura Cottom, Consultant Microbiologist, Glasgow Royal Infirmary, NHS GG & C
- Prof. J Peter Donnelly, EORTC Infectious Diseases Group, Brussels, Belgium
- Antonio Pagliuca, Professor of Haematology, King's College, London
- Dr. Jacqueline Sneddon, Project Lead, Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland

Declarations of interest were received from all peer reviewers. All contributions from peer reviewers were considered by the author and Evidence Review Committee. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Lorna Thompson, Health Services Researcher
- Lucian Gaianu, Senior Health Economist
- Carolyn Sleith, Information Scientist
- Paula O'Brien, Project Team Member
- Anne O'Connor, Admin Officer
- Members of the SHTG Evidence Review Committee

Published April 2019

References

1. Fung M, Kim J, Marty FM, Schwarzinger M, Koo S. Meta-analysis and cost comparison of empirical versus pre-emptive antifungal strategies in hematologic malignancy patients with high-risk febrile neutropenia. PLoS One. 2015;10(11):e0140930.
2. Morrissey CO, Gilroy NM, Macesic N, Walker P, Ananda-Rajah M, May M*, et al.* Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014. Intern Med J. 2014;44(12b):1298-314.
3. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother. 2017;72(Suppl 1):i19-28.
4. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K*, et al.* Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24 Suppl 1:e1-38.
5. Vazquez L, Salavert M, Gayoso J, Lizasoain M, Ruiz Camps I, Di Benedetto N*, et al.* Delphi-based study and analysis of key risk factors for invasive fungal infection in haematological patients. Rev Esp Quimioter. 2017;30(2):103-17.
6. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T*, et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis: 2008;46(12):1813-21.
7. Bio-Rad laboratories. Platelia Aspergillus Ag. 2013 [cited 2019 Mar 08]; Available from: http://www.bio-rad.com/webroot/web/pdf/inserts/CDG/en/62794_881115_EN.pdf
8. Leeflang MM, Debets-Ossenkopp YJ, Wang J, Visser CE, Scholten RJ, Hooft L*, et al.* Galactomannan detection for invasive aspergillosis in immunocompromised patients. The Cochrane Database of Systematic Reviews. 2015, Issue 12.
9. Rath P-M, Steinmann J. Overview of commercially available PCR assays for the detection of Aspergillus spp. DNA in patient samples. Front in Microbiol. 2018;9:740.
10. Cruciani M, Mengoli C, Loeffler J, Donnelly P, Barnes R, Jones BL*, et al.* Polymerase chain reaction blood tests for the diagnosis of invasive aspergillosis in immunocompromised people. Cochrane Database of Systematic Reviews. 2015 Issue 10.
11. Colombo AL, de Almeida Junior JN, Slavin MA, Chen SC, Sorrell TC. Candida and invasive mould diseases in non-neutropenic critically ill patients and patients with haematological cancer. Lancet Infect Dis. 2017;17(11):e344-56.
12. ISD Scotland. Cancer incidence in Scotland (2016). 2018 [cited 2019 Mar 08]; Available from: https://www.isdscotland.org/Health-Topics/Cancer/Publications/data-tables2017.asp?id=2148#2148
13. Morrissey CO, Chen SC, Sorrell TC, Milliken S, Bardy PG, Bradstock KF*, et al.* Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. Lancet Infect Dis. 2013;13(6):519-28.
14. Tan BH, Low JG, Chlebicka NL, Kurup A, Cheah FK, Lin RT*, et al.* Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study. Int J Infect Dis. 2011;15(5):e350-6.
15. Hebart H, Klingspor L, Klingebiel T, Loeffler J, Tollemar J, Ljungman P*, et al.* A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. Bone Marrow Transplant. 2009;43(7):553-61.
16. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F*, et al.* Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis. 2009;48(8):1042-51.

17. Santolaya ME, Alvarez AM, Acuna M, Aviles CL, Salgado C, Tordecilla J*, et al.* Efficacy of pre-emptive versus empirical antifungal therapy in children with cancer and high-risk febrile neutropenia: a randomized clinical trial. J Antimicrob Chemother. 2018;73(10):2860-6.
18. Yuan W, Ren J, Guo X, Cai S. Preemptive antifungal therapy for febrile neutropenic hematological malignancy patients in China. Med Sci Monit. 2016;22:4226-32.
19. Health Protection Scotland. Scottish one health antimicrobial use and antimicrobial resistance in 2017. [cited 2019 Mar 08] Available from: https://www.hps.scot.nhs.uk/haiic/amr/spotlightdetail.aspx?id=22826
20. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17(12):e383-92.
21. Ceesay MM, Sadique Z, Harris R, Ehrlich A, Adams EJ, Pagliuca A. Prospective evaluation of the cost of diagnosis and treatment of invasive fungal disease in a cohort of adult haematology patients in the UK. J Antimicrob Chemother. 2015;70(4):1175-81.
22. Mao N, Lesher B, Liu Q, Qin L, Chen Y, Gao X*, et al.* Economic analysis of empiric versus diagnostic-driven strategies for immunocompromised patients with suspected fungal infections in the People's Republic of China. Clinicoecon Outcomes Res. 2016;8:275-85.
23. Barnes R, Earnshaw S, Herbrecht R, Morrissey O, Slavin M, Bow E*, et al.* Economic comparison of an empirical versus diagnostic-driven strategy for treating invasive fungal disease in immunocompromised atients. Clin Ther. 2015;37(6):1317-28.
24. Macesic N, Morrissey CO, Liew D, Bohensky MA, Chen SC, Gilroy NM*, et al.* Is a biomarker-based diagnostic strategy for invasive aspergillosis cost effective in high-risk haematology patients? Med Mycol. 2017;55(7):705-12.