Pharmacologic Principles and Clinical Evidence for the Management of IFDs and Mucormycosis

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Disclosures

- Honoraria:
  - Gilead
  - Schering-Plough
  - Merck

Outline

- Antifungal drug armamentarium for treatment of mucormycosis
  - Liposomal amphotericin
  - Posaconazole
  - Isavuconazole

- Opportunities for improvement

A Tale of two cities

Case 1

- 53 male, pre-B ALL, diabetes
- #1. induction (CALG-B protocol), IPA (lung nodule, Asp PCR +)
  - Rx: L-AmB→ caspo 3 mo
  - Posa prophylaxis 600mg/d
- #2. consolidation, RLL"possible IPA" neg serum GM/ Asp PCR, no BAL
- Rx: L-AmB 3 wks→ vori with radiological regression (4/52) *BUT* then progression (10/52)

Keighley C, Kok J, Pollet S, Chen S (ASID 2015)

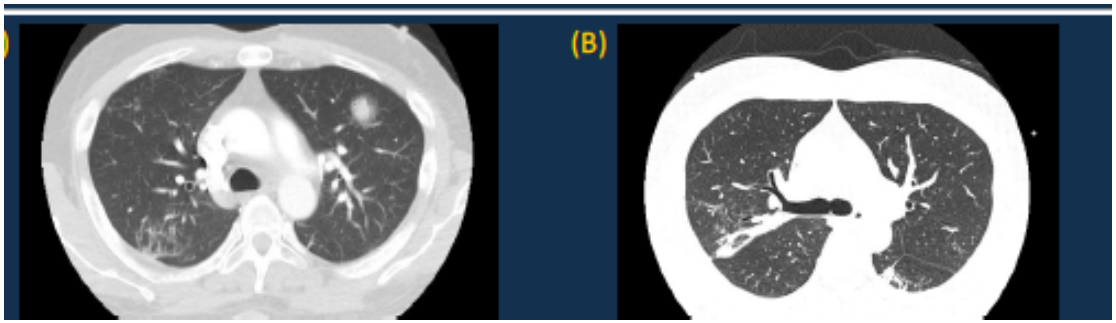
Case 1

#3. 6/52 later on vori ,levels therapeutic, LUL nodule with halo
-*Lichtheimia* in sputum

-Rx L-AmB 5mg/kg (3/52) PLUS posa 300mg IV/d

-posa TDM: 1809 ng/ml D7

-changed to posa oral suspension 200mg QID



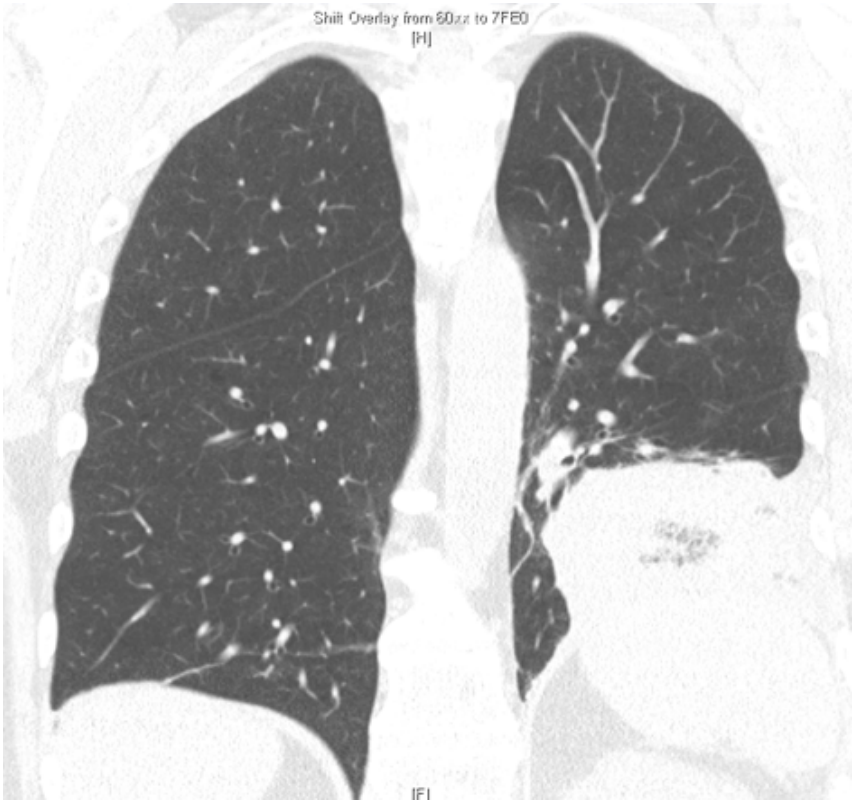
Keighley C et al. (ASID 2015)

Case 2

- 59 yo male gardener
- Aplastic anaemia Nov 2014
- ATGAM, Methylpred 45mg 3d; Cyclosporin 200mg BD; Pred 45mg/d
- Posa prophylaxis
  - 600mg/d oral suspension
- TDM day7: 300ng/L

