

Antifungal Stewardship

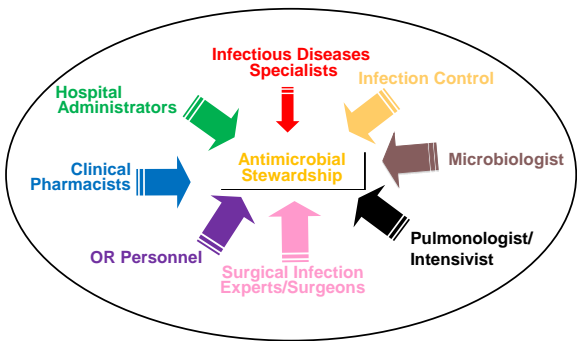
Methee Chayakulkeeree, MD, PhD, FECMM

Division of Infectious Diseases and Tropical Medicine
Department of Medicine
Faculty of Medicine Siriraj Hospital
Mahidol University

What is ASP?

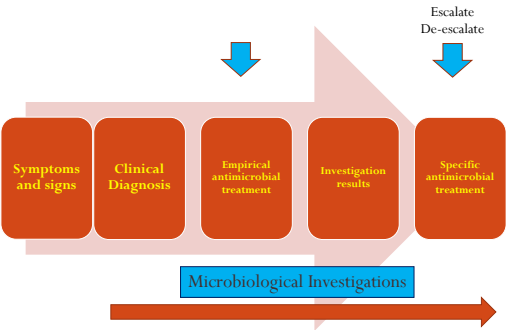
Antimicrobial Stewardship Program (ASP) is a key component of multifaceted approach to preventing emergence of antimicrobial resistance (AMR)

Building The (Dream) Team



Courtesy Dr. Pinya Rattana-umpawan

Antimicrobial Therapy



Antifungal Stewardship

- Antifungal stewardship
 - Coordinated interventions to monitor and direct the appropriate use of antifungal agents
 - In order to achieve the best **clinical outcomes** and **minimize selective pressure** and **adverse events**
- Parallel to ASPs whereby antifungal prescribing is optimized
 - Spectrum of activity
 - Pharmacokinetic and pharmacodynamic (PK-PD) properties
 - Duration
 - Route of administration

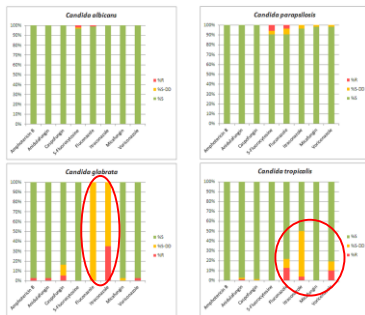
Virulence. 2017; 8(6): 658–672.

Differs from Antibacterial Stewardship

- Antibacterial
 - Clear relationship between antimicrobial usage and resistance
 - Clear relationship between clinical failure and resistance
 - Focus on **“start smart then focus”** (smart empirical therapy and step down appropriately)
- Antifungal
 - Focuses mainly on
 - Targeting treatment by identifying IFD
 - Reducing empiric treatment
 - Using diagnostics
 - Optimising treatment
 - TDM
 - Controlling costs

Agrawal S, et al J Antimicrob Chemother 2016;71:37-42.

Antifungal Susceptibility of *Candida*



Tan TY., et al. Med Mycol 2016; 54: 417-7

Problems

- How to do antifungal stewardship if...
 - You cannot diagnose the condition you are interested in
 - No formal surveillance is ongoing
 - Epidemiology
 - Resistance
- Antifungal expenditure continues to rise
 - Completely out of proportion with the scale of the problem
- Plethora of “Guidelines”
 - Based on low quality evidence

Harrison D et al Health Technol Assess 2013; 17(3):1-156
Pagano L et al. Haematologica 2006; 91: 1068-1075
Pagano L et al. Clin Infect Dis 2007; 45: 1161-1170

