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Therapeutic Options: Where do we stand? Where do we go?

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Transparency Declaration

Research Grants: 3M, Actelion, Astellas, AstraZeneca, Basilea, Bayer, F2G, Genzyme, Gilead, GSK, Merck/MSD, Medicines Company, MedPace, Miltenyi, Pfizer, Sanofi Pasteur, Scynexis, Seres, Viropharma

Advisory Boards: Amplyx, Anacor, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Matinas, Merck/MSD, Scynexis, Seres, Summit, Vical, Vifor

Speaker Honoraria: Astellas, Basilea, Gilead, Merck/MSD

Shareholder: N/A

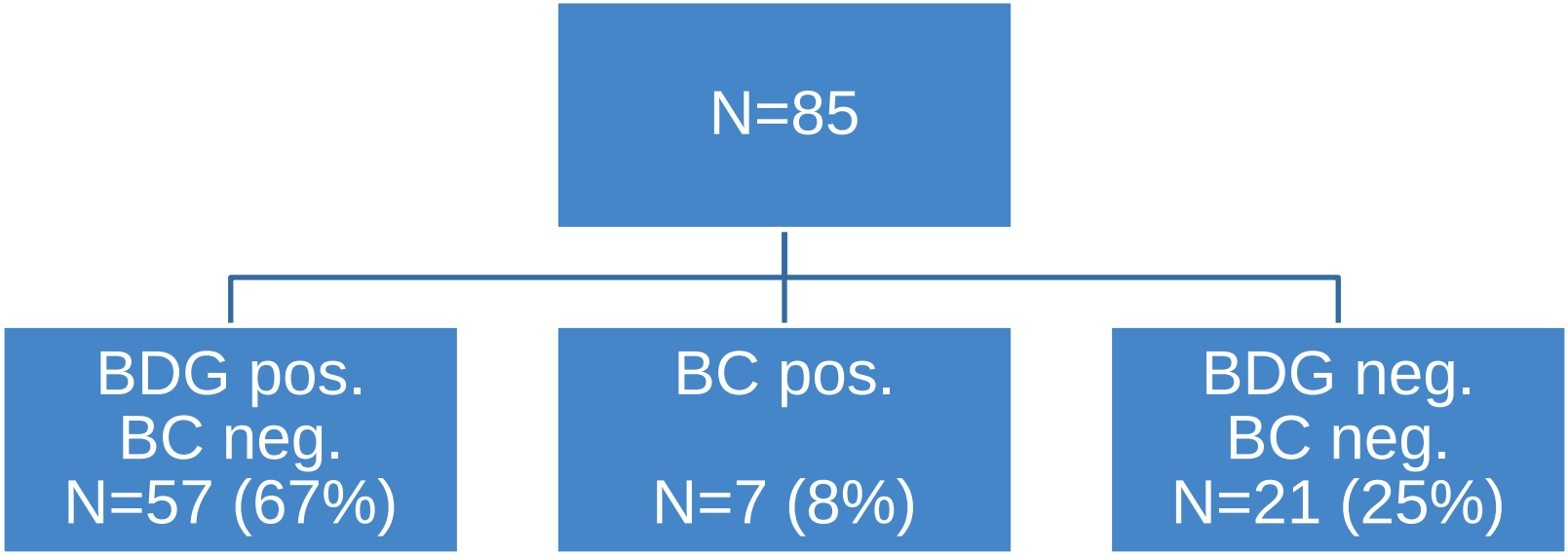
How to use 1,3-ß-D-glucan?

- 85 of 2148 ICU patients had all of the below:
  1. CVC
  2. Antibiotic treatment
  3. 2 of: dialysis, surgery, pancreatitis, steroids/immunosuppression, parenteral nutrition
  4. 1 of: fever, hypothermia, hypotension, leukocytosis, acidosis, or CRP↑

- Received echinocandin treatment and
  - ➢ Diagnostic screening
    - – Day 1 and 2: Blood culture
    - – Day 1, 2, and 3: β-D-Glucan

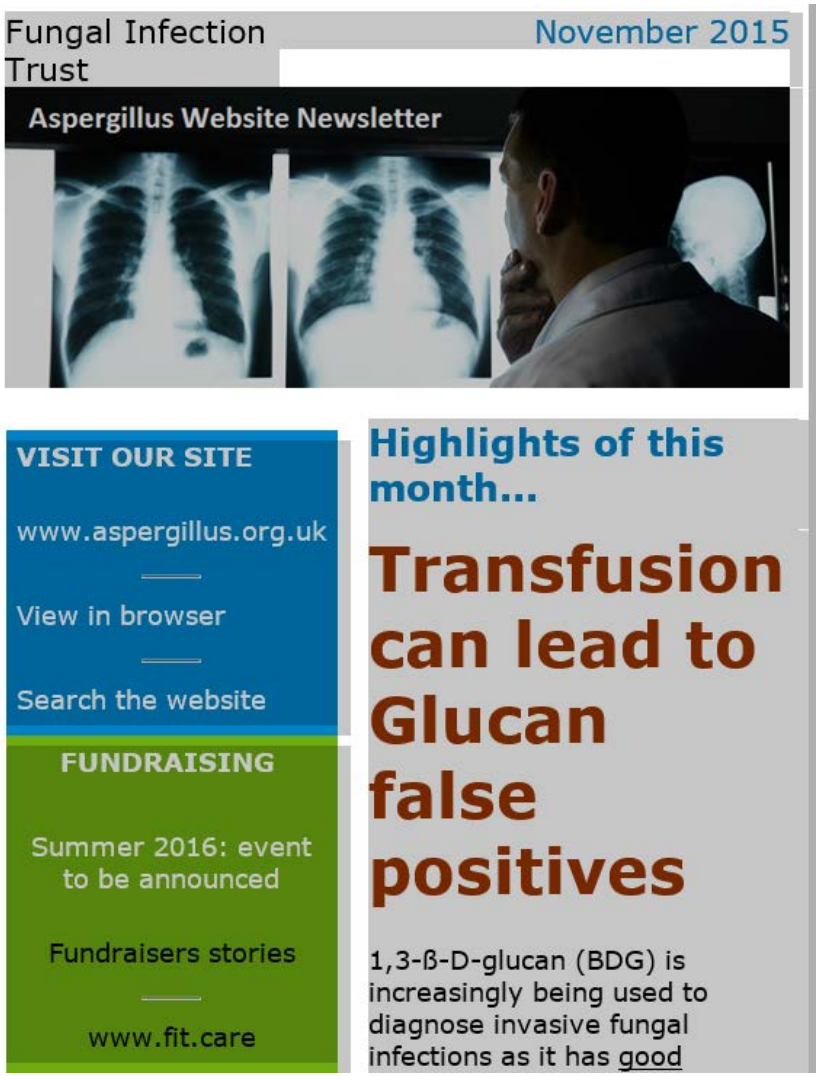
Nucci M et al. ICAAC 2014; M-1754.

How to use 1,3-ß-D-glucan?



Nucci M et al. ICAAC 2014; M-1754.

How to use 1,3-ß-D-glucan?


Fungal Infection Trust

November 2015

Aspergillus Website Newsletter

VISIT OUR SITE

www.aspergillus.org.uk

View in browser

Search the website

FUNDRAISING

Summer 2016: event to be announced

Fundraisers stories

www.fit.care

Highlights of this month...

