Controversies in Antimicrobial Treatment for Sepsis

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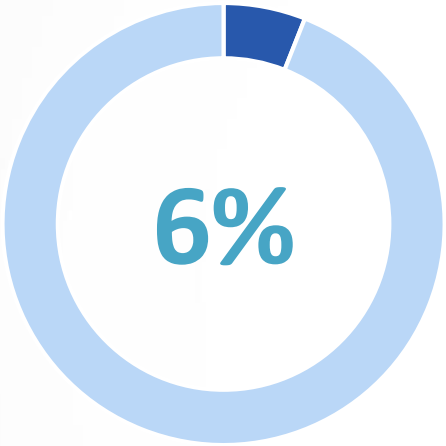
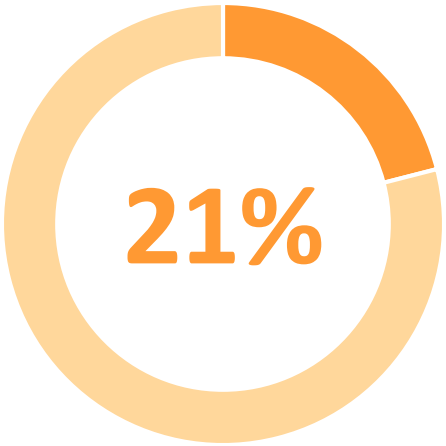
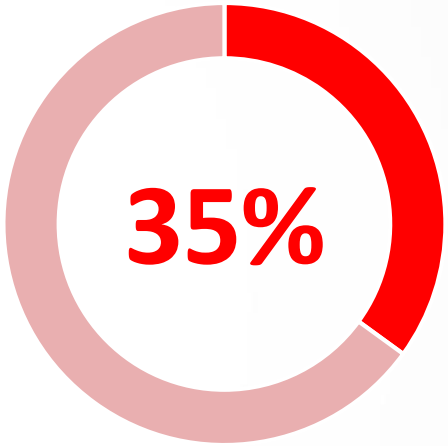
Burden of sepsis in the US



of hospitalized patients



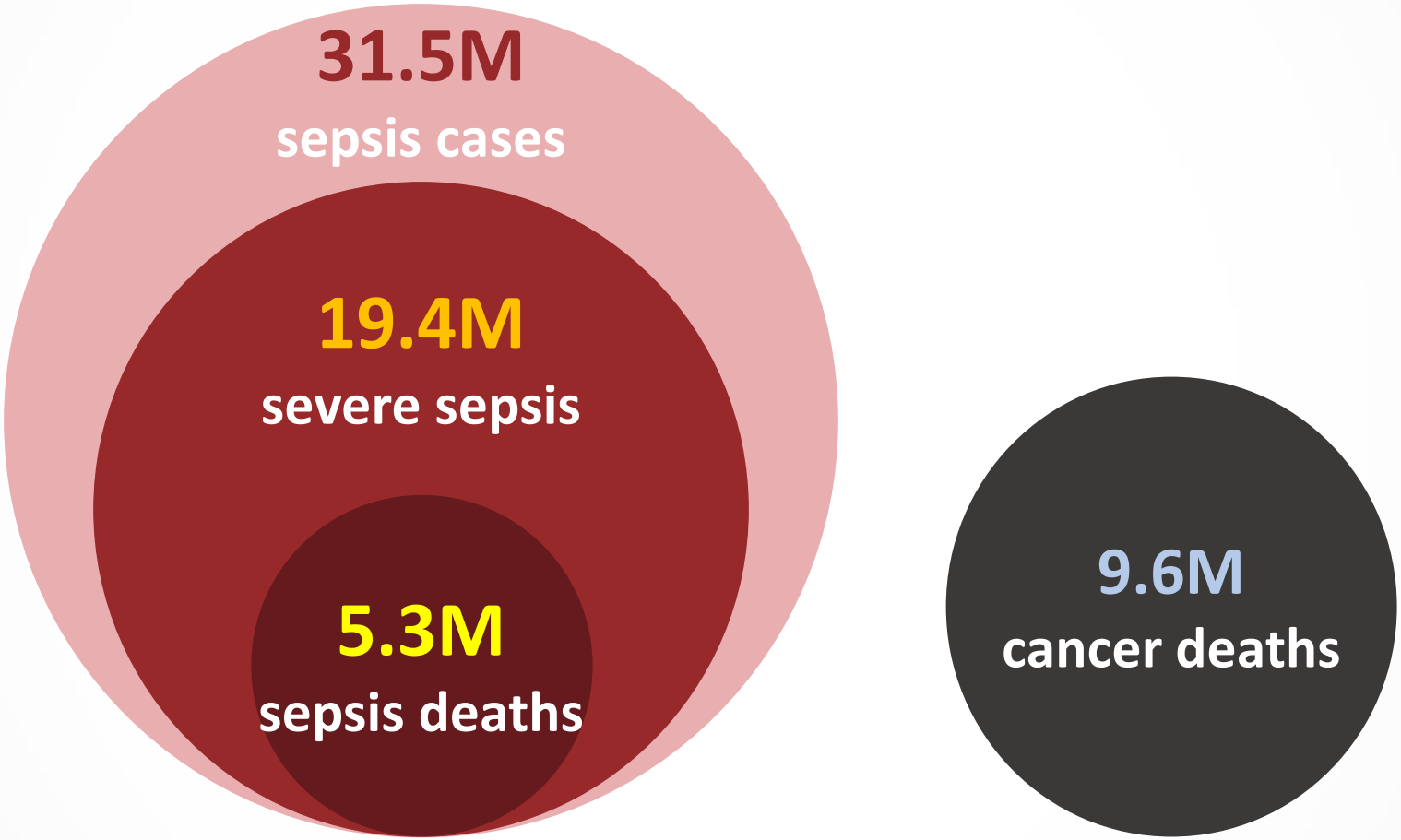
dies in the hospital or are discharged to hospice



of all hospitalizations that culminated in death

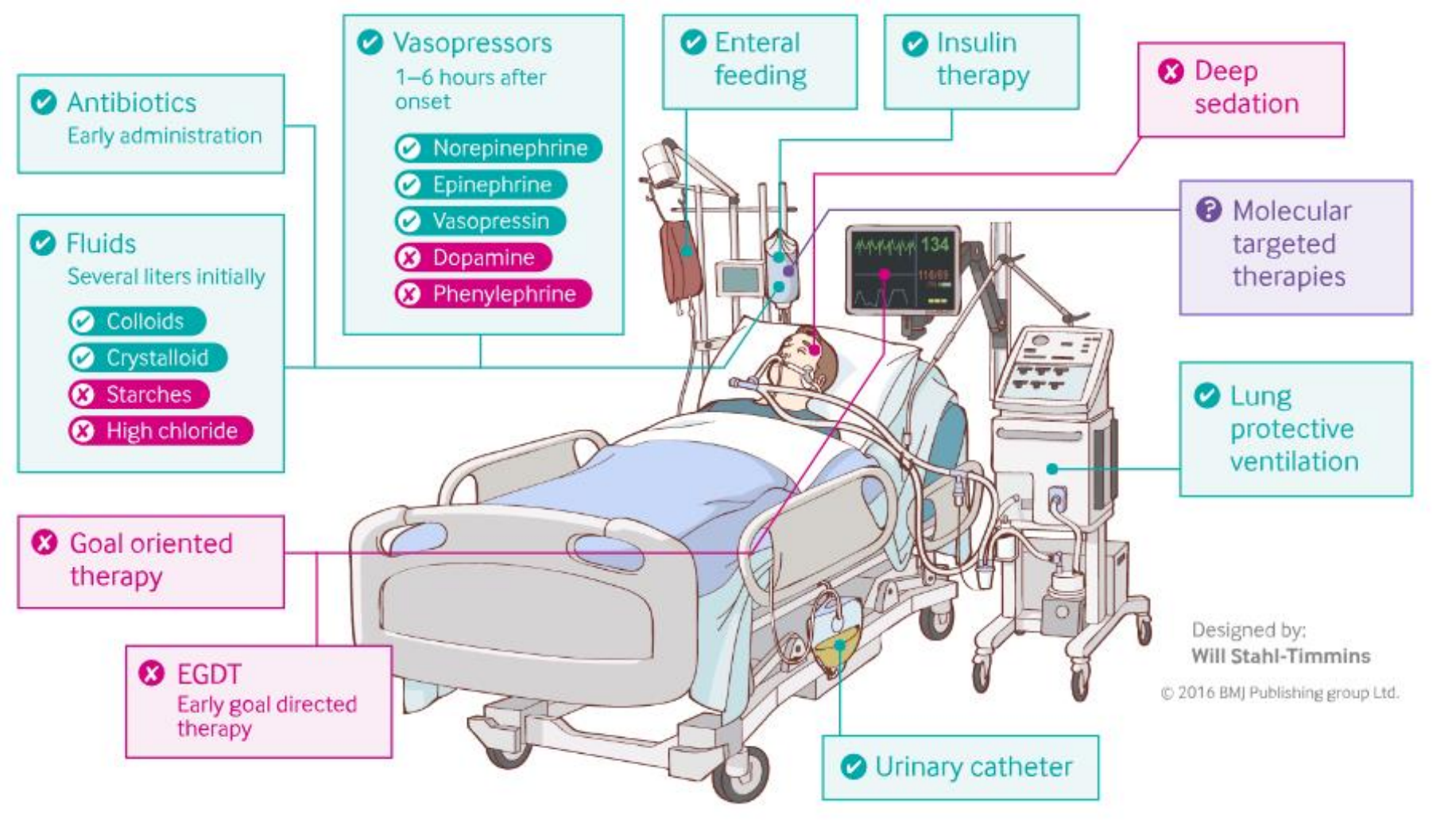
Rhee C et al. JAMA 2017;318(13):1241-1249

Global burden of sepsis



Fleischmann C et al. Am J Respir Crit Care Med 2016;193(3):259-272
GBD 2017 Causes of Death Collaborators. Lancet 2018;392(10159):1736-1788

Treatment for sepsis



Gotts JE et al. BMJ 2016;353:i1585

Principles of antimicrobial treatment for sepsis

Early initiation

Broad empirical coverage

De-escalation

There have been controversies on management for sepsis …

- Corticosteroids
- Goal-directed therapy
- Fluid resuscitation
- Molecular targeted therapies

… and many more

… and antimicrobial treatment is no exception

Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Infec
STAT
Sepsi

IDSA Sepsis

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Early Administration of Antibiotics for Suspected Sepsis

OPTION 1

Do Not Administer Antibiotics

Michael Klompas, M.D., M.P.H.

OPTION 2

Administer Antibiotics Immediately

Laura Evans, M.D.

Antibiotics within 1 hr

Hour-1 bundle

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).

