

Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy

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Abstract

Antifungal prophylaxis can be recommended in patients undergoing induction chemotherapy for acute myeloid leukemia and treatment for grade 2 or greater or chronic extensive graft versus host disease. The evidence for prophylaxis is less clear in other clinical settings although certain groups such as patients with prolonged neutropenia after stem cell transplants using bone marrow or cord blood sources and with impaired cell mediated immunity secondary to treatments such as Alemtuzumab are at high risk. The decision to use prophylaxis and which agent to use will be influenced by effectiveness, number needed to treat and the likelihood of toxicity and drug interactions. The availability of rapid diagnostic tests for fungal infection and institutional epidemiology will also influence the need for and choice of prophylaxis. Whilst prophylaxis can be beneficial, it may impede the ability to make a rapid diagnosis of fungal infection by reducing the yield of diagnostic tests and change the epidemiology of fungal infection. As non-culture based diagnostic tests are refined and become more available there may be a shift from prophylaxis to early diagnosis and treatment.

Candida infections were previously the leading cause of invasive fungal infection (IFI) during prolonged neutropenia and transplantation.^{1,2} The introduction of novel antifungal, antiviral and antineoplastic agents over the past 10 years, however, has led to a shift in fungal epidemiology;^{3–5} in most centres, invasive mould infections (e.g. *Aspergillus*) are now the major infectious cause of morbidity and mortality in patients with haematological malignancy. In patients with solid tumours, mould infections are rare,⁶ and invasive candidiasis (IC) remains the most common fungal infection.⁷ Most IFIs are diagnosed late and mortality remains high. Unless techniques enabling earlier diagnosis of IFI are refined, prophylaxis

will remain an important 'preventive' strategy for patients at high risk of developing an IFI.⁸

Rationale for antifungal prophylaxis

Determining a patient's risk of developing an IFI provides a practical approach to deciding if antifungal prophylaxis is warranted. The patient population, types of chemotherapy and interventions being used, and the incidence of IFIs in a treating centre (which can vary between centres treating the same population), can all influence a patient's risk.⁹ This risk, however, is not static; changes in practice, increased detection of moulds in the

environment and the presence of building works may all influence a patient's risk of acquiring an IFI. The incidence of IFI within a centre may also be underestimated, particularly if autopsies are not routinely performed.¹⁰

The availability and use of diagnostic tests within a centre – and the experience of a centre in interpreting those tests – may influence whether an infection is diagnosed early, when the outcome is likely to be better; or later, when the outcome is likely to be worse.¹¹ Potential for the latter scenario has tipped the scale towards the more frequent use of prophylaxis in many centres.¹² Whether a more intensive IFI surveillance regimen could be used instead of prophylaxis in high-risk patients is unknown.

McQuay and Moore suggest clinicians pose four questions before adopting prophylaxis: How serious is the event you are trying to prevent (i.e. invasive fungal disease)? How difficult would the event be to treat if it did occur? Is the proposed prophylaxis safe and well tolerated? Is the prophylaxis likely to be effective?¹³

The effectiveness of prophylaxis is often quantified in terms of the number needed to treat (NNT) to prevent one IFI where $NNT = 1/ARR$. The absolute risk reduction (ARR) is calculated by subtracting the incidence of IFI in the intervention group from the incidence of IFI in the control group. For example, in one meta-analysis, prophylactic itraconazole (when effective serum levels were achieved) reduced the incidence of IFI by 53%.¹⁴ This would translate into a relatively low NNT (approximately 13) in a centre where the incidence of IFIs was 15%; however, the NNT would increase to 38 in a centre with an incidence of only 5%. The NNT, along with an estimate of an individual patient's IFI risk, can be a guide to the overall or net value of a prophylactic agent and help shape individual and institutional practice.

Factors to consider when choosing a prophylactic agent

Epidemiological trends, the incidence of infection within a centre and whether those infections are predominantly due to yeasts, moulds or both, will help guide the choice of prophylactic agent. However, clinicians should also take into account drug-related factors such as prophylactic effectiveness; toxicity profile (particularly in patients with pre-existing organ impairment); the likelihood and seriousness of drug interactions; the need for, availability and cost of therapeutic drug monitoring (TDM); the drug's cost and the availability and requirement for an intravenous (IV) route (e.g. mucositis, grade 4 graft versus host disease (GVHD), ileus, neutropenic enterocolitis, malabsorption). The likely duration of infectious risk – and thus, the required duration of pro-

phylaxis, the need for a loading dose and when the drug should be commenced in relation to chemotherapy, should also be considered.