Transfusion can lead to Glucan false positives

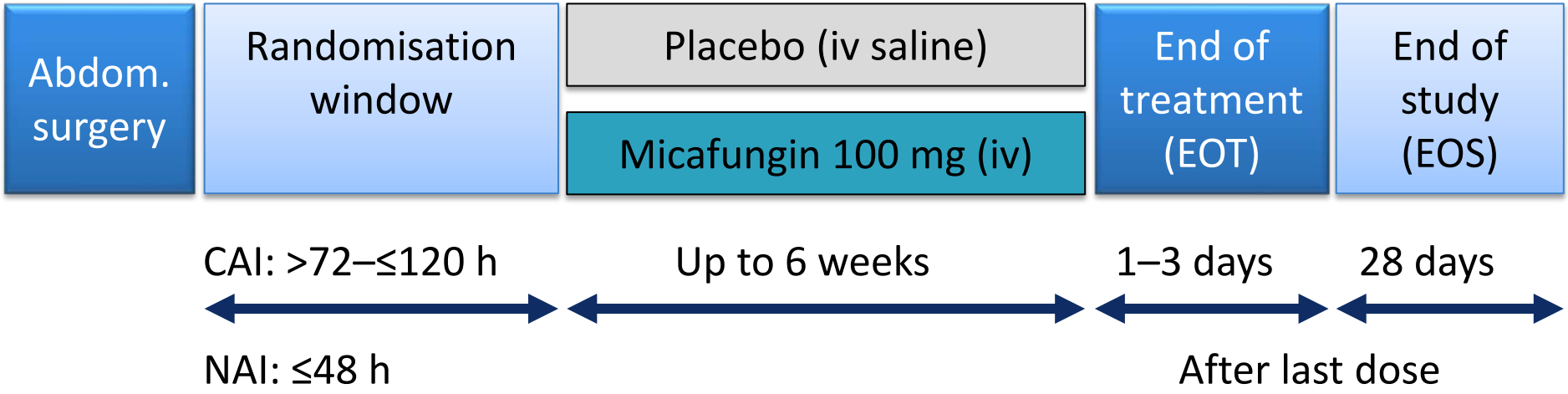
1,3-ß-D-glucan (BDG) is increasingly being used to diagnose invasive fungal infections as it has good

BDG more appropriate

- To rule out IFI
- In ICU settings

Liss BJ et al. Mycoses 2016.

Pre-Emptive Tx of Invasive Candidiasis Study Design

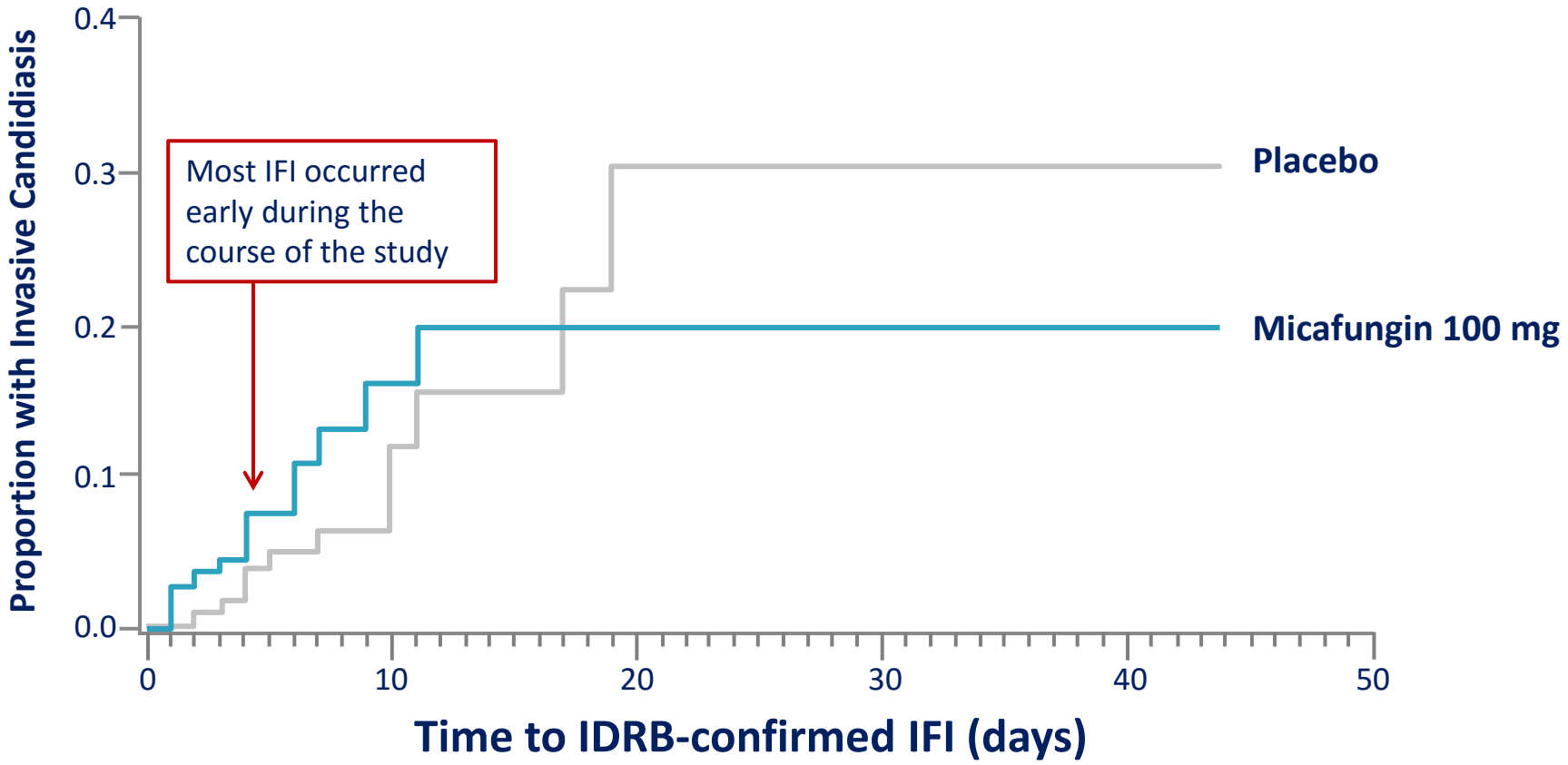


EOT occurred when:

- Condition of patient improved
- Confirmation of IFI
- Alternative antifungal therapy
- Death

Knitsch W et al. Clin Infect Dis 2015; 61(11):1671–8.

Pre-Emptive Tx of Invasive Candidiasis
Time to IDRB-Confirmed IC



No difference between placebo and micafungin 100 mg in time to first IFI.

Knitsch W et al. Clin Infect Dis 2015; 61(11):1671–8.

Targeted Treatment of Candidaemia
Echinocandins

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Compound	SoR	QoE	Reference	Comment
Anidulafungin 200/100	A	I	Reboli NEJM 2007	• Broad spectrum • Resistance rare • Fungicidal • Local epidemiology • C. parapsilosis, C. krusei • Safety profile • Less drug-drug interactions than caspofungin
Caspofungin 70/50	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	• Largely as above
Micafungin 100	A	I	Kuse Lancet 2007 Pappas CID 2007	• Largely as above • Consider EMA warning label

Cornely OA et al. Clin Microbiol Infect 2012.

Targeted Treatment of Candidaemia
Polyenes

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
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Compound	SoR	QoE	Reference	Comment
Amphotericin B, deoxycholate, any dose	D	I	Ullmann CID 2006 Bates CID 2001 Anaissie CID 1996 Rex NEJM 1994 Philips EJCMID 1995 Mora-Duarte NEJM 2002	
Amphotericin B, liposomal	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	•Similar efficacy as micafungin •Higher toxicity than micafungin
Amphotericin B, lipid complex	C	II_a	Anaissie ICAAC 1995 Ito CID 2005	
Amphotericin B, colloidal dispersion	D	II_u	Noskin CID 1998	•Mostly immunocompromised patients (HCT, haem/onc or SOT) rather than ICU patients

HCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation.

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Targeted Treatment of Candidaemia
Azoles

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Compound	SoR	QoE	Reference	Comment
Fluconazole	C	I	Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1995 Reboli NEJM 2007 Tuil CCM 2003 Abele-Horn Infect 1996 Leroy CCM 2009 Gafter-Gvili Mayo Clin Proc 2008	• Limited spectrum • Inferiority to anidulafungin (especially in the subgroup with high APACHE scores), • *C. parapsilosis*
Itraconazole	D	II_a	Tuil CCM 2003 (abstract)	
Posaconazole	D	III	No reference found	• PO only
Voriconazole	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	• Limited spectrum compared to echinocandins • Drug-drug interactions • IV in renal impairment • Need for TDM

TDM, Therapeutic drug monitoring.

