Monotherapy vs combination therapy; clinical results

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Disclosure

(potential) conflict of interest	None
For this meeting possibly relevant relationships with companies	Company names
• Sponsoring or research funding • Fee or other (financial) compensation • Shareholder • Other relationship, namely …	• • • •

Reasons for combination therapy

Why combination therapy?

- Increased spectrum of coverage –independent
- Increased spectrum of coverage –fixed
  - Amoxicillin/ clavulanic acid
- Penetration at different sites of infection
- Synergism: increased activity of 2 antimicrobials

Reasons for combination therapy

Increased spectrum of coverage – independent

- Example: pneumonia
  - Penicillin + ciprofloxacin

Streptococcus pneumoniae

Legionella

Reasons for combination therapy

Increased spectrum of coverage – fixed

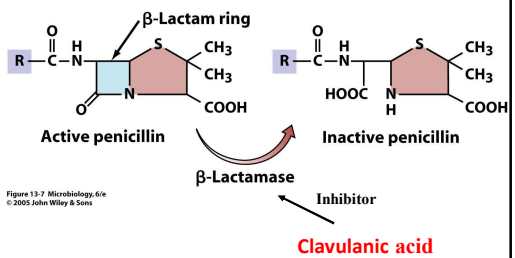

Figure 13-7 Microbiology, 6/e
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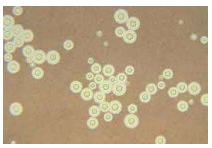
Augmentin is amoxicillin + clavulanic acid

Reasons for combination therapy

Penetration at different sites of infection

- Example:



Disseminated cryptococcosis

Flucytosine (5-FC) ⟶ Penetrates in CSF

Amphotericin B ⟶ Hardly penetrates in CSF

Reasons for combination therapy

Synergism

- Increased activity of an antimicrobial by adding a second antimicrobial

- Two drugs act on different sites or within different pathways

Synergy

Synergism -various methods-

- In vitro studies:
  - Checkerboards
  - Time kill curves
- In vivo animal studies:
  - Checkerboards
  - Time kill curves
  - Survival studies

Synergy

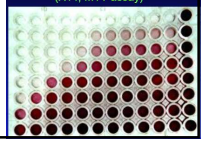
Fractional inhibitory concentration (FIC) index

- Tool to determine synergy or antagonism in vitro
- Calculated using a checkerboard
- Cave: differences in interpretation!

$$FIC = \frac{MIC_{combination}\ a}{MIC_{alone}\ a} + \frac{MIC_{combination}\ b}{MIC_{alone}\ b}$$

	Nguyen AAC 1995	Walsh AAC 1996	Eliopoulos Lorian	Moody ASM
synergism	<1	≤0.5	≤0.5	≤0.5
additive	1	0.5-1	0.5-1	
indifferent	1-2	>1-4		>0.5-4
antagonistic	>2	>4	>1	>4

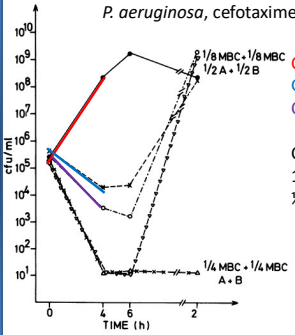
Colorimetric assays (XTT, MTT assay)



Synergy

Killing-curve method

P. aeruginosa, cefotaxime + gentamicin



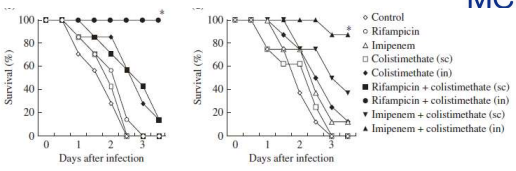
Control
Gentamicin (4mg/l; 1/4 MBC)
Cefotaxime (32 mg/l; 1/4 MBC)

Combinations:
1/8 MBC: 2 mg/l G+ 16 mg/l C
¼ MBC: 4 mg/l G + 32mg/l C

Hallander, AAC, p743, 1982

Synergy

Survival studies



- VAP-pneumonia mouse model
- Multidrug resistant *P. aeruginosa*
- Intranasal infection
- maximum synergistic effects: colistin + rifampicin
- Second best: imipenem plus colistin

Aoki, JAC,p534, 2009

Preclinical studies

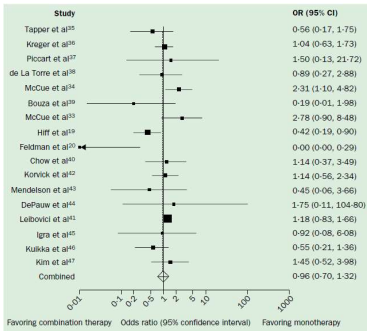
- Checkerboards: there are synergistic combinations
- Killing-curves: these are combinations with additive or synergistic effect
- Survival studies: these are combinations with additive or synergistic effect