The results of meta-analyses

The role of meta-analyses in assessing antifungal prophylaxis has been contentious. Meta-analyses may be useful for exploring end-points that cannot easily be studied in smaller clinical trials; pooled results increase statistical power. However, their validity is dependent on the quality and homogeneity of the studies included in the analysis. Publication bias can also lead to the inclusion of more positive trials.

Different authors have debated the appropriateness of using end-points such as 'IFI-related mortality' versus 'all-cause mortality' and criticized the techniques (and related conclusions) of others.^{14,15} For example, a study which demonstrates a decline in IFI rates and/or IFI-related mortality without an all-cause mortality benefit may simply reflect the difficulty of establishing a diagnosis in those receiving prophylaxis, rather than the actual prevention of IFI. These discussions are worth reading before reviewing the various prophylaxis meta-analyses (detailed summary tables are available from the author upon request).

The most comprehensive meta-analysis to date compared systemic antifungals with placebo, no intervention or non-systemic antifungal agents for prophylaxis in patients with cancer (largely haematological) after chemotherapy or haematopoietic stem cell transplantation (HSCT).¹⁶ Patients who received prophylaxis had a significant reduction in all-cause mortality. Allogeneic HSCT recipients benefited the most with significant reductions in all-cause mortality, fungal-related mortality and documented IFI. Patients with acute leukaemia had a borderline statistically significant reduction in all-cause mortality but a significant reduction in fungal-related mortality and documented IFI. The number of autologous HSCT recipients was not large enough to draw any firm conclusions but a trend towards a reduction in documented IFI and fungal-related mortality was observed in this group.¹⁶

This meta-analysis also compared outcomes between drugs. Two recent studies included in the meta-analysis compared oral posaconazole with oral fluconazole or itraconazole.^{17,18} Compared with fluconazole alone, posaconazole led to a significant reduction in all-cause mortality, fungal-related mortality and documented IFI. However, not enough patients received itraconazole to allow a valid comparison.

Overall, meta-analyses support the use of prophylaxis in allogeneic HSCT and some acute leukaemia therapy.

Itraconazole is more effective than fluconazole for preventing aspergillosis but is associated with more side-effects^{14,16} and requires systemic levels of >500 ng/mL for efficacy, which are more reliably achieved with the oral solution (level 1 evidence).¹⁴

Evidence-based recommendations for antifungal prophylaxis

Detailed tables summarizing the current evidence base for prophylaxis in patients with profound neutropenia due to haematological malignancy or HSCT is available from the authors upon request. See Table 1 for a summary of the recommendations discussed below.

Prophylaxis for HSCT: early, during neutropenia

The role of fluconazole prophylaxis in HSCT was clearly established in the 1990s (level II evidence).^{2,19} Fluconazole was protective against IFI and led to a reduction in overall mortality when given for 75 days post-bone marrow transplant (BMT)² compared with stopping prophylaxis at the time of engraftment.¹⁹ The effect on mortality persisted in allogeneic HSCT recipients after 8 years of follow up.²⁰ In these studies, *Candida* species caused the majority of IFIs. However, changes in practice, including the use of peripheral blood stem cells rather than bone marrow, growth factors and reduced intensity conditioning regimens, have shortened the duration of post-transplant neutropenia and reduced conditioning

Table 1 Summary of recommendations for antifungal prophylaxis in patients with haematological malignancy or profound neutropenia >10 days

