ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

THE UNIVERSITY OF SYDNEY

CIDM
centre for infectious diseases & microbiology

Antifungal stewardship: best practice

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www.wslhd.health.nsw.gov.au/CIDM-PH

DISCLOSURES

- Untied educational grants from MSD Australia, F2G Ltd. Manchester, UK
- Antifungal Advisory Board of MSD Australia, Gilead Sciences Inc., F2G Ltd.
- Speakers Fees, Gilead Sciences, Inc.

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Agenda

- Why is antifungal stewardship (“AFS”…. AMS) important ?
  - **Slow down “AMR” (or “AFR”); which fungi to worry about?**
- What is AMS?
  - AMS strategies - what can we learn from bacteria (and viruses)
  - Who does it?
- What is the evidence supporting it?

AMR: a global problem

WHO declared AMR as one of the

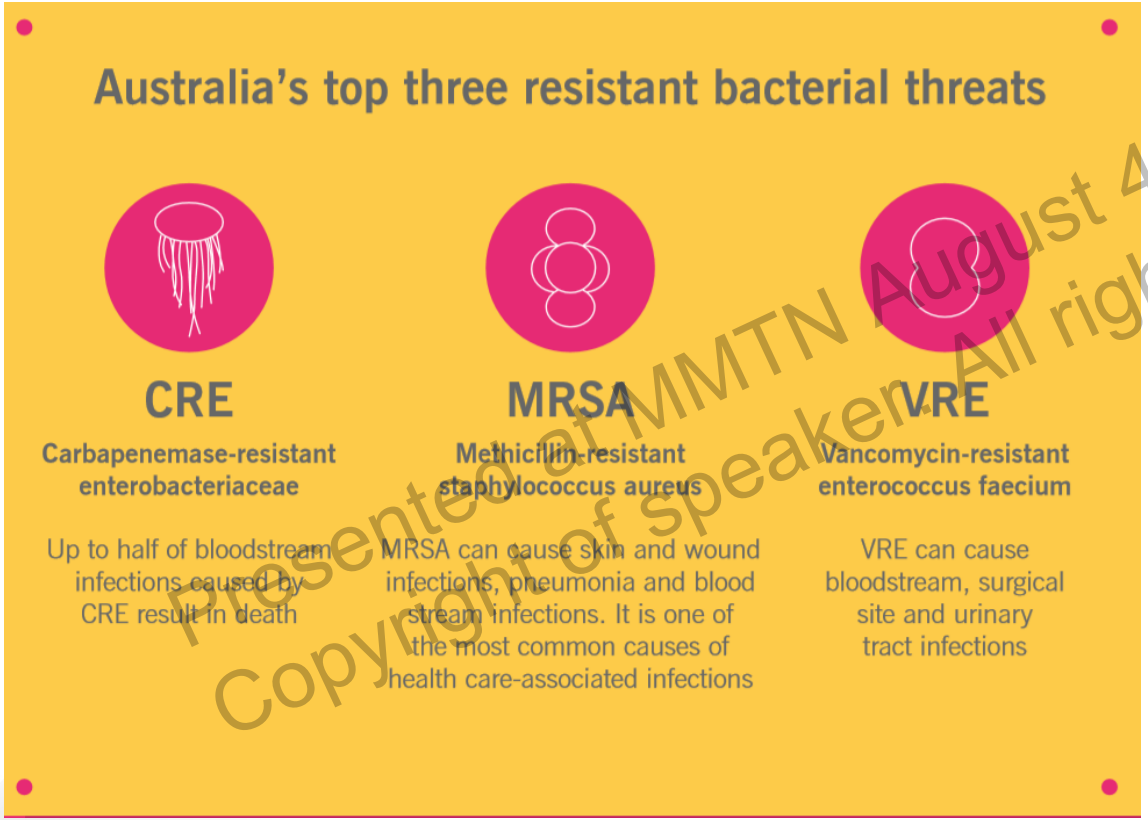
Top 10

global health threats

- 700,000 deaths/year globally
- 500,000 multi-drug resistant TB/year
- 58,000 newborns die/year in India
- 870,000 disability adjusted life years/year in EU

https://www.who.int/publications/i/item/global-action-plan-on-antimicrobial-resistance