Clinical studies

Clinical studies

Clinical studies

Clinical studies



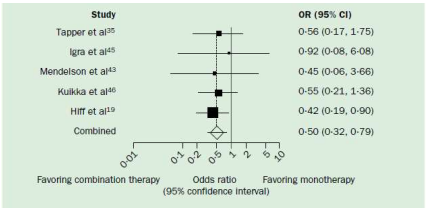
Gram-negative bacteremia

17 studies

Safdar Lancet Infect Dis 2004

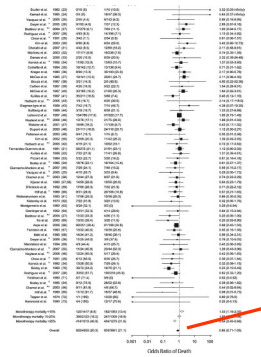
Clinical studies

Pseudomonas only – reduction in mortality



Safdar Lancet Infect Dis 2004

Clinical studies

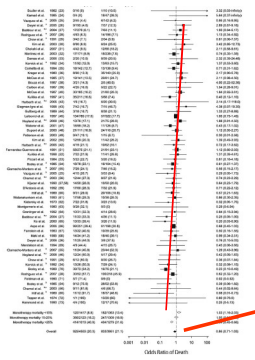


Survival for serious infections associated with sepsis and septic shock

0.86 (0.71-1.03)

Kumar et al CCM 2010

Clinical studies



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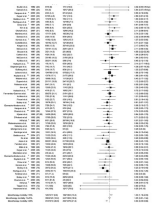


Monotherapy mortality <15%
Monotherapy mortality 15-25%
Monotherapy mortality >25%

1.53 (1.16-2.03)
1.05 (0.81-1.34)
0.54 (0.45-0.66)

Kumar et al CCM 2010

Clinical studies

Treatment of KPC-producing *K. pneumoniae* strains

- multicenter retrospective cohort study, (3 large Italian teaching hospitals)
- 125 patients with bloodstream infections caused by KPC-producing Kp
- Outcome: death within 30 days of the first positive blood culture
- Analysis:
  - Monotherapy vs combination therapy?
  - Other factors influencing outcome?

Tumbarello, CID,2012;55(7):943–50

Clinical studies

- Based on antibiograms after bloodstream infection onset:
  - Reported after 72–120 hours median 76 hours
  - 75/125, 60% of the empirical regimens were classified as inadequate
- The ineffective drugs were:
  - ß-lactam–ß-lactamase inhibitor combinations in 31 (41.3%)
  - carbapenems in 25 (33.3%)
  - aminoglycosides in 8 (10.7%)
  - fluoroquinolones in 6 (8%)
  - cephalosporins in 4 (5.3%)

Tumbarello, CID,2012;55(7):943–50

Clinical studies

Univariate analysis antibiotic regimen

Variable	No. (%) of Patients		*P* Value	OR (95% CI)
	Nonsurvivors (n = 50)	Survivors (n = 75)		
Postantibiogram antimicrobial regimens				
Monotherapy	25 (48.1)	21 (28.7)	.02	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	.28	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	.37	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	.09	1.66 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[a]	10 (19.2)	11 (15.1)	.54	1.17 (.71–1.96)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.26 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[b]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	.002	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	<.001	…

Monotherapy more in nonsurvivors

Combination-therapy more in survivors

3-drug Combination-therapy even more significant

Tumbarello, CID,2012;55(7):943–50

Clinical studies

Survival

Overall mortality rate 41.6%

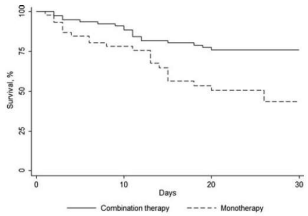


Figure 2. Kaplan-Meier curves showing the impact of combination therapy (solid line) versus monotherapy (dotted line) on 30-day mortality of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

Tumbarello, CID,2012;55(7):943–50

Clinical studies

Multivariate analysis

- outcome independently predicted by 3 factors:
  - presence of septic shock
  - high APACHE III score
  - **inadequate empirical therapy**
- **Supports combination therapy mainly to an increase antimicrobial spectrum**
- **But is misused to support synergism**

Tumbarello, CID,2012;55(7):943–50

Clinical studies

Example clinical studies synergism

- Colistin plus carbapenem vs colistin mono
- What is micro-organisms we want to study this on?
  - **Colistin S and Carbapenem R**
  - GNB that are carbapenem S should not be included