2016 SSC Guidelines for Sepsis and Septic Shock

Fixed target of 1 hour: PRO

- Supported by multiple large observational studies
- Benefit is biologically plausible
- Potential risk of delaying therapy is high
- Early administration would be beneficial in pts without shock to prevent deterioration into organ dysfunction

- If overuse is of concern, effort should be focused on de-escalation and discontinuation

Fixed target of 1 hour: CON

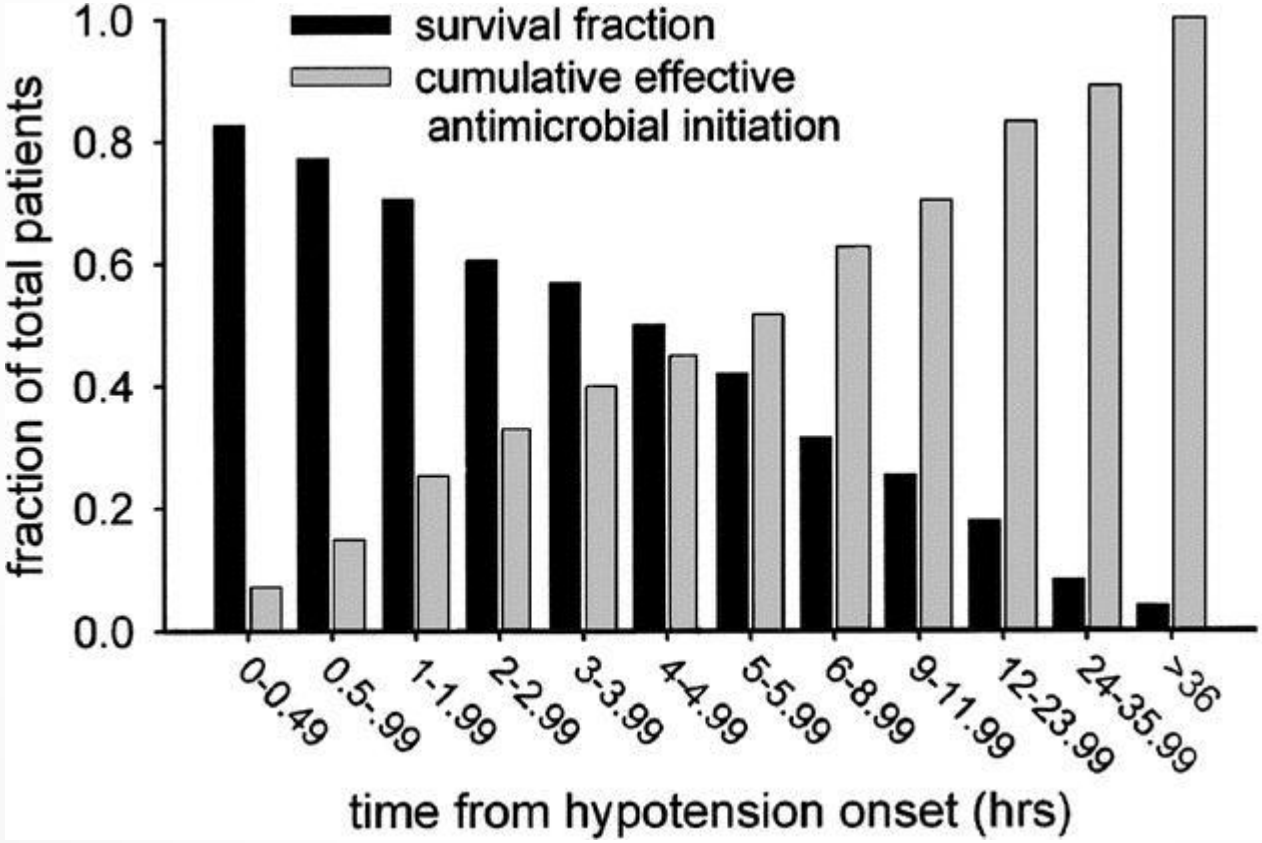
- Evidence for the benefit of <1 hr administration is weak for septic patients *without* shock
- Existing studies share common limitations

- Implementation might cause unexpected negative consequences
  - Excessive use of antibiotics
  - Delayed work-up for alternative diagnosis

- Benefit of such policy has never been tested in real life

Fixed target of 1 hour: Current evidence

- Multicenter retrospective, North Am; 2,154 patients w/ **septic shock**
- 77.9% documented infections, 34.2% bloodstream infection
- Overall mortality 58.0%



7.6% decrease in surv per hour

ABx < 1 hr vs. later
OR 1.67 (1.12-2.48)

Kumar A et al. Crit Care Med 2006;34(6):1589-96

Fixed target of 1 hour: Current evidence

- Multinational (SSC)
- 17,990 pts w/ **severe sepsis and septic shock** admitted to ICU
- Overall mortality 29.7%

Time to Antibiotics (Hr)	OR[a]	95% CI	*p*	Probability of Mortality (%)[b]	95% CI
0–1[c]	1.00			24.6	23.2–26.0
1–2	1.07	0.97–1.18	0.165	25.9	24.5–27.2
2–3	1.14	1.02–1.26	0.021	27.0	25.3–28.7
3–4	1.19	1.04–1.35	0.009	27.9	25.6–30.1
4–5	1.24	1.06–1.45	0.006	28.8	25.9–31.7
5–6	1.47	1.22–1.76	< 0.001	32.3	28.5–36.2
> 6	1.52	1.36–1.70	< 0.001	33.1	30.9–35.3

OR = odds ratio.

[a]Hospital mortality odds ratio referent group is 0–1 hr for the time to antibiotics and is adjusted by the sepsis severity score (SSS), ICU admission source (ED, ward, vs ICU), and geographic region (Europe, United States, and South America).

[b]Probability of hospital mortality is estimated using the generalized estimating equation population averaged logistic regression model and is based on the subject having the following characteristics: from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

[c]Antibiotics administered in the first hour are the referent group and thus the odds ratio by definition is 1.00 while the 95% CI and the p value are not generated by the regression model.

Ferrer R et al. Crit Care Med 2014;42(8):1749-1755

Fixed target of 1 hour: Current evidence

- Additional analysis of multicenter RCT (US)
- 291 pts w/ **septic shock** presented to ED
- Median time from triage to ABx: **115 min** (IQR 65-175)
- Overall mortality **18.9%**

Table 4. Inhospital mortality: Triage to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
≤1 hr	65	16.9	2.6	1.18	0.57–2.46	1.81	0.74–4.44
>1 hr	226	19.5					
≤2 hrs	155	21.3	−5.1	0.71	0.39–1.30	1.07	0.54–2.16
>2 hrs	136	16.2					
≤3 hrs	223	20.6	−7.4	0.59	0.27–1.27	0.66	0.27–1.63
>3 hrs	68	13.2					
≤4 hrs	255	20.4	−12.1	0.35	0.10–1.20	0.39	0.08–1.90
>4 hrs	36	8.3					
≤5 hrs	274	19.7	−13.8	0.25	0.03–1.96	0.69	0.07–6.86
>5 hrs	17	5.9					
≤6 hrs	281	19.6	−19.6	—	—	—	—
>6 hrs	10	0					

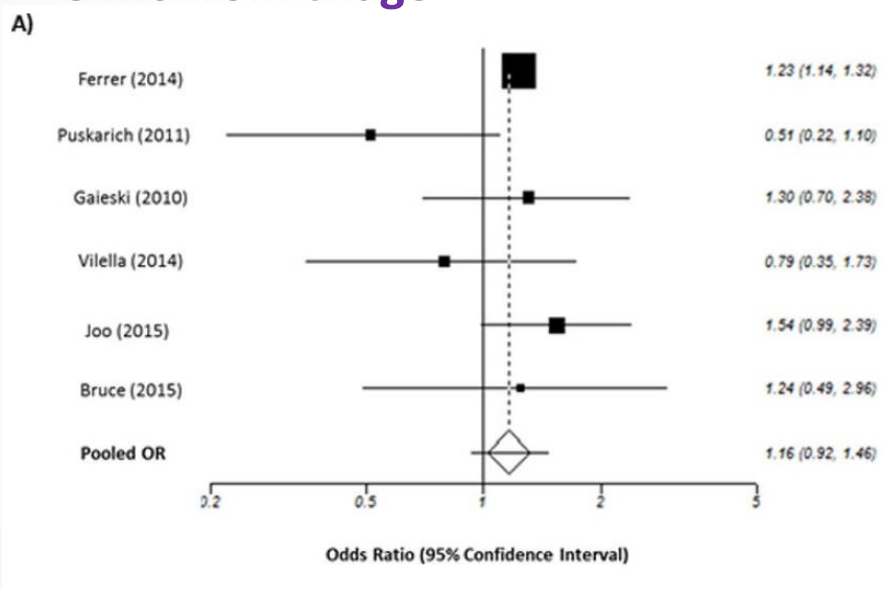
[a]Odds of death with increasing delays in antibiotic administration.

Puskarich MA et al. Crit Care Med 2011;39(9):2066-71

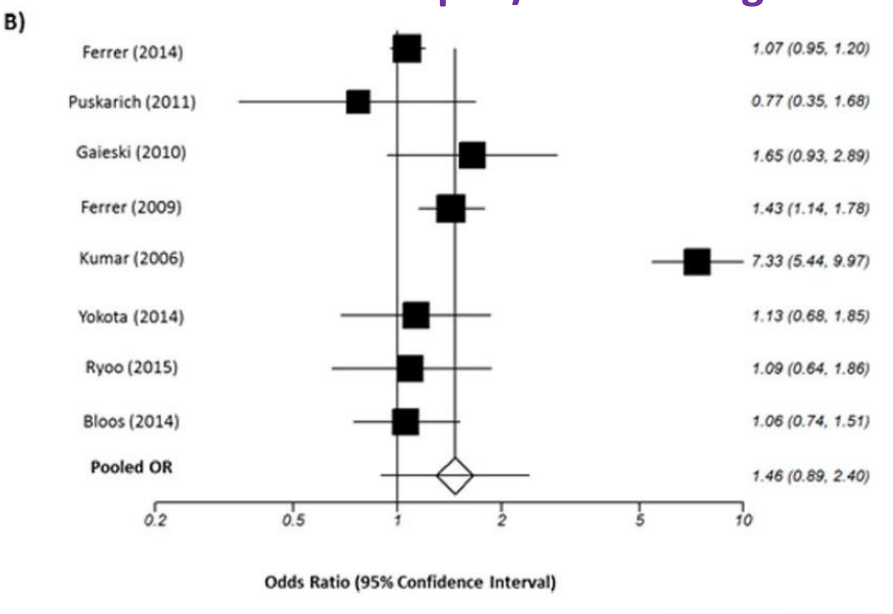
Fixed target of 1 hour: Current evidence

- Systematic review/meta-analysis (2015)
- 36 studies included, 11 for full meta-analysis

3 hrs from triage



1 hr from severe sepsis/shock recognition



Sterling SA et al. Crit Care Med 2015;43:1907-15

Fixed target of 1 hour: Current evidence

- Multicenter, prospective; 3 EDs in the Netherlands
- 1,168 pts w/ **sepsis**; 85% received ABx < 3hr
- Overall mortality 10.0%

