Antibiotic Combination Therapy:
A Double-Edged Sword?

Megan Luther, Pharm.D.
In Vitro PK/PD Fellow
Providence Veterans Affairs Medical Center
Adjunct Assistant Professor of Pharmacy
University of Rhode Island

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Objectives

- Discuss the history and supportive data for combination therapy in treating various infections.
- Identify the rationale for antibiotic combination therapy as it pertains to outcomes and resistance development.
- Understand the limitations and disadvantages of combination therapy as it relates to adverse events and antagonistic antibacterial activity.

"There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Alexander Fleming

HIV

Highly Active Antiretroviral Therapy (HAART)

- 2 NRTIs +

One of the following:

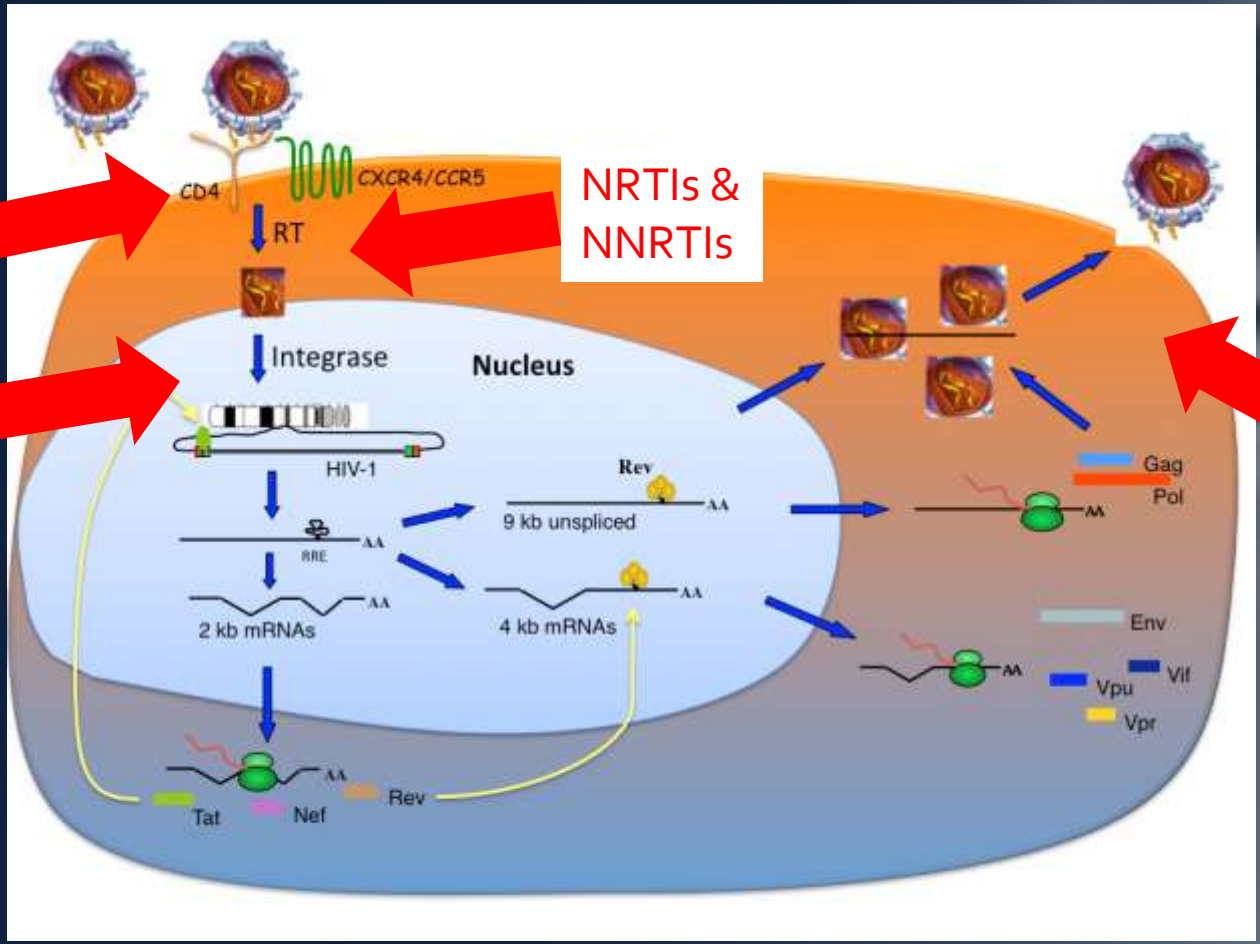
- NNRTI
- PI
- Integrase Strand Transfer Inhibitor (INSTI) (raltegravir)
- CCR5 Antagonist (maraviroc)
- Fusion inhibitor (enfuvirtide)

Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf . [6Feb2013]

Mechanisms of Action

Entry/
Fusion
Inhibitors

INSTIs
(raltegravir)



NRTIs &
NNRTIs

Protease
Inhibitors

Image courtesy of www.intechopen.com

Combination Therapy in HIV

- Effective HAART reduces viral load
- Decreases rates of resistance
- Prevents transmission

Tuberculosis

- Standard treatment with 4 medications
  - Isoniazid
  - Rifampin
  - Ethambutol
  - Pyrazinamide

American Thoracic Society, CDC, and Infectious Disease Society of America. Treatment of Tuberculosis. Am J Respir Crit Care Med. 2003;167:602-62

