

- 3 Schauburger CW, Rooney BL, Beguin EA, Schaper AM, Spindler J. Evaluating the thirty minute interval in emergency cesarean sections. *J Am Coll Surg* 1994;179:151-5.
- 4 Roemer VM, Heger-Romermann G. [Emergency cesarean section—basic data]. *Zeitschrift Geburtshilfe Perinatol* 1992;196:95-9. (In German.)
- 5 Chauhan SP, Roach H, Naef RW, Magann EF, Morrison JC, Martin JN Jr. Cesarean section for suspected fetal distress. Does the decision-incision time make a difference? *J Reprod Med* 1997;42:347-52.
- 6 Dunphy BC, Robinson JN, Sheil OM, Nicholls JSD, Gillmer MDG. Caesarean section for fetal distress, the interval from decision to delivery, and the relative risk of poor neonatal condition. *J Obstet Gynaecol* 1991;11:241-4.
- 7 MacKenzie IZ, Cooke I. Prospective 12 month study of 30 minute decision to delivery intervals for "emergency" caesarean section. *BMJ* 2001;322:1334-5.
- 8 James D. Caesarean section for fetal distress. *BMJ* 2001;322:1316-7.
- 9 Confidential Enquiries into Maternal Deaths. *Why mothers die 1997-1999: the fifth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom*. No 5. London: RCOG Press; 2001.
- 10 American College of Obstetricians and Gynecologists technical bulletin. Fetal heart rate patterns: monitoring, interpretation, and management. No 207, Jul 1995 (replaces No 132, Sept 1989). *Int J Gynaecol Obstet* 1995;51:65-74.
- 11 MacKenzie IZ, Cooke I. What is a reasonable time from decision-to-delivery by caesarean section? Evidence from 415 deliveries. *Br J Obstet Gynaecol* 2002;109:498-504.
- 12 Goodwin TM, Belai I, Hernandez P, Durand M, Paul RH. Asphyxial complications in the term newborn with severe umbilical acidemia. *Am J Obstet Gynaecol* 1002;167:1506-12.

(Accepted 31 December 2003)
doi 10.1136/bmj.38031.775845.7C

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

Mical Paul, Ishay Benuri-Silbiger, Karla Soares-Weiser, Leonard Leibovici

Abstract

Objective To compare β lactam monotherapy with β lactam-aminoglycoside combination therapy for severe infections.

Data sources Medline, Embase, Lilacs, Cochrane Library, and conference proceedings, to 2003; references of included studies; contact with all authors. No restrictions, such as language, year of publication, or publication status.

Study selection All randomised trials of β lactam monotherapy compared with β lactam-aminoglycoside combination therapy for patients without neutropenia who fulfilled criteria for sepsis.

Data selection Two reviewers independently applied selection criteria, performed quality assessment, and extracted the data. The primary outcome assessed was all cause fatality by intention to treat. Relative risks were pooled with the random effect model (relative risk < 1 favours monotherapy).

Results 64 trials with 7586 patients were included. There was no difference in all cause fatality (relative risk 0.90, 95% confidence interval 0.77 to 1.06). 12 studies compared the same β lactam (1.02, 0.76 to 1.38), and 31 studies compared different β lactams (0.85, 0.69 to 1.05). Clinical failure was more common with combination treatment overall (0.87, 0.78 to 0.97) and among studies comparing different β lactams (0.76, 0.68 to 0.86). There was no advantage to combination therapy among patients with Gram negative infections (1835 patients) or *Pseudomonas aeruginosa* infections (426 patients). There was no difference in the rate of development of resistance. Nephrotoxicity was significantly more common with combination therapy (0.36, 0.28 to 0.47). Heterogeneity was not significant for these comparisons.

Conclusions In the treatment of sepsis the addition of an aminoglycoside to β lactams should be

discouraged. Fatality remains unchanged, while the risk for adverse events is increased.

Introduction

Treatment with a combination of β lactam and an aminoglycoside is purported to be superior to β lactam alone for sepsis on the basis of potential advantages such as in vitro synergism and prevention of development of resistance.¹⁻⁷ Textbooks and guidelines advise the combination for specific pathogens, such as *Pseudomonas aeruginosa* and other Gram negative bacteria, and for infections commonly caused by these pathogens.^{8,9} In aiming for optimal antibiotic treatment of severe infections, hospital clinicians tend to use combination therapy despite the lack of direct evidence for its effectiveness. Observational studies show that 56% of patients with septic shock in the intensive care unit¹⁰ are given β lactam-aminoglycoside combination therapy.

We performed a systematic review and meta-analysis of randomised trials comparing β lactam-aminoglycoside combination therapy with β lactam monotherapy for severe infections in patients without neutropenia.

Methods

We searched Medline, Embase, Lilacs, the Cochrane Library (all up to March 2003), conference proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (1995-2002), and citations of included trials (see bmj.com for details).

We included all randomised and quasi-randomised trials that compared any β lactam monotherapy with any


Department of
Medicine E and
Infectious Diseases
Unit, Rabin Medical
Centre, Beilinson
Campus,
Petah-Tikva 49100,
Israel
Mical Paul
consultant


Department of
Medicine E, Rabin
Medical Centre,
Beilinson Campus,
Petah-Tikva

Ishay
Benuri-Silbiger
researcher
Karla Soares-Weiser
coordinator of clinical
research
Leonard Leibovici
associate professor

Correspondence to:
M Paul
mica@zahav.net.il

BMJ 2004;328:668-72

 A full list of references to excluded studies can be found on bmj.com

 This is the abridged version of an article that was posted on bmj.com on 2 March 2004: <http://bmj.com/cgi/doi/10.1136/bmj.38028.520995.63>

combination of a β lactam and an aminoglycoside for severe infections. Severe infection was defined as clinical evidence of infection, plus evidence of a systemic response to infection.¹¹ We excluded studies with a drop-out rate above 30%, unless intention to treat analysis was given for mortality or failure outcomes, and studies with more than 15% of patients with neutropenia, neonates, and preterm babies.

