Hospital
Vila Franca de Xira

Monoterapia vs Terapêutica combinada

Sinergismo vs antagonismo

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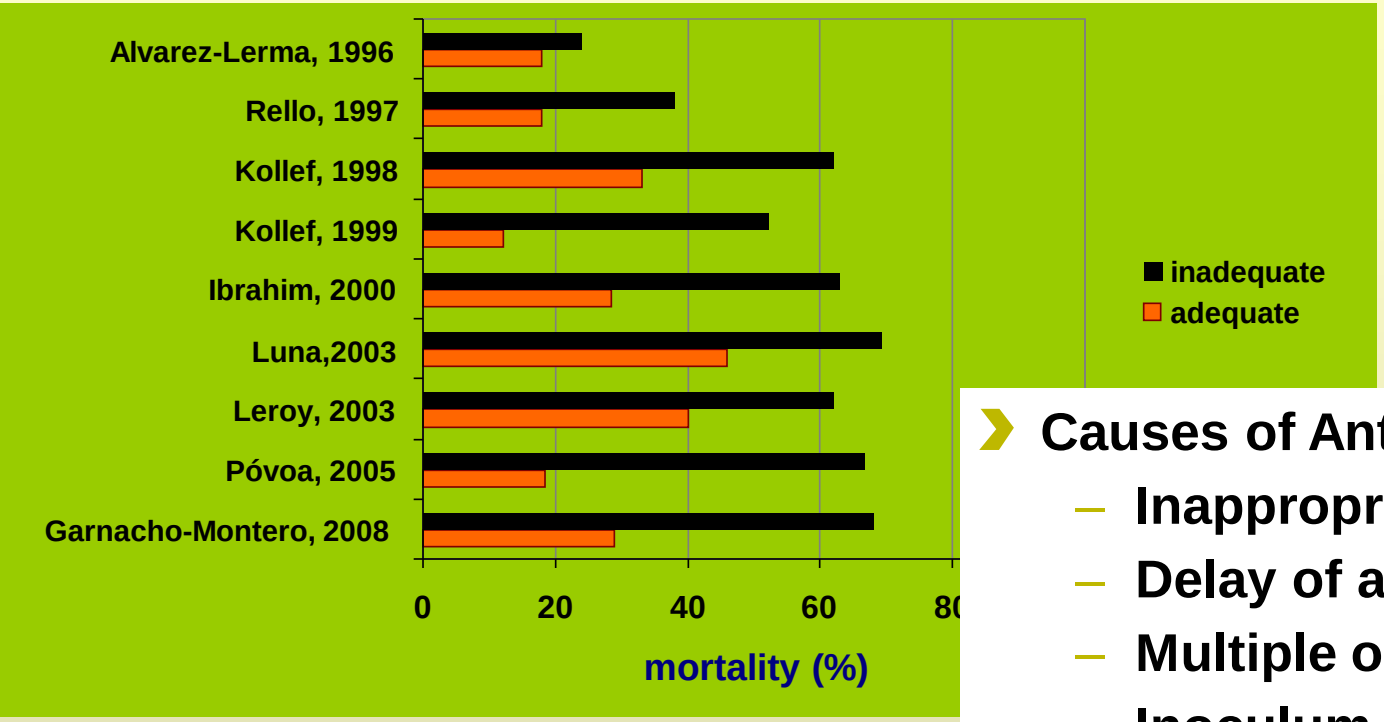
Goals of Antibiotic therapy

To kill the infecting bacteria

- Decrease inflamation
- Reduce the inoculum
- Prevent resistance

Importance of adequacy – MIC and PK/PD

Initial antibiotic therapy and mortality - VAP



- **Causes of Antibiotic Failure**
  - **Inappropriate antibiotics**
  - **Delay of antibiotic therapy**
  - **Multiple organ failure**
  - **Inoculum**
  - **Insufficient dose**
  - **Biofilms**

Alvarez-Lerma ICM 1996;22:387
Kollef Chest. 1998;113:412
Ibrahim Chest. 2000;118:146
Leroy ICM 2003;29:2170
Garnacho-Montero JAC 2008;61:1434

Rello. AJRCCM
Kollef Chest. 19
Luna. Chest. 19
Póvoa ERJ 2005;25:804

Can the Antibiotic Strategy be design to further improve patient outcome? – Combining antibiotics

Surviving Sepsis Guidelines

2a. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

Surviving Sepsis Campaign

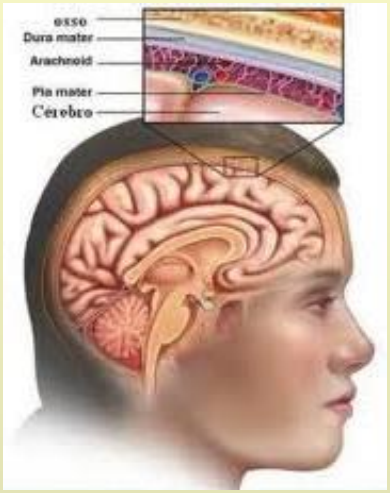
Advantages / Disadvantages

- Achieve broader cover for the empiric therapy
- Treatment of mixed infections
- Prevention of the development of resistance
- Reduce toxicity
- Achieve antibacterial sinergysm

- Antagonism – drug to drug interaction
- Adverse events
- Development of antimicrobial resistance
- Increased costs

Bacterial Meningitis

- If risk factors for ***Listeria monocytogenes***:



- Age > 50 years or < 2 months
- Diabetes
- Alchoolism
- Immunosupression
- Malignancy

3rd Gen Cephalosporin + Ampicillin

Tunkel AR et al. *CID* 2004; 39 :1267-1284

Peritonite

Primária (Monomicrobiana)	Secundária (Polimicrobiana)	Terciária (Polimicrobiana)
E. coli *Klebsiella* spp. *Streptococcus* spp. *Enterococcus* spp. Outros bacilos Gram negativos	**Peritonite Secundária Grave**	*Enterococci* *Pseudomonas* *S. epidermidis* *Candida*

Cefalosporina 3ª

Fluoroquinolon

Piperacilina Tazobactam

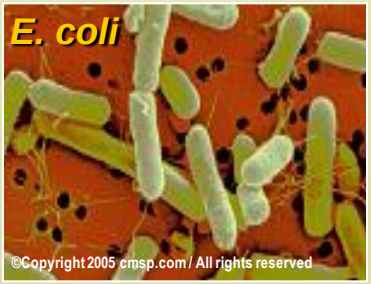
Carbapenem

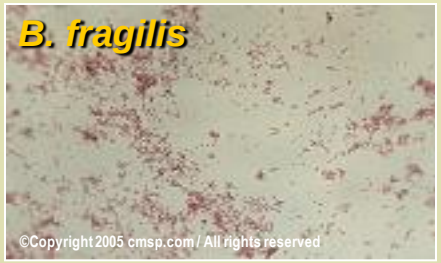
Cefalosporina de 3ª ou 4ª G + Metronidazol

Ciprofloxacina + Metronidazol

Fluoroquinolona + Metronidazol

Terapêutica combinada de acordo com as etiologias identificadas / prováveis





Barie PS. *J Chemother*. 1999;11:464-477.
LaRoche M, Harding G. *Eur J Clin Microbiol Infect Dis*. 1998;17:542-550.