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

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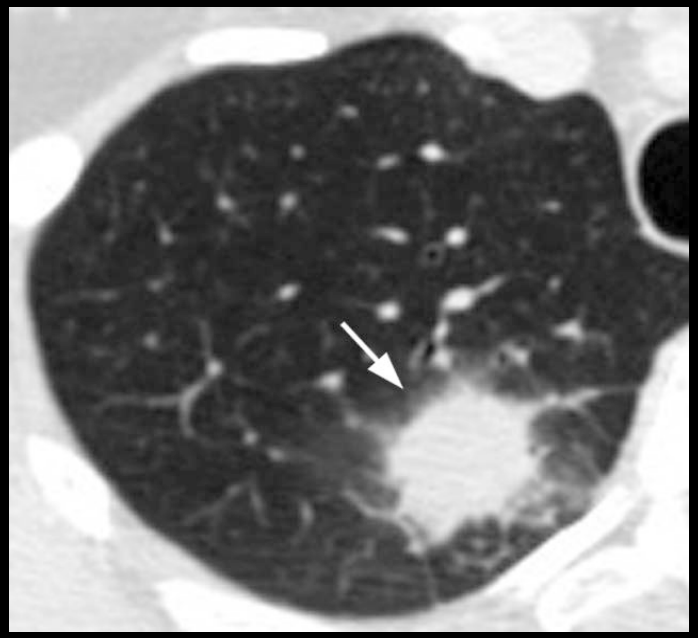
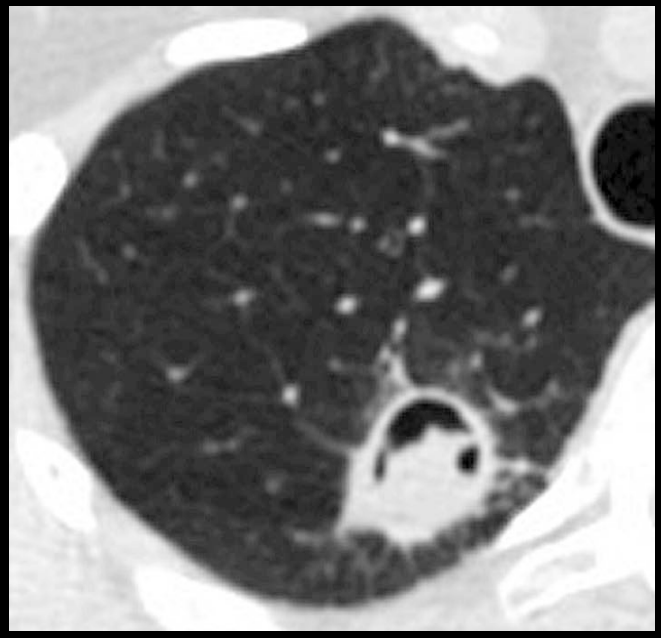
Typical CT Morphology of Invasive Aspergillosis



nodular infiltrate with a surrounding halo

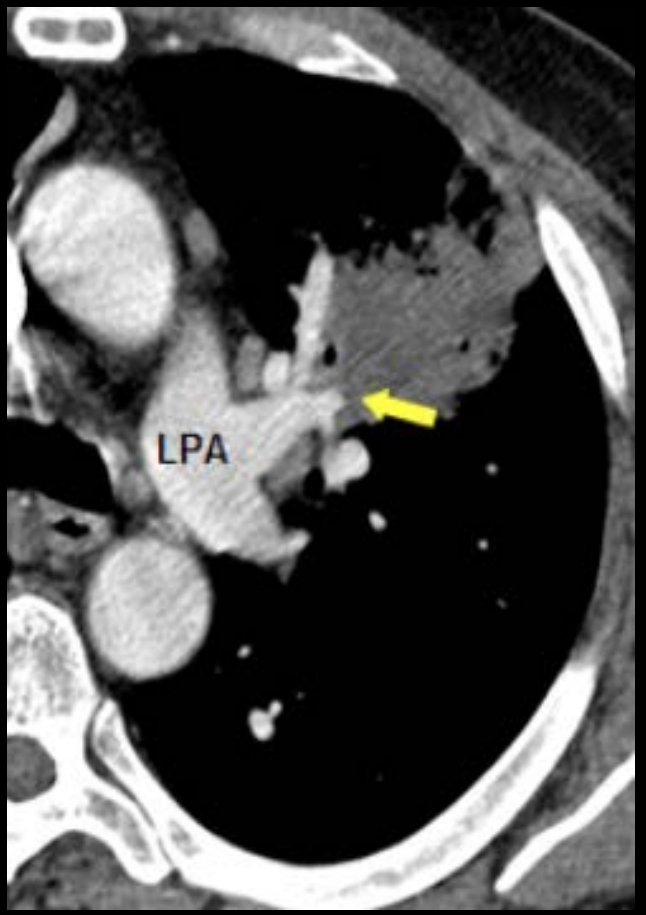


air-crescent

Cornely OA.

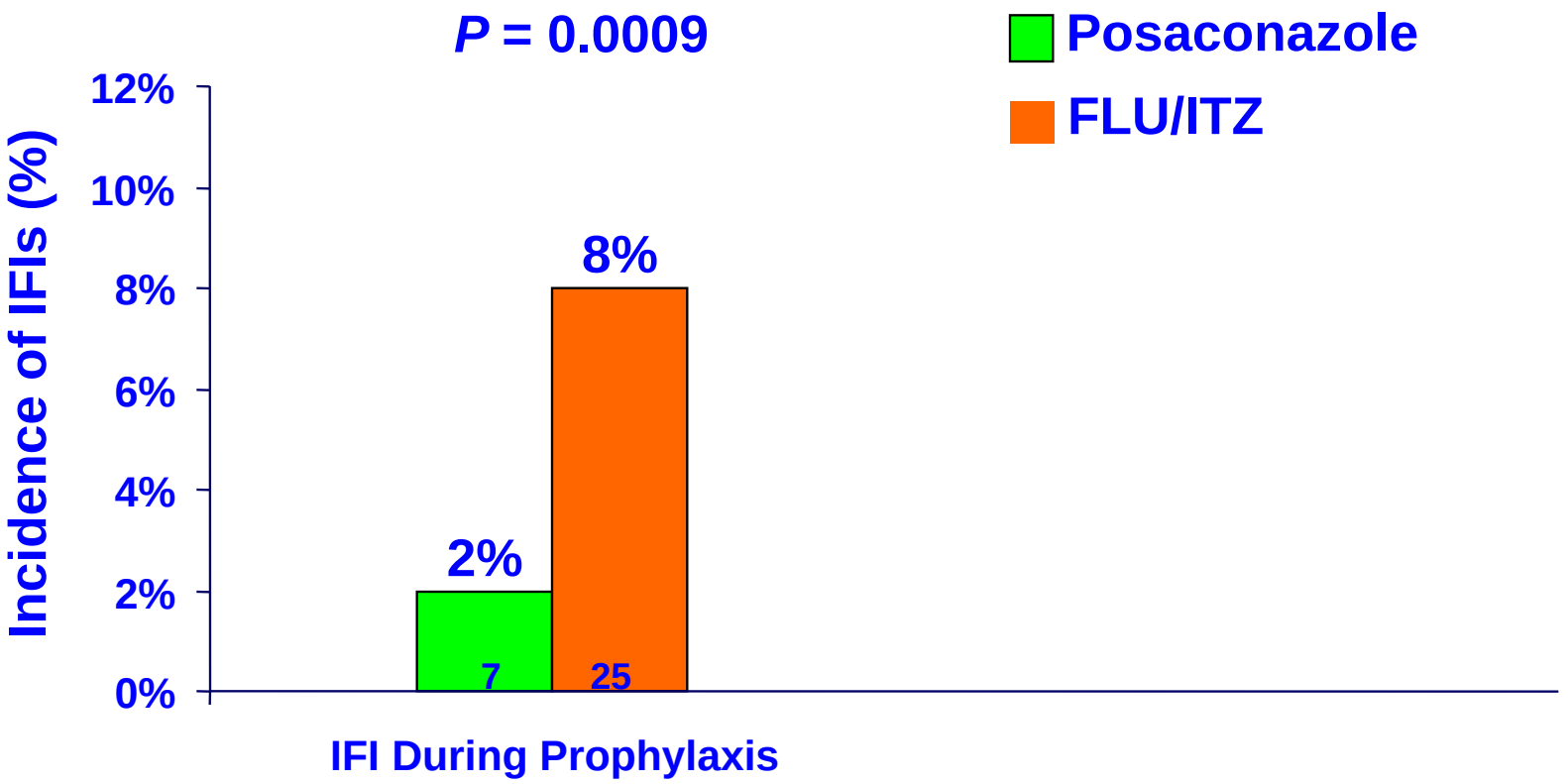
Invasive Fungal Infection – Angiography

- Lung embolism protocol
- Lung artery occluded or destroyed
- Angio-invasive growth of moulds



