

Monotherapy versus Combined therapy: pros and cons

MONOTHERAPY



COMBINATION THERAPY



We concede :

- Endocarditis :
 - streptococcal (enterococcal)
 - staphylococcal ??

We do not concede :

- mixed typical/atypical pulmonary infections (new fluoroquinolones)
- mixed aerobic/anaerobic infections (carbapenems)
- gram (-) meningitis (3-4th generation cephalo)
(meropenem)



Theoretical advantages of combination therapy

- Broader spectrum of coverage (especially in nosocomial infections)
- Potentially synergistic interaction
- Possibility of minimising emergence of [®]



Treatment in neutropenic patients

- Historically : 50-84% mortality in gram(-) rods bacteremia before 70's
- Improved impressively by
 - ureidopenicillin
 - +
 - aminoglycoside
 - Klastersky Cancer '73
 - EORTC JID '78
- extended to other "severe" infections



Treatment of neutropenic patients

- EORTC (and others) advocated combination therapy for decades
- However
 - shifting spectrum of causative agents of bacteremia
 - introduction of new agents with extended spectrum of activityrenewed the interest in monotherapy (J. Maertens Acta Clin. Belg. 1998)



Antimicrobial activity of 15 drugs against the six most frequently isolated gram-negative (5,847 strains) from the 1997 SENTRY Antimicrobial Surveillance Program.

Antimicrobial agent	<i>Pseudomonas aeruginosa</i> (n = 1,135) % resistant	<i>Acinetobacter species</i> (n = 224) % resistant	<i>Escherichia coli</i> (n = 2,527) % resistant	<i>Klebsiella species</i> (n = 1,089) % resistant	<i>Enterobacter species</i> (n = 647) % resistant	<i>Serratia marcescens</i> (n = 225) % resistant
<i>Broad-spectrum</i>						
Cefepime	9.7	17.4	0.0	0.6	0.5	4.0
Ceftazidime	12.8	17.0	1.0/3.0*	2.9/5.9*	21.6	6.7
Piperacillin/ tazobactam	9.3	13.9	2.5	4.4	10.8	11.1
Imipenem	8.3	3.6	0.1	0.2	0.5	2.2
Gentamicin	11.9	22.3	2.9	2.8	5.6	7.1
Ciprofloxacin	13.3	24.1	2.1	2.7	4.3	7.1



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1983, p. 435-439

SERUM BACTERICIDAL ACTIVITY OF CEFTAZIDIME AND
CEFOPERAZONE ALONE OR IN COMBINATION WITH AMIKACIN
AGAINST *PSEUDOMONAS AERUGINOSA* AND *KLEBSIELLA*
PNEUMONIAE

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Sera of volunteers receiving ceftazidime (2g) or amikacin (500mg), alone or in combination, or cefoperazone (2,4 or 6g) or cefoperazone (2g) with amikacin (500mg) were evaluated for bactericidal activity against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Serum bactericidal activities were similar for ceftazidime and ceftazidime plus amikacin, but were definitely lower for amikacin alone.



Median SBAs and percentage of sera with SBA \geq 1:8

Organism	Antibiotic (dose)	SBA			
		1h		6h	
		Median % Sera SBA titer \geq 1 : 8		Median % Sera titer \geq 1 : 8	
P. aeruginosa	Amikacin (0.5g)	1 : 2	11	<1 :	1
	Ceftazidime (2.0g)	1 : 64	9	1 : 8	74
	Amikacin (0.5g) + ceftazidime (2.0g)	1 : 64	10	1 : 8	81



Treatment of neutropenic patients

Several large scale trials published since 10 years, showing similar efficacy of :

- ceftazidime/piperacillin- tobra (De Pauw Ann. Int. Med., '94)
 - 696 episodes 61-62% satisfact. response
- Imipenem/ ceftazidime \pm amikacin (Rolston Arch. Int Med,'92)
 - 750 épisodes 72-71/59% satisfact. response
- Meropenem/ ceftazidime \pm amikacin (Cometta AAC, 1996)
 - 56-52% satisfact. response
- Place of cefepime alone ? (in units with high rate of β -lactam hyperproducing Enterobacter, Citrobacter, Serratia,...)



Review of prospective studies in gram (-) bacteremia Combination > Monotherapy

- EORTC (NEJM, 1987)
 - Main difference in *P.aeruginosa* infection
- KORVICK et al. (AAC, 1992)
 - 230 cases of *K.pneumoniae*
 - no difference (82-80%) except if : hypo TA within 3 days of BC (+) : 76%-50% ($p < 0.05$)
- Hill et al. (Am J Med 1989)
 - 200 cases of *P. aeruginosa*
 - Survival 73%-53% ($p 0.02$)
 - but 3/4 of monotherapy was aminoglycoside alone !



