Controversies in Antifungal Management in SOT

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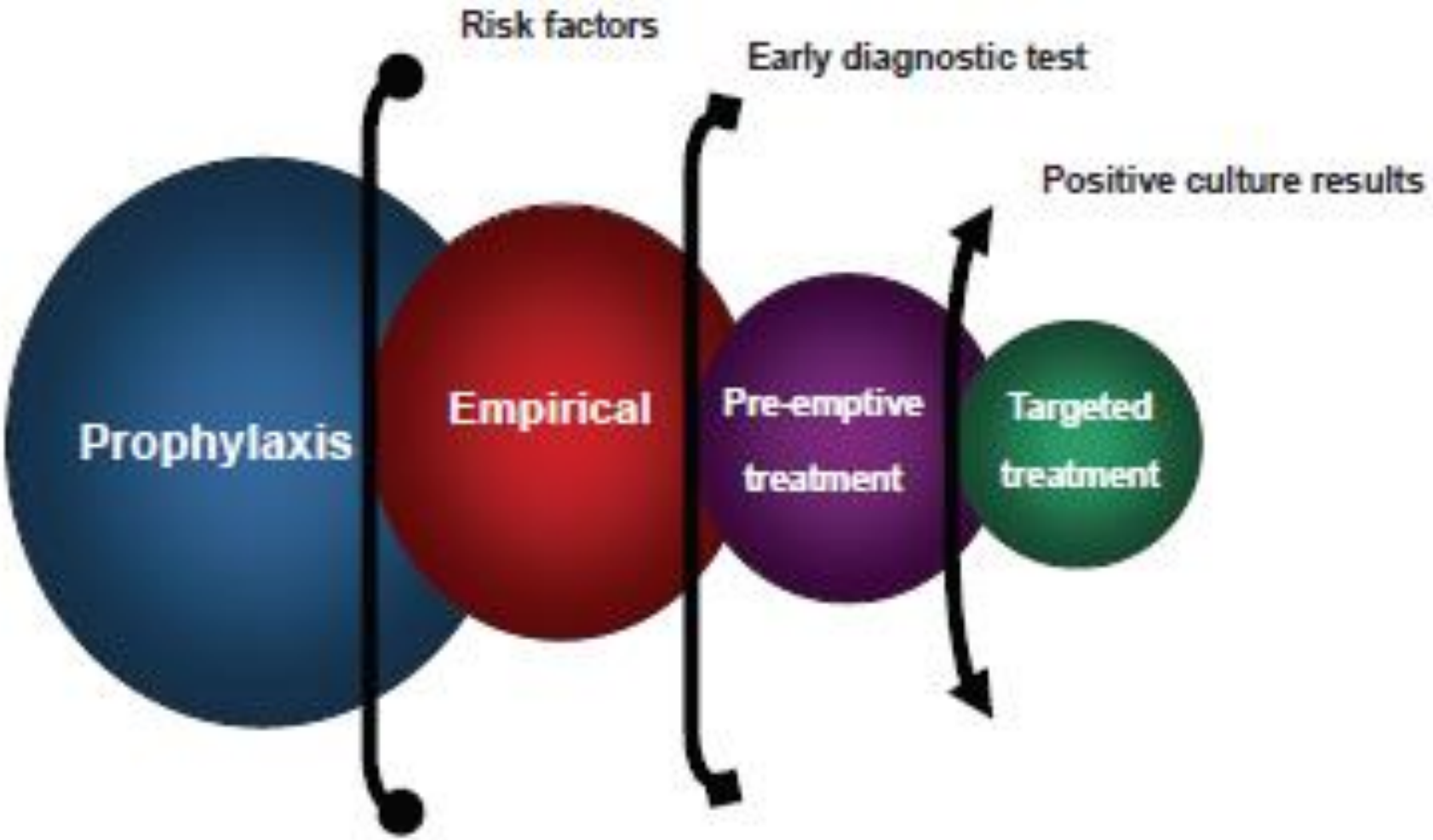
Why Controversies

1. Absence of evidence
   – Absence of evidence ≠ Evidence of absence
2. Quality of evidence
3. Efficacy vs. Effectiveness



