Problems and Solutions in Fungal Infection

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THE UNIVERSITY OF SYDNEY

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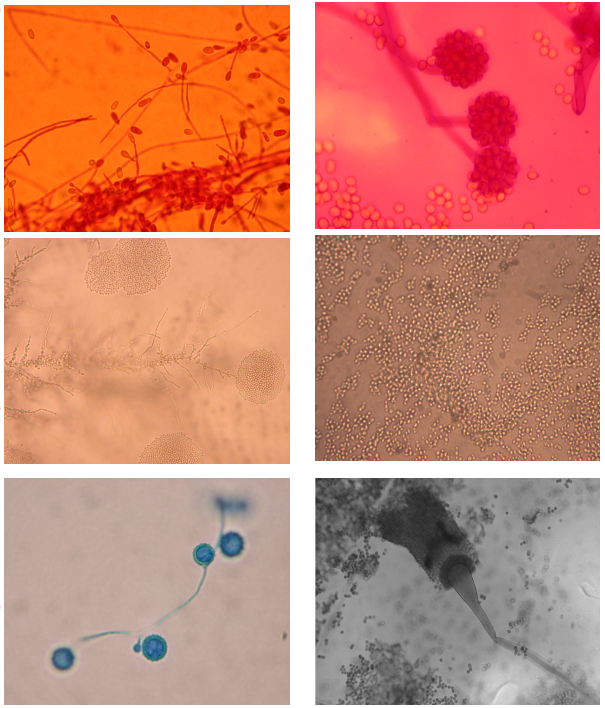
Fungal infections are increasing as immunocompromised populations continue to expand globally.

The current range of anti-fungal drug classes is limited.

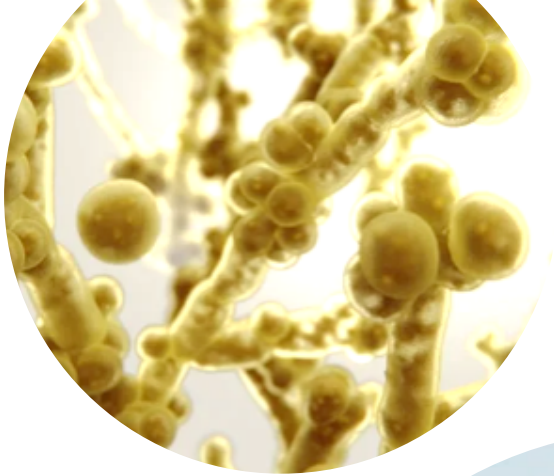
Access to antifungals and diagnostics is severely limited, especially in high-burden settings.

Disease is poorly understood and under-researched, receiving less than 1.5% of all infectious disease research funding



Photos credit: Ana Alastruey-Izquierdo, **Instituto de Salud Carlos III , Spain**