→changed to posa 200mg QID

- Non-resolving LLL pneumonia

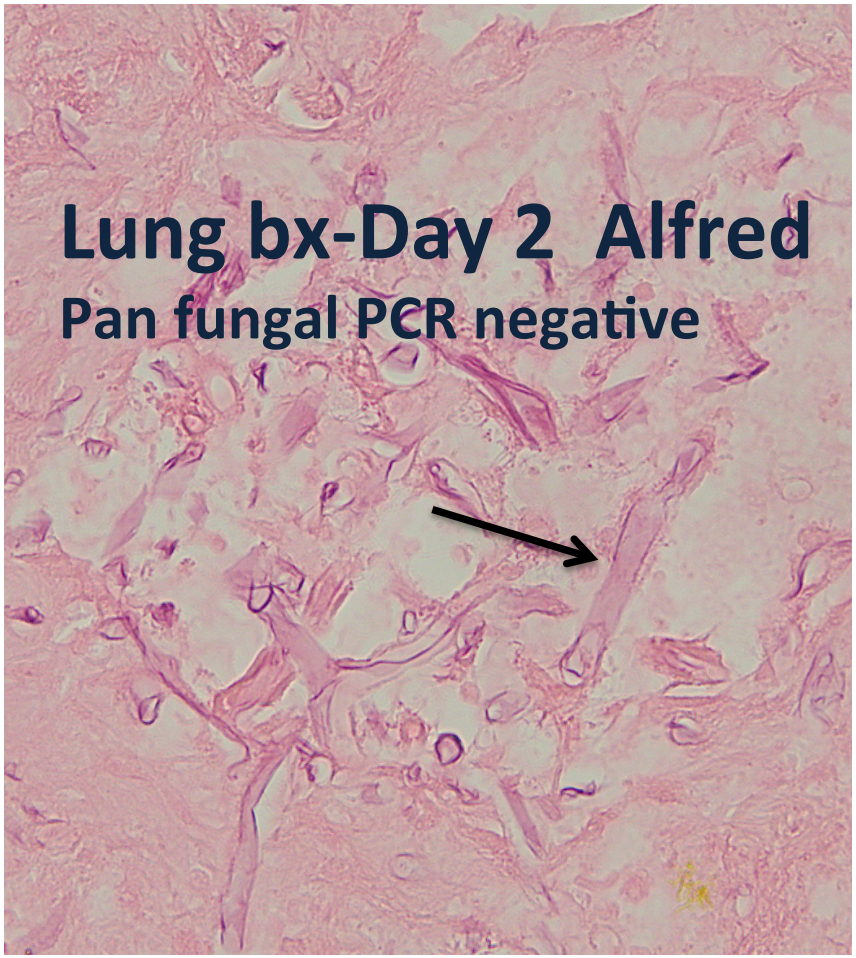


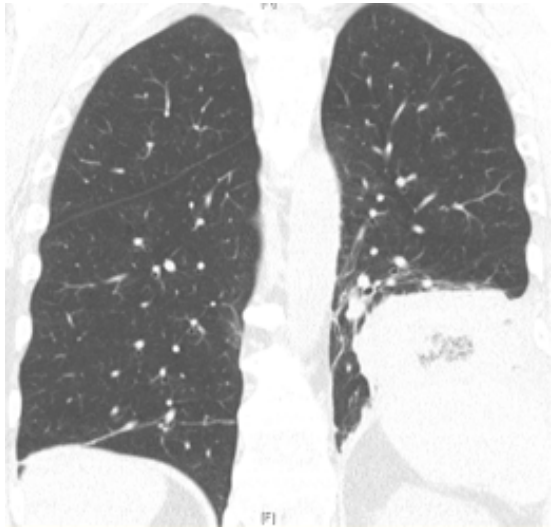
Graves B et al ISHAM 2015

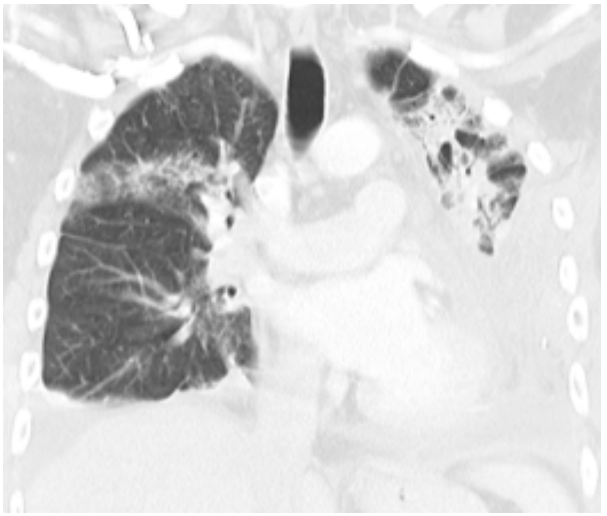
Case 2

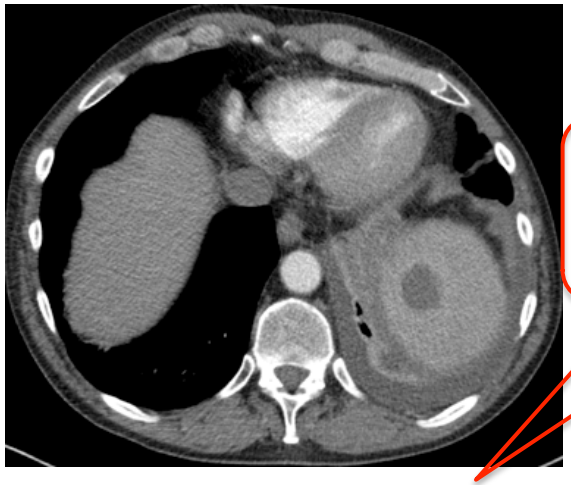
Background

- Chronic kidney disease
  - Focal and segmental hyalinosis & sclerosis, Nov 2012
  - Baseline eGFR 80ml/min