<u>Preventive administration</u> of a drug without attributable signs or symptoms

Starting antifungal in **<u>high-risk pts with clinical signs & symptoms</u>**, but without micro documentation

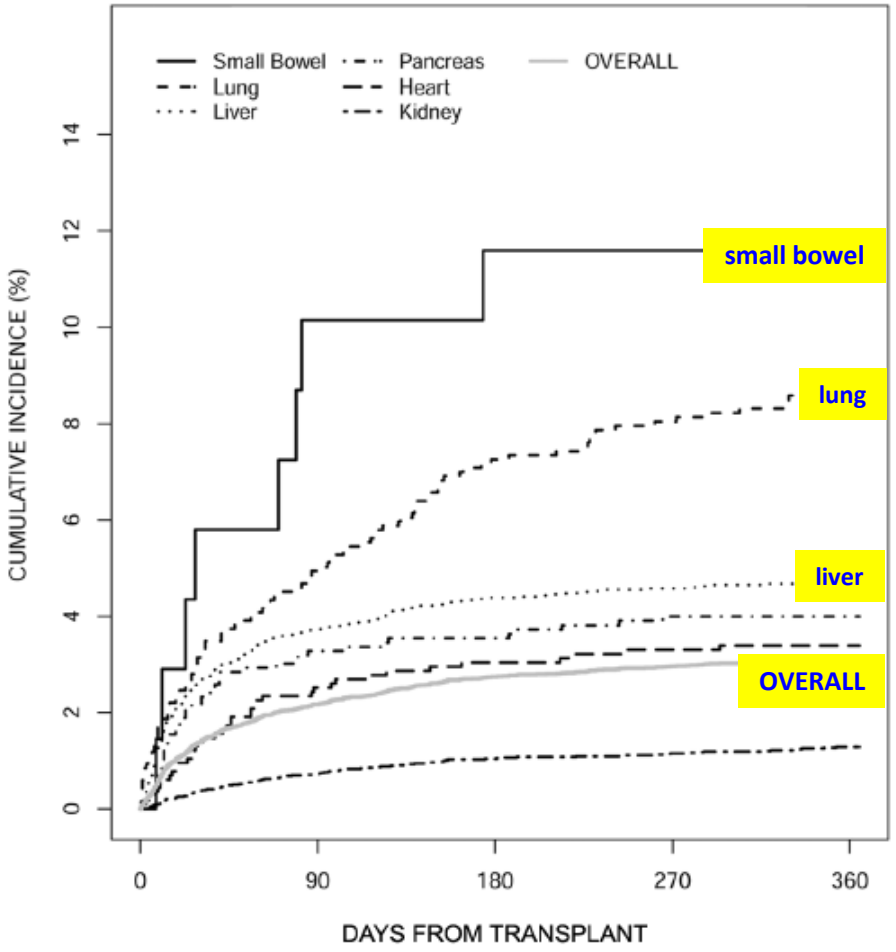
Decision to treat is **<u>based on an early diagnostic test</u>**

Treatment after **<u>diagnosis is confirmed</u>**

Outline

1. Prophylaxis: universal, targeted, or none?
2. Empiric treatment: when, how?
3. Targeted treatment: What are the options?

IFI Following SOT: Cumulative Incidence



Pappas PG, et al. *Clin Infect Dis*. 2010; 50:1101–1111.

Table 1
Epidemiology of invasive fungal infection in solid organ transplant recipients

Organ Transplanted	IFIs in Order of Decreasing Frequency
Kidney	*Candida* > *Crypto* > *Aspergillus* > Endemic mycoses > Molds > PJP
Liver	*Candida* > *Aspergillus* > *Crypto* > Endemic mycoses > Molds > PJP
Pancreas	*Candida* > Endemic mycoses > *Aspergillus* ≈ *Crypto* > Molds > PJP
Lung	*Aspergillus* > *Candida* > Molds > *Crypto* > PJP > Endemic mycoses
Heart	*Candida* > *Aspergillus* > Molds > *Crypto* > Endemic mycoses > PJP
Small bowel	*Candida* > *Crypto* > *Aspergillus* > Endemic mycoses > Molds > PJP

Data from: Pappas PG, et al. *Clin Infect Dis*. 2010; 50:1101–1111.