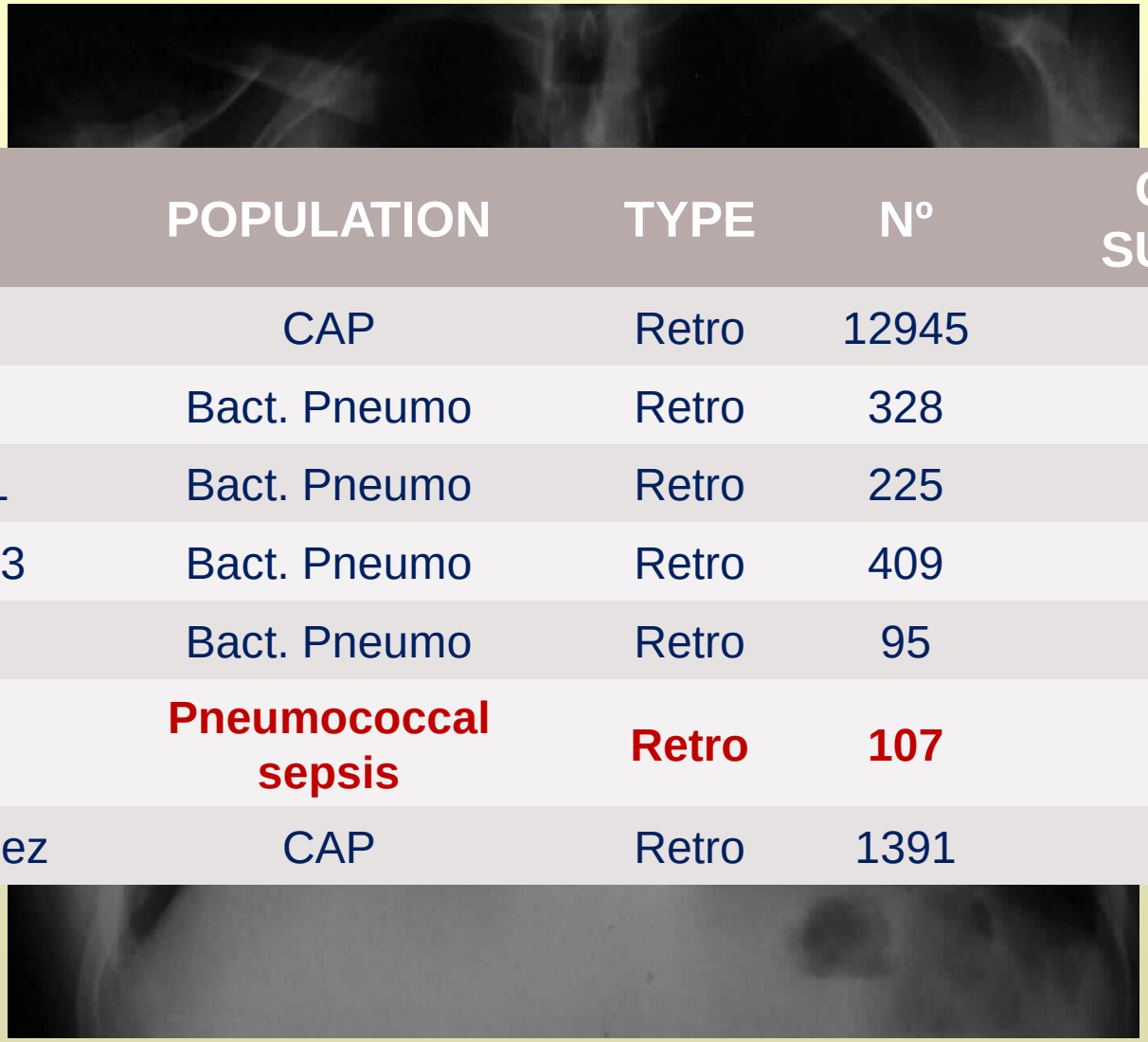
Abdominal Infections

Table 3
Comparison of randomized controlled trials of monotherapy versus combination therapy for abdominal sepsis

Author, Year	Total # pts, N	Experimental Therapy	Control Therapy	Mortality (%)	RR (CI)	*P* Value
Schentag 1983[142]	98	Moxalactam	Clindamycin + tobramycin	7/49 (14) v 6/49 (12)	1.17	1
Poenaru 1990[133]	104	Imipenem	Clindamycin/ metronidazole + tobramycin	4/52(8) v 9/52 (17)	.47	.235
Solomkin 1990[143]	162	Imipenem	Clindamycin + tobramycin	11/81(14) v 14/81 (17)	.82	.664
Fink 1991[141]	40	Ticarcillin-clavulanate	Clindamycin + gentamicin	3/20(15) v 5/25(20)	.75	.716
Dupont 2000[140]	204	Pipercillin-tazobactam	Pipercillin-tazobactam + amikacin	19/99 (19) v 22/105 (21)	0.9	.862

Bochud PY et al. *Crit Care Med* 2004; 32:S495-512

Community-Acquired Pneumonia

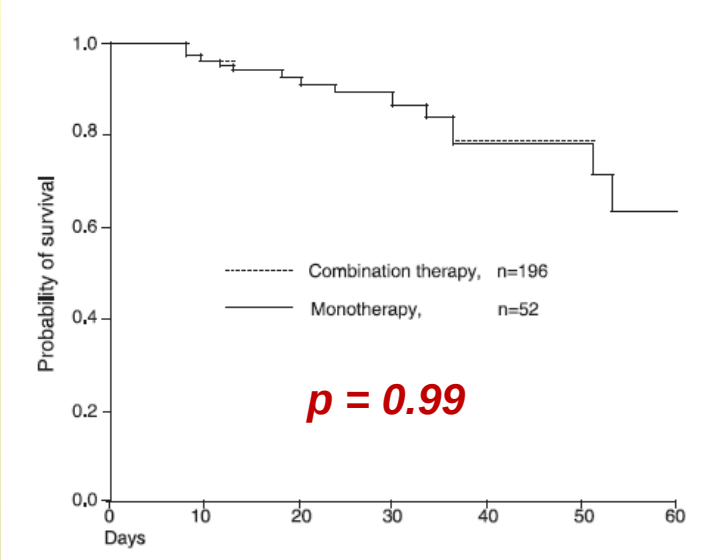


AUTHOR	POPULATION	TYPE	Nº	COMBO SUPERIOR
Gleason	CAP	Retro	12945	Yes
Mufson, 1999	Bact. Pneumo	Retro	328	Yes
Waterer, 2001	Bact. Pneumo	Retro	225	Yes
Martinez, 2003	Bact. Pneumo	Retro	409	Yes
Weiss, 2004	Bact. Pneumo	Retro	95	Yes
Harbarth	**Pneumococcal sepsis**	**Retro**	**107**	**No**
Garcia-Vasquez	CAP	Retro	1391	Yes

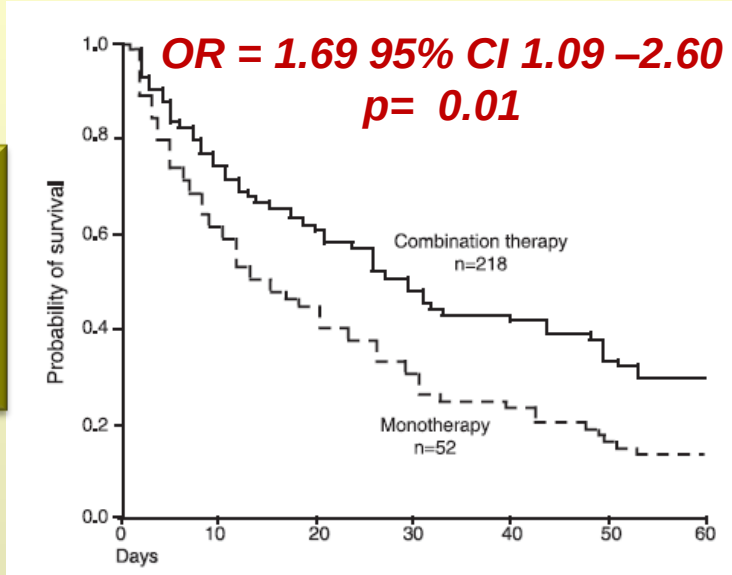
Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock

- Prospective observational cohort study of 529 adults with severe CAP

No Shock



Shock



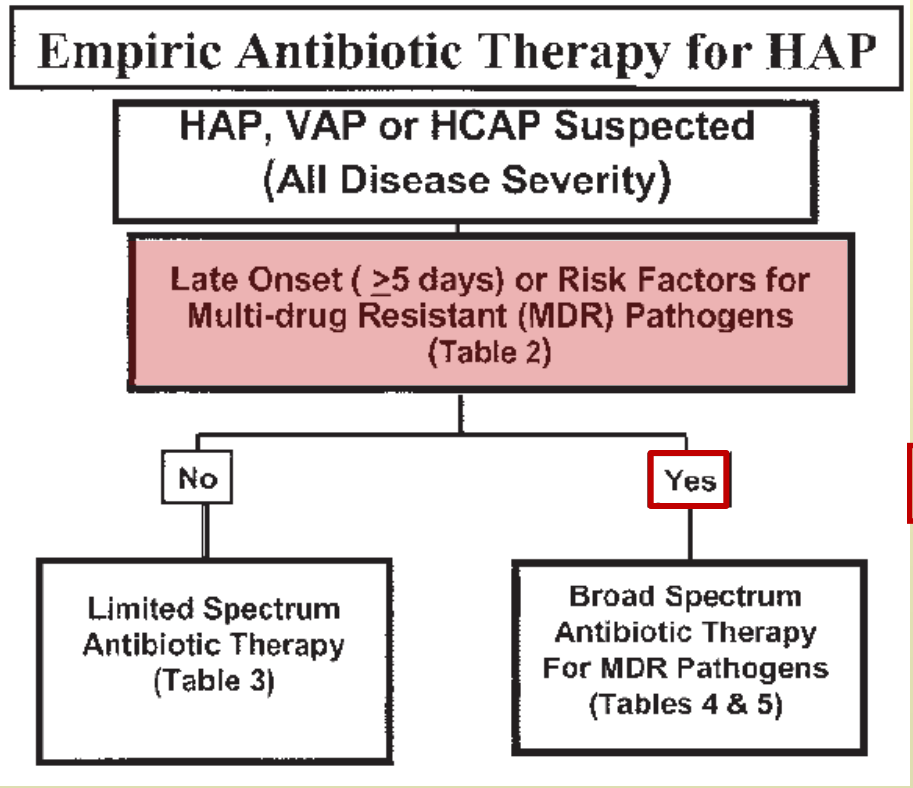
Even when monotherapy was appropriate, it achieved a lower 28-day survival than an adequate antibiotic combination OR 1,64 (1,01-2,64)