AMR: a national (Aussie) problem



Prof. John Turnidge
Dr. Jan bell
Prof Karin Thursky

AURA
(Antimicrobial Use and Resistance in Australia) Report 2019

No mention of fungi

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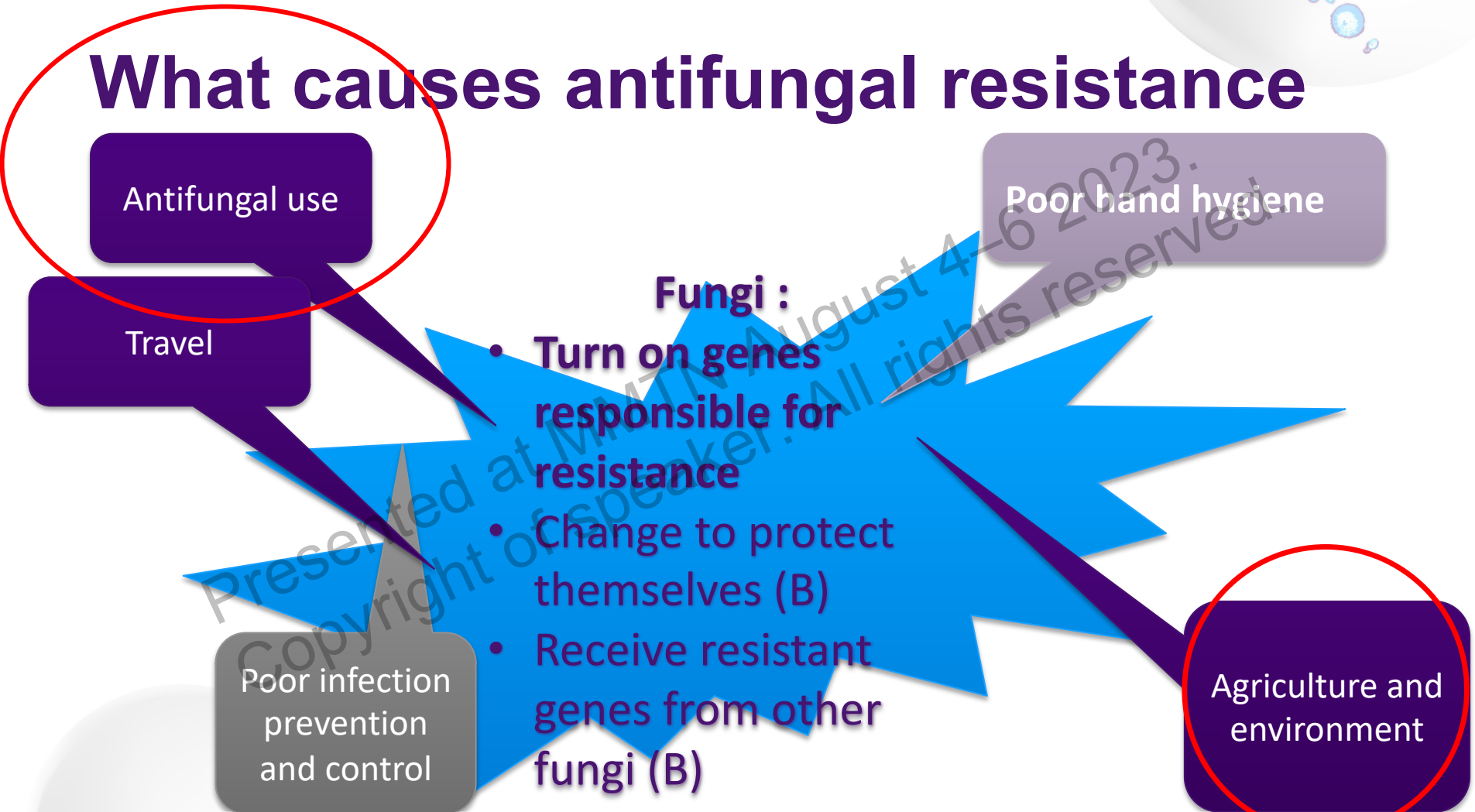
What causes antifungal resistance



The main players

- *Candida* species – *N. glabratus*, ***C. auris***, *C. tropicalis*, others
- *Aspergillus fumigatus* complex (***A. fumigatus* sensu stricto**)
- Increasingly – ***Lomentospora***, *Fusarium*, Mucorales
- Non-*Candida* uncommon (rare) yeasts

Inherited and acquired resistance: yeasts

Fungus (examples)	Inherent "R"	Acquired"R"
N. glabratus	Triazoles	Echinocandins
'C. krusei'	Triazoles	Echinocandins
C. auris	Azoles, (AMB, S Asia)	Echinocandins
Trichosporon	Echinocandins, AMB	Fluconazole
Saccharomyces/ Malassezia	Echinocandins	Fluconazole
Rhodotorula	Triazoles	
Saprochaete/ Magnusiomyces	Echinocandins	

Gamaletsou, Walsh and Sipsas, Turk J Hematol 2018 25: 1-11

Inherited and acquired resistance: moulds

Fungus	Inherent resistance	Acquired resistance
A. fumigatus	Fluconazole	Voriconazole, isavuconazole
A. terreus	Fluconazole, AMB	Voriconazole, isavuconazole
A. flavus	Fluconazole, AMB	Voriconazole, isavuconazole
Mucorales	Fluconazole, voriconazole	?
Fusarium spp.	Echinocandins, variably to AMB, triazoles	?
Lomentospora prolificans	Pan-resistant	?