PROPHYLAXIS

Antifungal Prophylaxis: Problems

- Cost
- Overtreatment
- Toxicity
- Drug interactions
- Antifungal resistance
- Interferes with biomarkers
- Breakthrough IFD
- Survival benefit?

Goodman. NEJM, 1992
Cornelly NEJM, 2007

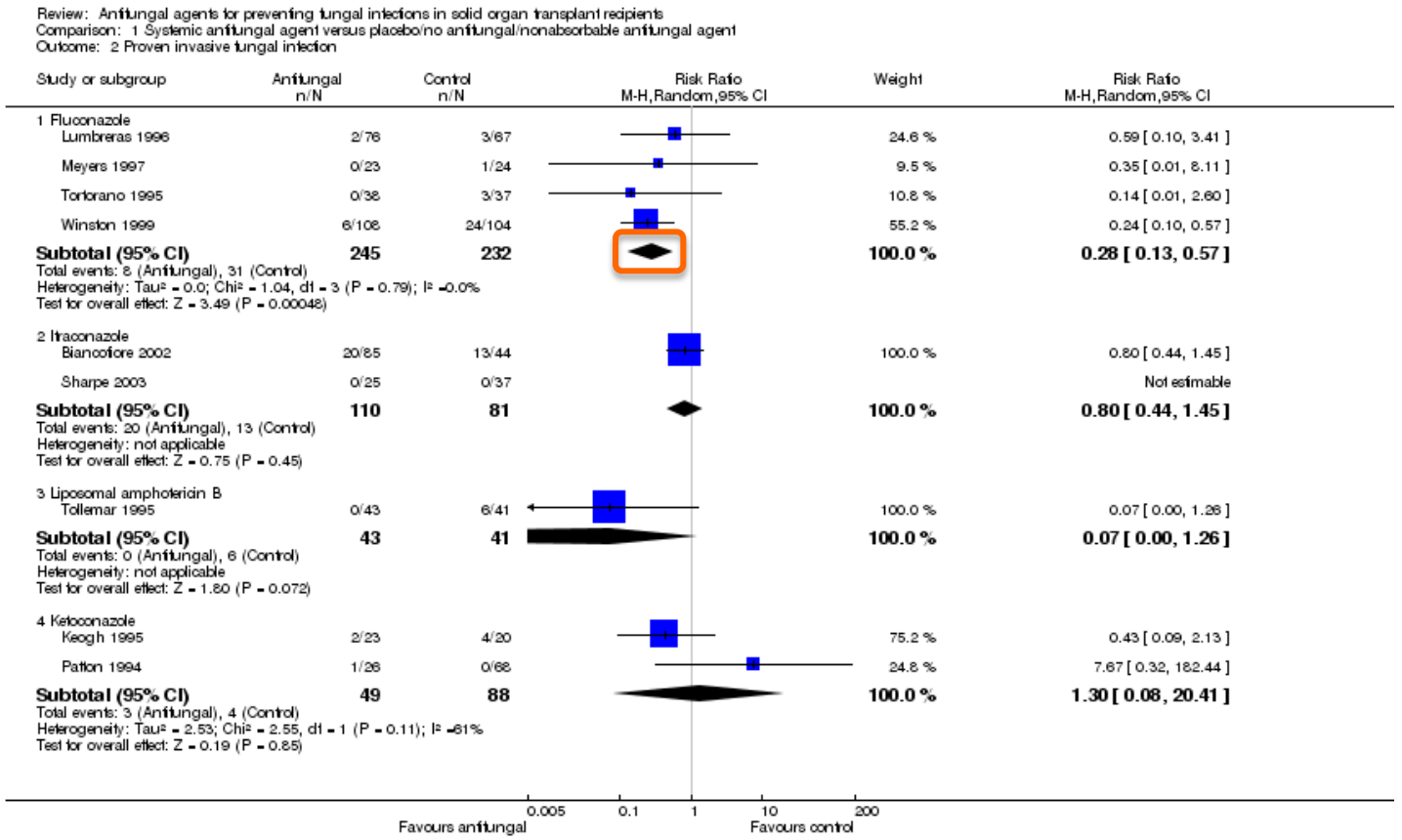
Prophylaxis: Cochrane Review

- Fluconazole **significantly reduced risk of proven IFIs** in liver tx recipients compared with placebo or non-absorbable antifungals (RR 0.28, 95% CI 0.13 to 0.57)
  - NNT to prevent 1 IFI