Combination antibiotic therapy seems to increase ICU survival in patients with severe CAP and shock

Rodriguez A (CAPUCI group) Crit Care Med 2007; 35: 1493

Ventilator Associated Pneumonia

ATS GUIDELINES



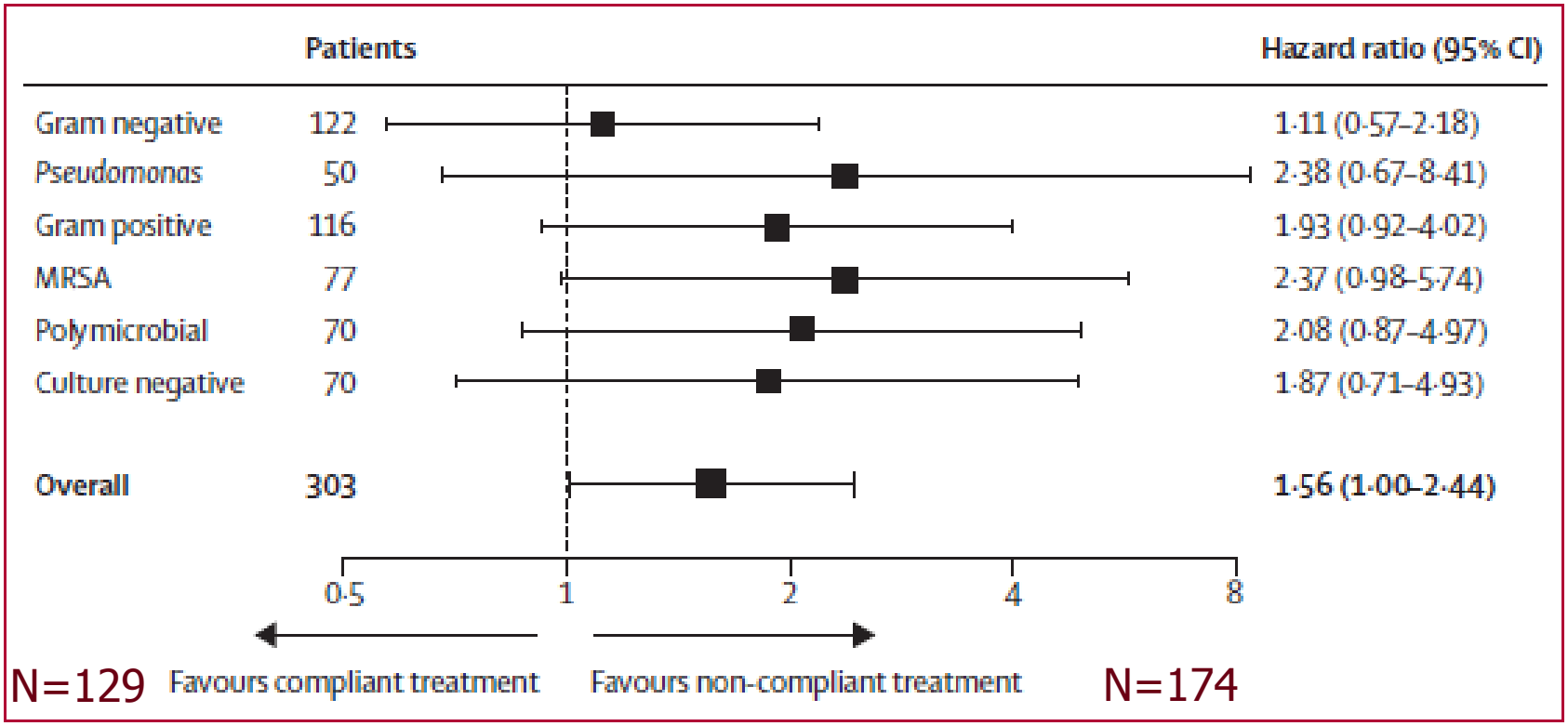
Potential Pathogens	Combination Antibiotic Therapy*
Pathogens listed in Table 3 and MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL+)† *Acinetobacter* species†	Antipseudomonal cephalosporin (cefepime, ceftazidime) *or* Antipseudomonal carbepenem (imipenem or meropenem) *or* β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) *plus* Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin) *or* Aminoglycoside (amikacin, gentamicin, or tobramycin) *plus*
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Linezolid or vancomycin‡

AJRCCM 2005; 171: 388-416

Ventilator Associated Pneumonia

Combination therapy

Compliance with ATS/IDSA Guidelines



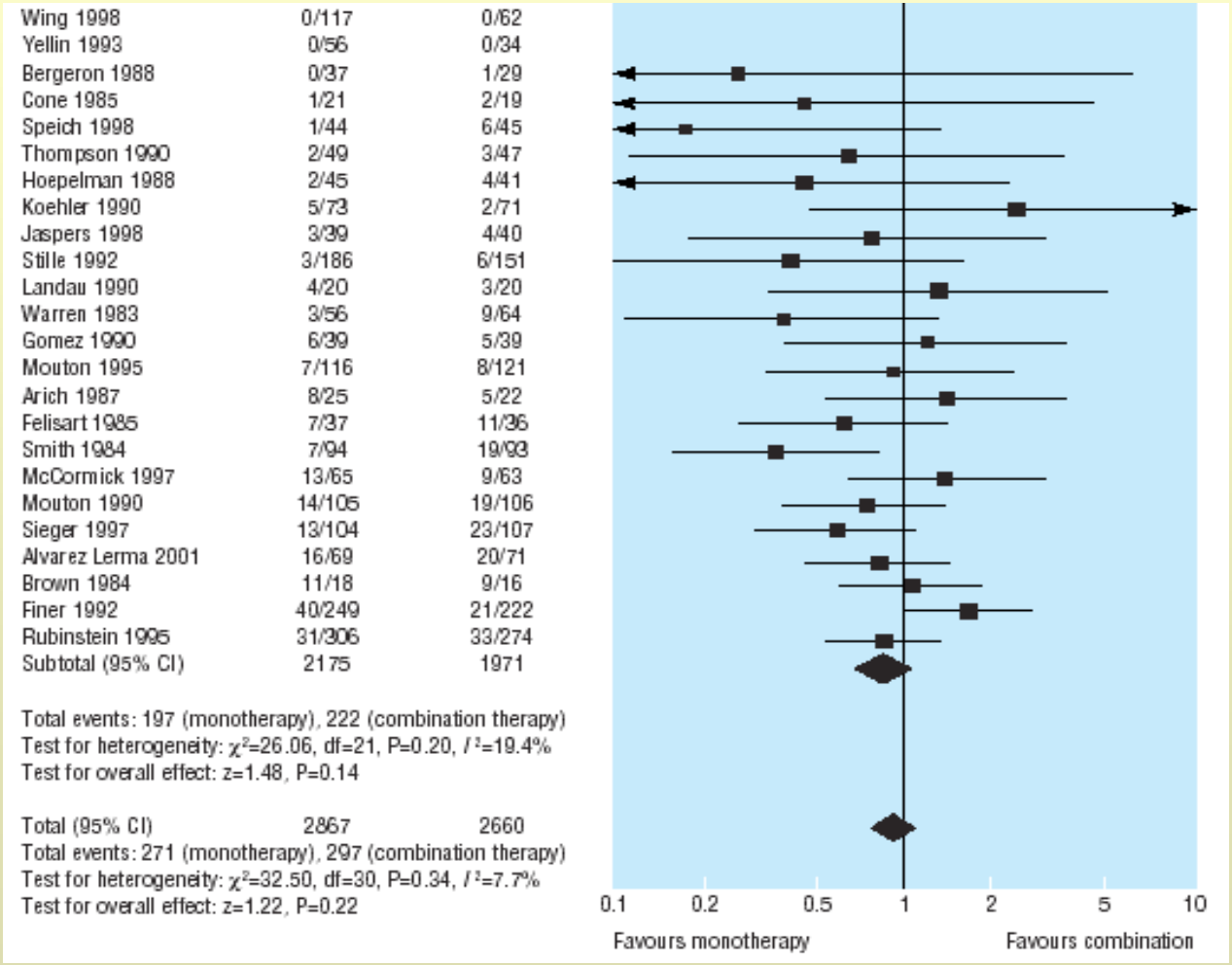
Single drug for Gram Negative infections – 154