Stanzani M et al. Clin Infect Dis 2015; 60(11): 1603-1610.

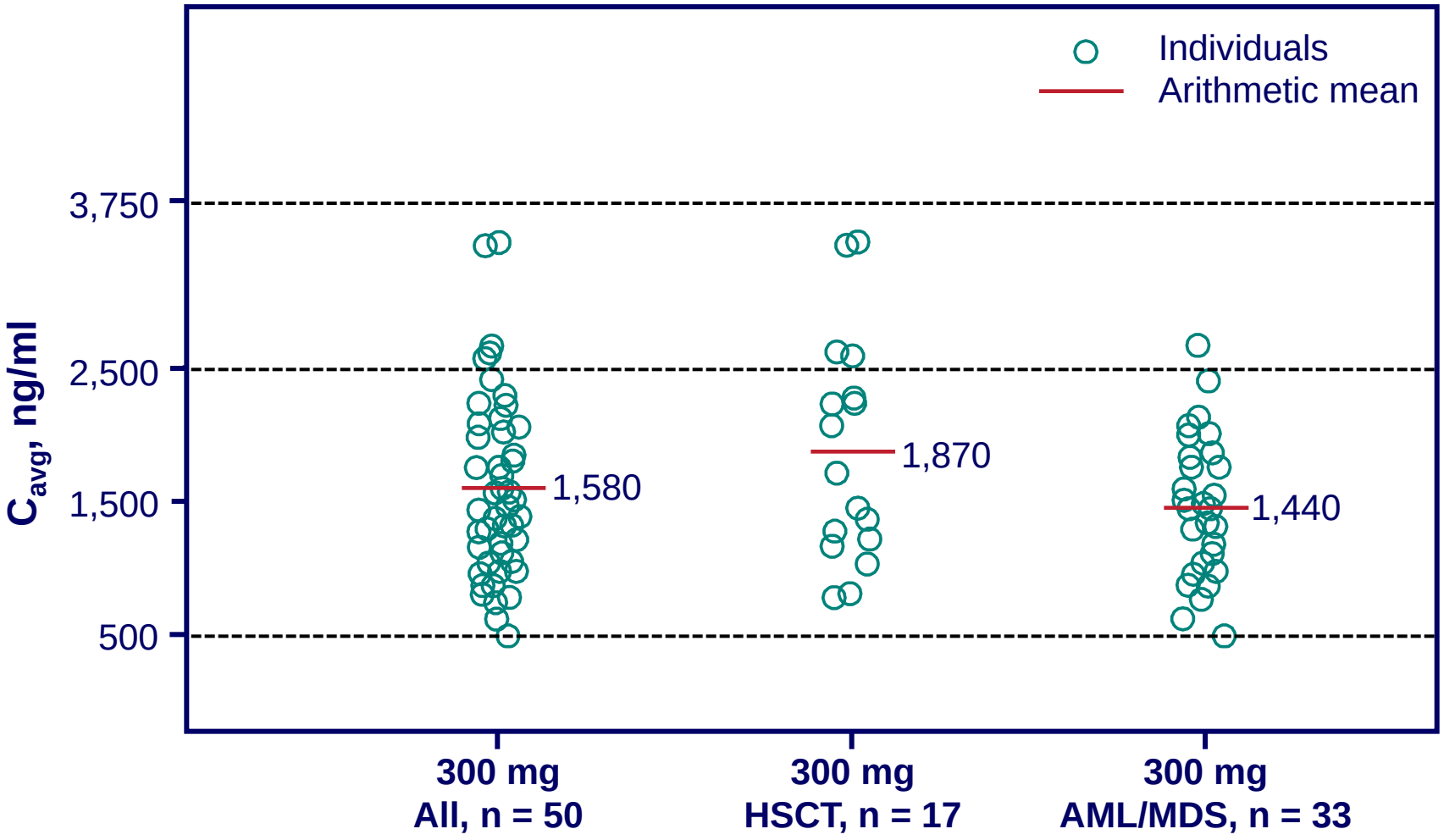
Posaconazole vs. Fluconazole/Itraconazole Incidence of Breakthrough IFI



Cornely OA et al. N Engl J Med 2007.

Posaconazole Tablet Phase III Observed Individual C_{avg}

Multiple dosing of 300 mg QD, BID on day 1, serial PK-evaluable cohort



Cornely OA et al. J Antimicrob Chemother 2016; 71(3): 718-26.

Posaconazol IV Phase III Pharmacokinetics

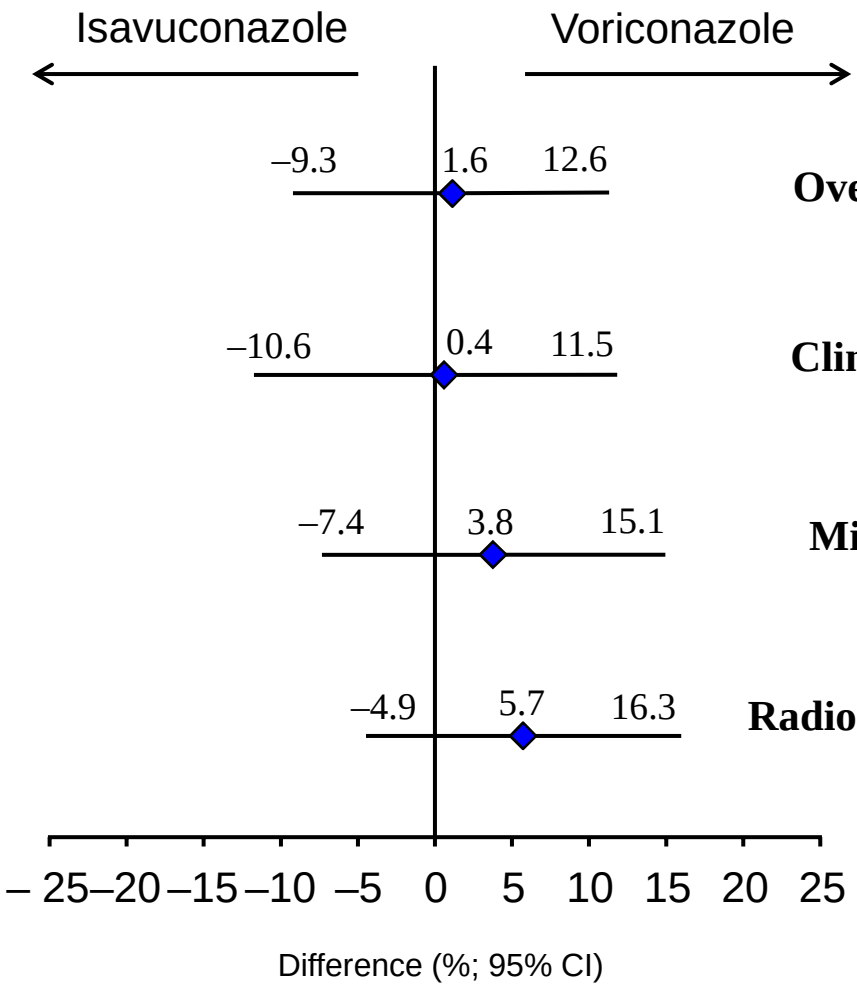
- 46/49 patients (94%) attained the exposure target of C_{avg} ≥500 ng/mL and ≤2,500 ng/mL

PK Steady State C_{avg} Criteria	AML n = 30	HSCT n = 19	Total n = 49
<500 ng/mL, n (%)	0	0	0
≥500 and ≤2,500 ng/mL, n (%)	28 (93)	18 (95)	46 (94)
>2,500 and ≤3,650 ng/mL, n (%)	2 (7)	1 (5)	3 (6)
>3,650 ng/mL, n (%)	0	0	0

- Steady state C_{avg} was similar in AML/MDS (1,470 ng/mL) and allogeneic HSCT (1,560 ng/mL) patients

Cornely OA et al. 53rd ICAAC, Denver, September 10-13, 2013.

