CIDARA THERAPEUTICS

TIMM 2019

Integrated Symposium

Nice, France

October 2019

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CIDARA THERAPEUTICS

Prevention & Management of IFI-
Mind the Gap(s)!

Integrated Symposium - TIMM 2019
Nice, Acropolis Convention Center, Nice, France

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11 October 2019
Cidara Therapeutics Integrated Symposium
TIMM-9, Nice France

Is it time to rethink echinocandin dosing?

Russell Lewis
Associate Professor, Infectious Diseases
Department of Medical and Surgical Sciences
University of Bologna

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Treatment of Candidemia / Invasive Candidiasis
Unmet Needs

Bart-Jan Kullberg, M.D.
Center for Expertise in Mycology Radboudumc/cwz
Radboud University Medical Center
Nijmegen, The Netherlands

Radboudumc Center for Infectious Diseases

Radboudumc

4

Rezafungin for Treatment of Invasive Candidiasis

George R. Thompson III, MD
Associate Professor
Division of Infectious Diseases
Department of Internal Medicine
Department of Medical Microbiology and Immunology
University of California-Davis Medical Center

UCDAVIS
UNIVERSITY OF CALIFORNIA

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PREVENTION OF INVASIVE FUNGAL INFECTIONS IN VULNERABLE HOSTS

KIEREN A. MARR MD, MBA
PROFESSOR OF MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE
DIRECTOR, TRANSPLANT AND ONCOLOGY INFECTIOUS DISEASES
VICE CHAIR OF MEDICINE FOR INNOVATION IN HEALTHCARE IMPLEMENTATION

CIDARA THERAPEUTICS

Prevention & Management of IFI- Mind the Gap(s)!

Integrated Symposium – TIMM 2019

Nice, Acropolis Convention Center, Nice, France

Welcome and Opening Remarks

Oliver A. Cornely MD, FACP, FIDSA, FAAM, FECMM

Director and Chair, Translational Research & Clinical Trials Center
University of Cologne

Consultant, Infectious Diseases
Director, European Mycology Excellence Center
University Hospital of Cologne

HOUSEKEEPING

Mobile phones

Question cards

Microphones

Mind The Gaps!

Epidemiology

Resistance

Drug-drug interactions

… to mention just a few …

Vendredi, le 11 octobre en Europe

79 candidaemia cases → **TIMM is an orphan disease meeting**

Dimanche, le 10 novembre → **We all love Sundays, but**
29 dead by that Day 30 (37%)

Candidemia incidence is increasing

Non-albicans proportion is increasing

Koehler P et al. Clin Microbiol Infect 2019; 25(10): 1200-1212.

Resistance

C. parapsilosis	x	Fluconazole
C. glabrata	x	Azoles, echinocandins
C. auris	x	MDR → XDR → PDR
A. fumigatus	x	Azoles
A. flavus	x	Amphotericin

Drug-Drug Interactions

New drugs in oncology

- Are welcome advances
- Many increase risk for IFI
- Usually interact with triazoles
- Such interaction not evaluated in oncology drug development

Mind the Gaps!

16:50 - 17:05	PK/PD Optimized Echinocandin Dosing	Russel E. Lewis
17:05 - 17:20	Unmet Needs for Treatment of IC/Candidemia	Bart J. Kullberg
17:20 - 17:40	Rezafungin for Treatment of Candidemia/IC	George R. Thompson
17:40 - 18:00	Current Challenges for prophylaxis of IFI	Kieren Marr
18:00 - 18:10	Q&A	Panel
18:10 - 18:15	Closing Remarks	Oliver A. Cornely

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Is it time to rethink echinocandin dosing?

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ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

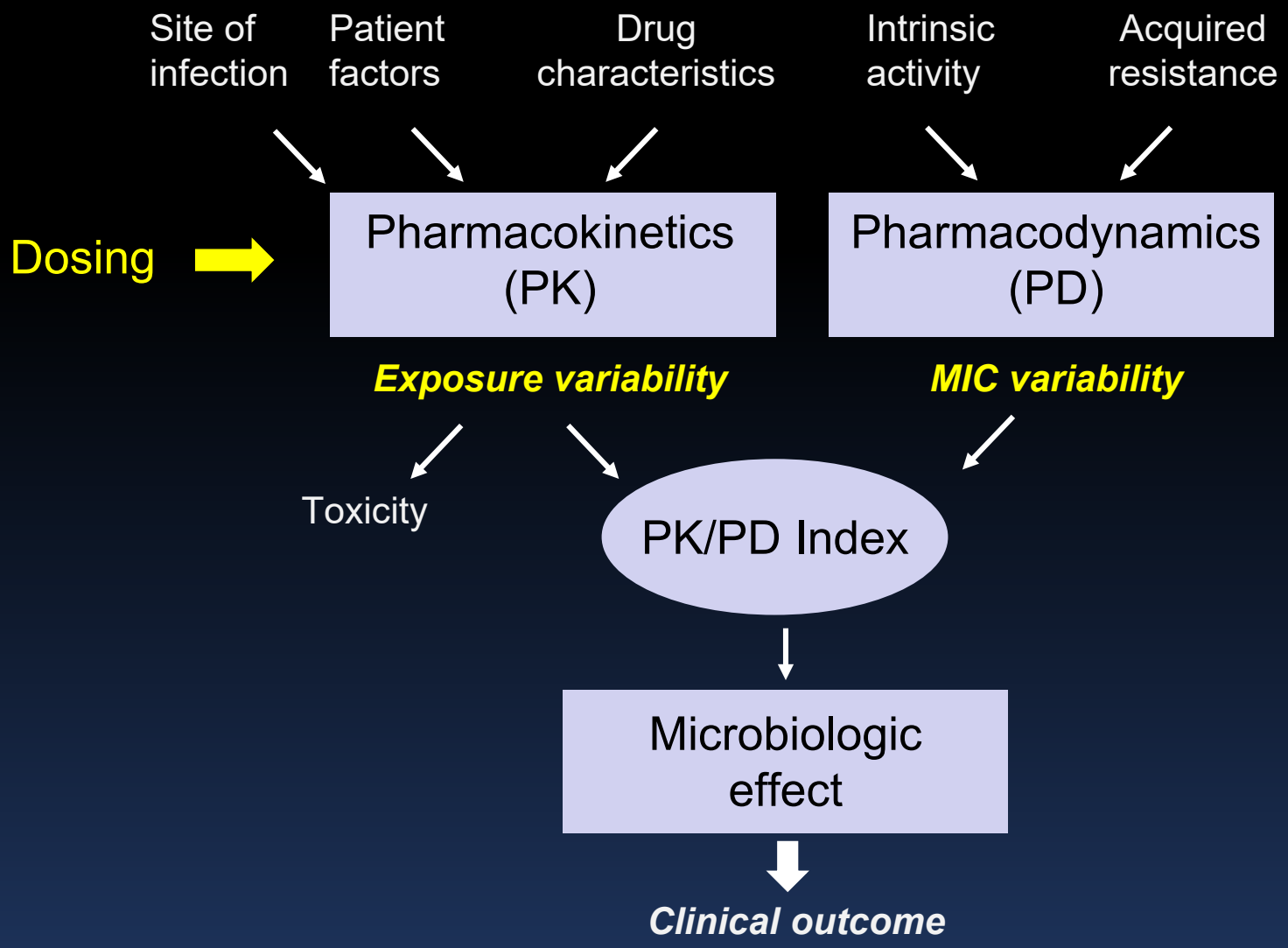
Disclosures

- Research support: Merck Inc.
- Advisory committees: Gilead, Cidara, F2G

“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D.
(1849-1919)

The uncertain science of antibiotic dosing



Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Echinocandin exposures are variable in critically-ill patients

- **Pharmacokinetic point prevalence study (n=68 ICUs):[1]**
  - **Included patients receiving caspofungin/ anidulafungin**
    - **Cmax, AUC_{0-24}, Cmin** ~50% lower values than reported in healthy volunteers
    - **Cmax, AUC_{0-24}, Cmin** ~40% lower values than reported in previous ICU PK studies

- **Empirical micafungin in ICU patients with sepsis, organ failure and *Candida* colonization (EMPIRICUS trial):[2,3]**
  - **Empirical micafungin 100 mg/day was not associated with improved fungal-free survival vs. placebo by day 28**
  - **Measured micafungin blood concentrations were lower than expected → increased clearance (low albumin) and obesity[4]**

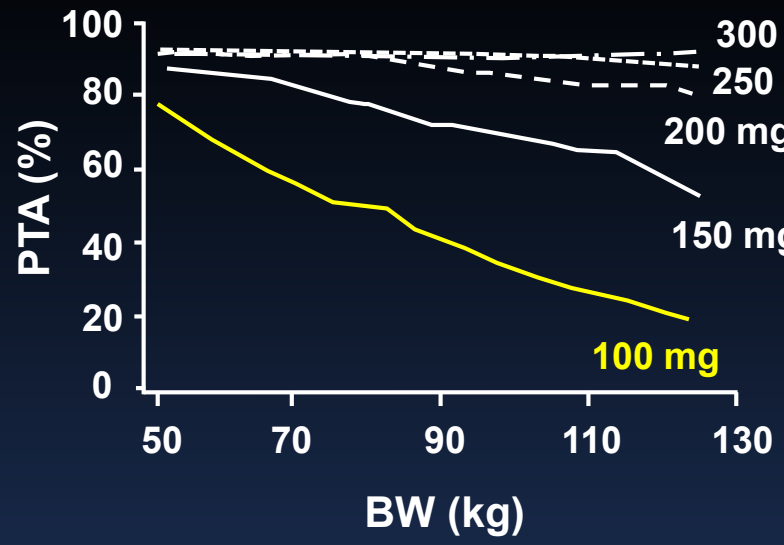
[1] Sinnollareddy M et al. *Crit Care* 2015;19(1):1.
[2] Timsit JF, et al. *JAMA* 2016;316(15):1555–64.
[3] Jullien V, et al. *J Antimicrob Chemother* 2017;72(1):181–9.
[4] Lempers et al. Antimicrob Agents Chemother 2015; 59: 4403 – 9

Micafungin 100 mg/day probability of target attainment (PTA)*

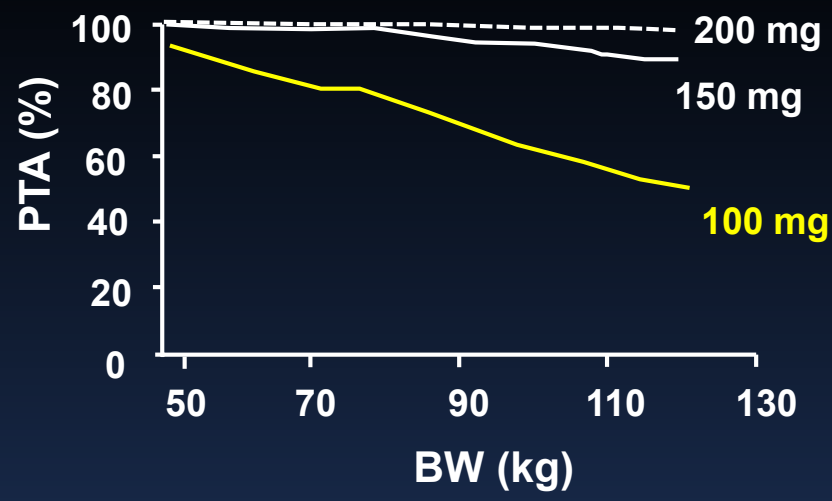
A PK/PD autopsy of the EMPIRICUS trial

PTA* was ≥ 90% in *Candida albicans* and *Candida glabrata* infections, except when the MIC was ≥0.015 mg/L

***C. albicans* MIC=0.016 mg/L; SOFA < 10**



***C. albicans* MIC=0.016 mg/L; SOFA ≥ 10 (25% decrease in clearance)**



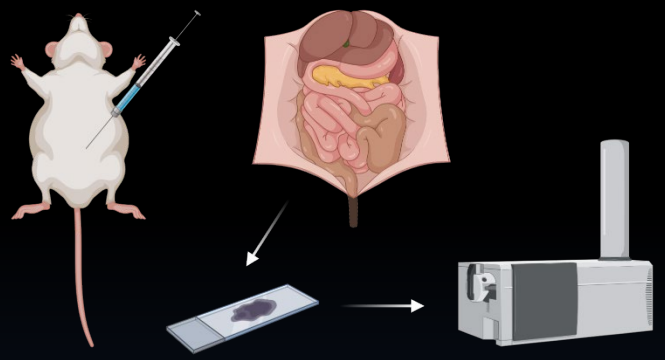
Median patient weight: 84.5 kg (48-141)

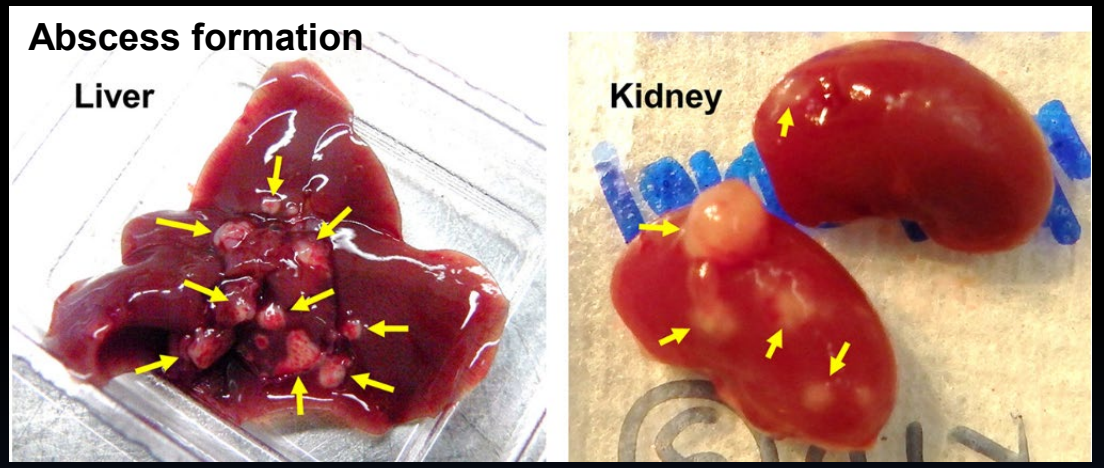
Jullien V, et al. *J Antimicrob Chemother* 2017;72(1):181–9.

* Total micafungin AUC/MIC > 5000

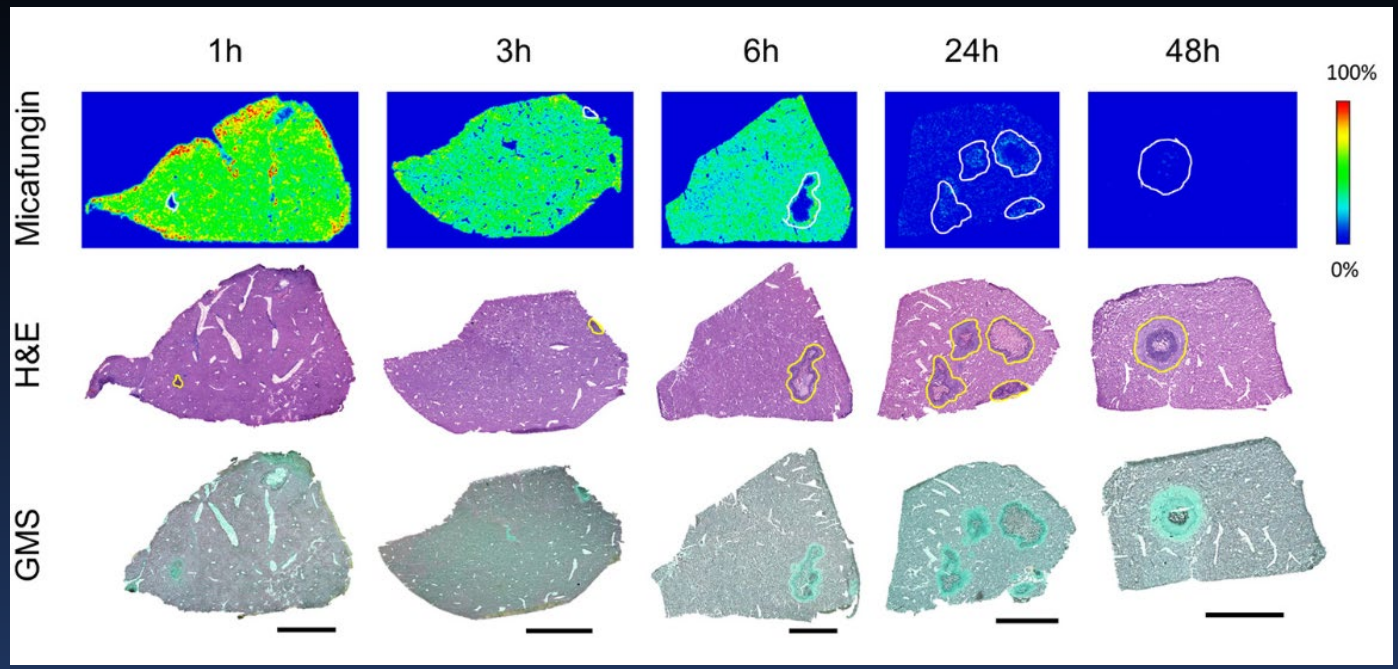
Echinocandin drug penetration at the site of infection
Intraabdominal abscess model

IP infection model: 1x10^7 *C. albicans* with sterile stool





Matrix-assisted desorption ionization mass spectrometry imaging technology

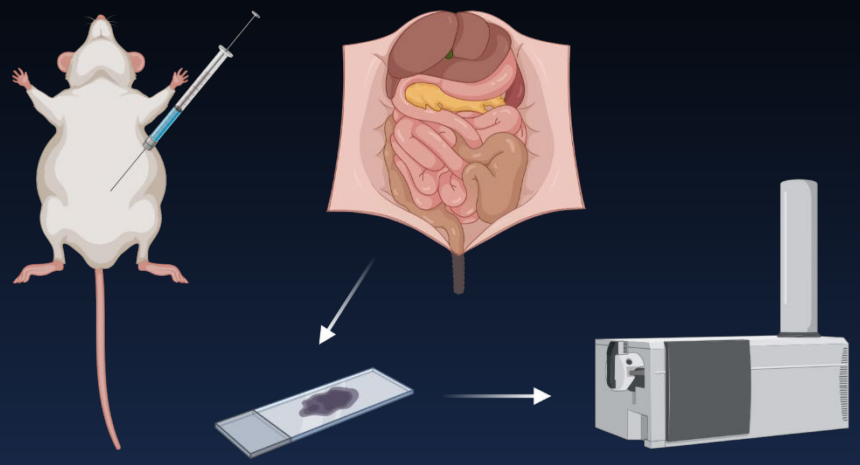


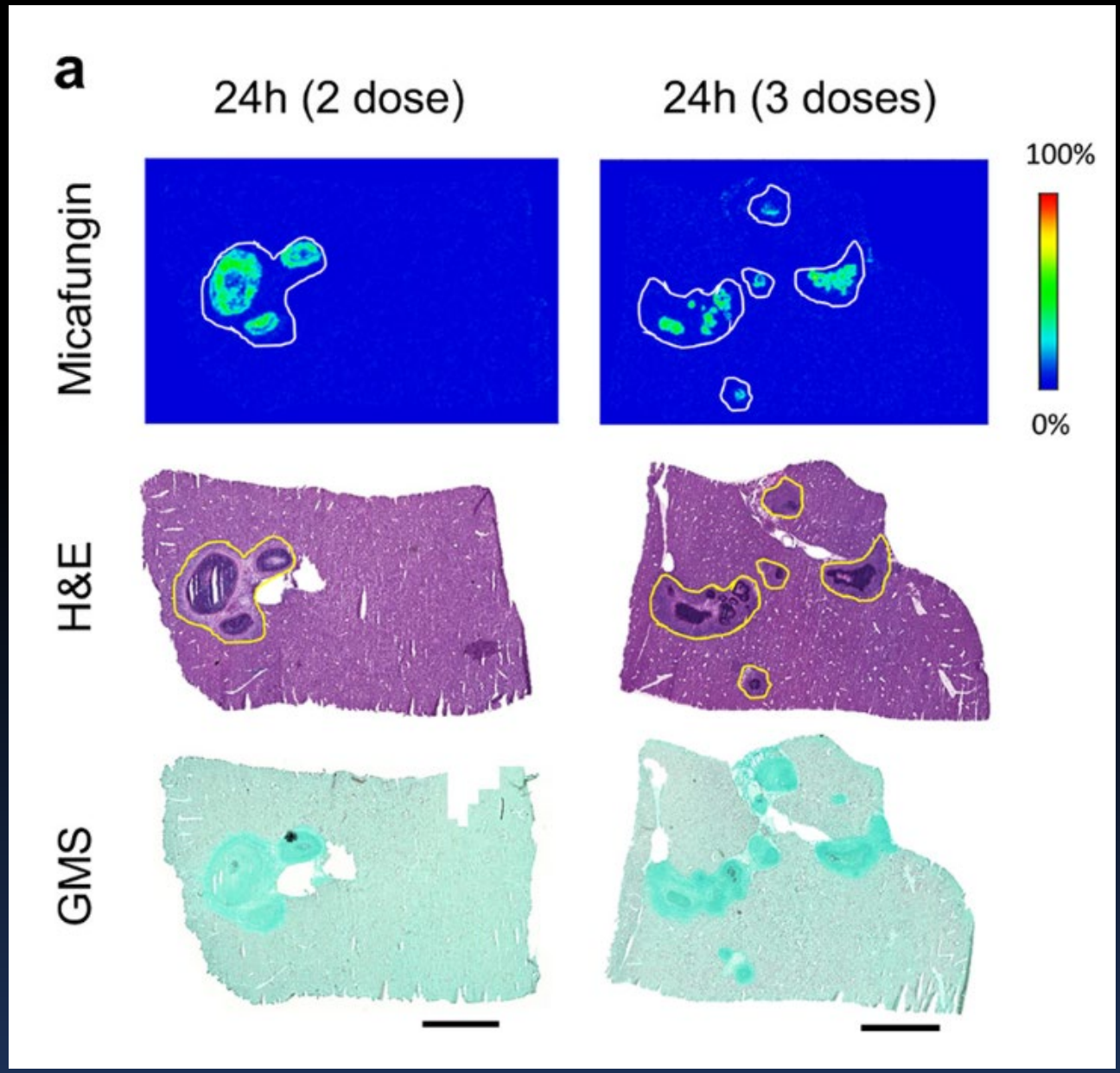
Liver lesions after single dose experiment

Zhao Y et al. Antimicrob Agents Chemother 2017;61(10).