Review of prospective studies in gram (-) bacteremia Combination = monotherapy

- 5 prospective studies

- Piccart et al. (AAC, 1984)

- 50 cancer patients randomized

Cefoperazone	78%	Clinical response
Cefoperazone + Amika	81%	

- Fainstein et al. (JAC, 1983)

- 37 cancer patients, randomized

Ceftazidime	94%	Clinical response
Ceftazidime + tobra	95%	

10 P.aeruginosa on both groups : successful for all



Review of prospective studies in gram (-) bacteremia Combination = monotherapy

– Chow et al. (Ann. Int Med, 1991)

- 129 patients- Enterobacter. Observational

	Full group	Severely ill
β -lactam	83%	50%
β -lactam + amino	84%	73%

– Leyland et al. (JAC, 1992)

- 36 neutropenic patients, randomized

Imipenem	Equally effective
Piperacillin + gentamicin	



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1997, p. 1127-1135

MONOTHERAPY VERSUS β -LACTAM-AMINOGLYCOSIDE
COMBINATION TREATMENT FOR GRAM-NEGATIVE
BACTEREMIA : A PROSPECTIVE, OBSERVATIONAL STUDY

LEONARD LEIBOVICI et al.



LEIBOVICI et Al., AAC, 1997

Mortality and antibiotic treatment : univariate analysis

Antibiotic treatment	No. of patients who died/Total No. of patients (%)	
	Empirical treatment	Definitive Treatment
- Inappropriate treatment	228/670 (34)	52/205 (25)
- Appropriate treatment		
β-lactam	131/789 (17)	109/816 (13)
- Aminoglycoside	59/249 (24)	44/193 (23)
- Aminoglycoside plus β-lactam	62/337 (19)	57/442 (-15)
	NS	NS

* p0.01



Review of prospective studies in gram (-) bacteremia Combination = Monotherapy

- LEIBOVICI et al. (AAC, 1997)
 - 2124 patients (8 years)

β-lactam	19%	mortality
β-lactam + amino	17%	
 - No difference in :
 - rates of persistent blood cultures
 - duration of febrile disease
 - duration of hospital stay
 - outcome of Enterobacter infection (72 cases)
 - Trend (not stat. significant)

in	P.aeruginosa(O.R. 0,7)
	neutropenic pat. without a source (O.R. 0,5)



Is combination therapy mandatory in P.aeruginosa septicemia ?

Two retrospective studies

- Vidal et al. (Arch Int Med, 1996)

- 189 episodes

- No difference

- Siegman et al. (Int J Inf Dis, 1998)

- 123 patients → 57 after exclusion

- early mortality (48h)

- inappropriate therapy

- Monotherapy (47 cases) : 14%

- Combination (15 cases) : 13%

mortality

- No difference



Hospital acquired bronchopneumonia (HAP)

- Non neutropic animal model; Mimosz et al., JAC 1998

Enterobacter bronchopneumonia

® ceftazidime

wild type

stable derepressed
type

Cefepime ± amikacin

- - same bactericidal activity against both types
 - same bacterial killing in the lungs
 - same AUIC 24 h



HAP - Human Trials (1)

- Lack of clinical data to support combination therapy in all cases
- Old data outdated with the new
 - 3-4th generation cephalosporins
 - Carbapenems
 - Fluoroquinolones
- Achieving
 - high serum levels
 - high levels in extracellular fluid of pulmonary tissues (no special diffusion barrier)



HAP - Human Trials (2)

- Summary of 7 randomized trials comparing monotherapy versus combination (1.010 cases) (1983-1993) Arbo- Snydman (Sem Resp Infect-1993)

Mono : cefoperazone or ceftazidim or meropenem

Combinations : Aminoglycoside + β -lactam

P.aeruginosa : 14% Ventilation : 25%

Mortality : 14%

→ | Mono : 82% Clinical efficacy
| Combination : 72%



HAP - Human Trials (3)

- More conflicting/limited data in severe VAP
 - consider (at least transient) combination therapy in contrast to mild to moderate HAP



Does combination therapy prevent the emergence of resistance ?