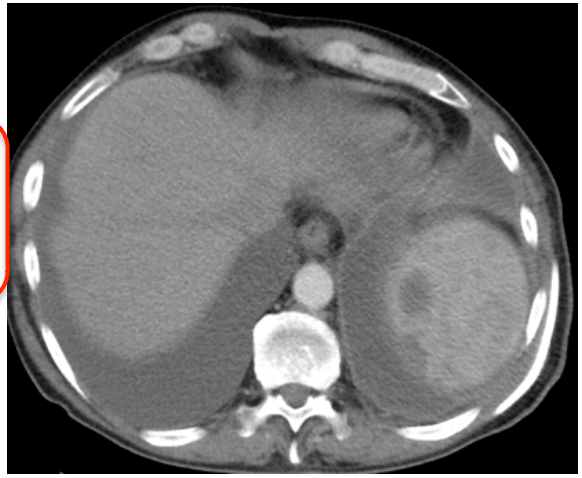








LLL lobectomy
D4 Alfred



D1 Rx 16/12/14

Surgery D8 24/12/14

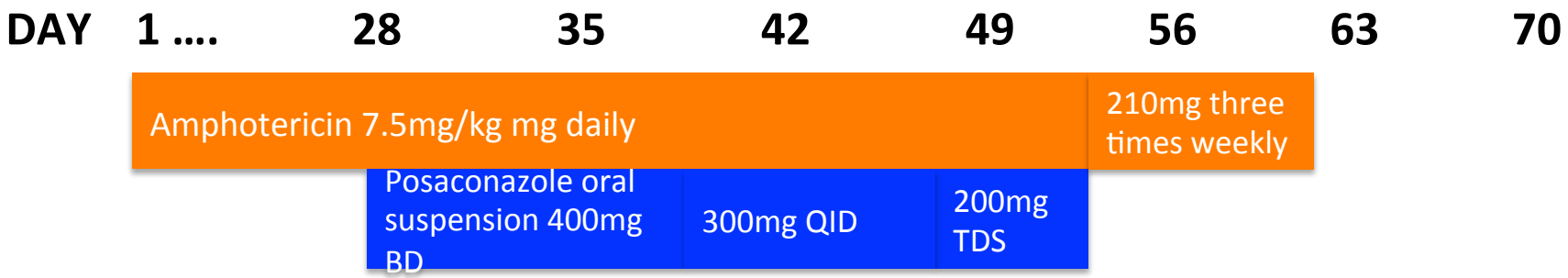
12/1/15

DAY **1** **7** **8** **14** **21** **28** **35**

Amphotericin 7.5mg/kg daily

Caspofungin

Posaconazole oral suspension 400mg BD

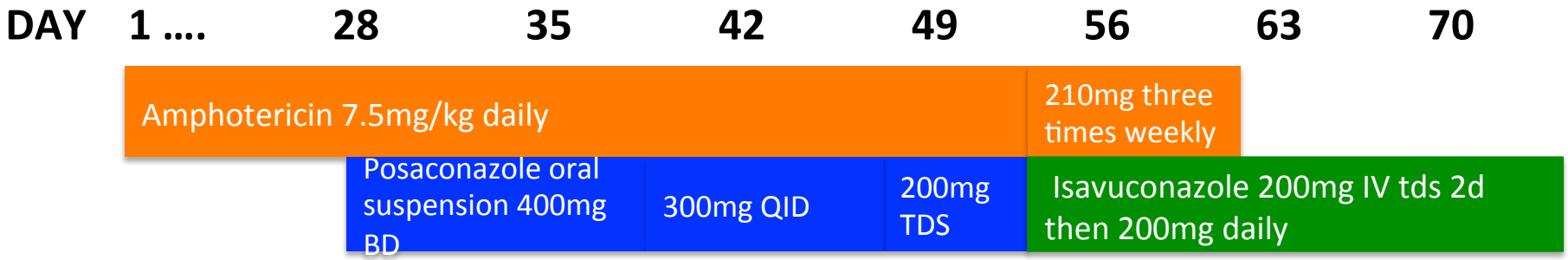


Posaconazole level (ng/ml)	**380**	**290**
Renal Function (creatinine)	**65**	**196**

- R pleural effusion drained – transudate, no evidence of mucormycosis
- Persisting nausea requiring dose reduction of Posaconazole
- Deteriorating renal function BUT clinically stable

What would you do?

- LAmB 5mg/d
- Combination Rx:
  - LAmB 5 mg/d and posa 300mg/d IV
  - LAmB 5mg/d & echinocandin
- Posa 300mg/d IV
- Isavuconazole



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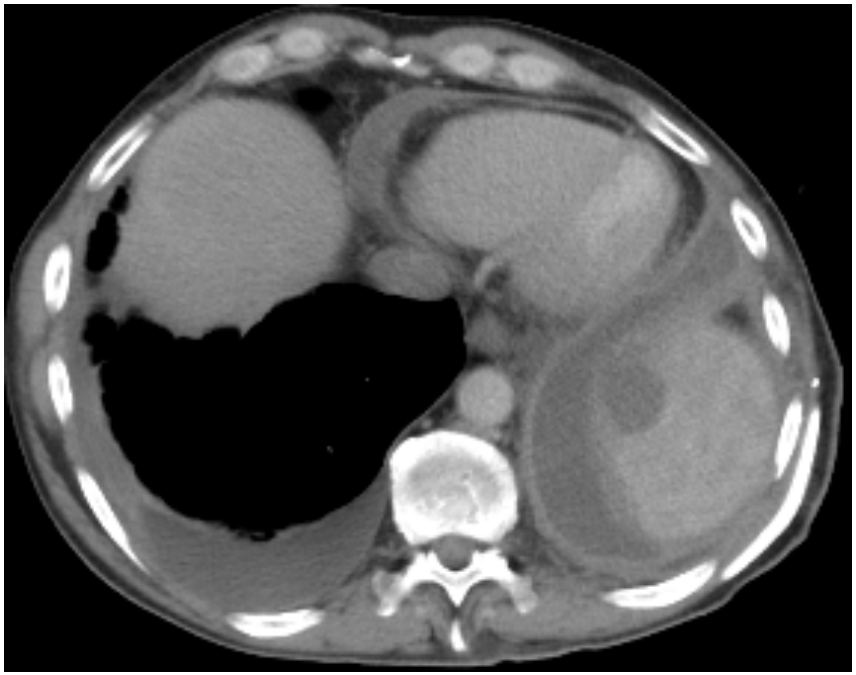
- Persisting nausea requiring dose reduction of Posaconazole
- Deteriorating renal function

