CRE: Treatment Challenges

Michael Satlin, MD, MS
Instructor in Medicine
Transplantation-Oncology Infectious Diseases Program
Division of Infectious Diseases
Weill Cornell Medical College
June 22, 2013

Faculty Disclosure

I have no potential conflicts of interest to disclose

Clinical Case

- 51 year-old woman with relapsed lymphoma that responded to a salvage chemotherapeutic regimen
- After receiving total body irradiation and cyclophosphamide, she had an allogeneic bone marrow transplant from an unrelated donor
- 1 day before infusion of her donor stem cells (Day -1): she had a fever → started on piperacillin-tazobactam (as per protocol of fever and neutropenia)
  - Cultures from that day were negative and fever resolved
- Day +9: She started coughing up blood, became short of breath and required supplemental oxygen in the setting of a very low platelet count. No new fevers.

Clinical Case: Hospital course

- Chest x-ray showed bilateral pulmonary infiltrates.
- Had a bronchoscopy and bronchoalveolar lavage (BAL) that showed blood in right middle and lower lobes. Admitted to the ICU.
- Thought to most likely represent diffuse alveolar hemorrhage (DAH).
- Vancomycin added to cover MRSA and voriconazole added to cover an invasive mould infection. Pip-tazo continued. Methylprednisolone added for DAH.
- Symptoms improved. Bacterial and fungal cultures from BAL were negative. Remained neutropenic.

Clinical Case: A turn for the worse

- Day + 16: 9 am: Reported increasing shortness of breath.
- 11 am: Developed acute respiratory failure requiring intubation and mechanical ventilation. No fever.
- Blood cultures collected at noon. Pip-tazo discontinued, meropenem started at 1 pm.
- 6 pm: Started on vasopressors for hypotension. Fever to 39.
- Midnight: Blood cultures flagged positive for gram-negative rods
- 2 am (next day): given 1 dose of tobramycin. Multi-organ system failure progresses.
- 9 am: Infectious Diseases recommends polymyxin B. Gets at 11 am.
- Noon: Becomes asystolic and pronounced dead.

Clinical Case: Microbiology results

- 10 hours after death:

Source / Body Site		Broviac
Blood Bottle(s) Stain Report		Micro Results Date: August 14, 2011 Time: 23:24 Aerobic and Anaerobic bottle:
Final Report		Micro Results Date: August 16, 2011 Time: 09:06 **CONTACT PRECAUTIONS**
Preliminary Report	H	Micro Results Date: August 15, 2011 Time: 22:58 Klebsiella pneumoniae Susceptibility testing results to follow
Organism	H	Klebsiella pneumoniae
Method	H	Minimum Inhibitory Concentration
Ampicillin		>=32 R
Aztreonam		>=64 R
Cefepime		>=64 R
Ceftazidime		>=64 R
Ceftriaxone		>=64 R
Gentamicin		<=1 S
Levofloxacin		<=0.12 S
Meropenem		>=16 R
Tigecycline		1 S
Trimeth/Sulfamethoxazole		S

- Isolate resistant to tobramycin (MIC ≥16 on Vitek2)
- Etest set up for polymyxin B that evening. The morning after her death, an MIC of 0.5 reported.

Objectives: Treatment Challenges

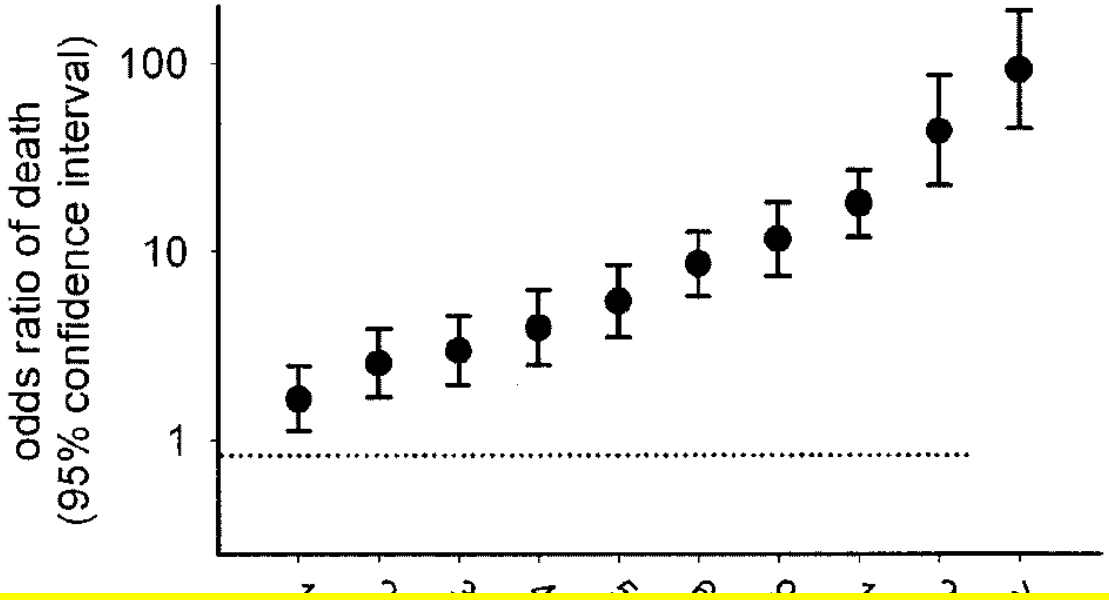
- 1st problem: We don't know who is infected with CRE on presentation.
  - Delay in appropriate therapy = increased mortality
- 2nd problem: What do we do once we know or highly suspect a patient is infected with CRE?
  - Outline our current antimicrobial armamentarium vs. CRE
    - Discuss the severe limitations of each of these options
  - Combination therapy
- Alternative strategies:
  - Prolonged infusion of carbapenems
  - Inhaled antimicrobials
  - New antimicrobial agents

Poor Outcomes with CRE Infections

- Patients with CRE infections consistently have high mortality rates (40-50%)[1,2]
- These high mortality rates far exceed those for CSE infections, even after adjusting for comorbidities and severity of illness[3,4]
- An important factor in these high mortality rates may be that it often takes 2-4 days to identify CRE from clinical specimens.
  - So, unless patients are started on empirical polymyxin, they have long delays until they receive active therapy

[1]Patel G, et al. Infect Control Hosp Epidemiol 2008. [2]Tumbarello M, et al. Clin Infect Dis 2012.
[3]Gasink LB, et al. Infect Control Hosp Epidemiol 2009. [4]Ben-David D, et al. Clin Microbiol Infect 2012.