Emerging AMR

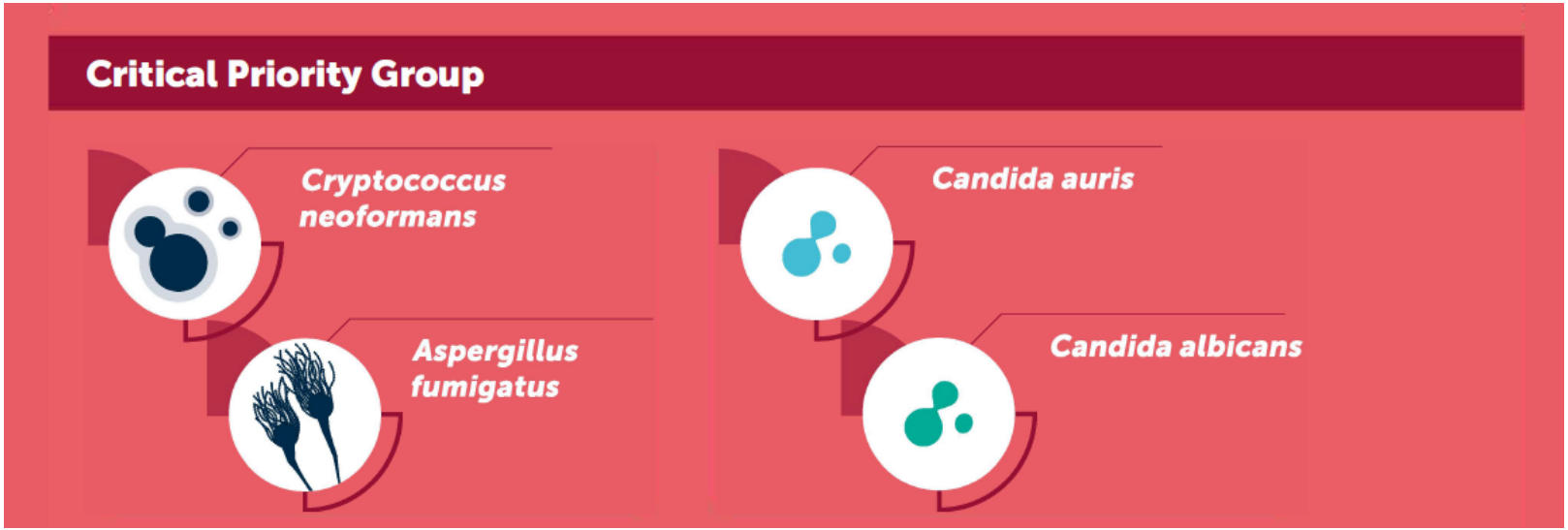


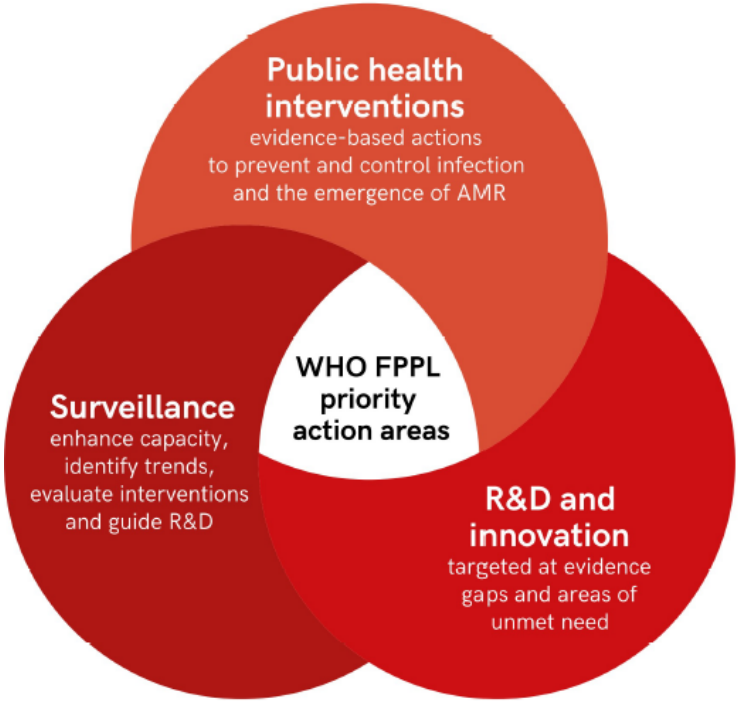
Candida auris

- Often multidrug resistant. Some are pan-resistant.
- Resistant to standard IPC strategies.
- *C. auris* first cases reported in Japan in 2009, since reported in over 55 countries.
- Where did it come from?

Azole resistant *Aspergillus fumigatus*

- Emerged over the last decade.
- Worsens clinical outcomes.
- Driven by environmental agricultural contamination.
- Rates seem exceptionally high in areas of China and SEA (90%!)


Critical Priority Group
Cryptococcus neoformans
Aspergillus fumigatus
Candida auris
Candida albicans



AFR: Antifungal Resistance; R&D: Research and Development; WHO FPPL: World Health Organization fungal priority pathogens list.

(Selected) problems with fungal infections in ICU

Early diagnosis and treatment of fungal infections

Optimal use of antifungals in ICU

Infection prevention and control

Getting treatment started early

IC - Burden and mortality

- EPIC-II showed 50% of ICU patients are infected at any given time.