Table 3 The hazard for 28-day mortality as a function of time to antibiotics in ED patients with suspected infection in three categories of illness severity

	Crude model (HR (95% CI)	Corrected model (HR (95% CI)	*P* (Corrected model)
PIRO group 1 to 7 (n = 413)			
Antibiotics <1 hour (reference category)	1	1	0.422[a]
Antibiotics 1–3 hours	0.95 (0.17-5.18)	2.55 (0.36-18.25)	0.352
Antibiotics >3 hours	1.98 (0.36-10.78)	5.31 (0.43-68.16)	0.191
PIRO group 8 to 14 (n = 532)			
Antibiotics <1 hour (reference category)	1	1	0.676[a]
Antibiotics 1–3 hours	1.11 (0.62-1.99)	1.25 (0.62-2.31)	0.488
Antibiotics >3 hours	0.65 (0.22-1.90)	0.86 (0.28-2.63)	0.786
PIRO group >14 (n = 223)			
Antibiotics <1 hour (reference category)	1	1	0.978[a]
Antibiotics 1–3 hours	1.10 (0.62-1.97)	0.99 (0.53-1.87)	0.983
Antibiotics >3 hours	0.93 (0.36-2.43)	1.11 (0.40-3.08)	0.849

De Groot et al. Crit Care 2015;19:194

Fixed target of 1 hour: Current evidence

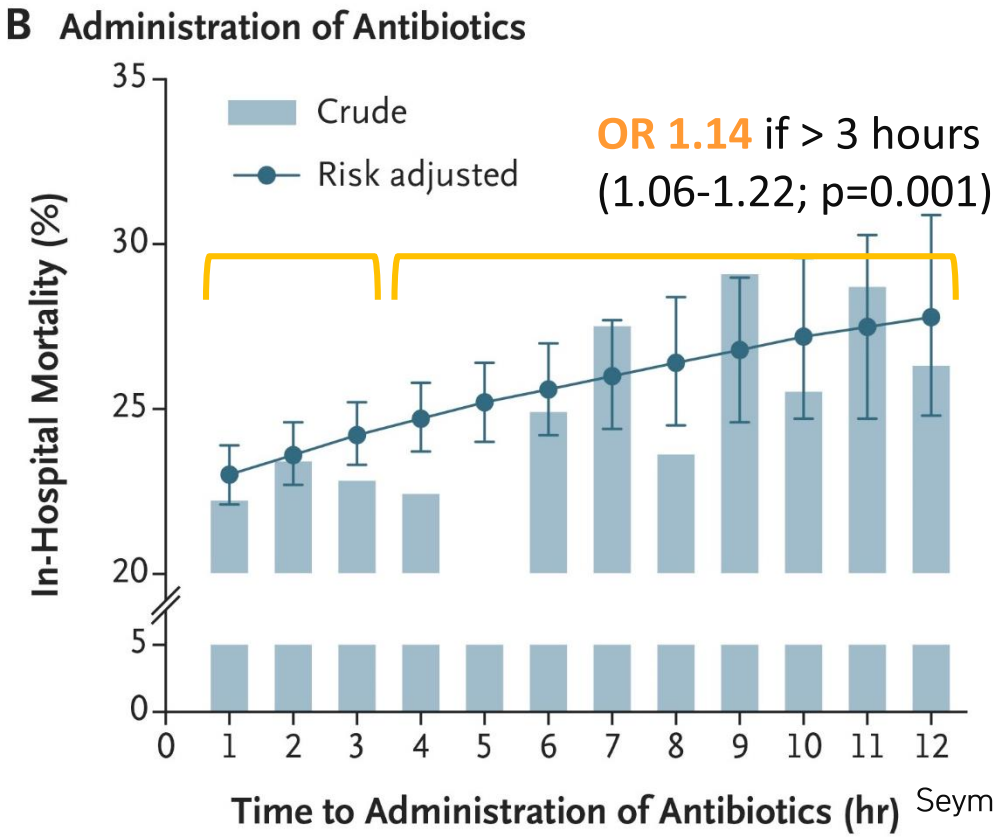
- 35,000 random patients w/ **sepsis (ICD code)** presented to 21 EDs in the Kaiser Permanente Northern California 2010-2013
- Observed mort: 3.9% (sepsis), 8.8% (severe sepsis), 26.0% (shock)
- Median time of ABx: **2.1** hours (IQR 1.4-3.1)

Subgroup	OR for mortality per hour until antibiotics			Absolute increase of mortality per hour until antibiotics		
	OR	95% CI	p	Percent	95% CI	p
Sepsis	1.09	1.00-1.19	0.046	0.3%	0.01-0.6%	0.04
Severe sepsis	1.07	1.01-1.24	0.014	0.4%	0.1-0.8%	0.02
Septic shock	1.14	1.06-1.23	0.001	1.8%	0.8-3.0%	0.001

Liu VX et al. Am J Respir Crit Care Med 2017;196(7):856-863

Fixed target of 1 hour: Current evidence

- 49,331 patients w/ **sepsis and septic shock** reported to the NY State Dept of Health 2014-2016
- 82.5% completed 3-hour bundle within 3 hours
- Median time of ABx: **0.95** hours (IQR 0.35-1.95)



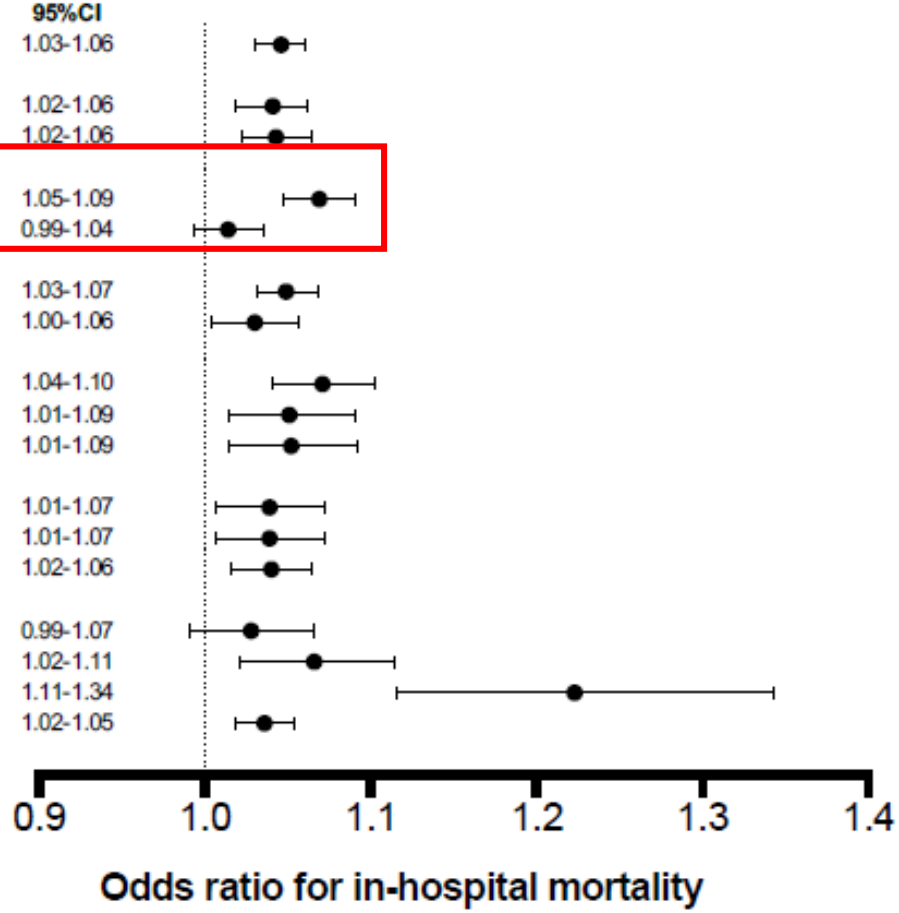
OR 1.14 if > 3 hours (1.06-1.22; p=0.001)

OR 1.04 per hour (1.06-1.06; p<0.001)

Seymour W et al. N Engl J Med 2017;376:2235-2244

Fixed target of 1 hour: Current evidence

Model	No.	Odds ratio	95%CI
All cases	49,331	1.04	1.03-1.06
Gender			
Male	25,689	1.04	1.02-1.06
Female	23,634	1.03	1.02-1.06
Vasopressors			
Yes	16,721	1.07	1.05-1.09
No	32,610	1.01	0.99-1.04
Admission source			
Home	33,464	1.05	1.03-1.07
Other	15,867	1.03	1.00-1.06
Comorbidities			
Congestive heart failure	10,092	1.07	1.04-1.10
Hemodialysis	5,207	1.05	1.01-1.09
Chronic respiratory failure	5,738	1.05	1.01-1.09
Source of infection			
Respiratory	19,839	1.04	1.01-1.07
Urinary	13,439	1.04	1.01-1.07
Other	16,053	1.04	1.02-1.06
Bacteremia			
Gram positive	7,175	1.03	0.99-1.07
Gram negative	6,431	1.07	1.02-1.11
Other	965	1.22	1.11-1.34
None	34,757	1.04	1.02-1.05

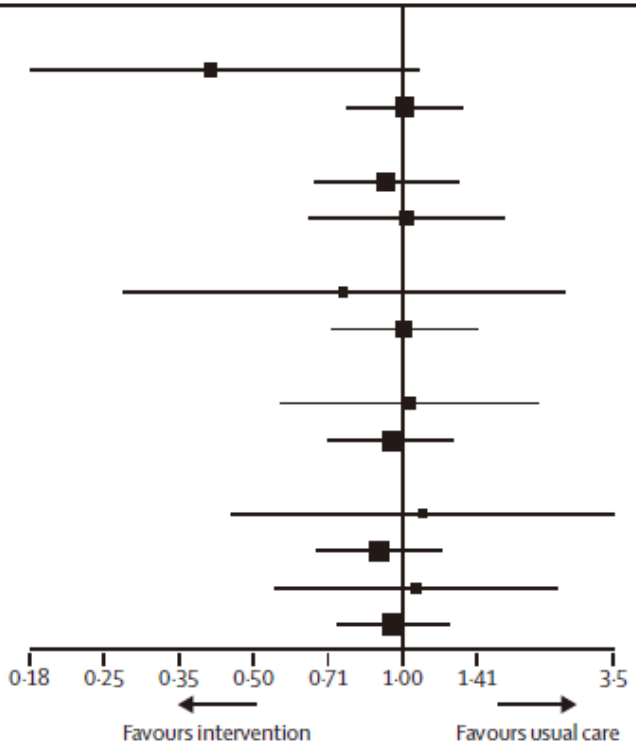


Seymour W et al. N Engl J Med 2017;376:2235-2244

Fixed target of 1 hour: Current evidence

- Randomized controlled trial: **pre-hospital EMS CTRX** vs. usual care
- 2,672 pts (1,535 intervention vs. 1,137 usual care)
- Estimated time gain to ABx in intervention group: **96 min**

