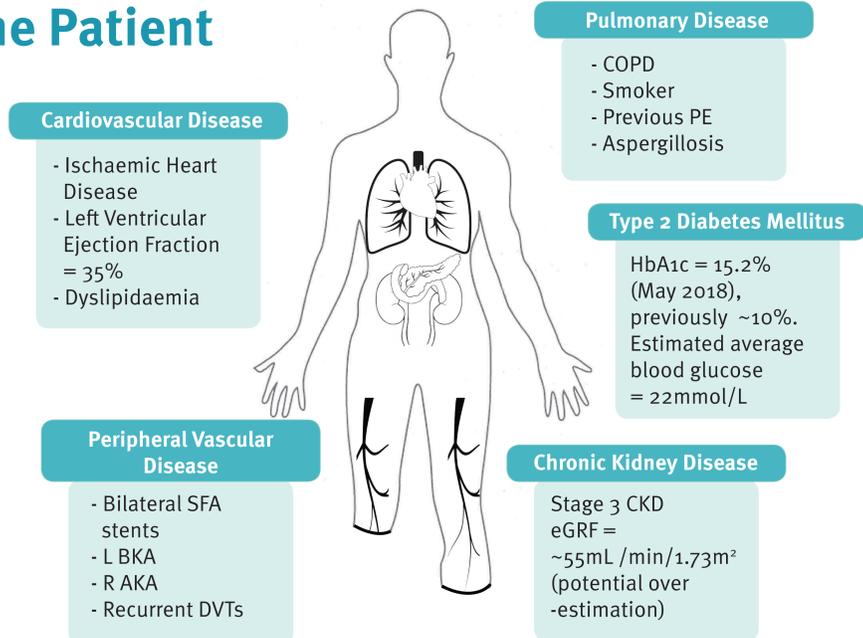


Challenges of concurrent life-long antifungal and anticoagulant therapy: a case study

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The Patient



A 72-year old male was admitted to the rehabilitation ward of a large tertiary hospital following an above knee amputation. In the previous year he was diagnosed with histologically proven aspergillus pulmonary mycetoma and commenced on lifelong itraconazole therapy. He also had a history of multiple unprovoked venous thromboembolisms, the most recent being in January 2019, which triggered lifelong dabigatran therapy. Itraconazole inhibits p-glycoprotein increasing dabigatran plasma concentrations and consequently bleeding risk. Therefore, alternative antifungal and anticoagulant options were investigated.



The Options

Antifungal Options for Invasive Aspergillosis²

- Amphotericin B** → effective but limited by infusion reactions and toxicity
→ parenteral therapy unsuitable given risks of long-term IV access
- Echinocandins** → not routinely recommended for primary treatment
→ parenteral therapy unsuitable given risks of long-term IV access
- Triazoles with mould activity** → preferred agents and favourable given oral formulations
→ complicated by inhibition of cytochrome P450 enzymes and p-glycoprotein

Anticoagulant Options for Prevention of Recurrent Venous Thromboembolism (VTE)

- Heparins** → effective but limited by parenteral route
- Warfarin** → multiple limitations for patient including history of labile INRs
→ favourable due to INR monitoring, oral formulation and PBS eligibility
- Direct Oral Anticoagulants** → preferred agents due to standardised dosing and oral formulations
→ caution in renal impairment
→ substrates for cytochrome P450 enzymes and p-glycoprotein, which complicates use

Predicted Pharmacokinetic Interactions:³⁻⁶

	Itraconazole	Isavuconazole	Posaconazole	Voriconazole	TGA indicated for prevention of recurrent VTE?	PBS indicated for prevention of recurrent VTE?	Therapeutic Drug Monitoring
Dabigatran	× P-gp	× P-gp	× P-gp	✓	✓	×	Available but therapeutic range not established
Rivaroxaban	× CYP3A4,5 × P-gp	× CYP3A4,5 × P-gp	× CYP3A4,5 × P-gp	× CYP3A4,5	✓	✓	
Apixaban	× CYP3A4,5 × P-gp	× CYP3A4,5 × P-gp	× CYP3A4,5 × P-gp	× CYP3A4,5	✓	✓	
Warfarin	× CYP3A4,5 × CYP2C9	× CYP3A4,5	× CYP3A4,5	× CYP3A4,5 × CYP2C9 × CYP2C19	✓	✓	✓
TGA indicated for invasive aspergillosis?	✓	✓	✓*	✓	* If intolerant of, or disease that is refractory to, alternative therapy		
PBS indicated for invasive aspergillosis?	✓	×	✓*	✓**	** Patient must be immunocompromised		
Therapeutic Drug Monitoring	✓	×	✓	✓			

The Outcome

Voriconazole and dabigatran appear to be a suitable combination, however due to PBS limitations, itraconazole was the preferred option by the respiratory team. Therefore, despite drug interactions, warfarin was chosen due to its well-established monitoring system. However, concerns were raised by the patient and various allied health members.

- These concerns were mitigated through a collaborative effort from the multi-disciplinary team.
- Physiotherapists and occupational therapists provided extra rehabilitation to improve vehicle and wheelchair transfers
 - Social workers encouraged family involvement and helped alleviate financial burden by arranging extra care packages
 - Pharmacists and dietitians provided education to increase the patient's understanding, empowerment and acceptance

As a result, this patient was successfully discharged on stable itraconazole and warfarin therapy.

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