Clinical setting	Recommended prophylaxis (grading of recommendation)	Alternative agent (grading of recommendation)
AML: intensive chemotherapy or induction, re-induction	Posaconazole solution 200 mg oral tds (with fatty food/drink). Start 24 h after last anthracycline or on day of chemotherapy in patients not receiving anthracycline. Continue until neutropenia has resolved and patient in complete remission (B)	Itraconazole 200 mg oral bd (B)†‡
AML: consolidation with high dose therapy	Posaconazole solution 200 mg oral tds (with fatty food/drink). Start 24 h after last anthracycline or on day of chemotherapy in patients not receiving anthracycline. Continue until neutropenia has resolved and patient in complete remission (C)	Itraconazole 200 mg oral bd (C)†
AML: less intensive chemotherapy or standard consolidation	Fluconazole 200 mg/day. Start on admission and continue until neutropenia resolved (D) or no prophylaxis if mucositis unlikely (D)§	
Autologous HSCT	Fluconazole 200–400 mg/day. Start on admission and continue until neutropenia resolved (C) or no prophylaxis if mucositis unlikely§	
Standard allogeneic HSCT, pre-engraftment, e.g. sibling, matched, peripheral blood stem cell source	Fluconazole 400 mg oral daily from admission to day 75 (B)	
Higher risk allogeneic HSCT, pre-engraftment, e.g. cord blood, unrelated donor transplant with bone marrow stem cell source or likely delayed engraftment	Posaconazole solution 200 mg oral tds with fatty food/drink. No grading – see text for discussion. Start after conditioning. Continue until neutropenia resolved. If no GVHD, use fluconazole through to day 75 (D)	Itraconazole 200 mg oral bd (B)‡ Fluconazole 400 mg daily (B)
Allogeneic HSCT grade 2–4 or chronic extensive GVHD	Posaconazole solution 200 mg oral tds until day 112 post-onset GVHD or resolution (B). Monitor cyclosporin, tacrolimus levels and consider dose reduction (see section by Worth <i>et al.</i>)	Itraconazole 200 mg oral bd (B)†‡

†Refer back to the text for discussion of intravenous alternatives, including amphotericin B; ‡Itraconazole solution 200 mg oral bd may be used as an alternative to posaconazole in patients/centres where mould infections are infrequent; §Superficial or oropharyngeal candidiasis may occur if systemic prophylaxis is not used. Itraconazole capsules are an alternative only when turnaround times for drug levels are short (≤2 days). AML, acute myeloid leukaemia; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation.

toxicity and mucositis. Invasive mould infections are now a greater risk for allogeneic HSCT recipients than IC.^{3,4} Although the fluconazole prophylaxis studies were well-conducted, randomized control trials (RCTs) supported by meta-analyses, we have assigned a B grading to the prophylactic use of fluconazole in this setting because of the changes in practice since the studies were first conducted. While the incidence of mould infection is still low in autologous transplants, there is less evidence for the use of fluconazole prophylaxis in this group of patients (grade C recommendation).

Itraconazole and voriconazole have a broader spectrum of activity than fluconazole, offering protection against *Aspergillus* and other moulds. While clearly effective for reducing IFI (level 1 evidence),^{21,22} itraconazole is not an ideal drug in the early post-transplant setting due to drug–drug interactions (e.g. cyclophosphamide²³ and toxicity; approximately 30% of patients need to cease itraconazole for toxicity-related reasons, primarily gastrointestinal intolerance and abnormal liver function tests.^{21,22} Many of these drug interactions are shared by voriconazole. A recent RCT compared the use of voriconazole and fluconazole for 100–180 days post transplant, for the prevention of IFIs in standard risk allogeneic BMT patients. All patients underwent serum galactomannan (GM) monitoring. There were no differences in fungal-free survival rates between the two groups at 6 and 12 months.²⁴

The duration of neutropenia is likely to be longer and the incidence of IFI greater in the early post-transplant period following a matched unrelated donor transplant or if cord blood or bone marrow was used as the source of stem cells. However, there have been no prophylaxis studies specific to these clinical settings. The use of a mould-active agent, such as itraconazole or posaconazole, may be justified in this group, particularly if an institution's incidence of IFI in this population is over 10% or there are additional patient risk factors such as pre-existing neutropenia or severe mucositis (grade D recommendation). Otherwise, fluconazole 400 mg daily is recommended.

