Mould-active antifungal prophylaxis: A gap analysis of prescribing appropriateness

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INTRODUCTION

- Invasive fungal infections (IFIs) are a common and very serious complication of immune deficiency in haematology patients (1). Antifungals are used for the prevention of IFIs (1). Lower risk patients receive anti-candida prophylaxis, whereas higher-risk patients receive mould-active prophylaxis.(2)
- The first line choice of primary and secondary mould-active prophylaxis are respectively, posaconazole and voriconazole (2). Liposomal amphotericin B is the second line choice where azoles are contraindicated (2).
- Mould-active antifungals should be prescribed vigilantly due to risks of resistance, cost ,variable pharmacokinetics and high adverse effect profile. (3-6)
- The national data in Australia shows that the rate of appropriateness of antifungal prophylaxis in haematology inpatients is 95.1% (7)

AIM

- Compare the appropriateness of prophylactic mould-active antifungals use in haematology inpatients of a regional hospital to the national data as per the guidelines and identify the gaps in appropriate prescribing.

METHODS

- A cohort retrospective study including a gap analysis
- **Inclusion criteria:**
  - Hematology inpatients prescribed mould active prophylaxis at Launceston General Hospital
  - From 1st July 2021 to 31st January 2022
- **Exclusion criteria**:
  - Patients with active mould infection receiving treatment
- A list of patients prescribed mould-active antifungals was prepared from antimicrobial recording system (Guidance MS®) and dispensing records
- Digital Medical Records for each patient were used to compare the indication against the eviQ guidelines (2)

Risk classification	Clinical examples	Recommended prophylaxis
High-risk	• Acute myeloid leukemia • Acute lymphoblastic leukaemia • Graft Versus Host Disease • Allogeneic HSCT expected neutropenia > 14 days	Mould-active prophylaxis
Low risk	• Selected autologous HSCT • Allogeneic HSCT with expected neutropenia < 14 days • intensive/dose escalated therapy for lymphoma	Anti-Candida prophylaxis
Very low risk	• Standard chemotherapy for lymphoma • Chronic myeloid leukaemia • Other myeloproliferative neoplasms	No prophylaxis

Table 1: Risk classification for Antifungal prophylaxis in haematology patients adapted from eviQ (2)

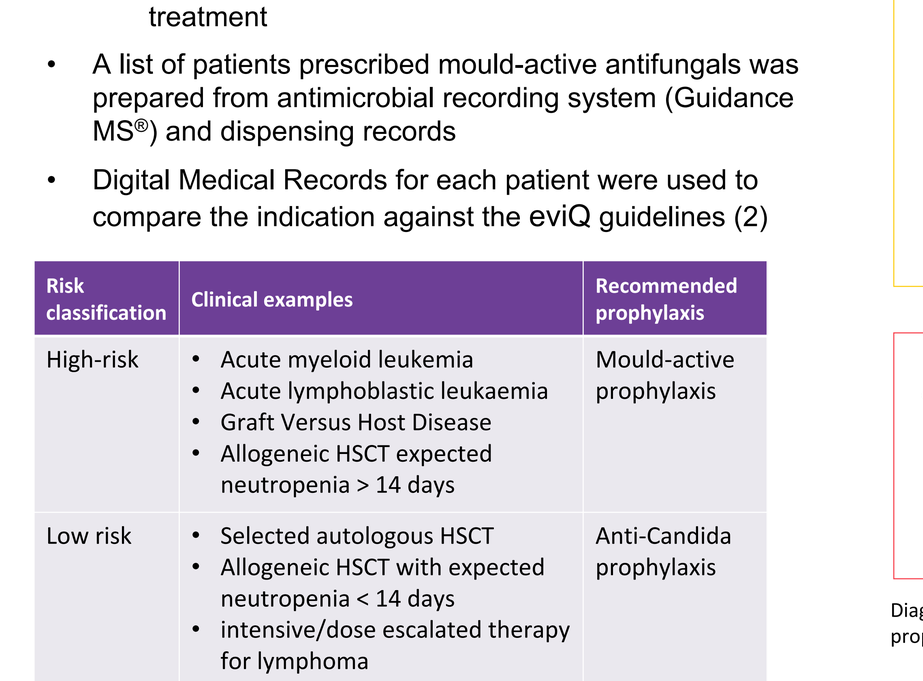

Diagram 1: Process of assessing appropriateness of mould-active prophylaxis prescribing

Statistical analysis

- Normality was assessed using Shapiro-wilk test. A one sample T-test was used to compare the mean with the national rate of 95.4%. SPSS 28 was used for statistical analysis. Excel was used for data collection and gap analysis.

RESULTS

- Out of the 20 haematology inpatients prescribed prophylactic mould-active antifungals, 10 (50%) were prescribed prophylactic mould-active antifungals as per the guidelines.
- This was significantly ($p<0.001$) lower than the national rate of appropriate antifungal prophylaxis for haematology inpatients.