- *Candida* spp. caused a significant burden of disease -

Pathogen	%	Mortality
Candida spp (843/4947)	17%	43%
Gram positive bacteria (2315/4947)	47%	25%
Gram negative bacteria (3077/4947)	62%	29%

IC - Diagnostics

- Diagnosis is not easy – in one study 50% of first positive blood cultures from 152 episodes of candidemia had a fungal density of ≤1 colony-forming unit (CFU)/mL, challenging even molecular diagnostic tools.

IC - Early treatment reduces mortality

Delayed antifungal treatment is harmful mortality of candidemia is 10% if antifungals are introduced in the 12 h following the first positive blood culture, vs >30% if treatment is delayed for more than 48 h.

Even more marked in septic shock – 28d mortality 60% <24hr vs 90% >24hrs.

- REF Morrell AAC 2005; Kollef CID 2012

IC – who is at risk?

Major

Candida are commensals of the gut and skin, with low numbers in the healthy microbiome

Invasion is 2ry to

Increased numbers -
Antibiotics, immunosuppression and corticosteroids, Diabetes mellitus

Increased permeability -
Mucositis, malignancy, surgery, prosthetic material (biofilm)

Other

Hyperalimentation (TPN)

Urinary catheterization

Mechanical ventilation

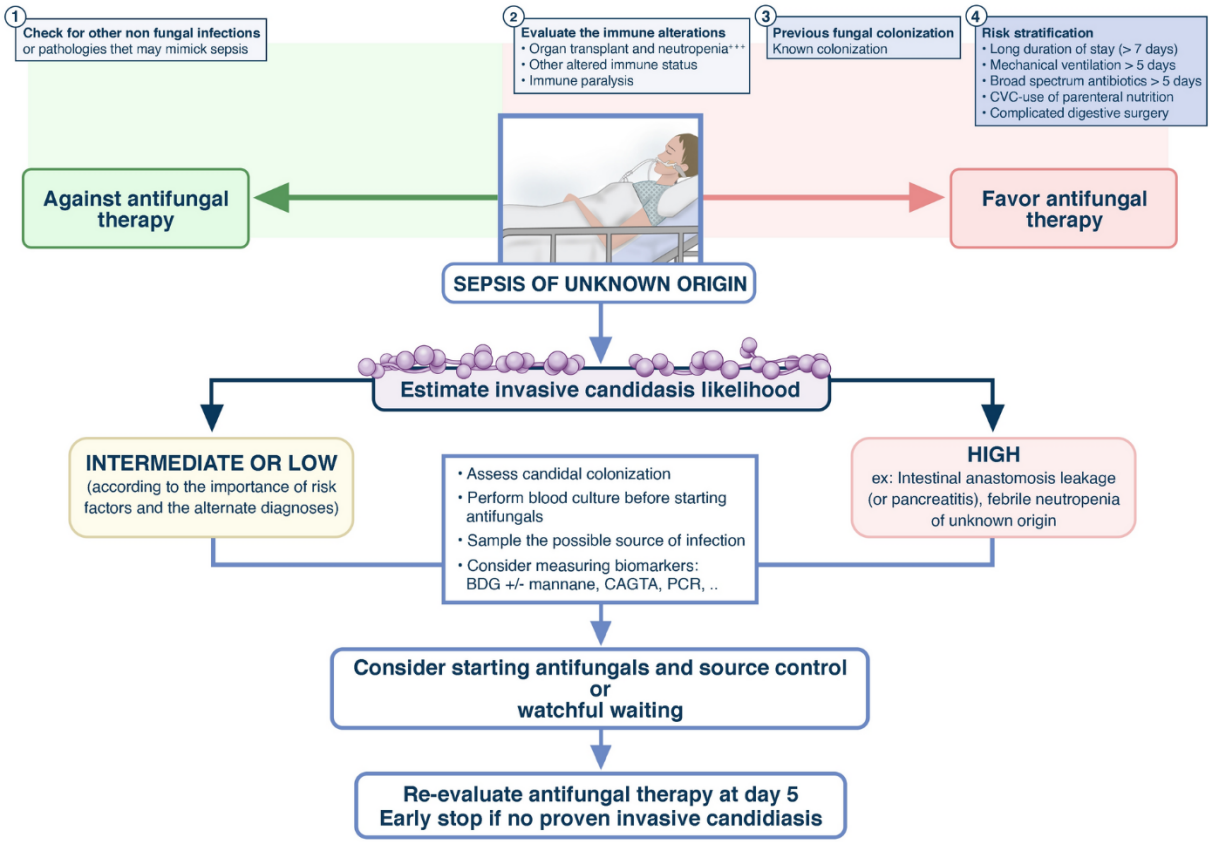
Prior *Candida* colonisation

Previous ICU stay

Concomitant bacterial infection

Antifungal strategies – Invasive *Candidiasis* in ICU

Empiric	Pre-emptive	Probabilistic	Definitive
Clinical triggers – fevers, consistent signs	Non-culture triggers – colonization, biomarkers	Score-based triggers – e.g. Candida score	Microbiologically confirmed disease, with targeted therapy
Ineffective in multiple trials Golan Ann Int Med 2005 (fluconazole) Timsit JAMA 2016 (micafungin)	**Questionable value** Mannan too insensitive, BDG too non-spec (?consecutive) Bloos Int Care Med 2022 (CandiSep)	**Complex, helpful, but not deterministic** Assessed in Australia, PPV 10% Playford CID 2016(CandiSep)	