Echinocandin drug penetration at the site of infection

Intraabdominal abscess model multiple micafungin doses



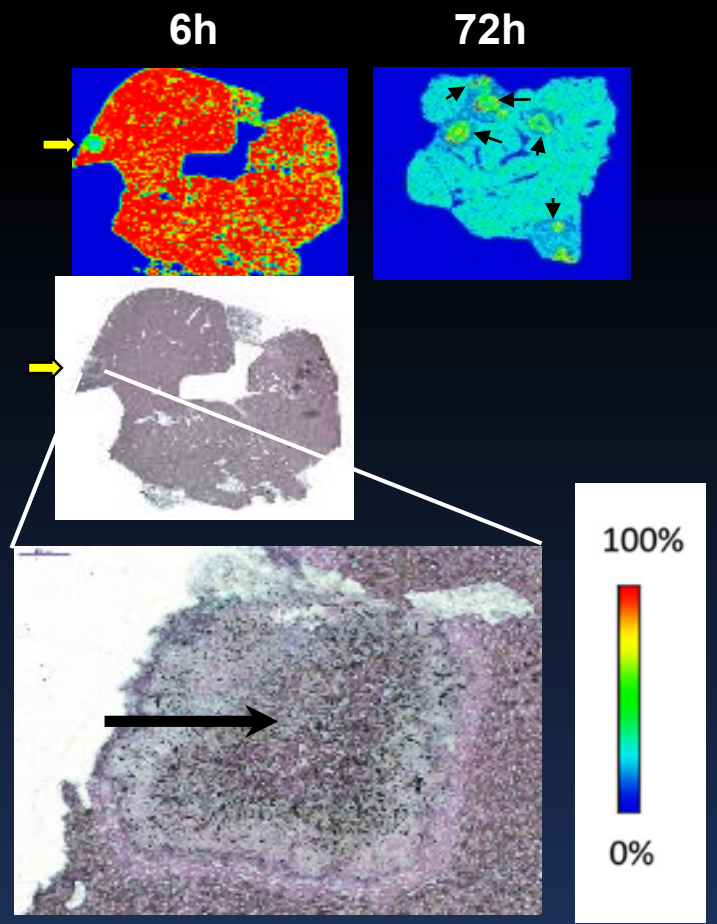


Liver lesions after 2-3 micafungin doses

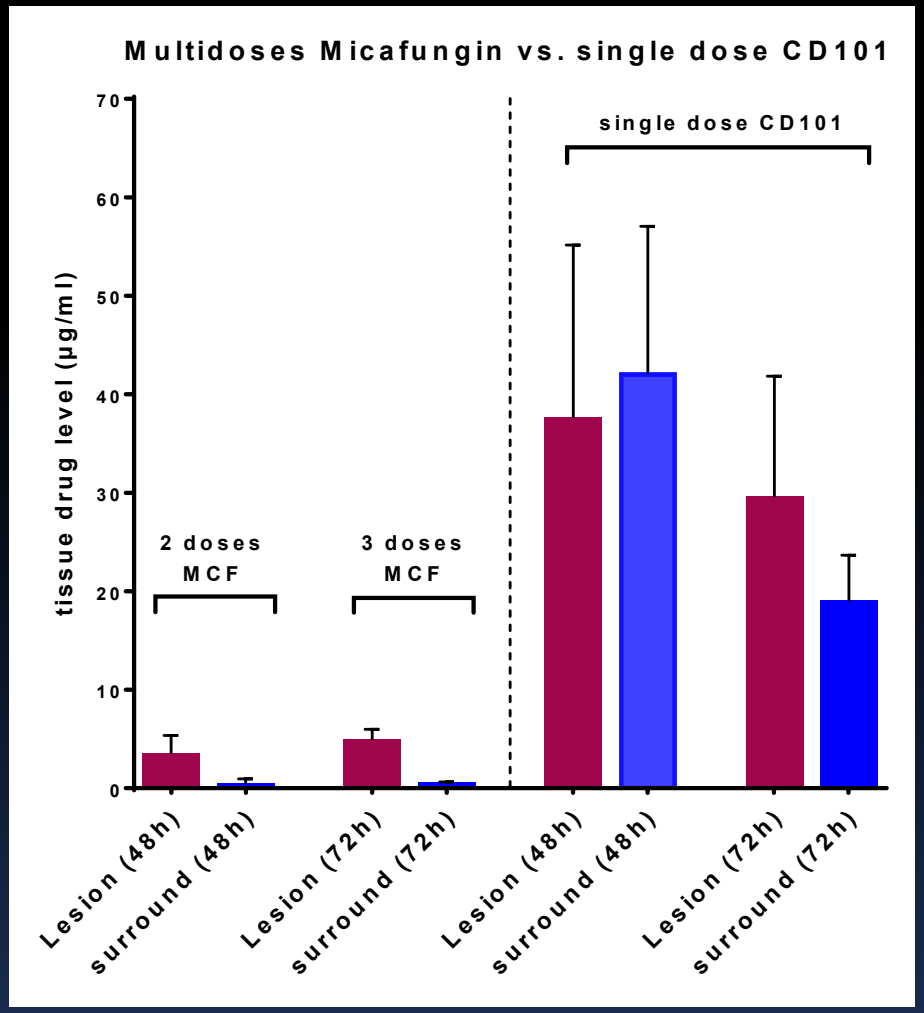
Zhao Y et al. *Antimicrob Agents Chemother* 2017;61(10).

Rezafungin penetration at the site of infection

Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

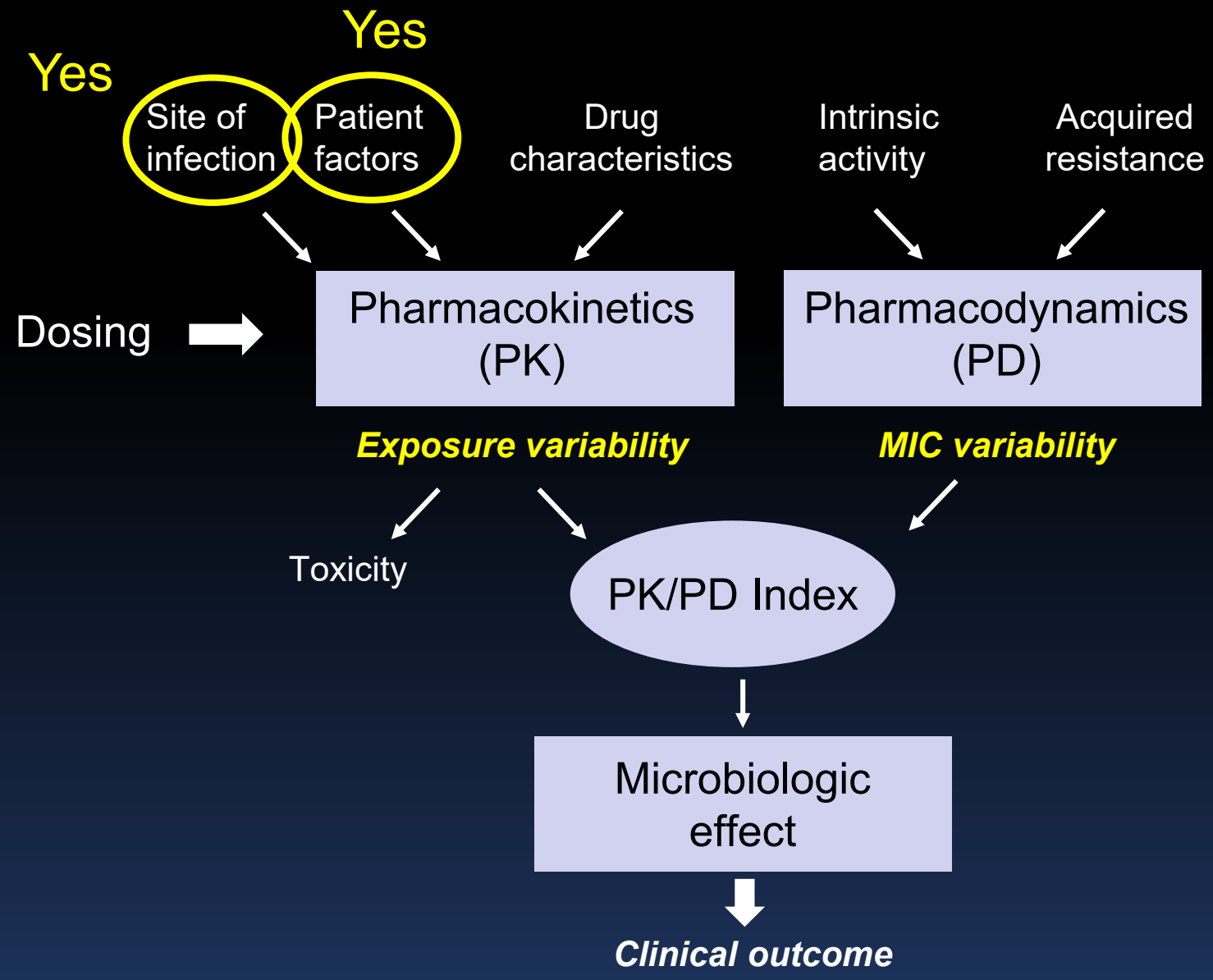


Fungi location stained by GMS



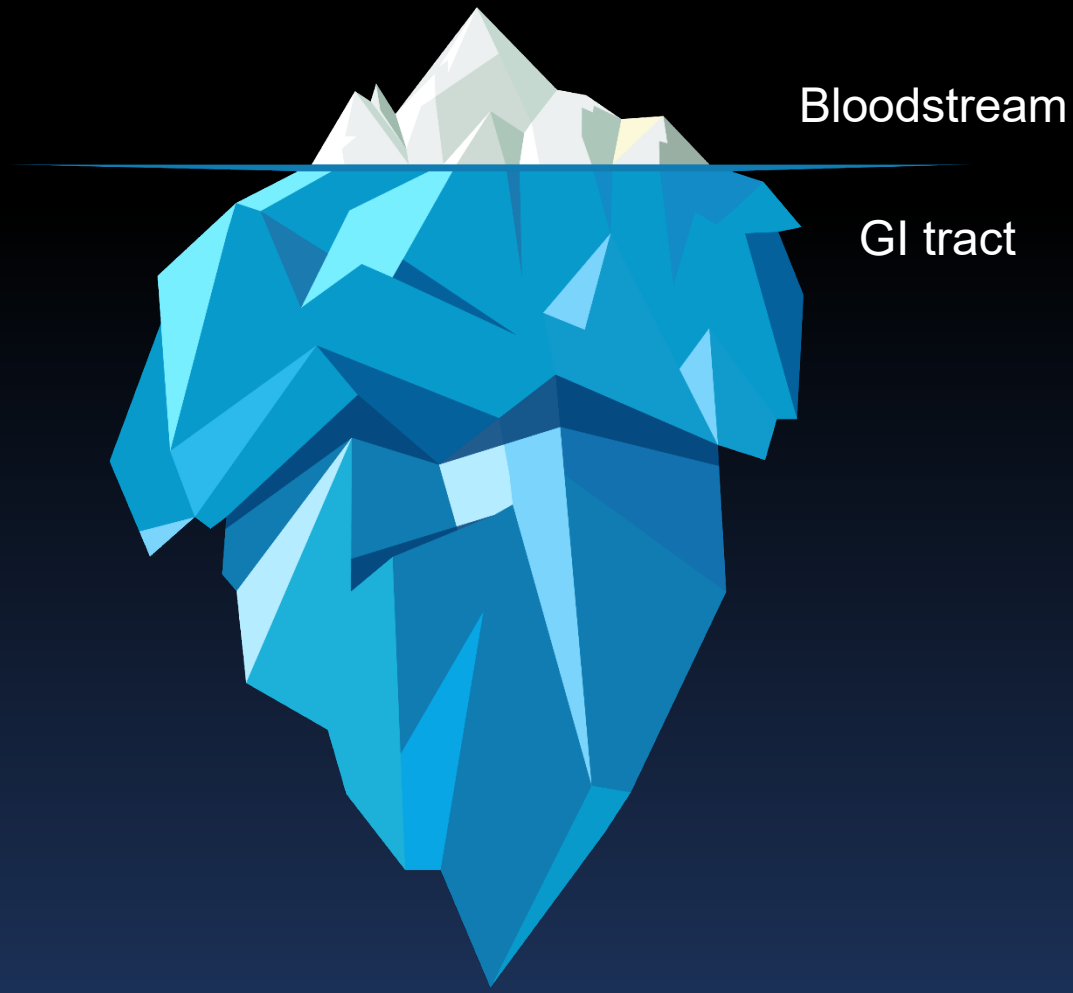
Zhao, Perlin et al, AAC July 2017

Time to rethink dosing?

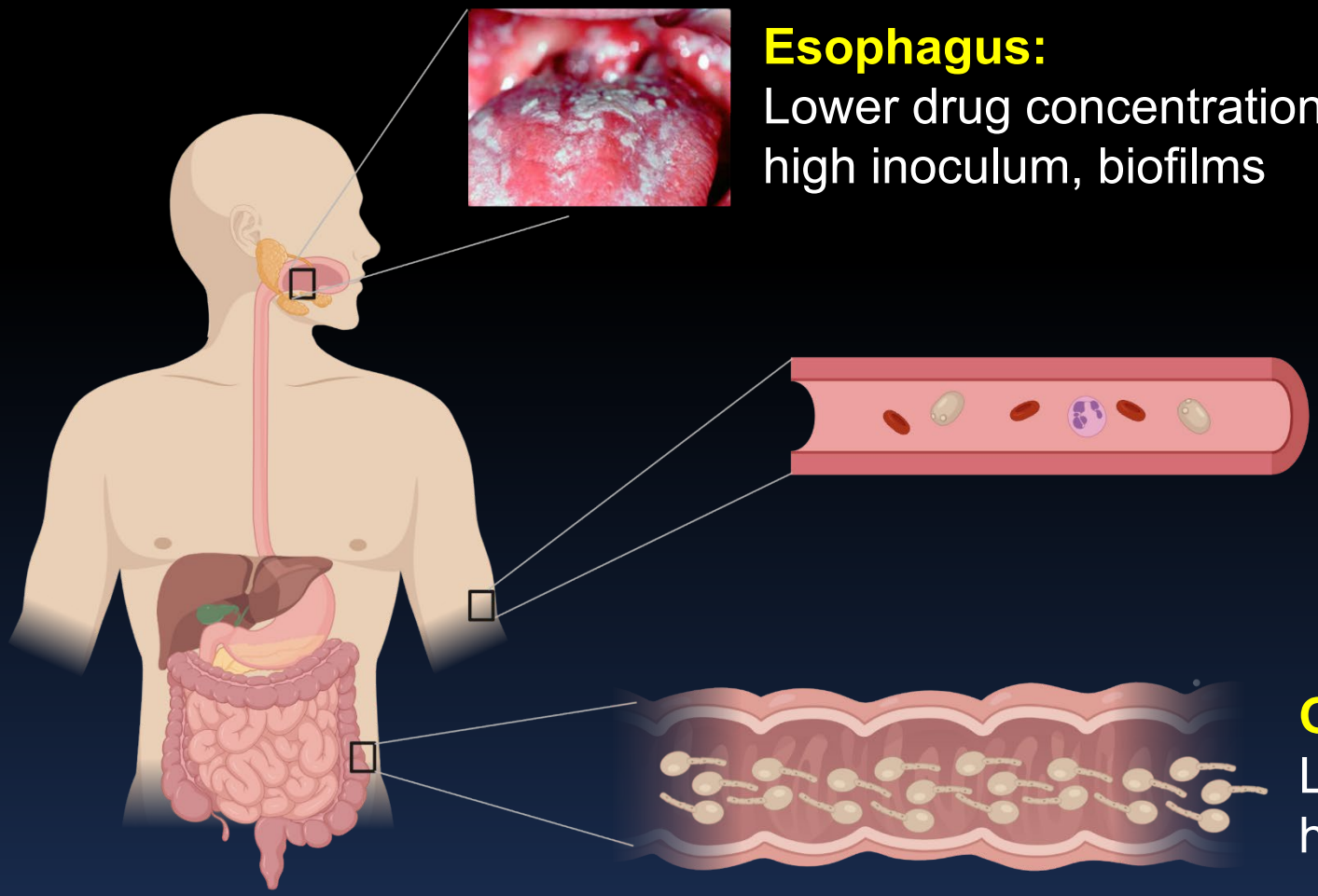


Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Where do we find echinocandin resistance?



Where do we look for echinocandin resistance?



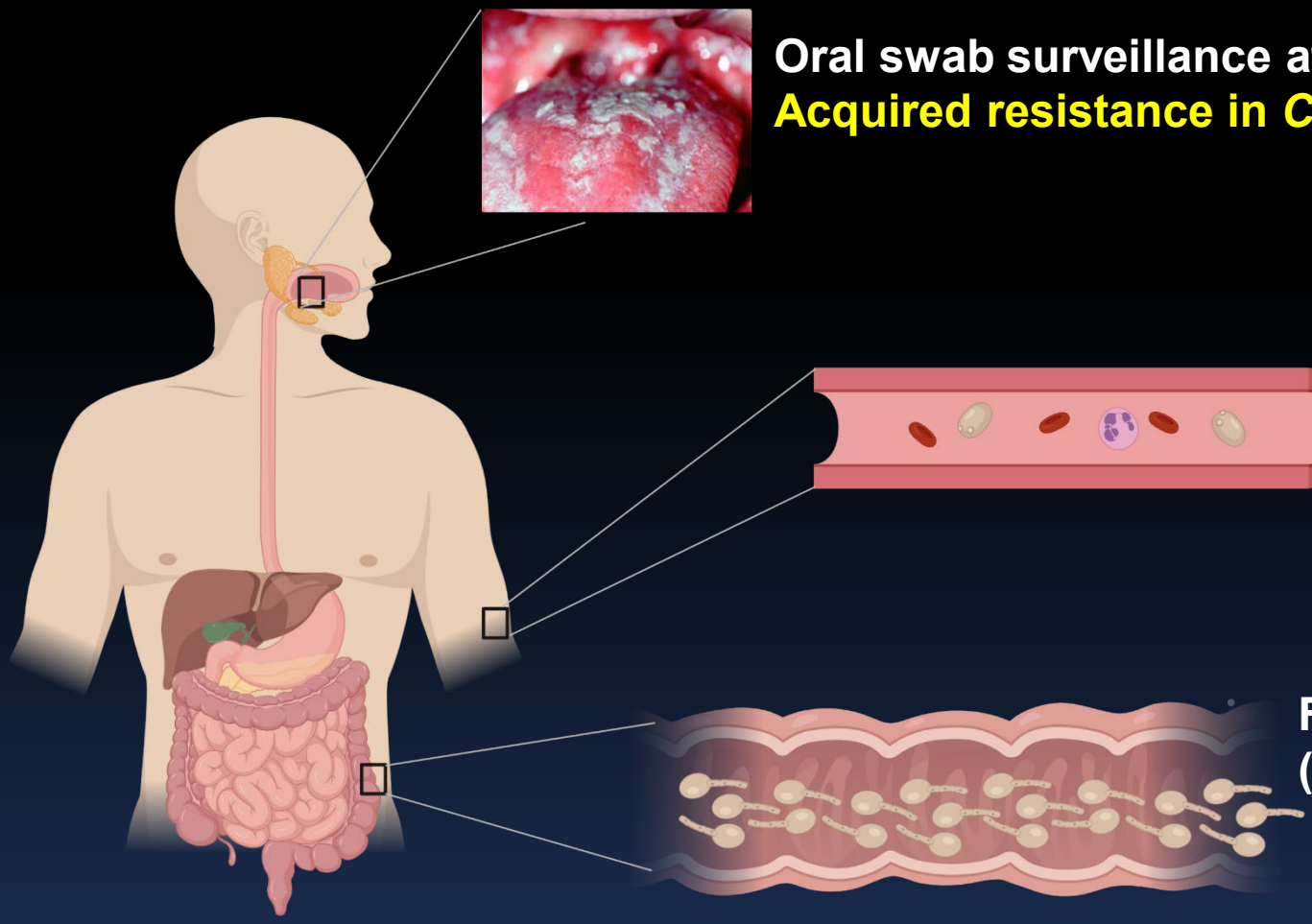
Esophagus:
Lower drug concentrations,
high inoculum, biofilms

Bloodstream:
High drug concentrations,
low inoculum

Gut:
Low drug concentrations,
high inoculum, biofilms?

Healey et al. *Antimicrob Agents Chemother* 2017;61(12).

Where do we look for echinocandin resistance?