Invasive Aspergillosis – Treatment Response Isavuconazole vs Voriconazole



	ISA	VRC
Overall Response	50/143 (35%)	47/129 (36%)
Clinical Response	85/137 (62%)	73/121 (60%)
Microbiological Response	54/143 (38%)	53/129 (41%)
Radiological Response	41/141 (29%)	42/127 (33%)

Maertens J et al. Lancet 2015.

Invasive Aspergillosis – Safety Isavuconazole vs Voriconazole

Most frequent treatment-emerging adverse events by system organ class

System Organ Class	Isavuconazole N = 257	Voriconazole N = 259	p-value
Overall, n (%)	247 (96.1)	255 (98.5)	
Gastrointestinal disorders	174 (67.7%)	180 (69.5%)	
Infections and infestations	152 (59.1%)	158 (61.0%)	
General disorders & admin. site conditions	148 (57.6%)	144 (55.6%)	
Respiratory, thoracic & mediastinal disorders	143 (55.6%)	147 (56.8%)	
Metabolism and nutrition disorders	108 (42.0%)	121 (46.7%)	
Nervous system disorders	95 (37.0%)	89 (34.4%)	
Skin and subcutaneous tissue disorders	**86 (33.5%)**	**110 (42.5%)**	**0.037**
Investigations (abnormal laboratory tests)	85 (33.1%)	96 (37.1%)	
Blood and lymphatic system disorders	77 (30.0%)	82 (31.7%)	
Psychiatric disorders	70 (27.2%)	86 (33.2%)	
Eye disorders	**39 (15.2%)**	**69 (26.6%)**	**0.002**
Hepatobiliary disorders	**23 (8.9%)**	**42 (16.2%)**	**0.016**

Maertens J et al. Lancet 2015.

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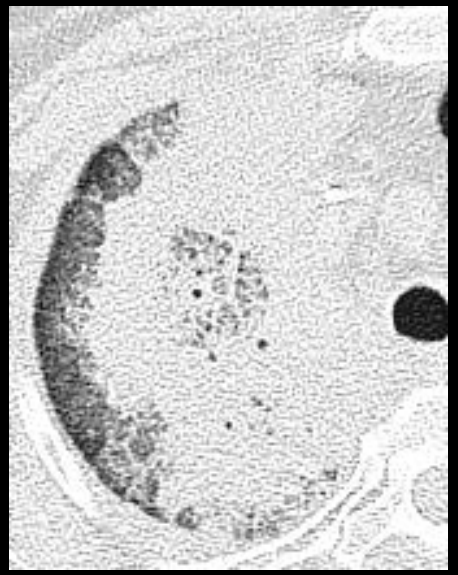
Mucormycosis – Inverse Halo Sign

d1

d8



d15

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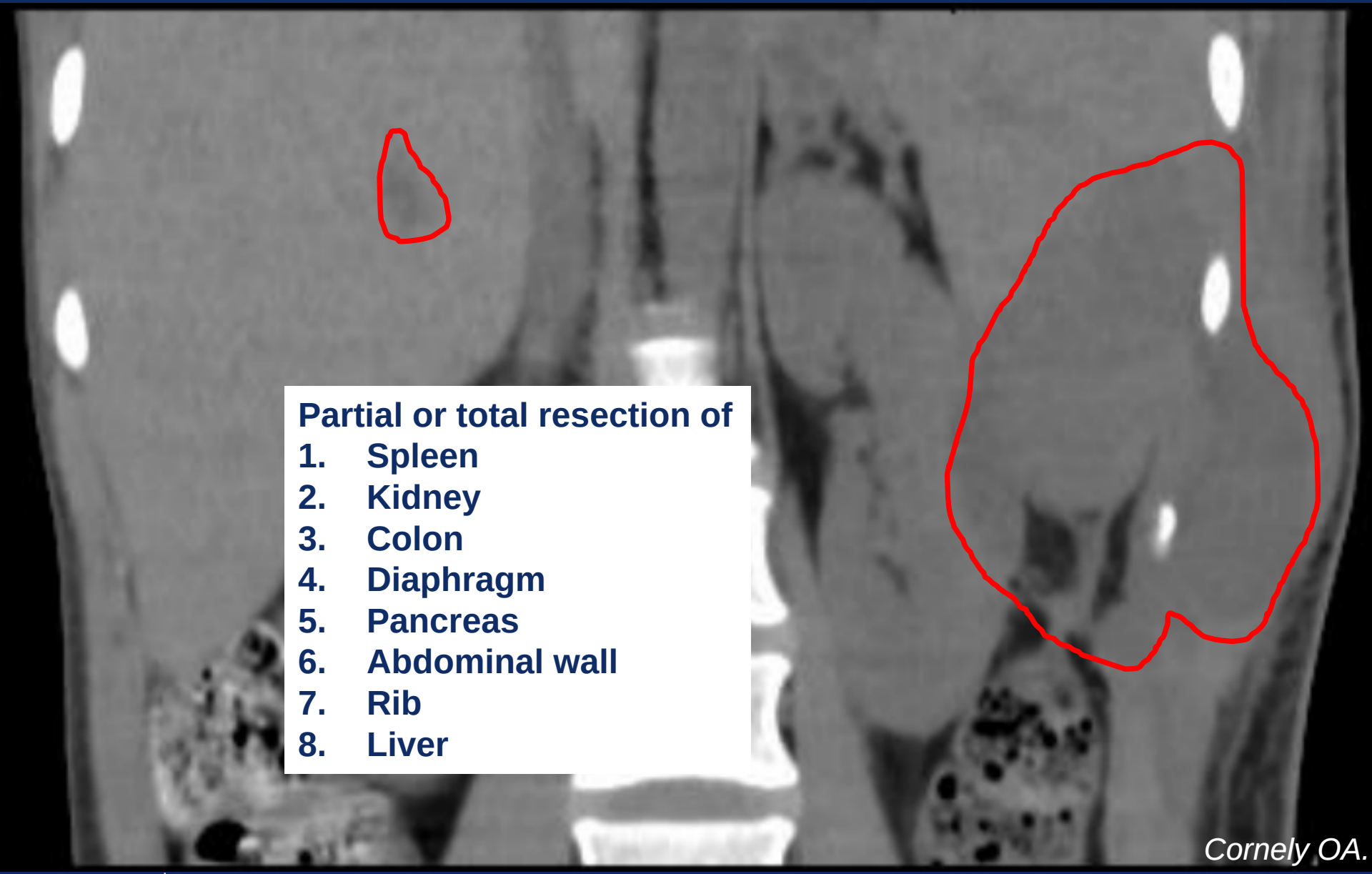
Mucormycosis – 21 y/o ALL Patient