1 Check for other non fungal infections
or pathologies thet may mimick sepsis
2 Evaluate the immune alterations
• Organ transplant and neutropenia+++
• Other altered immune status
• Immune paralysis
3 Previous fungal colonization
Known colonization
4 Risk stratification
• Long duration of stay (> 7 days)
• Mechanical ventilation > 5 days
• Broad spectrum antibiotics > 5 days
• CVC-use of parenteral nutrition
• Complicated digestive surgery
Against antifungal therapy
Favor antifungal therapy
SEPSIS OF UNKNOWN ORIGIN
Estimate invasive candidasis likelihood
INTERMEDIATE OR LOW
(according to the importance of risk factors and the alternate diagnoses)
• Assess candidal colonization
• Perform blood culture before starting antifungals
• Sample the possible source of infection
• Consider measuring biomarkers: BDG +/- mannane, CAGTA, PCR, ..
HIGH
ex: Intestinal anastomosis leakage (or pancreatitis), febrile neutropenia of unknown origin
Consider starting antifungals and source control
or
watchful waiting
Re-evaluate antifungal therapy at day 5
Early stop if no proven invasive candidiasis

Molecular assays

- PCR sensitivities 90-95% and specificities 90-92% (candidemia) *Sensitivity is reduced in intra-abdominal candidiasis (86-91%) and specificity varies widely (33-97%)*

- Positive results can occur in colonized patients

- Lower limit of detection ≤10 colony forming units (CFU)/mL, so may still miss early or low burden infections (e.g. *N. glabrata*)

- 5 most common species are targeted by commercial multiplex kits -

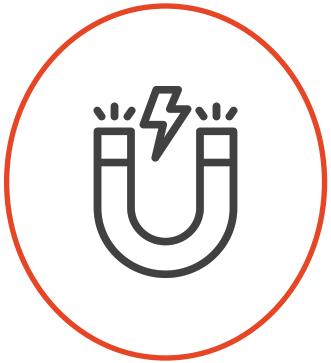
C. albicans	***C. tropicalis***
C. parapsilosis	***P. kudriavzevii***
N. glabrata	