Mechanisms of Action

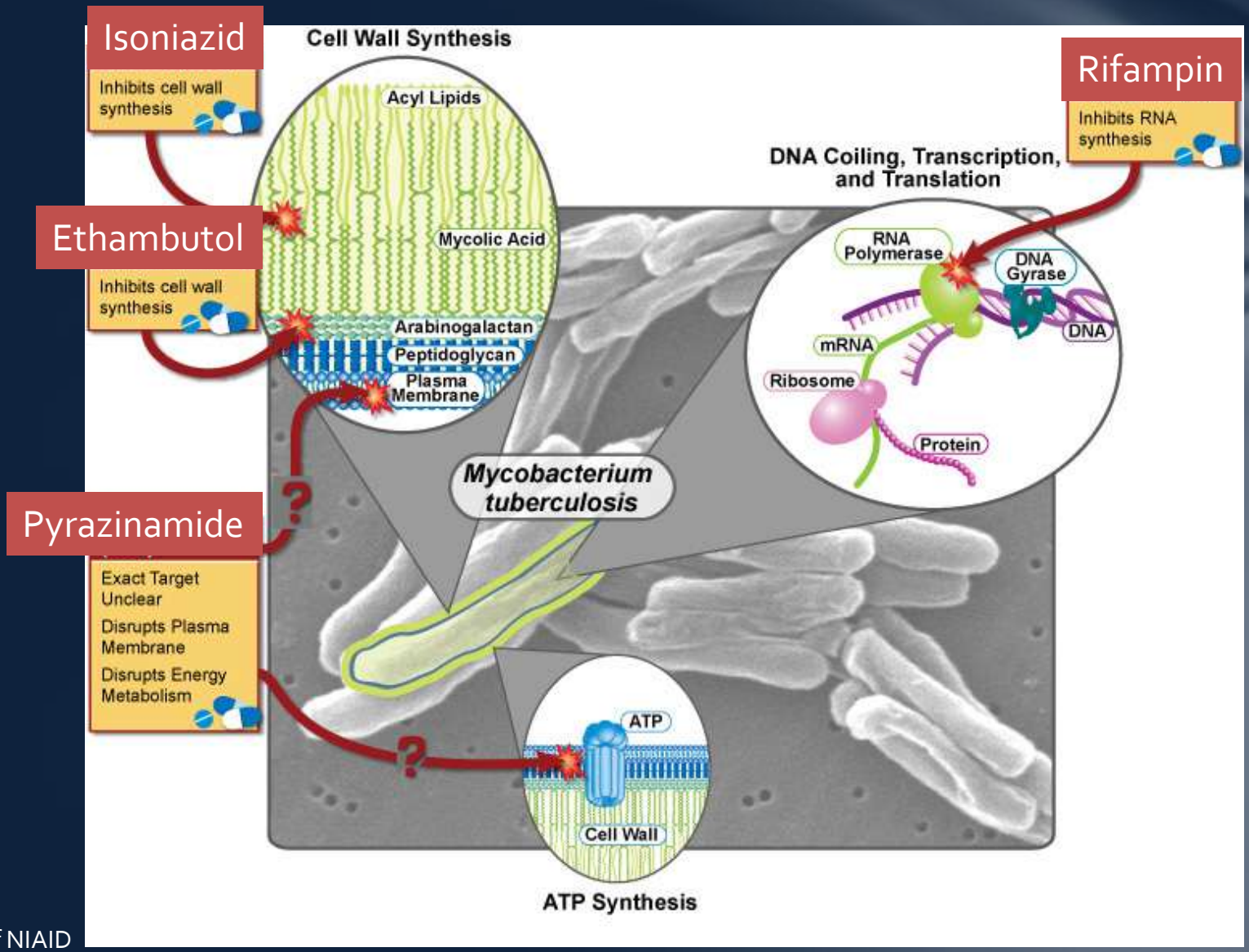


Image courtesy of NIAID

History of Antibiotic Combinations

- Sulfamethoxazole/ Trimethoprim
  - Complementary mechanisms

- Amoxicillin/ clavulanate
  - Overcome resistance

Resistance

- Sulphonamides (1935)
  - By 1948, 80% of *Neisseria gonorrhea* were resistant
- Penicillin (1941)
  - By 1946, ~14% of *Staphylococcus aureus* were resistant
- Rifampin
  - Rapid resistance
  - Always used in combination with other antibiotics when treating active infections

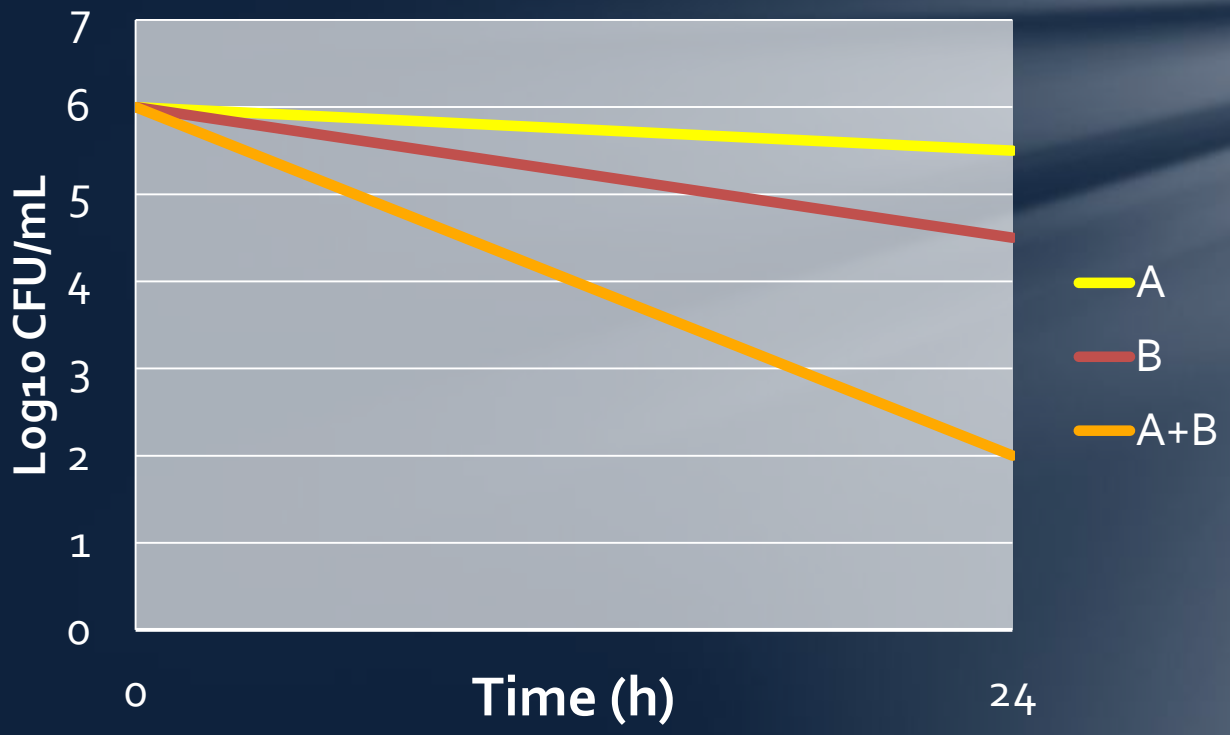
Varley AJ, Sule J, Absalom AR. Principles of antibiotic therapy. Contin Educ Anaesth Crit Care Pain. 2009. 9(6):184-8.