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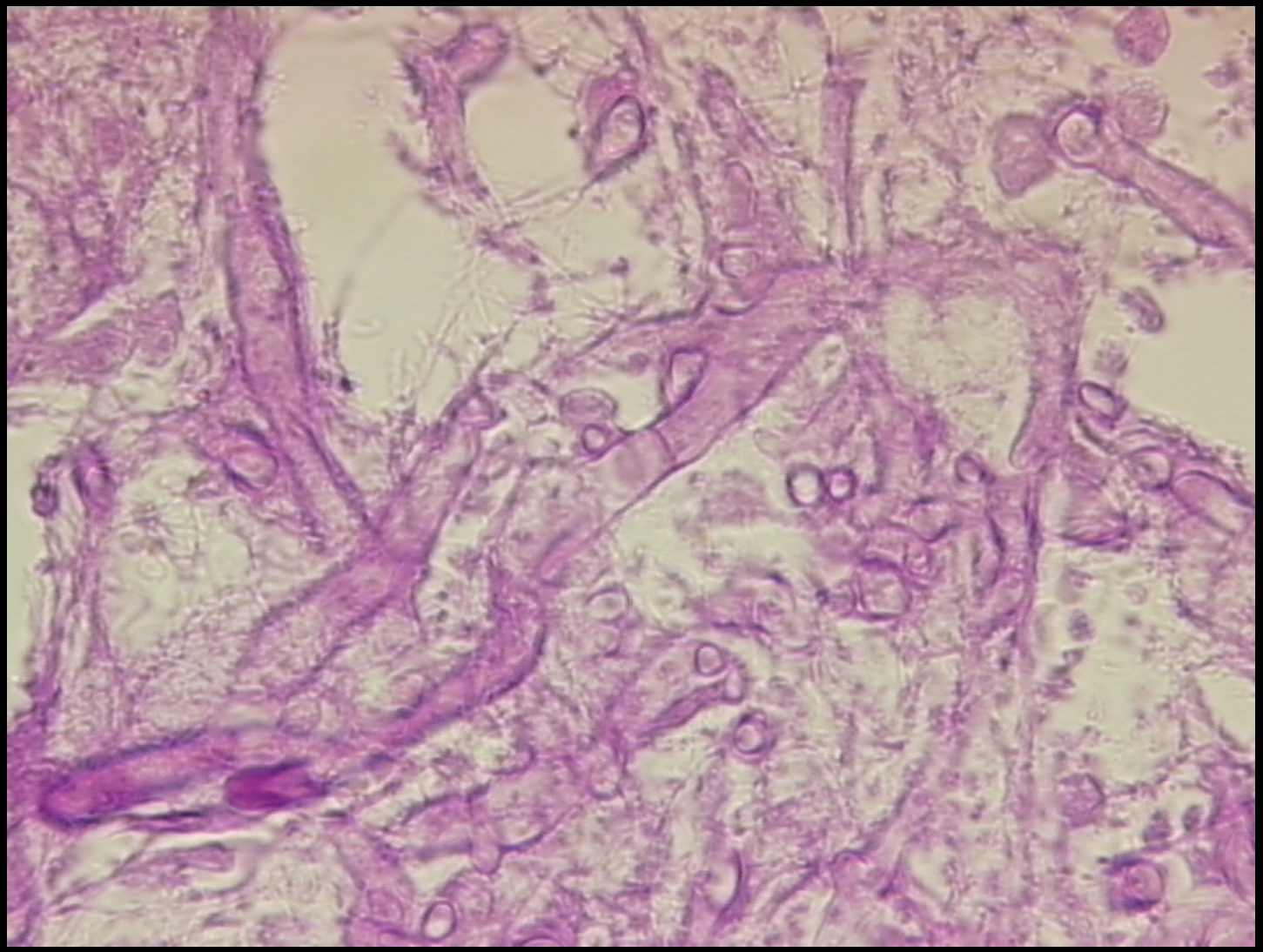
Histology of the Spleen, PAS x100

2016



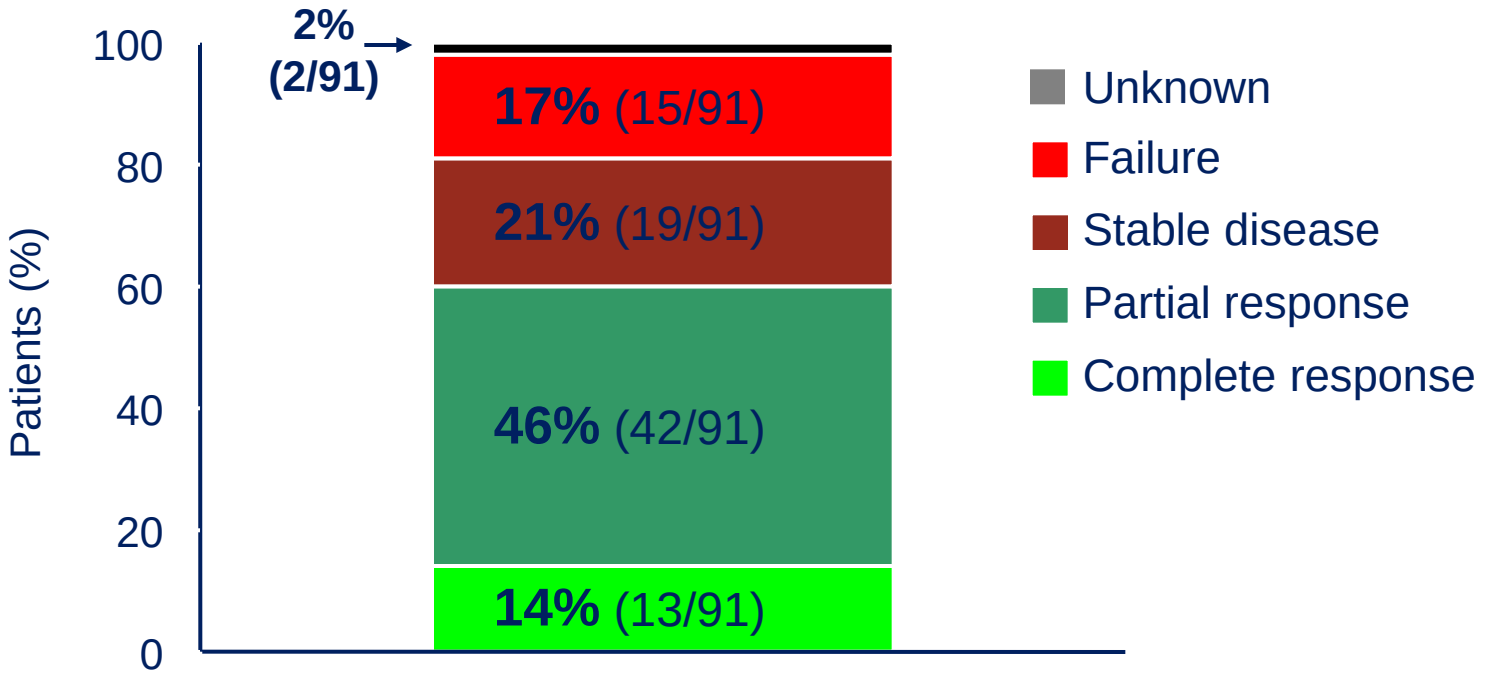
Cornely OA.

Histology Proves Invasive Fungal Disease

1885

Paltauf A. Archiv für pathologische Anatomie 1885; 102 (25): 543-564.