Prophylaxis for HSCT: late after engraftment

Attention has recently focused on assessing risk factors for IFI and changing fungal epidemiology. This risk-adjusted approach has practical implications for clinicians. Most centres, including those in Australia, report that pre-engraftment, invasive mould infections are rare; most infections occur in the late post-transplant period, usually in the context of grade 3–4 GVHD.^{3,4,25–29} Ullmann *et al.*, instituted prophylaxis as soon as GVHD (of grade 2 or greater severity or meeting the criteria for chronic

extensive) was diagnosed.¹⁸ This study demonstrated a reduction in IFI in patients receiving posaconazole compared with those receiving fluconazole or itraconazole (level II evidence). However, there were too few patients receiving itraconazole to adequately assess its activity independently. Posaconazole is only available in oral suspension so patients with severe GVHD involving the gastrointestinal tract were not well represented in this study. Despite these limitations, the recommendation for a mould-active agent such as posaconazole in patients who develop \geq grade 2 or chronic, extensive GVHD, can still be assigned a B grading. Clinicians, however, are encouraged to consider the NNT in their institution as well as the grade of a patient's GVHD and likely need for ongoing immunosuppression when instituting prophylaxis; grade 2 GVHD, which is steroid responsive, will not impart the same IFI risk as grade 4 GVHD where the incidence of IFI approaches 50%⁴ and second- and third-line treatment is often required.

Prophylaxis for neutropenia in haematological malignancy

There is a wide range of immunosuppressive regimens for treatment of haematological malignancy. Most prophylaxis studies have been conducted in specific clinical settings, making it difficult to generalize findings to other chemotherapy regimens.

Cornely *et al.*, studied posaconazole versus fluconazole or itraconazole prophylaxis in patients undergoing induction chemotherapy for acute myeloid leukaemia (AML). The results of this trial were encouraging, particularly the improved overall survival rate and reduced incidence of IFI, although diagnosis of IFI relied heavily on GM testing (level II evidence).¹⁷ Thus, we have assigned a B grading to the use of posaconazole in this setting. The study's design does limit our ability to extrapolate its findings, as most patients were undergoing their first cycle of chemotherapy.¹² Whether the favourable results also apply to consolidation chemotherapy, when the incidence of IFI is usually lower, is thus, unclear.³⁰ Consolidation chemotherapy can be as intense as remission induction therapy, particularly in newer treatment regimens; in our opinion mould-active prophylaxis should be used for this type of consolidation therapy (grade C recommendation). The study was also not powered or designed to separate the potential effect of itraconazole from fluconazole so it is unclear whether itraconazole would have been as effective as posaconazole. It does, however, remain an alternative to posaconazole (grade B recommendation). Fluconazole 200 mg/day is an alternative to both for patients receiving less aggressive therapy for AML,

including regimens associated with mucositis and candidaemia (grade D recommendation).

If HSCT or further intensive chemotherapy is planned for the future, a more aggressive approach to antifungal prophylaxis is indicated, as the development of IFI may complicate or delay transplant and/or definitive treatment, leading to a poorer outcome or relapse of haematological malignancy.

Alternatives to oral agents in high-risk patients

Posaconazole is currently only available as an oral formulation. Cornely *et al.*, allowed clinicians to substitute IV conventional amphotericin B (amphotericin B deoxycholate (AmB-D)) for oral posaconazole for up to 4 days; however, patients were discontinued from the study if IV therapy was required for longer.

IV prophylaxis may be used when patients are unable to take oral agents, e.g. GVHD or mucositis. IV formulations of fluconazole, itraconazole and voriconazole have been studied in the setting of allogeneic HSCT.²⁴ Other IV formulations have also been evaluated. Daily micafungin in HSCT recipients during neutropenia was found to be equivalent to fluconazole (level II evidence), but the incidence of *Aspergillus* in this study was too low to assess its potential benefit.³¹ Trials of low-dose AmB-D prophylaxis have been small and inconclusive.^{32,33} Four trials have studied the intermittent administration of lipid amphotericin B products (level III–IV evidence). The first was a non-blinded study of 219 neutropenic episodes in 132 patients with haematological malignancy (predominantly AML) receiving chemotherapy likely to induce long-term neutropenia or undergoing HSCT. Liposomal amphotericin B (L-AMB), 50 mg on alternate days, was compared with no prophylaxis. Prophylaxis reduced the incidence of IFI, including invasive aspergillosis (IA), although most of the *Aspergillus* infections in the placebo arm were probable, not proven.³⁴ The second study compared amphotericin B lipid complex (ABLC), 2.5 mg/kg, administered three times weekly to patients with newly diagnosed AML or high-risk myelodysplasia (MDS) undergoing induction chemotherapy, with a historical control group that had received prophylactic L-AMB, 3 mg/kg, three times weekly. The two regimens led to equivalent rates of IFI.³⁵ The final two studies were small safety studies of L-AMB prophylaxis (7.5–10 mg/kg weekly) in allogeneic HSCT recipients with GVHD³⁶ and neutropenic patients with acute leukaemia or allogeneic HSCT.³⁷ The high doses of L-AMB used in these studies were not well tolerated by allogeneic HSCT recipients due to infusion-related toxicity³⁷ and elevations of serum creatinine.³⁶