    - 14 (intermediate risk)
    - 6 (high risk)
- **No mortality benefit** (RR 0.84, 95% CI 0.54 to 1.30

Cochrane Database of Systematic Reviews
19 JUL 2004 DOI: 10.1002/14651858.CD004291.pub2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004291.pub2/full#CD004291-fig-00102

Antifungals for preventing IFI in SOT recipients

PROVEN IFI



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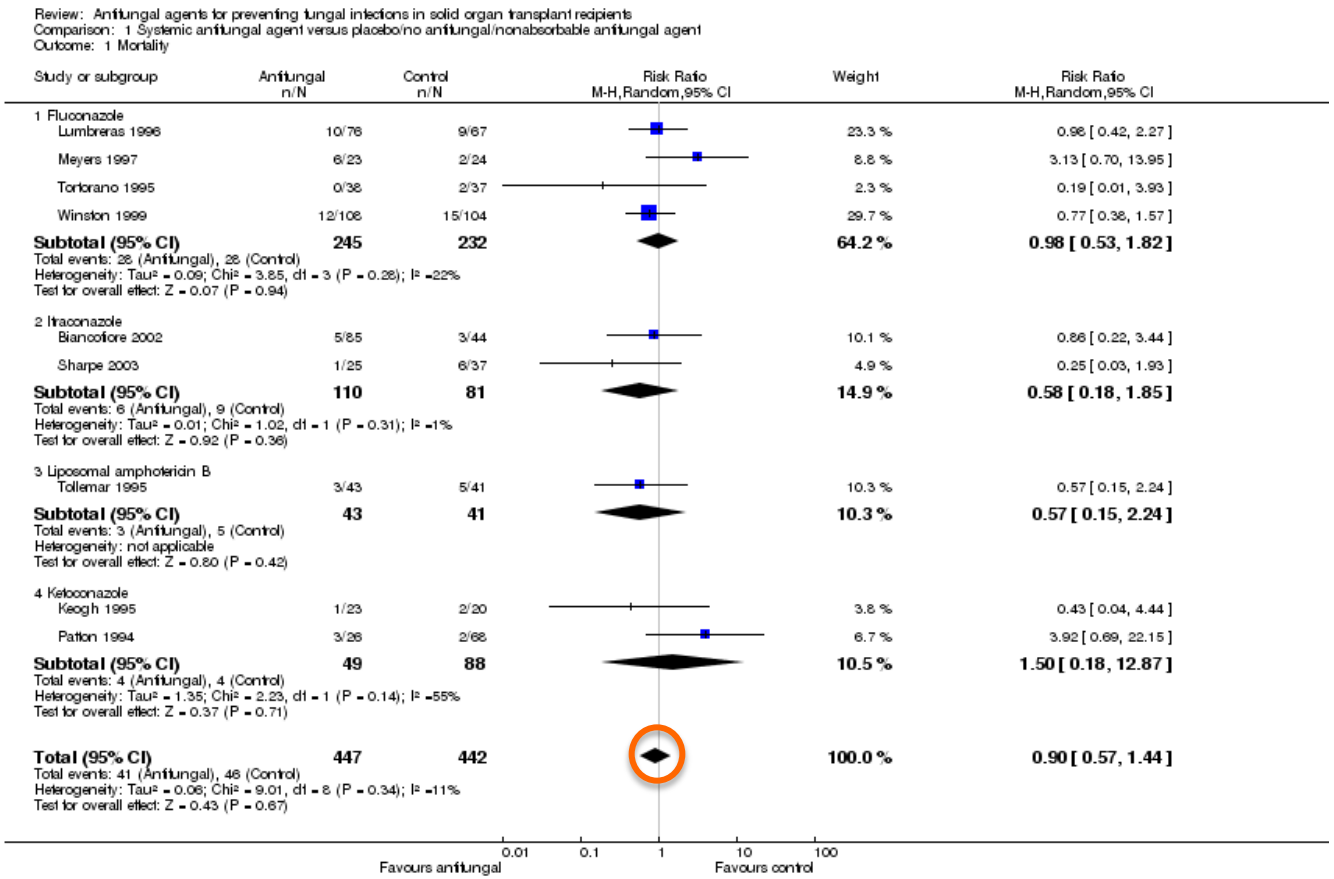
Antifungals for preventing IFI in SOT recipients