Rationale for Combination Therapy

- Synergy or additivity
- Decrease resistance
- Broaden spectrum

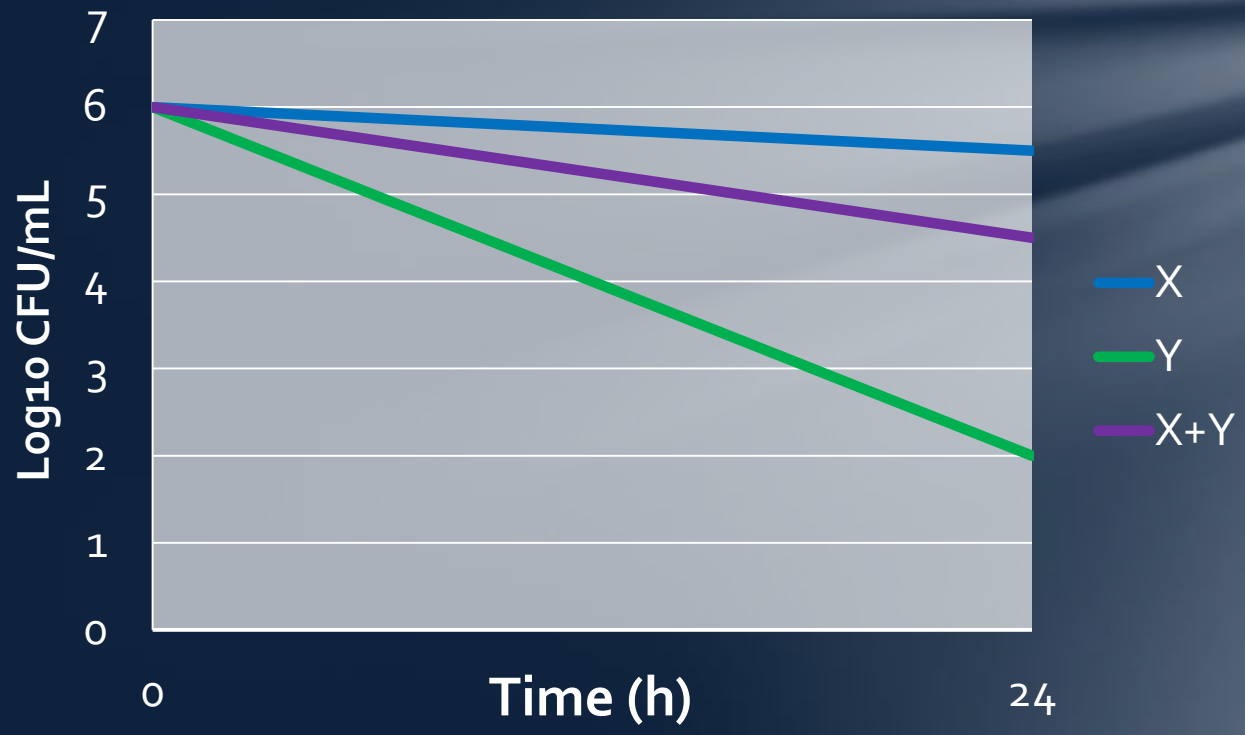
Synergy

- >2 log greater activity for the combination than its most active constituent



Antagonism

- >2log decrease in activity for the combination than its most active constituent



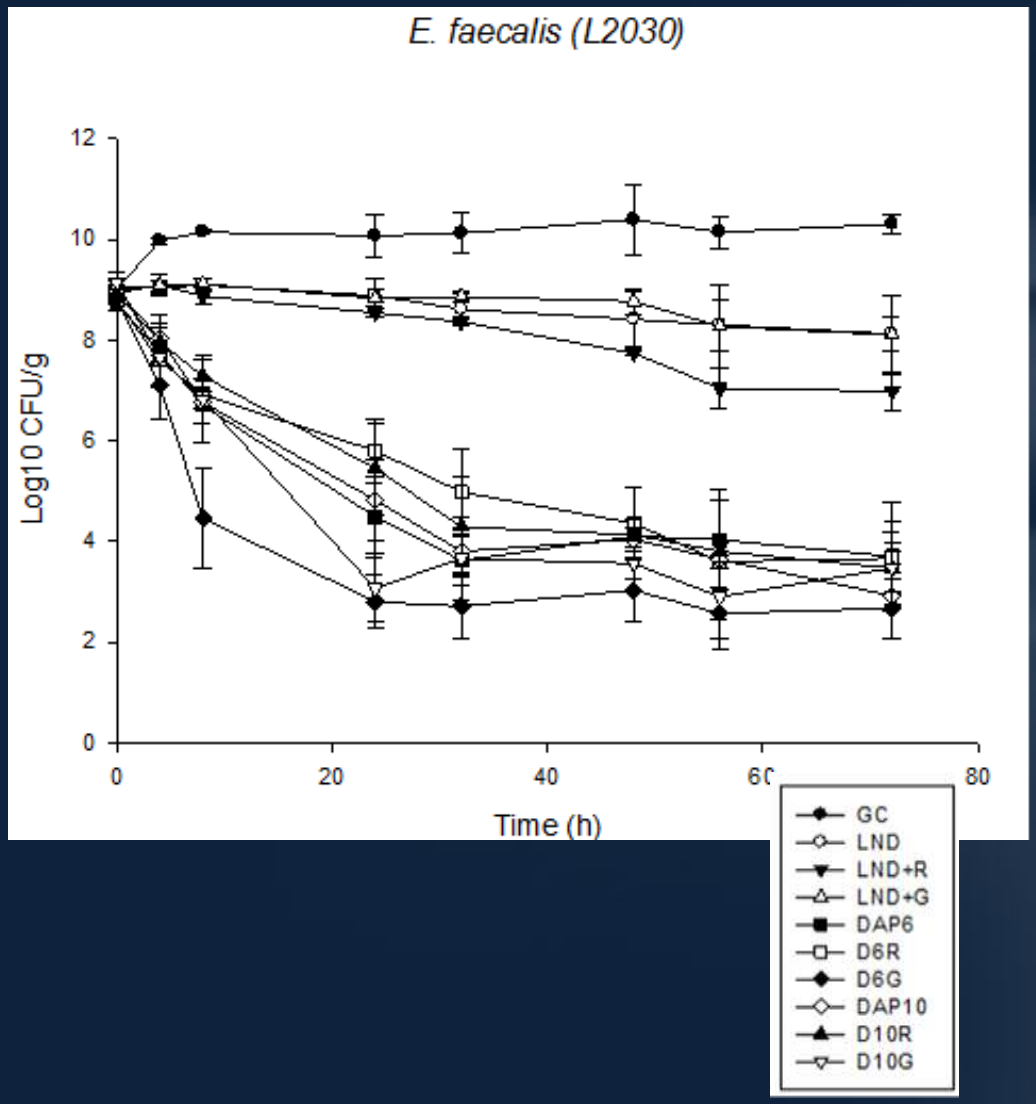
Synergy

- Penicillin- Gentamicin
  - Penicillin is bacteriostatic against enterococci
  - Aminoglycosides are inactive against enterococci
  - Combination is bactericidal
  - Issues with administration

"Evaluating the Activity of Daptomycin or Linezolid Alone or in Combination with Rifampin or Gentamicin on Enterococci in an In Vitro Pharmacodynamic Model with Simulated Endocardial Vegetations"