- MOELLERING (CID, 1998)
 - Milatovic and Braveny (Eur J Clin. Microb. 1987)
 - Resistant organisms emerged during therapy in : 4.7-13.4%
 - Trend toward less frequent emergence of R in patients receiving combination therapy
 - The most frequent : P.aeruginosa : 16.7-24.5%
 - No proof in several studies as :
 - Nichols and Maki : Chemoterapia 1985(LRT infection)
 - Bodey Arch. Int Med 1985 (410 septicemia)



Combination therapy as a tool to prevent emergence of bacterial resistance

Mouton Infection 1999

- Animal experiments :
 - Scarse data on non P.aeruginosa micro-organisms :
Usually : no difference
 - Few controlled studies (apart from endocarditis) on P.aeruginosa
 - | With aminosides (see table)
 - | With quinolones (see figure)



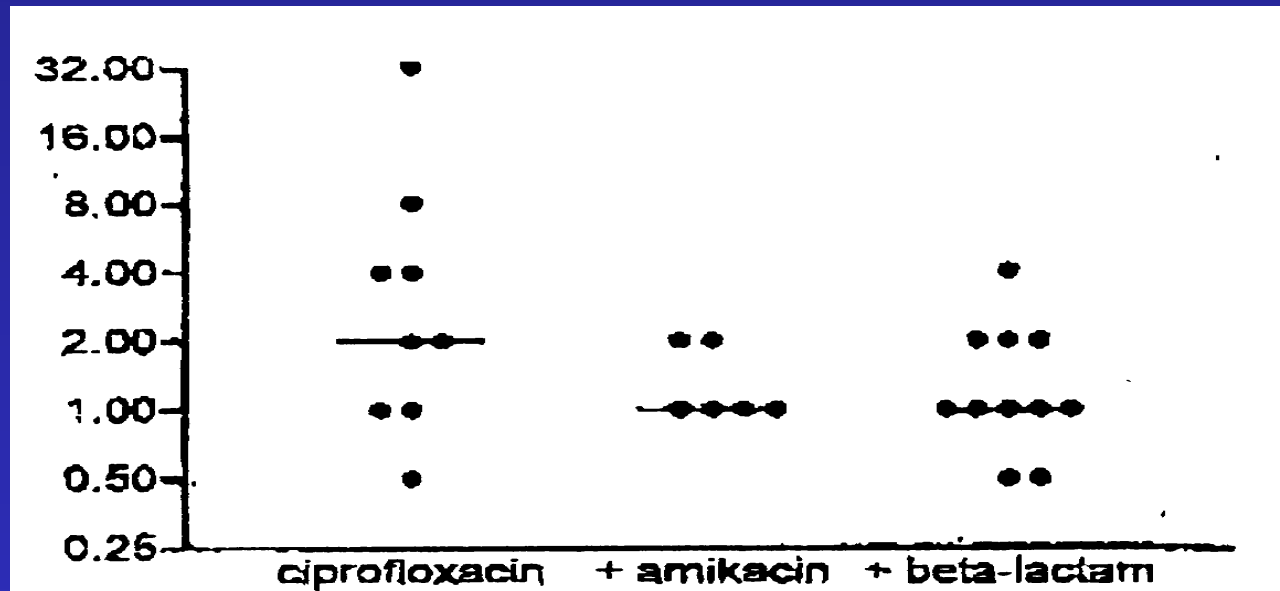
Number of animals with resistant subpopulations of *P.aeruginosa* after therapy in relation to the total number of animals treated during single drug therapy and combination therapy

References	Beta-Lactam	
	Single	Combination
Johnson and Thompson 1986	5/20 6/20	0/20 2/20
Johnson et al. 1985	8/20 4/20	1/20 0/20
Lumish and Norden 1976	19/29 5/15	0/16 0/15
	Mouton Infection 1999	



Combination therapy and bacterial resistance

Increase MIC



Increase in MIC for ciprofloxacin of *Pseudomonas aeruginosa* during monotherapy or combination therapy with amikacin and with β -lactam. The lines are medians.

Mouton Infection 1999



Combination therapy as a tool to prevent emergence of bacterial resistance

- Controlled Human Trials

- 2 old studies on cystic fibrosis

- With azlocillin

- or ticarcillin

- ± aminoglycoside

- less resistant strains in combination

BUT : low intrinsic activity of these drugs in comparison with new compounds ⇒ ?



... Conclusive data that combination antibiotic therapy for nosocomial bloodstream infections prevents the subsequent emergence of antibiotic resistance are lacking

Kollef CID 2000



Possible indications for combination antibiotic therapy

- Immunosuppressed patient
 - *Pseudomonas aeruginosa*
 - *Klebsiella spp.*
 - *Enterobacter spp.*
- Severely ill patient

Chow-Yu Int J Ant.Ag, 1999



Indications for monotherapy

- Less virulent organism
 - *E. coli*,...
- Nosocomial gram-negative rod
 - *Serratia spp.*
 - *Citrobacter spp.*
 - *Providencia spp.*
 - *Morganella morganii*
- Urinary tract or intravascular catheter portal
- Well, stable patient
- Immunocompetent



Conclusion

- Choice of treatment should be tailored individually to each patient according to clinical/biological factors
- (short term) combination therapy may be considered in certain instances
- However, monotherapy should be sufficient in most clinical situations