MORTALITY



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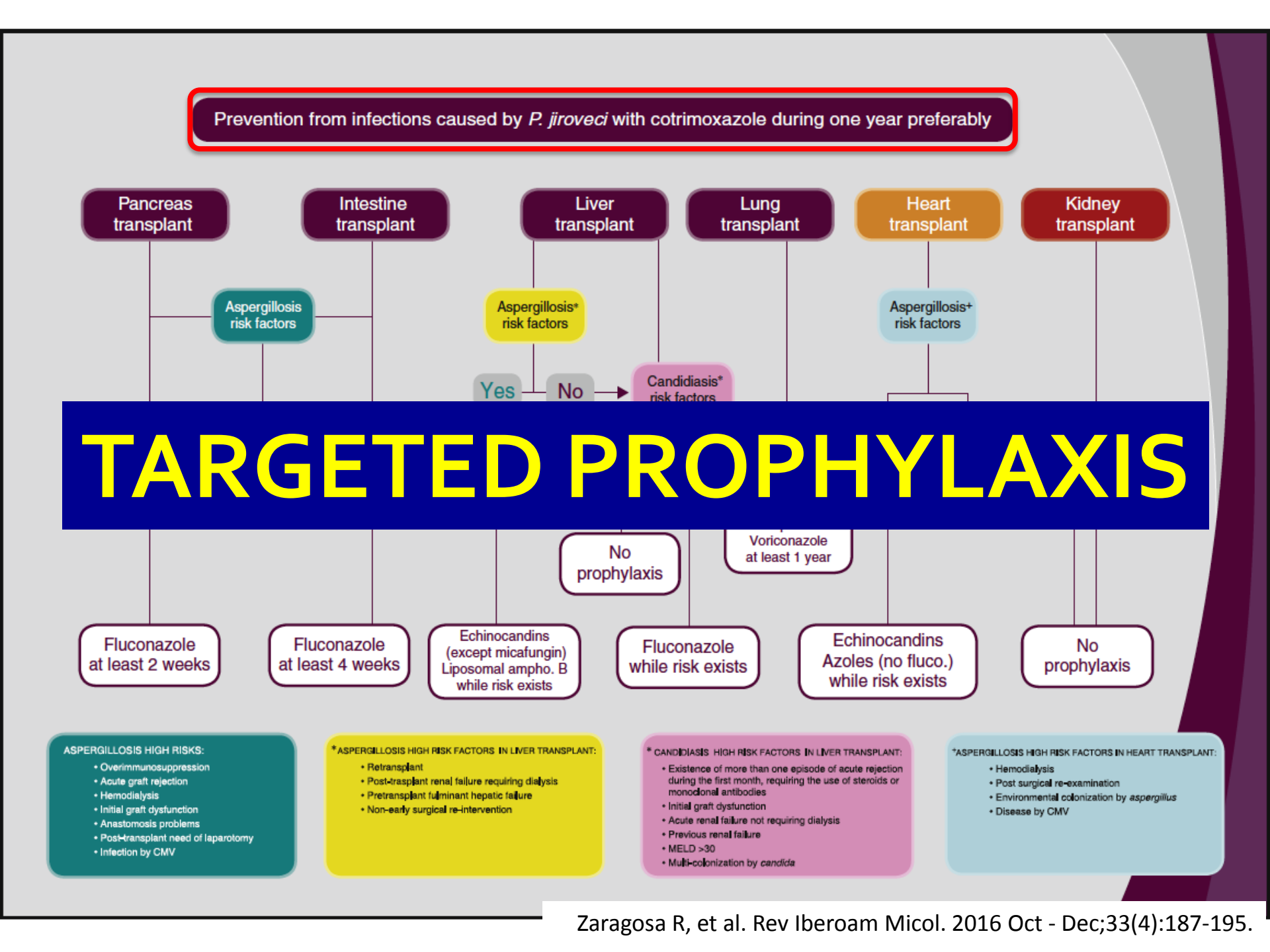