- *Enterococcus faecalis*
- *Enterococcus faecium*

Enterococcus faecalis



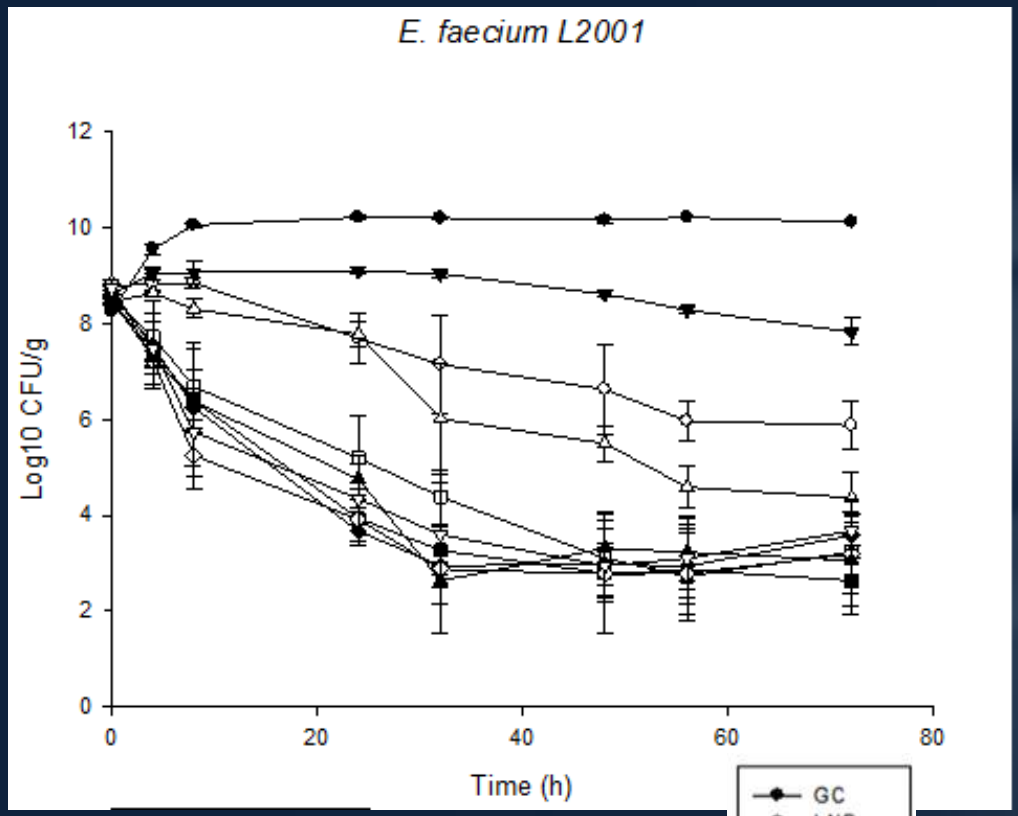
GC

L
LG
LR

D6
D6R
D10R
D10G
D10
D6G

- All daptomycin-containing regimens demonstrated significantly greater kill (decrease in CFU/g) than all linezolid-containing regimens. ($p<0.001$)
- D6G had more kill at 8h than any other regimen ($p=0.001$), however it is not different from the daptomycin-containing regimens at 24h.

Enterococcus faecium



GC

LR

L

LG

D10G

D6G

D6R

D10

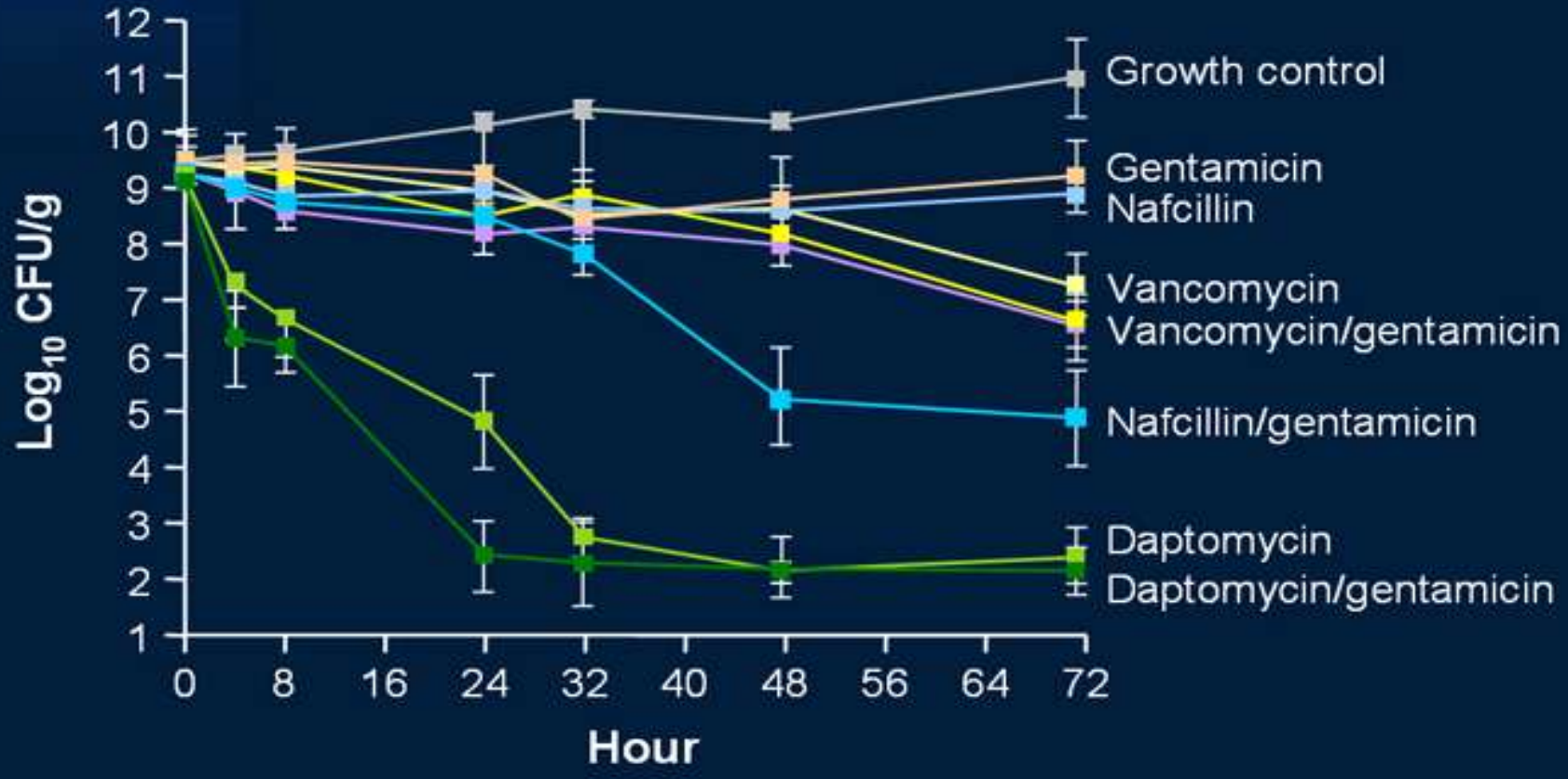
D10R

D6

- Rifampin delayed the cidality of daptomycin by at least 1 log CFU/g at each timepoint.
- Rifampin attenuated linezolid; the combination was not significantly different from the growth control. ($p>0.05$)
- D6G demonstrated the greatest kill at 24h, and was significantly better than all linezolid-containing regimens and D6R. ($p<0.013$)

Daptomycin-containing regimens demonstrated more activity than linezolid-containing regimens at 24 and 48h ($p\leq0.005$)

In Vitro Pharmacodynamic Model: MSSA in Simulated Endocardial Vegetations



MSSA=methicillin-susceptible *Staphylococcus aureus*; CFU=colony-forming unit.