Oral swab surveillance after ≥ 7 days of echinocandins[2]
Acquired resistance in *C. glabrata* 21.6%

SENTRY 2006-2016, single center studies[1,2]
Echinocandin resistance rate: 3-12%

FKS mutant *Candida* isolates detected in 24% (6/25) patients exposed to echinocandins[4,5]
- ***C. glabrata* 29%**
- ***C. albicans* 14%**

[1]Pfaller M et al. *Open Forum Infect Dis* 2019;6 (Supplement_1):S79–94.
[2]Alexander et al. Clin Infect Dis 56:1724-32.
[3]Jensen RH, Johansen HK, Soes LM, et al. *Antimicrob Agents Chemother.* 2016;60(3):1500-1508.
[4]Shields RK, Nguyen MH, Press EG, Clancy CJ. *Antimicrob. Agents Chemother.* 2014;58(12):7601-7605.
[5]Prigent et. al. *Antimicrobial Agents Chemother.* 2016; Nov 15, 2016.

The GI tract as the major source of echinocandin resistance

1.5x10^{8}CFU *C. glabrata* → PIP/Tazo → Dexamethasome immunosuppression

Caspofungin 5 mg/kg
(humanized dose)

Caspofungin 20 mg/kg
(4x humanized dose)

↔ CFU in stool vs. control
(FKS mutants in 10% mice)

10^7-10^8 CFU/stool

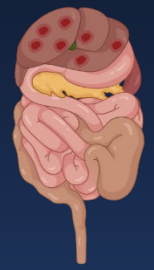
Transient ↓ then ↑
(100% mice with FKS mutants)

No positive BC
during caspofungin treatment

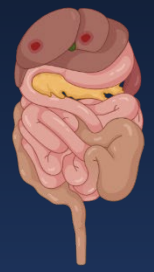
Controls 50%

No positive BC
during caspofungin treatment

Organ dissemination in 60% of mice
(No FKS mutants)
Mean small intestine-3.8 µg/mL
Mean large intestine-9.1 µg/mL



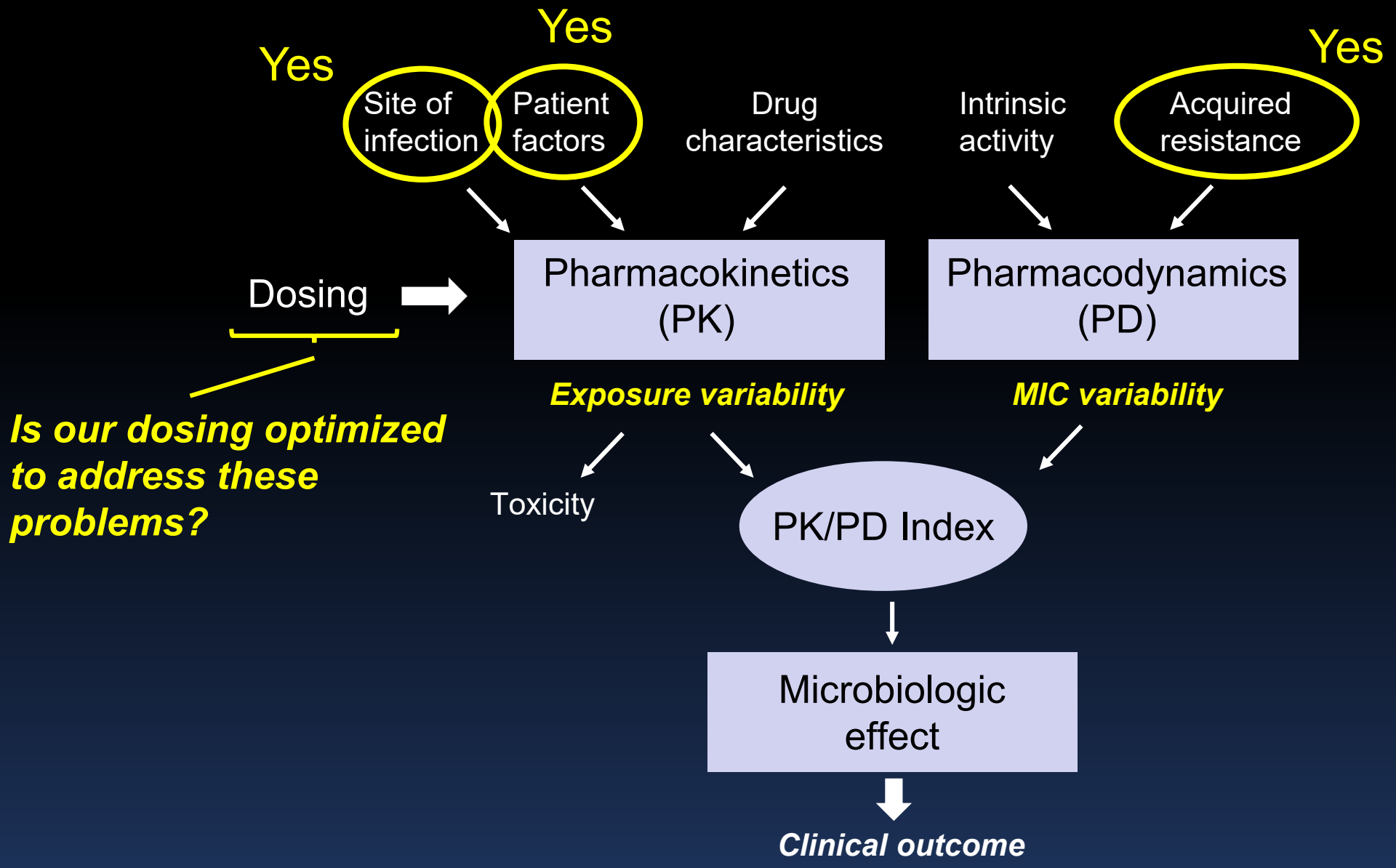
Controls 70%
(No FKS mutants)



Organ dissemination in 30% of mice
(ALL FKS mutants)
Mean small intestine-36.2 µg/mL
Mean large intestine-22.2 µg/mL

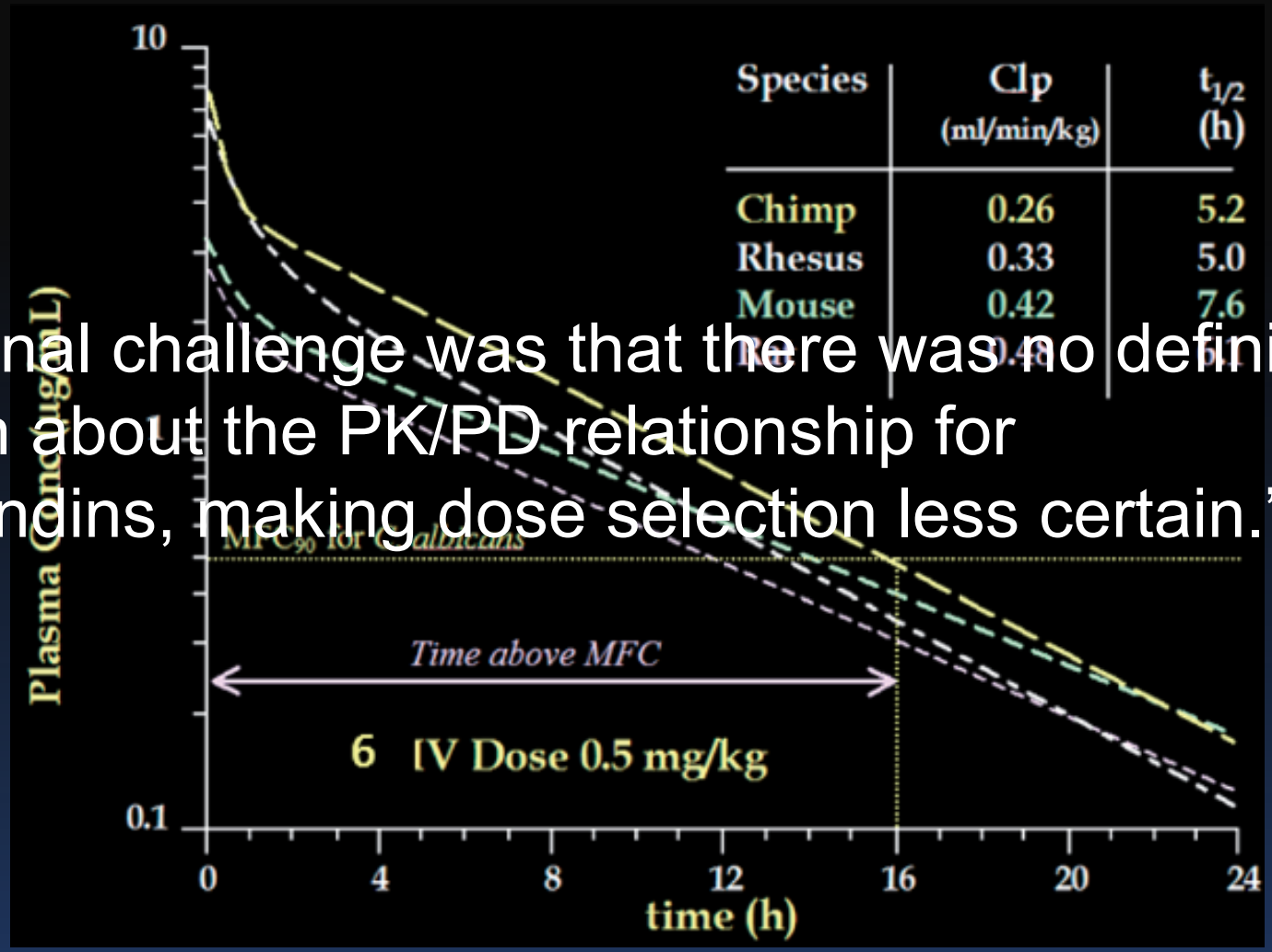
Healey et al. *Antimicrob Agents Chemother* 2017;61(12).

Time to rethink dosing?



Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Currently-recommended echinocandin dosing schemes were not developed from PK/PD principles



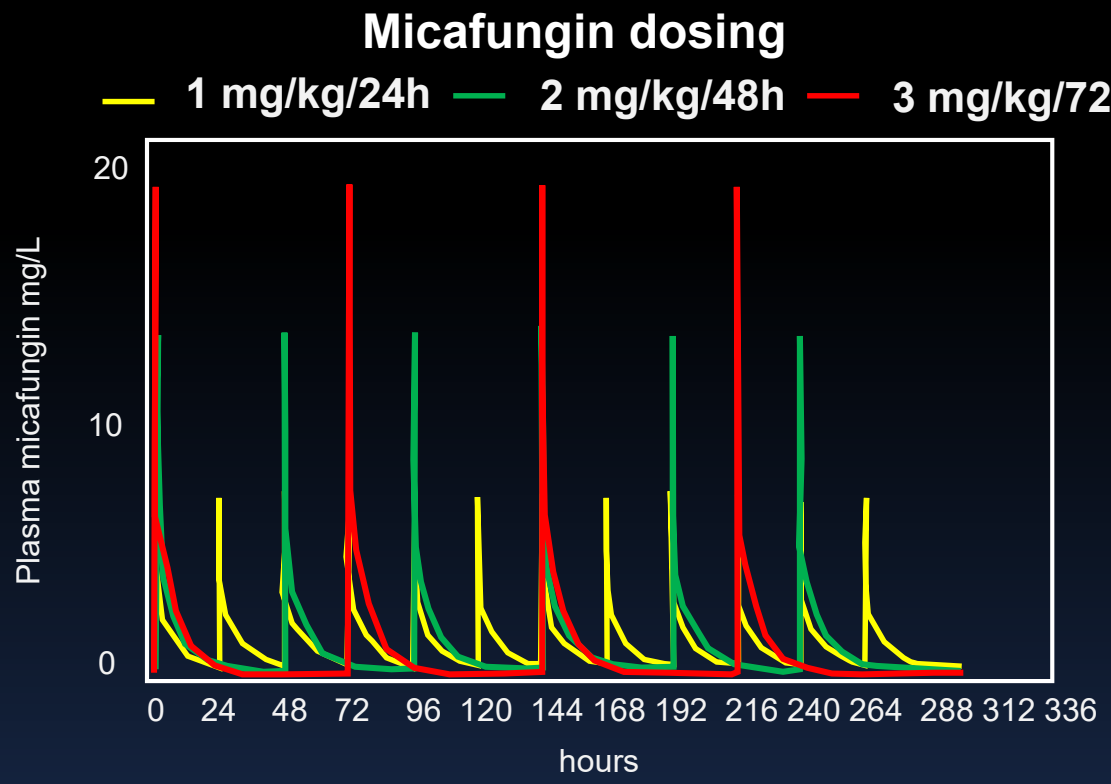
"An additional challenge was that there was no definitive information about the PK/PD relationship for pneumocandins, making dose selection less certain."

Balkovec JM. *Nat Prod Rep* 2014;**31**(1):15–34.

What have we learned about echinocandin PK/PD from animal models?

Rabbit model of invasive candidiasas

Micafungin Cmax/MIC and AUC/MIC correate with efficacy

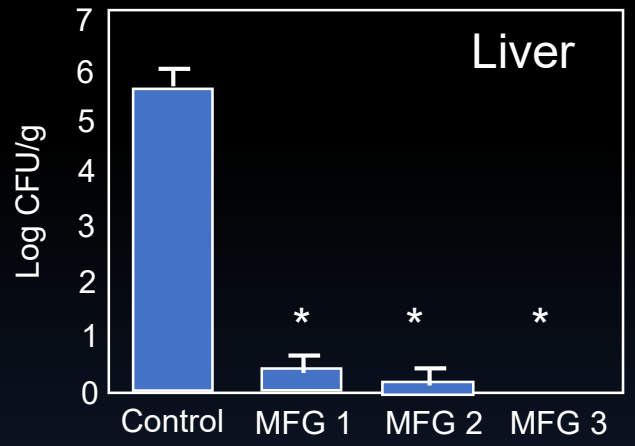


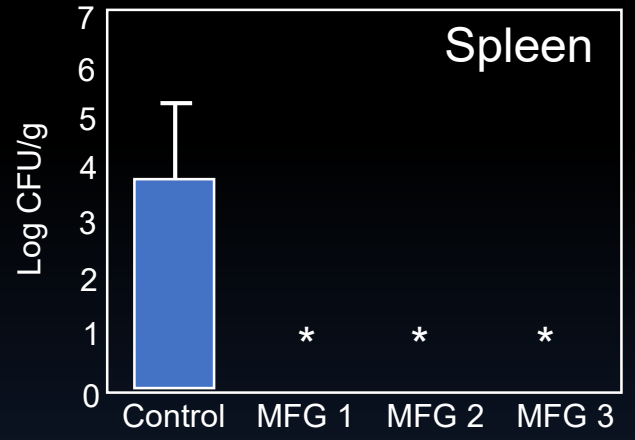
Mean AUC $_{0\text{-}312}$ similar for all three regimens

Petraitiene R, Petraitis V, Hope WW, Walsh TJ. Clin Infect Dis 2015;61:S643–51.

Larger infrequent doses maximize echinocandin antifungal activity

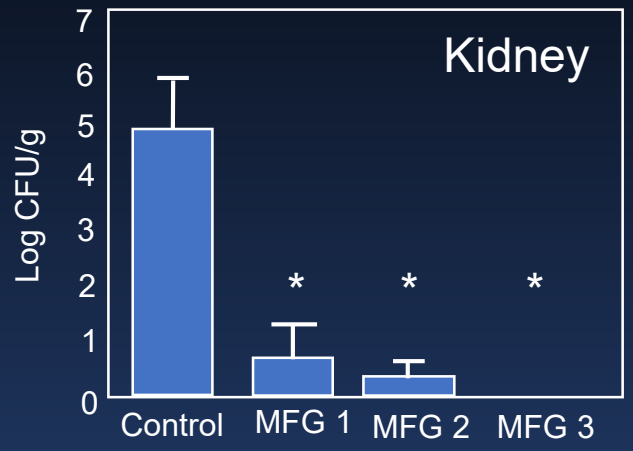
Neutropenic rabbit model of invasive candidiasis





C. albicans MIC 0.125 mg/L (CLSI)

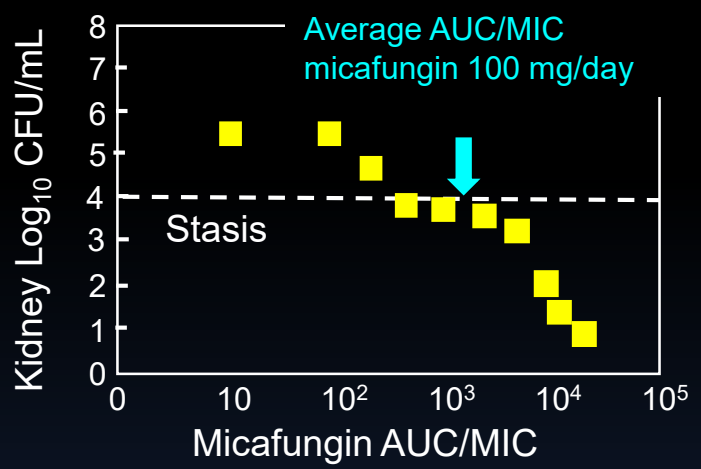
When AUC/MIC is equivalent, dosing regimens that acheive a higher Cmax/MIC exhibit improved killing



* P< 0.05 vs. control

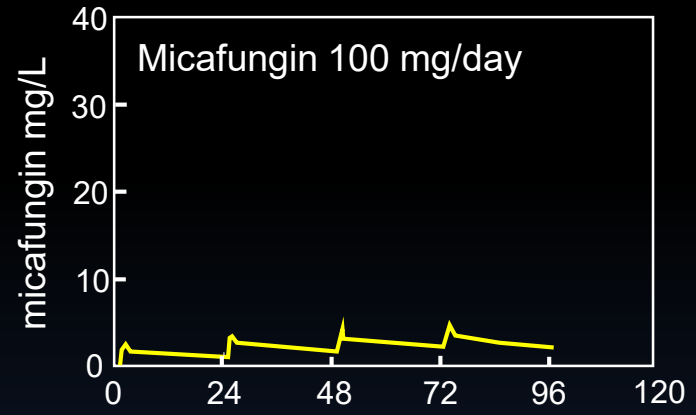
Petraitiene R, Petraitis V, Hope WW, Walsh TJ. Clin Infect Dis 2015;61:S643–51.

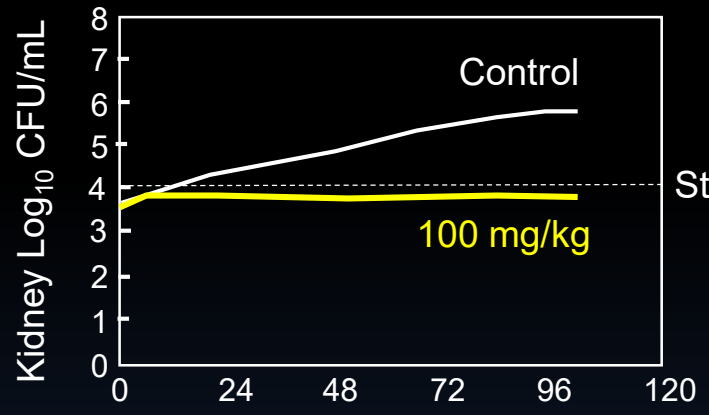
Echinocandins are not fungicidal against *C. glabrata* in neutropenic models at currently recommended doses

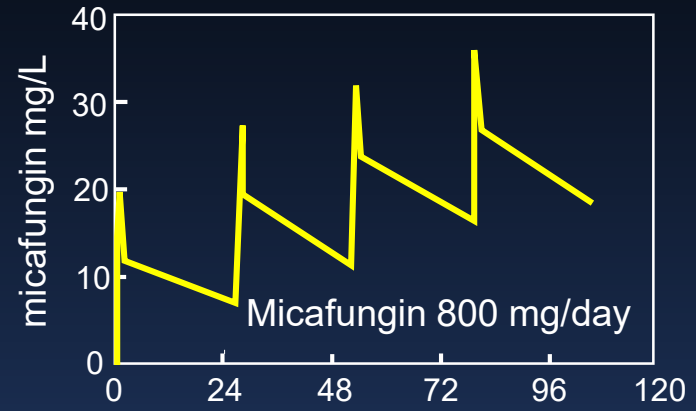


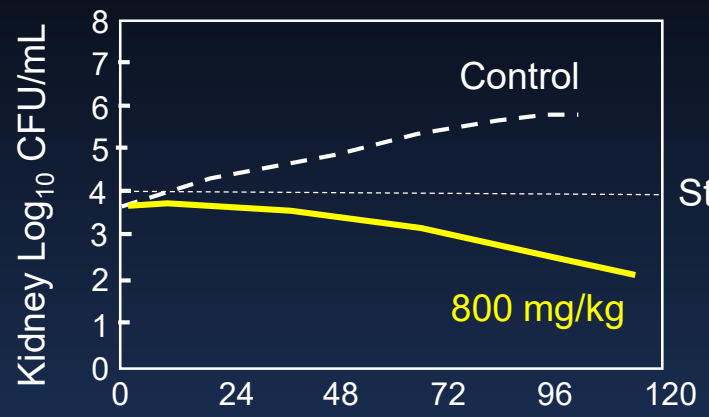
Humanized dosing, neutropenic murine model of *C. glabrata* fungemia (MIC 0.06 mg/L)

Model predictions





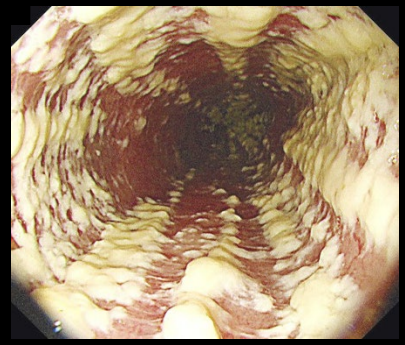




Time (hrs)

Howard S et al. *Antimicrob Agents Chemother* 2011;55(10):4880–7.

Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: Dosing strategy optimization



% of patients with indicated result

	Mycological response at EOT?*			Clinical relapse at 2 weeks?**		
Micafungin dosing regimen	Success (n=260)	Failure (n=56)	Total (n=316)	Yes (n=29)	No (n=278)	Total (n=307)
150 mg QD	145 (78.8)	39 (21.2)	184	22 (12.2)	159 (87.9)	181
300 mg QOD	115 (87.1)	17 (12.9)	132	7 (5.6)	119 (94.4)	126

P=0.056

P=0.051

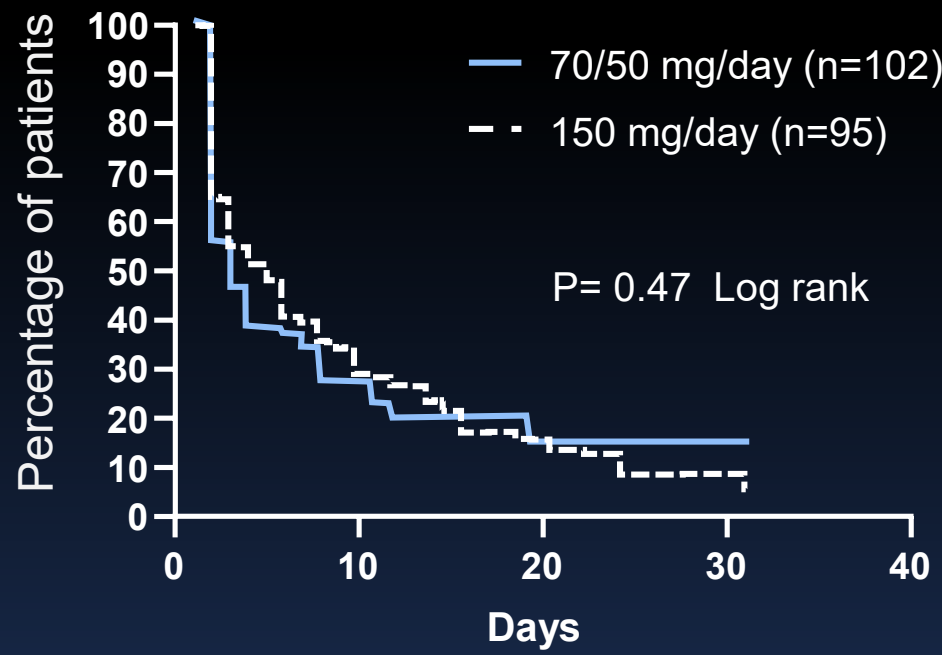
The dosing regimen that acheives a higher Cmax/MIC was assocaited with improved clinical success and lower relapse rates

de Wet et al. Aliment. Pharmacol. Ther. 21:899–907.
Andes DR, et al. *Antimicrob Agents Chemother* 2013;57(11):5714–6.

Caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Conclusion: Both dosing regimens were equivalent and safe

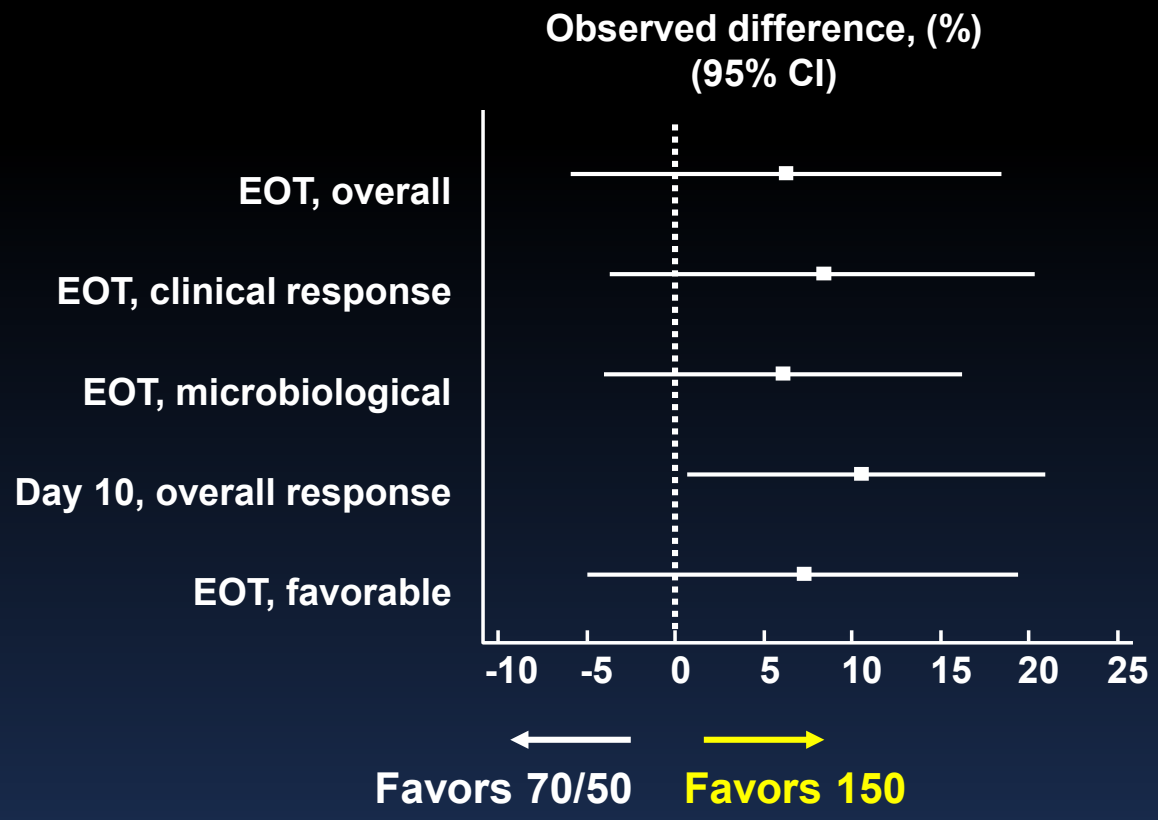
Time to clearance of blood cultures

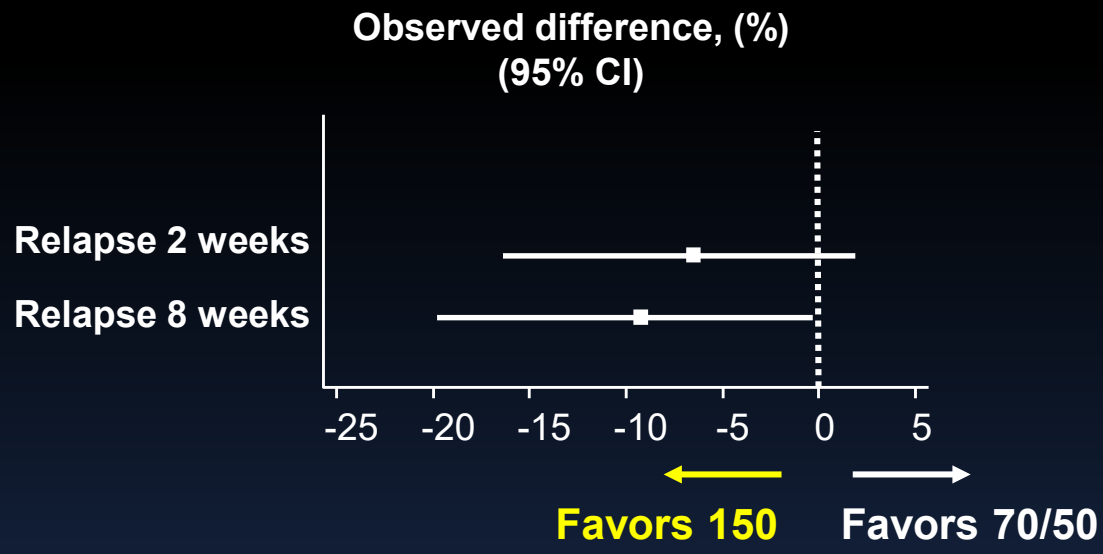


Design hypothesis: Higher caspofungin dose is safe and non-inferior Δ <15%.
Study was not powered to evaluate superiority of caspofungin higher dose

Betts RF et al. *Clin Infect Dis* 2009;48(12):1676–84.
Pea F, Lewis RE. *J Antimicrob Chemother* 2018;73(suppl_1):i33–43.

Multicenter double-blind trial of caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

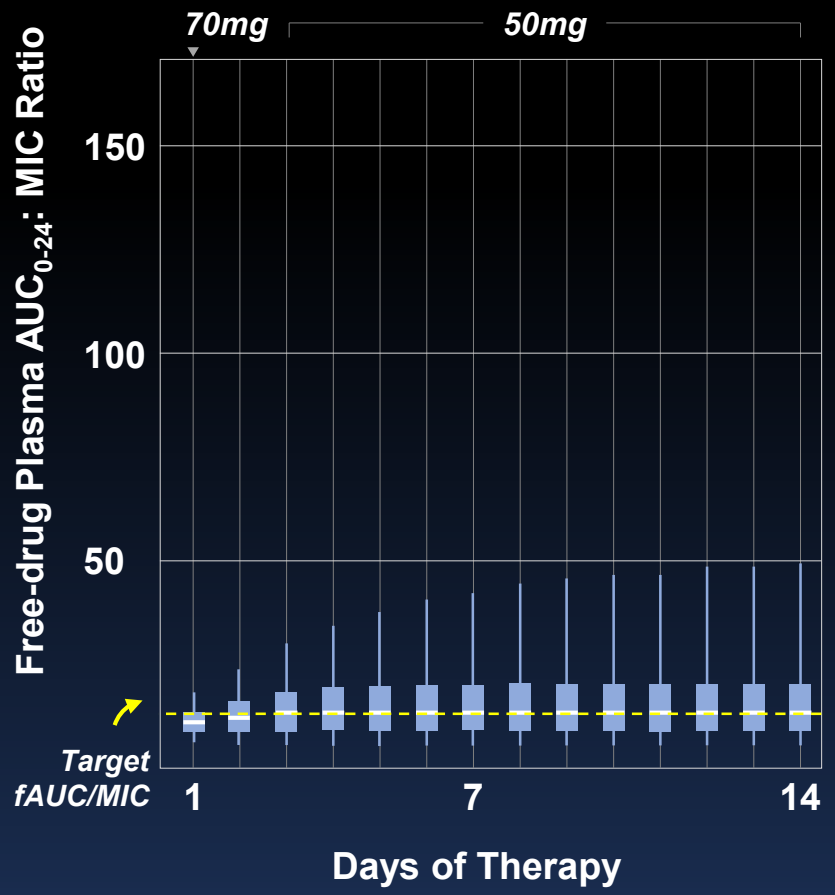




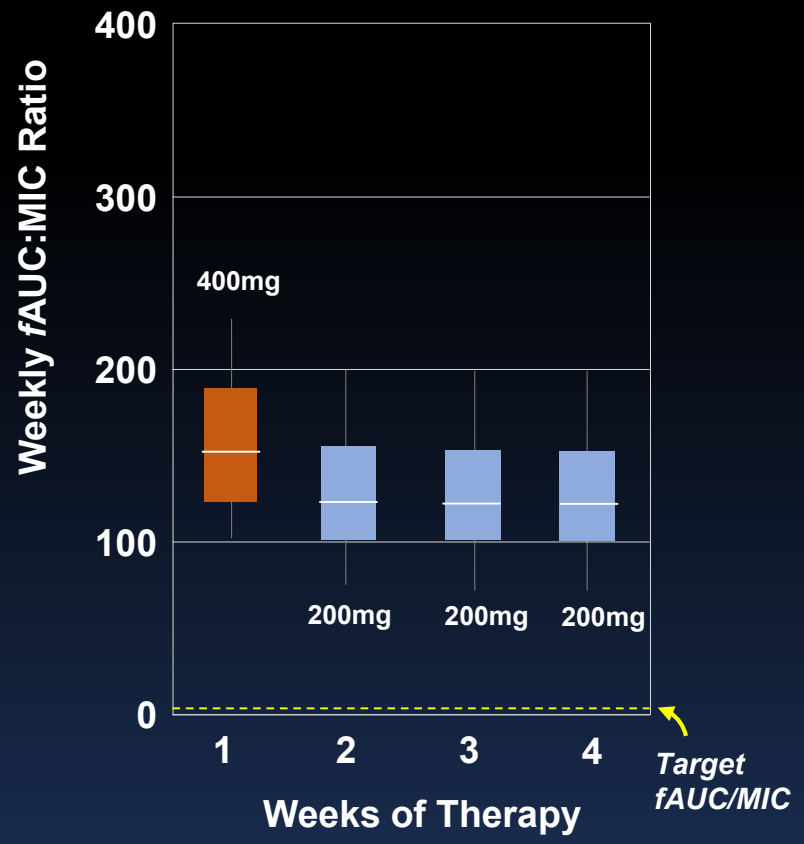
Betts RF et al. *Clin Infect Dis* 2009;48(12):1676–84.
Pea F, Lewis RE. *J Antimicrob Chemother* 2018;73(suppl_1):i33–43.

Comparison of caspofungin vs. rezafungin PK/PD target attainment (C. glabrata MIC 0.25 mg/L)

Caspofungin (14 daily doses)



Rezafungin (4 weekly doses)



MIC=0.25 for caspofungin. MIC=0.12 for CD101

Bader et al. Emerging Candida glabrata Resistance and Echinocandin Dosing: A Call to Arms! IDWeek 2016

Bader et al. Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018; revised with Phase 2 results.

Novel echinocandin dosing approaches during micafungin prophylaxis

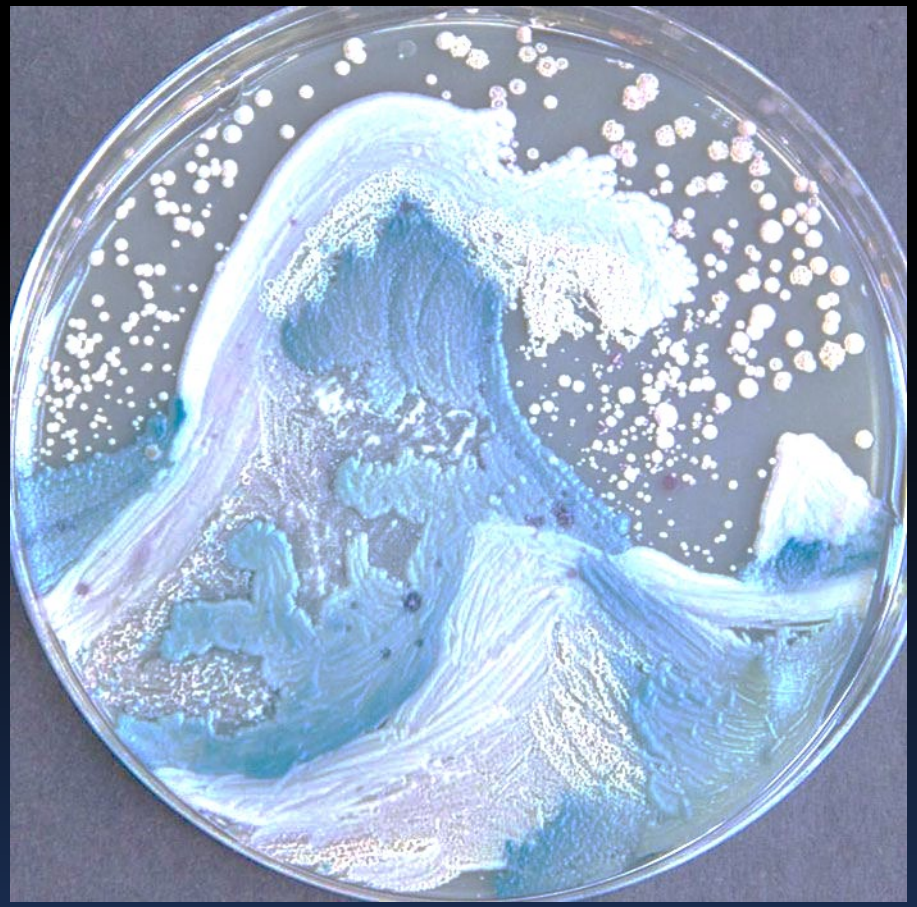
- Intermittent administration of higher-dose micafungin (≥ 5 doses of 300 mg 2-3 times weekly) was well tolerated in patients with acute leukemia and allogeneic SCT recipients[1]
- Intermittent higher-dose micafungin was safe in children[2,3]
- Equivalent weekly AUCs have been confirmed for 300 mg twice weekly dosing of micafungin (3hr infusion) → possible 700 mg once weekly? [4]

[1] Neofytos et al. Clin Infect Dis 2015;61:S652-61.
[2] Mehta et al. Biol Blood Marrow Transplant 2010; 16:1458-62.
[3] Bochennek et al. J Antimicrob Chemother 2015;70:1527-30.
[4] Muilwijk EJ et al. J Antimicrob Chemolther 2018;73:3095-3101

Summary

- Preclinical and clinical evidence suggest current echinocandin dosing approaches need revision for some patient groups
- Acquired echinocandin resistance can be detected at much higher frequency in the GI tract than bloodstream, and likely serves as a reservoir for future breakthrough infection
- Evidence that PK/PD optimization of echinocandin dosing might improve clinical efficacy, reduce relapse, and enhance dosing convenience

Thank you!



"The Great Wave of *Candida*"
Cristina Marcos

The Great Wave off Kanagawa
Katsushika Hokusai

Treatment of Candidemia / Invasive Candidiasis
Unmet Needs

Bart-Jan Kullberg, M.D.
Center for Expertise in Mycology Radboudumc/cwz
Radboud University Medical Center
Nijmegen, The Netherlands

Radboudumc Center for Infectious Diseases

Radboudumc

Disclosures

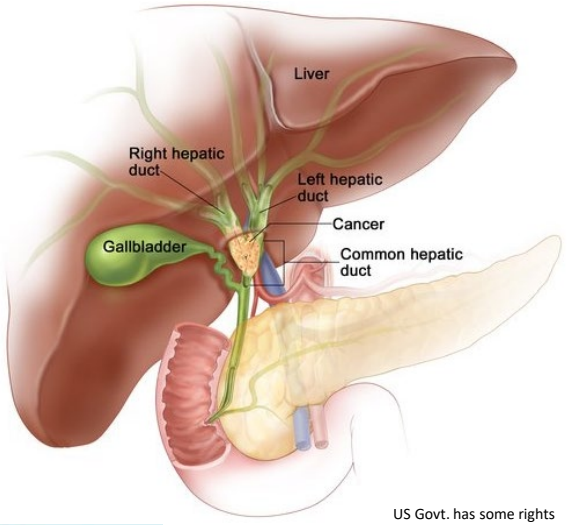
- Scientific advisor for Amplyx, Cidara, and Scynexis
- Participated in CME with support from Cidara and Pfizer.

Case Study

- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma

- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin

- Possible suture leak
- Abdominal CT inconclusive
- Blood cultures (still) negative



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Candida colonizing the gut

- What is the likelyhood of invasive candidasis?
- How can we diagnose invasive (abdominal) candidiasis?
- Should she have received antifungal prophylaxis?
- Should she receive empiric antifungal therapy?
- If so, aimed at which *Candida* species?

Unmet Needs

- ✓ Can we prevent invasive candidiasis in the ICU?

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Antifungal prophylaxis in the ICU

- *Does it work?*
  - Yes, some reduction of incidence

- *Does it work well enough?*
  - No … Less than optimal results:

Incidence			*P*	Reference	Year
Control		***Prophylaxis***			
17%	→	10%	n.s.	Ostrosky-Zeichner	2014
15%	→	8.5%	0.01	Pelz	2001
10%	→	4%	0.02	Garbino	2002
9%	→	2%	n.s.	Eggimann	1999

- *Has it been associated with reduced mortality?*
  - No … In none of the studies:

Mortality			*P*	Reference	Year
Control		***Prophylaxis***			
14%	→	17%	n.s.	Ostrosky-Zeichner	2014
12%	→	11%	n.s.	Pelz	2001
41%	→	39%	n.s.	Garbino	2002
50%	→	30%	n.s.	Eggimann	1999

MSG-01: Echinocandin prophylaxis in high-risk ICU patients

Randomised, double-blind, multicentre study of caspofungin vs. placebo

- Adult patients >48 h in ICU
- Mechanical ventilation
- Central venous catheter
- Broad-spectrum antibiotics
- ≥1 of: TPN, dialysis, major surgery, pancreatitis, steroids/immunosuppressants

MITT[1], N=186	Caspofungin[2]	Placebo	Difference *P*
Invasive candidiasis proven/probable[3], after baseline	9.8%	16.7%	P=0.14
Proven invasive candidiasis	1.0%	4.8%	P=0.11
Mortality	16.7%	14.3%	P=0.35
Length of stay			n.s.

Conclusions: 1. No support for antifungal prophylaxis among ICU patients
2. We are unable to identify the patient at risk for candidiasis

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[1] Modified intent-to-treat group: eligible patients without candidiasis at baseline, who received ≥1 dose of study drug
[2] Caspofungin has not been licenced for prophylactic use
[3] Probable candidiasis (EORTC/MSG): 2x ß-glucan>80 AND clinical signs

Ostrosky-Zeichner L, et al.
Clin Infect Dis 2014; 58(9):1219–26

Unmet Needs

- ✓ Can we treat invasive candidiasis in the ICU earlier?