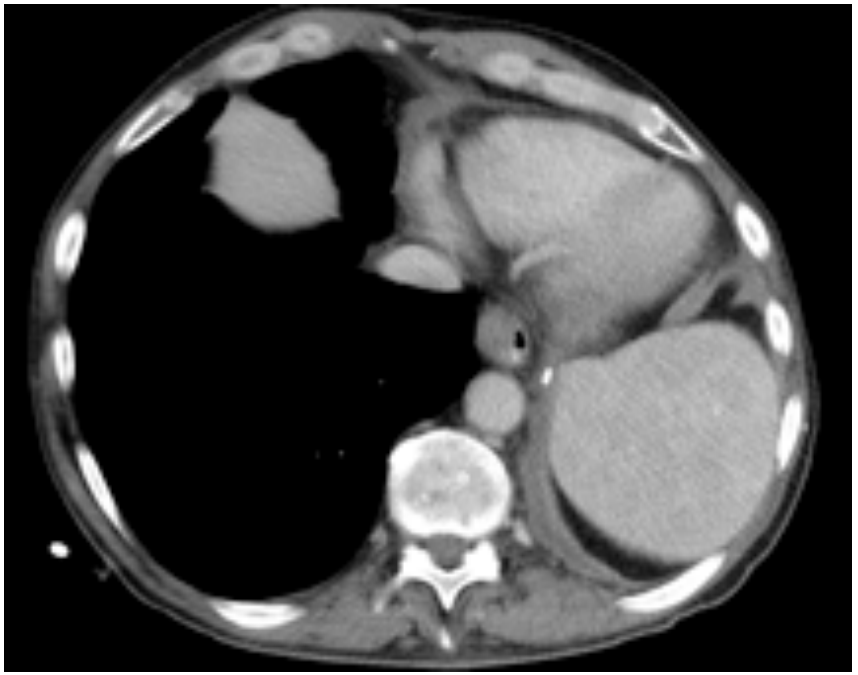
The isavuconazole levels are in the range as observed during phase III randomized registration trials. Thus there is no dose adjustment necessary, if well tolerated.

Sample ID	Analyte	Conc [ng/mL]
Day 3, pre-dose	BAL4815	2520
Day 3, pre-dose	BAL4815	2540
Day 5, pre-dose	BAL4815	2540
Day 5, pre-dose	BAL4815	2580
Day 7, pre-dose	BAL4815	2550
Day 7, pre-dose	BAL4815	2490

Case 2: progress



10 days prior to isavuconazole



11 wks of isavuconazole

Mucormycosis: Principles of management

- High index of suspicion
- Prompt diagnosis with h
- Rapid initiation of ge systemic antifungal therapy
- Debr ue, debride
- Reve l of underlying predisposing conditions

FUNGAL EMERGENCY!

» Kontoyiannis Blood 2011

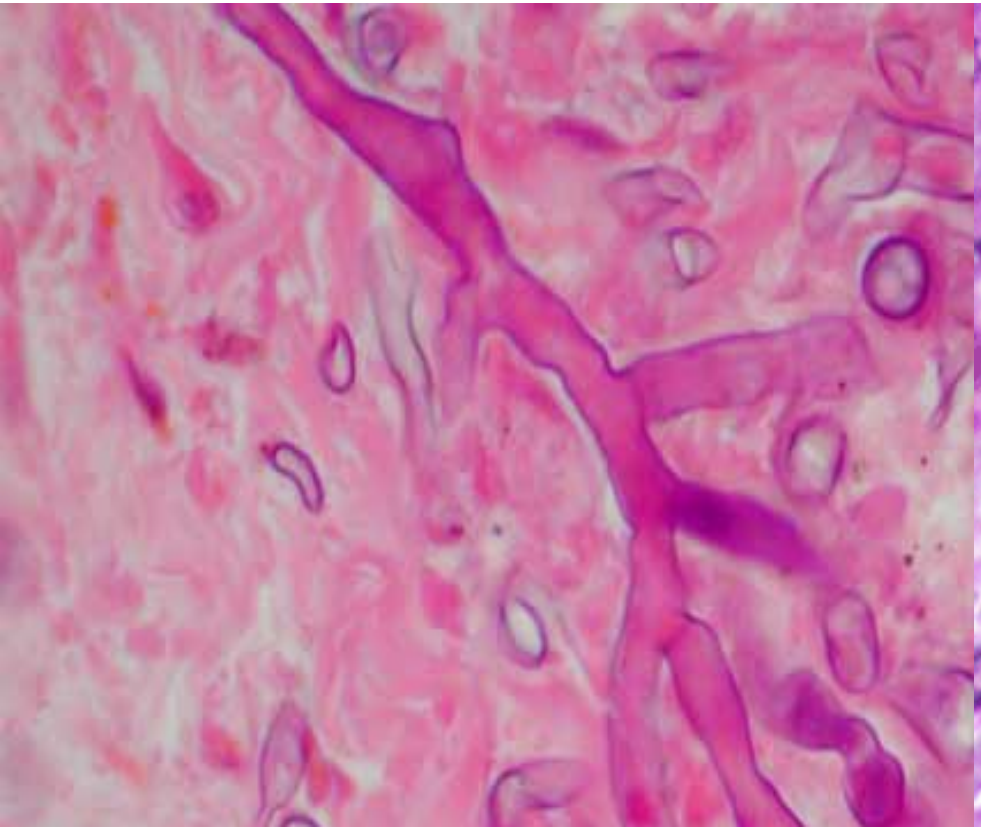
Does microbiology help?