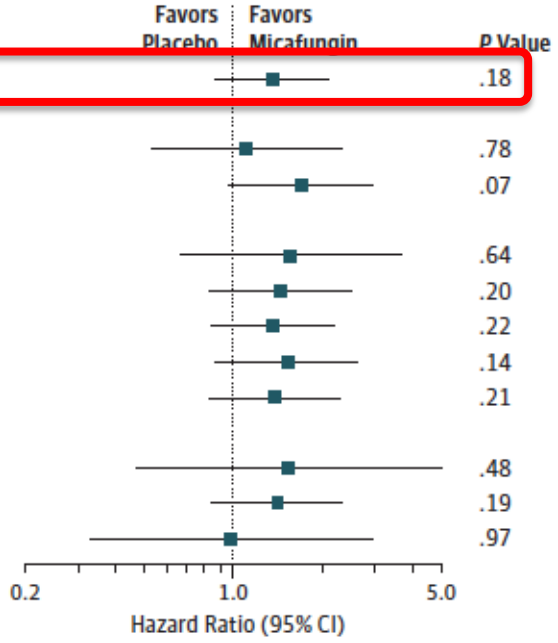
Zaragosa R, et al. Rev Iberoam Micol. 2016 Oct - Dec;33(4):187-195.

EMPIRICAL TREATMENT

Empirical Micafungin Treatment

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



Timsit JF, et al. JAMA. 2016 Oct 18;316(15):1555-1564.

TARGETED TREATMENT

Targeted Treatment Options

- Candidiasis:
  - Echinocandin
  - Fluconazole
- Aspergillosis:
  - Voriconazole
  - Amphotericin B

Isavuconazole

- Extended-spectrum triazole
  - Active against yeasts, moulds & dimorphic fungi
- Water soluble i.v. formulation
- Excellent oral bioavailability
  - No food interactions
- Predictable pharmacokinetics