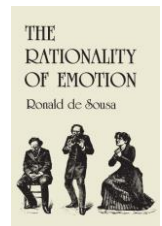
Areas Where Antifungal Use is Inappropriate/Irrational

- Prophylaxis of low risk patients
- Empirical therapy
 - Treating patients who do not have fungal infection
 - Haematology, intensive care
 - Treating patients already on prophylaxis
- Unnecessary prolongation of treatment
 - When to stop
 - When to switch iv to oral

Prophylaxis Empirical Pre-emptive Targeted

Reason vs. Emotion

- Infection associated with significant morbidity and mortality
- Delays in treatment associated with poorer outcome
- Signs and symptoms of systemic infection are non-specific
- Conventional diagnostic techniques **traditionally were** suboptimal
- FEAR led us to use empirical antifungals despite lack of evidence of efficacy



Diagnostic Strategy

Perform in patients likely to have invasive fungal infection and treat them with the safest and most effective drug

Do not perform in patients unlikely to have invasive fungal disease and adopt a WAIT-and-SEE policy

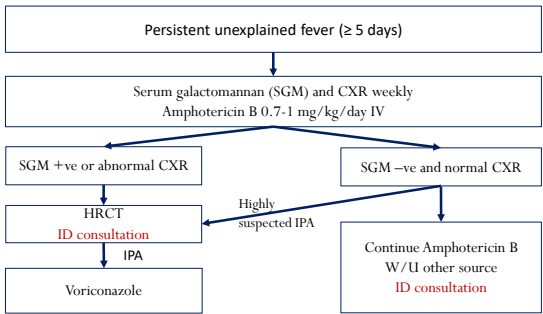
Principle of AMS/AFS

1. Education & guideline implementation
2. Drug use evaluation form
3. Antibiotic/antifungal restriction
 - Pre-prescription authorization
 - Post-prescription authorization
4. Prospective audit & feedback
5. De-escalation Therapy
6. OPAT
7. IV-to-PO conversion

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Empirical antifungal therapy in febrile neutropenia
Siriraj clinical policy



Freifeld A. et al. Clinical Infectious Diseases 2011;52(4):e56-e93

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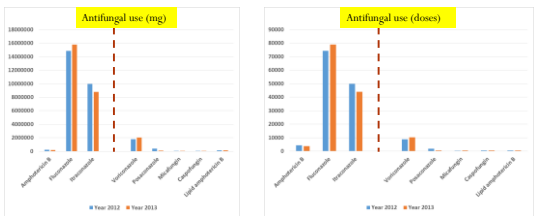
Control of Antimicrobial Use in Siriraj Hospital

No restriction	Drug use evaluation (DUE)	Restricted ATBs
<ul style="list-style-type: none">▪ Penicillins▪ Cephalosporins▪ Aminoglycosides▪ Fluoroquinolones	<ul style="list-style-type: none">▪ Piperacillin/tazobactam▪ Imipenem▪ Meropenem▪ Ertapenem	<ul style="list-style-type: none">• Colistin• Linezolid• Tigecycline

Control of Antifungal Use in Siriraj Hospital

No restriction	Restricted antifungals
<ul style="list-style-type: none">• Amphotericin B deoxycholate• Fluconazole• Itraconazole cab/cap	<ul style="list-style-type: none">• Liposomal amphotericin B• Itraconazole solution• Voriconazole• Posaconazole• Echinocandins<ul style="list-style-type: none">• Caspofungin• Micafungin

Antifungal Use in Siriraj Hospital



DUE/Restriction/Audit

- Pros:
 - Highly effective
 - Provide education opportunity
- Cons:
 - Need dedicated / full-time personnel
 - Loss of prescribing autonomy
 - Potential in patient safety due to a delayed initiation of therapy
 - Difficult for outpatients

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De-escalation Antifungal Therapy

Fluconazole susceptibility in *Candida* spp.