- Blood cultures negative
- 30-50% of histopathology proven cases have **NEGATIVE** cultures
- GM is negative
- Beta D glucan is negative
- PCR is investigational

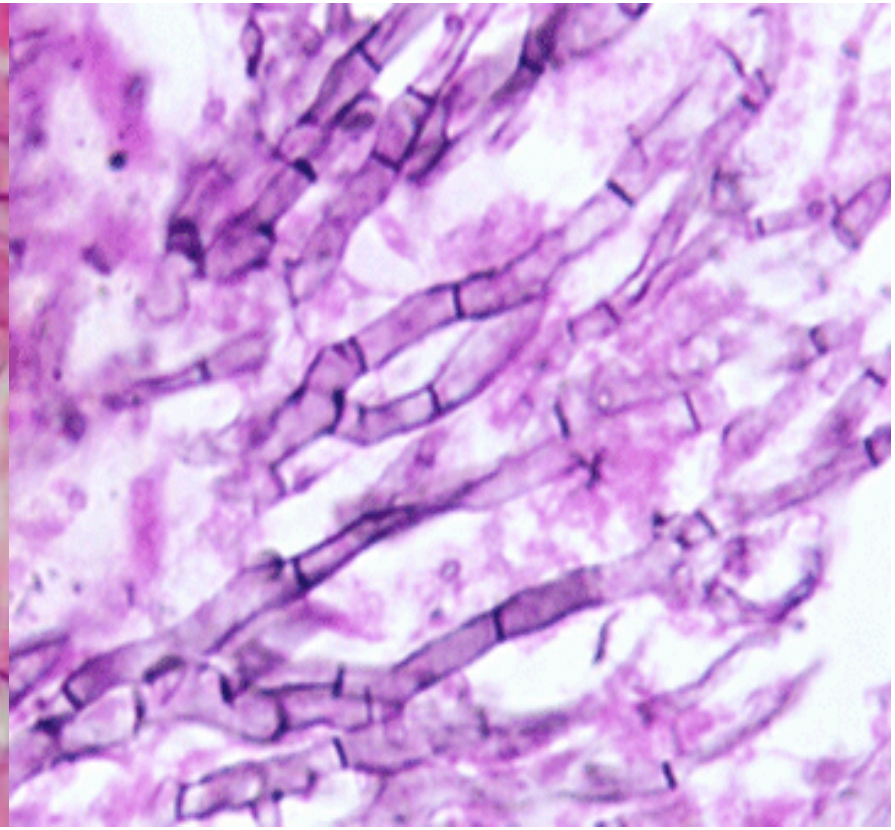
» Kontoyiannis Blood 2011
» Tacke et al Mycoses 2014