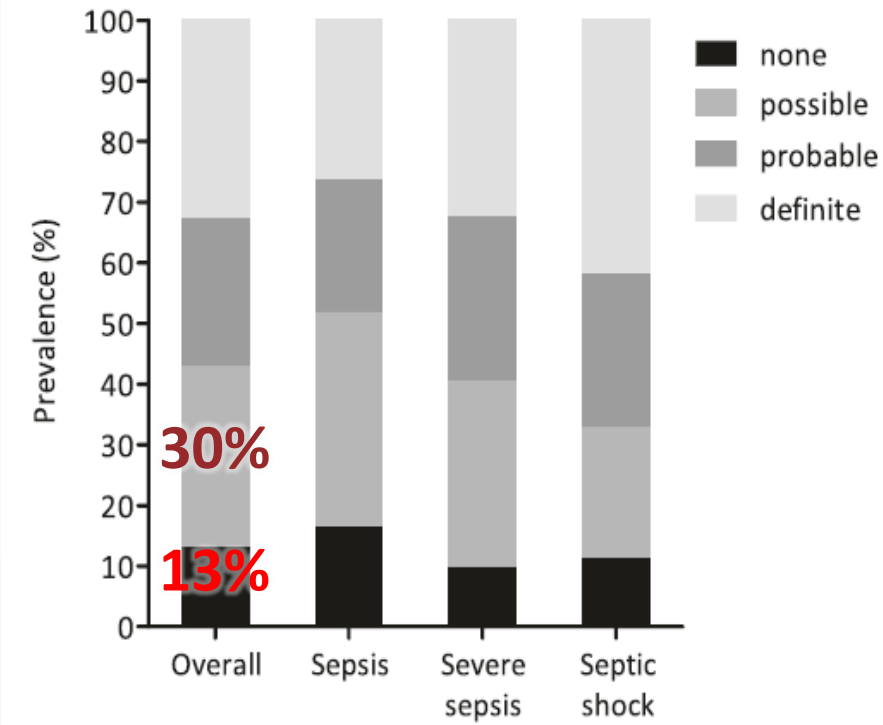
	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	p value
Age (years)				
<65	12/276 (4%)	6/336 (2%)	0·41 (0·16–1·08)	0·10
≥65	81/860 (9%)	114/1199 (10%)	1·01 (0·77–1·32)	1·00
qSOFA (prehospital)				
<2	59/872 (7%)	71/1132 (6%)	0·93 (0·66–1·29)	0·72
2	25/180 (14%)	45/318 (14%)	1·02 (0·65–1·60)	1·00
NEWS (prehospital)				
<5	7/146 (5%)	7/192 (4%)	0·76 (0·27–2·12)	0·80
≥5	53/622 (9%)	71/827 (9%)	1·01 (0·72–1·42)	1·00
SBP (prehospital)				
≤100	15/112 (13%)	25/181 (14%)	1·03 (0·57–1·87)	1·00
>100	75/1001 (7%)	95/1337 (7%)	0·95 (0·71–1·27)	0·78
Severity of sepsis				
Sepsis	8/424 (2%)	12/579 (2%)	1·10 (0·45–2·66)	1·00
Severe sepsis	74/656 (11%)	88/868 (10%)	0·90 (0·67–1·20)	0·53
Septic shock	10/37 (27%)	19/66 (29%)	1·07 (0·56–2·04)	0·85
Overall	**93/1136 (8%)**	**120/1535 (8%)**	**0·95 (0·74–1·24)**	**0·78**



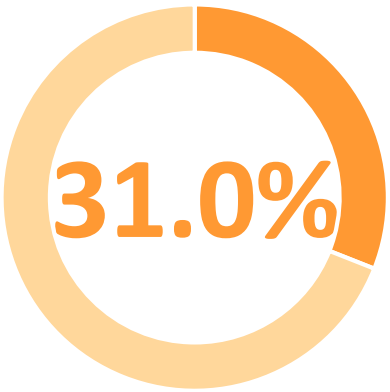
Alam N et al. Lancet Respir Dis 2018;6:40-50

Many patients with presumed sepsis actually do not have sepsis

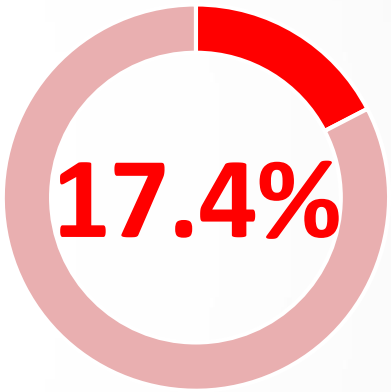
2,579 pts in 2 Dutch ICUs



Approx. 1M pts in the US



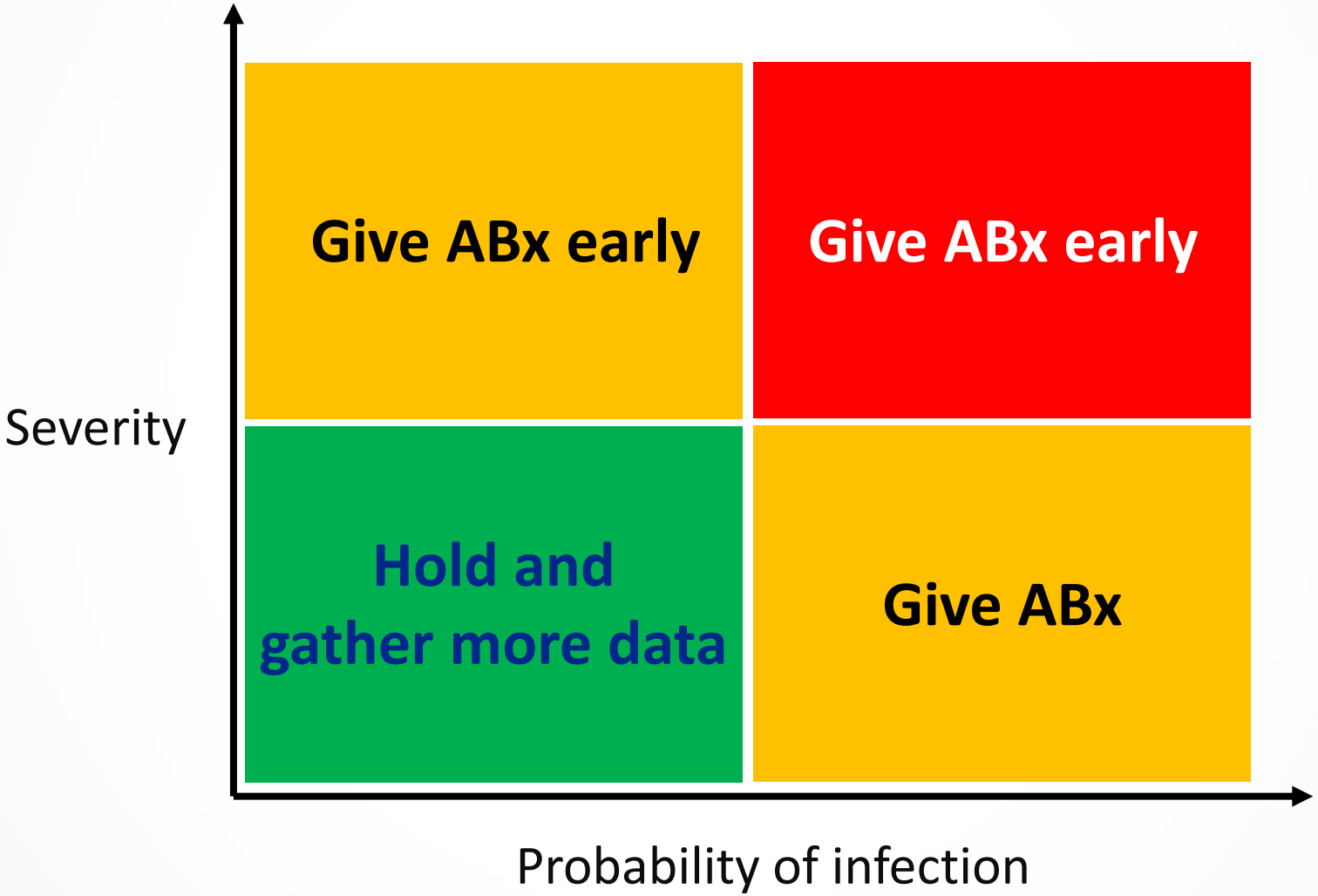
PPV of qSOFA for infection



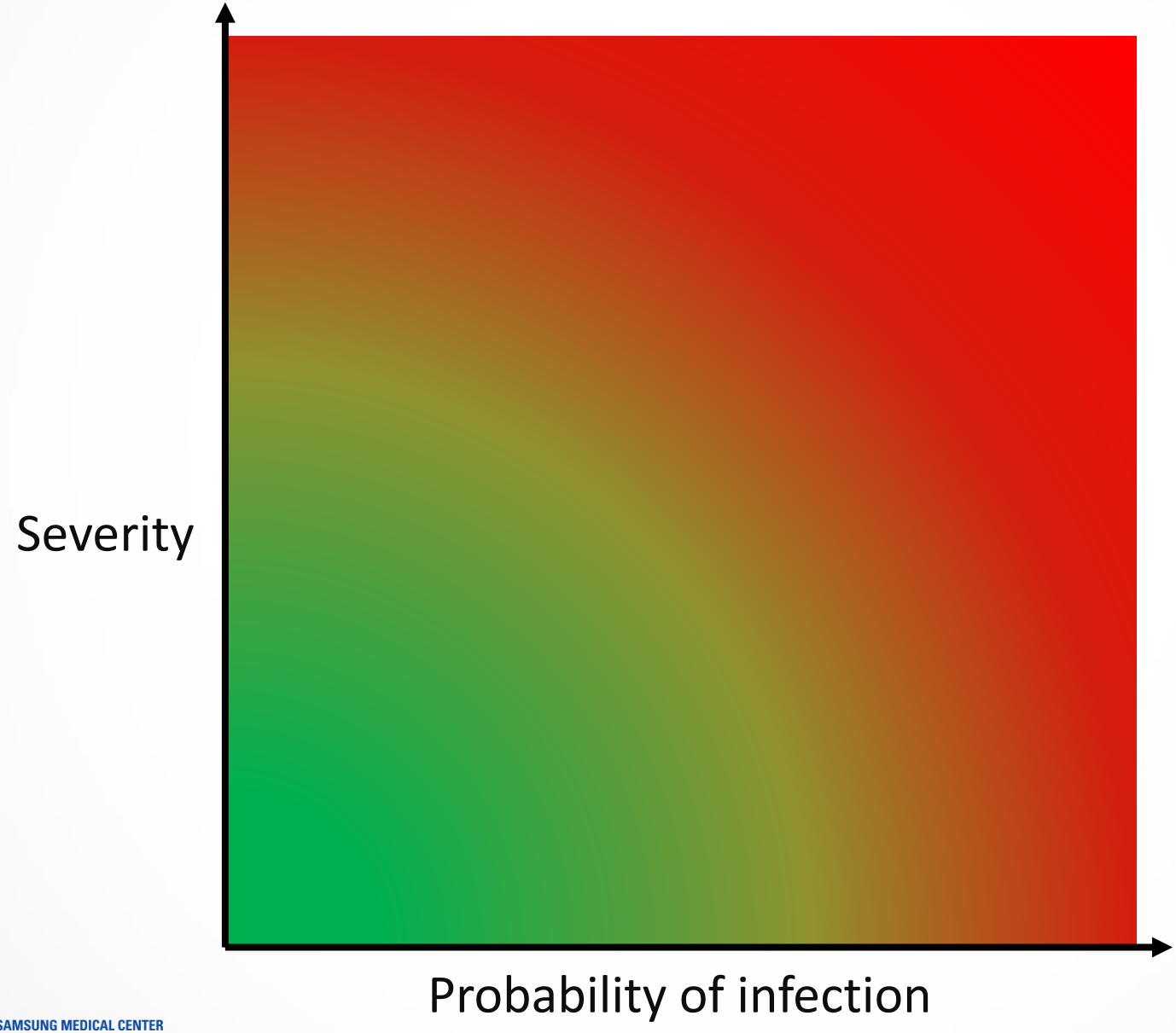
PPV of qSOFA for sepsis

Klein Klouwenberg PMC et al. Crit Care 2015;19:319
Anand V et al. Chest 2019 (advance online pub)

An ideal decision-making



Reality



Fixed target of 1 hour: What do we need?