No coverage of MRSA - 24

Kett, Lancet Inf Dis 2011; 11:181

Ventilator Associated Pneumonia

Combination therapy



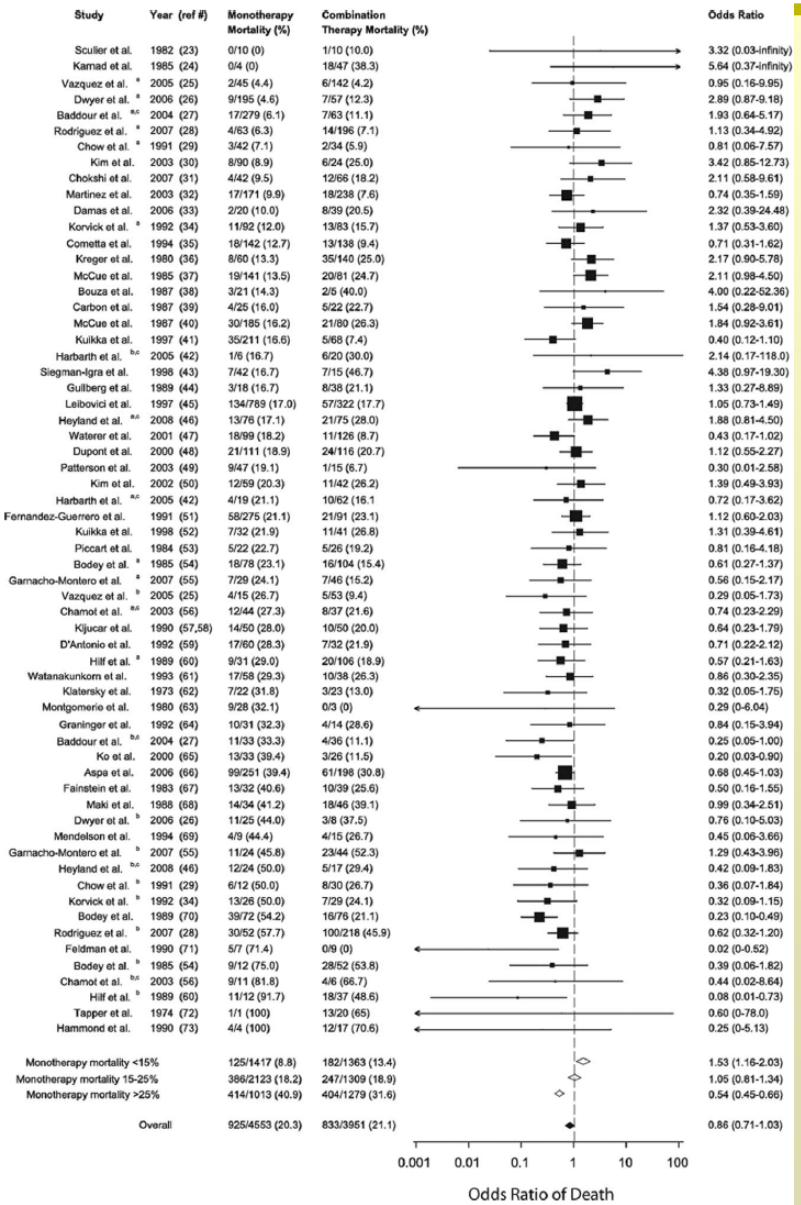
No advantage of combination therapy

- Gram negative infections (N=1835)
- Pseudomonas aeruginosa (N=426)

Paul. BMJ 2004; doi:10.1136/bmj.38028.520995.63

Sepsis

Combination therapy



- Meta-analysis of 62 eligible datasets OR (death/clinical failure)

  0.856 (95% CI, 0.713–1.027)

  (p= 0.094)

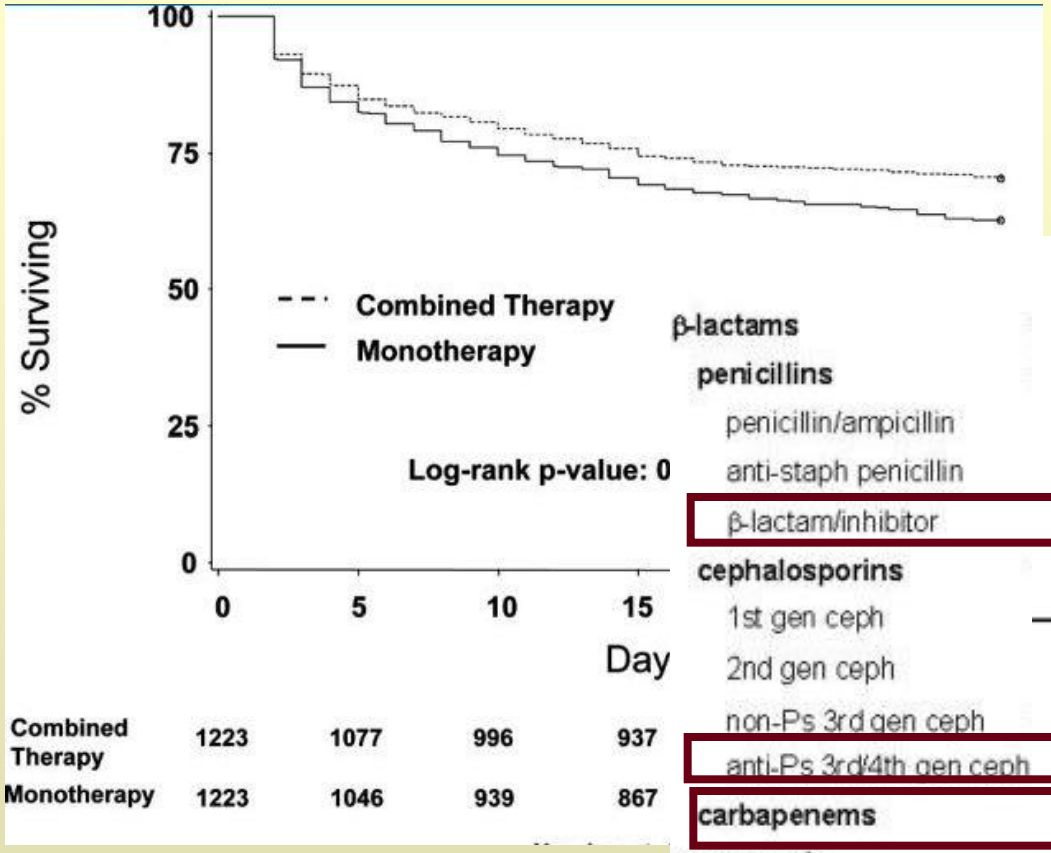
- Combination therapy demonstrates a significant advantage over monotherapy **when the rate of death/clinical failure exceeds 25%**

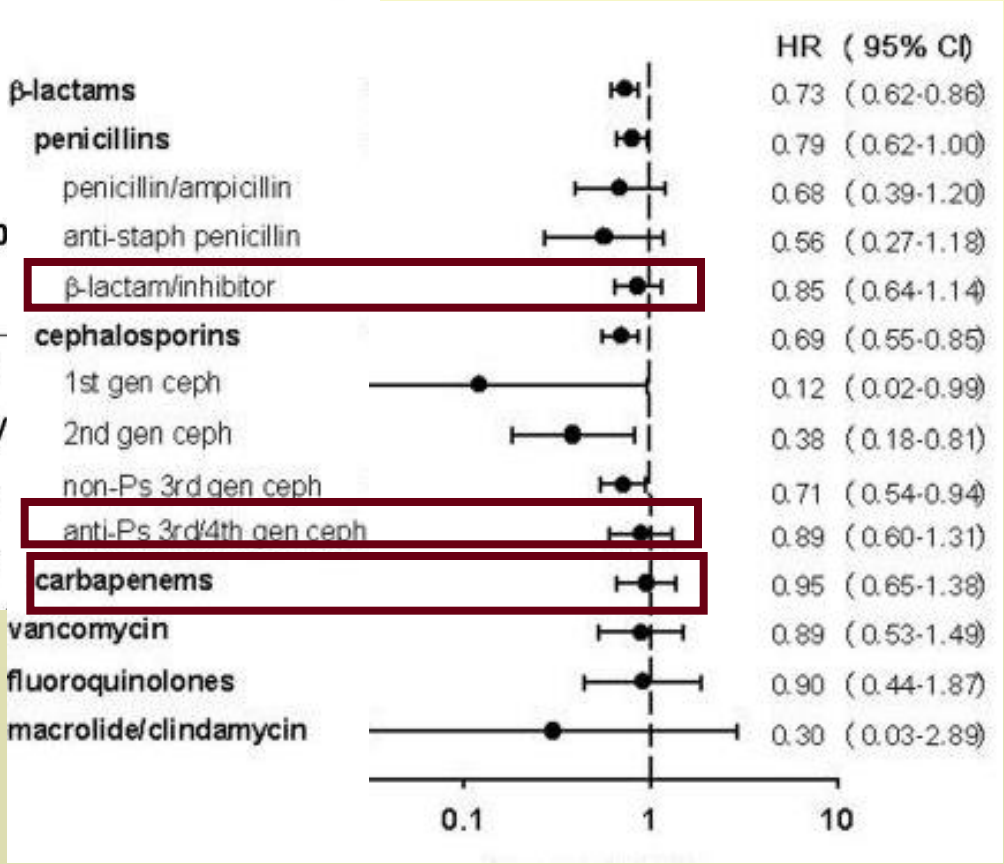
  OR 0.54; 95% CI, 0.45– 0.66 (p = 0.0001)