- *Candida albicans* - S
- *Candida parapsilosis* - S
- *Candida tropicalis* - S or SDD or R
- *Candida krusei* - R
- *Candida glabrata* - SDD or R



S – Susceptible; SDD – Susceptible dose dependent; R – Resistant

Empirical Treatment With Echinocandins:
De-escalation VS. Maintenance of Treatment

Variable	Deescalation (n=44)	Maintenance (n = 75)	P-value
APACHEII	19 (14–24)	23 (17–26)	0.022
SOFA	7 (4–9)	0 (6–12)	0.013
Fluconazole S or SDD	44 (100)	56 (74.7)	< 0.001
30-d mortality	5 (11.4)	33 (44.0)	< 0.001
90-d mortality	7 (15.9)	44 (58.7)	< 0.001

Garnacho-Montero J, et al. Critical Care Medicine 2018, 46(3):384-393

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IV-to-PO

- Cryptococcosis : AMB → fluconazole
- Histoplasmosis : AMB → itraconazole
- Talaromycosis : AMB → itraconazole
- Aspergillosis: IV Voriconazole → oral
- Candidiasis: AMB/ IV fluconazole → oral flucoconazole
- Mucormycosis : AMB → itraconazole

Need for Antifungal Stewardship?

- Antimicrobial stewardship (AMS) has largely focused on the judicious use of antibiotics
- Antifungal agents have received less attention

YES

- Deficiencies in prescribing behavior
- High drug cost
- Potential for toxicities, especially with long term use
- Significant drug interactions

Ananda-Rajah M et al. Curr Opin Infect Dis. 2012;25:107-115

Considerations for AFS

Need less	Need more
<ul style="list-style-type: none">• No empirical treatment until definite diagnosis• Diagnostic and therapeutic option available<ul style="list-style-type: none">• Histoplasmosis• Penicilliosis• Mucormycosis	<ul style="list-style-type: none">• Use of antifungal agents in colonization<ul style="list-style-type: none">▪ Candidiasis• Overuse in critically ill or immunocompromised patients• No definite criteria for empirical treatment (ICU)• No accurate and/or rapid diagnostic test<ul style="list-style-type: none">• Aspergillosis• Candidiasis

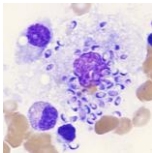
Scenario 1: A 30-year old woman



- HIV-positive
- Low grade fever for 1 month
- Multiple discrete skin lesions

Skin scrape wright stain

Diagnosis: Talaromycosis

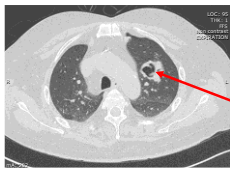


แนวทางการรักษา Amphotericin B

- ผสมใน 5% DW เท่านั้นจนได้ความเข้มข้นสุดท้ายไม่เกิน 0.1 mg/ml และบริหารอย่างช้าๆ 4-6 ชม.
- ให้ paracetamol 500 mg และ chlorpheniramine 1 เม็ดรับประทาน หรือ 1 amp ฉีดก่อนให้ยา 30 นาที เพื่อป้องกันไข้ และอาการหนาวสั่น
- หากผู้ป่วยมีอาการหนาวสั่นมากและเกร็ง อาจพิจารณาให้ hydrocortisone injection
- ผู้ป่วยที่ไม่จำกัดน้ำควรให้ NSS 500 -1000 ml IV 1-2 ชม. ก่อนให้ยา เพื่อป้องกันพิษต่อไต
- ให้ Potassium supplement เพื่อรักษากาเวโปตัสเซียมต่ำที่เกิดจากยา

ตัวอย่าง

Scenario 2: A 50-year old man post kidney transplantation



Possible IPA

Probable IPA

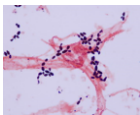
Serum galactomannan: positive
Culture from lung aspiration: *A. fumigatus*