*The clinical significance of *in vitro* data has not been established.

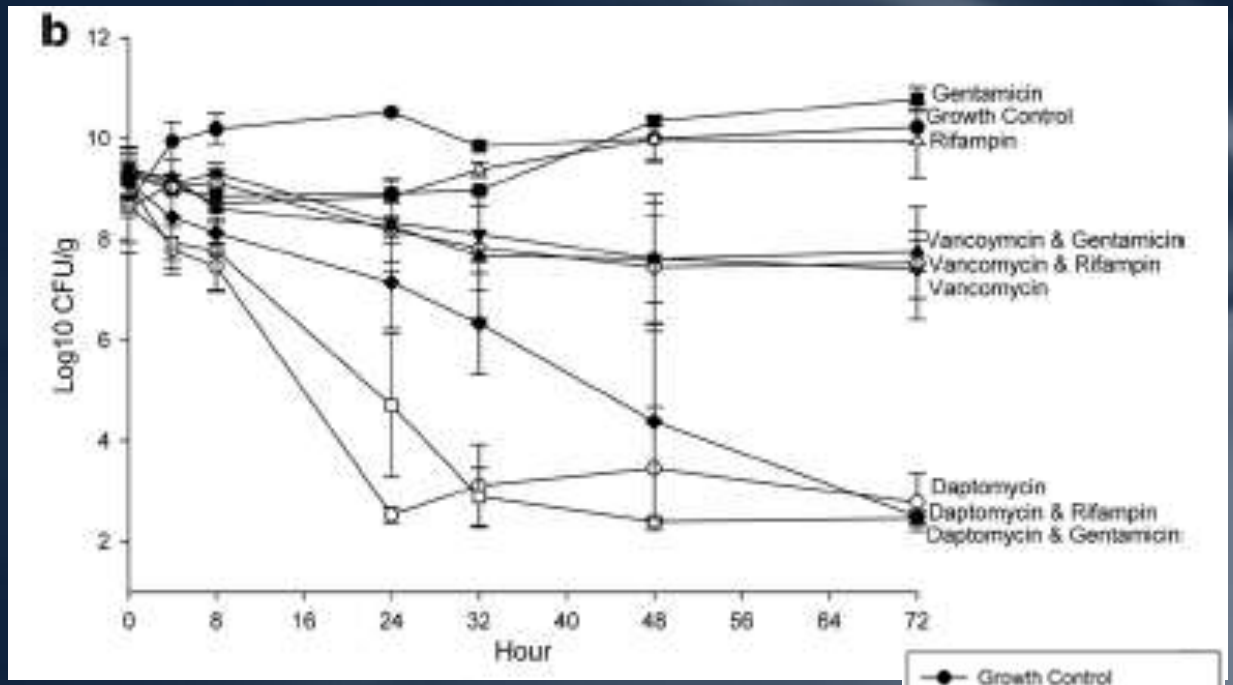
LaPlante KL, Rybak MJ. Impact of high-inoculum *Staphylococcus aureus* on the activities of nafcillin, vancomycin, linezolid, and daptomycin alone and in combination with gentamicin, in an in vitro pharmacodynamic model. *Antimicrob Agents Chemother*. 2004;48:4665-4672.

"Activities of Daptomycin and Vancomycin Alone and in Combination with Rifampin and Gentamicin against Biofilm-Forming MRSA Isolates in an Experimental Model of Endocarditis"

LaPlante KL, Woodmansee S. AAC. 2009 Sep; 53(9):3880-6.

Staphylococcus

- Vancomycin was bacteriostatic (<3log kill)
- Daptomycin was bactericidal (>3log kill)
- Addition of rifampin or gentamicin antagonized/ delayed activity at 24h, and demonstrated no added activity at 72h.



- At 24h, daptomycin monotherapy had significantly better activity than daptomycin in combination with rifampin or gentamicin. (p=0.03 and p=0.001)

LaPlante KL, Woodmansee S. AAC. 2009 Sep; 53(9):3880-6.

Adding Rifampin

Pro:

- highly active against staph
- excellent tissue penetration

Con:

- Significant adverse effects (increased transaminases & drug interactions)
- Rapid resistance development (21% of patients with *S. aureus* native-valve endocarditis)

Biofilm- Recommend waiting until blood cultures have cleared S. aureus before addition of rifampin, to minimize the risk of development of resistance

Levine DP, Intern Med 1991;115:674-80.
Simon GL, Rev Infect Dis 1983;5(Suppl 3):S507-8.
Cosgrove S, Clin Infect Dis. (2008) 46 S386-S393.

Adding Gentamicin

Pro:

- 3-5 days of low-dose synergistic gent+vanco (MRSA bacteremia and native-valve IE) appears to reduce the duration of bacteremia by ~1day in patients with MSSA native-valve endocarditis (AHA IE)

Con:

- Nephrotoxicity- low dose, short course gent (plus vanco or naf/oxa) vs daptomycin monotherapy- pt receiving combination (26.3%) therapy were significantly (p=0.004) more likely to develop renal dysfunction than were those who received daptomycin (11%)

Korzeniowski O, Ann Intern Med 1982;97:496-503
Abrams B, Ann Intern Med 1979;90:789-91
Fowler VG Jr, N Engl J Med 2006;355:653-65

Persistent *Staphylococcus aureus* bacteremia

- Retrospective study at Northwestern – Jan. 2001- Sept. 2004
- pSAB (> 7 days of bacteremia) vs nonpersistent SAB (< 3 days of bacteremia).
- Identified 84 patients with pSAB and 152 nonpersistent SAB

RESULTS:

- MRSA (OR, 5.22; 95% [CI], 2.63-10.38)
- Intravascular catheter/foreign body use (OR, 2.37; 95% CI, 1.11-3.96)
- Chronic renal failure/HD (OR, 2.08; 95% CI, 1.09-3.96)
- > 2 sites of infection (OR, 3.31; 95% CI, 1.17-9.38)
- Infective endocarditis (OR, 10.30; 95% CI, 2.98-35.64)

Hawkins C, Huang J, Jin N, Noskin GA, Zembower TR, Bolon M. Arch intern Med 2007 Sep 24; 167(17):1861-7.