Kumar A et al. Crit Care Medicine 2010; 38 :1651-1654

Sepsis

Combination therapy





Kumar, Crit Care Med. 2010;38:1773

Synergism

- "*In vitro*" for many antibiotic combinations

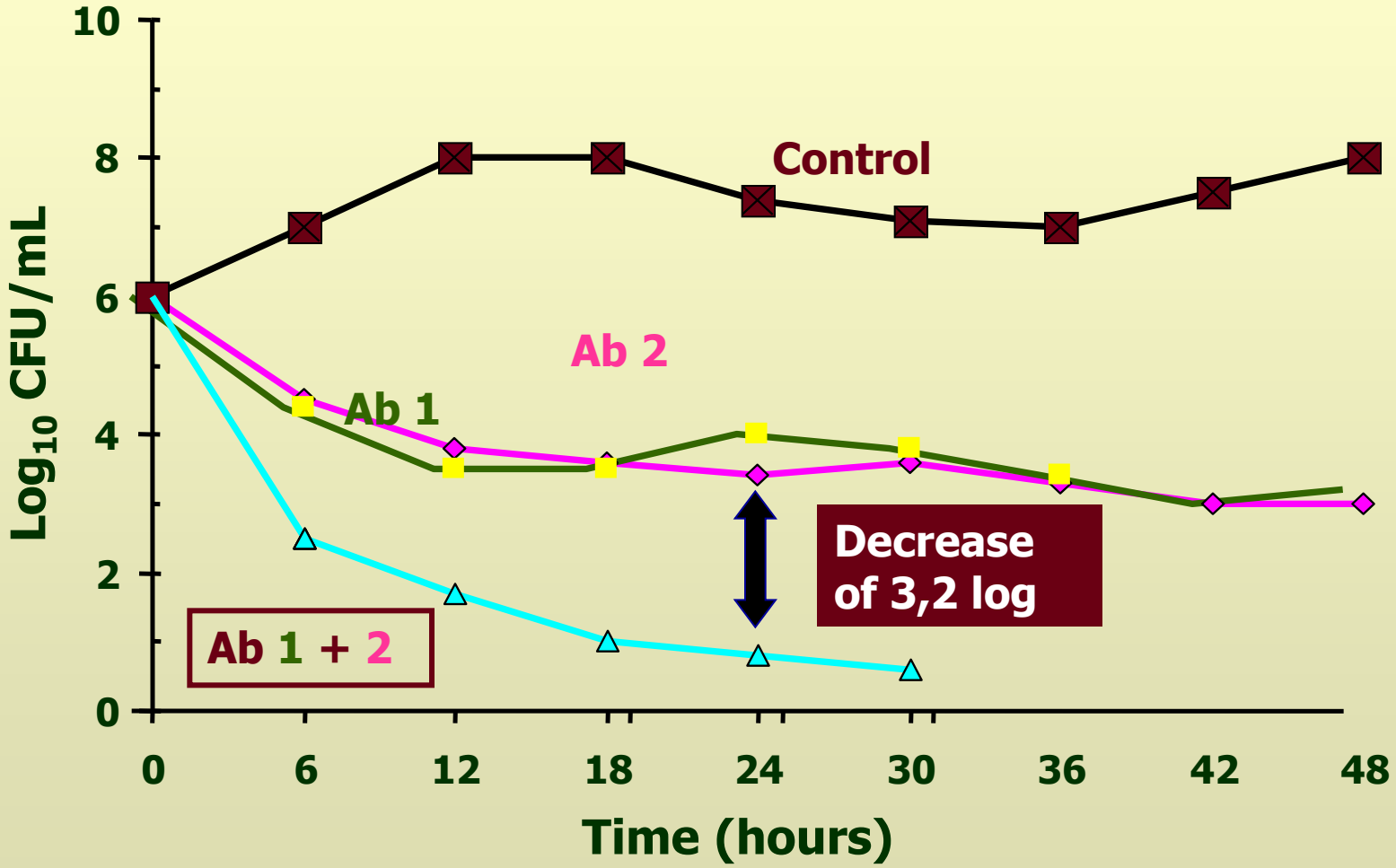
Calandra T et al. Am J Med 1986; 80: 45. Kumar A et al. ICAAC Proc 2004; 26: A-1296; Darras-Joly C et al. Antimicrob Agents Chemother 1996; 40: 2147; Giamarellou H. Am J Med 1986; 80: 126. Giamarellou H et al. Antimicrob Agents Chemother 1984; 25: 534.

- Clinical studies of infection (including endocarditis, Gram negative bacteremia and neutropenic infections)

Anderson ET et al. Chemotherapy 1978;24(1):45–54. Bouza E et al. Med Clin North Am 2000;84(6):1357–89; De Jongh CA et al. Am J Med 1986;80(5C):96–100.

- Specific types of infection:
  - HIV
  - Tuberculosis
  - Helicobacter pylori

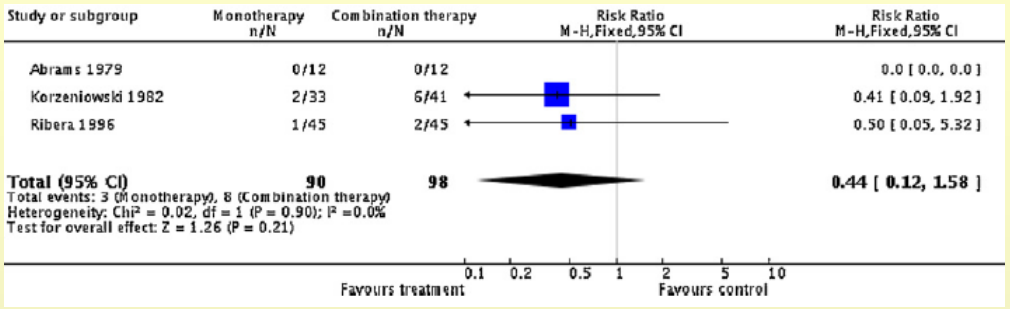
Synergism of antibiotics (*In vitro*)

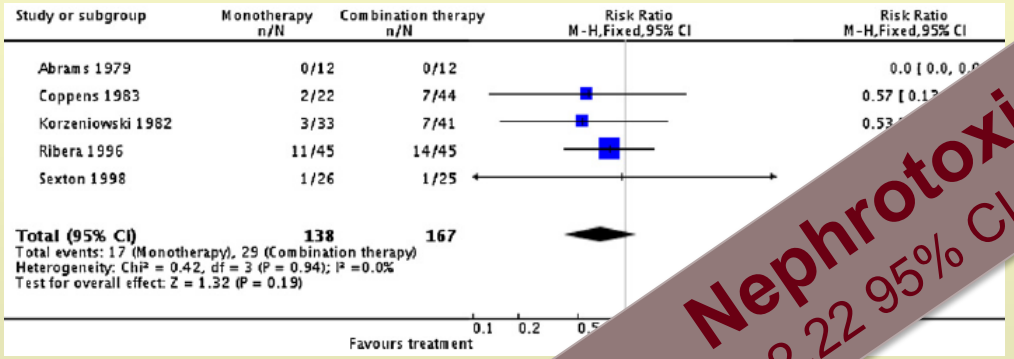


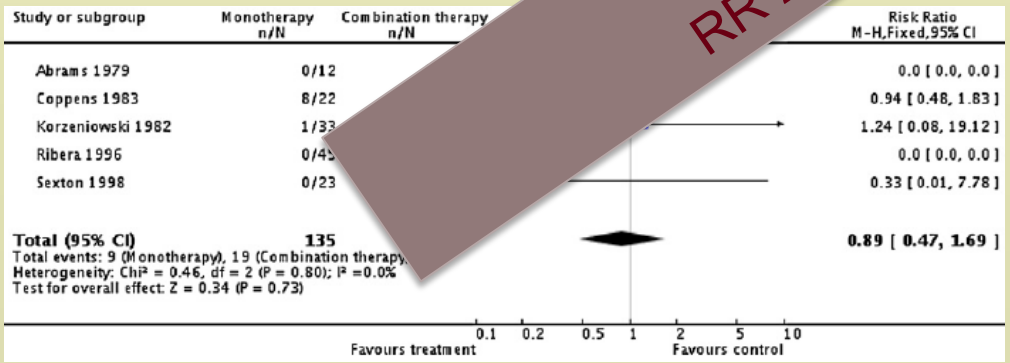
Is clinical proof necessary?