Proven IPA

Diagnosis: Invasive pulmonary aspergillosis
Treatment: Voriconazole (pre-authorization, dose, route, duration, check DI, TDM)

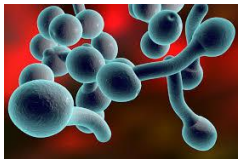
Scenario 3: A 60-year old man

- Admitted in ICU
- Colonic surgery with anastomosis leakage
- Broad spectrum antibiotic
- Central line indwelling
- Budding yeasts in urine and sputum
- Blood culture → budding yeast



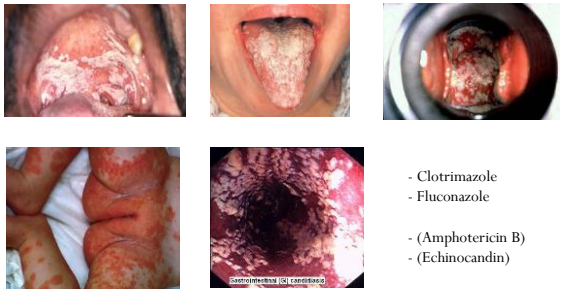
Diagnosis: Suspected candidemia
Treatment: Amphotericin B
Liposomal amphotericin B in kidney failure patients (pre-authorization)
Echinocandins (pre-authorization, proven *Candida* species with fluconazole resistance or severe disease)
→ De-escalatio therapy to fluconazole when appropriate

Invasive Candidiasis



- ✓ Candidemia* (most common)
- ✓ Disseminated candidiasis
- ✓ Deep organ candidiasis
 - ✓ Intra-abdominal candidiasis*
 - ✓ Endovascular candidiasis
 - ✓ Others

Mucocutaneous Candidiasis



Candiduria

- Asymptomatic candiduria
 - No treatment unless high risk for dissemination
 - Focus on elimination of predisposing factors
- Consider treatment in patients with high risk for dissemination
 - Urologic manipulations
 - Short course fluconazole or amphotericin B
 - Neutropenic patients and low birth weight infants
 - Treat as invasive candidiasis

Risk Factors for Candidemia

- Healthcare-related**

 - Critical illness; long-term ICU stay
 - Abdominal surgery; with anastomotic leakage
 - Broad-spectrum antibiotics
 - Central vascular catheter
 - Total parenteral nutrition
 - Hemodialysis
 - Solid organ transplantation
 - Glucocorticoid / chemotherapy
- Host-related**

 - Acute necrotizing pancreatitis
 - Hematologic malignancies
 - Solid-organ tumors
 - Neonates - low birth weight, and preterm infants
 - Candida colonization; particularly if multifocal

1. Kullberg, BJ., and Arendrup, MC. N Engl J Med 2015;373:1445-56
2. Chakrabarti, A. Intensive Care Med. 2015, 41, 285-295

Antifungal Susceptibility

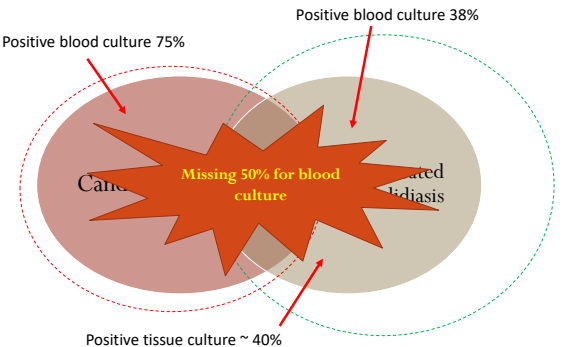
Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Amphotericin B	Echinocandins
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S → R	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S → R
<i>C. glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S to I	S
<i>C. krusei</i>	R	S-DD to R	S	S	S to I	S

S-DD, Susceptible dose-dependent; I, Intermediate; S, Susceptible

Prior azole exposure is associated with azole resistance
Increasing non-albicans Candida species