"Use of Antistaphylococcal Beta lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia due to MRSA"

- 7 cases of MRSA bacteremia
- Refractory to a number of vancomycin-based and daptomycin-based regimens
- Addition of high-dose ASBLs (eg nafcillin 2g IV q4h) to high-dose daptomycin (8-10mg/kg/day) resulted in rapid bacteremia clearance

Dhand A, Bayer AS, Pogliano J, Yang SJ, et al. Use of antistaphylococcal B-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: Role of enhanced daptomycin binding. CID 2011;53(2):158-63.

Daptomycin and Antistaphylococcal Beta Lactams

- See-saw effect between daptomycin resistance and ASBL susceptibility (mecA independent)
- Daptomycin Nonsusceptible MRSA
  - Enhanced daptomycin binding
  - Increased bactericidal activity
  - Decrease in positive surface charge

Dhand A, Bayer AS, Pogliano J, Yang SJ, et al. Use of antistaphylococcal B-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: Role of enhanced daptomycin binding. CID 2011;53(2):158-63.

Daptomycin plus Ceftaroline

- Ceftaroline possesses MRSA activity
- Case report
  - Complex patient case with endocarditis with renal failure- treated with daptomycin in combination with ceftaroline
    - Clearance of daptomycin nonsusceptible strain
- IVPD model
  - Simulated the development of daptomycin nonsusceptibility and evaluated activity of daptomycin plus ceftaroline

Rose W; Antimicrob Agents Chemother. 2012 Oct;56(10):5296-302.

Combination Therapy with Daptomycin and Ceftaroline

- Simulated the development of daptomycin nonsusceptibility and evaluated activity of daptomycin plus ceftaroline in an IVPD model
- DAP 6mg/kg q48h was bactericidal but resulted in regrowth and nonsusceptibility (MIC 2-4mcg/mL)
- Addition of ceftaroline after emergence of resistance enhanced killing
- Initial combination therapy produced rapid and sustained bactericidal activity and prevented resistance.

Rose W; Antimicrob Agents Chemother. 2012 Oct;56(10):5296-302.

Rationale

- Both in vivo- and in vitro-derived daptomycin resistance resulted in bacteria with more fluid cell membranes.
- Ceftaroline exposure enhanced daptomycin-induced depolarization
  (81.7% versus 72.3%; p = 0.03)
- Fluorescence-labeled daptomycin was bound over 7-fold more in ceftaroline-exposed cells.

Werth, BJ Rybak MJ; Antimicrob Agents Chemother. 2013 Jan;57(1):66-73

"In Vitro Bactericidal Activities of Linezolid in Combination with Vancomycin, Gentamicin, Ciprofloxacin, Fusidic Acid, and Rifampin against *Staphylococcus aureus*"

- MRSA and MSSA strains
- Ciprofloxacin and vancomycin alone were bactericidal
  - Addition of linezolid antagonized
- Others in combination prevented selection of resistant mutants

Grohs P, Kitzis MD, Gutmann L. AAC. Jan 2003; 418-420.

"Role of Rifampin for Treatment of Orthopedic Implant- Related Staphylococcal Infections"

- 33 patients with PJI
- Includes *S. aureus* and *S. epidermidis*
- Treated with flucloxacillin or vancomycin with either rifampin or placebo for 2 weeks, then ciprofloxacin plus rifampin or ciprofloxacin plus placebo

Zimmerli W, Widmer AF, Blatter M, Ochsner PE for the Foreign-Body Infection Study Group. JAMA. 1998; 279:1537-41.

Ciprofloxacin plus Rifampin

- Cure
  - 12 out of 12 (100%) patients in the rifampin combination group
  - 7 out of 12 (58%) patients in the placebo combination group
- Risk of failure lower in the ciprofloxacin-rifampin group ($p<0.02$)

Zimmerli W, Widmer AF, Blatter M, Ochsner PE for the Foreign-Body Infection Study Group. JAMA. 1998; 279:1537-41.

"Outcome and Predictors of Treatment Failure in Total Hip/ Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*"

- Retrospective chart review
- 98 patients with PJI
- Includes retention and replacement
- Long-term suppressive antibiotic therapy included

Senneville E, Joulie D, Legout L, Valette M, et al. CID 2011; 53(4):334-40.

Rifampin Combinations

- Protective
  - Adequate empirical postsurgical antibiotic therapy (p=0.04)
  - Rifampin-quinolone therapy (p=0.001)
  - Rifampin combination therapy (p=0.002)
- Lower risk of treatment failure with rifampin-quinolone vs other combinations (p=0.003)

Senneville E, Joulie D, Legout L, Valette M, et al. CID 2011; 53(4):334-40.

"A Large Multicenter Study of MSSA & MRSA Prosthetic Joint Infections Managed with Implant Retention"

- 345 episodes of prosthetic joint infection (PJI)
- Treated with debridement, antibiotics, and implant retention (DAIR)

- Rifampin-based combinations exhibited an independent protective effect.

Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, et al. CID 2013; 56(2):184-94.

Pseudomonas

- Combination therapy was the rule
- Antipseudomonal beta lactam
  - Piperacillin
  - Ceftazidime
  - Cefepime
  - Imipenem
  - Aztreonam

+

- Aminoglycoside
  - Tobramycin
  - Gentamycin
  - Amikacin

OR

- Fluoroquinolone
  - Ciprofloxacin
  - Levofloxacin

History of Combination Therapy

- Mortality rate
  - Combination therapy (27%)
  - Monotherapy (47%) ($p<0.02$)

- Monotherapy was often an aminoglycoside

Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989 Nov; 87(5):540-5.

"Does combination antimicrobial therapy reduce mortality in Gram-negative bacteremia? A meta-analysis."

- 17 studies
- Outcome: mortality
- Overall gram negative bacteremia
  - 0.96 (95%CI 0.70-1.32)
- Pseudomonas
  - 0.50 (95%CI 0.30-0.79)

Safdar N, Handelsman J, Maki DG. Lancet Infect Dis. Aug 2004; 4(8):519-27.

"Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials"

- 64 trials with 7586 patients
  - No difference in all-cause mortality

(0.90, 95% CI 0.77-1.06)

- Subset of Pseudomonas infections (426 patients)
  - No difference in all-cause mortality

(1.50, 95% CI 0.07-32.84)

Paul M, Benuri-Silbinger I, Soares-Welser K, Levbovici L. BMJ 2004 Mar 20;328(7441):668.