The Lab	Real Life
Use of measured antibiotic concentrations administered at precise time points and tested against a standard inoculum of bacteria	› Antibiotic concentrations in the host is determined by: – dose, volume distribution and elimination rate of atb – patient's age, volume status, weight, renal and hepatic function, hypoalbuminemia – site of infection › Bacterial load is highly variable

Endocarditis







Nephrotoxicity
RR 2.22 95% CI 1.11-4.35

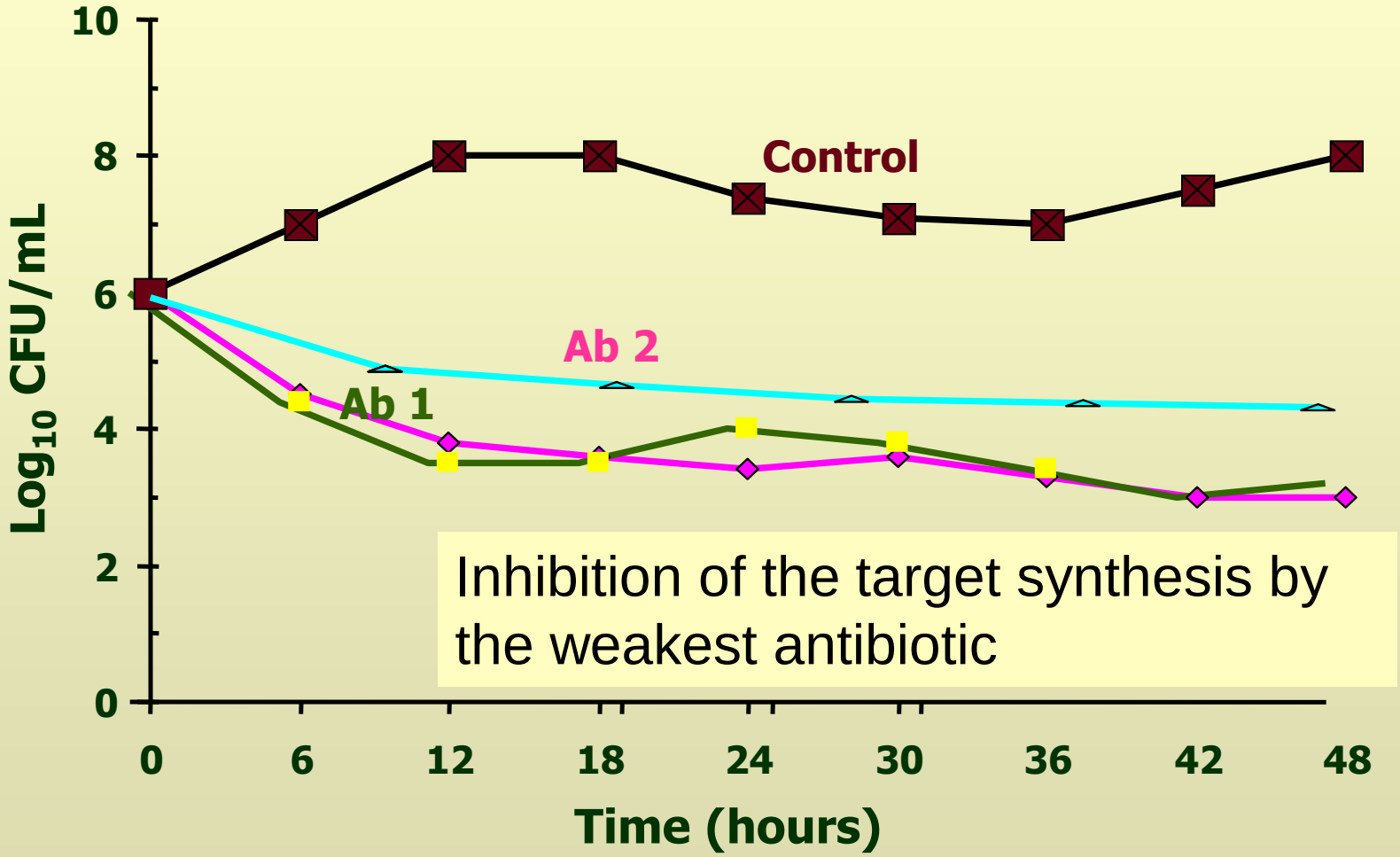
M lity
OR 0. 0.12-1.58

Clinical Failure
OR 0.69 95% CI 0.40-1.19

Bacteriological Failure
OR 0.89 95% CI 0.47-1.69

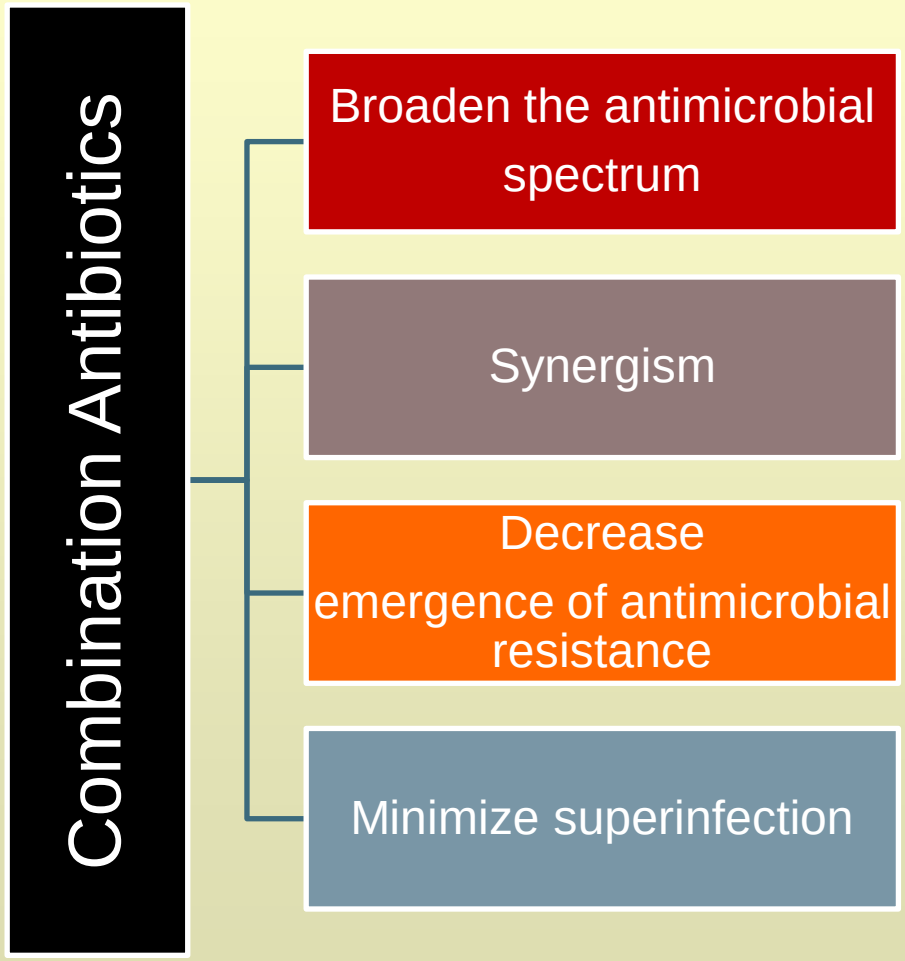
Leibovici L *International Journal of Antimicrobial Agents* 2010; 36S: S46–S49

Antagonism of antibiotics (*In vitro)*



Inhibition of the target synthesis by the weakest antibiotic

Pseudomonas aeruginosa
Acinetobacter baumannii



In vitro synergism

- Wide ranges of results
- Dependent on several methodological factors:
  - method of synergy test used
  - susceptibility patterns of the isolates
  - concentrations of antibiotics used
- The greatest likelihood of synergy is an **aminoglycoside** with an antipseudomonal penicillin (~ 90%), and then, in decreasing order, with a cephalosporin (~ 80%) or a carbapenem (~ 50%).
- The interaction of **fluoroquinolones** combined with β-lactams or aminoglycosides was usually autonomous (additive) or indifferent.
- For quinolone combinations plus antipseudomonal β-lactams, the β-lactam drug accomplished most of the bacterial killing.

Ps aeruginosa Bacteremia

Table 2 Logistic regression analysis of the risk factors for 28-day mortality in patients with adequate empirical therapy

Variable	Univariate analysis	*P*	Multivariate analysis	*P*
	OR (95% CI)		OR (95% CI)	
Age	1.00 (0.96-1.04)	.98		
Male gender	0.48 (0.14-1.76)	.27		
Underlying disease				
Solid organ malignancy	1.22 (0.42-3.56)	.71		
Hematologic malignancy	2.33 (0.84-6.46)	.10		
Structural lung disease	0.25 (0.03-2.31)	.22		
Neurologic disease	0.21 (0.02-1.81)	.15		
Congestive heart failure	2.96 (0.26-34.42)	.39		
Hemodialysis	0.69 (0.06-8.05)	.77		
Immunosuppression	0.62 (0.20-1.93)	.41		
McCabe score				
Non-fatal	0.57 (0.09-3.38)	.54		
Ultimately fatal	1.20 (0.24-6.11)	.83		
Rapidly fatal	1.0 (referent)			
APACHE II score	1.04 (0.97-1.11)	.32		
Pitt bacteremia score	1.21 (0.96-1.51)	.10		
CPIS	1.06 (0.73-1.54)	.77		
Type of pneumonia				
Community-acquired	1.00 (0.16-6.26)	.99		
Healthcare-associated	0.74 (1.12-4.73)	.75		
Hospital- acquired	1.02 (0.19-5.37)	.98		
Ventilator-associated	1.0 (referent)			
MDR-*P. aeruginosa*	0.43 (0.08-2.30)	.32		
Previous antibiotic therapy	1.42 (0.53-3.86)	.49		
Initial manifestation within 24 h				
Sepsis	0.36 (0.11-1.17)	.09	0.07 (0.01-0.49)	0.008
Severe sepsis	0.29 (0.07-1.21)	.09	0.13 (0.02-0.89)	0.04
Septic shock	1.0 (referent)			
Type of adequate empirical therapy				
Monotherapy	0.38 (0.14-1.06)	.06	0.05 (0.01-0.34)	0.002
Combination therapy	1.0 (referent)			

The **absence of septic shock at the time of bacteremia** (AOR 0.07; 95% CI, 0.01-0.49; p = 0.008), and **combination therapy** (AOR 0.05; 95% CI 0.01-0.34; p = 0.002) as variables that were independently associated with decreased all-cause 28-day mortality

No significant difference in terms of the emergence of antimicrobial resistance (21.9% and 12.1% respectively; p = 0.29).