FOR DEFINITIVE DIAGNOSIS TISSUE IS NECESSARY

Rhizopus

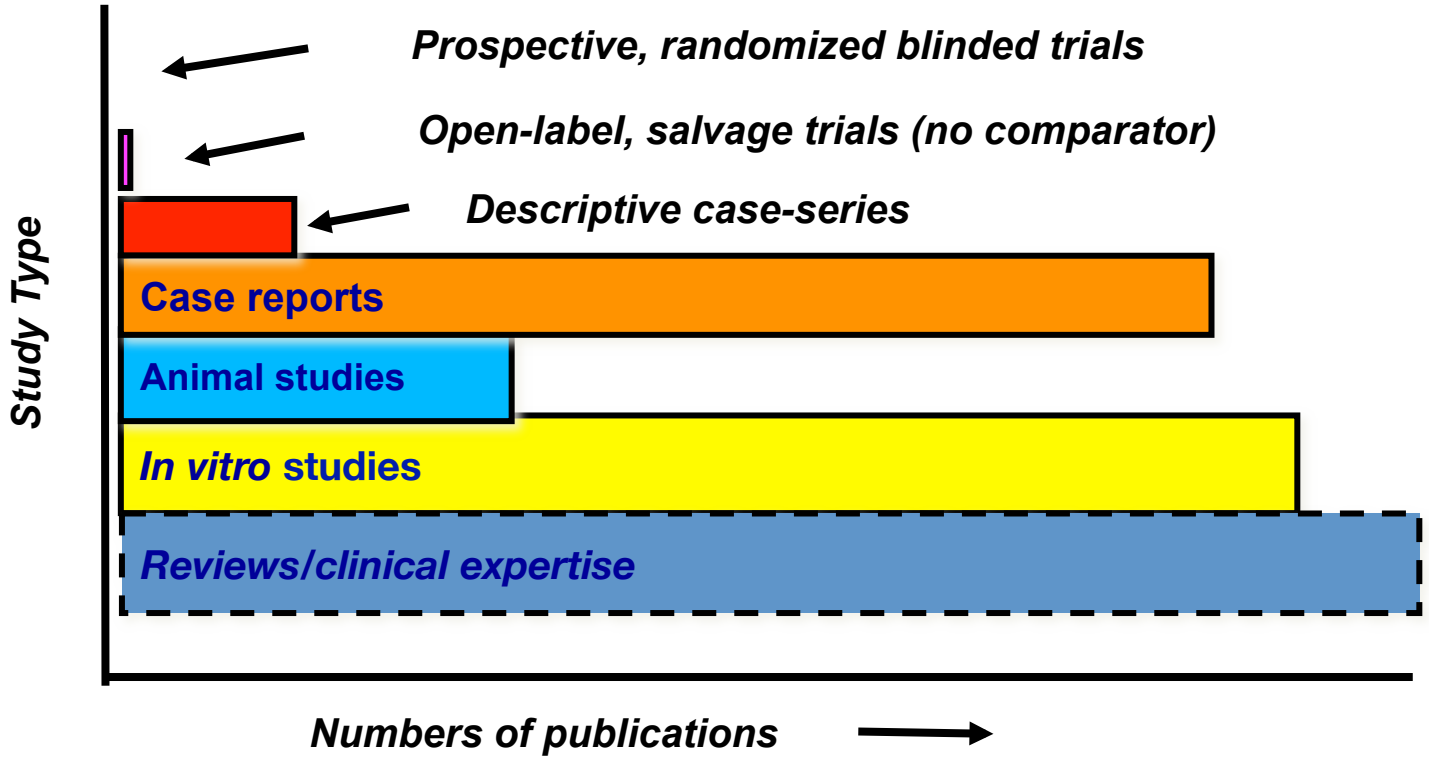


Aspergillus



Mucormycosis has Large ribbon like irregular aseptate hyphae

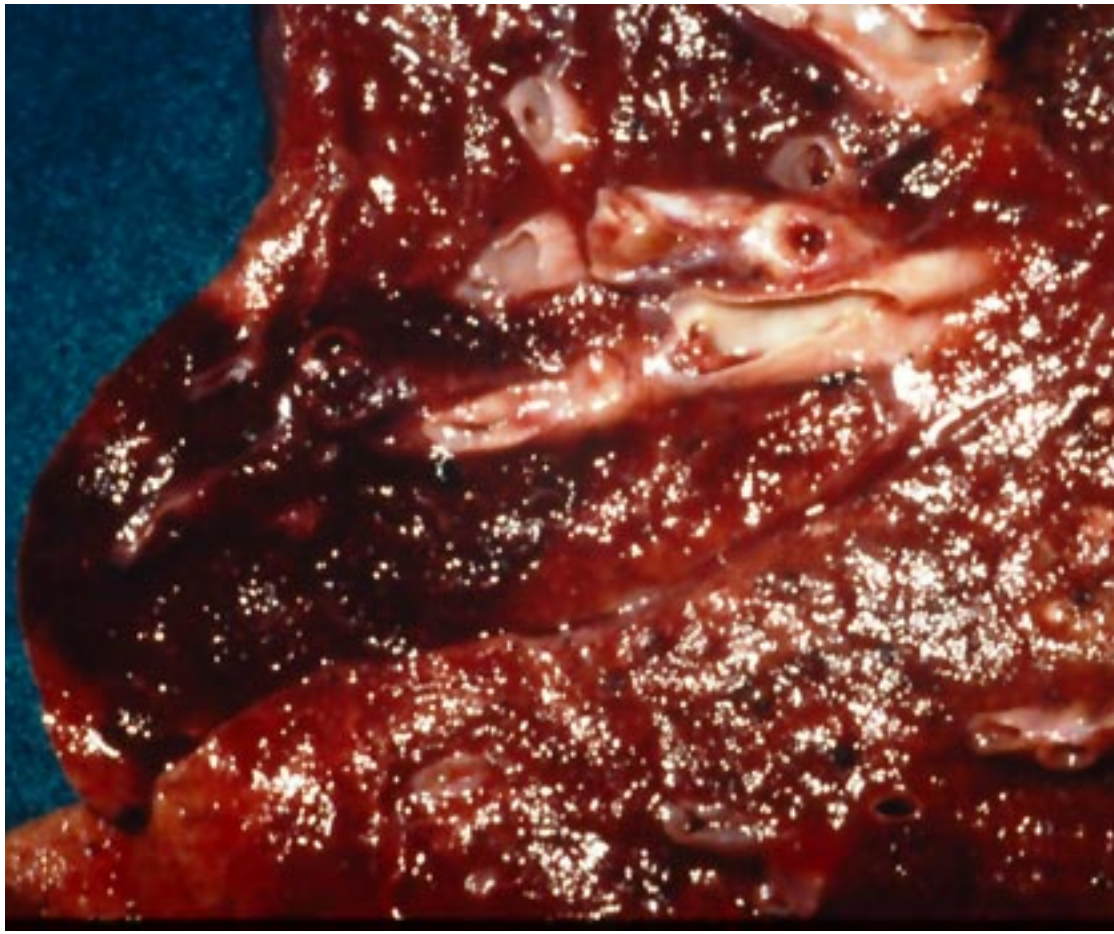
Evidence for the treatment of mucormycosis



Mucormycosis: target site & adjunctive therapies

- Surgery

- Adjunctive:
  - Hyperbaric therapy
  - Iron starvation:
  - unresolved



Amphotericin B is the back bone

Table 5. Treatment administered to 929 patients with zygomycosis, 425 of whom survived.

Treatment	No. (%) of all patients	No. of patients who survived/total no. who received the treatment (%)
Amphotericin B formulation		
Deoxycholate	532 (57)	324/532 (61)
Lipid	116 (12)	80/116 (69)

Reports 1940-2003

Responses vary from 30-71%

Roden et al CID 2005

Mucormycosis: posaconazole salvage studies

Study	Study design	N. of patients [n]	Survival [n/%]
Greenberg 2006[52]	Compassionate	24	19 (79%) at Day 90 post baseline
van Burik 2006[53]	Compassionate	91 (including 11 pts of study 1)	65 (62%) at 1 mo post end-of-therapy

Open label non-randomised multicentre, 1999-2001

Retrospective study of compassionate use program, 2001-2004

Greenberg et al AAC 2006

Van Burik et al CID 2006

Registry data

ECMM (European Confederation of Medical Mycology), 2005-2007

- n=230, median age 50 yrs (1 mo-87 yrs); children <14 yrs = 17
- Overall mortality 47%
- Factors associated with decreased mortality (OR):
  - Amphotericin B +/- posaconazole 0.14 p=0,006
  - Posaconazole & other in combination or sequential 0.09 p=0.0003
  - Surgery 0.21 p<0.001