"Impact of Definitive Therapy with Beta Lactam Monotherapy or Combination with an Aminoglycoside or a Quinolone for *Pseudomonas aeruginosa* Bacteremia"

- Susceptible to beta-lactam *and* either aminoglycoside *or* quinolone
- Primary outcome: treatment success
- Monotherapy (65%) vs Combination (85%) (p=0.1)

Bliziotis IA, Petrosillo N, Michalopoulos A, Samonis G, Falagas ME. PloS One. 2011; 6(10):e26470.

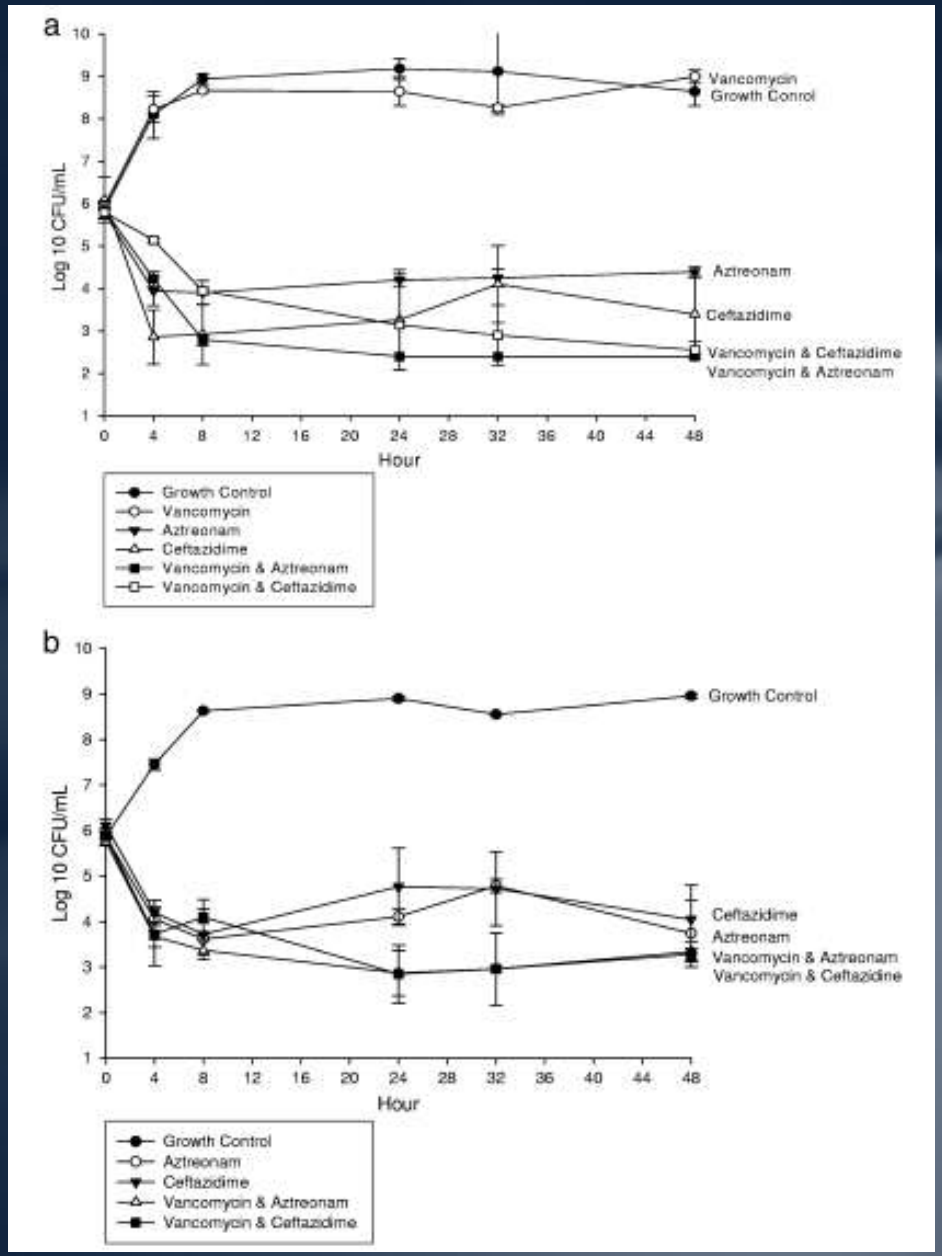
Gram positive antibiotics in gram negative bacteria

- "Evaluating Aztreonam and Ceftazidime Pharmacodynamics with *Escherichia coli* in Combination with Daptomycin, Linezolid, or Vancomycin in an In Vitro Pharmacodynamic Model"

Laplante KL, Sakoulas G. AAC. 2009 October; 53(10):4549-4555.

Vancomycin

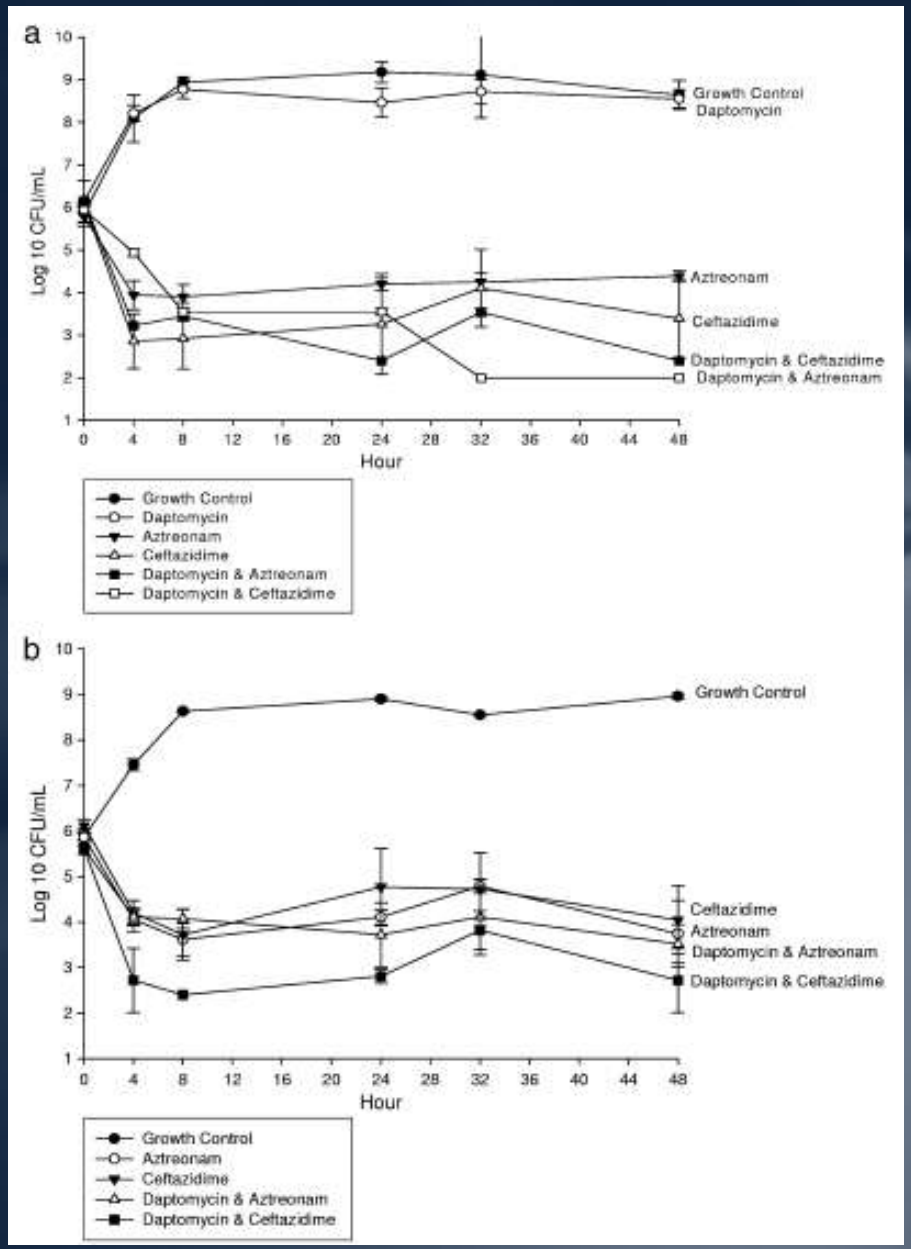
- Vancomycin enhanced activity of aztreonam and ceftazidime at 24 and 48h.
- Vancomycin demonstrated synergy with aztreonam at 48h against 1 strain.