Patients with septic shock: The importance of timely, appropriate therapy



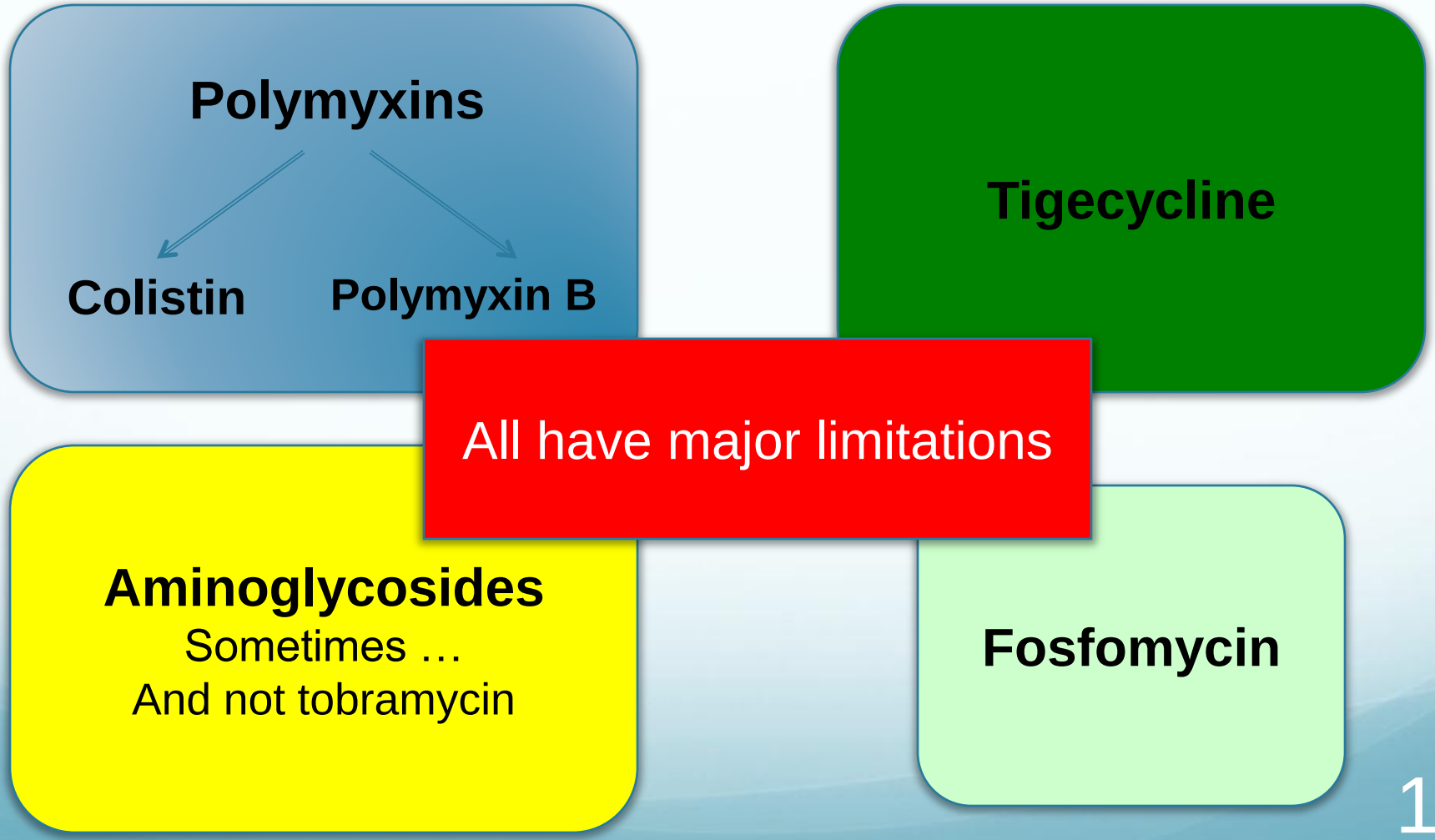
Two things are needed to combat this problem:

1) Predictive models that can identify who is at high risk for CRE infection (and should get empirical CRE-active tx)
2) Rapid molecular diagnostics that can be done from blood culture bottles or directly from clinical specimens

Kumar A, et al. Crit Care Med 2006.

The antimicrobial armamentarium

- What agents are left that are active vs. CRE?



Problems with Polymyxins

- 1) Toxicities
  - Nephrotoxicity: 40-60% with either colistin[1] or polymyxin B[2]
  - Neurotoxicity[3]: paresthesias, visual alterations, ataxia, neuromuscular blockade; less common
- 2) Poor PK/PD data
  - Example: we don't know how to dose in renal failure[4]
  - Very few labs that will check levels
- 3) Unreliable susceptibility testing by Etest[5]
- 4) Emergence of resistance on therapy[6]

[1]Pogue JM, et al. Clin Infect Dis. [2]Kubin CJ, et al. J Infect 2012. [3]Lim LM, et al. Pharmacotherapy 2010. [4]Zavascki AP, et al. Clin Infect Dis 2008. [5]Tan TY, et al. Clin Microbiol Infect. 2007. [6]Lee J, et al. J Clin Microbiol 2009.