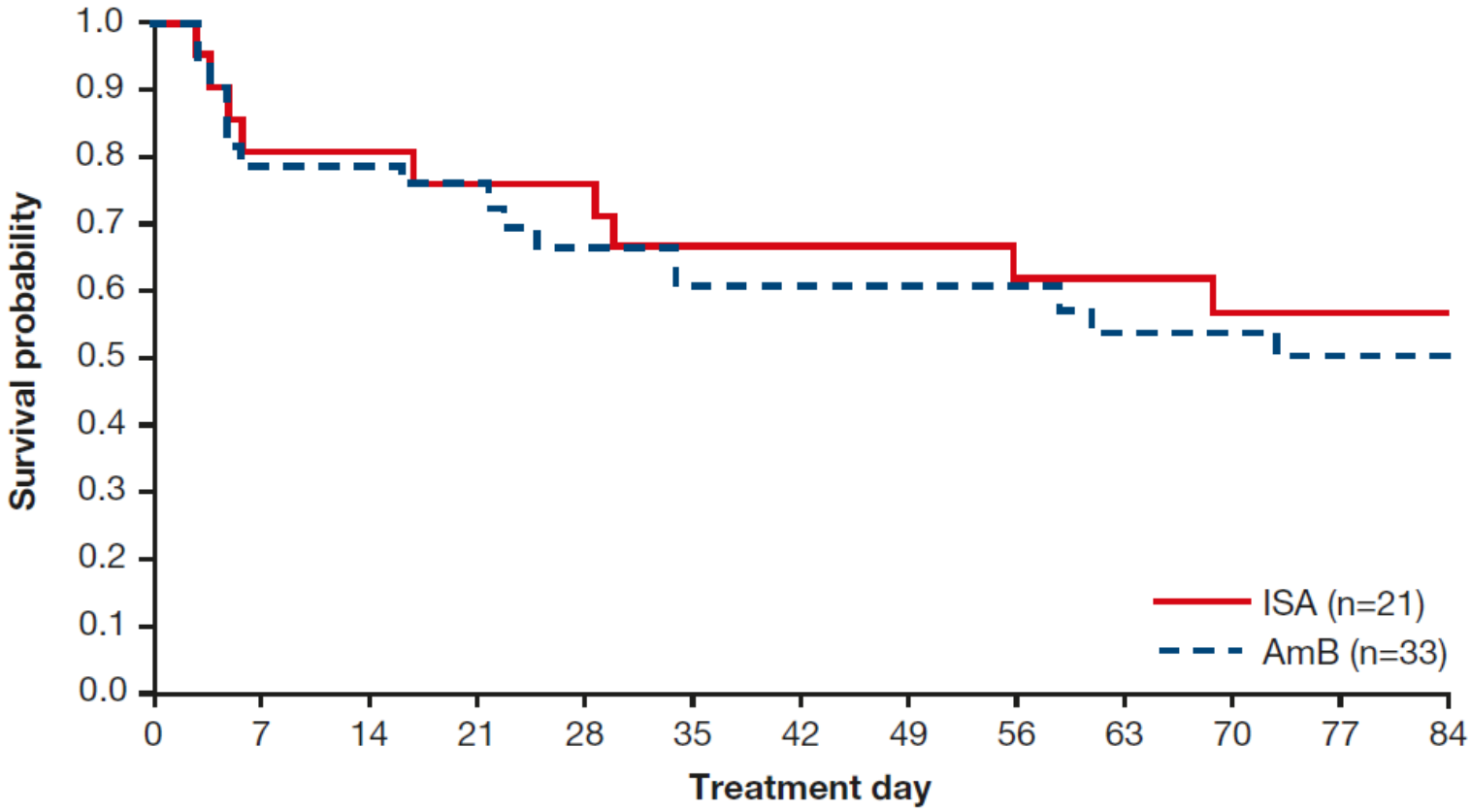
Posaconazole Oral Suspension
Outcome of Mucormycosis



- 38% (35/91) of patients died while on POS or within 30d F/U
- 43% (15/35) of deaths were attributed to mucormycosis

van Burik A et al. CID 2006; 42: e61-65.

Isavuconazole versus Amphotericin B Regimens Matched Control Comparison



No. of Subjects at Risk

ISA	21	17	17	16	16	14	14	14	14	13	12	12	12
AmB	33	26	26	25	22	20	20	20	18	16	16	14	14

Marty F, …,Vehreschild MJGT. VITAL-FungiScope. Lancet ID 2016.

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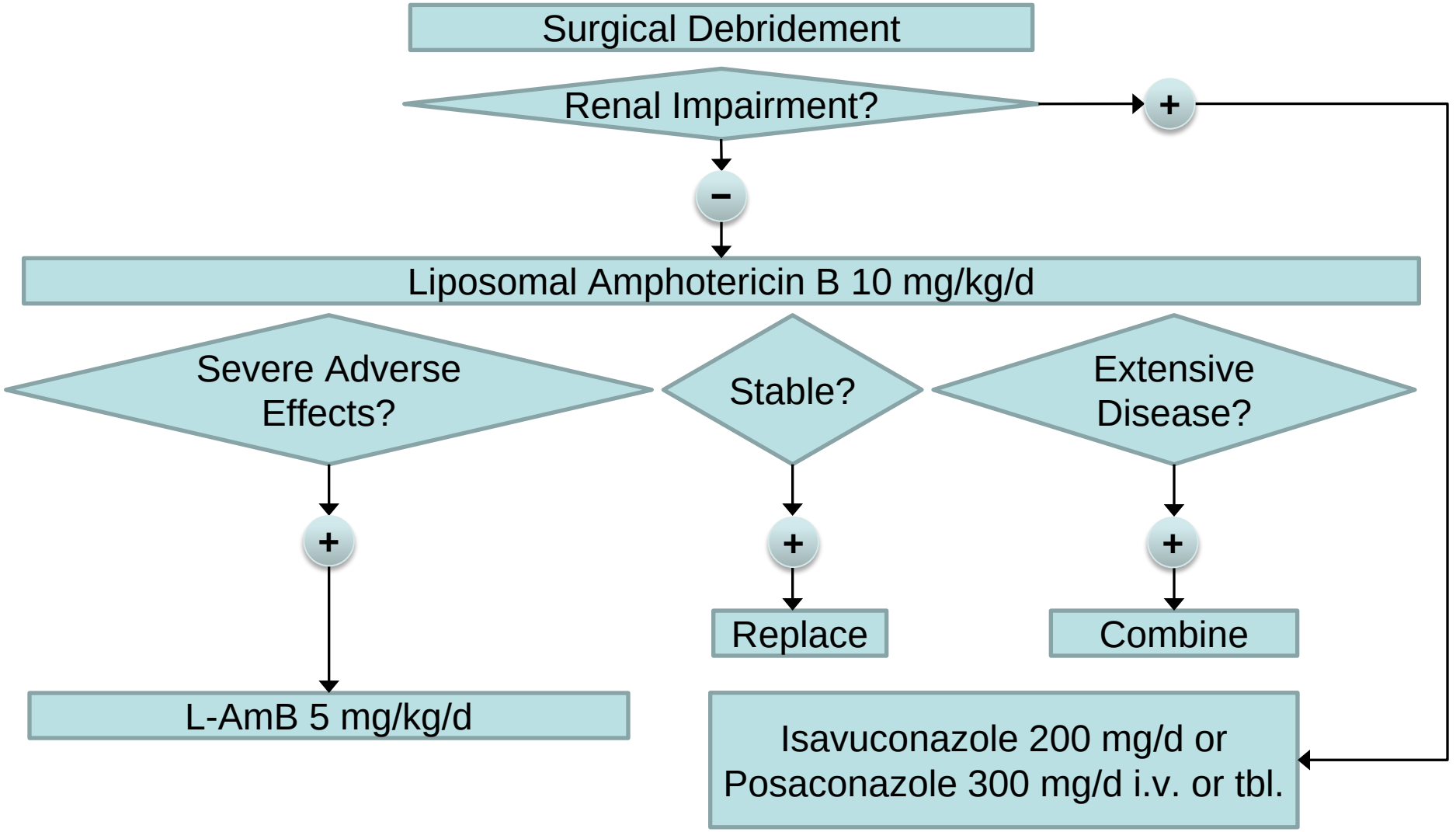
Mucormycosis – Treatment-Algorithm 2016



Where do we stand? Where do we go?

Today

Candidiasis

- Echinocandins 1st line

Aspergillosis

- Posaconazole Prophylaxis in H/O
- Voriconazole 1st line

Mucormycosis

- Liposomal Ampho 1st line
- Posaconazole 2nd line
- Isavuconazole 2nd line

Tomorrow?