Skiada et al. CMI 2011

FUNGISCOPE global registry 2006-2009

- n=41, mortality 49%

Ruping et al JAC 2010

Posaconazole "targets" for treatment: genesis

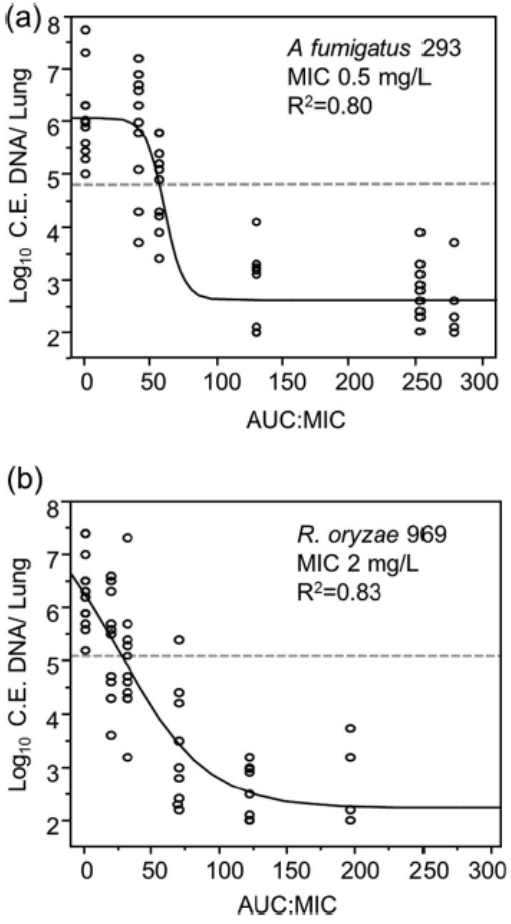
- Prob/prov IA; posa n=107, controls n=86, 1999-2001
- PK analysis n=67
- Exposure-response relationship observed in salvage treatment of IA
- NO upper threshold but target >1000ng/ml

		Plasma C_{max}		Plasma C_{avg}		
Quartile	No. of subjects[a]	Mean ng/mL	CV, %	Mean ng/mL	CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

Walsh et al CID 2007

Determining the optimal PD target for mucor

- Neutropenic murine model of pulmonary infection with *A. fumigatus* & *R. oryzae*
- AUC/MIC >100 assoc. with maximal early antifungal response in BOTH models
- Target achievable with new posa formulations up to an MIC of 0.125ug/ml



Lewis et al AAC 2014

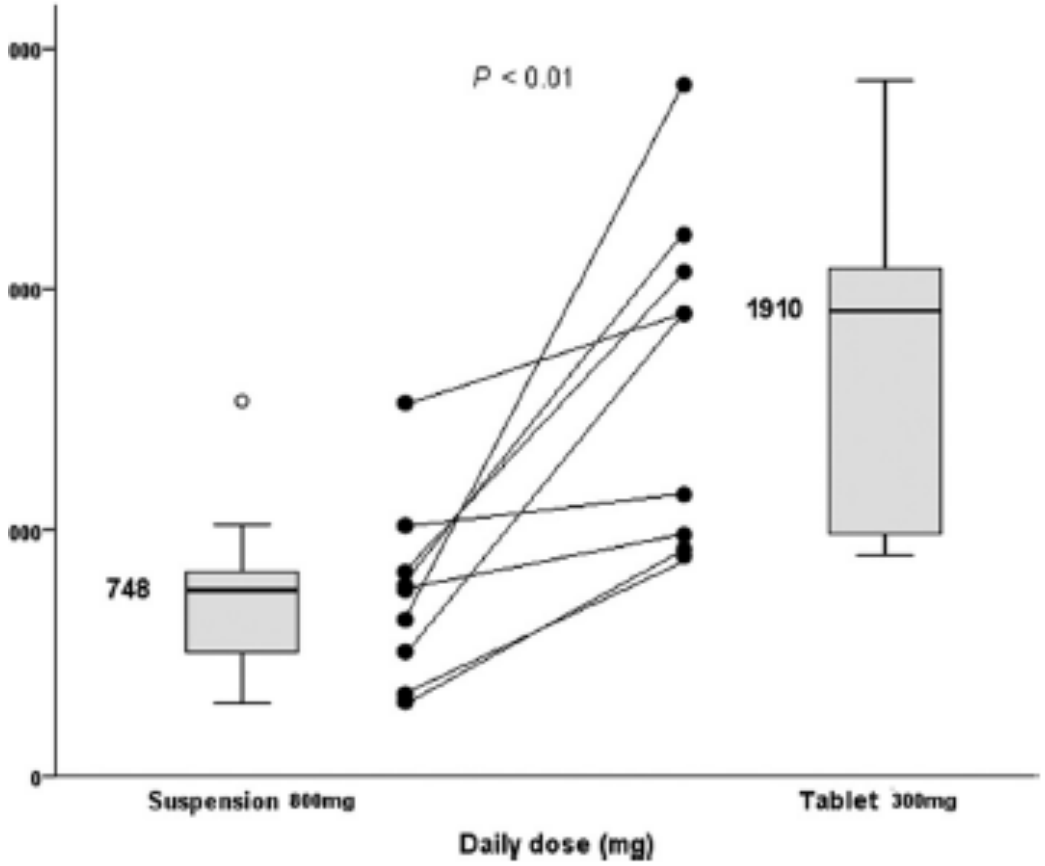
Comparison of posa oral suspension vs. tablets

	Posaconazole suspension	Posaconazole Tablet
	Treatment - Invasive Aspergillosis Study 0041	Prophylaxis in AML and HSCT Study 5615
	200 mg QID (hospitalized) then 400 mg BID	300 mg QD (Day 1, 300 mg BID)[a]
Quartile	pC_{av} Range (ng/mL)	pC_{av} Range (ng/mL)
Q1	55 – 277	442 – 1,223
Q2	290 – 544	1,240 – 1,710
Q3	550 – 861	1,719 – 2,291
Q4	877 – 2,010	2,304 – 9,523

MSD, data on file

Posaconazole tablets in the real world

- Suspension to tablets, 800mg/d
- n=12 leuk, IFDs in 9
- Treatment target (>1000ng/ml)
  - 83% tablets vs. 24% suspension



"almost all patients are now being transitioned to tablets"