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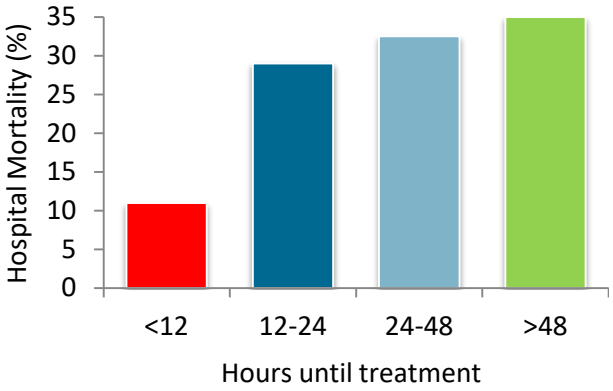
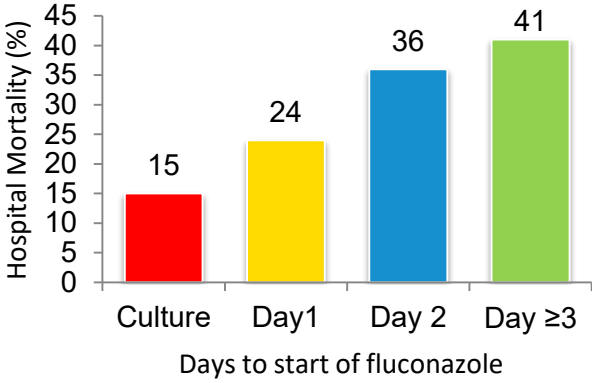
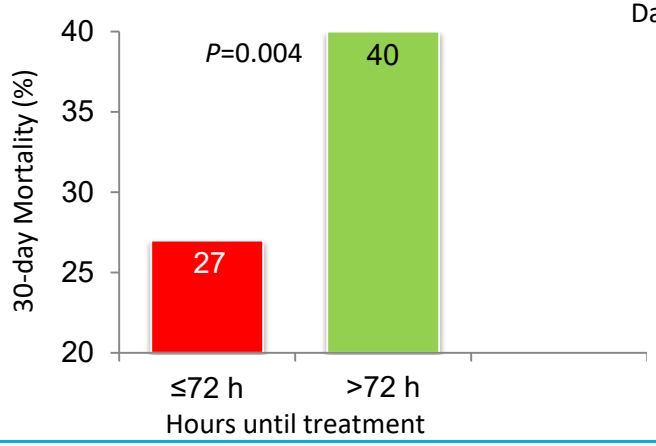
Candidemia: Importance of early appropriate treatment



157 patients – 2001–2004
Initiation of antifungal therapy <12 to >48 h after culture sample
Morrell M, et al. *AAC* 2005



230 patients – 4 centres – 2002–2005
Initiation of fluconazole 0 to ≥3 days
Garey KW, et al. *Clin Infect Dis* 2006



446 patients – 2001–2009
Intent to treat: 31.6–36.3% - N.S.
Shown: when Rx for <24 h classified as inappropriate
Grim SA, et al. *J Antimicrob Chemother* 2012

Empirical micafungin in ICU patients with sepsis, organ failure and *Candida* colonization

Randomised, double-blind, multicenter study of micafungin vs. placebo

- Non-neutropenic adult patients in ICU
- Mechanical ventilation ≥5 days
- Broad-spectrum antibiotics ≥4 days
- ≥1 Site colonized with *Candida* species
- New ICU-acquired sepsis
- ≥1 Additonal organ dysfunction

MITT[1], N=251	Micafungin (14 days)	Placebo	Difference
28-day Survival free of proven fungal infection	68%	60%	HR 1.35 (0.87-2.08)
Survival (d28)	70%	70%	HR 1.04 (0.64-1.67)
Invasive fungal infections	9%	12%	Δ 2.8% (-5.0, 10.8)

Conclusions: 1. No support for empirical antifungals among ICU patients
2. We are unable to identify the patient at risk for candidiasis

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[1]Modified intent-to-treat group: patients who received ≥1 dose of study drug

Timsit JF, et al. JAMA 2016; 315(15):1555–64

Unmet Needs

- ✓ Are we able to identify the patient with invasive candidiasis?

Abdominal candidiasis – The missing 50%

2-year retrospective cohort, U Pittsburg Medical Center

Patients	N
Candidemia Intraabdominal candidiasis	161 163
Intraabdominal candidiasis ▪ GI tract source ▪ Secondary peritonitis/abscess (post GI leak, surgery)	163 103
▪ Hepatobiliary/pancreatic source ▪ Secondary peritonitis/abscess, panceatits/cholangitis ▪ Primary peritonitis	 52 8
Mortality (100 days)	28%
Bacterial co-infection	67%
Candidemia	6%

Vergidis P, Clancy CJ et al, PLoS ONE 2016:11(4);e015247

Unmet Needs

- ✓ Can we detect invasive candidiasis in the ICU earlier?

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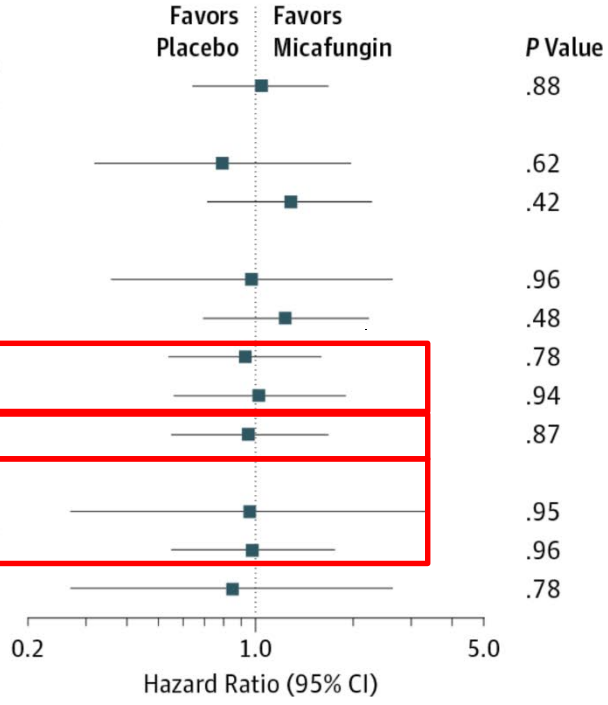
Determinants for success of Micafungin in ICU patients with Sepsis, Organ failure, and Candida colonization

28-Days' Survival

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



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Timsit JF, et al. *JAMA* 2016; 315(15):1555–64

T2 *Candida* in ICU patients at high risk of candidemia / invasive candidiasis in Europe

- Adult patients in ICU (N=126)
- Initiation of antifungal treatment (prophylactic/empiric)
  OR
- T>38°C despite 3 days of Broad-spectrum Abx
  AND ≥2 risk factors:
  - Abdominal surgery
  - Secondary peritonitis
  - Central venous catheter
  - TPN
  - Hemodialysis
  - Steroids/immunosuppressants
  - Liver transplant

Candidiasis*	N	Sensitivity	Specificity	PPV	NPV
Proven	11 (9%)				
- BC	5/11	45%	100%	100%	95%
- T2	6/11	55%	93%	50%	96%
- Mannan Ag	4/11	36%	94%	36%	94%
Likely	6 (5%)				
Proven + Likely	17 (14%)				
- BC	5/17	29%	100%	100%	90%
- T2	10/17	59%	96%	83%	94%
- Mannan Ag	7/17	41%	96%	64%	91%
Possible	11 (9%)				
Prov+Poss+Likely	28 (22%)				
- BC	5/28	18%	100%	100%	81%
- T2	11/28	39%	97%	92%	85%

T2

- False positives?
  3 putative FP in this study
- Sensitivity better than BC but underwhelming (with current gold standard)

Proven: +ve BC or normally sterile site
Likely: Colonization ≥2 sites AND either SIRS or Mannan Ag>250
Possible: Colonization ≥2 sites +MAg>125 OR Mag≥250 OR Colonized + SIRS despite ABx

Arendrup et al, Open Forum Infect Dis 2019

Fungal Immunogenetics for Personalized Therapy

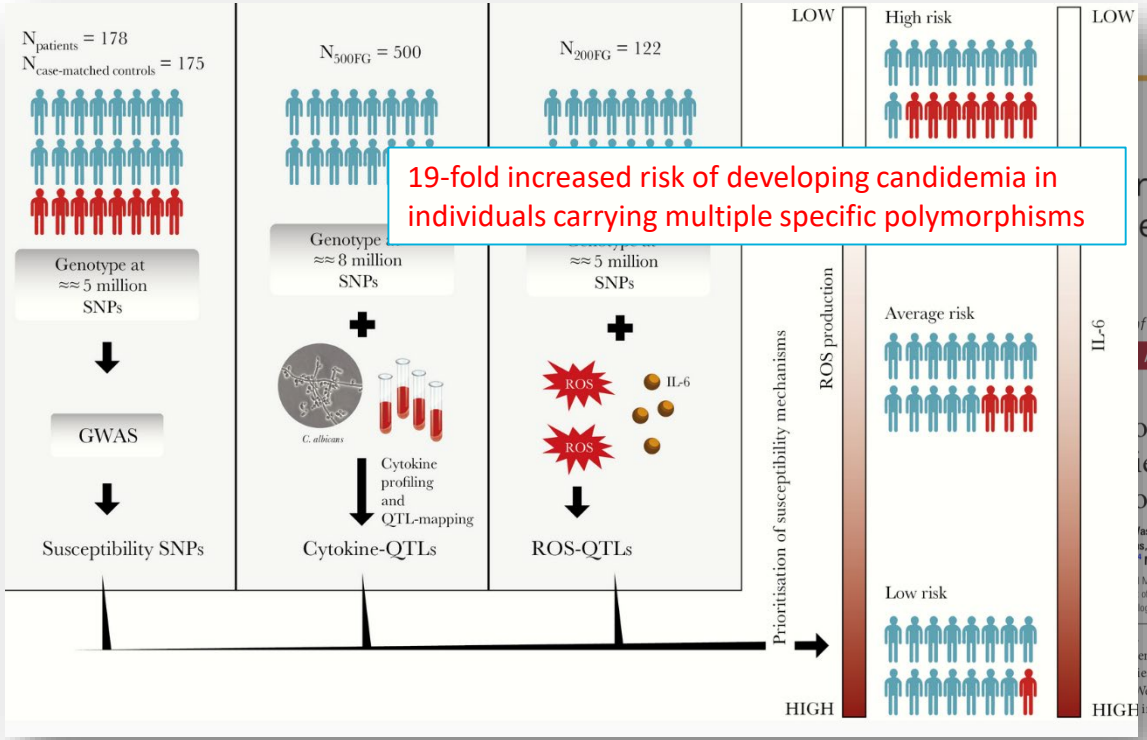
nature COMMUNICATIONS

Host susceptibility to candidiasis in an ICU cohort

ARTICLE

Received 7 Jan 2014 | Accepted 11 Jul 2014 | Published 8 Sep 2014 DOI: 10.1038/ncomms5675

Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia



19-fold increased risk of developing candidemia in individuals carrying multiple specific polymorphisms

roach identifies
e candidaemia

f Infectious Diseases

ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

ome-Wide Functional Genomics Approach
es Susceptibility Pathways to Fungal Bloodstream
on in Humans

asiliki Matzaraki,[1,2,a] Raúl Aguirre-Gamboa,[2,a] Mark S. Gresnigt,[1] Xiaojing Chu,[2] Melissa D. Johnson,[3] Marije Oosting,[1] s,[1] Sebo Withoff,[2] Iris Jonkers,[2] John R. Perfect,[3] Frank L. van de Veerdonk,[1] Bart-Jan Kullberg,[1] Leo A. B. Joosten,[1] Yang Li,[2] Mihai G. Netea,[1,5] and Vinod Kumar[1,2]

Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands; [2] University of Groningen, University Medical Center of Genetics, the Netherlands; [3]Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; [4] K.G. Jebsen Coeliac Disease Research Centre, gy, University of Oslo, Norway; [5] Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

Candidemia, one of the most common causes of fungal bloodstream infection, leads to mortality rates up to 40% ents. Understanding genetic mechanisms for differential susceptibility to candidemia may aid in designing host- ies.

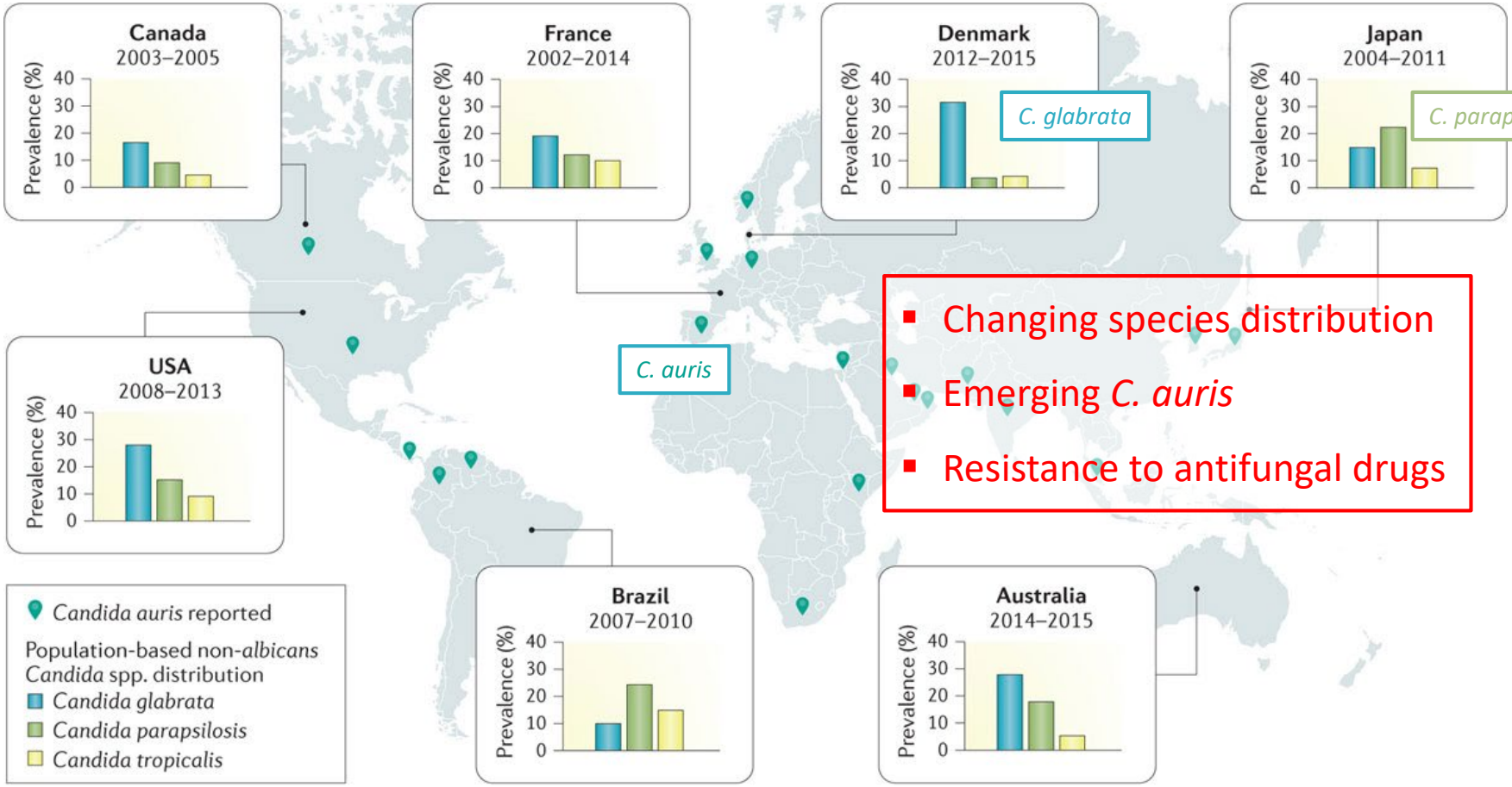
Ve performed the first genome-wide association study on candidemia, and we integrated these data with variants that in different cellular systems stimulated with *Candida albicans*.

Kumar et al, Nat Commm 2014; Matzaraki et al, PLoS One 2017; Jaeger et al. J Infect Dis 2019

Unmet Needs

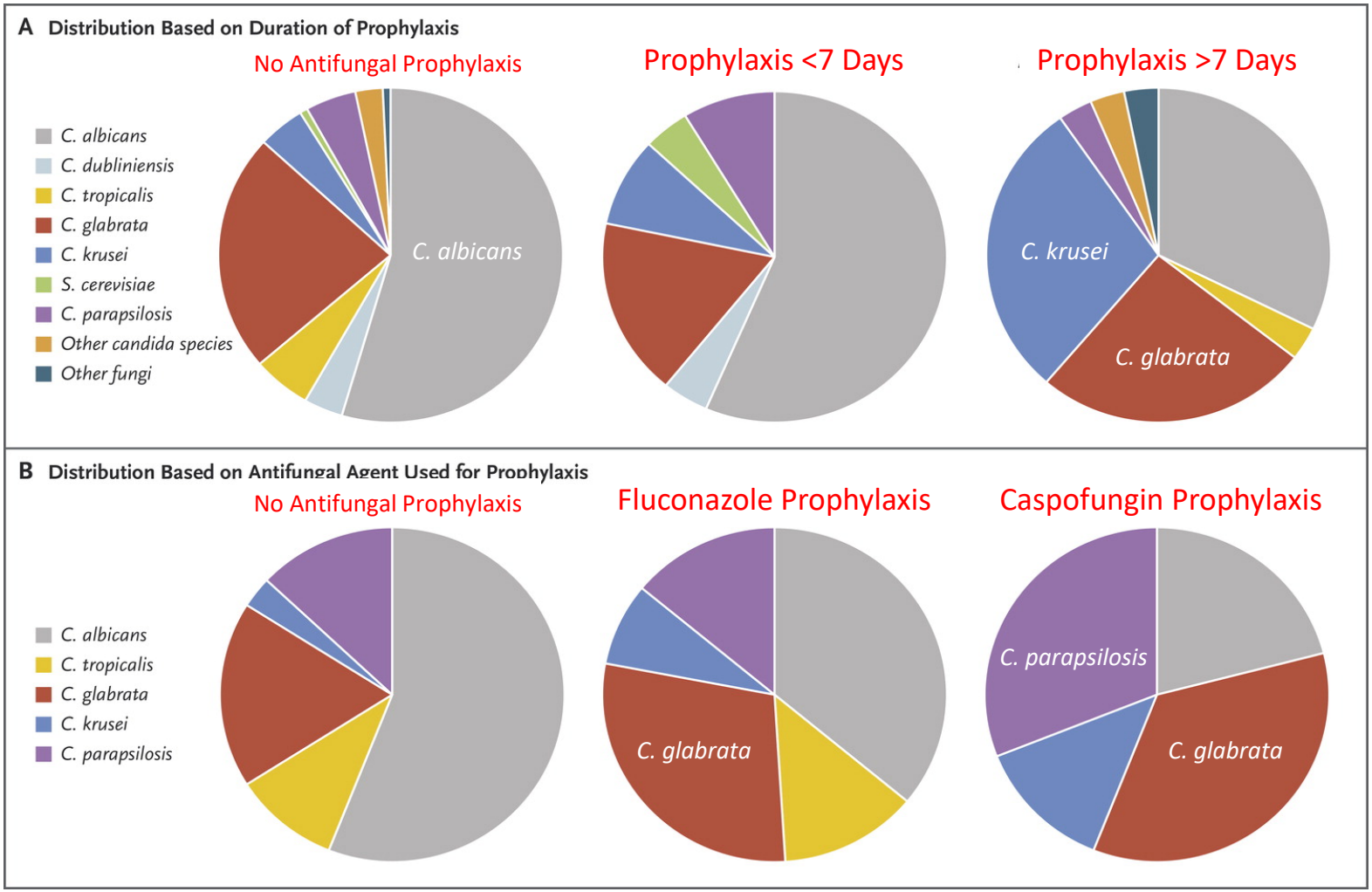
- ✓ Can we cover the emerging spectrum of *Candida* species?

Changing epidemiology of invasive candidiasis



Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ
Invasive candidiasis. Nat Rev Dis Primers 2018: 4; 18026

Distribution of *Candida* species according to prophylaxis used



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Kullberg BJ, Arendrup MC. N Engl J Med 2015;373:1445-1456

Unmet Needs

- ✓ Can we select the most effective initial antifungal drug?