Gamaletsou, Walsh and Sipsas, Turk J Hematol 2018 25: 1-11

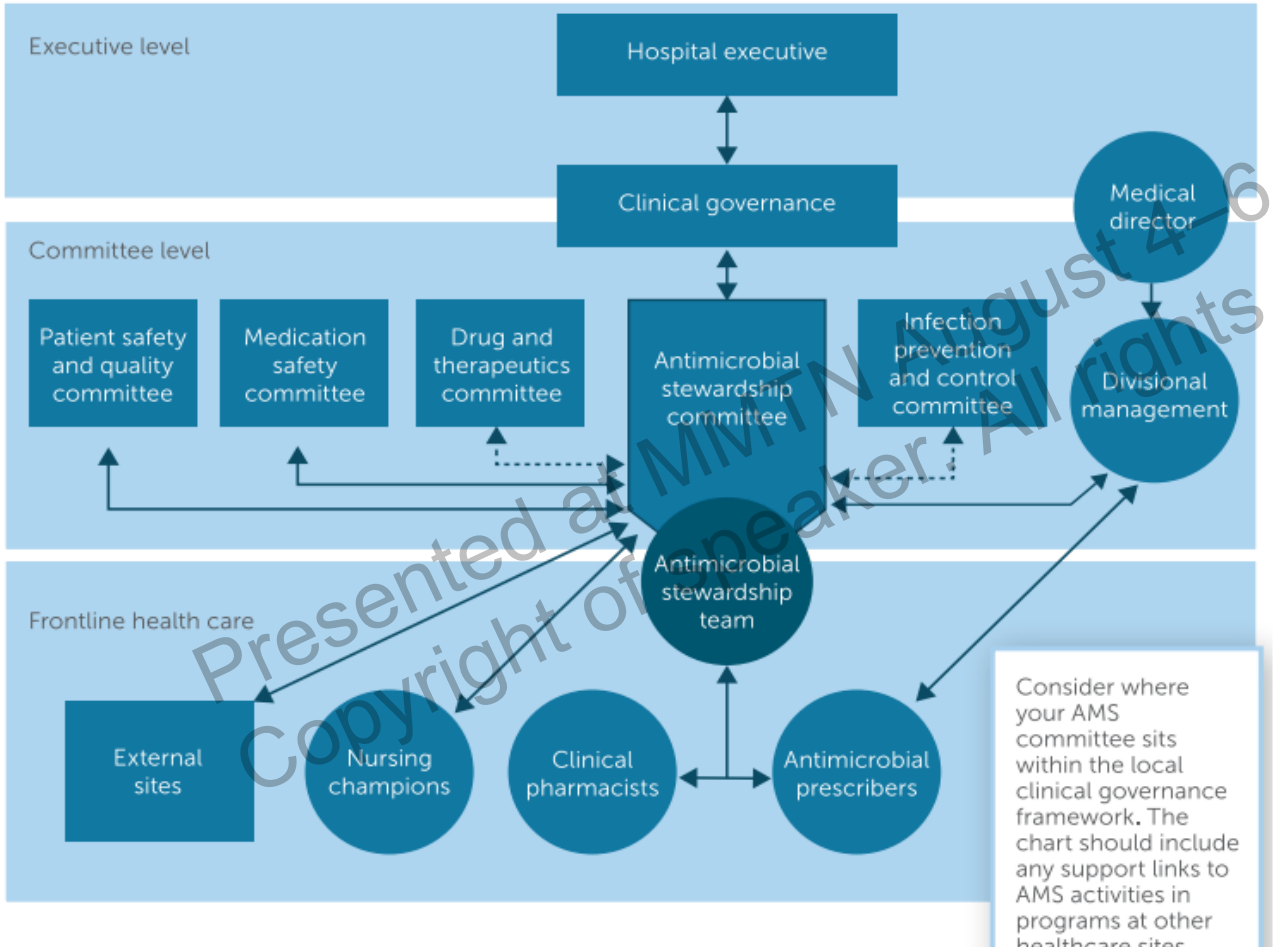
ANTIMICROBIAL STEWARDSHIP (AMS)