Modified from CID 2009; 48:503-35

Invasive Candidiasis



Clancy and Nguyen CID 2013;56:1284-1292

Diagnostic Tests



Tests	Sensitivity	Specificity	Turn-around time
Blood culture	21-71	NA	24-48 hours
Beta-D glucan antigen	65-100	31-79	24 hours
Candida mannan antigen and anti-mannan antibody	83	86	24 hours
PCR			
- In house	82-98	97-98	6-12 hours
- SeptiFast	48-72	99	3-4 hours
- T2 Candida panel	91	94	3-5 hours

Kullberg BJ and Arendrup MC.N Engl J Med 2015;373:1445-56

Candidiasis Guidelines

	Non-neutropenia			
	IDSA guidelines 2016		ESCMID guidelines 2012	
	Recommendation	Evidence	SoR	QoE
Echinocandins (caspofungin, micafungin, anidulafungin)	Strong	Moderate	A	I
Liposomal amphotericin B 3-5 mg/kg/day	Strong	Low	B	I
Fluconazole 400-800 mg/day	Strong	Moderate	C	I
Voriconazole 6/3 mg/kg/day	-	-	B	I
Amphotericin B lipid complex 5 mg/kg/day	Strong	Low	C	II
Amphotericin B deoxycholate 0.7-1 mg/kg/day	-	-	D	I

Pappas PG, et al. CID 2016;62:e1-50, Cornely OA, et al. Clin Microbiol Infect 2012; 18 (Suppl. 7): 19-37

Candidiasis Guidelines

	Neutropenia			
	IDSA guidelines 2016		ESCMID guidelines 2012	
	Recommendation	Evidence	SoR	QoE
Echinocandins (caspofungin, micafungin, anidulafungin)	Strong	Moderate	A (Cas, Mic) B (Anid)	II
Liposomal amphotericin B 3-5 mg/kg/day	Strong	Moderate	B	II
Fluconazole 400-800 mg/day	Weak	Low	C	II
Voriconazole 6/3 mg/kg/day	Weak	Low	C	II
Amphotericin B lipid complex 5 mg/kg/day	Strong	Low	C	II
Amphotericin B deoxycholate 0.7-1 mg/kg/day	-	-	D	II

Pappas PG, et al. CID 2016;62:e1-50, Cornely OA, et al. Clin Microbiol Infect 2012; 18 (Suppl. 7): 19-37

Specific Antifungal Treatment of Candidiasis:
De-escalation therapy

Candida spp.	Drug of choice
C. albicans	Fluconazole
C. parapsilosis	Fluconazole
C. tropicalis	Fluconazole (increased resistance)
C. glabrata and C. krusei	Echinocandins

Important

- Eye exam*
- Remove central line*
- For candidemia: treatment duration is **2 weeks after blood culture negative**

Empirical Antifungal Therapy for Invasive Candidiasis

Neutropenia

- Prolonged neutropenia
- Still febrile after 4 days of broad-spectrum anti-bacterial therapy
- Aim to cover both invasive candidiasis and aspergillosis
- Antifungal treatment
 - Echinocandins
 - Amphotericin B

Non-neutropenia

- High risk for candidemia/invasive candidiasis
- No clear guideline
- Antifungal treatment
 - Echinocandins
 - Amphotericin B
 - Fluconazole (mild disease)

The Challenges of Antifungal De-escalation

- Current guidelines (IDSA, ESCMID) **underappreciate** the challenges of de-escalation in the empiric context
- Clinicians are often reluctant to de-escalate therapy when a seriously ill patient is improving on broad-spectrum treatment
- Less than 40% of echinocandin-treated candidemic patients with fluconazole-susceptible isolates were de-escalated to fluconazole
- Only 50% of patients with less severe disease or C. albicans underwent de-escalation

Question

A 50-year-old woman with poorly controlled diabetes mellitus, presented with fever and right eye pain for 1 week.