Candidiasis

- Oral glucan synthesis inhibitors

Aspergillosis

- Isavuconazole 1st line
- Posaconazole 1st line

Mucormycosis

- Isavuconazole 1st line

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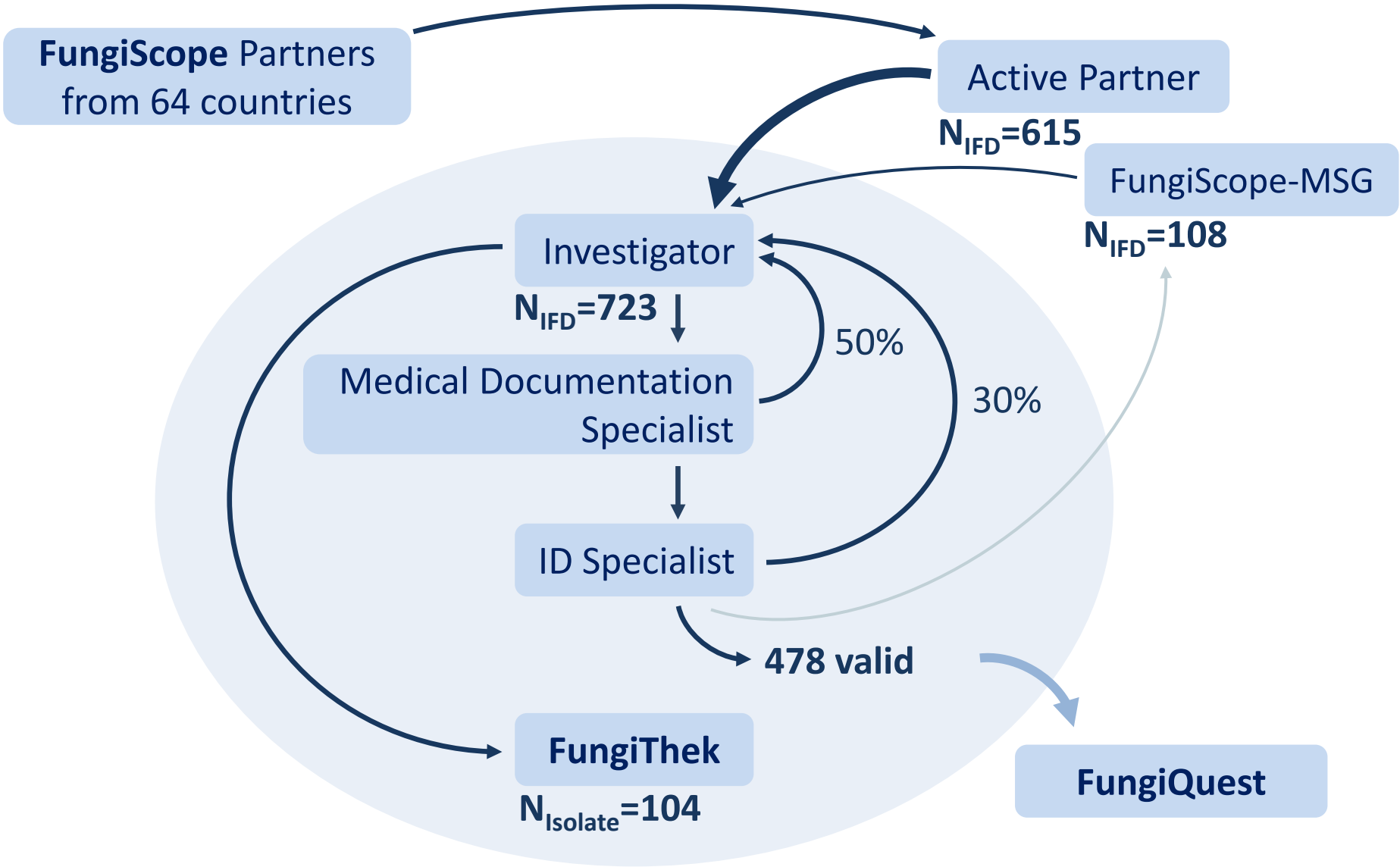
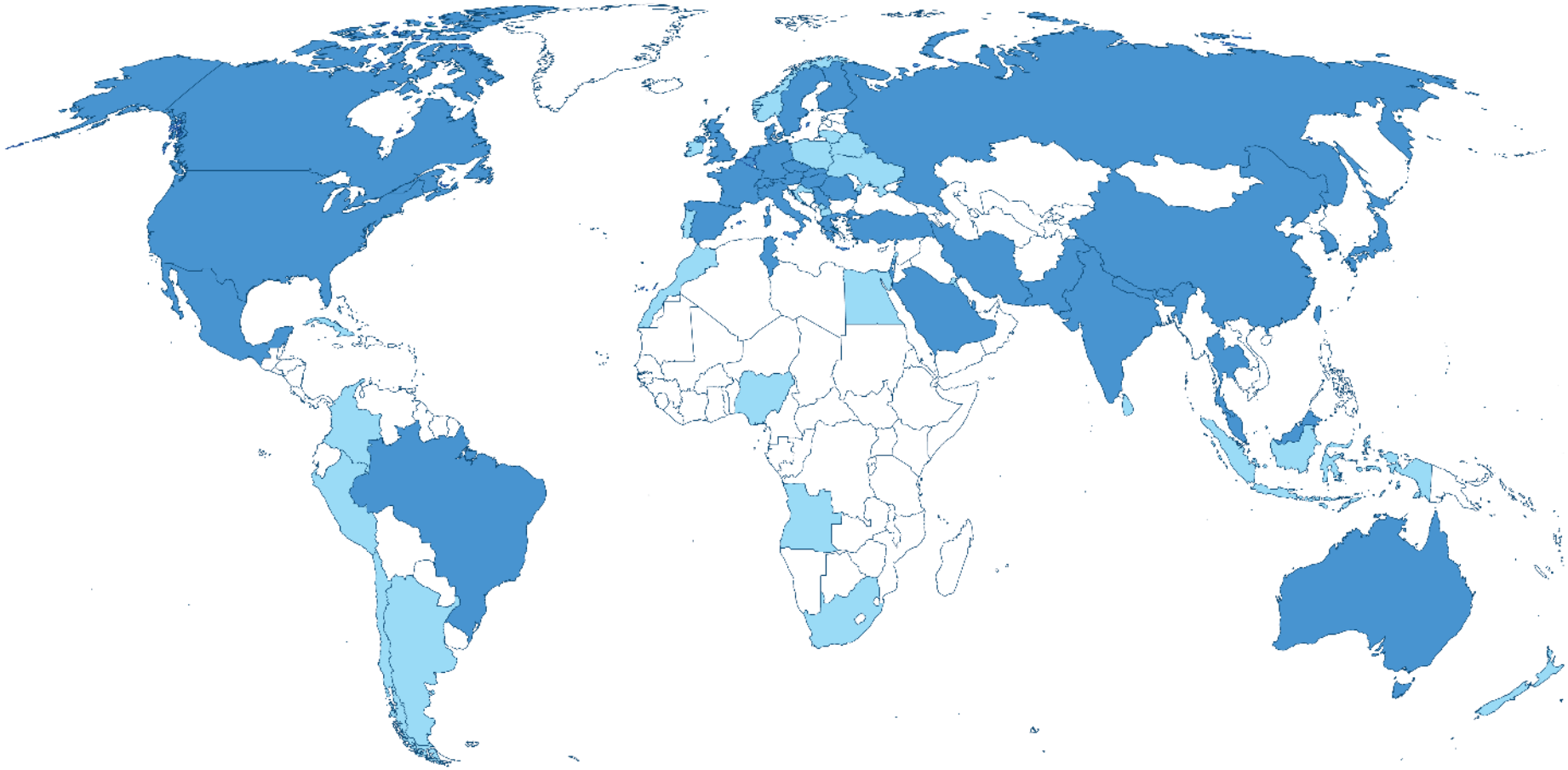
FungiScope – Quality Control



FungiScope – 478 Validated Rare IFI Cases



Collaborators in 64 Countries

www.fungiscope.net

www.fungiquest.net