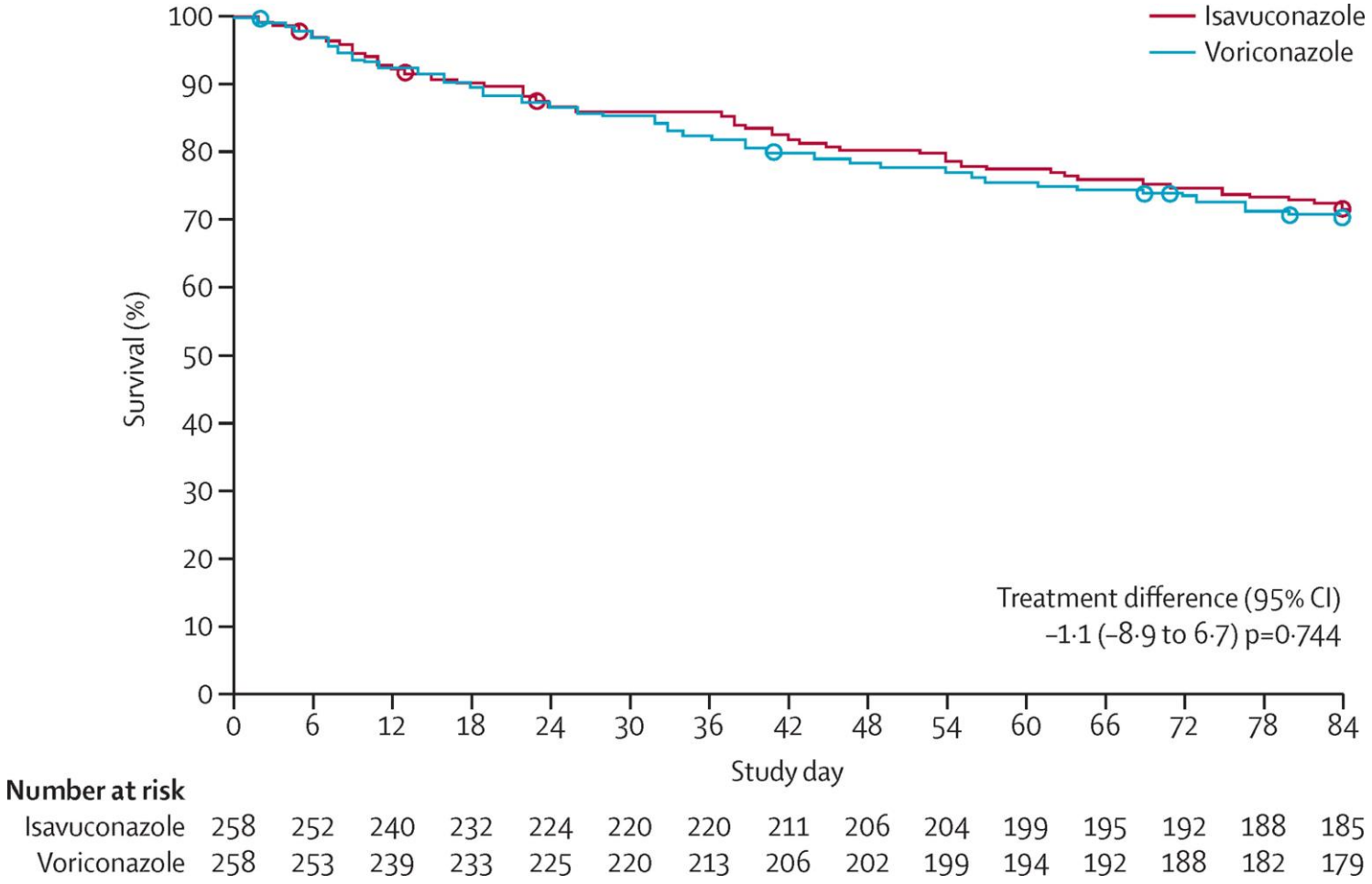
Miceli MH, et al. *Clin Infect Dis*. 2015;61(10):1558–65.

SECURE Trial: Efficacy Outcomes

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
All-cause mortality			
ITT population	258	258	
Day 42 all-cause mortality	48 (19%)	52 (20%)	−1·0% (−7·8 to 5·7)
Deaths	45 (17%)	50 (19%)	..
Unknown survival status†	3 (1%)	2 (1%)	..
Day 84 all-cause mortality	75 (29%)	80 (31%)	−1·4% (−9·2 to 6·3)
Deaths	72 (28%)	75 (29%)	..
Unknown survival status†	3 (1%)	5 (2%)	..
mITT population	143	129	
Day 42 all-cause mortality	28 (20%)	30 (23%)	−2·6% (−12·2 to 6·9)
Day 84 all-cause mortality	43 (30%)	48 (37%)	−5·5% (−16·1 to 5·1)
myITT population	123	108	
Day 42 all-cause mortality	23 (19%)	24 (22%)	−2·7% (−12·9 to 7·5)
Day 84 all-cause mortality	35 (28%)	39 (36%)	−5·7% (−17·1 to 5·6)

Maertens JA, et al. *Lancet* 2016; 387: 760–69.

SECURE Trial: Survival



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SECURE: Secondary Outcome

DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Maertens JA, et al. *Lancet* 2016; 387: 760–69.

Conclusions

- Prophylaxis
  - Risk stratification, followed by targeted prophylaxis
  - Centre-specific
- Empiric treatment
  - No robust evidence to support routine use
- Targeted therapy
  - Isavuconazole ?drug of the future

Thank You!