- **Proof of benefit**
  - Randomized controlled trial is not feasible
  - Cluster randomized trial on ED policy
  - Quasiexperimental study (e.g., before-and-after)

- **Feasibility & implementation**
  - System improvement to accelerate drug delivery, especially in the ED

- **Antimicrobial stewardship**
  - Institution-specific guidance
  - De-escalation and discontinuation

Combination therapy

Why combine?

Rationale	Antimicrobial coverage	Example
Broader coverage	Do not overlap	Metronidazole + cephalosporins
Reduce the risk of inappropriate ABx	Overlap	PTZ + FQ/AG
Additive/synergistic effect	Overlap	Ampicillin + AG for enterococci
Reduce the risk of emergence of resistance	Overlap	Tuberculosis HIV
Immunomodulating effect	Irrelevant	Macrolides

Empirical treatment for VAP

MRSA Activity (if risk present)

- Vancomycin
- Linezolid

+

Anti-pseudomonal Beta-lactams

- Piperacillin-tazobactam
- Cefepime or Ceftazidime
- Carbapenems
- Aztreonam

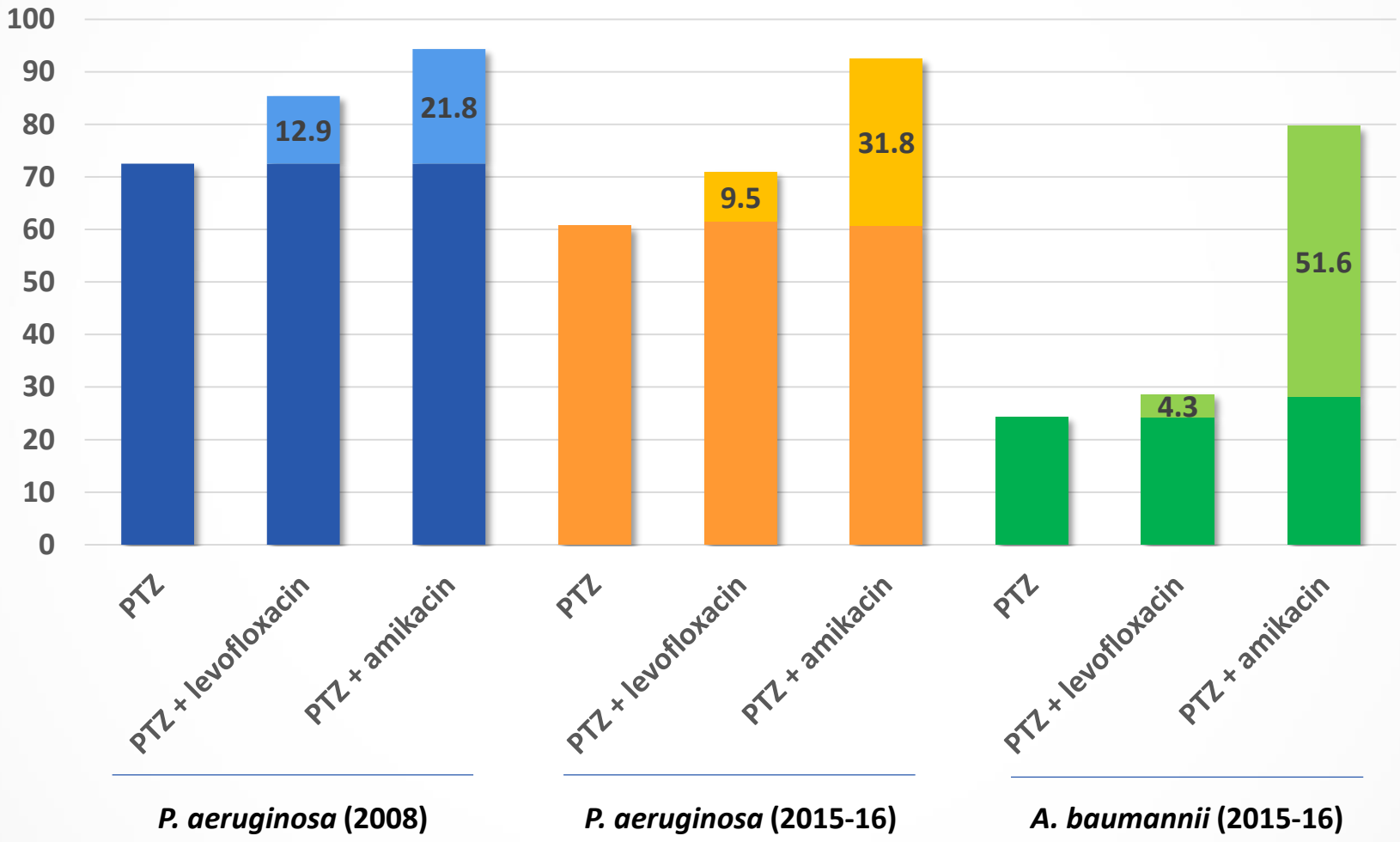
+

Anti-pseudomonal Non-beta-lactams

- FQ
- AG
- Polymyxins

2016 ATS/IDSA HAP/VAP Guidelines

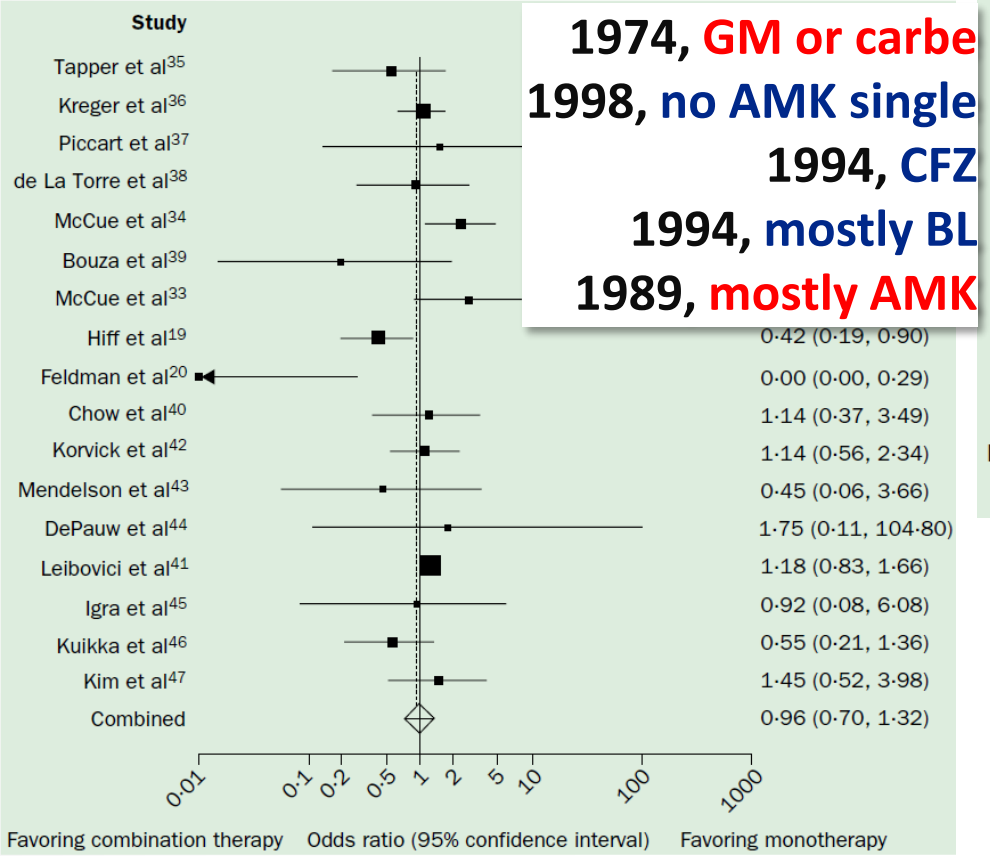
Susceptibility of non-fermenters to combination regimens



Huh K et al. Diagn Microbiol Infect Dis 2013;76:477-82
KARSNet, 2015-16 (unpublished data)

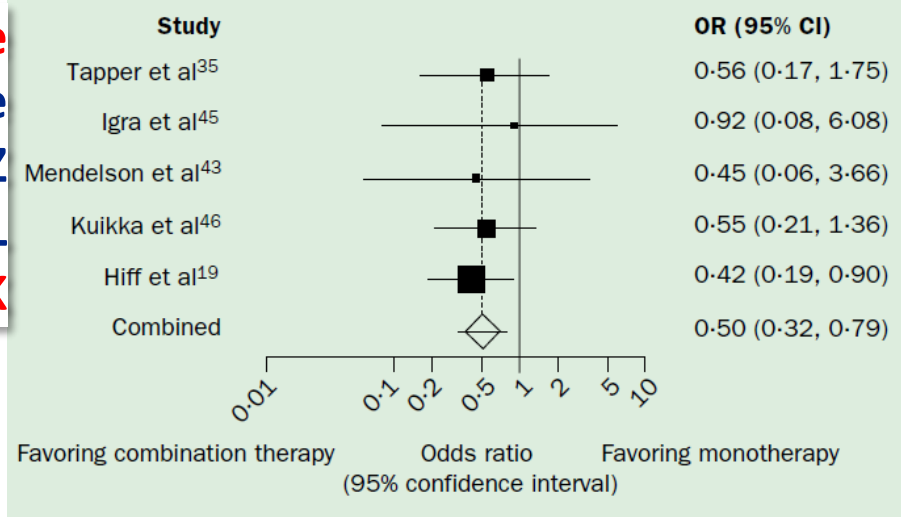
Combination therapy: Meta-analysis on gram-negative bacteremia