However, the 2-week bacteria eradication rate (54.5% vs. 18.8%, p = 0.04) and the 4-week **eradication rate** (54.5% vs. 28.1%, p = 0.04) were significantly higher in the combination therapy group than the monotherapy group.

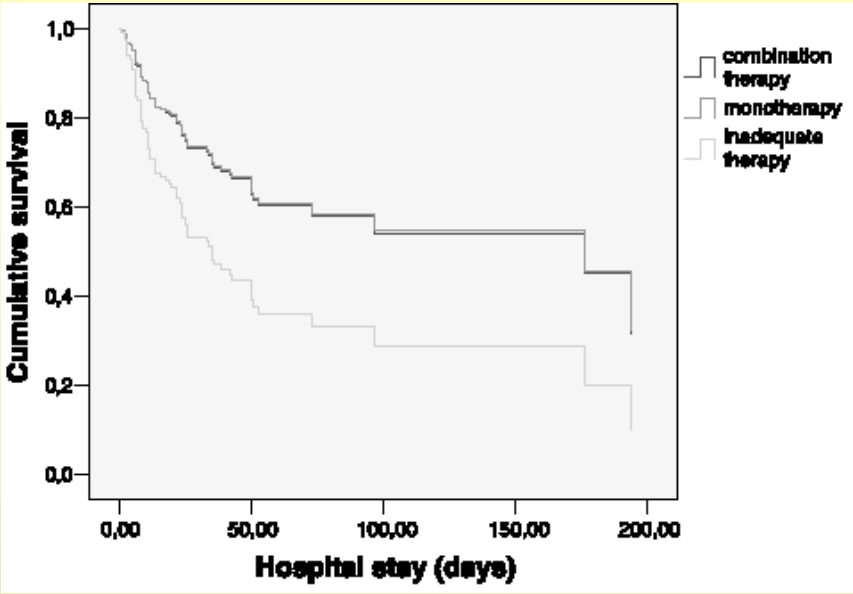
Park et al. *BMC Infectious Diseases* 2012, 12:308

Ps aeruginosa VAP

- Retrospective, observational, cohort study
- 183 episodes of monomicrobial P. aeruginosa VAP

Table 5. Variables independently associated with mortality using Cox proportional regression analysis

	aHR	95% CI	*p*
Age	1.02	1.01–1.04	.005
Chronic cardiac failure	1.90	1.04–3.47	.035
Effective empirical therapy			.02
Combined therapy	1		
Monotherapy	0.90	0.50–1.63	.73
Inappropriate therapy	1.85	1.07–3.10	.02



- Initial use of combination therapy significantly reduces the likelihood of inappropriate therapy, which is associated with higher risk of death.
- However, administration of only one effective antimicrobial or combination therapy provides similar outcomes, suggesting that switching to monotherapy once the susceptibility is documented is feasible and safe.

Garnacho-Montero J *Crit Care Med* 2007; 35: 1888

Acinetobacter baumannii

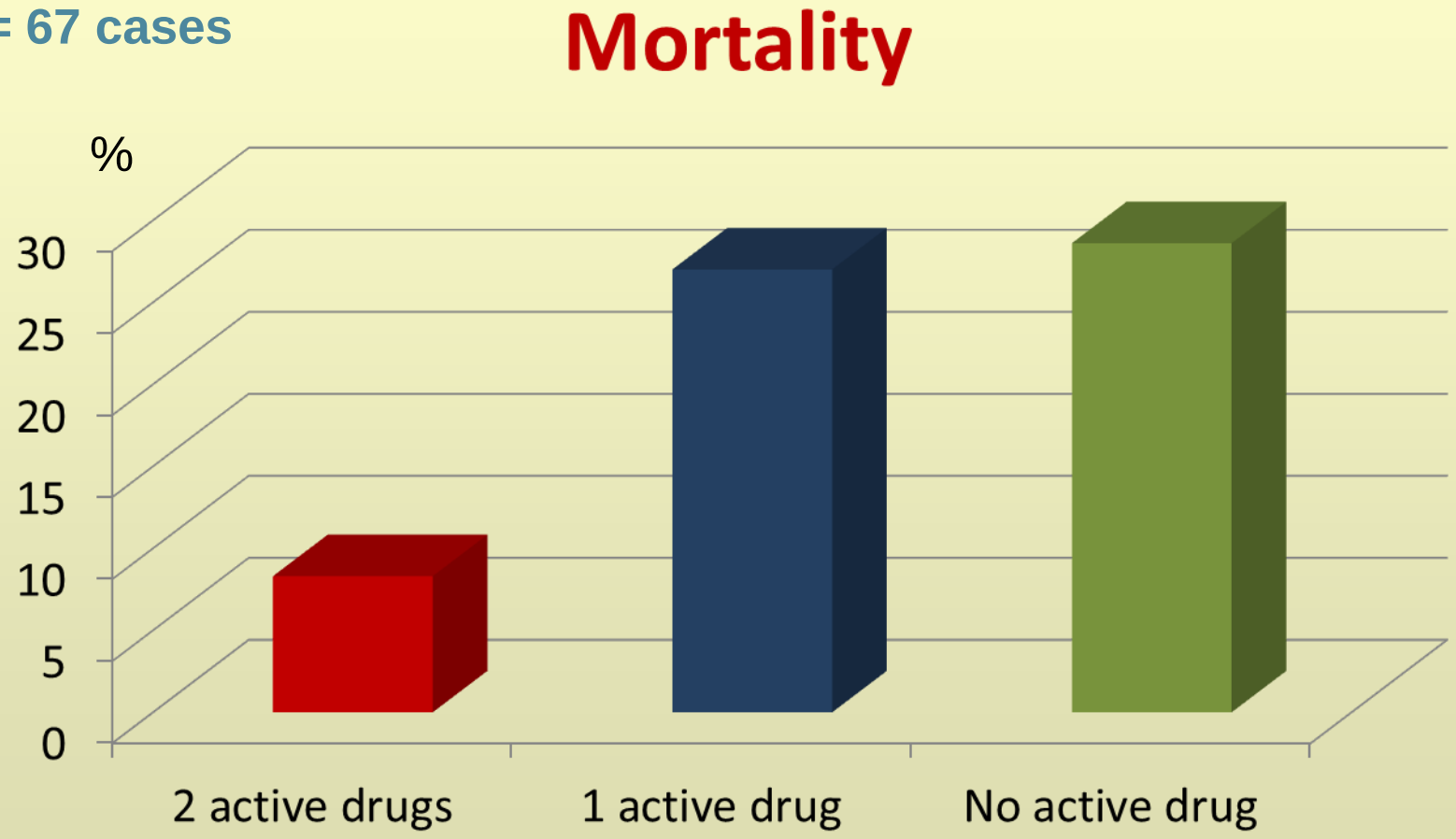
In vitro synergism

	Colistin	Tigecycline	Carbapenems	Sulbactam	Aminoglyc	Rifampicin	Others
Colistin		+	+	+			Pipt/tazo
Tigecycline			+	+	+		
Carbapenems				+	+	+	
Sulbactam						+	Cefepime Fosfomycin

- **Colistin + Tigecycline**: better with Tigecycline 200 mg q12h
- **Colistin + Carbapenem**:
  - *In vitro* synergy rates of 77% (95% CI: 64 to 87%)
  - **Meropenem was more synergistic than imipenem**
- **Carbapenem + Aminoglycoside**: probably no better than carbapenem (imipenem) monotherapy
- **Carbapenem + Rifampicin**: no clinical benefit
- Triple combination therapy of **meropenem,sulbactam and colistin** has consistently shown very high levels of synergy.