Treatment for candidemia

IDSA 2016

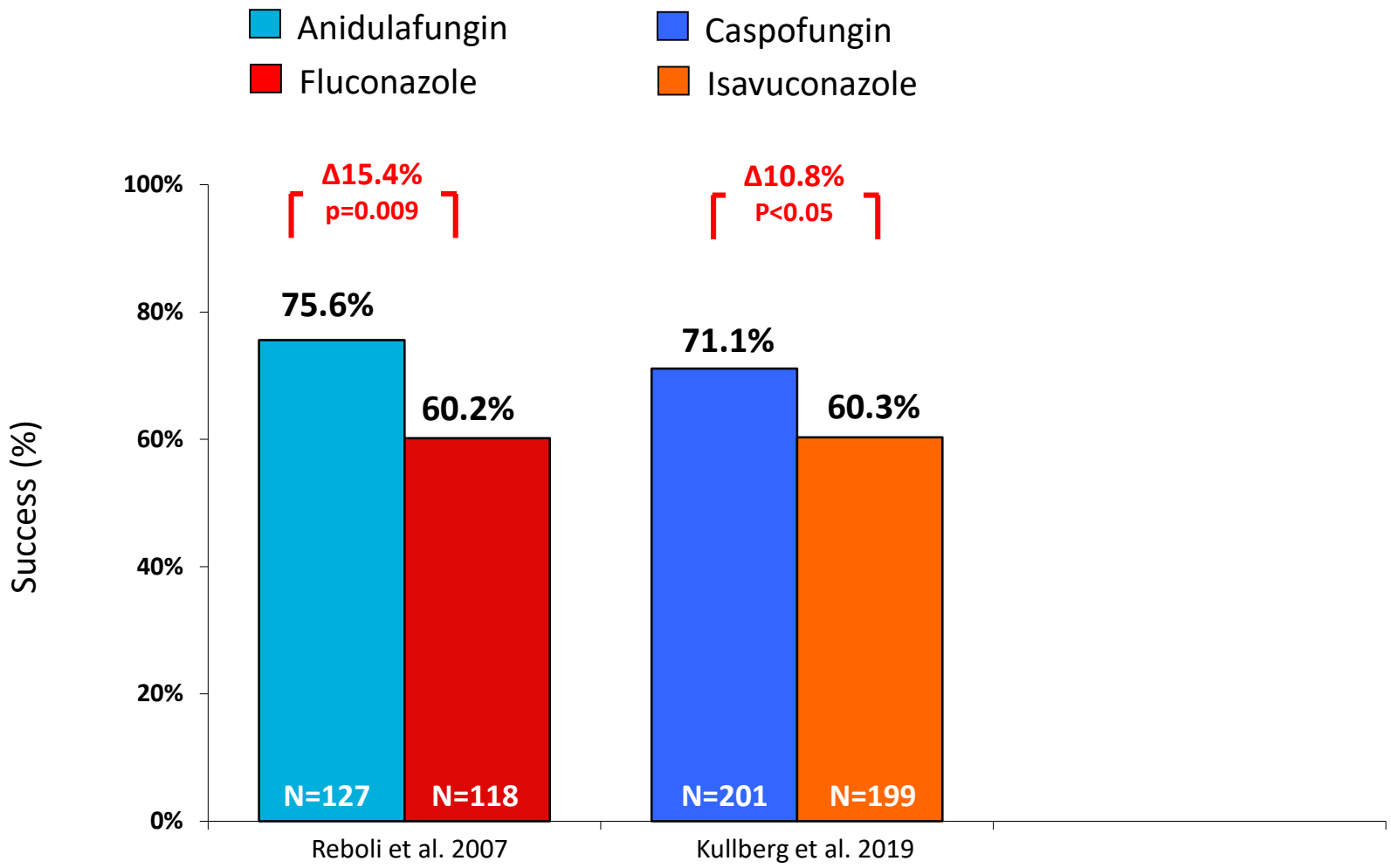
Compound	Recommendation	Evidence
Initial therapy		
Anidulafungin 200→100 mg	Strong	High
Caspofungin 70→50 mg	Strong	High
Micafungin 100 mg	Strong	High

ESCMID 2012

Compound	Recommendation	Evidence
Anidulafungin 200→100 mg	A I	I
Caspofungin 70→50 mg	A I	I
Micafungin 100 mg	A I	I
L-Amphotericin B 3 mg/kg	B I	I
Voriconazole 6→3 mg/kg bid	B I	I
Fluconazole 400→800 mg	C I	I

Pappas PG et al. Clin Infect Dis 2016;62(4):409–17
Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37

Echinocandin superior to azole for candidemia



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Reboli AC, et al. N Engl J Med 2007; 356(24):2472–82
Kullberg BJ, et al. Clin Infect Dis 2019;68(12):1981–9

Case Study (2)

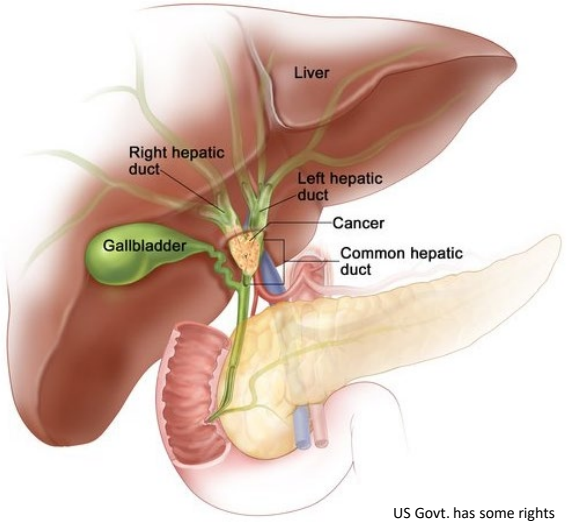
- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma

- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin

- Rule out suture leak

- Repeat abdominal CT negative
- Blood cultures negative
- T2 *Candida* positive: *C. krusei/glabrata*
- Started on caspofungin

- Afebrile, clinically stable
- Ready for discharge – which antifungal – if any?



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Unmet Needs

- ✓ Do we know the optimal duration of treatment?

Early echinocandin to azole stepdown in candidemia patients

All pts started on iv anidulafungin	All patients	Early (≥ Day 5) switch population
	% (N) [95% CI]	% (N) [95% CI]
MITT population (N)	250	102
Global success at EOT	68% (170/250) [62.2–73.8]	79% (81/102) [71.6–87.3]
Mortality (ITT population)	23% (65/282)	14% (14/102)
Success at end of iv therapy	83% (208/250) [78.6–87.8]	95% (97/102) [90.3–99.3]

Current practice:

- ✓ Start all patients on echinocandin
- ✓ Continue echinocandin until stabilization
- ✓ DO switch early after stabilization and negative follow-up blood culture, if azole-susceptible

Unknowns:

- ✓ What if ready for early discharge / azole-resistant / azole drug-drug interactions?

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EOT, end of therapy; MITT analysis: missing/unknown values set as failures

Vazquez J, et al. *BMC Infect Dis* 2014:14;97

Summary thoughts – Unmet needs

- Changing epidemiology / species distribution / resistance / emerging species at least partly under pressure of prophylactic/empiric antifungal use
- Non-culture *Candida* detection and biomarker studies mostly underwhelming but nevertheless the way to go
- Need to better identify patients at risk for candidemia/invasive candidiasis (with conventional methods or immunogenetics)
- Supporting data on superiority of echinocandins for candidemia/invasive candidiasis
- Rapid step down to azoles in stabilized patients is feasible, but limited by susceptibility and drug-drug interactions
- Need for additional iv/oral antifungal classes with broad spectrum, deep tissue penetration for in/outpatient use

Reviewed in: Kullberg & Arendrup. N Engl J Med 2015;373:1445-1456 *and*
Pappas, Lionakis, Arendrup, Ostrosky-Zeichner, & Kullberg. Invasive candidiasis. Nat Rev Dis Primers 2018: 4; 18026

Thank you

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Rezafungin for Treatment of Invasive Candidiasis

George R. Thompson III, MD
Associate Professor
Division of Infectious Diseases
Department of Internal Medicine
Department of Medical Microbiology and Immunology
University of California-Davis Medical Center

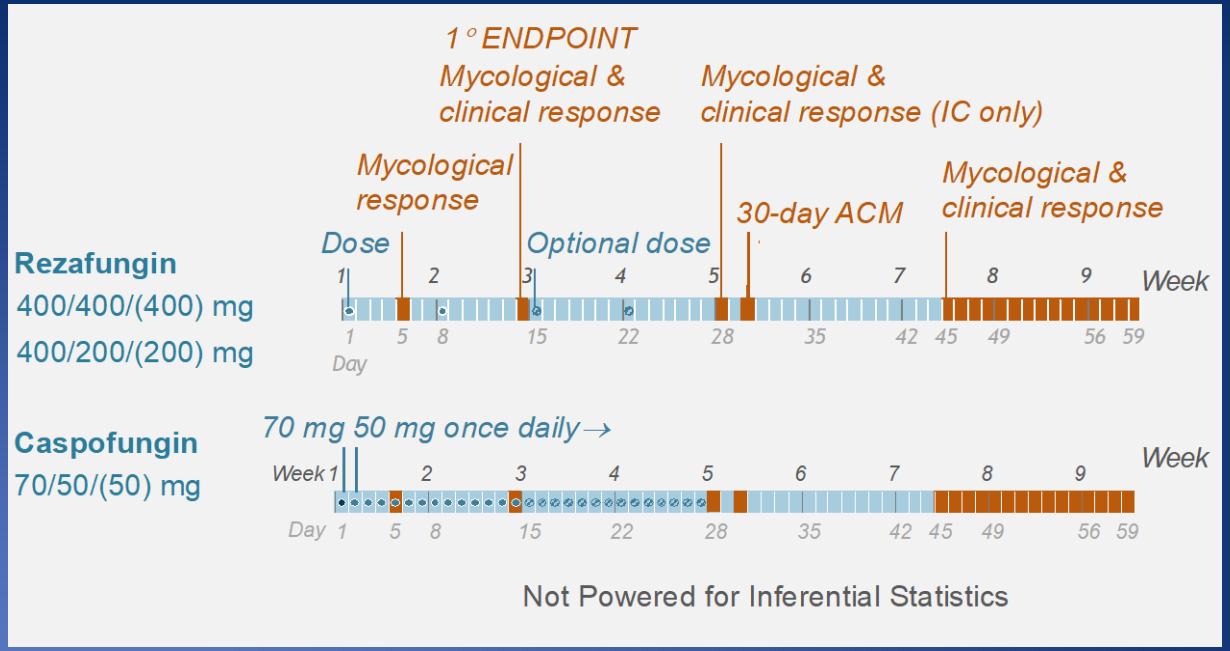
UCDAVIS
UNIVERSITY OF CALIFORNIA

Disclosures / Acknowledgments

- **G. R. Thompson**: Cidara Therapeutics (investigator, research support); Mayne (investigator, research support); Astellas (consultant, investigator, consulting fee, research support); Scynexis (investigator, research support); Vical (consultant, consulting fee)
- Editorial support was provided by T. Chung (Scribant Medical) and funded by Cidara Therapeutics.

STRIVE Phase 2 Trial of Rezafungin Treatment

Documented Candidemia & Invasive Candidiasis



Objectives

To establish:

- Safety and tolerability
- Clinical and mycological efficacy across timepoints
- Efficacy vs caspofungin
- Dosing regimen for Phase 3

Clinicaltrials.gov; NCT02734862

Demographics and Baseline Characteristics

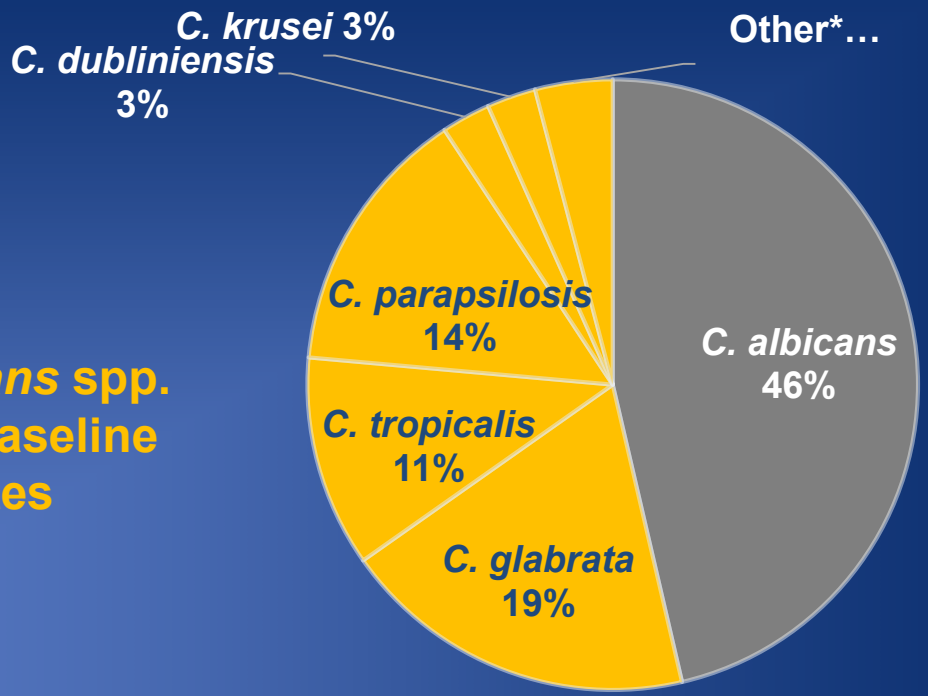
ITT Population

Parameter	Rezafungin 400 mg Wk 1 / 400 mg QWk N=81	Rezafungin 400 mg Wk1 / 200 mg QWk N=57	Caspofungin 70 mg Day 1 / 50 mg QD N=69
Age, Mean [Range]	60 y [24-88]	60 y [24-91]	59 y [24-93]
Diagnosis			
Candidemia	76.5%	80.7%	81.2%
IC	23.5%	19.3%	18.8%
APACHE II[a]			
0-9	28.4%	26.3%	24.6%
10-19	48.1%	45.6%	53.6%
≥20	21.0%	24.6%	13.0%
Mean score	13.4	14.1	14.0

[a]Subjects with scores not calculated/missing not shown.

Candida Species at Enrollment

mITT Population



C. fermentati, C. intermedia, C. kefyr, C. metapsilosis, C. rugosa, C. utilis (n=1 each), and *C. guilliermondii* (n=2)

Non-*albicans* spp. ~54% of baseline isolates

Total number of isolates: 196

Primary Outcome: Overall Response

Day 14 – mITT Population

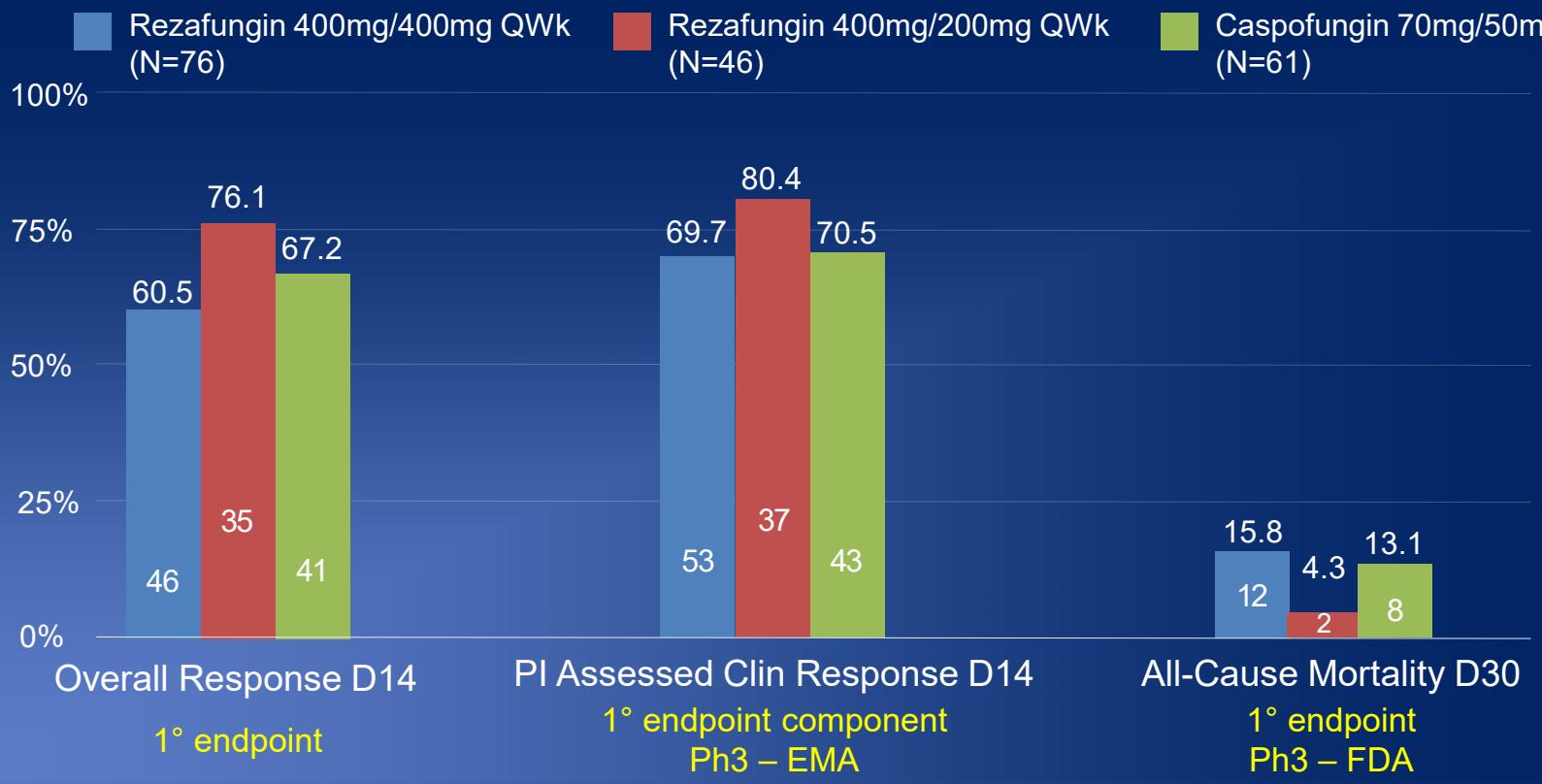
Overall Response n (%)	Rezafungin 400 mg Wk 1 / 400 mg QWk N=76	Rezafungin 400 mg Wk1 / 200 mg QWk N=46	Caspofungin 70 mg Day 1 / 50 mg QD N=61
Success	46 (60.5)	35 (76.1)	41 (67.2)
Failure	20 (26.3)	8 (17.4)	17 (27.9)

Overall Response = mycological success AND resolution of signs attributable to candidemia/IC

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown.
mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).

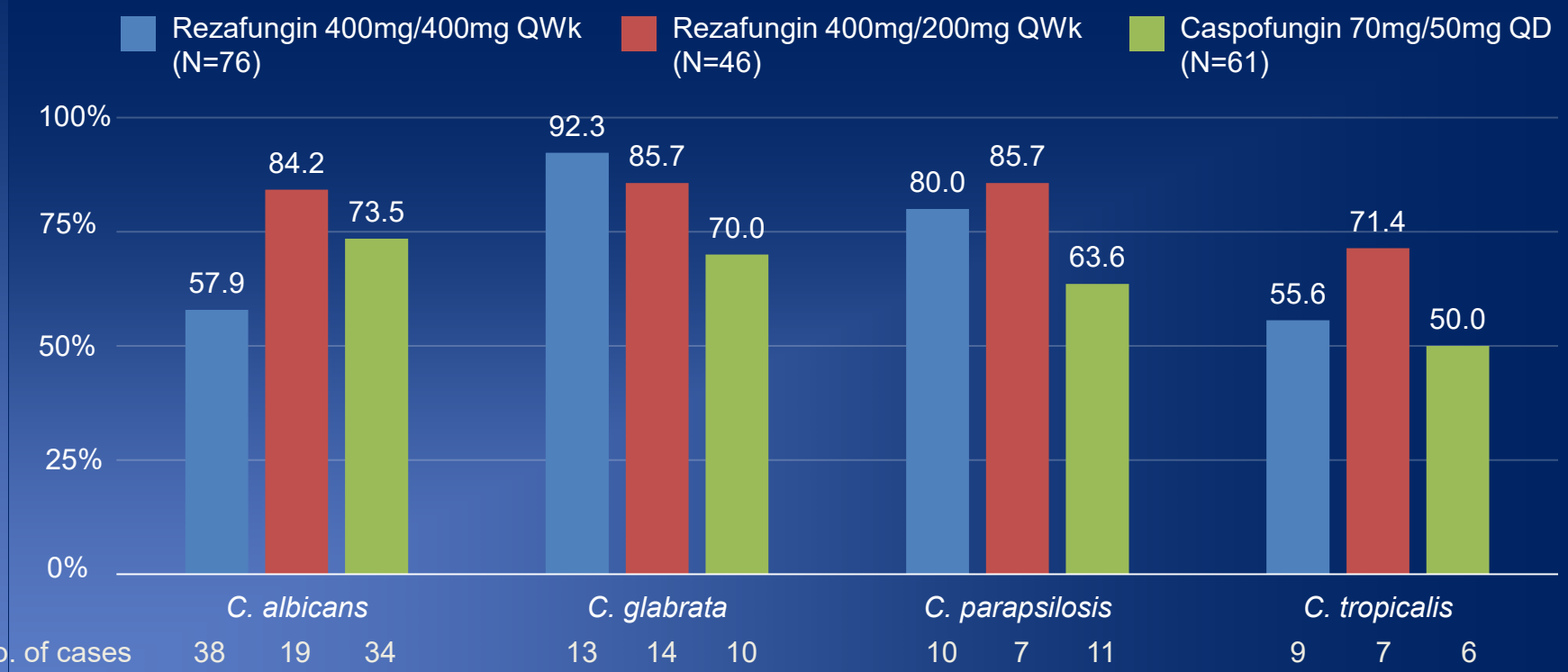
Summary of Rezafungin Efficacy Results

mITT Population



PI Assessment of Clinical Response by *Candida* spp.