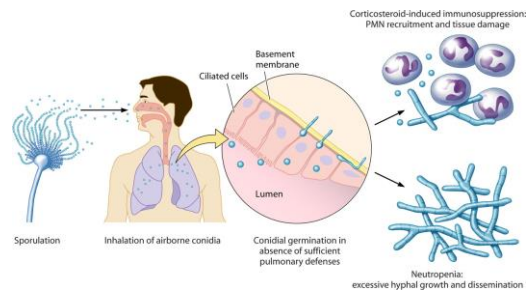
Physical examination revealed chemosis, proptosis, ophthalmoplegia and blurred vision at her right eye. CT scan show a soft tissue mass at her sphenoid sinus, extending into her right eye and cavernous sinus.

Biopsy of the sphenoid sinus was performed and showed inflammation with tissue invasion by **dichotomous branching septate hyphae**. Serum galactomannan was negative. Serum creatinine is 0.6 mg/dL.

What is the antifungal drug of choice?

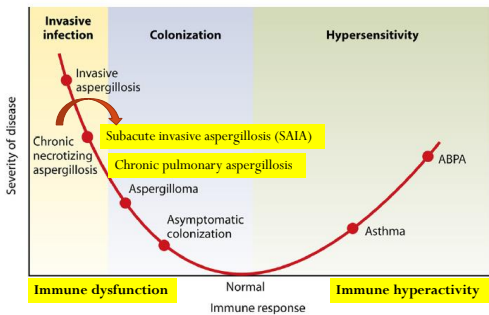
A. Amphotericin B deoxycholate
B. Liposomal amphotericin B
C. Voriconazole
D. Posaconazole
E. Caspofungin

Aspergillosis - pathogenesis



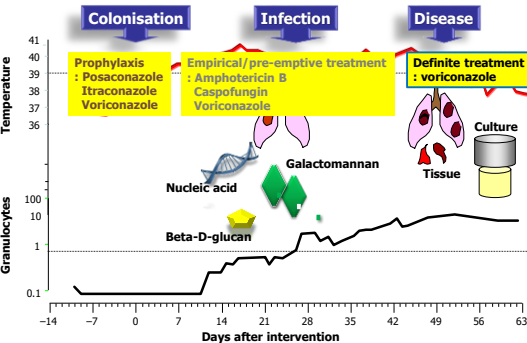
CLINICAL MICROBIOLOGY REVIEWS, July 2009

Pulmonary Aspergillosis: Spectrum



CLINICAL MICROBIOLOGY REVIEWS, July 2009

Invasive Pulmonary Aspergillosis in Neutropenics



Diagnosis of Aspergillosis Using Galactomannan

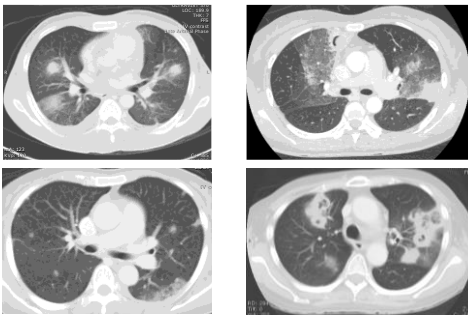
Galactomannan for diagnosis

- Serum and BAL galactomannan
 - In hematologic malignancies and HSCT
 - Sensitivity and specificity about 70-80%
 - Decreased sensitivity in patients receiving mold-active agents (e.g. amphotericin B, posaconazole, etc)
 - BAL galactomannan can be used in patients receiving mold-active antifungal agents
- Galactomannan can be used for treatment monitoring

Patterson TF, et al. Clin Infect Dis 2016;63(4):e1-60

Chest CT:

Halo sign, Nodules, Air crescent sign, Cavities



2016 IDSA Guidelines for Management of Invasive Aspergillosis

Primary treatment

- ✓ Voriconazole (strong recommendation; high-quality evidence)