Carbapenemase-producing *Kl. pneumoniae*

n= 67 cases



Daikos GL et al *AAC* 2009; 53: 1868-1873

Carbapenemase-producing *Kl. pneumoniae*

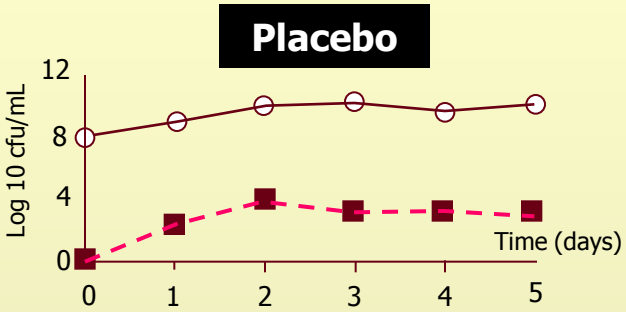
Qureshi ZA et al. AAC 2012; 56: 2108-2113

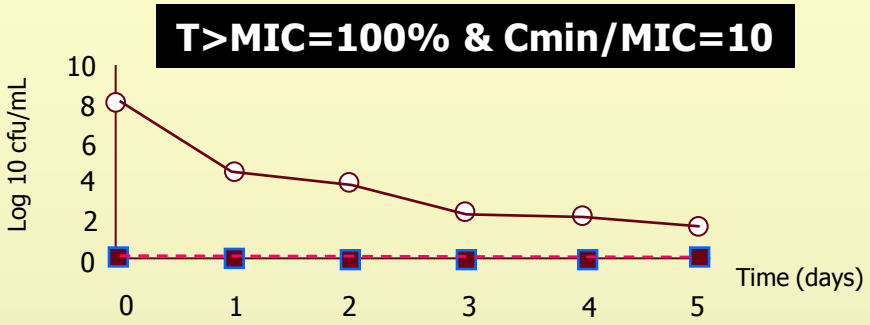
- **The 28-day mortality was 13.3% in the CT vs. 57.8% in the M group (P = 0.01).**
- **In the multivariate analysis, definitive therapy with a combination regimen was independently associated with survival (OR 0.07 ;95% CI 0.009-0.71; p = 0.02).**
- Despite *in vitro* susceptibility, patients who received monotherapy with colistin-polymyxin B or tigecycline had a higher mortality of 66.7%.
- Colistin/Tigecycline + carbapenem: most common (mortality - 12.5%).

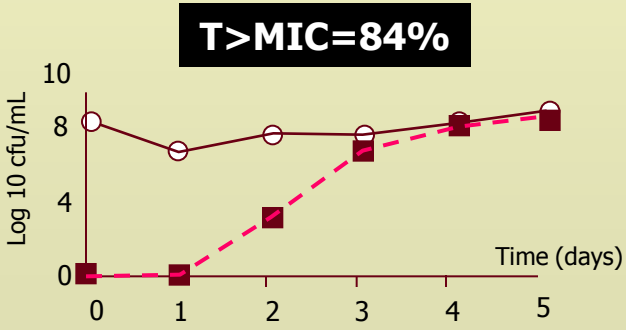
Zarkotou O et al. CMI 2011; 17: 1798-1803

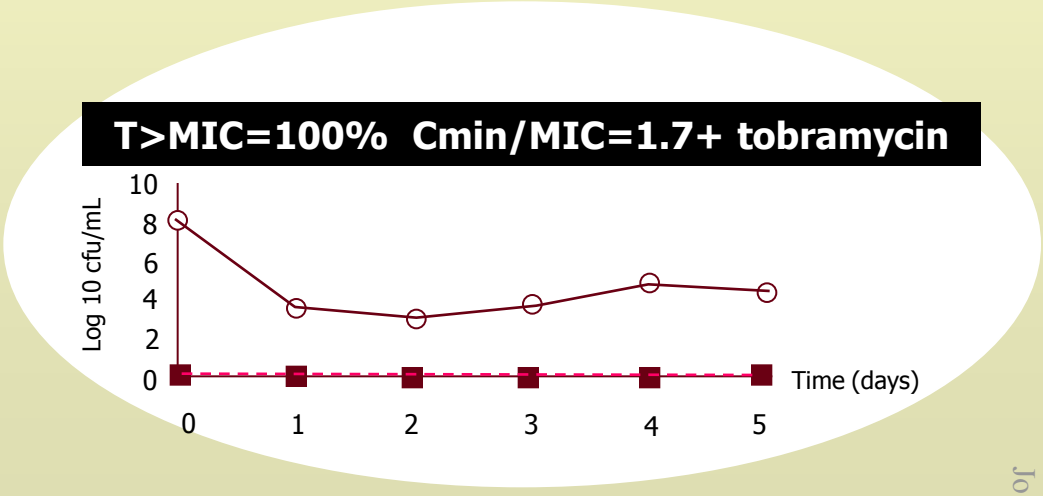
- **Overall mortality was 52.8% and infection mortality was 34%**
- Appropriate antimicrobial therapy was administered to 35 patients (66%)
- In the appropriate group: mortality in CT was significantly lower than in M group (0% vs. 46,7%; p= 0.001)
- **In univariate analysis, combinations of active antimicrobials (p 0.001) were significantly associated with survival**.

Resistance induction: Optimisation of minimum concentration/MIC ratio

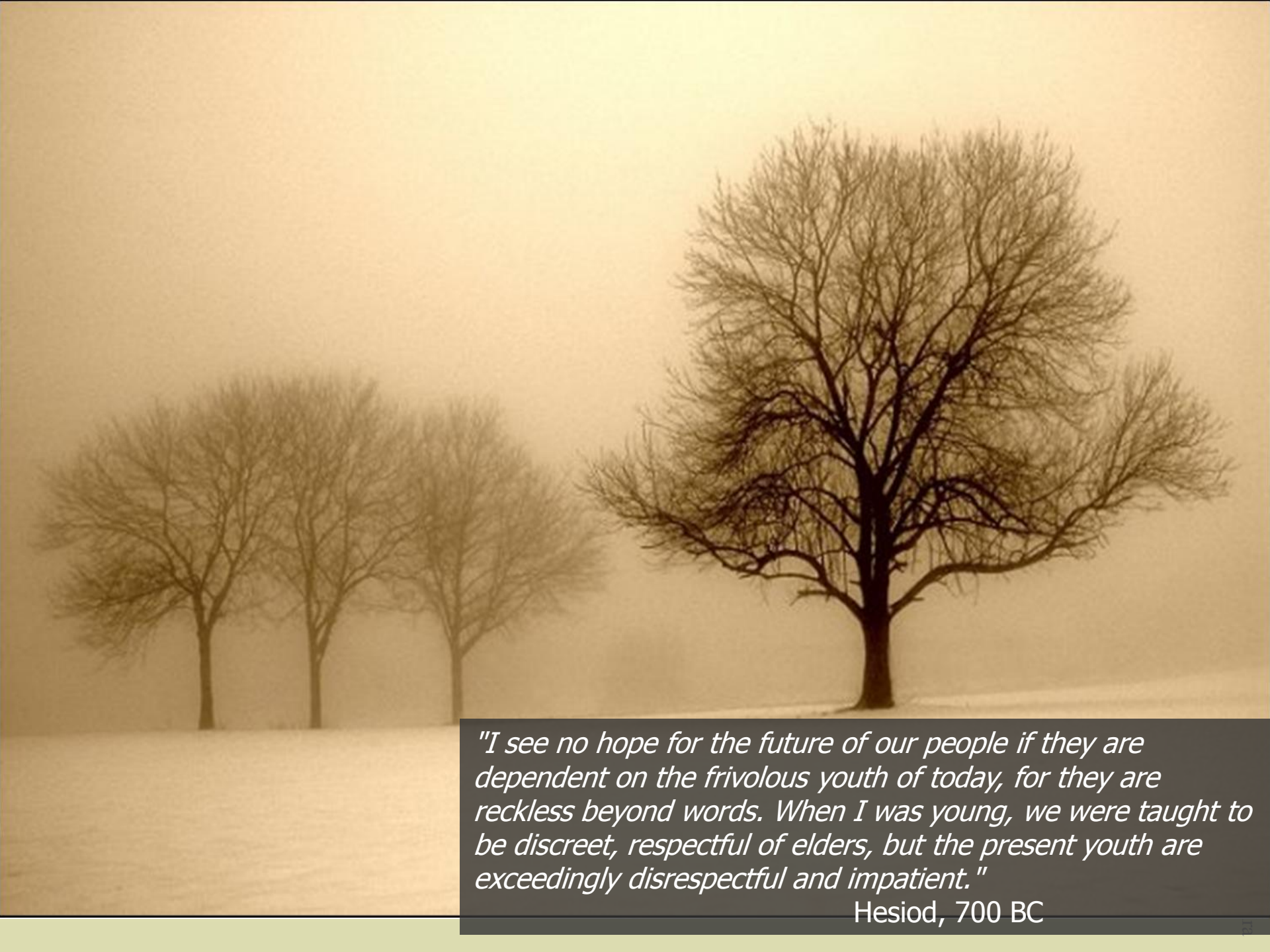








Tam Antimicrob Agents Chemother 2005; 49. 4920


"I see no hope for the future of our people if they are dependent on the frivolous youth of today, for they are reckless beyond words. When I was young, we were taught to be discreet, respectful of elders, but the present youth are exceedingly disrespectful and impatient."
Hesiod, 700 BC