Day 14 – mITT Population



Overall Response
Day 5 – mITT Population

Overall Response n (%)	Rezafungin 400 mg Wk1/ 400 mg QWk N=76	Rezafungin 400 mg Wk1/ 200 mg QWk N=46	All Rezafungin (Pooled) N=122	Caspofungin 70 mg Day 1 50 mg QD N=61
Success	42 (55.3)	34 (73.9)	76 (62.3)	34 (55.7)
Failure	24 (31.6)	10 (21.7)	34 (27.9)	24 (39.3)

Day 5 outcomes reflect the initial dose of 400 mg in both RZF-treated arms

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown.
mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).

Mycological Response

Day 14 – mITT Population (Patients with Candidemia Only)

Mycological Response n (%)	Rezafungin 400 mg Wk 1 / 400 mg QWk N=57	Rezafungin 400 mg Wk1 / 200 mg QWk N=36	Caspofungin 70 mg Day 1 / 50 mg QD N=48
Success	38 (66.7)	25 (69.4)	32 (66.7)
Failure	14 (24.6)	8 (22.2)	14 (29.2)

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown.
mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).

Summary of Adverse Events

Safety Population

Adverse Event n (%)	Rezafungin 400 mg Wk1/ 400 mg QWk N=81	Rezafungin 400 mg Wk1/ 200 mg QWk N=53	Rezafungin (Pooled) N=134	Caspofungin 70 mg Day 1 50 mg QD N=68
≥1 TEAE	71 (87.7)	49 (92.5)	120 (89.6)	55 (80.9)
Severe	29 (35.8)	17 (32.1)	46 (34.3)	26 (38.2)
Study drug–related	7 (8.6)	6 (11.3)	13 (9.7)	9 (13.2)
TEAE leading to study D/C	6 (7.4)	1 (1.9)	7 (5.2)	4 (5.9)
Serious AE	35 (43.2)	28 (52.8)	63 (47.0)	29 (42.6)
Study drug–related	1 (1.2)	1 (1.9)	2 (1.5)	2 (2.9)

D/C=discontinuation; TEAE (treatment-emergent adverse event)=AE that occurs after first dose of study drug is administered.

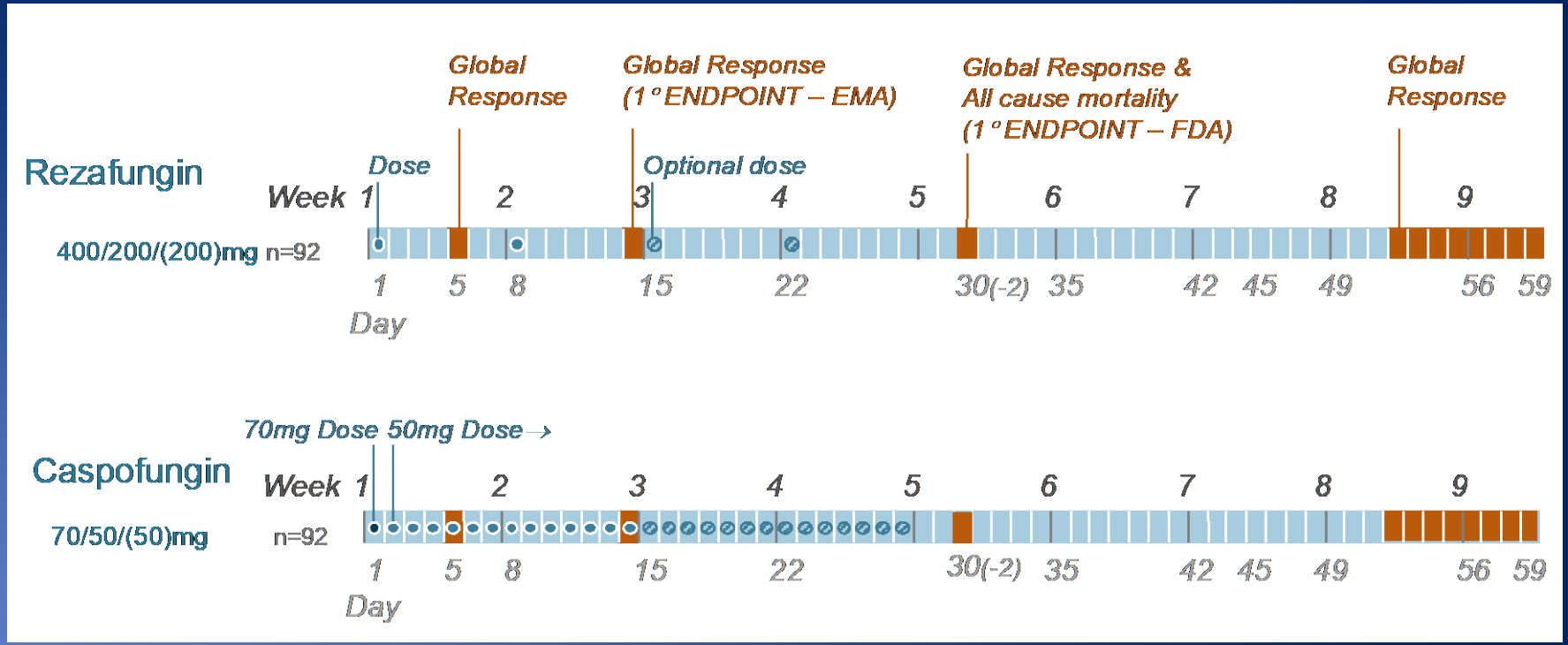
Treatment-Emergent Adverse Events (≥10%)

Safety Population

Preferred Term n (%)	Rezafungin 400 mg Wk1/400 mg QWk N=81	Rezafungin 400 mg Wk1/200 mg QWk N=53	Rezafungin (Pooled) N=134	Caspofungin 70 mg Day 1/ 50 mg QD N=68
Hypokalemia	13 (16.0)	9 (17.0)	22 (16.4)	9 (13.2)
Diarrhea	7 (8.6)	11 (20.8)	18 (13.4)	10 (14.7)
Vomiting	6 (7.4)	8 (15.1)	14 (10.4)	5 (7.4)
Pyrexia	9 (11.1)	4 (7.5)	13 (9.7)	6 (8.8)
Anemia	6 (7.4)	7 (13.2)	13 (9.7)	4 (5.9)
Nausea	4 (4.9)	8 (15.1)	12 (9.0)	6 (8.8)
Abdominal Pain	5 (6.2)	6 (11.3)	11 (8.2)	5 (7.4)
Septic Shock	9 (11.1)	1 (1.9)	10 (7.5)	3 (4.4)

Ongoing Phase 3 ReSTORE Trial

Rezafungin Treatment of Candidemia & Invasive Candidiasis



Summary

- ✓ **STRIVE findings which established rezafungin**
  - Clinical safety and tolerability
  - Efficacy (clinical and mycological) across time points and versus caspofungin
  - Once weekly dosing of 400 mg Week 1 / 200 mg Qweek

- ✓ **Results of STRIVE support ongoing phase 3 development** of rezafungin for treatment of candidemia and invasive candidiasis and prophylaxis of IFI

- ✓ Stop by poster #436 on Sunday for more details on STRIVE

PREVENTION OF INVASIVE FUNGAL INFECTIONS IN VULNERABLE HOSTS

KIEREN A. MARR MD, MBA

PROFESSOR OF MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE

DIRECTOR, TRANSPLANT AND ONCOLOGY INFECTIOUS DISEASES

VICE CHAIR OF MEDICINE FOR INNOVATION IN HEALTHCARE IMPLEMENTATION

COMMERCIAL ACTIVITY DISCLOSURE

- CONSULTANT / ADVISORY BOARD
  - AMPLYX, CHIMERIX, CIDARA, MERCK
- EDITORIAL ROLES
  - UPTODATE
- LICENSED TECHNOLOGY / OWNERSHIP
  - MYCOMED TECHNOLOGIES

OUTLINE

- PROPHYLAXIS – FOUNDATION AND HISTORY
- REAL-LIFE EPIDEMIOLOGY
- TRIAL DESIGN
  - RESPECT: 1-DRUG PREVENTION WITH REZAFUNGIN
- FUTURE POTENTIALS: UNMET NEEDS IN HEMATOLOGIC MALIGNANCIES

The New England
Journal of Medicine

Volume 326 MARCH 26, 1992 Number 13

A CONTROLLED TRIAL OF FLUCONAZOLE TO PREVENT FUNGAL INFECTIONS IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION

Jesse L. Goodman, M.D., Drew J. Winston, M.D., Ronald A. Greenfield, M.D., Pranatharthi H. Chandrasekar, M.D., Barry Fox, M.D., Herbert Kaizer, M.D., Richard K. Shadduck, M.D., Thomas C. Shea, M.D., Patrick Stiff, M.D., David J. Friedman, M.D., Ph.D., William G. Powderly, M.D., Jeffrey L. Silber, M.D., Harold Horowitz, M.D., Alan Lichtin, M.D., Steven N. Wolff, M.D., Kenneth F. Mangan, M.D., Samuel M. Silver, M.D., Ph.D., Daniel Weisdorf, M.D., Winston G. Ho, M.D., Gene Gilbert, Ph.D., and Donald Buell, M.D.

Efficacy and Safety of Fluconazole Prophylaxis for Fungal Infections after Marrow Transplantation—A Prospective, Randomized, Double-Blind Study

Monica A. Slavin, Barbara Osborne, Robyn Adams, Marcia J. Levenstein, H. Gary Schoch, Allen R. Feldman, Joel D. Meyers,* and Raleigh A. Bowden

Fred Hutchinson Cancer Research Center, Seattle; Pfizer Medica Division, New York, New York; Royal Melbourne Hospital Melbourne, Australi

705-713.

Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients

A Multicenter, Randomized Trial

Drew J. Winston, MD; Richard T. Maziarz, MD; Pranatharthi H. Chandrasekar, MD; Hillard M. Lazarus, MD; Mitchell Goldman, MD; Jeffrey L. Blumer, PhD, MD; Gerhard J. Leitz, MD, PhD; and Mary C. Territo, MD

blood

2004 103: 1527-1533
Prepublished online October 2, 2003;
doi:10.1182/blood-2003-08-2644

Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants

Kieren A. Marr, Fulvio Crippa, Wendy Leisenring, Maggie Hoyle, Michael Boeckh, S. Arunmozhi Balajee, W. Garrett Nichols, Benjamin Musher and Lawrence Corey

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

blood

Prepublished online Sep 8, 2010;
doi:10.1182/blood-2010-02-268151

Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HCT)

John R Wingard, Shelly L Carter, Thomas J Walsh, Joanne Kurtzberg, Trudy N Small, Lindsey R Baden, Iris D Gersten, Adam M Mendizabal, Helen L Leather, Dennis L Confer, Richard T Maziarz, Edward A Stadtmauer, Javier Bolaños-Meade, Janice Brown, John F DiPersio, Michael Boeckh and Kieren A Marr

AZOLE PROPHYLAXIS - BMT

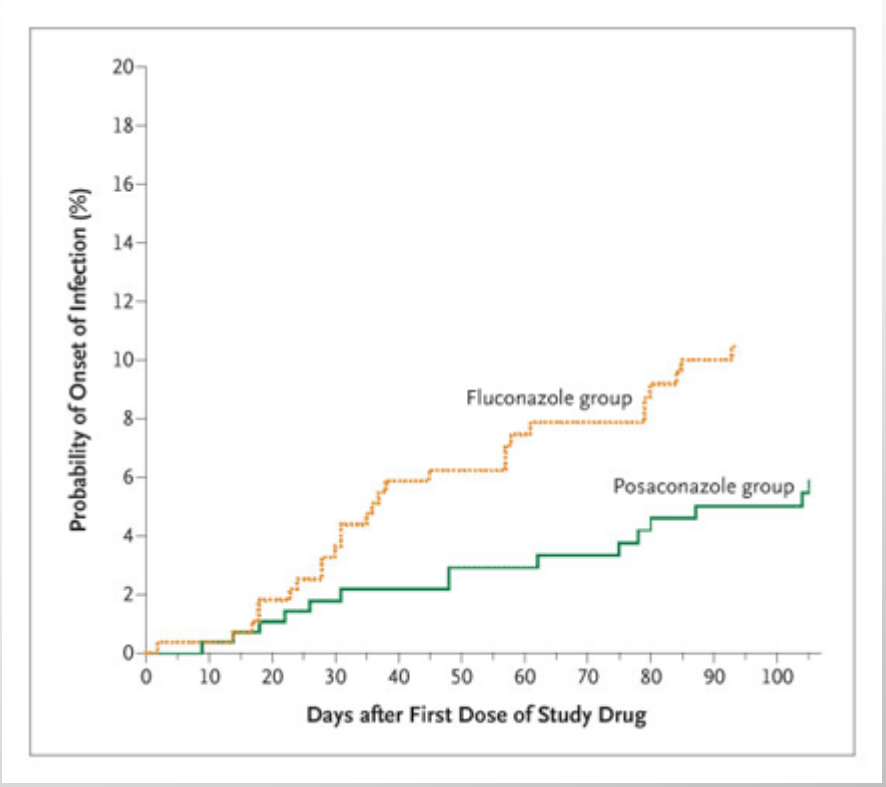
- FLUCONAZOLE PREVENTS CANDIDIASIS
  - NEW COMPARATOR FOR MOLD-ACTIVE AZOLES
- TWO RANDOMIZED TRIALS EVALUATING ITRACONAZOLE SOLUTION IN BMT PATIENTS
  - BOTH
    - DECREASED INVASIVE ASPERGILLOSIS IN ITRACONAZOLE ARM
    - TREND TO WORSE SURVIVAL IN ITRACONAZOLE ARM
    - TOXICITIES OF DRUG
      - GI TRACT TOXICITIES
      - DRUG INTERACTIONS

Is decreased IA "caused" by informative censoring ?

Winston et al. Ann Intern Med. 2003;138:705-713.
Marr et al, Blood 2004 103(4): 1527-33

POSACONAZOLE

- POSACONAZOLE VS. FLUCONAZOLE (N=600 PATIENTS)
  - DRUG WITH DIAGNOSIS OF GVHD
- APPROVED FOR PROPHYLAXIS IN BMT & AML/MDS



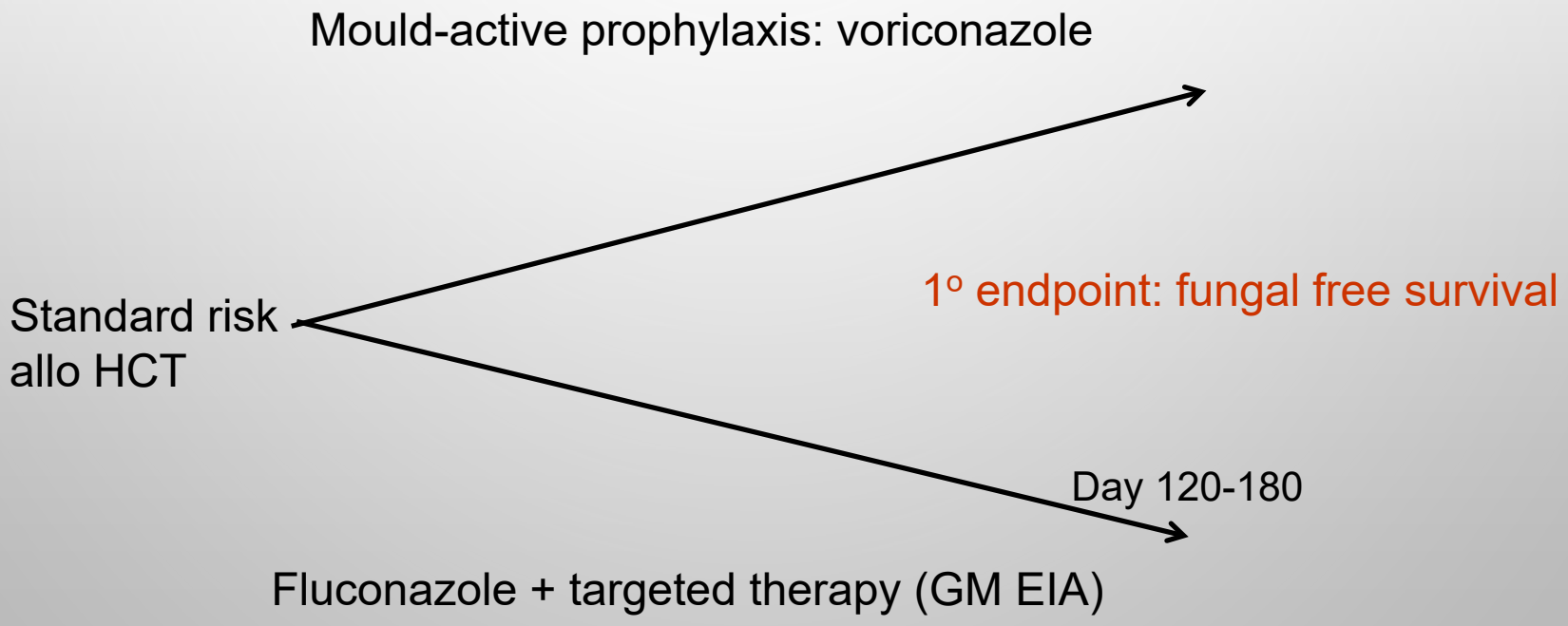
Ullmann et al. New Eng J Med 356;4 (2007)

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation

John R. Wingard,[1] Shelly L. Carter,[2] Thomas J. Walsh,[3] Joanne Kurtzberg,[4] Trudy N. Small,[5] Lindsey R. Baden,[6] Iris D. Gersten,[2] Adam M. Mendizabal,[2] Helen L. Leather,[1] Dennis L. Confer,[7] Richard T. Maziarz,[8] Edward A. Stadtmauer,[9] Javier Bolaños-Meade,[10] Janice Brown,[11] John F. DiPersio,[12] Michael Boeckh,[13] and Kieren A. Marr,[10,13] for The Blood and Marrow Transplant Clinical Trials Network

Blood; 116(24):5111-5118 (2010)

600 PATIENTS ENROLLED IN NHLBI BMT CTN PROTOCOL 0101



ANTIFUNGAL PROPHYLAXIS TRIALS IN BMT PATIENTS

Ullmann trial **Characteristics**	**POS** **n (%)**	**FLU** **n (%)**	***P*** **Value**
Study Period (120 days)			
Total	**16 (5)**	**27 (9)**	**0.07**
***Aspergillus* spp.**	**7 (2)**	**21 (7)**	**0.006**

N=600 total patients (301 POS group, 299 FLU group).

BMT CTN trial **Characteristics**	**VORI** **n (%)**	**FLU** **n (%)**	***P*** **Value**
Study Period (180 days)			
Total	**14 (4.6)**	**24 (8.1)**	**0.11**
***Aspergillus* spp.**	**9 (3.0)**	**17 (5.8)**	**0.09**

N=600 total patients (305 VORI group, 295 FLU group).