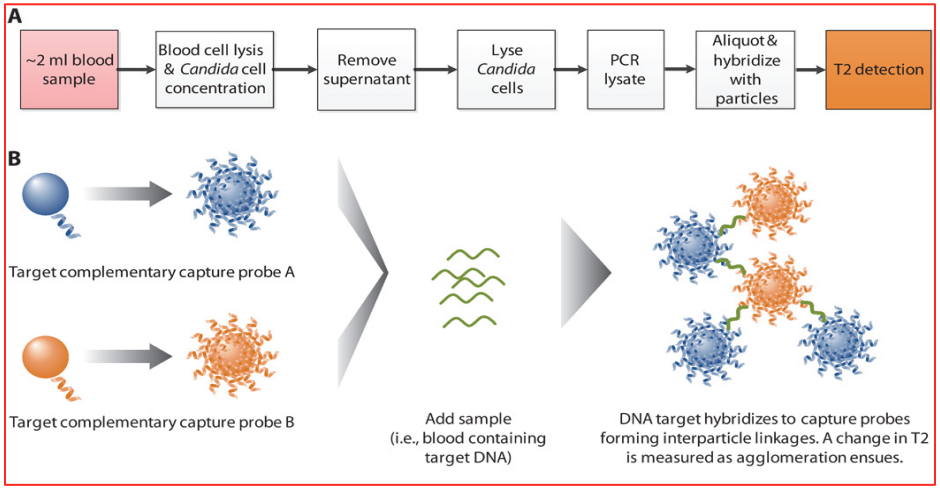
T2Candida

- Detects *Candida* in whole blood
- Mechanical lysis of cells, DNA amplification, detection by amplicon-induced agglomeration of super magnetic particles via T2 resonance measurement
- Sensitivity 89-91% and specificity 98-99%
- Limit of detection 1CFU/mL
- Result available after 3-4hours

A	*C. albicans*	*C. tropicalis*
B	*C. parapsilosis*	
C	*N. glabrata*	*P. kudriavzevii*

- Utility in follow-up blood cultures – detection of non-viable yeast





Treatment

- Guidelines from ASID, IDSA, and ESCMID

- **Echinocandins** 1st line therapy
  - -Network meta-analysis on data from 13 trials (3528 patients)
  - -Odds ratio (OR) 0.66; 95% confidence interval (CI) 0.45-094; P=0.02

- **Azoles** 2nd line initial therapy and usual step-down therapy
  - -~15% less effective
  - -May be 1st line in central nervous system, eye, urinary tract infections (due to better penetration)

- **Amphotericin B** effective, but
  - -Toxicities
  - -Used where intolerance/resistance to echinocandins and/or azole and in certain deep-seated infections (e.g. endocarditis, meningoencephalitis, endophthalmitis)
-

Conclusion

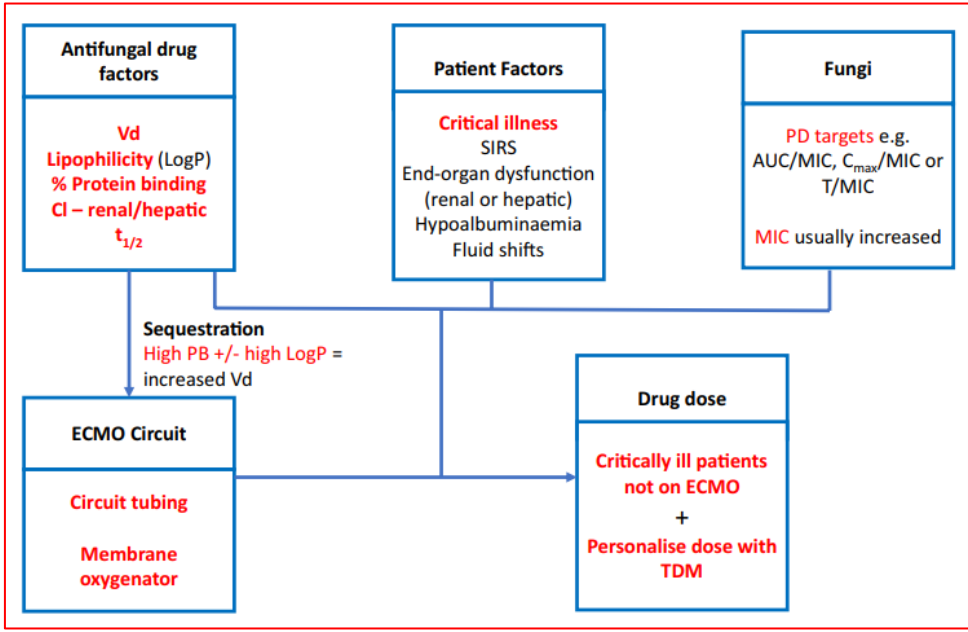
These considerations apply to IA, CAPA, IAPA, mucor and others. We risk going from under-recognition and under-treatment to overestimation of IFIs and the overuse of antifungal drugs.

This highlights the importance of a multidisciplinary approach to the management of IFIs, taking into account clinical, radiological, histological, and biological data.

Getting dosing right

What factors impact required antifungal dose in ICU

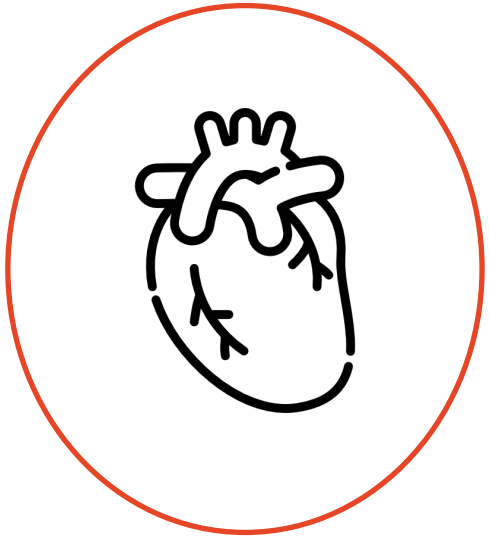
- Drug
- Patient
- Fungi
- Interventions – ECMO, CRT



REF Lyster H *Clin Pharmacokinet*. 2023

ECMO - azoles

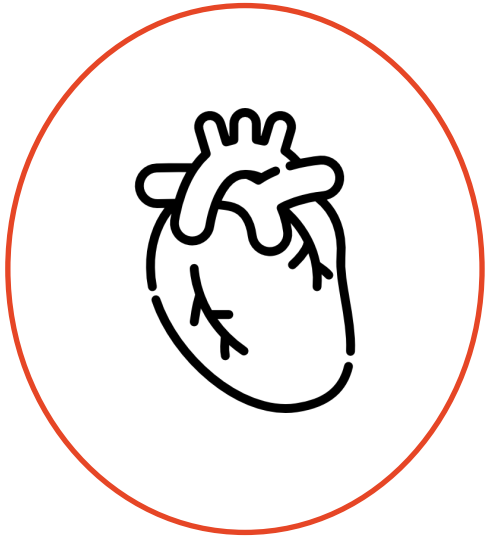
Drug	PB% (Vd)	Sequestration	Dosing advice
Fluconazole	12% (0.7L/kg)	Min circuit loss	May required increased LD
Voriconazole	58% (4.6 L/kg)	Mod-sig circuit loss	Conflicting data, standard dose - TDM
Posaconazole	>98% (1774 L)	Mod-sig circuit loss	TDM guided
Isavuconazole	>98% (450 L)	Mod-sig circuit loss	TDM guided



REF Lyster H *Clin Pharmacokinet*. 2023

ECMO - others

Drug	PB% (Vd)	Sequestration	Dosing advice
Anidulafungin	>99% (30-50 L)	Mod circuit loss	Insuff data- standard dose
Caspofungin	97% (NA)	Mod circuit loss	Insuff data- standard dose
Micafungin	>99% (0.39 L/kg)	Mod circuit loss	Contradictory data – standard dose (?higher)
Amphotericin	>90 (0.5-2 L/kg for dAmB; 0.05-2.2 for L-AmB)	dAmB min circuit loss L-AmB mod circuit loss	Conflicting data for L-AmB, preference for dAmB



REF Lyster H *Clin Pharmacokinet*. 2023

RRT

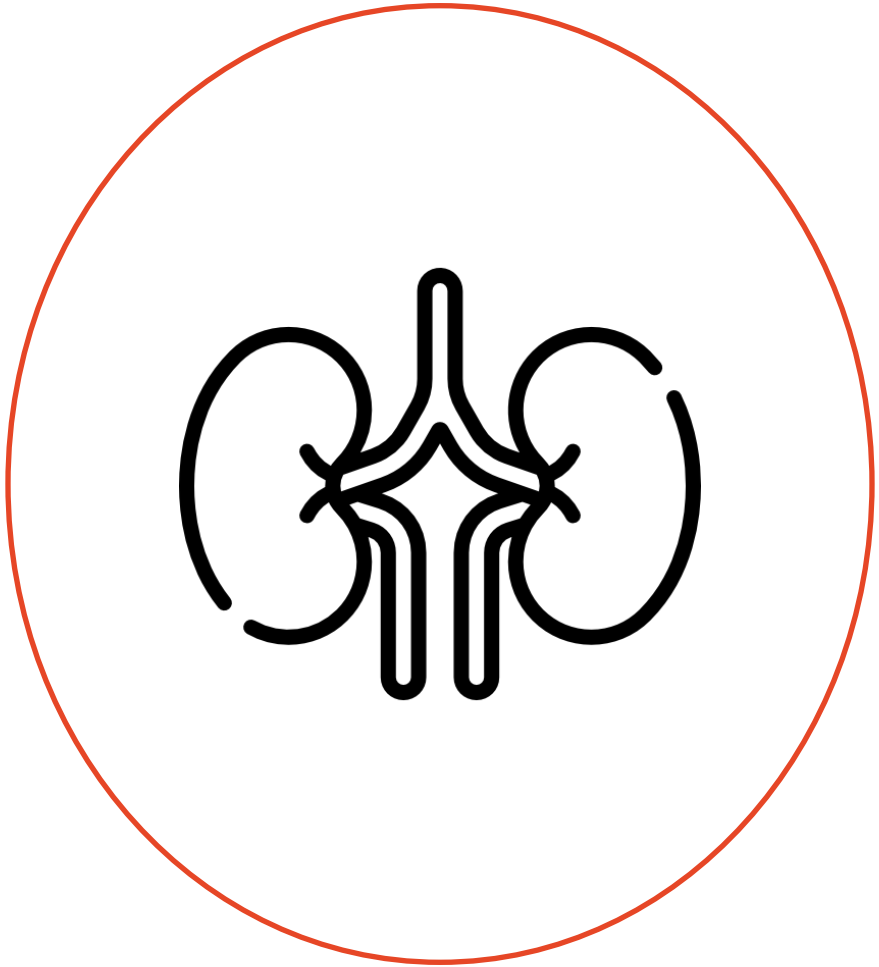
Dose adjustment only required for

fluconazole - increase
(*800mg LD followed by 400mg Q12H*)

flucytosine - decrease
(*reduce according to CrCl*)

itraconazole - increase
(*from 200-300mg Q12H D1 then Q24H*)

REF Roger *Curr Fungal Infect Rep.* 2018



TDM for antifungals in critical care

Drug	Parameters	Target	Recommendation
Fluconazole	NS	NS	Neither recommend nor discourage
Voriconazole	C_{min}	2-6mg/L	Yes
Posaconazole	C_{min}	0.5–0.7 mg/L (prophylaxis) / > 1 mg/L (treatment)	Neither recommend nor discourage
Isavuconazole	NS	NS	Neither recommend nor discourage
Itraconazole	C_{min}	> 0.5–1 mg/L	Neither recommend nor discourage

REF Abdul-Aziz MH *Intensive Care Med*. 2020

TDM for antifungals in critical care

Drug	Parameters	Target	Recommendation
Echinocandins	NS	NS	Neither recommend nor discourage
Flucytosine	C_{max} C_{min}	< 100 mg/L ≥ 25 mg/L	Neither recommend nor discourage
Amphotericin B	Not possible	Not possible	Not possible

REF Abdul-Aziz MH *Intensive Care Med*. 2020

Preventing infections from occurring

Fungal IPC in critical care

- Fungal infections are a significant threat in critical care settings due to patients' compromised immunity and invasive procedures.
- *Candida auris*, a multidrug-resistant fungal pathogen, poses a severe risk and typifies the threat.
- Whilst early diagnosis and treatment are vital, prevention is even more so.

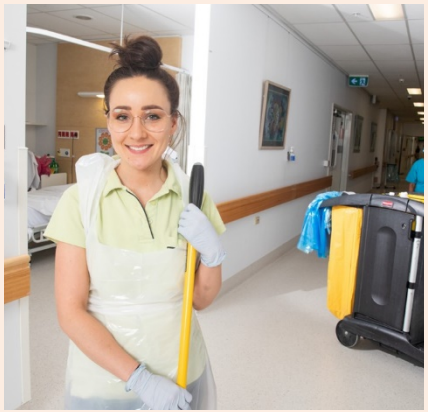
Fungal IPC in critical care

Hand Hygiene Consistent handwashing with soap and water or alcohol-based sanitizers.

Isolation Precautions Contact precautions for known or suspected *Candida auris (*or other drug resistant *Candida*) cases. Combined with **environmental Cleaning.** Note that *Candida auris* can persist on surfaces and equipment.

Standard CLABSI precautions and early removal of infected lines.

Antifungal Prophylaxis in relevant patient groups (not routine)



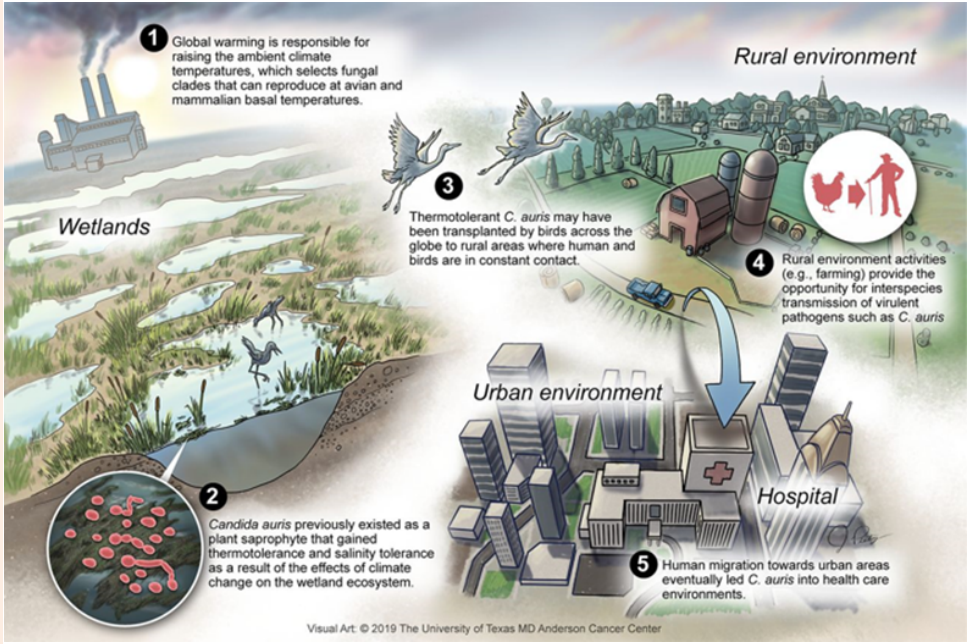
Keeping *C. auris* out?

- **Surveillance swabs** need to be considered – PCR for rapid result, followed by culture for sensitivities and epidemiology.

- Axilla and groin swabs are preferred.

- Note that patient cannot be de-isolated until >1yr swab negative.

- **Antifungal stewardship**



(Selected) solutions for fungal infections in ICU

For **early diagnosis,** better tests are on the way.

Careful stewardship of antifungals is vital.

Antifungal dosing remains challenging.

Improved access to TDM, ideally real time, is a challenge.

IPC to detect threats, reduce infections, and prevent transmission is especially important (and hard) in ICU.

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sydney.edu.au/medicine-health/about/our-people/academic-staff/justin-beardsley.html

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