- Systematic approach to optimising use of antimicrobials (antifungals)
- Aim:
  - Reduce inappropriate antifungal use
  - Improve patient outcomes
  - Reduce adverse effects/toxicity
  - *Reduce development of antimicrobial resistance*
  - Reduce costs

Essential AMS strategies

1. Establish a multidisciplinary AMS team
2. AMS policy (restricted antimicrobial formulary)
3. Education to prescribers, pharmacists, nurses and consumers
4. Implement clinical guidelines consistent with eTG (e-therapeutic guidelines); local bodies
5. Review antimicrobial prescribing with intervention and feedbackMonitor antimicrobial use and outcomes

AMS structure (team)



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AMS policy and antimicrobial formulary restrictions

Pharmacy formulary - List of medications available for use in a hospital

- Determined by hospital Drug and Therapeutics Committee

Formulary restrictions

- Formulary may include further restrictions of use either
  - By prescriber (e.g. infectious diseases only)
  - By indication (e.g. piperacillin/tazobactam for febrile neutropenia)
  - Determined by AMS committee
- Commonly used “traffic light system”

Antimicrobial formulary

Antimicrobial category	Details and examples
Unrestricted	• Can be prescribed without an approval • Examples include benzylpenicillin and doxycycline
Restricted or 'protected'	• Require an approval within a nominated time of the medicine being prescribed (e.g. within 24 hours) • Individual prescription review is required for prolonged use (beyond 48–72 hours) • Examples include broad-spectrum antimicrobials with potential to promote resistance – such as ceftriaxone, vancomycin, ciprofloxacin and meropenem – and those that are common targets for antimicrobial stewardship programs
Highly restricted	• Require discussion with a nominated expert to obtain approval before the medicine can be initiated, to ensure that use is appropriate and to enable ongoing patient follow-up • Often, a full, formal, specialist clinical consultation for these patients is also recommended • Examples include antimicrobials viewed as last-line agents and reserved for highly resistant pathogens, or medicines with high potential toxicity or high cost, such as echinocandins, colistin and linezolid

Management restricted approvals

- There are a few approaches tailored to hospitals workflow/resources:

1. Electronic approval system/Clinical Decision Support
    - 3rd party e.g. *Guidance, eASY, IDEA3S, TheraDOC, Treat*
2. AMS Pager
3. AMS hotline

ANTIMICROBIAL ADVICE AND APPROVALS

- Electronic decision support and approval system
  - **MANDATORY** to obtain approvals for restricted antimicrobials
- Training for interns, jRMOs

Education

- Passive
- *Active*
- Opportunistic: AMS rounds
- *E-resources*
- Clinical guidelines: AFWG, ANZMIG, IDSA, ECMM
- Phone apps

Review Antimicrobial prescribing

- Regular antimicrobial review and feedback to prescriber is the **Cornerstone of AMS**
- Most widely practice AMS strategy
- Importance of starting antimicrobials without delay (e.g. in severe sepsis) and review of microbiology (usually 48 hours turn around)

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Common interventions

1. Intravenous to oral (IV-to-Oral) switch
2. De-escalation (cf. escalation)
3. Dose optimisation
4. Therapeutic drug monitoring
5. Microbiology interpretation
6. Duration advice

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Intravenous to oral

- Guidelines
- Dependent on fungal infection (ID consult)
  - e.g. amphotericin B formulation use in cryptococcosis
  - e.g. candidiasis (echinocandin to azole)
- Dependent on antifungal agent
  - Azoles vs. other agents
- Dependent on host co-morbidity (renal dysfunction)

IV-ORAL SWITCH

Western Sydney Local Health District Antimicrobial Stewardship Program
IV TO ORAL SWITCH

Consider conversion from IV to ORAL antibiotics when ALL of the following apply:

1. Temperature <38^{0}C for 24 hours
2. Improving signs and symptoms
3. Oral/nasogastric intake tolerated
4. Suitable ORAL alternative available
5. Patient likely to be adherent with oral therapy
6. Patient has not been diagnosed with one of the conditions below:

Conditions where IV to Oral switch may NOT be appropriate:	
Bone and Joint Infections	Deep seated abscess
Cystic Fibrosis	Meningitis
Endocarditis	Bacteraemia