Comparison of beta-lactams to polymyxin (and gentamicin) for *Pseudomonas aeruginosa* bacteremia

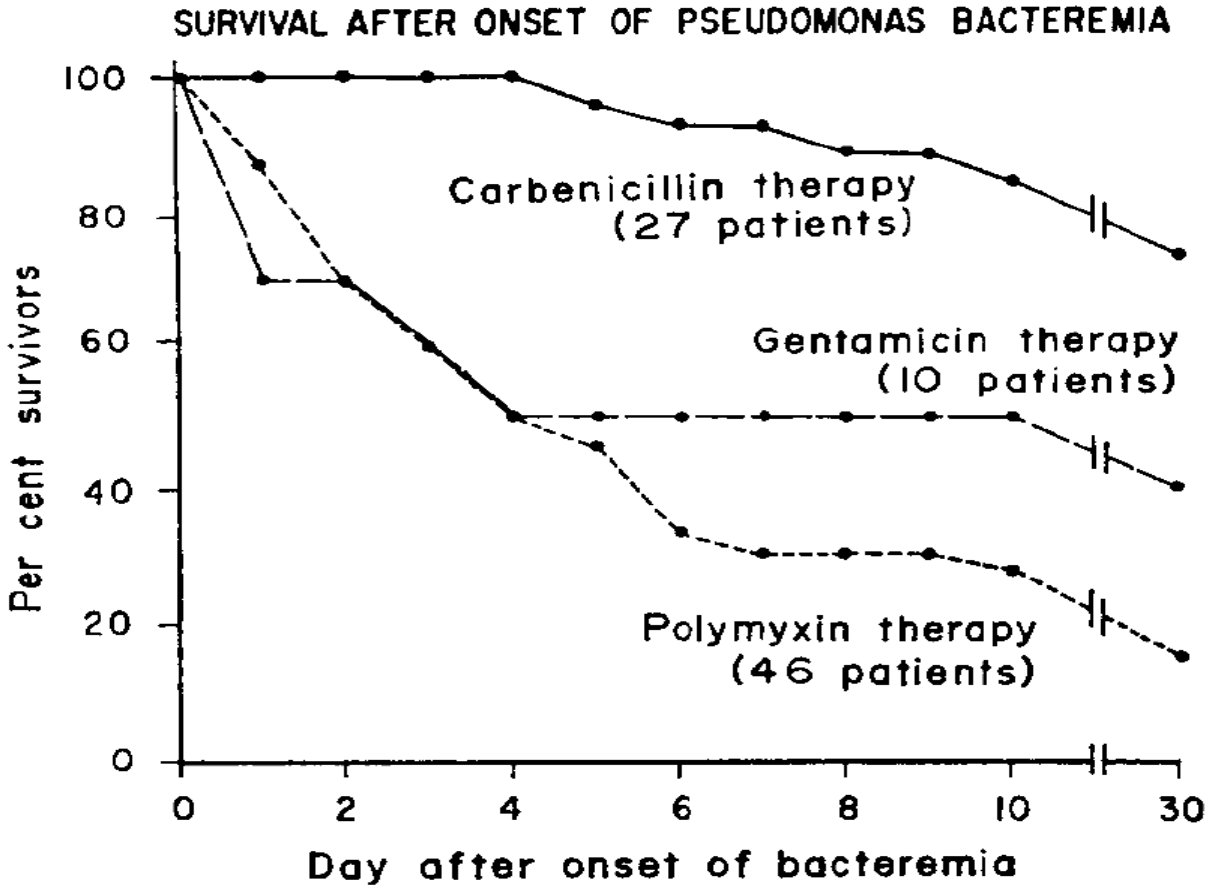
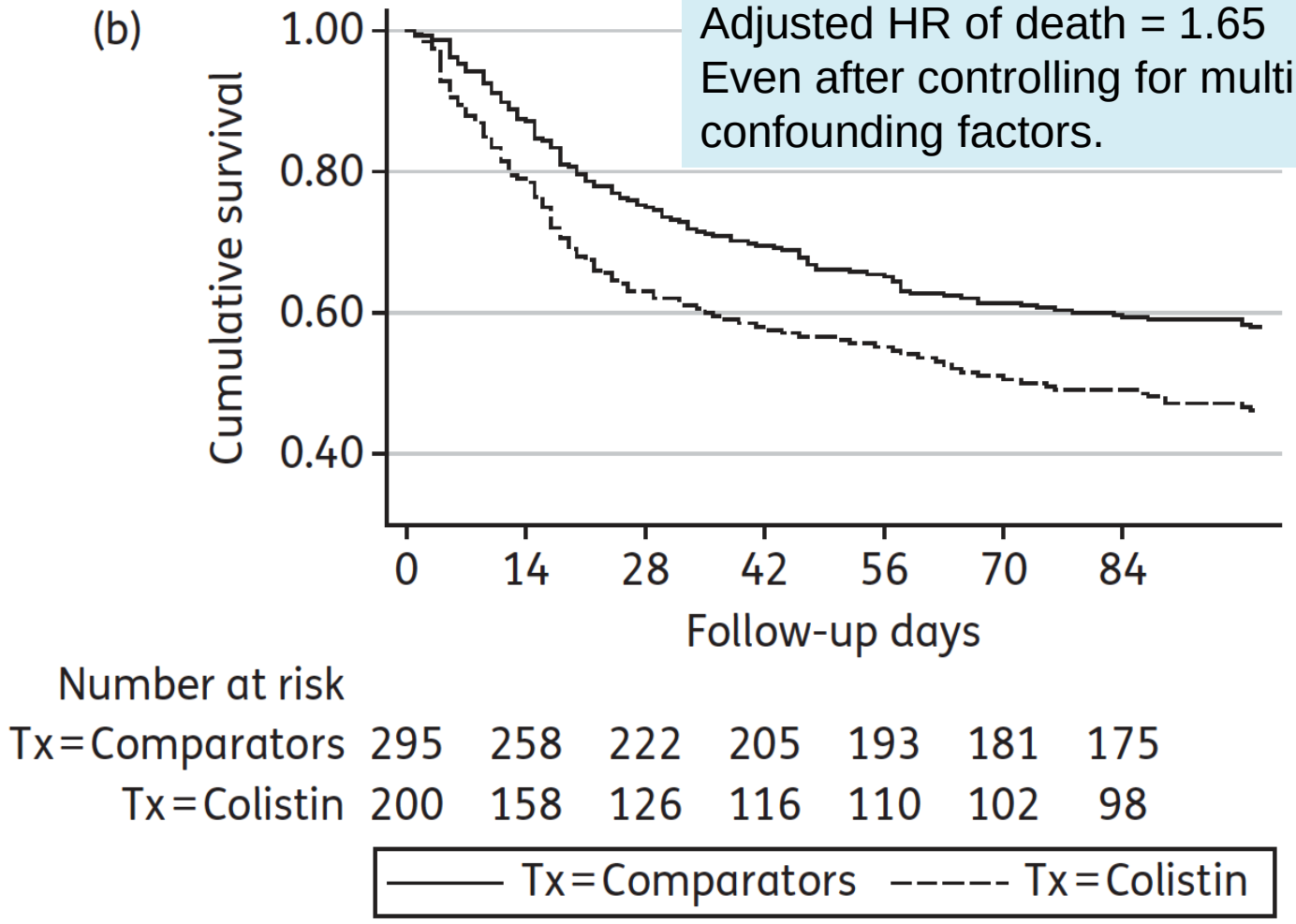


Fig. 5. Effect of antibiotic therapy on survival after onset of Pseudomonas *septicemia in cancer patients.*

Bodey GP, et al. Eur J Cancer 1973.