Jung et al AAC 2014

Mucor: combination therapy

- Polyene-echinocandin
  - Polyene-caspo vs. polyene alone for rhino-cerebral 1994-2006
  - Successful outcomes 100% (6/6) vs. 45% (14/31) *BUT* majority diabetics 83%, neutropenia 12%, HSCT =2

» Reed et al. CID 2008

- L-AmB-posa (oral suspension 600mg/d to 3200mg/d)
  - n=32, 2007-2012 SEIFEM & Fungiscope
  - Outcomes:
    - 56% favourable (CR/PR) at 90 d
    - Mortality 59% at 3 mo
  - L-AmB-posa-deferasirox in 3

» Pagano et al. Haematologica 2014

Isavuconazole

- Favourable PK & physico-chemical properties
  - Prodrug isavuconazonium sulfate
  - Linear, predictable PK
  - Bioavailability >98% (indep. gastric pH, food)
  - IV→ oral (200mg tds 2d then 200mg daily)
  - T1/2=130h, OD
  - Moderate inter-individual PK variability (22-37%)
  - CYP3A4 metabolism (no adjustment with renal or hepatic failure, cyclodextrin absent)

Ananda-Rajah MR, Kontoyiannis DP Future Microbiol 2015, in press

Isavuconazole: clinical efficacy

- Mucorales: posa retains greatest in vitro activity
  - Posa MIC 1-4 ug/ml
  - Isavu 4-16 µg/ml

- VITAL study[1] :IFDs in patients with or without renal impairment, n= 149

Outcome	Primary n= 21	Salvage n=16	Total n=37
All cause mortality through D42	7 (33%)	7 (44%)	14 (38%)
Success (CR/PR) EOT, n=35	6 (32%)	5 (31%)	11 (31%)

- Isavu duration in 5 pts with CR=179-735 d
- Successful outcomes with MICs (0.25 to >16 µg/mL) in 14 baseline isolates

[1]Marty et al ID Week 2014

Ananda-Rajah MR, Kontoyiannis DP Future Microbiol 2015, in press

Mucormycosis: practice guidelines

Guideline, year	First line	Salvage
Aust/NZ Consensus Guidelines IMD, 2014[1]	L-AmB B -5-10mg/kg in CNS/ disseminated disease	Posa oral suspension C
ESCMID/ECM, 2014[2]	-Surgical debridement & antifungal AIIu -L-AmB ≥5mg/kg AIIu -Posa oral suspension BIIu	Posa oral suspension AIIu

[1]Blyth et al Int Med J 2014: NHMRC B=good, C=satisfactory

[2]Cornely et al CMI 2014: A=strong, B=moderate support

TDM is one element of an antifungal stewardship program

Characteristic	Comments
Process measures	
Antifungal drug consumption	
	Large fluctuations in small [illegible] because of the effect of outlier patients
Minimum standards of prescribing	
Documentation of treatment rationale	The reason(s) for prescription should be recorded in the
Dose optimization using therapeutic drug monitoring (TDM)	Resources should be available to ensure that the pharmac pharmacodynamic endpoints proposed for voriconazole optimize clinical efficacy and minimize toxicity are rapidly attained [75]
	The utility of TDM for posoconazole is unclear
	TDM for itraconazole is well established
Therapeutic streamlining	
De-escalation of empiric antifungal therapy	Assisted by the high negative predictive value of NCBTs such as galactomannan and *Aspergillus* PCR in the appropriate clinical context
	Best studied in neutropenic patients
De-escalation from broad to narrower spectrum drugs	Guided by susceptibility results and clinical response
Intravenous to oral switch therapy	Can decrease health-care costs/adverse events without compromising outcomes
	Suitable for agents with high oral bioavailability, for example, voriconazole
Timeliness and completeness of diagnostic investigations when IFD suspected	Improved diagnosis to guide therapy, such as ceasing or modifying antifungal therapy
Concordance of prescribing with institutional guidelines using an indication-driven approach	Clinical audit can be a labour-intensive process requiring chart review, online tools, for example, computerized decision support system or point prevalence surveys.
	May be best performed targeting areas where there is reasonable quality evidence and/or institutional guidelines [illegible] antifungal prophylaxis [illegible]
	[illegible] timeliness, appropriateness and adequacy of initial antifungal therapy
Outcome measures	
IFD incidence in targeted groups	Targeted surveillance of patients at highest risk for IFDs, that is, allogeneic HSCT recipients and patients with AML undergoing chemotherapy for initial remission; refractory or relapsed disease.
	Requires prospective surveillance
	Evolves in response to changing practices, for example, formulary changes
Antifungal drug expenditure	Patient quality and safety initiatives encompass AFS programmes and should not be driven by cost
	Subject to fluctuations in purchase contracts, formulary changes, variations in ordering
	Targeting specific high-cost drugs, for example, liposomal amphotericin, intravenous voriconazole, [illegible] efficient means [illegible]
Structural measures	[illegible] practice guidelines

Process measures
-treatment rationale
-**dose optimisation using TDM**
-descalation of empiric therapy
-IV to oral switch
-diagnostic aggressiveness

Outcome measures
-IFD incidence/surveillance
-drug expenditure

Structural measures
-clinical practice guidelines

Ananda-Rajah, Slavin, Thursky; Curr Opin Infect Dis 2011

Key Points

- L-AmB is the backbone of therapy for mucormycosis
  - Combination therapy with azoles or echinocandins unresolved
- Posaconazole & isavuconazole for salvage, step down therapy, favourable PK allowing earlier switch
- Good outcomes not solely dependent on choice of antifungal drug
  - Co-ordinated response (MDM: bronchoscopists, pharmacy, lab, clinicians)
  - Early diagnosis, prompt initiation of treatment, surgery, hyperbaric therapy
  - Antifungal stewardship
  - Knowledge of local epidemiology
- Epidemiology: fragmented, publication delays, incomplete case-capture
- Guidelines struggle to keep pace with change