WSLHD Antimicrobial Stewardship Committee October 2015 Copyright WSLHD

Dose optimisation

- Certain indications for dose optimisation include
  - **Increase dose:**
    - Tissue penetration (e.g. meningitis, CNS, sanctuary sites)
    - Fungi with higher MICs (*N. glabratus, A. fumigatus*)
    - Augmented renal clearance (eGFR >130)
    - Sepsis/Septic shock, hypoalbuminemia
    - Extracoropeal Membrane Oxygenation (ECMO)
  - **Decrease dose:**
    - Renal impairment (eGFR<50)
  - **Depends on drug:**
    - Obesity, renal replacement therapy, drug interactions

TDM

Active process of individualising a dose by maintaining plasma/blood concentration

- Iterative process: **Give dose**

Measuring a concentration of a drug

Adjust dose /continue dose

Sources of PK variability

- Compliance
- Age –neonates, children, elderly
- Physiology- gender, pregnancy, albumin levels, renal impairment
- Drug-drug interactions, food interactions
- Genetic polymorphisms on metabolism

Duration

This is the most commonly requested advice

- Magic numbers based on convention vs. best evidence based medicine:
  - 6, 12 weeks? 6 months, 1 year, “don’t know”
- Can depend on clinical response but usually guided by Therapeutic Guidelines: Antibiotic

Evidence supporting AMS

- Benefits of effective AMS programs:
  - Reduced antimicrobial utilisation
  - Reduced acquisition costs of antimicrobials
  - Improved appropriateness of prescribing
  - Reduced adverse effects associated with antimicrobial use
  - Reduced Length Of Stay
- Balancing measures:
  - No increase in infection related mortality or morbidity

Entirety of published evidence up to 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

CrossMark

Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs

Styliani Karanika,[a] Suresh Paudel,[a] Christos Grigoras,[a] Alireza Kalbasi,[b] Eleftherios Mylonakis[a]

Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, Rhode Island, USA[a]; Medical Oncology Department, Dana-Farber Cancer Institute, Boston, Massachusetts, USA[b]

- 25,000 publications, 26 studies were analysed
- Compared pre vs post AMS program (range 6 mo – 6 y)

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AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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Total antimicrobial utilisation reduced by

20% (95% CI 7.5-30%)

Antifungal utilisation reduced by

40% (95% CI 16-62%)

Reduced Length of Stay

15%

Reduced antimicrobial costs

35%

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The AMS Team: fictional

- AMS Ward Rounds
  - Mondays, Wednesdays & Fridays @ 10:30am

Team

- ID Doctors
- AMS Pharmacists (dedicated)
- Infection Prevention & Control Team
- Clinical Microbiologist, Mycology scientist

What the AMS team does?

- Education
- Interpreting microbiology results
- TDM
- Advice, JMO support
  - De-escalation
  - Dose optimisation
  - IV to Oral Switch
  - Appropriate duration, cessation
  - Directed therapy/Broadening cover

Always happy to answer questions on the round!

There are no dumb questions

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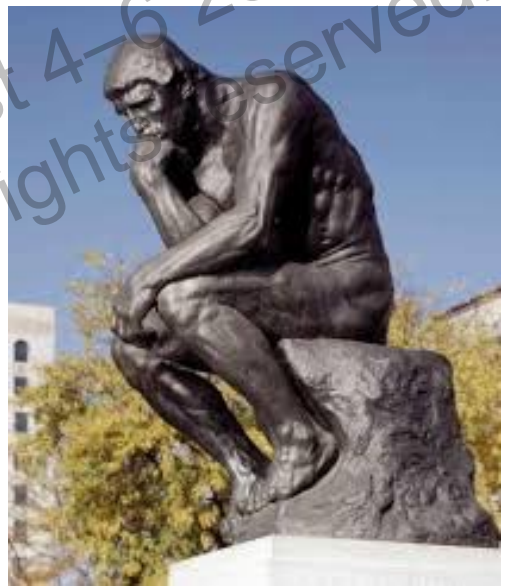
AMS Philosophy

Patient safety & quality of care

- Education vs enforcement
- Improve antibiotic literacy
- Minimise additional work load
- Maximise efficiency of the system



THANK YOU !

Factors influencing the outcome of antifungal therapy

Van t' Wout J. 1996

Immunological status
Underlying disease
Site of disease
Prosthetic material

HOST

resistance

FUNGUS

ANTIFUNGAL DRUG

efficacy

Virulence
Propensity to disseminate
Species
Drug resistance

Prompt aggressive therapy
Compliance
Drug pharmacokinetics
- tissue penetration
- drug inactivation

Elizabeth Johnson, with permission, PH England

Where can I learn more?

AUSTRALIAN MEDICINES HANDBOOK

MIMS ONLINE

UpToDate®

TRUVEN HEALTH ANALYTICS
MICROMEDEX® SOLUTIONS

SANFORD GUIDE
熱病 Antimicrobial Therapy

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