Risk reduction 0.037 vs. 0.04

ISAVUCONAZOLE

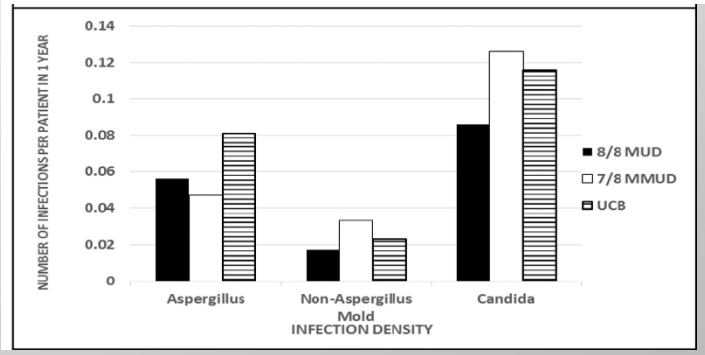
- APPROVED FOR THERAPY OF INVASIVE ASPERGILLOSIS
- OBSERVATIONS: USED FREQUENTLY, ESPECIALLY WITH LIVER TOXICITIES, PEOPLE WITH LONG QT
- REPORTS OF FREQUENT BREAKTHROUGH
- REASONS UNKNOWN
  - BIAS?
  - ANTIFUNGAL LEVELS? (TDM)
  - RESISTANCE? AT LEAST ONE CASE OF TR34-L98H RESISTANT *A. FUMIGATUS* BREAKTHROUGH REPORTED

Rauch et al. Clin Infect Dis 2018; Fontana et al. Clin Infect Dis 2019; Belanger et al. EID 2019

REAL-WORLD EPIDEMIOLOGY

- CIBMTR STUDY – ACUTE LEUKEMIA WITH ALTERNATIVE DONORS: MATCHED, UNRELATED DONORS (MUD), MISMATCHED, UNRELATED DONORS (MMUD) AND CORD BLOOD (UCB)
- INCIDENCE OF IFI REMAINS HIGH
- "PREVENTABLE IFI":
  - BOTH IA AND CANDIDIASIS

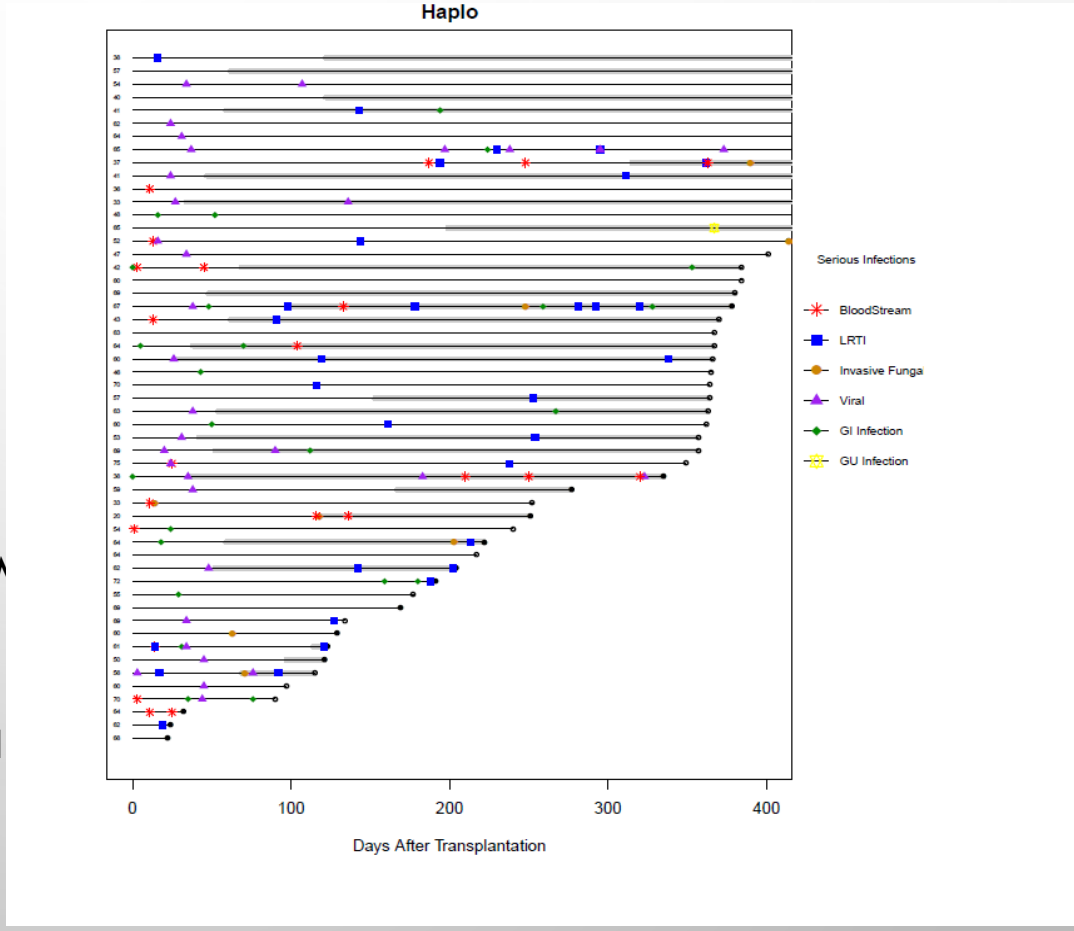
	MUD % (95% CI)	MMUD* % (95% CI)	UCB* % (95% CI)	p-value
Transplant Outcomes				
OS	69% (66 – 72%)	60% (54 – 66%)	51% (47 – 55%)	<0.0001
LFS	56% (56 – 72%)	49% (43 – 54%)	44% (40 – 48%)	<0.0001
Relapse	27% (24 – 30%)	25% (20 – 30%)	24% (21 – 28%)	0.43
NRM	14% (12–16%)	27% (22 – 32%)	33% (29 – 36%)	<0.0001
Infection Incidence				
Bacterial	59% (57 – 64%)	65% (59 – 70%)	72% (68 – 76%)	<0.0001
Viral	45% (42 – 48%)	53% (47 – 59%)	68% (64 – 72%)	<0.0001
Fungal	10% (8–12%)	16% (12–20%)	18% 15–21%)	0.0001



Ballen et al. BBMT 2016 22(9)

REAL – WORLD RECURRENT INFECTIONS

- INFECTIOUS MORBIDITY BETTER APPRECIATED AS CUMULATIVE, RECURRENT EVENTS
- SWIMMER-LANE PLOTS: PROVIDE CONTROL FOR INFORMATIVE CENSORING AND DEMONSTRATES 'REAL-LIFE' FAILURE
- A LOT OF MORBIDITY DESPITE EFFECTIVE PREVENTION ALGORITHM
- HETEROGENEITY
- IFI OCCUR LARGELY BEFORE DEATH



SUCCESS = BALANCE

<u>Benefits</u>

Prevent IFI
- morbidity
- mortality

Secondary

<u>Risks</u>

Toxicities
Drug interactions
Drug resistance
Costs

Each drug has different benefits and risks when utilized in different settings

PNEUMOCYSTIS INFECTION FRENCH BMT OBSERVATION

- ONLY 45% OF 139 CONSECUTIVE PATIENTS RECEIVED FULL COURSE OF TMP/SMX
  - 60 PATIENTS SWITCHED DUE TO SIDE EFFECT
  - 18 CONFIRMED PCP CASES (12.9% INCIDENCE)
- FREQUENT FAILURE DUE TO POOR TOLERABILITY IN REAL-WORLD

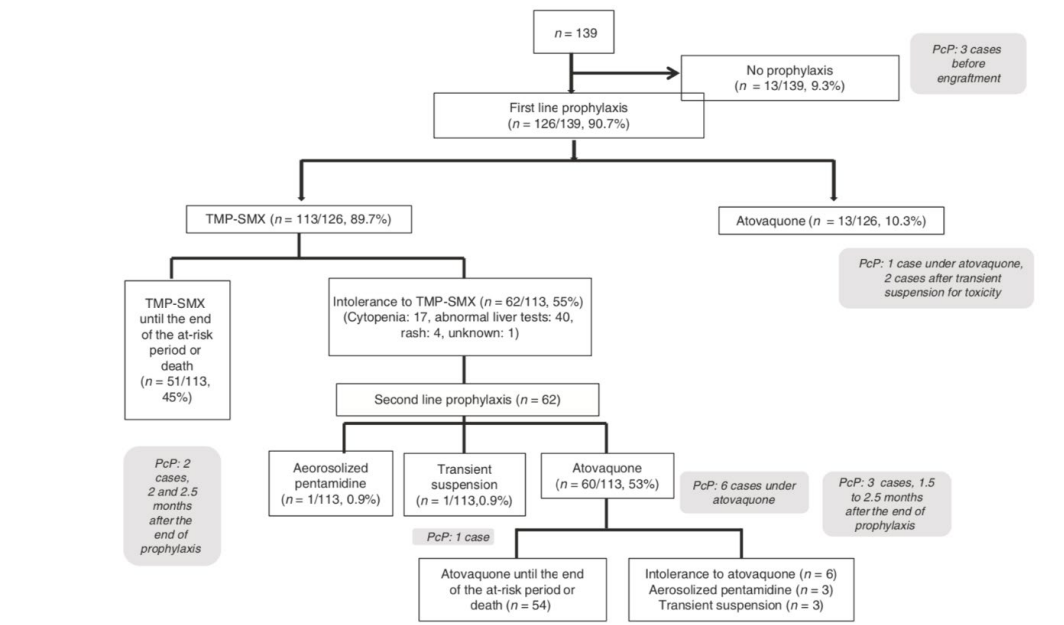


Fig. 1 Flow chart of pneumocystis prophylaxis in 139 consecutive allogeneic HCT recipients

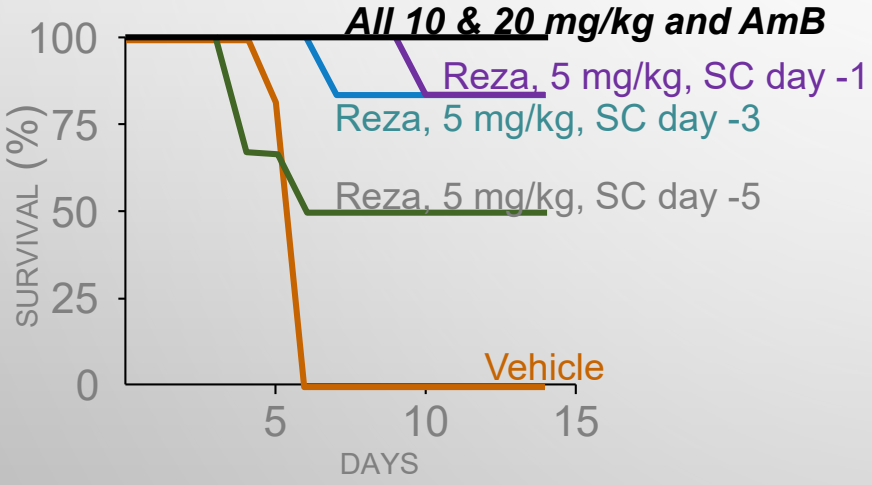
Redjoul et al. BMT 2019 54: 1082-88

REZAFUNGIN ANTIFUNGAL PROPHYLAXIS: RATIONALE

- ONCE – WEEKLY INFUSION
- NO CYTOCHROME P450 INTERACTIONS
- PRECLINICAL, CLINICAL ACTIVITY AGAINST *CANDIDA* SPP.
- PRECLINICAL ACTIVITY AGAINST *ASPERGILLUS* & PCP

Rezafungin
Aspergillosis & PCP models

Aspergillosis in neutropenic mice:
Equivalent survival in humanized doses relative to AmB

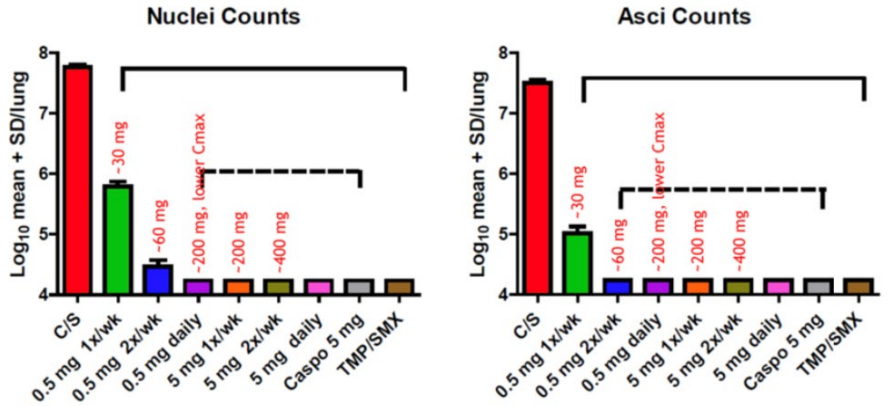


10 mg/kg ≈ human dose of 200mg
20 mg/kg ≈ human dose of 400mg

ECCMID and EHA 2017

PCP in neutropenic and steroid-suppressed mice:
Equivalent reduction in cysts and trophic forms relative to TMP/SMX

Log_{10} mean nuclei and asci counts after 42 days of study drug administration.



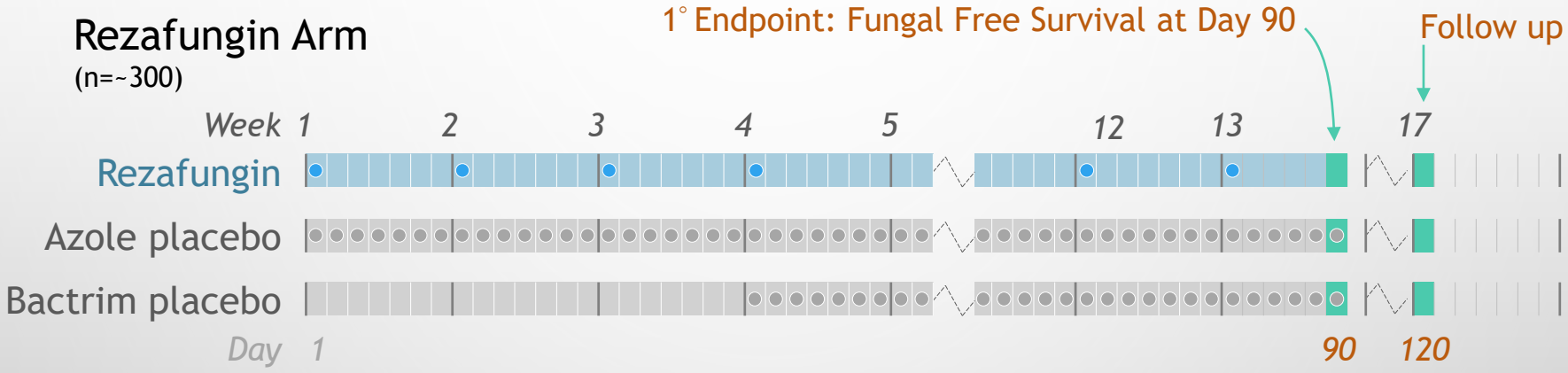
Cushion et al. TCT, Feb 2019

RESPECT TRIAL ANTIFUNGAL PROPHYLAXIS IN BMT

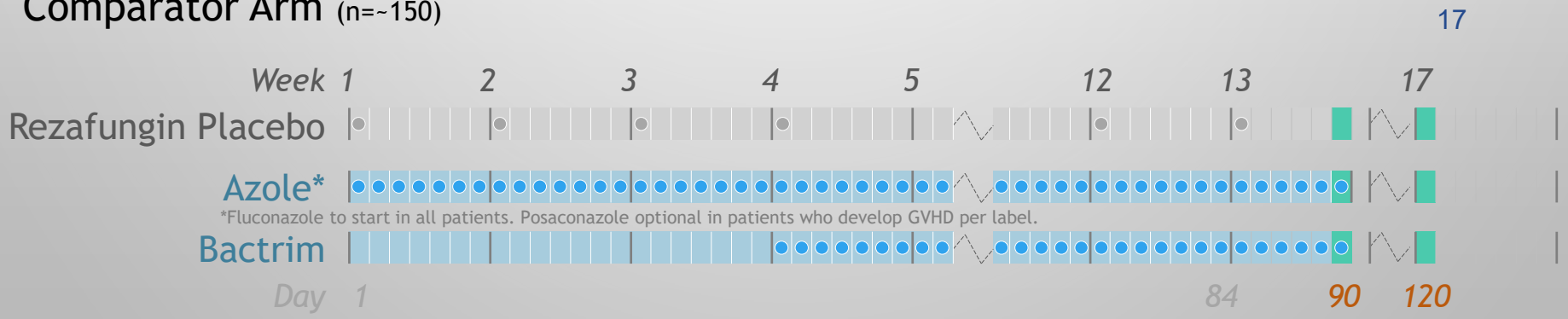
- TO START Q12020 IN EUROPE
- RANDOMIZED, DOUBLE-BLIND COMPARISON OF ONCE WEEKLY REZAFUNGIN VS. STANDARD ANTIFUNGAL PROPHYLAXIS (AZOLE + TMP-SMX) AFTER ALLOBMT
- DESIGN (462, 2:1 RANDOMIZATION)
  - STANDARD-RISK ALLOGENEIC BMT (NO CBT, AML NOT IN MORPHOLOGIC REMISSION, RECENT IFI)
  - 90 DAYS REZA VS. CURRENT STANDARD (FLUCONAZOLE WITH POSA FOR GVHD & TMP/SMX)
  - POWERED TO MEASURE NON-INFERIORITY OF FUNGAL – FREE SURVIVAL & SUPERIORITY OF PROPHYLAXIS SUCCESS

RESPECT PHASE 3 TRIAL

Rezafungin Arm
(n=~300)



Comparator Arm (n=~150)



FUTURE APPLICATIONS? UNMET NEEDS IN HEMATOLOGY

- INFECTIOUS RISKS POORLY DESCRIBED IN CLINICAL DEVELOPMENT
- EXPERIENCE UNDERLINING COMPLEX SECONDARY RISKS FOR IFI IN SEVERAL DRUGS
- MANY CONTRAINDICATIONS TO AZOLES DUE TO CYTOCHROME P450 INTERACTIONS

New chemotherapic agents already in use or coming in Hematology

AML

1. FLT3-inhibitors (Quizartinib, Midostaurin, Sorafenib)
2. Monoclonal antibodies anti-CD33 (Gentuzumab)
3. Arsenic Trioxide
4. IDH1-2 inhibitors
5. Combined liposomal cytarabine and daublastine (CTX1)

Lymphomas (low and high grade)

1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Rituximab, Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)

Hodgkin's Lymphoma

1. Monoclonal antibodies anti-CD30 (Brentuximab)
2. IgG4 anti-PD-1 (Nivolumab)

ALL

1. Monoclonal antibodies
   a. anti-CD19 (Blinatuzumab)
   b. anti -CD22 (Inotuzumab)
2. TK inhibitors (Imatinib, Nilotinib, Dasatinib, Ponatinib)

Multiple Myeloma

1. IMIDS (Talidomide, Lenalidomide Pomalidomide)
2. Proteosome inhibitors (Bortezomib, Carfizomib)
3. Monoclonal antibodies
   a. anti-CD38 (Daratumumab)
   b. anti-CD319 (Elotuzumab)

CLL

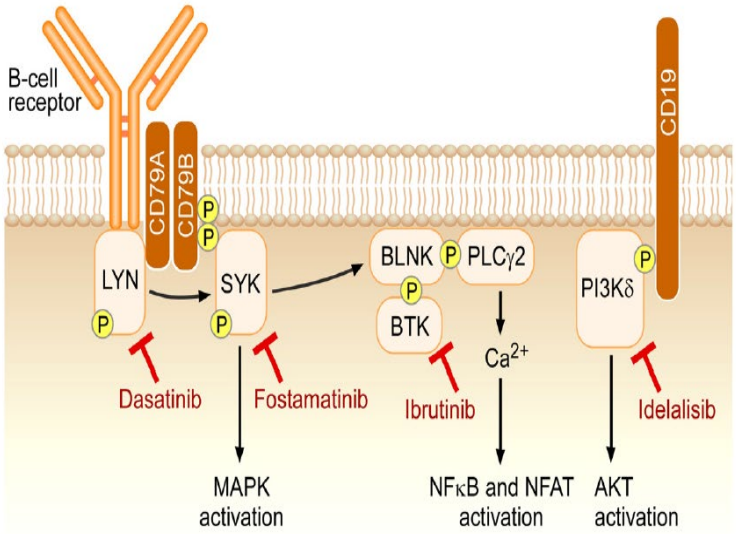
1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)
4. Anti apoptotic BCL-2 (Venetoclax)

Slide: L. Pagano

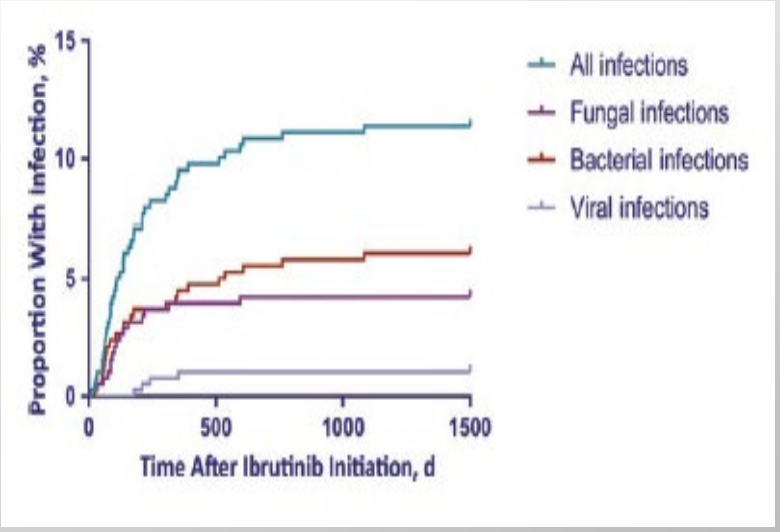
IFI RISKS ARE COMPLEX AND SOMETIMES UNEXPECTED

- RISKS REPRESENT
  - CUMULATIVE FUNCTION OF HOST RISKS (EX. AGE, LUNG DISEASE), UNDERLYING DISEASE, PRIOR THERAPIES
  - MANY DRUGS (EX. CHECKPOINT INHIBITORS) CAUSE INFLAMMATORY SYNDROMES THAT REQUIRE SECONDARY IMMUNOSUPPRESSION
    - EXAMPLE: IFI AFTER STEROIDS GIVEN FOR PNEUMONITIS, COLITIS
  - NON-SPECIFIC EFFECTS OF 'TARGETED' DRUGS

TYROSINE KINASE INHIBITORS



- DRUGS TARGET B CELL RECEPTOR, INHIBIT ACTIVATION AT DIFFERENT SIGNALING TARGETS. USED FOR CLL, LYMPHOMAS
- IFI RISKS COMPLICATED. EXAMPLE IBRUTINIB (BRUTON'S TK INHIBITOR)
  - SINGLE-CENTER REVIEW: 11% INCIDENCE INFECTION
  - RELATIVELY HIGH INCIDENCE IFI (ESPECIALLY PCP & IA)
  - CNS ASPERGILLOSIS
  - MECHANISTIC STUDIES REVEAL INHIBITION OF MACROPHAGE AND PMN KILLING
- LIMITED OPTIONS FOR PROPHYLAXIS DRIVING EXPLORATION OF ALTERNATIVES



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92; Bercusson A. Blood 2018 132(18): 1985-88; Blez et al. Haematologica 2019 (in press); Lee et al. Am J. Hematol 2017; 92

CONCLUSIONS

- LONG HISTORY OF STUDIES IN BMT DEMONSTRATE UTILITY OF ANTI-FUNGAL PROPHYLAXIS IN TRIALS
  - ANTI-CANDIDA, ASPERGILLUS AND PJP
- REAL-LIFE OUTCOMES COMPLICATED BY INABILITY TO TAKE PREVENTATIVE DRUGS FOR A LONG PERIOD OF TIME (DRUG INTERACTIONS, TOXICITIES)
- NEW STUDY TO START NEXT YEAR:
  - REZAFUNGIN 1-DRUG PROPHYLAXIS VS. STANDARD APPROACH
  - DESIGN CONSIDERS LESSONS LEARNED
- EVOLVING COMPLEX FIELD WITH UNMET NEEDS IN OTHER VULNERABLE HOSTS, ESPECIALLY WITH TARGETED BIOLOGICS

THANK YOU