Laplante KL, Sakoulas G. AAC. 2009 October; 53(10):4549-4555.

Daptomycin

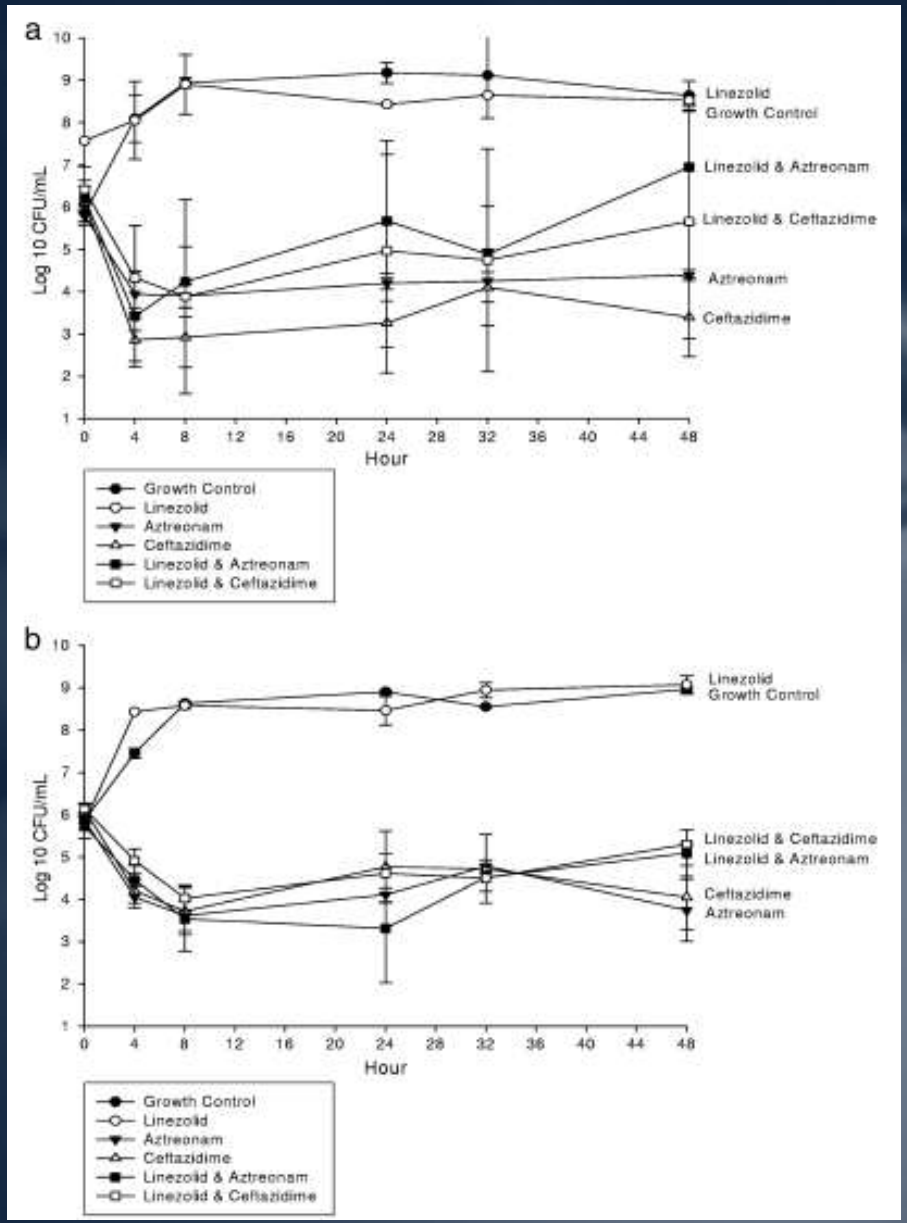
- Daptomycin mostly enhanced activity of aztreonam and ceftazidime at 24 and 48h.
- Daptomycin demonstrated synergy with ceftazidime at 24h against 1 strain.



Laplante KL, Sakoulas G. AAC. 2009 October; 53(10):4549-4555.

Linezolid

- Linezolid attenuated activity of aztreonam and ceftazidime at 24 and 48h.
- Linezolid antagonized activity of aztreonam and ceftazidime at 48h against 1 strain of *E. coli*.



Laplante KL, Sakoulas G. AAC. 2009 October; 53(10):4549-4555.

Disadvantages

- Antagonism
- Risk of adverse effects
- Drug- drug interactions
- Risk for superinfection
- Increased costs

Antagonism

- Not much clinical data
  - Chlortetracycline and penicillin
- Mostly in vitro
  - Relevance?

Jawetz E, Gunnison JB, Speck RS, Coleman VR. Studies on antibiotic synergism and antagonism; the interference of chloramphenicol with the action of penicillin. AMA Arch Intern Med. 1951 Mar; 87(3):349-59.

Conclusion

- Combination therapy may be helpful in certain infections where the benefits outweigh the risks

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Megan Luther, Pharm.D.

In Vitro PK/PD Fellow