Mortality: all gram-negatives



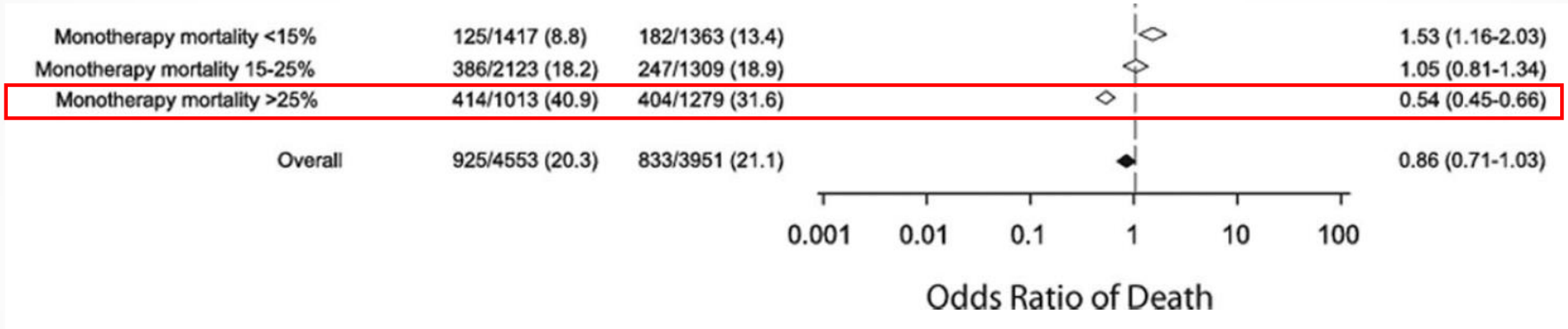
1974, GM or carbe
1998, no AMK single
1994, CFZ
1994, mostly BL
1989, mostly AMK

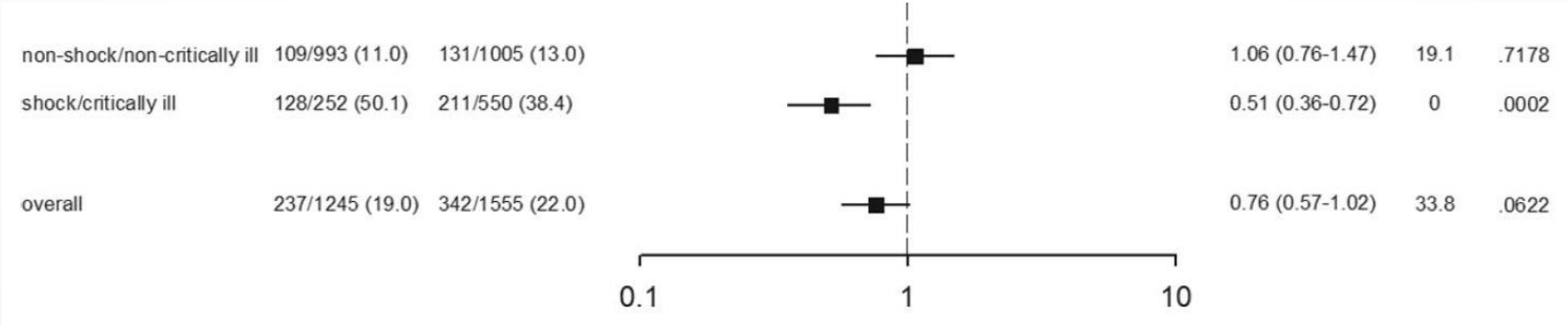
Mortality: *P. aeruginosa* only



Safdar N et al. Lancet Infect Dis 2004;4:519-27

Combination therapy: Meta-analysis/meta-regression on sepsis

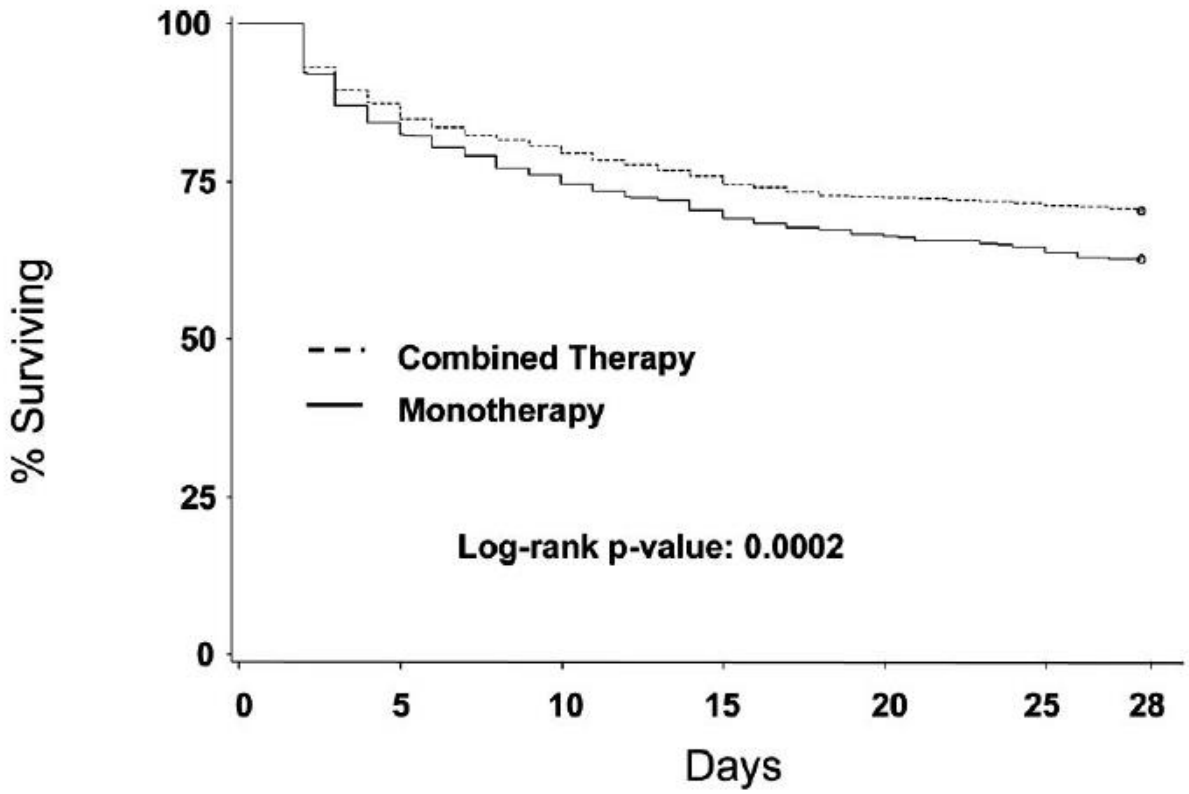




Kumar A et al. Crit Care Med 2010;38(8):1651-1664

Definitive combination therapy: A large retrospective study

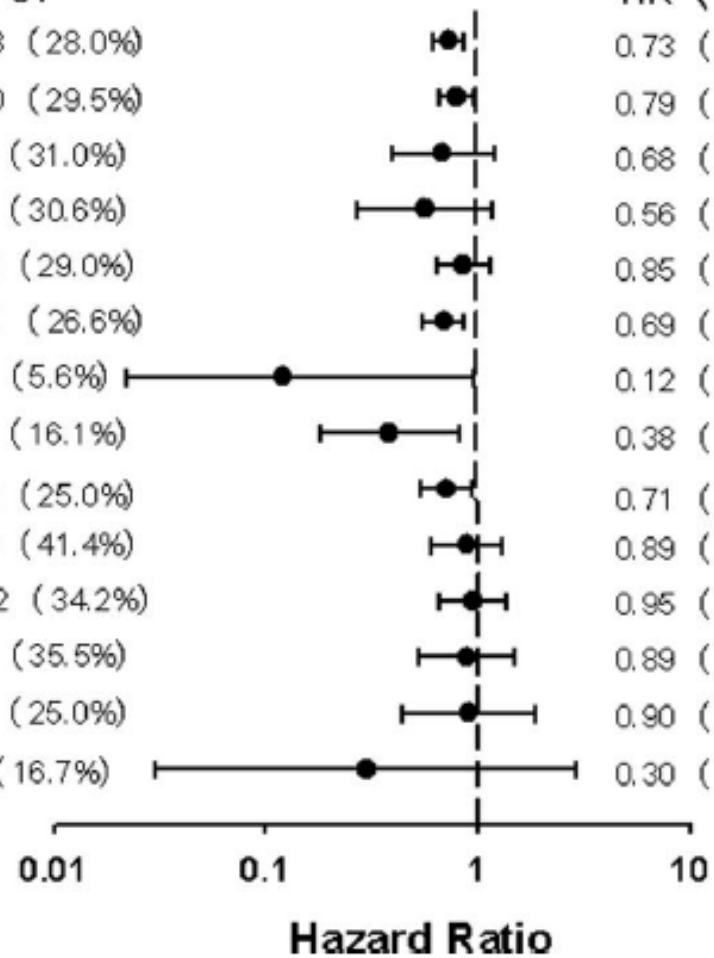
- Multicenter, retrospective, propensity matched
- 1,223 PS-matched pairs w/ **culture-positive septic shock**
  - Approx. 30% *E. coli*, ***8% P. aeruginosa***
- Primary outcome: 28-day mortality



Kumar A et al. Crit Care Med 2010;38(8):1773-1785

Definitive combination therapy: A large retrospective study

	# deaths/total (%) MT	# deaths/total (%) CT	HR (95% CI)	p value
β-lactams	339/930 (36.5%)	260/928 (28.0%)	0.73 (0.62-0.86)	.0002
penicillins	142/391 (36.3%)	118/400 (29.5%)	0.79 (0.62-1.00)	.05
penicillin/ampicillin	27/62 (43.6%)	22/71 (31.0%)	0.68 (0.39-1.20)	.19
anti-staph penicillin	19/40 (47.5%)	11/36 (30.6%)	0.56 (0.27-1.18)	.13
β-lactam/inhibitor	96/289 (33.2%)	85/293 (29.0%)	0.85 (0.64-1.14)	.28
cephalosporins	196/538 (38.6%)	139/511 (26.6%)	0.69 (0.55-0.85)	.0007
1st gen ceph	8/21 (28.1%)	1/18 (5.6%)	0.12 (0.02-0.99)	.049
2nd gen ceph	23/60 (38.3%)	10/62 (16.1%)	0.38 (0.18-0.81)	.01
non-Ps 3rd gen ceph	113/339 (33.3%)	83/332 (25.0%)	0.71 (0.54-0.94)	.02
anti-Ps 3rd/4th gen ceph	53/119 (44.5%)	48/116 (41.4%)	0.89 (0.60-1.31)	.54
carbapenems	56/154 (36.4%)	52/152 (34.2%)	0.95 (0.65-1.38)	.77
vancomycin	32/82 (39.0%)	27/76 (35.5%)	0.89 (0.53-1.49)	.66
fluoroquinolones	14/50 (28.0%)	15/60 (25.0%)	0.90 (0.44-1.87)	.79
macrolide/clindamycin	3/6 (50.0%)	1/6 (16.7%)	0.30 (0.03-2.89)	.30