In conclusion, clinicians may like to consider a lipid formulation of amphotericin B on alternate days or

three times a week (e.g. 50–250 mg L-AMB or 2.5 mg/kg ABLC) when oral posaconazole prophylaxis is not tolerated although the optimal dose and timing of these formulations, particularly in HSCT recipients, have not been well evaluated (grade C–D recommendation). Despite a lack of evidence, IV voriconazole or caspofungin are also sometimes used as alternatives in this setting. Patients at a higher risk of IFI should be carefully monitored for early signs of filamentous fungal infection if mould-active prophylaxis is not used.

Prophylaxis in other settings

Chemotherapy regimens associated with profound T-cell immunosuppression (as opposed to neutropenia) also impart a high risk for IFI, e.g. alemtuzumab (which has been associated with an IFI rate >10% in patients with lymphoproliferative disorders),³⁸ treatment for acute lymphoblastic leukaemia (ALL) (which may span many months and entail high doses of corticosteroids and regular vinca alkaloid therapy) and salvage therapy for non-Hodgkin lymphoma. Patients with these conditions are not routinely included in studies of antifungal prophylaxis³⁰ and thus, it is difficult to make recommendations for prophylaxis.

The regular dosing of vinca alkaloids and prolonged chemotherapy for the treatment of ALL can make azoles such as posaconazole, voriconazole or itraconazole difficult to administer due to the likelihood of drug–drug interactions. Similar difficulties may occur when choosing antifungal prophylaxis for salvage regimens for lymphoma.

Prophylaxis during treatment with alemtuzumab may be indicated in patients at very high risk of IFI, e.g. individuals whose underlying lymphoproliferative disease is not responding, where other immunosuppressive treatments have previously been given, or during periods of neutropenia (grade D recommendation).³⁸

Prophylaxis for neutropenia in solid tumour patients

Antifungal prophylaxis is not routinely recommended for patients undergoing treatment for solid tumours. However, *Candida* infections may develop in patients undergoing abdominal surgery or regimens causing intense mucositis.

Dosing and duration

A loading dose is not recommended for most patients receiving azoles for prophylaxis, as therapeutic levels need not be reached until the onset of neutropenia (after

chemotherapy or conditioning). A loading dose of itraconazole or voriconazole (but not fluconazole or posaconazole) may be considered to achieve therapeutic levels in patients presenting after prolonged neutropenia or with relapsed leukaemia.

For patients with AML or other haematological malignancies undergoing chemotherapy or autologous transplant, antifungal prophylaxis should continue until the neutropenia has resolved ($\text{ANC} > 0.5/\text{mm}^3$). Post-allogeneic transplant patients should continue fluconazole until Day 75 or the commencement of posaconazole for prophylaxis during GVHD treatment. Ullman *et al.*, administered posaconazole prophylaxis until Day 112 after the onset of treatment for GVHD (\geq grade 2 or chronic extensive); however, we recommend clinicians tailor the duration of an individual's prophylaxis according to the grade of GVHD and the amount of immunosuppressive therapy they require. It is important to be aware that doses of corticosteroids equivalent to prednisolone doses of >1 mg/kg for 0–13 days, and as low as 0.25–1 mg/kg for 14–27 days following allogeneic HSCT, have been independently associated with an increased risk of IA.⁴

It is difficult to recommend a duration of prophylaxis for alemtuzumab as IFI risk may persist for up to 12 months following its cessation.³⁸

Secondary prophylaxis after IFI

Secondary prophylaxis is given to patients presenting for further cycles of chemotherapy or HSCT after an IFI was diagnosed during a previous course of therapy. No systematic studies have been performed in this setting. Evidence is limited to case series only and no recommendation can be given for one agent over another.