	AML	ALL	CLL	NHL	CVID	Total n=20
Appropriate agent and indication	5(25%)	5(25%)	-	-	-	10 (50%)
Inappropriate second-line agent	5(25%)	-	-	-	-	5(25%)
Inappropriate Indication	-	-	1(5%)	3(15%)	1(5%)	5(25%)

AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukaemia; NHL: Non-Hodgkin lymphomas; CLL: Chronic lymphocytic leukemia; CVID: Common variable immune deficiency

Gaps in appropriate prescribing:

Inappropriate second-line agent

- Switching from posaconazole to liposomal amphotericin B: (n=4 [20%])
  - Due to a transient rise in LFTs while receiving posaconazole for AML with Idarubicin and cytarabine (n=2 [10%])
  - When given concurrently with venetoclax for AML (n=2 [10%])
- Use of posaconazole as secondary prophylaxis in a patient treated for IFI with voriconazole(n=1 [10%])

Inappropriate Indication

- Use of mould-active prophylaxis in low/very low-risk patients (n=5 [25%]).
  - Non-Hodgkin lymphomas (NHL) (n=3 [15%])
  - Chronic lymphocytic leukemia (CLL) (n=1 [5%])
  - Common variable immune deficiency (n=1 [5%])

Diagram 2: Gaps in appropriate prescribing of mould-active antifungal prophylaxis

DISCUSSION

The following gaps in appropriate prescribing of prophylactic mould-active antifungals were identified:

- **Switching from posaconazole to liposomal amphotericin B:**
  Evidence supporting efficacy of liposomal amphotericin B is limited(2). Amphotericin B is only available as an IV infusion and has higher toxicity compared to posaconazole (8). Thus, where possible posaconazole should be used.

  - **Transient rise in LFTs while on posaconazole:**
  Liver toxicity from posaconazole is not proven (9). Rises in LFTs are generally transient, multifactorial and should not warrant switching to a less effective agent (10).

  - **When given concurrently with venetoclax:**
  Posaconazole interacts with venetoclax increasing the effect of venetoclax, however the safety of posaconazole with reduced dose venetoclax is demonstrated in the literature (11) and is recommended by the guidelines (12). The presence of interaction should not warrant switching to amphotericin B and dose modification could be used instead.

- **Use of posaconazole as secondary prophylaxis in place of voriconazole:**
  This patient had a confirmed episode of aspergillosis and was treated with voriconazole then switched to posaconazole for prophylaxis. Australian guidelines recommend using the same treatment agent at therapeutic dose for prophylaxis in further episodes of immunodeficiency provided it is well tolerated and effective (2). This recommendation is based on a 2014 study showing safety and efficacy of continuing treatment regimen for secondary prophylaxis in allogeneic hematopoietic stem cell transplantation (13). It is difficult to predict the clinical outcomes of switching patients treated with voriconazole to posaconazole for secondary prophylaxis without further data.

- **Use of mould-active prophylaxis in low/very low-risk patients:**

  - **Non-Hodgkin lymphomas (NHL) and Chronic lymphocytic leukemia (CLL) :**

The basis for the risk assessment of IFIs in many guidelines is the SEIFEM-2004 study. This study included 11,802 patients with hematologic malignancies, 1104 and 3457 of which counted for CLL and NHL respectively. IFI rates for CLL and NHL were 0.5% and 1.6% respectively (14). The low rate of IFIs is the reason patients with these haematological malignancies do not routinely require mould active prophylaxis.

  - **Common variable immune deficiency (CVID):**

Patients with CVID do not generally exhibit increased susceptibility to fungal infections. Although CVID does weaken the immune system there is not sufficient evidence suggesting a link between the disease and IFIs, suggesting no evidence-based need for prophylaxis with the current level of literature (15).

Implications

- The gaps were discussed and compared with the available literature. The findings of this study will assist in developing antifungal stewardship interventions specifically targeted at the gaps highlighted and will help improve guideline compliance and evidence-based practice with mould-active antifungals.
- The findings may also provide insight for other similar size institutions in their journey of improving quality use of antimicrobials.

Limitations

- The national data from Douglas et. al, which the local data was compared with, looks at appropriateness of both mould and candida-active prophylaxis in haematology inpatients. The national data on only mould active antifungal is not published.
- A sample size of 20 patients is generally a small cohort. A larger cohort may show a different pattern of prescribing.
- This study does not address patients who did not receive mould-active prophylaxis while indicated. This is due to the limitations of the study design.
- the Australasian Antifungal Guidelines Steering Committee published an updated guideline in December 2021(16). This study did not assess appropriateness based on the updated 2021 consensus guidelines.

CONCLUSION

- The rate of appropriate mould-active prophylaxis prescribing at this regional hospital was significantly lower than the national rate. This study has identified some of the gaps in appropriate prescribing of mould-active antifungal prophylaxis. Further interventions should be made to address these gaps and a future study can use this data to evaluate the effectiveness of the said interventions.

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