What about recent studies?



Adjusted HR of death = 1.65
Even after controlling for multiple confounding factors.

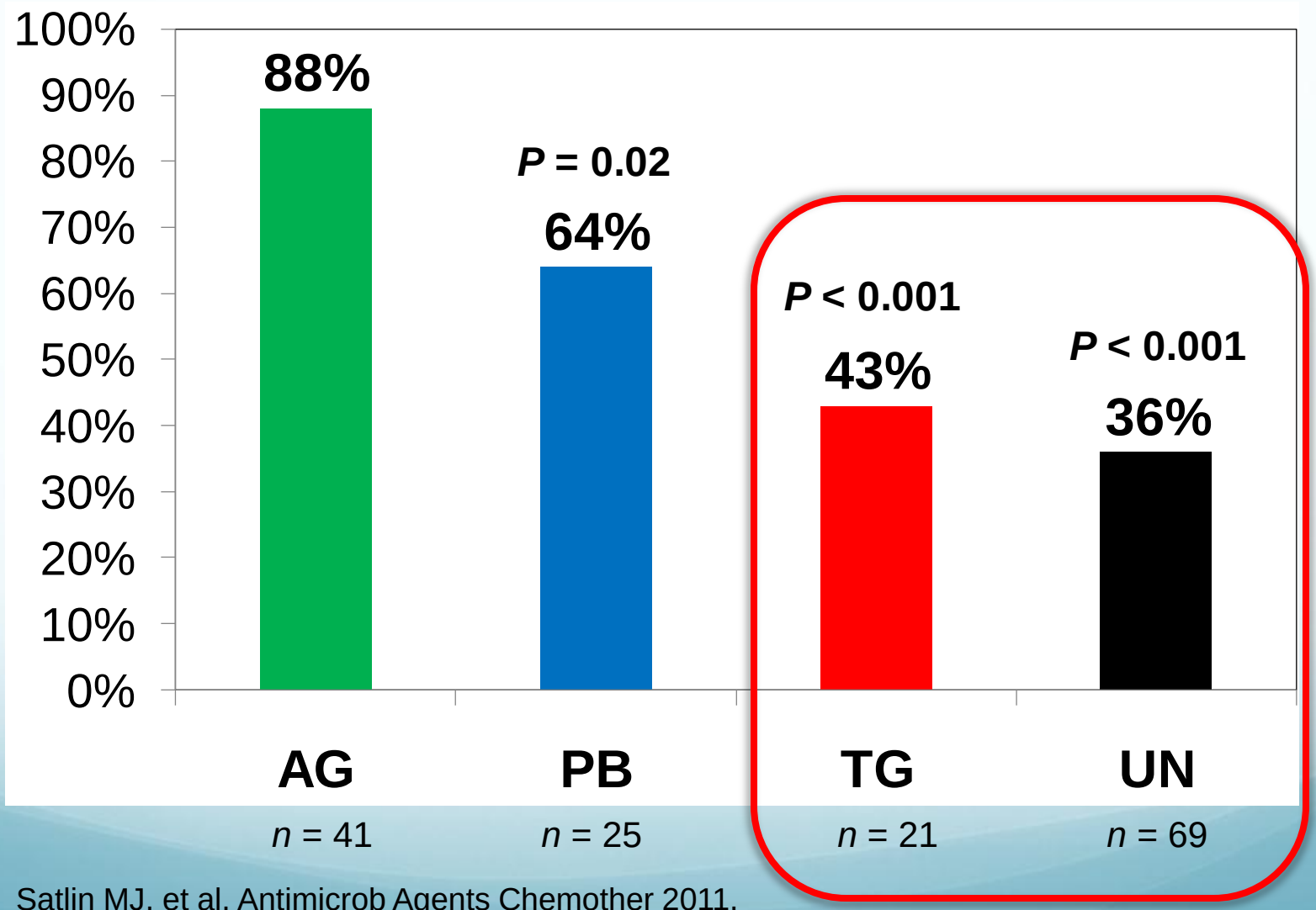
Paul M, et al. J Antimicrob Chemother 2010.

Troubles with Tigecycline

- 1) Not active vs. *Pseudomonas aeruginosa*
- 2) Bacteriostatic, not bactericidal
- 3) Low bloodstream and urine levels
  - Limits their use in bacteremias and UTIs
  - Only approved for complicated skin-soft tissue infection, complicated intraabdominal infection, and community-acquired pneumonia

MacGowan AP. J Antimicrob Chemother 2008.

Microbiologic Clearance Rates of CRKP Bacteriuria, by Cohort (%)



Satlin MJ, et al. Antimicrob Agents Chemother 2011.

RCTs comparing tigecycline to comparator agents since obtained FDA approval in 2005

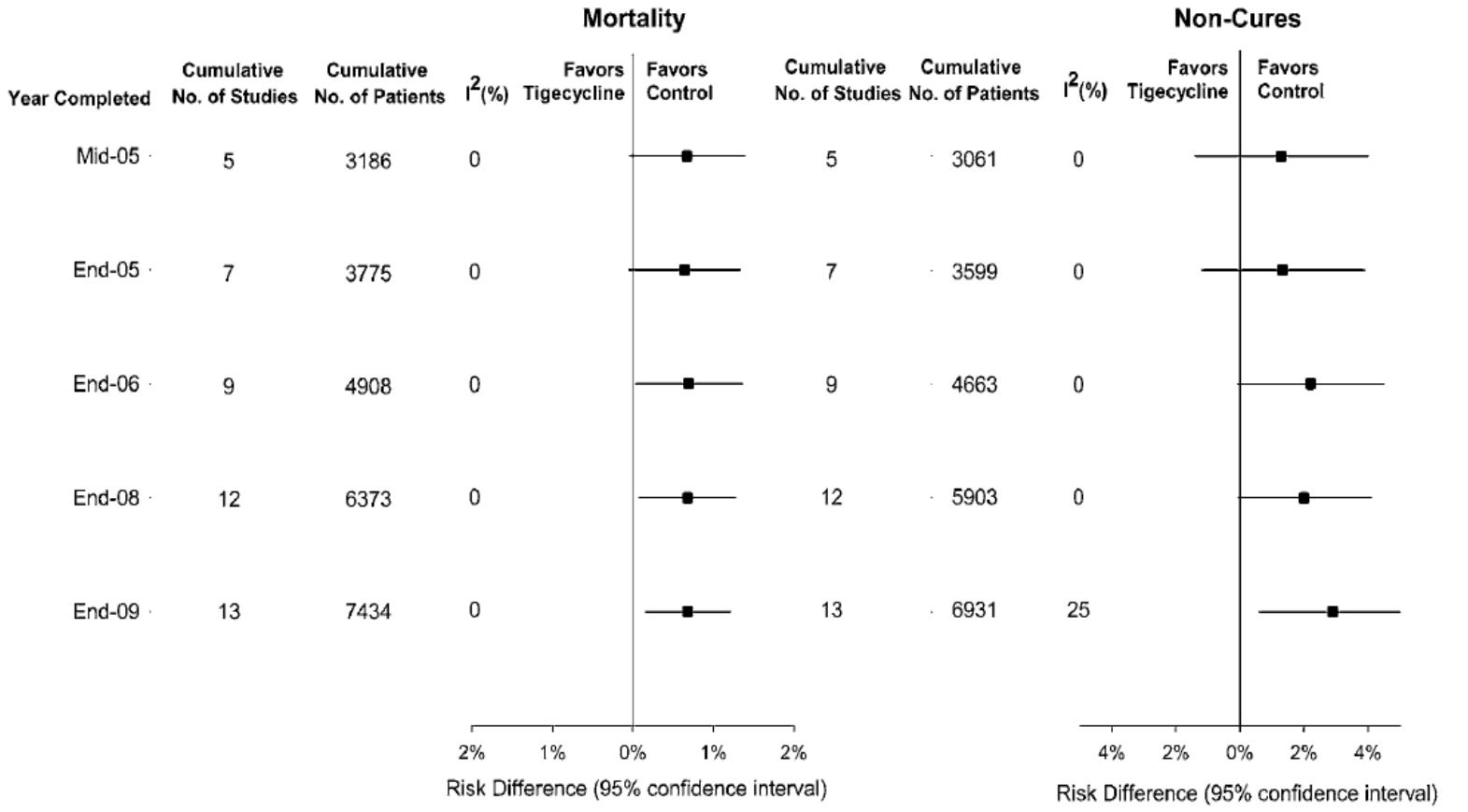


Figure 5. Cumulative mortality and cumulative noncure rate analyses for the tigecycline noninferiority trials identified in this meta-analysis from mid-2005 (the date when tigecycline received FDA approval as monotherapy for complicated intra-abdominal and skin infections) through the end of 2009 (the date by which the last study in this meta-analysis was completed).

Prasad P, et al. Clin Infect Dis 2012.

Are aminoglycosides active vs. CRE?

- Tobramycin almost never active vs. KPC- or MBL-producers[1,2]

Ref	Mechanism	Geographic location	Isolates (N)	Gent (%S)	Ami (%S)
1	KPC	New York	96	61	45
2	KPC	New York	99	59	14
3	KPC	Italy	125	94	0
4	KPC	Israel	88	93	5
5	KPC, VIM, IMP	SENTRY (N.Am, S.Am, Europe)	104	50	73
6	KPC, VIM, IMP	Crete	181	13	7
7	NDM	UK, India, Pakistan	107	3	0
8	NDM	Pakistan	64	22	20

[1]Bratu S, et al. J Antimicrob Chemother 2005. [2]Patel G, et al. Infect Control Hosp Epidemiol 2008. [3]Tumbarello M, et al. Clin Infect Dis 2012. [4]Hussein K, et al. Infect Control Hosp Epidemiol 2009. [5]Castanheira M, et al. Antimicrob Agents Chemother 2008. [6]Neonakis IK, et al. Chemotherapy 2010. [7]Kumarasamy KK, et al. Lancet Infect Dis 2010. [8]Perry J, et al. J Antimicrob Chemother 2011.

Even when they are active, aminoglycosides are suboptimal

- 1) Toxicities
  - Nephrotoxicity: 10-20% of patients have their kidney function reduced by at least 50%[1]
  - Otovestibular toxicity: Less common but can be irreversible[2]
- 2) Poor penetration into lungs[4], abscesses[5]
- 3) Clinical efficacy?

[1]Moore RD, et al. Ann Intern Med 1984. [2]Guthrie OW. Toxicology 2008.
[3]Brun-Buisson C, et al. Am J Respir Crit Care Med 2001. [4]Ristuccia AM, et al. Med Clin North Am 1982.

Aminoglycoside monotherapy for *Pseudomonas aeruginosa*

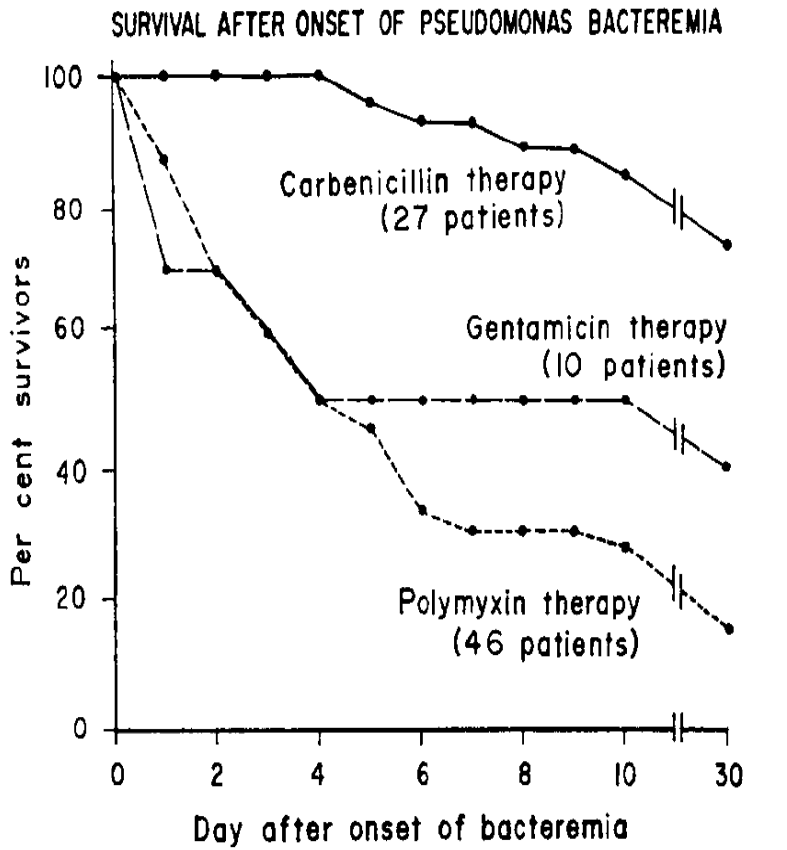


Fig. 5. Effect of antibiotic therapy on survival after onset of Pseudomonas *septicemia in cancer patients.*

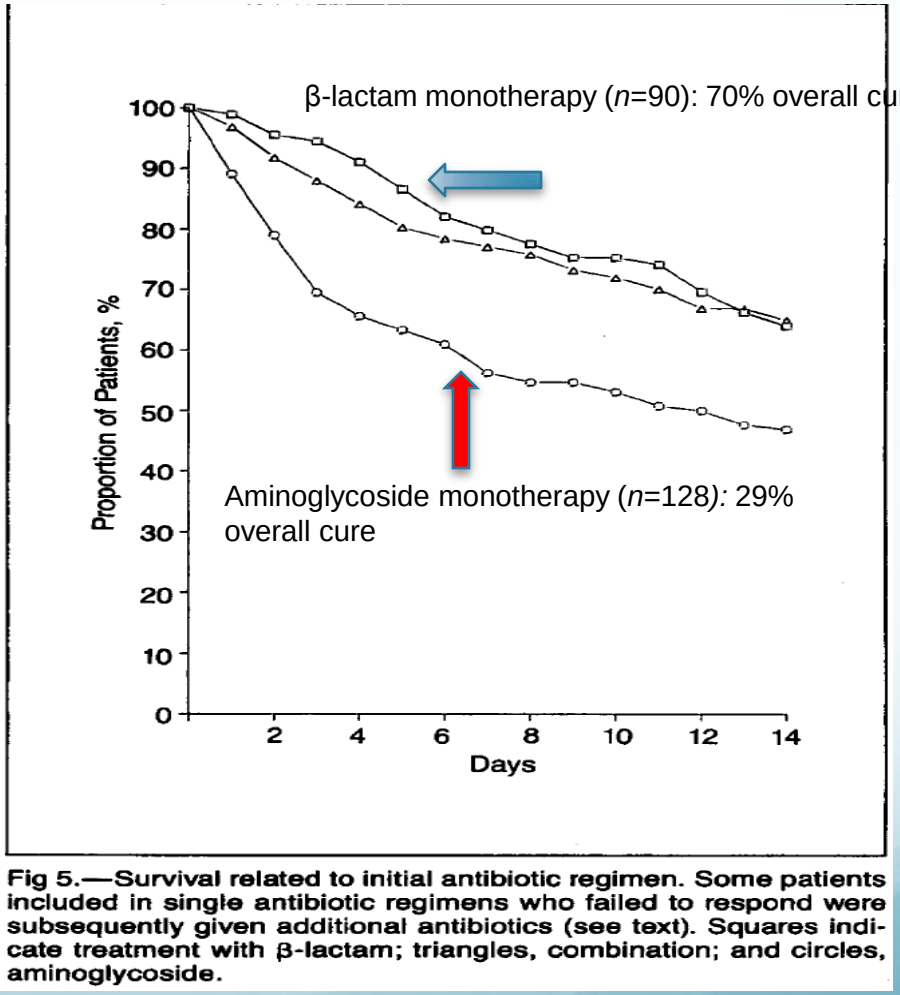
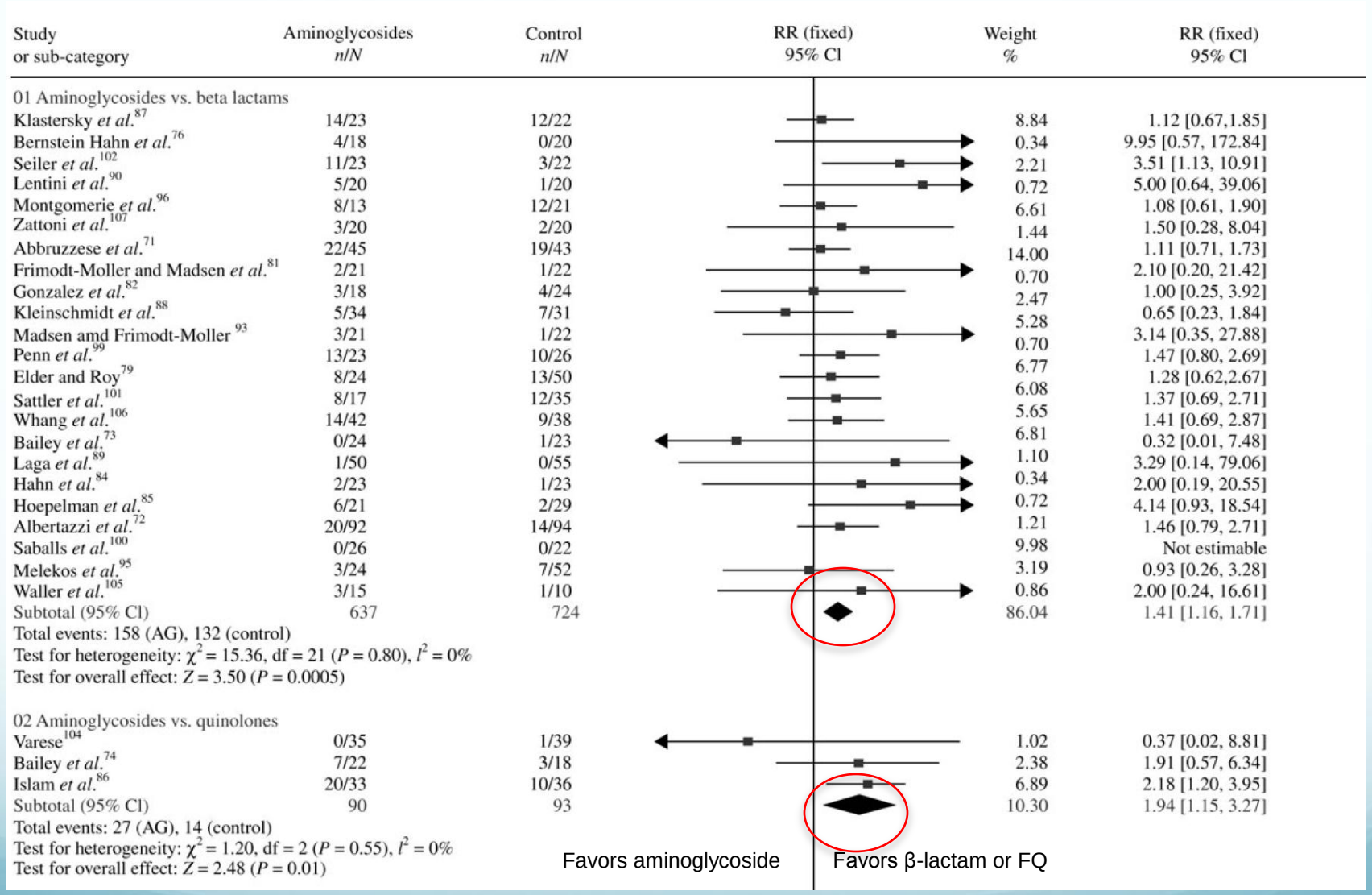


Fig 5.—Survival related to initial antibiotic regimen. Some patients included in single antibiotic regimens who failed to respond were subsequently given additional antibiotics (see text). Squares indicate treatment with β-lactam; triangles, combination; and circles, aminoglycoside.

Bodey GP, et al. Arch Int Med 1985.

Meta-analysis of RCTs of aminoglycosides as monotherapy: Microbiologic failure at the end of treatment



Vidal L, et al. J Antimicrob Chemother 2007.

Fosfomycin

- Seldom-used agent that inhibits peptidoglycan biosynthesis and is FDA-approved for UTIs
- Available as an IV formulation in Europe, only as a sachet in the U.S.
- Susceptibility rates of CRE: 45-93%[1,2]
- Resistance may develop rapidly on therapy[3]
- Study of 13 patients with CRKP UTI who received 3 doses[4]:
  - Only 6/13 had microbiologic cure

[1]Endimiani A, et al. Antimicrob Agents Chemother 2010. [2]Chen S, et al. Antimicrob Agents Chemother 2011.
[3]Karageorgopoulos DE, et al. J Antimicrob Chemother 2012. [4]Neuner EA, et al. Antimicrob Agents Chemother 2012.

Given the limitations of each of these agents individually, what about combination antimicrobial therapy for CRE infections?

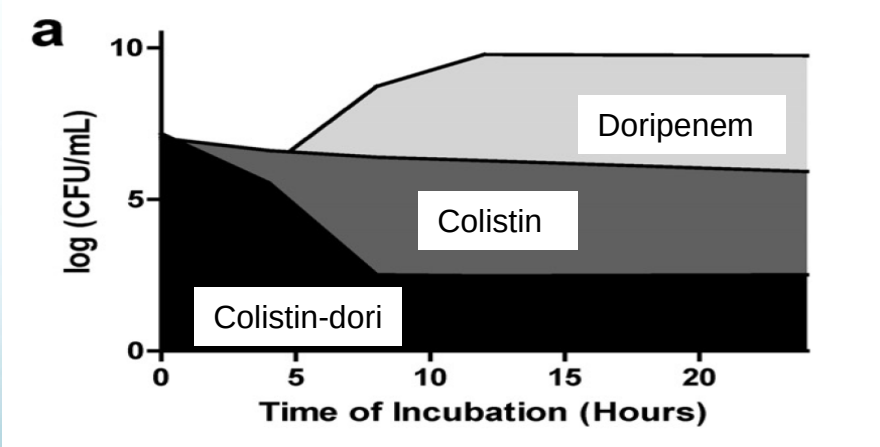
In vitro data

- Polymyxin-based combinations:
  - Polymyxin-rifampin and polymyxin-carbapenem
    - Time-kill assays for 16 KPC-producing *K.pneumoniae*[1]

Imipenem MIC_{50} >32 μg/mL Antibiotic (concentration, mg/L)	Change (mean ± SD) log cfu/mL at 4 h	Change (mean ± SD) log cfu/mL at 24 h	No. with decrease ≥3 log cfu/mL at 24 h
Polymyxin B (0.5 × MIC)	–2.5 ± 1.0	+2.1 ± 0.7	0/16
Polymyxin (0.5 × MIC) + rifampicin (1 μg/mL)	–3.6 ± 1.2	–4.4 ± 1.9	14/16
Polymyxin (0.5 × MIC) + imipenem (4 μg/mL)	–2.6 ± 1.6	–2.0 ± 3.7	10/16

    - 12 KPC-*Kp* isolates with colistin and doripenem MIC_{50} of 8 and 64μg/mL[2]

- Doripenem hydrolyzed at least 2-fold slower than imipenem vs. KPC, IMP and VIM[3]
- *In vitro* model: doripenem suppressed development of colistin resistance[4]



[1]Bratu S, et al. J Antimicrob Chemother 2005. [2]Jernigan MG, et al. Antimicrob Agents Chemother 2012.
[3]Queenan AM, et al. Antimicrob Agents Chemother 2010. [4]Deris ZZ, et al. Antimicrob Agents Chemother 2012.

In vitro data for other combinations

- Polymyxin-tigecycline:
  - *In vitro* synergy not as consistently and thoroughly documented as polymyxin-carbapenem[1,2]
  - Problem of low bloodstream levels of tigecycline
- Polymyxin-aminoglycoside:
  - Not as commonly synergistic as polymyxin-carbapenem[3] and combined nephrotoxicity
- Carbapenem-aminoglycoside
  - Neutropenic murine model: Unclear if any benefit to adding doripenem to amikacin[4]
- Double carbapenem therapy
  - Ertapenem takes one for the team[5]

[1]Pournaras S, et al. Int J Antimicrob Agents 2011. [2]Elemam A, et al. J Clin Microbiol 2010. [3]Jernigan MG, et al. Antimicrob Agents Chemother 2012. [4]Hirsch EB, et al. J Infect Dis 2013. [5]Bulik CC, et al. Antimicrob Agents Chemother 2011.

Clinical data for combination therapy

- 53 patients with KPC-*Kp* bacteremia from Greece[1]:
  - 35 received at least 48h active therapy

TABLE 3. Appropriate antimicrobial treatment for at least 48 h and infection mortality

Treatment for infection	*n* (%)	Infection mortality *n* (%)
Combination schemes	20 (57.1)	0
Tigecycline combined with		
Colistin	9 (26.5)	0
Gentamicin	3 (8.8)	0
Colistin + carbapenem	2 (5.9)	0
Carbapenem	1 (2.9)	0
Colistin + gentamicin	1 (2.9)	0
Amikacin	1 (2.9)	0
Colistin + gentamicin	2 (5.8)	0
Carbapenem + gentamicin	1 (2.9)	0
Monotherapy	15 (42.9)	7 (46.7)
Colistin	7 (20)	4 (66.7)
Tigecycline	5 (14.7)	2 (40)
Gentamicin	2 (5.9)	0
Carbapenem	1 (2.9)	1 (100)
Total	35	7 (20)

- 41 patients with KPC-*Kp* bacteremia from USA[2]:

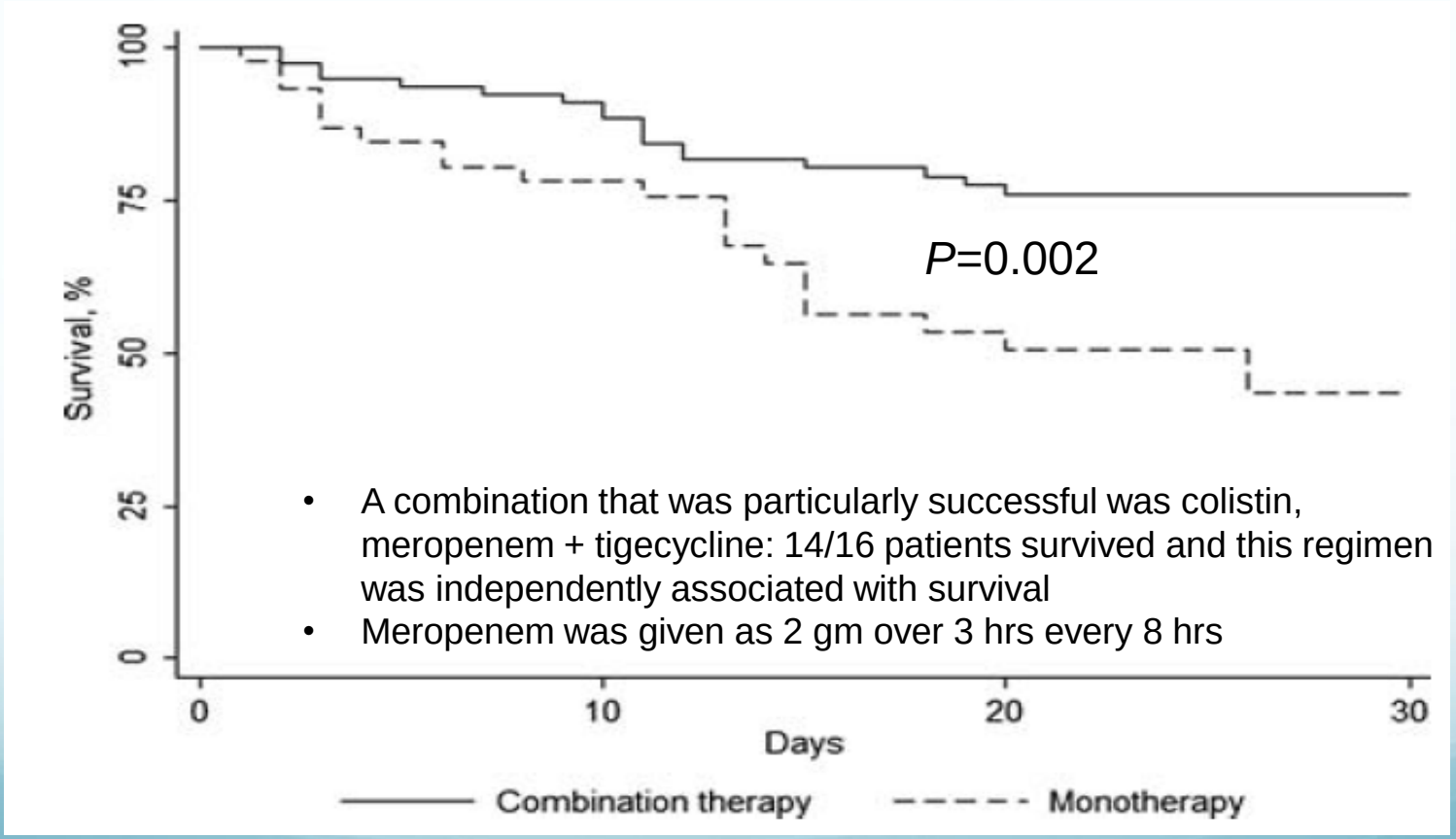
Definitive regimen	28-day mortality
Polymyxin alone	4/7 (57%)
Tigecycline alone	4/5 (80%)
Combination therapy	2/15 (13%)

Combination definitive therapy was independently associated with survival

[1]Zarkotou O, et al. Clin Micro Infect 2011. [2]Qureshi ZA, et al. Antimicrob Agents Chemother 2012.

Clinical data for combination therapy

- Largest observational study of KPC-*Kp* bacteremia (*n*=125). From Italy.



- A combination that was particularly successful was colistin, meropenem + tigecycline: 14/16 patients survived and this regimen was independently associated with survival
- Meropenem was given as 2 gm over 3 hrs every 8 hrs

Tumbarello M, et al. Clin Infect Dis 2012.

Take-home points: Treatment of CRE

- Rapid diagnostics are needed to decrease the time to identification of CRE (time is mortality)
- Our current antimicrobial armamentarium is extremely limited
- *In vitro* and observational clinical data support the use of polymyxin-based combination therapy
- Alternative approaches and new agents are needed (see Part II – Dr. Weinstein)