There have been reports of low reactivation rates of IFI with standard amphotericin B,³⁹ lipid formulations of amphotericin B or itraconazole,^{40–43} voriconazole⁴⁴ and caspofungin,^{45,46} compared with untreated controls. There is only one case report where posaconazole was given as initial treatment for zygomycosis and then used as secondary prophylaxis during allogeneic HSCT.⁴⁷

A review of 197 published cases of proven/probable aspergillosis in patients undergoing treatment for haematological malignancy or autologous HSCT reported a progression rate of 62% in patients receiving no antifungal therapy ($n = 23/42$) versus 16% in patients receiving antifungal therapy.⁴¹

Martino *et al.*, reviewed 129 proven/probable cases of aspergillosis and identified seven risk factors for recurrence: >20 days neutropenia, advanced disease at transplant, myeloablative conditioning, cytomegalovirus (CMV) disease, <6 weeks' antifungal therapy before

transplant, bone marrow or cord blood source, grade 2–4 GVHD + steroids ≥ 2 mg/kg/day for >20 days.⁴⁸ The risk of recurrence was 6% if 0–1 risk factors were present. This rose to 27% for 2–3 risk factors and 72% if >3 risk factors were present. Reactivation rates were 26–33%, regardless of the agent chosen and whether prophylaxis was used.⁴⁸

To minimize the chance of recurrence, clinicians should consider the timing of the transplant, duration of antifungal therapy prior to transplant, stem cell source (e.g. peripheral stem cells will reduce the period of neutropenia but increase the risk of chronic GVHD),⁴⁹ feasibility of surgical resection^{50,51} and the possibility of donor granulocyte cover for profound neutropenia.^{52–54} We refer you to the review by Grigg and Slavin, for further details on minimizing the risk of recurrent mould infections during neutropenia and transplantation.⁵⁵

Conclusions on prophylaxis – the risks and benefits

Despite the many antifungal prophylaxis studies and meta-analyses performed, few have shown an impact on overall mortality. Only two individual trials – fluconazole in (largely) allogeneic HSCT recipients² and posaconazole in patients with AML or MDS undergoing induction chemotherapy¹⁷ – had an impact on overall mortality. The decision to use prophylaxis, and which agent to use, will be informed by a risk–benefit assessment that takes into account reported reduction in IFI and mortality, patient risk factors, institutional fungal epidemiology, available diagnostic tools, risk of breakthrough infections, drug toxicity and drug–drug interactions.

Meta-analysis supports the use of prophylaxis in high-risk populations such as allogeneic HSCT and probably some cases of acute leukaemia. Posaconazole has shown benefit over fluconazole in subsets of these patients with GVHD (without a mortality benefit) or AML undergoing remission induction. If used, mould-active prophylaxis should cover the period of risk but existing risk assessment tools⁵⁶ and knowledge of duration of risk could benefit from further refinement.

Other considerations include the complications associated with mould-active agents such as toxicity and drug–drug interactions, which may be more complex than those observed with fluconazole, as discussed later in these guidelines (see the section by Worth *et al.* on p. 521).

When embarking on antifungal prophylaxis, clinicians should be aware of the impact that prophylaxis has on the epidemiology and diagnosis of breakthrough fungal infections. Marr *et al.*, showed that while the number of *Candida* species infections decreased after fluconazole

prophylaxis in HSCT recipients, the infections that did occur were more likely to involve a species less intrinsically susceptible to fluconazole such as *Candida krusei*.⁵⁷ This relationship has also been observed with mould-active agents, particularly voriconazole, where breakthrough infections with more resistant moulds such as zygomycosis^{58–61} and *Scedosporium prolificans*⁶⁰ have been reported. Breakthrough infections with resistant moulds may become more common as our use of broader spectrum agents such as posaconazole grows. Clinicians should consider using a more aggressive diagnostic regimen for breakthrough infections given the broader range of potential pathogens and the higher likelihood of resistant fungi.

Mould-active agents may also suppress early markers of fungal infection such as blood galactomannan (GM) antigen.⁶² Fewer cases of IA were diagnosed with GM testing in patients receiving posaconazole compared with those receiving fluconazole in the study by Cornely *et al.*¹⁷ This could delay the diagnosis of early IFI and result in poorer outcomes.

The cost of antifungal therapy and monitoring drug levels in patients who often have mucositis, nausea and vomiting (making drug absorption a concern) should be balanced against the cost of an IFI to the hospital and the patient, particularly where treatment of the underlying condition may be delayed or compromised.

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