Kumar A et al. Crit Care Med 2010;38(8):1773-1785

Definitive combination therapy: recent meta-analysis

- Broad-spectrum beta-lactam vs.
  beta-lactam + **aminoglycoside**

- **All-cause mortality:** RR 0.97 (95% CI 0.73-1.30)
- **Clinical failure:** RR 1.11 (95% CI 0.95-1.29)

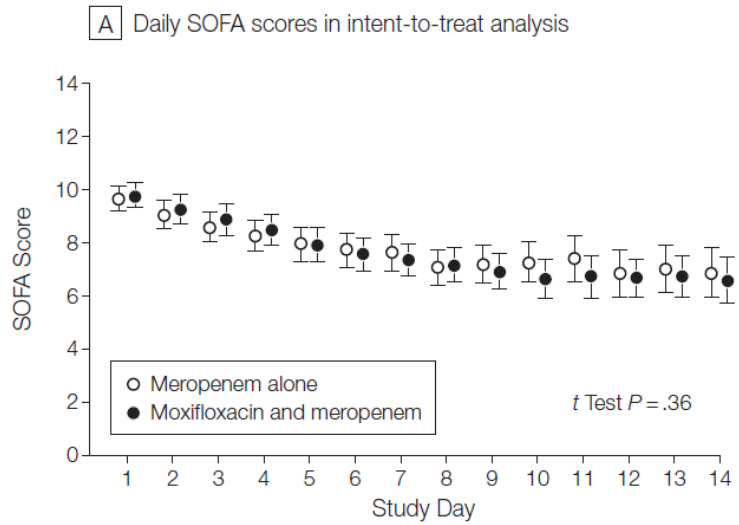
- **Nephrotoxicity:** RR 0.30 (95% CI 0.23-0.39)

Paul M et al. Cochrane Database Syst Rev 2014:Cd003344

Definitive combination therapy: RCT

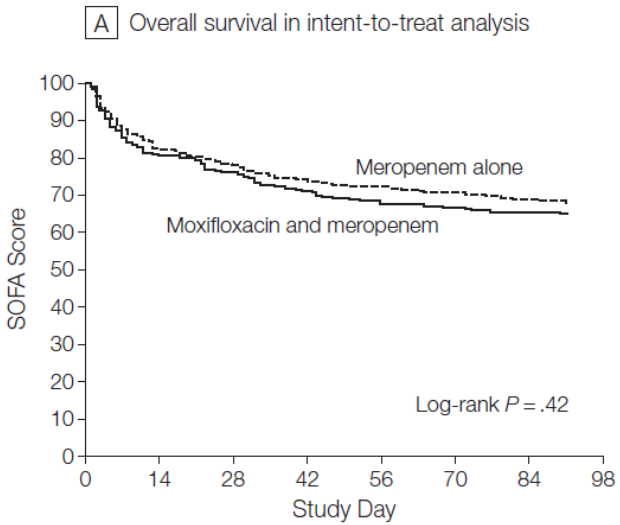
- RCT, open-label, 44 ICUs in Germany (2007-2010)
- 551 pts. w/ **severe sepsis or septic shock**
- Meropenem vs. **meropenem + moxifloxacin** (7-14 d)
- Primary outcome: daily SOFA score

Figure 2. Daily Sequential Organ Failure Assessment (SOFA) Scores



No. of evaluable patients							
Meropenem alone	249	212	167	137	124	103	89
Moxifloxacin and meropenem	255	209	179	153	125	95	81

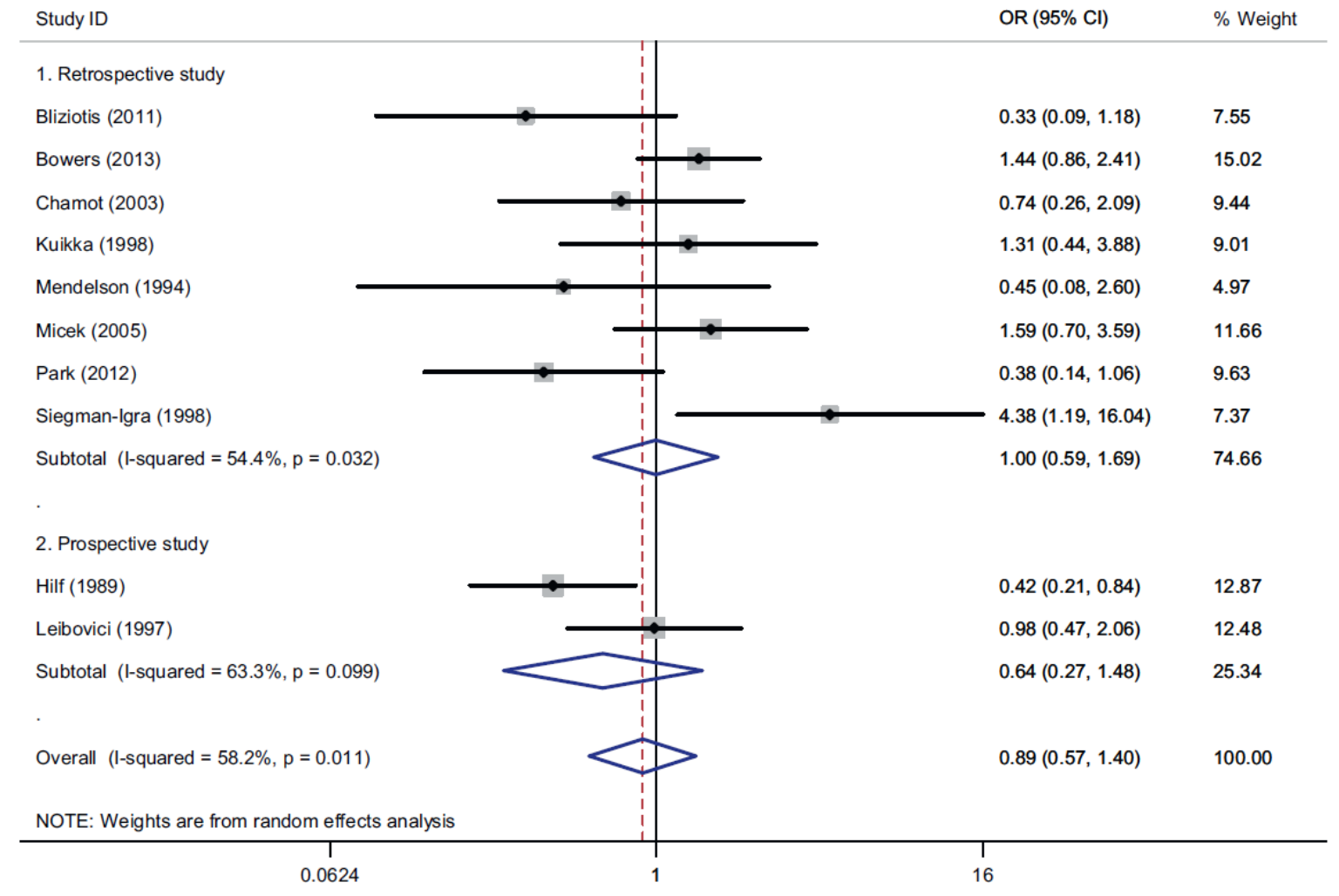
Figure 3. Overall Survival



No. of patients at risk							
Meropenem alone	273	222	211	193	188	184	179
Moxifloxacin and meropenem	276	224	210	193	186	180	177

Brunkhorst FM et al. JAMA 2012;307(22):2390-2399

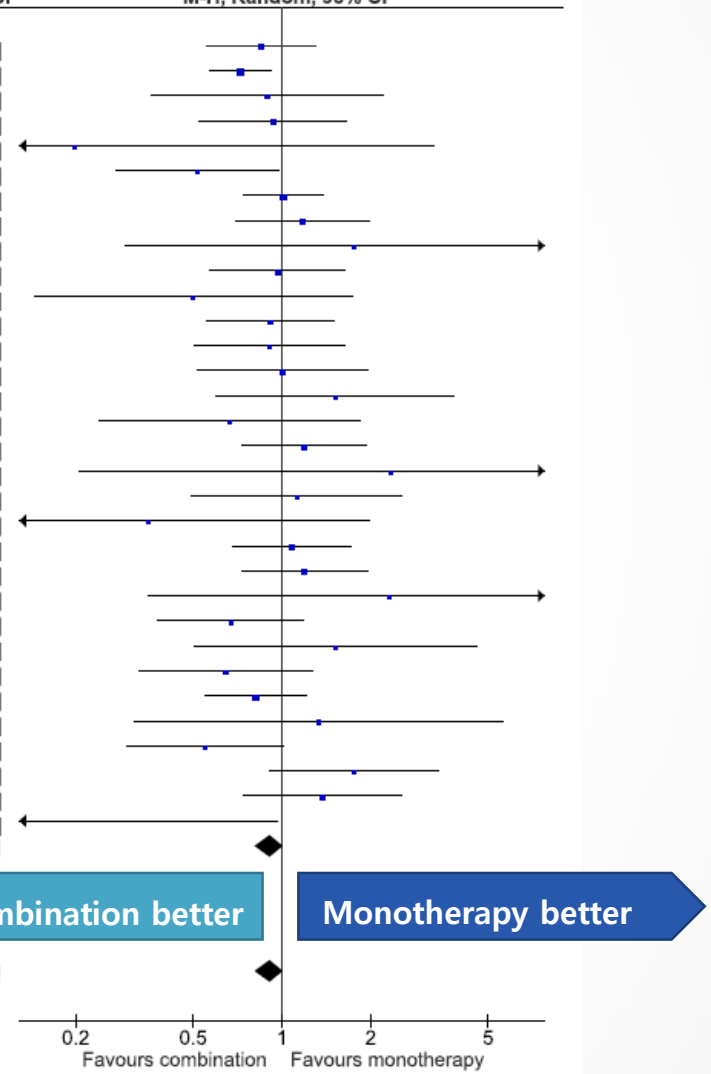
Definitive combination therapy: meta-analysis (*P. aeruginosa*)



Hu et al. Int J Antimicrob Agent 2013;42:492-496

Definitive combination therapy: CRGNB

Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Retrospective						
Aydemir et al. 2013	13	21	16	22	5.9%	0.85 [0.56, 1.30]
Batirel et al 2014	112	214	26	36	14.1%	0.72 [0.57, 0.92]
Capone et al 2013	12	37	4	11	1.4%	0.89 [0.36, 2.21]
Chuang et al 2014	7	15	52	104	3.4%	0.93 [0.53, 1.66]
Daikos et al. 2009	0	8	4	15	0.2%	0.20 [0.01, 3.27]
Daikos et al. 2014	11	39	12	22	2.9%	0.52 [0.28, 0.97]
Durante-Mangoni et al 2013	45	104	45	105	9.7%	1.01 [0.74, 1.38]
Falagas et al 2009	78	218	11	36	4.1%	1.17 [0.69, 1.98]
Falagas et al. 2008	7	16	1	4	0.4%	1.75 [0.29, 10.44]
Garnacho-Montero et al 2013	14	29	14	28	4.0%	0.97 [0.57, 1.64]
Hernadez-Torres et al. 2011	5	20	2	4	0.8%	0.50 [0.14, 1.73]
Jang et al 2009	11	19	14	22	4.5%	0.91 [0.55, 1.50]
Kontopidou et al. 2013	13	31	12	26	3.3%	0.91 [0.51, 1.63]
Ku et al.2012	7	19	26	71	2.6%	1.01 [0.52, 1.95]
Lim et al 2011	5	11	6	20	1.4%	1.52 [0.60, 3.84]
Lopez-Cortes et al 2014	4	23	12	46	1.2%	0.67 [0.24, 1.84]
Mouloudi et al. 2010	11	18	18	35	4.6%	1.19 [0.73, 1.94]
Navarro et al. 2012	10	17	0	1	0.2%	2.33 [0.21, 26.56]
Ozvatan et al. 2015	50	89	3	6	1.8%	1.12 [0.49, 2.55]
Papadimitriou et al. 2014	3	17	1	2	0.4%	0.35 [0.06, 1.98]
Parchem et al. 2016	19	41	21	49	5.1%	1.08 [0.68, 1.72]
Petrosillo et al 2014	35	105	17	61	4.6%	1.20 [0.74, 1.94]
Pintado et al 2008	15	52	1	8	0.3%	2.31 [0.35, 15.16]
Porwal et al 2014	13	29	8	12	3.5%	0.67 [0.38, 1.19]
Samonis et al. 2014	4	7	3	8	1.0%	1.52 [0.51, 4.58]
Simsek et al 2012	10	31	10	20	2.6%	0.65 [0.33, 1.26]
Sirijatuphat et al 2014	22	47	27	47	6.7%	0.81 [0.55, 1.21]
Souli et al 2008	8	12	1	2	0.6%	1.33 [0.32, 5.64]
Tumbarello et al 2012	14	51	11	22	3.1%	0.55 [0.30, 1.01]
Vardakas et al. 2014	26	37	6	15	2.7%	1.76 [0.91, 3.38]
Yilmaz et al 2015	30	53	7	17	3.0%	1.37 [0.74, 2.54]
Zarkotou et al. 2011	0	14	4	7	0.2%	0.06 [0.00, 0.97]
Subtotal (95% CI)		**1444**		**884**	**100.0%**	**0.91 [0.82, 1.02]**
Total events	614		395			
Heterogeneity: Tau² = 0.01; Chi² = 33.68, df = 31 (P = 0.34); I² = 8%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Total (95% CI)		**1444**		**884**	**100.0%**	**0.91 [0.82, 1.02]**
Total events	614		395			
Heterogeneity: Tau² = 0.01; Chi² = 33.68, df = 31 (P = 0.34); I² = 8%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Not applicable						

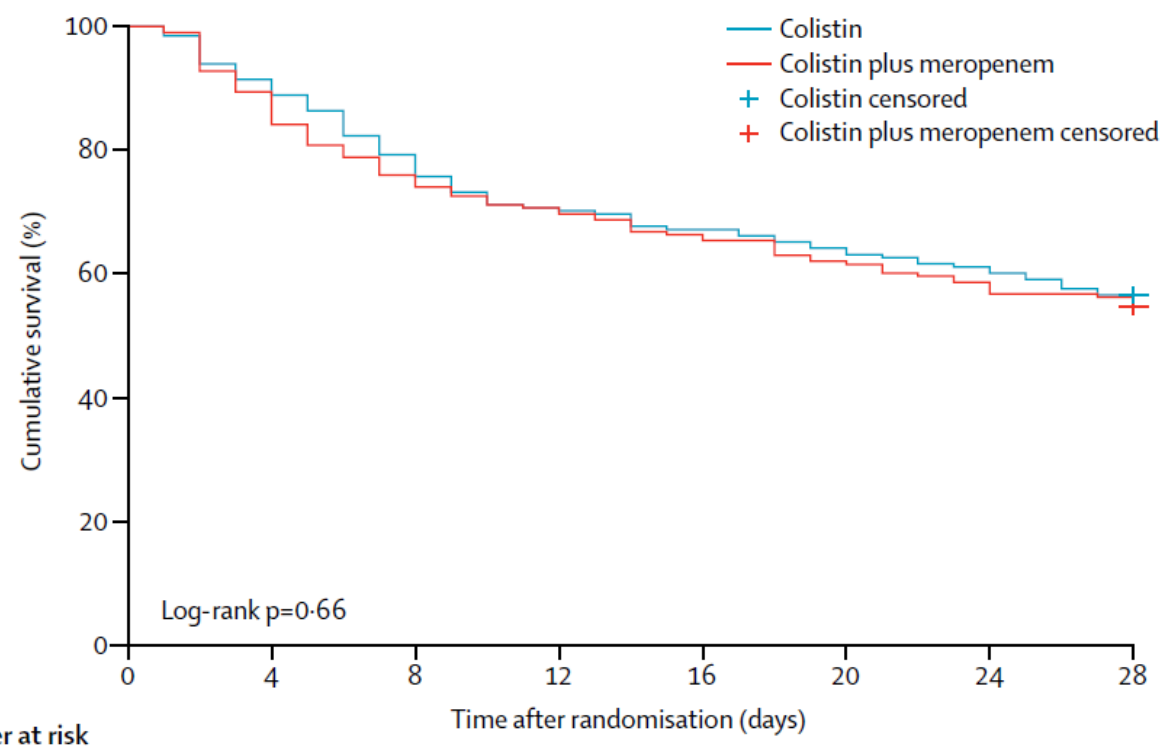


Vardakas KZ et al. Int J Antimicrob Agent. 2018;51:535-547

Definitive combination therapy: CRGNB

- RCT (Israel, Greece, Italy)
- 406 pts w/ BSI, VAP/HAP, UTI due to carbapenem-NS GNB
- Colistin (w/ loading) vs. **colistin + meropenem** (prolonged)

- Pneumonia or bacteremia: 87%
- *A. baumannii* 77%



Number at risk								
Colistin	197	175	149	138	132	124	118	111
Colistin–meropenem	207	174	153	144	136	127	118	116

Paul M et al. Lancet Infect Dis 2018;18:391-400

Definitive combination therapy: *S. aureus*

1. Gentamicin should not be used for treatment of NVE caused by MSSA or MRSA (*Class III; Level of Evidence B*).

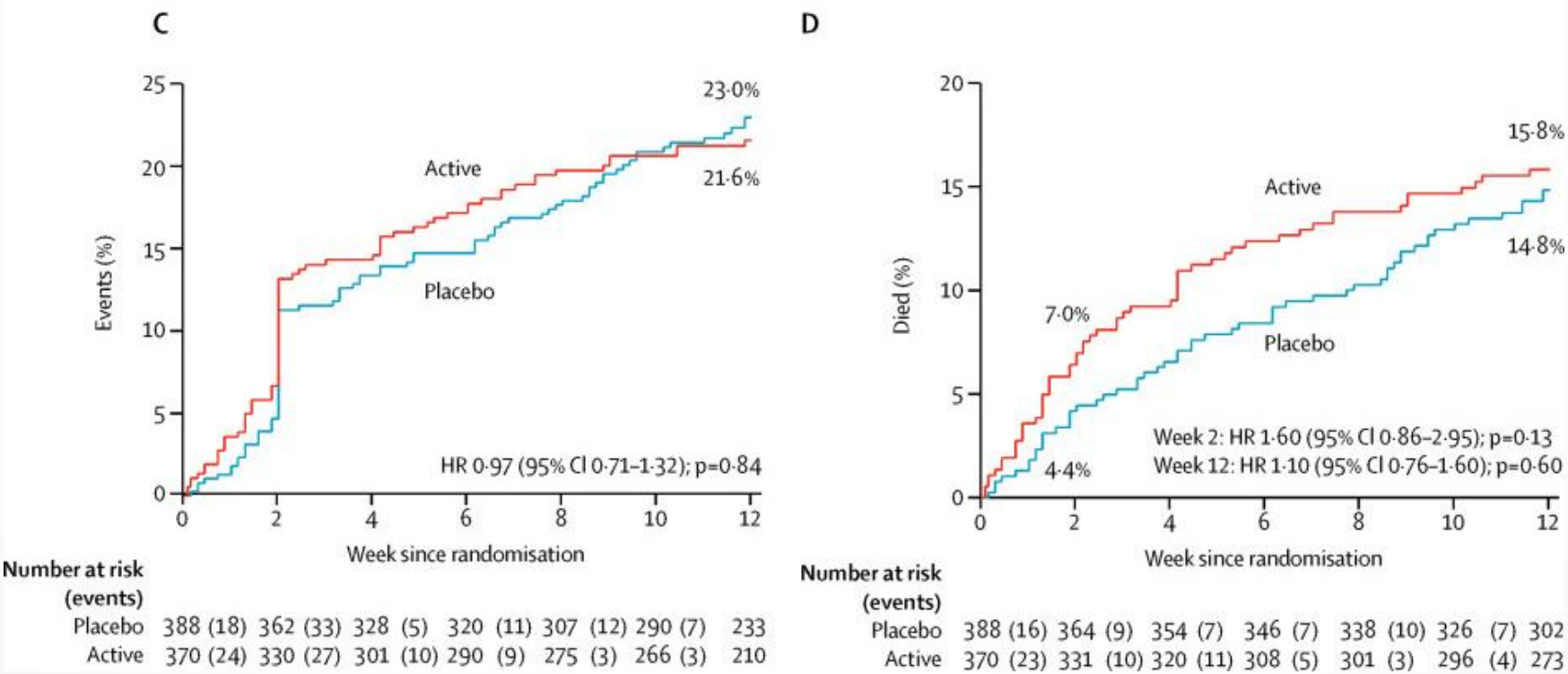
2015 AHA Guidelines for Infective Endocarditis

21. Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (A-II).
22. Addition of rifampin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (A-I).

2011 IDSA Guidelines for MRSA Infections

Definitive combination therapy: *S. aureus*

- RCT, double-blind, placebo-controlled (UK)
- 758 pts w/ *S. aureus* BSI
- Adjunctive **rifampin (active)** vs. placebo



Thwaites GE et al. Lancet. 2018;391(10121):668-678

Summary

1 hr goal for the initiation of antibiotics

- Biologically plausible and supported by many observational studies
- Evidence for a fixed 1 hr time goal is weaker for pts without shock
- Concerns regarding potential unwanted consequences have been raised (especially associated w/ regulatory mandates)
- How to implement will be a critical issue

Definitive combination therapy

- More recent studies and a RCT suggest the lack of benefit
- Some well-defined indications exist (e.g., enterococci, prosthesis)
- Some indications warrant further studies
  (e.g., carbapenem-resistant gram-negative, *P. aeruginosa*)