Paul, JAC,p2305,2014

Clinical studies

Bias in the existing studies

- Many studies included carbapenem susceptible strains
- Often observational retrospective design
  - Selection bias
  - Patients with carbapenem R strains are more likely to be more severily ill at baseline and have more comorbitity
    - That comorbidity will most likely determine the outcome
  - Choosing combination vs monotherapy was not random

Paul, JAC,p2305,2014

Clinical studies

Bias in the existing studies (2)

- For severe infection there are 7-10 variables known to determine outcome
- So, if you want to study one of them. You need 100rds-1000nds of patients in a study

Paul, JAC,p2305,2014

Clinical studies

Clinical studies

- Qureshi 2012:
  - KPC-producing *K. pneumoniae* bacteremia
  - in favor combination therapy, but based on 34 patients
- Tumbarello 2012: in favor of combination therapy but based on 16 patients
- Both studies had other biases
- **So, there are no data to support the use of combination therapy with carbapenem plus colistin over colistin mono for carbapenem R GNB**

Tumbarello, CID,2012;55(7):943–50
Qureshi,AAC,p2108,2012

Paul, JAC,p2305,2014

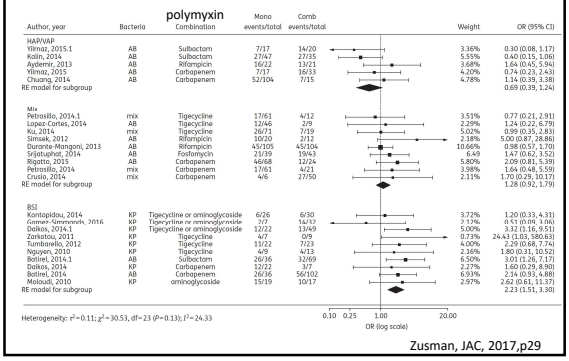
Clinical studies

Polymyxin mono vs combination for carba-R infections

- Evaluation of the available data
- 22 studies with 28 comparisons
- Infections due to carbapenem R or carbapenemase-producing bacteria

Zusman, JAC, 2017,p29

Meta-analysis



Zusman, JAC, 2017,p29

Polymyxin monotherapy vs combination with carbapanems

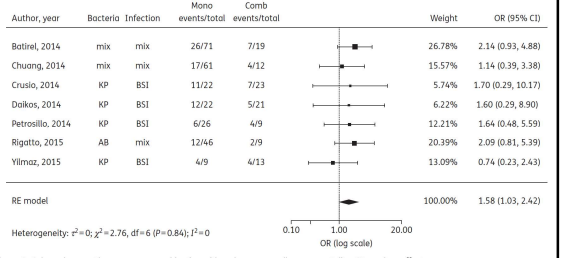


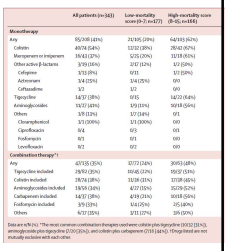
Figure 4. Polymyxin monotherapy versus combination with carbapenems, all-cause mortality. RE, random effects.

Zusman, JAC, 2017,p29

Clinical studies

Retrospective cohort 343 patients

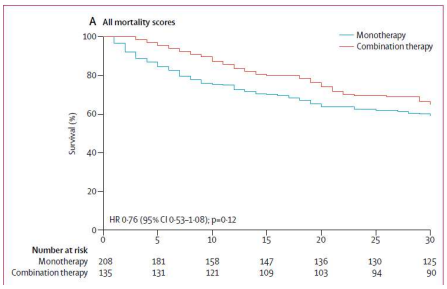
- Monomicrobial BSI with CPE
- 10 countries
- 26 hospitals
- 30-day all cause mortality
- Mono= 1 in-vitro active
- Combi= more than 1



Gutiérrez-Gutiérrez, 2017, Lancet ID

Clinical studies

Overall analysis

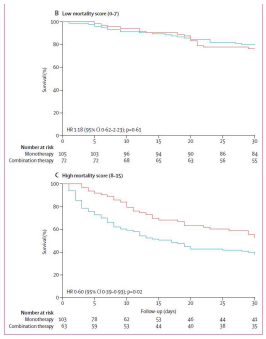


Suggests that there is superiority of combination therapy over monotherapy

Gutiérrez-Gutiérrez, 2017, Lancet ID

Clinical studies

Differences per mortality rate



More benefit in the high mortality group

Gutiérrez-Gutiérrez, 2017, Lancet ID

Conclusions

Conclusions

The evidence of combination therapy:

- Pre-clinical/ animal studies
  - Proven additivity and synergy for several combinations
  - Reduced mortality in mice
- Clinical studies:
  - Reduced mortality by increasing the antimicrobial spectrum
  - Limited evidence to support synergism in retrospective studies
  - No evidence from prospective studies
  - Reduced mortality for Pseudomonas infections
  - Be careful for bias in these studies