Duration: at least 6-12 weeks

Alternative therapies

- ✓ Liposomal AmB (strong recommendation; moderate-quality evidence)
- ✓ Isavuconazole (strong recommendation; moderate-quality evidence)
 - ✓ Has activity against mucormycosis
 - ✓ Less adverse effect than voriconazole in RCT
 - ✓ IV form: No cyclodextrin solution
- ✓ Combination antifungal therapy with voriconazole and an echinocandin
 - Considered in select patients with documented IPA (weak recommendation; moderate-quality evidence)

Patterson TF., et al. Clin Infect Dis 2016;63(4):e1-60

Voriconazole Pharmacokinetics

- Non-linear PK
 - Due to saturable metabolic enzymes required for clearance
- Steady state-5-6 days
 - With loading dose → 24 hours
- > 90% oral bioavailability (take before meal)
 - Reduced by fatty meal
 - Independent of gastric pH
- CYP2C19, 2C9 and 3A4 responsible for clearance of voriconazole
- Drug interactions: Rifampicin, sirolimus, statin, calcium channel blocker
 - Omeprazole may increase voriconazole level
- Voriconazole concentrations vary up to 100-fold in patients receiving fixed dosages

Purkins L., et al. Antimicrob Agents Chemother 2002; 46(8): 2546-53
Denning DW., et al. Clin Infect Dis 2002; 34(5):563-71

Recommended Voriconazole Concentration (2016 IDSA Guidelines)

- Aim for dosing to achieve a voriconazole trough of
 - > 1–1.5 µg/mL for efficacy
 - < 5–6 µg/mL to minimize toxicity, primarily CNS toxicity
- Visual changes
 - Elevated voriconazole concentration
 - Resolve spontaneously
 - No long-term sequelae

Patterson TF., et al. Clin Infect Dis 2016;63(4):e1-60

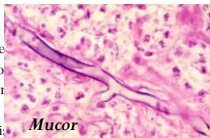
Voriconazole Dose Adjustment

Voriconazole trough level (mcg/ml)	Interventions
0.0 - 0.6	Increase dose by 100 mg/day
0.7 - 0.9	Increase dose by 50 mg/day
1.0 - 4.0	No change
4.1 – 5.5	Decrease dose by 50 mg/day
5.6 - 7.9	Hold dose Recheck daily trough level Restart at 100 mg/day less when trough level < 2.5
≥ 8.0	Hold dose Recheck daily trough level Restart at 50% dose reduction when trough level < 2.5

Poster Abstracts • OFID 2015:2 (Suppl 1)

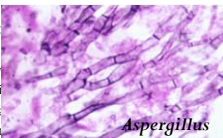
Question 1

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galactomannan was negative. What is the antifungal drug of choice?

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Mucor

Aspergillus

- A. Amphotericin B deoxycholate
- B. Liposomal amphotericin B
- C. Voriconazole
- D. Posaconazole
- E. Caspofungin

Antifungal Stewardship: Essential Elements

- Implement guidelines for antifungal use in institution
- Guidelines adapted to the local context
 - Recommendations for empiric therapy (use local guidelines)
 - Susceptibility testing
 - Rapid diagnostic tests (local facility):
 - HRCT
 - Galactomannan, beta D-glucan, PCR
 - Fungal culture, identification and susceptibility testing
 - De-escalation of empiric therapy
 - Dosing /dose adjustments
- Preprescription approval
- Postprescription review and feedback

Q and A

I have so
MUSHROOM
in my heart
for you



SAVE THE DATE

22 May 2020 (Fri)
Workshop on
Antimicrobial Stewardship Program

23-24 May 2020 (Sat-Sun)
Siriraj Infectious Disease Conference 2020

@ Siriraj Hospital, Bangkok

Contact: si.idconference@gmail.com
FB page: [Siriraj Infectious Disease Conference](#)

Organized by Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital