9° DITMO, Genova 22-23 Giugno 2017

Antifungals and Renal Injury

Russell Lewis
Infectious Diseases Unit, S. Orsola-Malpighi
Associate Professor
Department of Medical Sciences and Surgery
University of Bologna
russeledward.lewis@unibo.it

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Outline

- How large of problem is antifungal-associated renal injury?
- How can the risk of renal injury be reduced?
- Do we need to re-assess the renal-injury risk of liposomal amphotericin B?

Epidemiology of acute kidney injury reported in prospective cohort studies:

- Adult populations: 14-26%
- Pediatrics: 16%
- Higher risk subgroups:
  - Cancer patients with critical illness: 54%
  - Solid organ transplant (non-renal): 16.9%-56%

Most common causes:
Volume depletion, hypotension/vasodilation (sepsis), and nephrotoxic medications

Rosner, M. H. & Perazella, M. A. *Engl. J. Med.* **376,** 1770–1781 (2017).
Awdishu, L. & Mehta, R. L. *BMC Nephrol.* **18,** 124 (2017).
Rossi, A. P. & Vella, J. P.. *Transplantation* **100,** 506–514 (2016).
Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Acute kidney injury criteria

RIFLE (changes within 7 days)

	Creatine criteria	Urine output (UO) criteria
Risk	Cr↑ 1.5x baseline or GFR ↓ >25%	UO < 0.5 mL/kg/h x6h
Injury	Cr↑ 2x baseline or GFR ↓ >50%	UO < 0.5 mL/kg/h x12h
Failure	Cr↑ 3x baseline or GFR ↓ >75%	UO < 0.3 mL/kg/h x24h or anuria x 12h
Loss	Complete loss for > 4 weeks	
End stage	Complete loss for > 3 months	

Progression through the increasingly severe stages of RIFLE is marked by decreasing sensitivity and increasing specificity. Correlates with mortality in critically-ill patients

Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Acute kidney injury criteria

AKIN (changes within 48 hours)

	Creatinine criteria	Urine output criteria
Stage 1	Cr↑ ≥ 0.3 mg/dL or 150-200% of baseline	UO < 0.5 mL/kg/h x6h
Stage 2	Cr↑ 200-300% (2-3 fold) of baseline	UO < 0.5 mL/kg/h x12h
Stage 3	Cr↑ > 300% (> 3 fold) of baseline, or SeCr equal to 4 mg/L with acute increase of at least 0.5 mg/dL	UO < 0.3 mL/kg/h x24h or anuria x 12h

GFR was discarded (used as an alternative to Cr in the original RIFLE criteria). AKIN modification does not perform better than RIFLE.

Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Acute kidney injury criteria

KDIGO (changes within 48 hours)

Injury	**SeCr↑ ≥ 0.3 mg/dL within 48 hours;** **SeCr↑ 1.5x baseline within 7 days** **UO < 0.5 mL/kg/h x6h**
Stage 1	**Cr↑ 1.5-1.9x baseline or ↑ ≥ 0.3 mg/dL**
Stage 2	**Cr↑ 2-2.9x baseline**
Stage 3	**Cr↑ 3x baseline or SeCr ≥ 4 mg/dL *or*** ***Initiation of renal replacement therapy***

Kidney Disease Improving Global Outcomes

Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Limitations of injury criteria

- **Rely on function markers**
  - **SeCr, (estimated GFR), urine output**
- **Relationship between SeCr and GFR is non-linear, SeCr rises relatively late**
  - **Affected by fluid overload, sepsis, decreased creatinine generation, variable renal function**

Chu, R. *et al. Clin. J. Am. Soc. Nephrol.* **9,** 1175–1182 (2014).
Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Limitations

- **Many patients with histological evidence of kidney injury do not fulfill AKI clinical criteria**

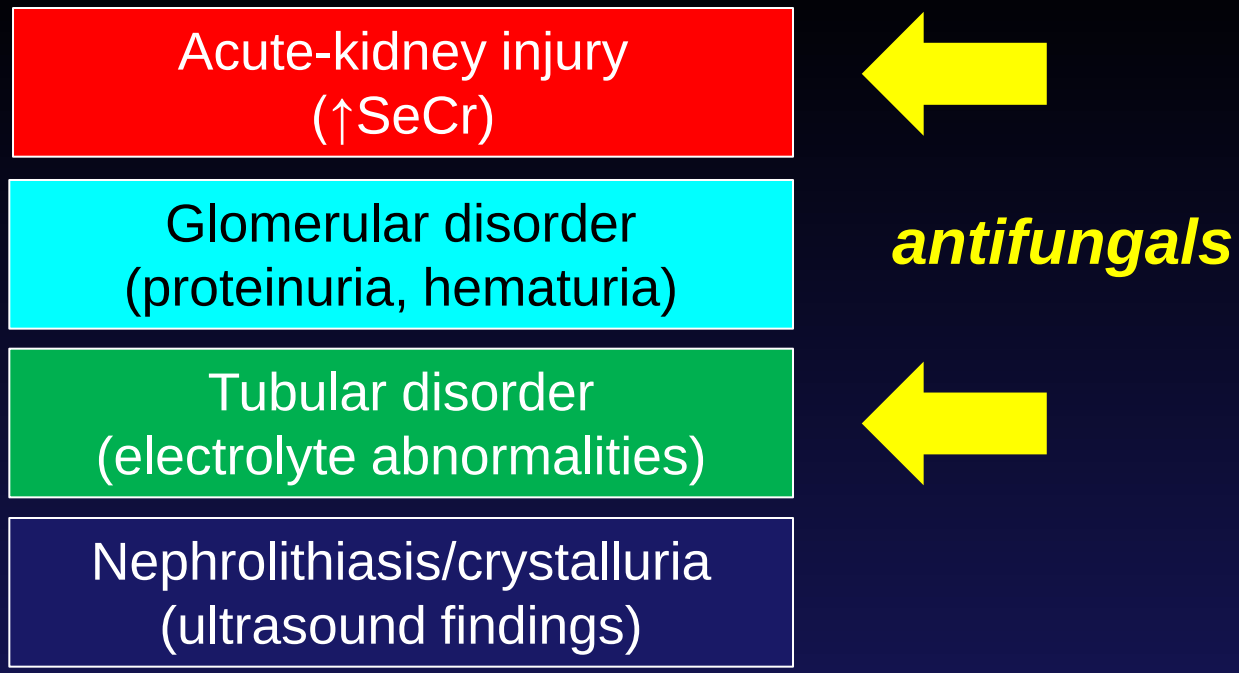
- **Alternative tests:**
  - **6h assessments of urinary output ± furosemide challenge (1-1.5 mg/kg IV bolus → 100 mL urine within 2 hours)**
  - **Troponin-like biomarkers? (cystatin-C, KIM-1, NGAL, N-acetyl β glucosamindase…etc.)**

Chu, R. *et al. Clin. J. Am. Soc. Nephrol.* **9,** 1175–1182 (2014).
Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Phenotype standardization of drug-induced kidney injury

Type A: Dose-dependent
(pharmacology of drug)

Type B: Iatrogenic
(e.g,. interstitial nephritis)



However, patient rarely receiving only one nephrotoxic medication

Mehta, R. L. *et al.* Phenotype standardization for drug-induced kidney disease. *Kidney Int.* **88,** 226–234 (2015).

Frequency of antifungal-induced kidney injury

Frequency of nephrotoxicity reported as doubling of baseline SeCr in clinical studies

Antifungal	Percent
AMB-d	33.2 %
ABLC	16.5 %
L-AMB	14.6%
Fluconazole	0.2%
Itraconazole	5.2 %
Voriconazole	0.3%
Posaconazole	0.2%
Isavuconazole	0.7%
Anidulafungin	0.2%
Micafungin	1.1%
Caspofungin	3%

However….

Hypokalemia: 15-30%
Hypomagnesaemia: 10-15%

In rare cases and overdoses, refractory hypokalemia persisted until antifungal was stopped

Girois, S. B., Chapuis, F., Decullier, E. & Revol, B. G. P. *Eur. J. Clin. Microbiol. Infect. Dis.* **25,** 138–149 (2006)
Data source: EMA SPCs

Frequency of antifungal-induced kidney injury

Frequency of nephrotoxicity reported as doubling of baseline SeCr in clinical studies

Antifungal	Percent	
AMB-d	33.2 %	
ABLC	16.5 %	
L-AMB	14.6%	
Fluconazole	0.2%	
Itraconazole	5.2 %	← hydroxypropyl-β-cyclodextrin (HPβCD)
Voriconazole	0.3%	← sulfobutylether-β-cyclodextrin (SBEβCD)
Posaconazole	0.2%	← sulfobutylether-β-cyclodextrin (SBEβCD)
Isavuconazole	0.7%	
Anidulafungin	0.2%	
Micafungin	1.1%	
Caspofungin	3%	

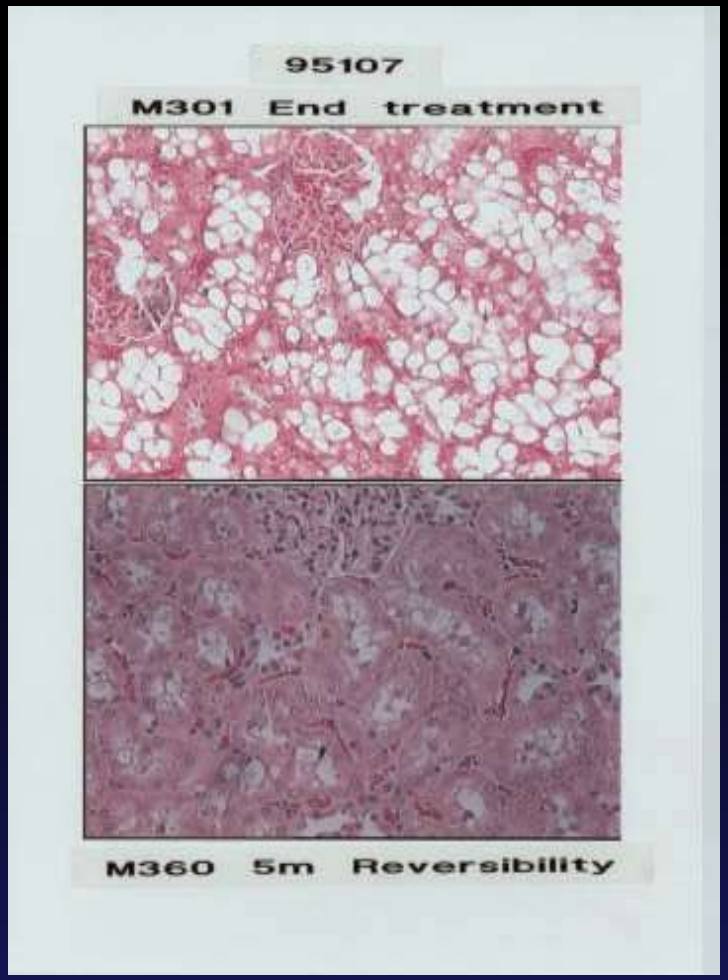
"…should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min) unless the risk justifies the use.."

Girois, S. B., Chapuis, F., Decullier, E. & Revol, B. G. P. *Eur. J. Clin. Microbiol. Infect. Dis.* **25,** 138–149 (2006)
Data source: EMA SPCs

Why the concern with cyclodextrans?

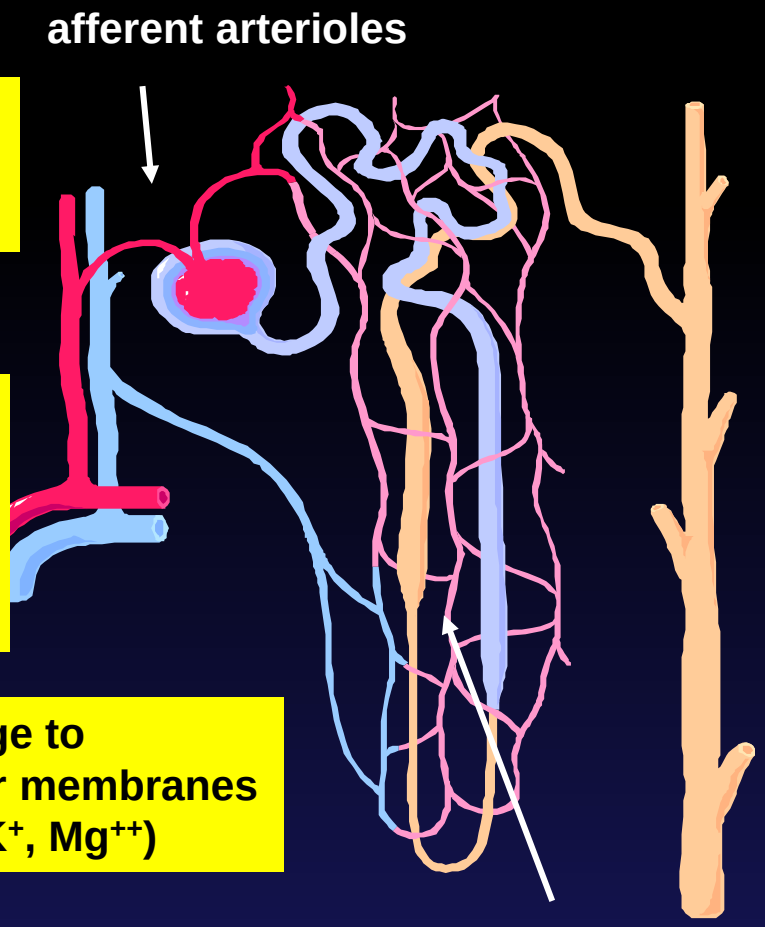
- Early unmodified cyclodextrans where re-absorbed and concentrated in kidney tubules, extracting lipid membrane components → cellular toxicity
- Current cyclodextrans (HPβCD, SBEβCD) are modified to avoid tubular reabsorption
- Prolonged SBEβCD exposure in animals (6 months) showed dose-related vacuolation of renal tubular cells, but was reversible after stopping therapy.

Not reported in humans,
No effect on renal function



Luke et al. J Pharmaceut Sciences 2010;99:3291-3301.

Mechanism of amphotericin B-induced nephrotoxicity



Intrarenal vasoconstriction (afferent arterioles)

Compensatory tubular-glomerular feedback (further constriction of afferent arterioles)

Direct damage to distal tubular membranes (wasting of K^+, Mg^{++})

Backleak of H^+ ions (distal tubular acidosis)

Ischemia and acute tubular necrosis

Clinical manifestations

- Hypokalemia
- Hypomagnesinemia
- ↑SeCr (↓GFR)
- ↑Blood urea nitrogen
- ↑Urinary FENa

A need for intravenous potassium administration of 80 to 120 mEq/day or higher is often needed .

Strategies used to reduce AMB-associated renal injury

- **Sodium loading (moderate evidence)**
  - moderate evidence from retrospective and prospective case series for amphotericin B deoxycholate
  - 1 liter /m^2 of 0.9 % NaCL with electrolyte supplementation as needed reduced nephrotoxicity of AMB-d (2x baseline sCR to 11.7%; severe hypokalemia (≤2.5 mmol/l) to 19.5%[1]
  - Does not prevent tubular toxicity (hypokalemia)
- **Continuous infusion of L-AMB? (conflicting evidence)**
  - Reduced intrarenal vascoconstriction, but tubular toxicity persists[2]
  - Clinical efficacy?
- **Liposomal formulation of AMB (strong evidence)**

[1] Girmenia, C. *et al. Support. Care Cancer* **13,** 987–992 (2005).
[2] Eriksson, U., Seifert, B. & Schaffner, A. *BMJ* **322,** 579–582 (2001).

Amp… liposom… …ey

Review: Amphotericin B deoxycholate versus liposomal amphotericin
Comparison: 1 Liposomal versus conventional amphotericin B
Outcome: 1 Increase in serum creatinine level ≥ two-fold increase fr…

Study or subgroup	Liposomal n/N	Conventional n/N
Prentice 1997	22/236	24/102
Leenders 1997	0/15	1/13
Leenders 1998	6/52	22/54
Walsh 1999	64/343	116/344
Bodhe 2002	Indian study (2002) …23	8/16
Johnson 2002a	Histoplasmosis (1995-1997)	9/24
Sundar 2004	Leishmaniasis 1/102	3/51
Hamill 2010	Cryptococcosis (1995-1998)	29/87
Sundar 2010	Leishmaniasis 2/304	1/108
Jadhav 2012	Fungisome (generic liposomal AMB in India)	
Total (95% CI)	**1353**	**819**

Total events: 139 (Liposomal), 214 (Conventional)
Heterogeneity: Tau² = 0.0; Chi² = 7.01, df = 9 (P = 0.64); I² =0.0%
Test for overall effect: Z = 7.39 (P < 0.00001)
Test for subgroup differences: Not applicable

0.0…
Favours liposomal

Review: Amphotericin B deoxychol…
Comparison: 1 Liposomal versus c…
Outcome: 1 Increase in serum crea…

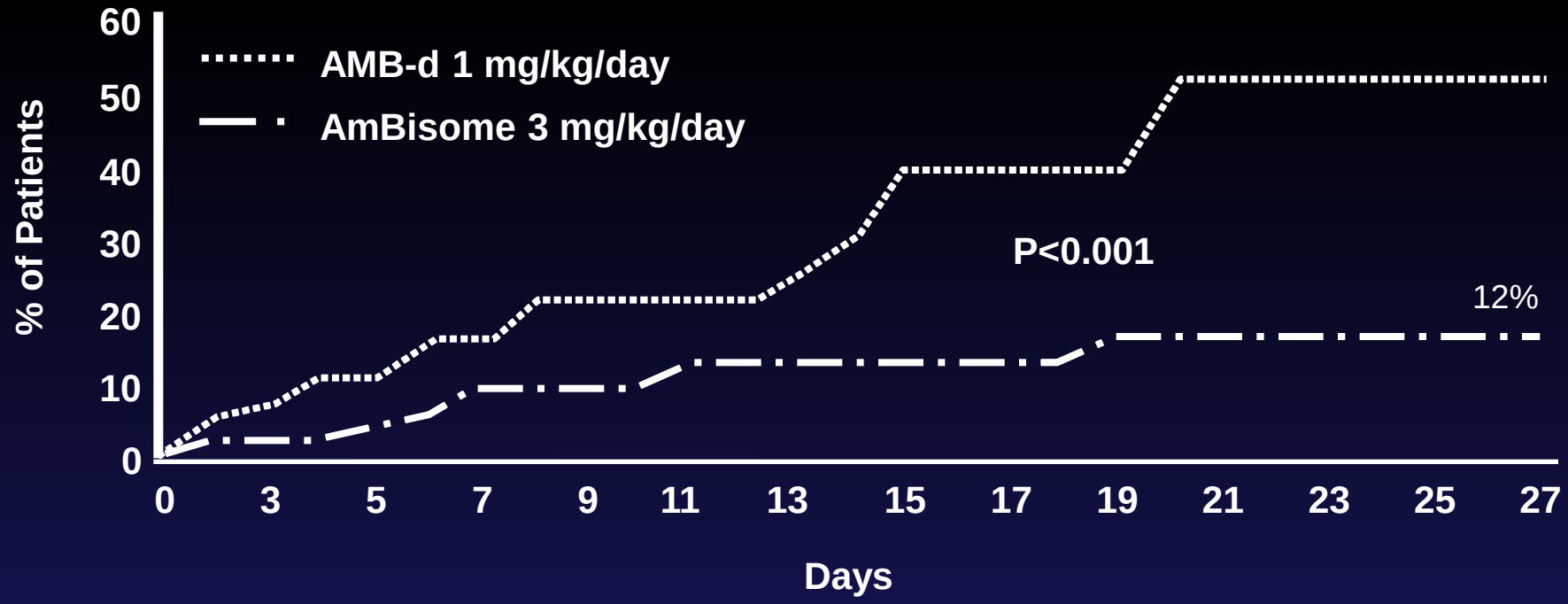
Study or subgroup Lipo…

Prentice 1997
Leenders 1997
Leenders 1998
Walsh 1999
Bodhe 2002
Johnson 2002a
Sundar 2004
Hamill 2010
Sundar 2010
Jadhav 2012

Total (95% CI)
Total events: 139 (Liposomal), 214
Heterogeneity: Tau² = 0.0; Chi² = 7
Test for overall effect: Z = 7.39 (P <
Test for subgroup differences: Not

Botero Aguirre, J. P. & Rest… …idney function. *Cochrane Databas…*

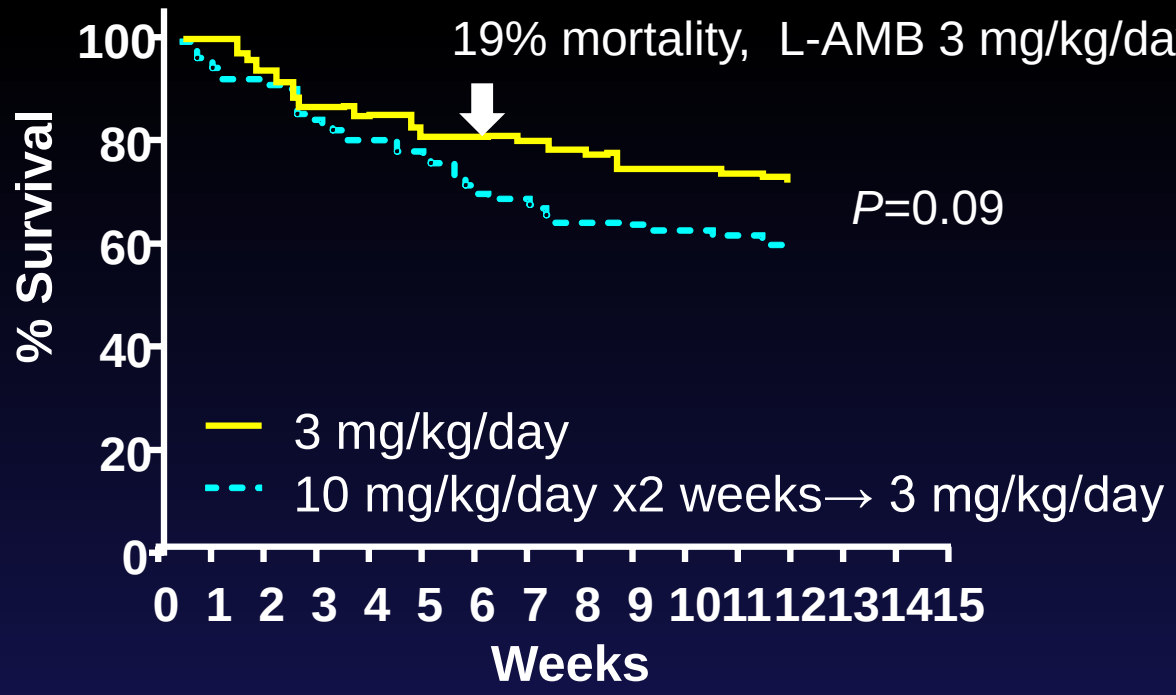
Time until nephrotoxicity: AmBisome vs AMB-d



Nephrotoxicity defined as doubling of serum creatinine

Prentice HG, et al. *Br J Haematol* 1997;98(3):711–8.

Liposomal amphotericin B efficacy in aspergillosis (Ambiload trial)



Doubling of baseline SeCr:
3 mg/kg (14%) vs.
10 mg/kg (31%), P=.005

K^+ < 3.0 mmol/L:
3 mg/kg (16%) vs.
10 mg/kg (30%), P=.015

median duration of study drug treatment in the modified intent-to-treat population was 15 days (range, 1–60 days) in the standard-dose group and 14 days (range, 1–57 days) in the high-dose group.

Cornely et al. *Clin Infect Dis* 2007;44:1289-97

What about “real-life” data?

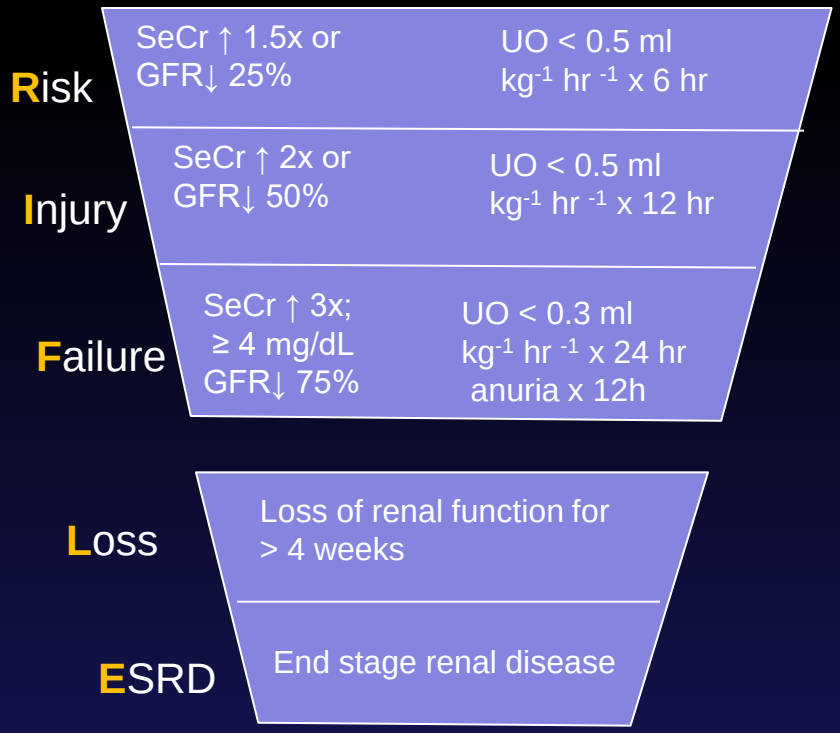
Best L-AMB toxicity data?

- Prospective, longitudinal study (2000-2002) of amphotericin B tolerability in 20 European centers (n=418)
  - Amphotericin B deoxycholate (62%)
  - Liposomal amphotericin B (27%)
  - Other lipid formulations (11%)

- Nephrotoxicity (≥ 50% increase SeCr) developed in 57% of patients, was associated with increased hospital LOS
  - Amphotericin B deoxycholate (67.5%)
  - Liposomal amphotericin B (30.7%)
  - Other lipid formulations (55.8%)

Ullmann et al. Clin Infect Dis 2006;43:e29-e38.

Better "real-life" data for amphotericin B nephrotoxicity?



Mixed patient population,
Less than 30% hematology

	AMB-D (n=236)	ABLC (n=90)	L-AMB (n=105)
Risk	50.6%	25.7%	22.0%
Injury	23.6%	5.7%	3.7%
Failure	11.5%	7.2%	2.4%

3 months later
(88%-no Injury)
(12%-Risk category only)

Ricci et al. Kidney International 2008;73:538-546.
Falci, Rosa & Pasqualotto. Mycoses 2015;59:104-112.

L-AMB retrospective cohort analysis
(Bologna, Seràgnoli Haematology Institute)

115 L-AMB treatment courses (2007-2014) in patients with hematological malignancies

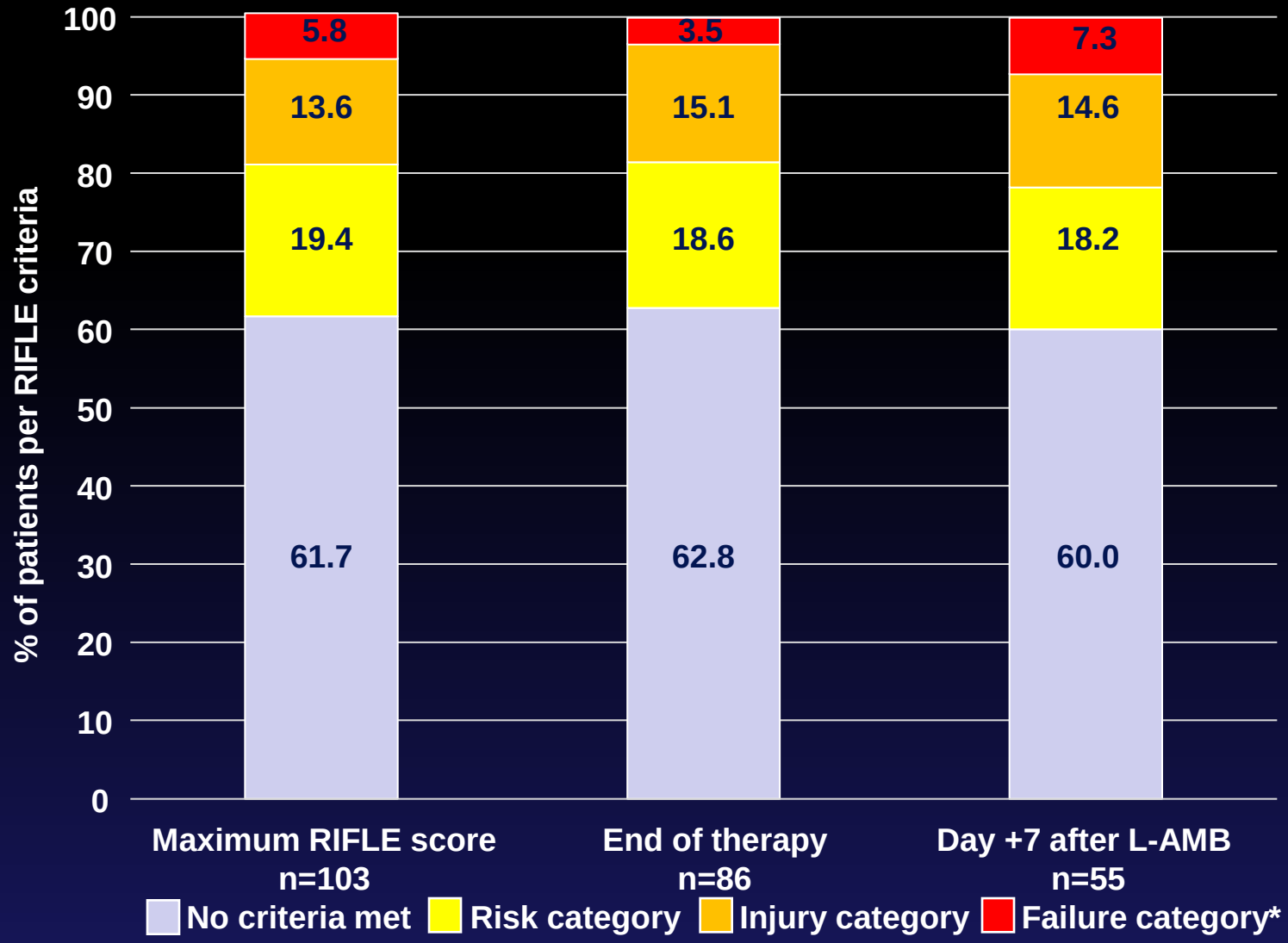
12 cases excluded because low- doses administered as prophylaxis (1 mg/kg daily or 10 mg/kg weekly)

103 L-AMB treatment courses
3 mg/kg/day (87%)
5 mg/kg/day (4.8%)
5 mg/kg/day→ 3 mg/kg/day (4.8%)

1° endpoint: Incidence of renal injury (RIFLE criteria)
2° endpoint: Concomitant drug risk factors

Stanzani, M. *et al. Antimicrob. Agents Chemother.* (2017)

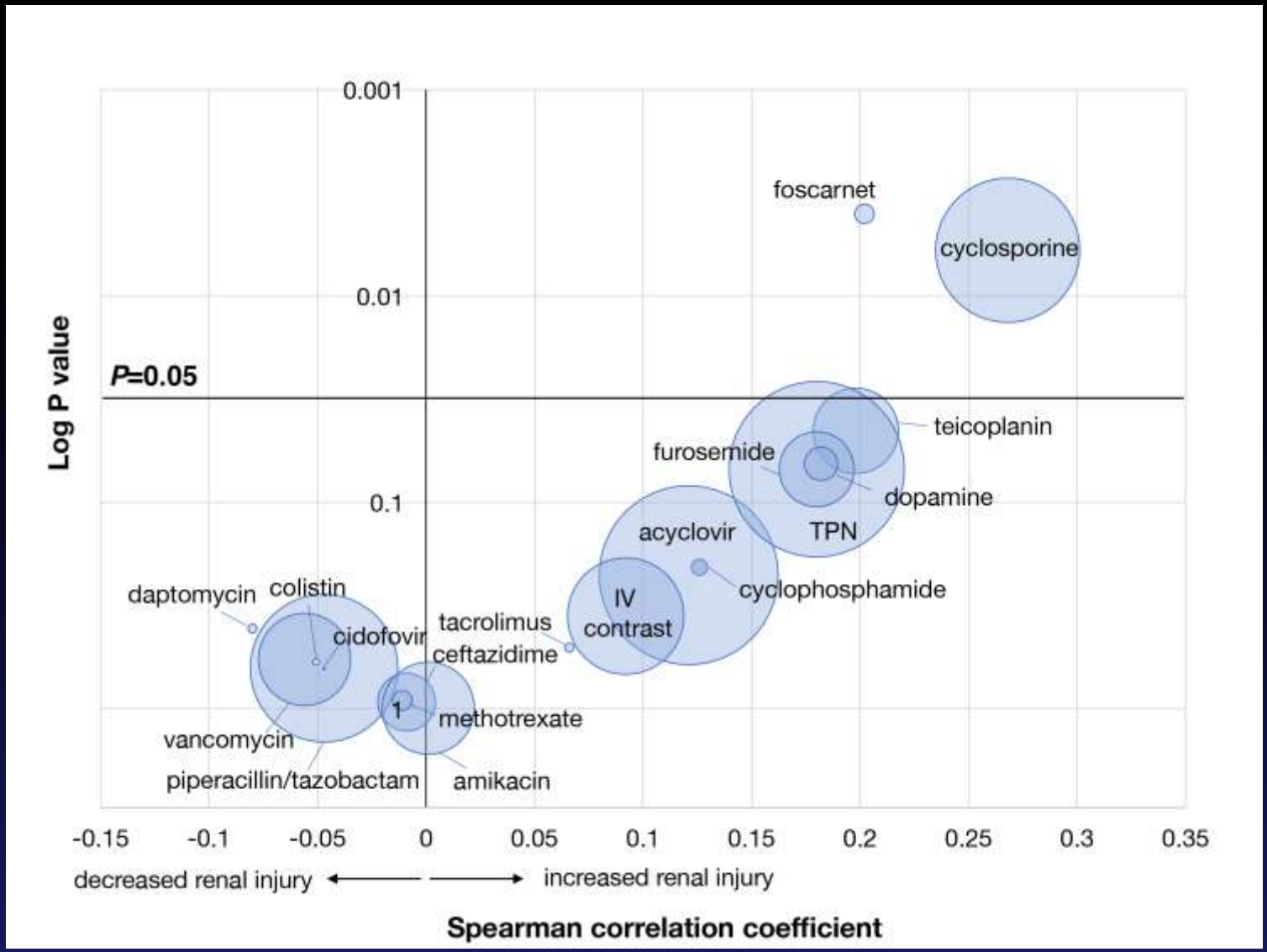
RIFLE categories met during L-AMB therapy



*all failure patients had multiorgan failure due to sepsis, hemorrhage and uncontrolled malignancy

Stanzani, M. *et al. Antimicrob. Agents Chemother.* (2017)

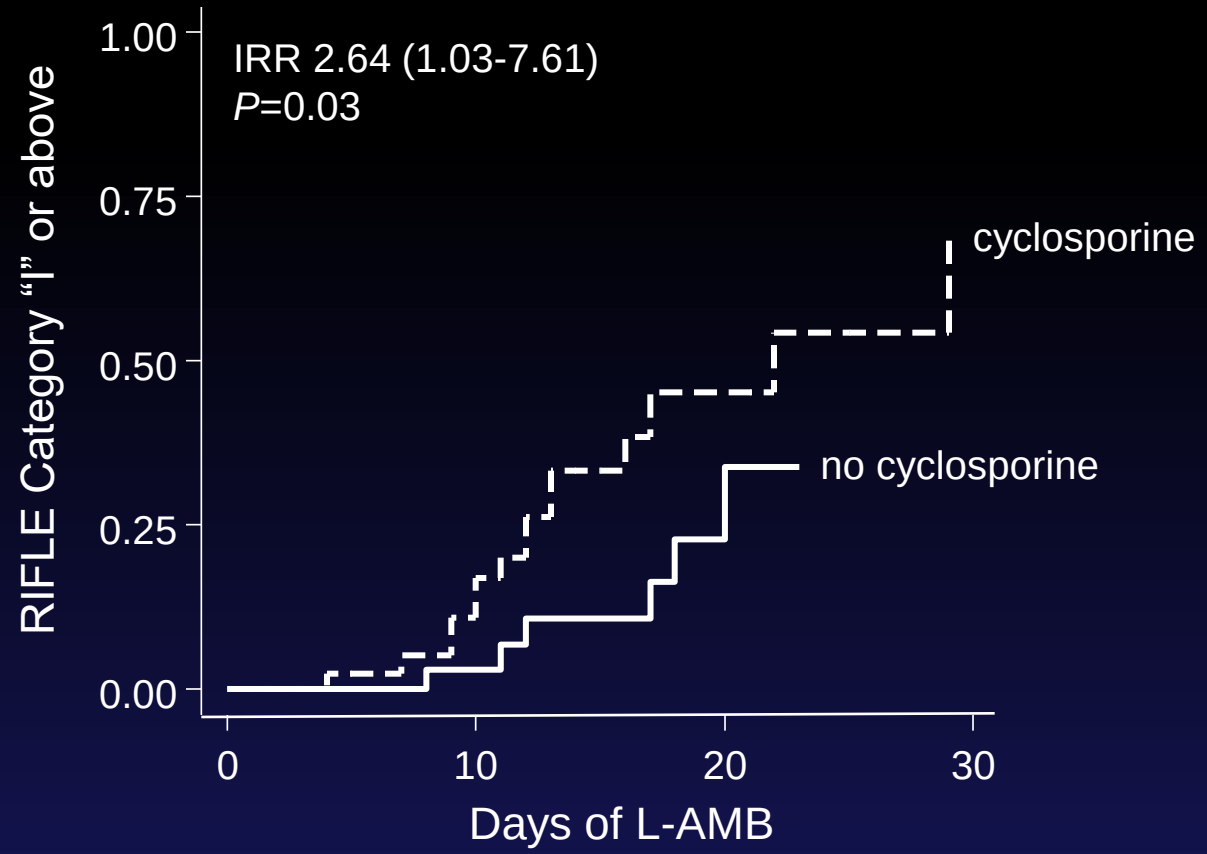
Impact of concomitant drugs on odds of progressing to injury category or greater



Stanzani, M. *et al*. *Antimicrob. Agents Chemother.* (2017)

Risk factors for meeting any RIFLE criteria

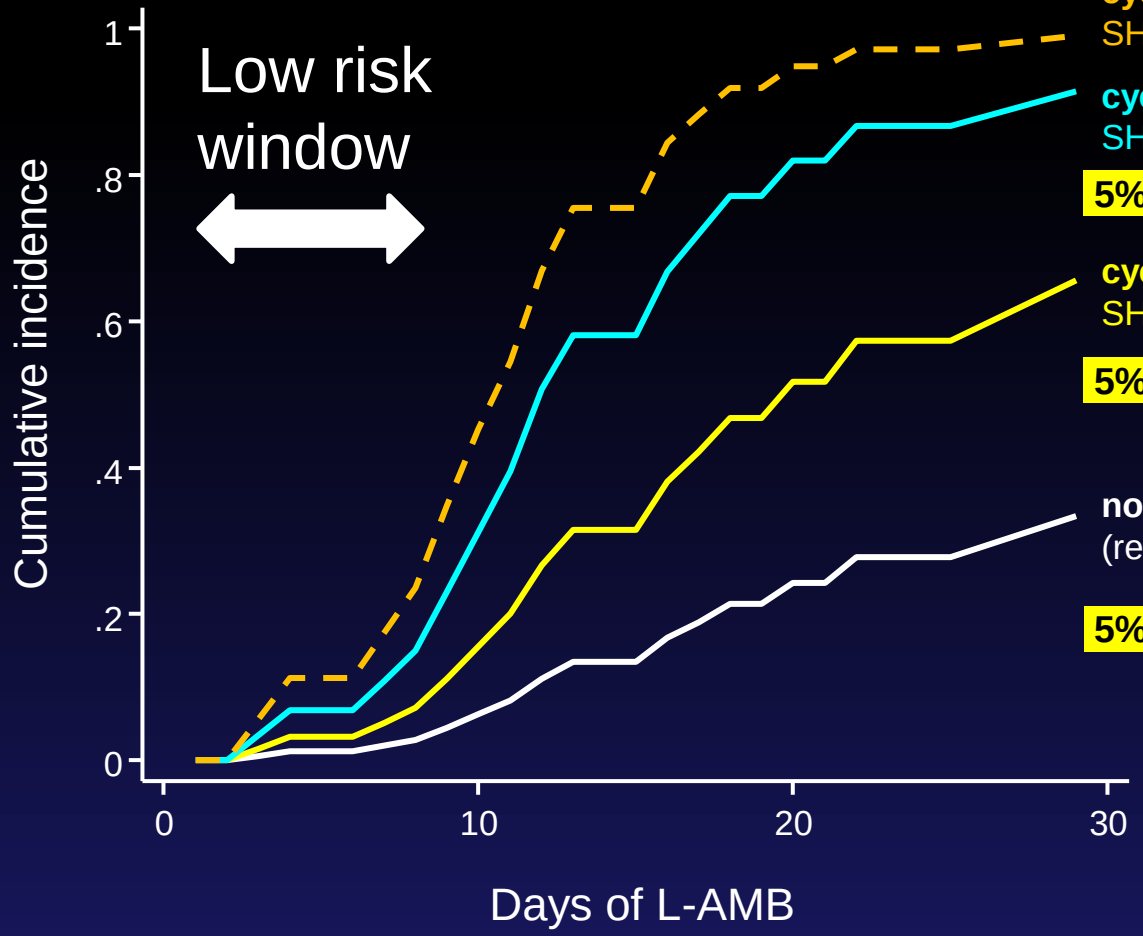
Allogeneic HSCT; *P*=0.06
Duration of L-AMB (median 13 vs. 8; *P*<0.0009)



no cyclosporine	61	28	7	2
cyclosporine	42	29	7	2

Stanzani, M. *et al. Antimicrob. Agents Chemother.* (2017)

L-AMB treatment window vs. risk of renal injury



cyclosporine + foscarnet
SHR 9.03 (3.68-22.14); *P*<0.0001

cyclosporine + furosemide
SHR 5.46 (1.89-15.74); *P*=0.002

5% cumulative incidence < 5 days

cyclosporine
SHR 2.62 (1.10-6.27); *P*=0.03

5% cumulative incidence: 9 days

no cyclosporine
(reference)

5% cumulative incidence: 12 days

Stanzani, M. *et al. Antimicrob. Agents Chemother.* (2017)

Avoid contrast-enhanced CT scans for invasive mould disease?

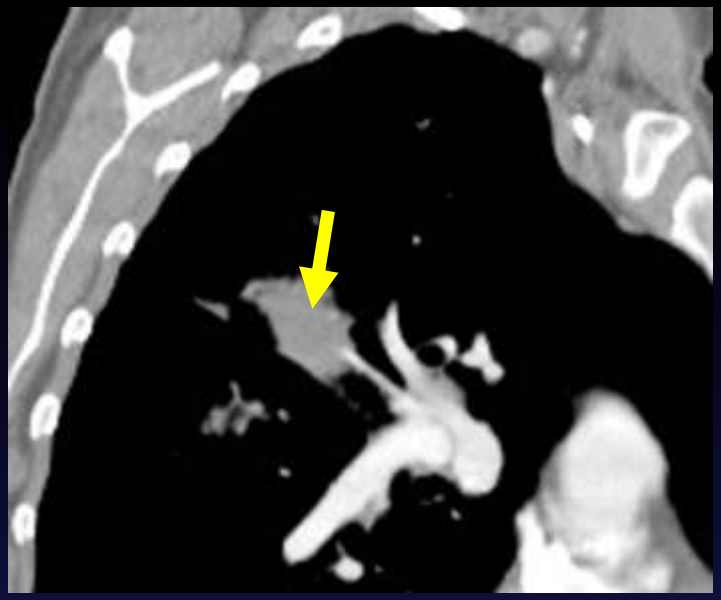
2016 Revised IDSA Aspergillosis Guidelines:

"Routine use of contrast during chest CT scan for suspicion of IPA is not recommended"
(*strong recommendation, moderate quality of evidence)*

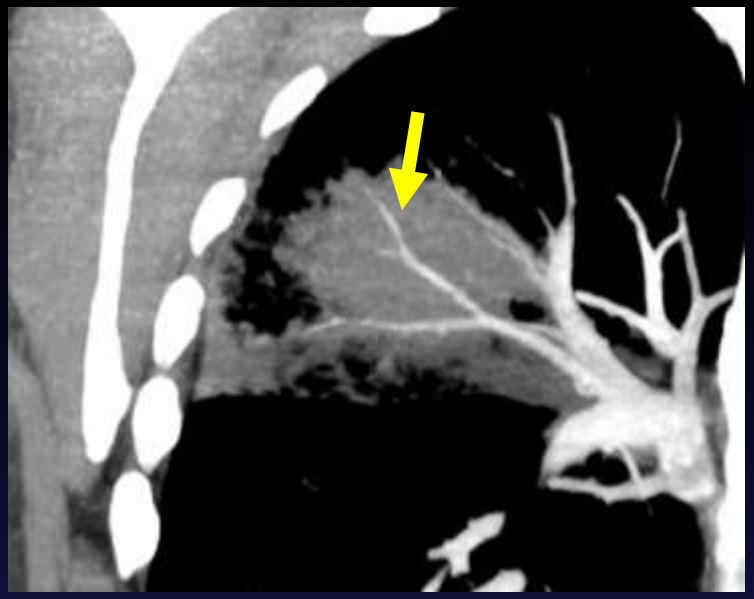
"Contrast is recommended when a nodule or a mass is close to a large vessel"
(*strong recommendation, moderate quality of evidence)*

Patterson et al. Clin Infect Dis 2016;63:e1-e60

CT pulmonary angiography (CTPA) can differentiate mould vs. bacterial pneumonia



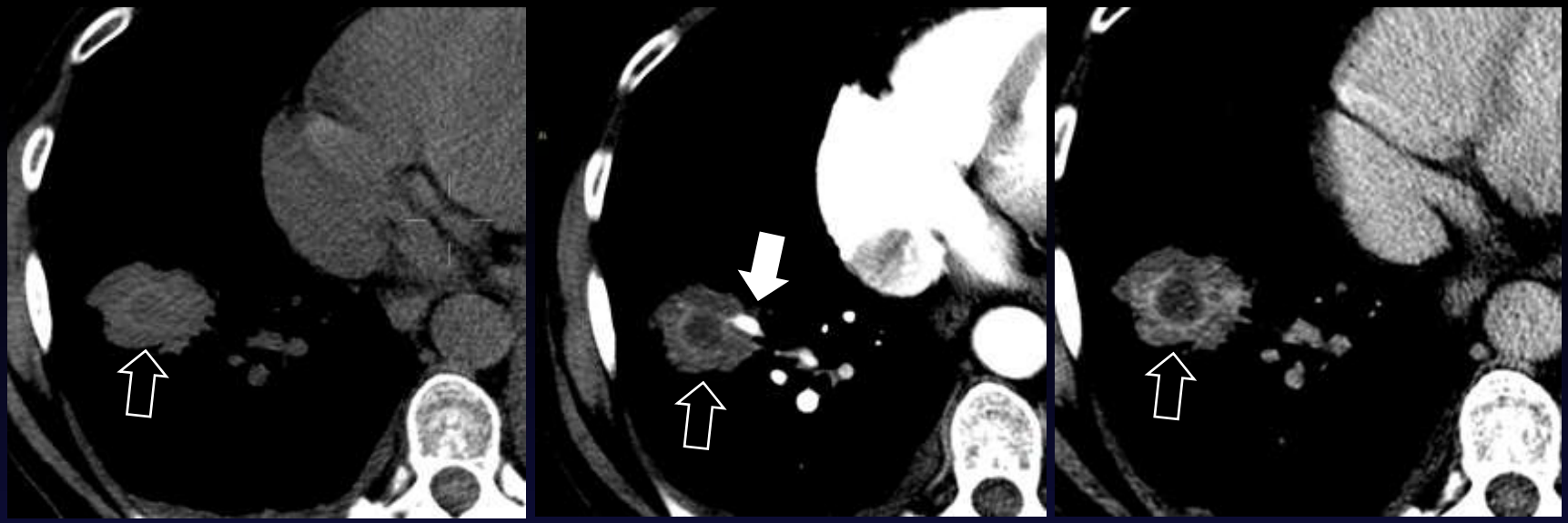
CTPA positive, proven mould disease by autopsy



CTPA negative, bacterial pneumonia

Stanzani et al. Clin Infect Dis 2012;54(5):610-6.

Contrast improved detection of the hypodense sign in invasive pulmonary aspergillosis

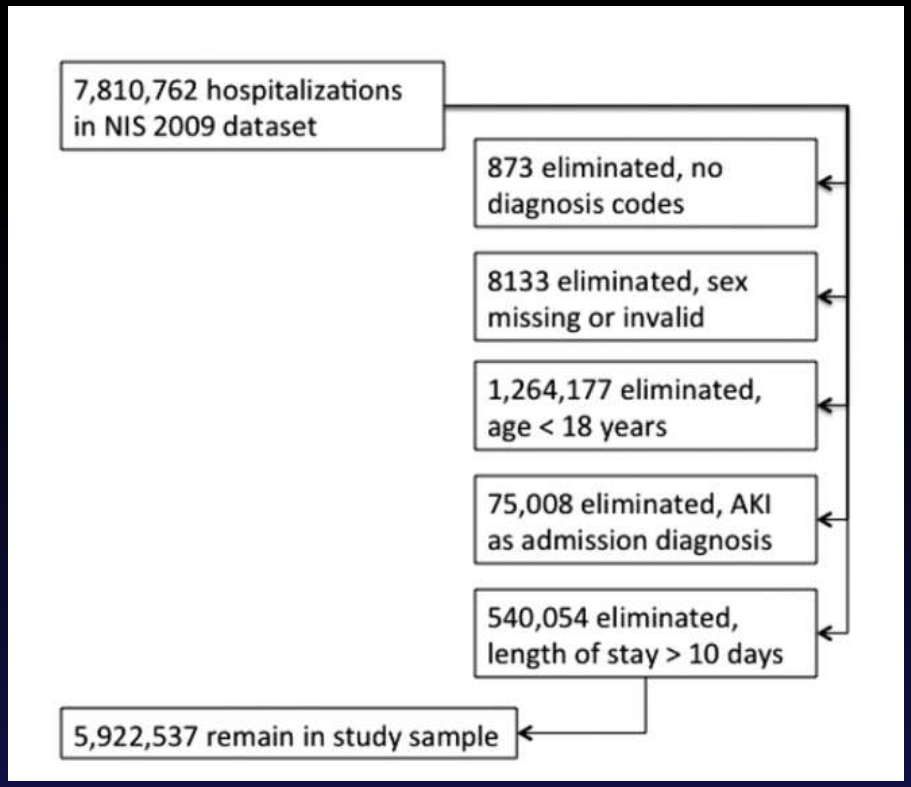


⇨ hypodense sign
vessel occlusion

➡ hypodense sign
vessel occlusion

Sassi et al. *Submitted*

Estimating the risk of radiocontrast-induced nephropathy

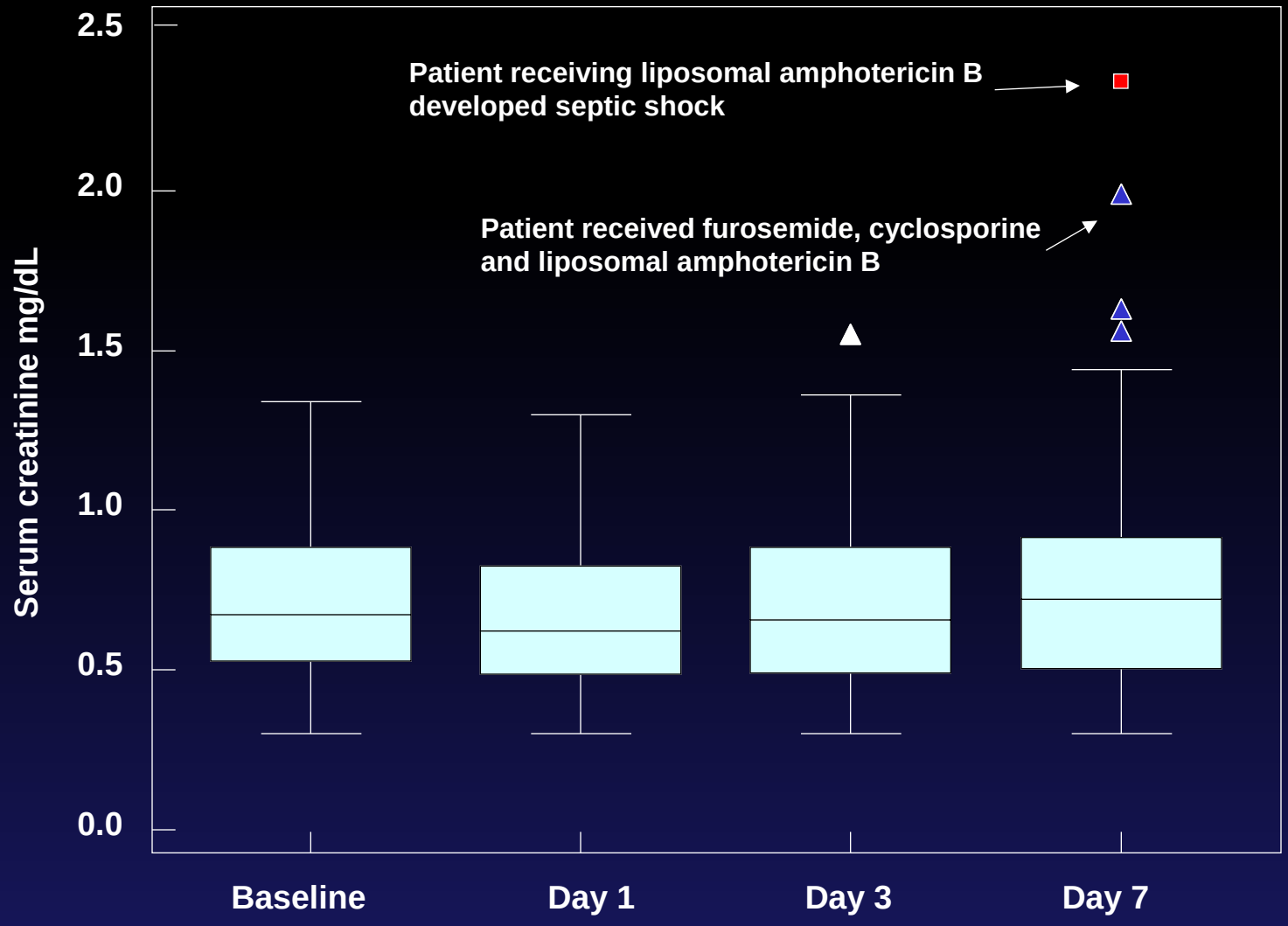


- Rates of acute kidney injury
  - No contrast: 5.5%
  - Contrast 5.6%
- Adjust. for comorbidities, odds ratio for renal injury associated with contrast administration:
  - OR 0.93 (95% CI 0.88-0.97)

Conclusion: risk for contrast-associated nephropathy may be overstated in the literature and overestimated by clinicians

Wilhelm-Leen, E., Montez-Rath, M. E. & Chertow, G. *J. Am. Soc. Nephrol*. **28,** 653–659 (2017).

CTPA-nephrotoxicity concerns (n=100 patients)



Stanzani et al. Clin Infect Dis 2015;60:1603-1610.

Coadministration of liposomal amphotericin B and contrast medium does not increase risk of kidney injury

Category	Contrast	Non-contrast	OR (95% CI)	P value
AKIN stage 1				
Unadjusted	19 (17)	16 (19)	0.86 (0.41-1.80)	0.69
Matched 1:1	12 (18)	13 (20)	0.87 (0.32-2.42)	0.80
AKIN stage 2				
Unadjusted	7 (6)	7 (8)	0.73 (0.25-2.16)	0.57
Matched 1:1	4 (6)	5 (8)	0.80 (0.21-2.98)	0.74
AKIN stage 3				
Unadjusted	6 (5)	1 (1)	4.67 (0.55-39.5)	0.12
Matched 1:1	3 (5)	0 (0)	10.5 (0.64-174)	0.20

Matched 1:1: adjustment for age, baseline kidney function,
And other clinical risk factors by propensity score

O'Horo, J. C. *et al. Antimicrob. Agents Chemother.* (2017).

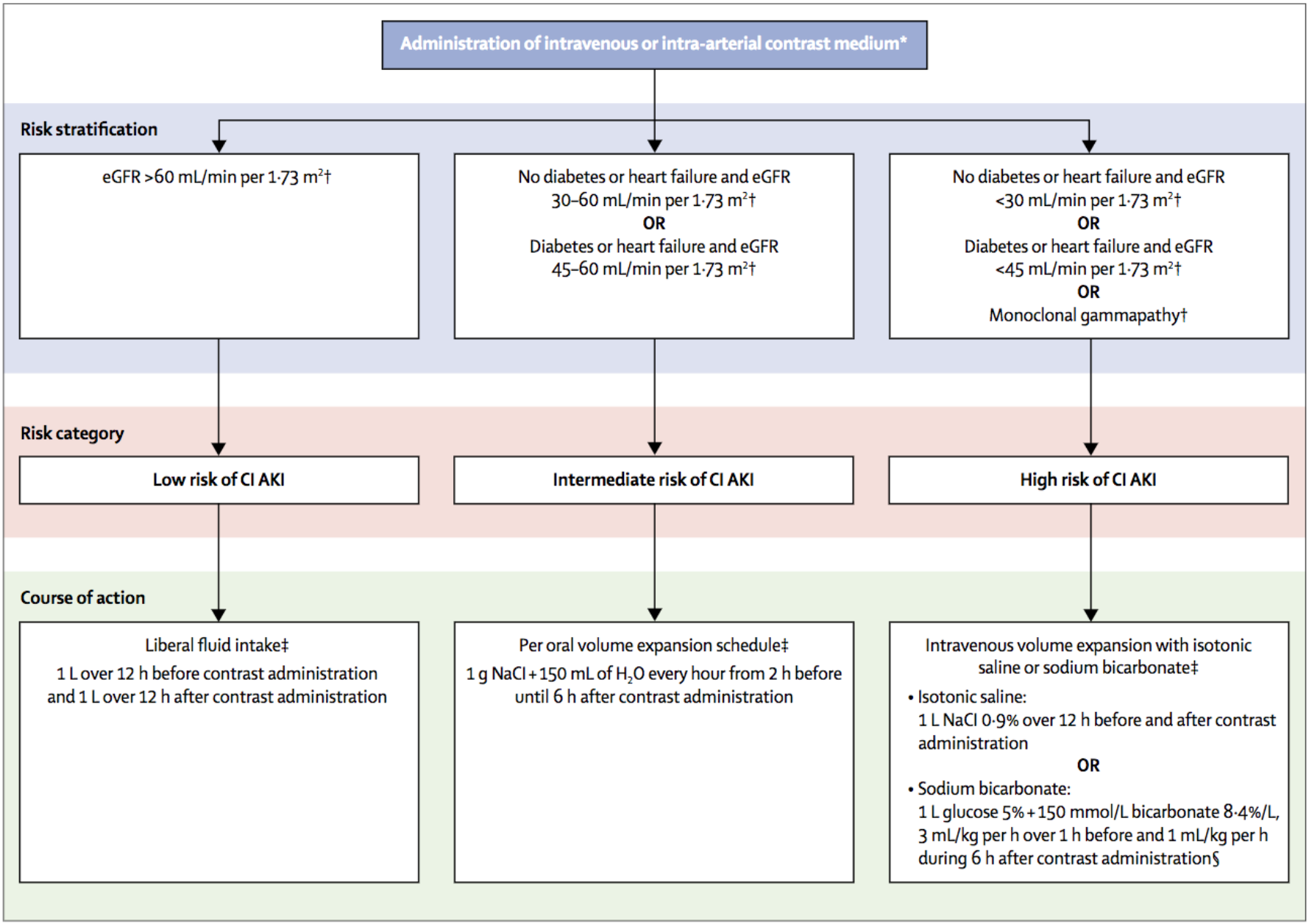
Physicians avoid using contrast in patients with more comorbidities because of the perceived risk of AKI.

The low risk of AKI attributable to contrast administration suggests such a strategy might not be warranted in many conditions. However, the risk of contrast-induced AKI is not zero, and therefore this risk should always be balanced against the consequences of an incomplete diagnostic or interventional work-up caused by avoiding contrast administration.

Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* **389,** 2139–2151 (2017).

Conclusions

- The risk of renal injury with antifungal therapy may be overstated by older literature
- Forms of renal injury have been observed with all antifungals, but are most prominent with amphotericin B formualtions
- Risk of L-AMB renal injury can be reduced by using
  - Recommended doses (3-5 mg/kg/day)
  - Adequate hydration and sodium loading
  - Avoidance of multiple concomitant nephrotoxic medication
  - Reassessing continued need after first 7-10 days of therapy



Only two-thirds of patients at risk for AKI are sufficiently volume expanded

Vanmassenhove, J., Kielstein, J., Jörres, A. & Biesen, W. V. *Lancet* 389, 2139–2151 (2017).

Patients routinely received hydration (250-500 mL 0.9% NaCl) before and after L-AMB infusions, and were managed with a standardized electrolyte replacement protocol for potassium replacement (goal K^+ = 4.0 mEq/L) and magnesium supplementation (5 g of $MgSO_4$ IV daily until serum K^+ levels normalized; thereafter oral Mg^{2+} supplementation was used at a daily dose of 535 mg (5.33 mEq) MgCl twice daily.