The primary outcome assessed was all cause fatality by the end of study follow up and up to 30 days. Secondary outcomes included treatment failure, defined as death, non-resolving primary infection, any modification to allocated antibiotics, or any therapeutic invasive intervention not defined by protocol; bacteriological failure, defined as persistence of primary pathogen; bacterial and fungal superinfections and colonisation; adverse events; and length of hospital stay. We separated studies that compared the same β lactam from studies that compared different β lactams. We performed subgroup analyses for *P aeruginosa* infections, any Gram negative infection, bacteraemia, and specific sources of infection.

Two reviewers independently applied inclusion and exclusion criteria and extracted the data. We extracted outcomes by intention to treat, unless the reasons for exclusions were not presented. In this case, we used the presented results (per protocol analysis) in the main analysis and compared them with results using all randomised patients and assuming failure for dropouts. We expected heterogeneity with respect to outcomes and used the random effects model, comparing it to a fixed effect model.¹² The effect of study quality measures was examined through sensitivity analysis.

We examined a funnel plot of the log of the relative risk against the weight to estimate potential selection bias (such as publication bias) and to assess whether effect estimates were associated with study size.

Results

We evaluated 144 eligible randomised trials and included 64 in the review (see bmj.com). The trials included 7586 patients, nearly all adults, and were performed between the years 1968-2001. The median number of patients per trial was 87 (range 20-580). The major conditions were severe sepsis, pneumonia, or Gram negative infections (41 trials), abdominal infections (11 trials), urinary tract infections (7 trials), and Gram positive infections (5 trials). Allocation to antibiotics was empirical in 56 trials. The same β lactam was compared in 20 trials, while all other trials compared one β lactam to a different, narrower spectrum β lactam combined with an aminoglycoside.

All cause fatality—Forty three trials including 5527 patients reported all cause fatality. There was no significant difference between monotherapy and combination therapy when we combined these studies (fig 1). There was no difference among the 12 studies with 1381 patients that compared the same β lactam or among studies that compared different β lactams. The heterogeneity for this comparison was low.

Treatment failure—We compared clinical and bacteriological failures in 63 and 43 trials, respectively. For both comparisons, monotherapy was not significantly different from combination therapy among studies that compared the same β lactam. Monotherapy was

significantly superior to combination therapy among studies that compared different β lactams. The overall comparison favoured monotherapy for clinical failure (0.87, 0.78 to 0.97; 6616 patients; number needed to treat 34, 20 to 147) and for bacteriological failure (0.86, 0.72 to 1.02; 3511 patients).

Subgroup analysis—Major effectiveness outcomes were compared within the defined patient subgroups: *P aeruginosa* infections, any Gram negative infection, bacteraemia, non-urinary tract infections, Gram positive infections, and endocarditis. We did not detect an advantage to combination therapy with any subgroup tested (see bmj.com).

Development of resistance—Combination therapy did not lower bacterial superinfection or colonisation rates, which we would have expected if combination therapy prevented the development of resistance. Relative risks tended to favour monotherapy for bacterial superinfections (0.79, 0.59 to 1.06). Rates of fungal superinfection were similar. Twenty six studies reported coverage rates of the allocated treatment, although outcomes were not related to coverage. Among studies with different β lactams, the monotherapy β lactam provided broader coverage than the combination β lactam in 13 studies, the opposite occurring in two studies. Combined coverage of the β lactam and the aminoglycoside equalled monotherapy in these studies.

Dropouts and adverse events—The dropout rate was 12.6% and similar in both study groups (1.01, 0.85 to 1.20, 24 studies, 3631 patients). Few patients (2%) discontinued treatment because of adverse events with no difference between study groups (0.89, 0.52 to 1.52, 15 studies, 3042 patients). Nephrotoxicity was more common with combination therapy in nearly all studies, and the combined relative risk was 0.36 (0.28 to 0.47, fig 2), corresponding to a number needed to harm of 15 (14 to 17) for combination therapy.

Sensitivity analysis—Sensitivity analyses were carried out for measures of study quality. All sensitivity comparisons were non-significant. The advantage of monotherapy was more significant in trials that used some type of blinding. The funnel plot for treatment failure generated a nearly symmetrical “funnel distribution” (see bmj.com).

Discussion

Main findings

In this systematic review of all randomised trials we have shown that β lactam-aminoglycoside combination therapy and β lactam monotherapy for the treatment of sepsis have similar effects in patients without neutropenia.

Twenty trials compared the same β lactam. All cause fatality, the most significant and objective outcome, was not reduced by the addition of aminoglycosides. Clinical and bacteriological failure, which may be prone to bias with non-blinded trials and are of much lesser relevance to patients, were not significantly different. However, rates of adverse events increased with the aminoglycoside. Nephrotoxicity was much more common with combination therapy.

Forty four trials compared a broad spectrum, usually novel, β lactam with a “routine” combination regimen. Rates of appropriate antibiotic treatment with combination therapy and monotherapy were

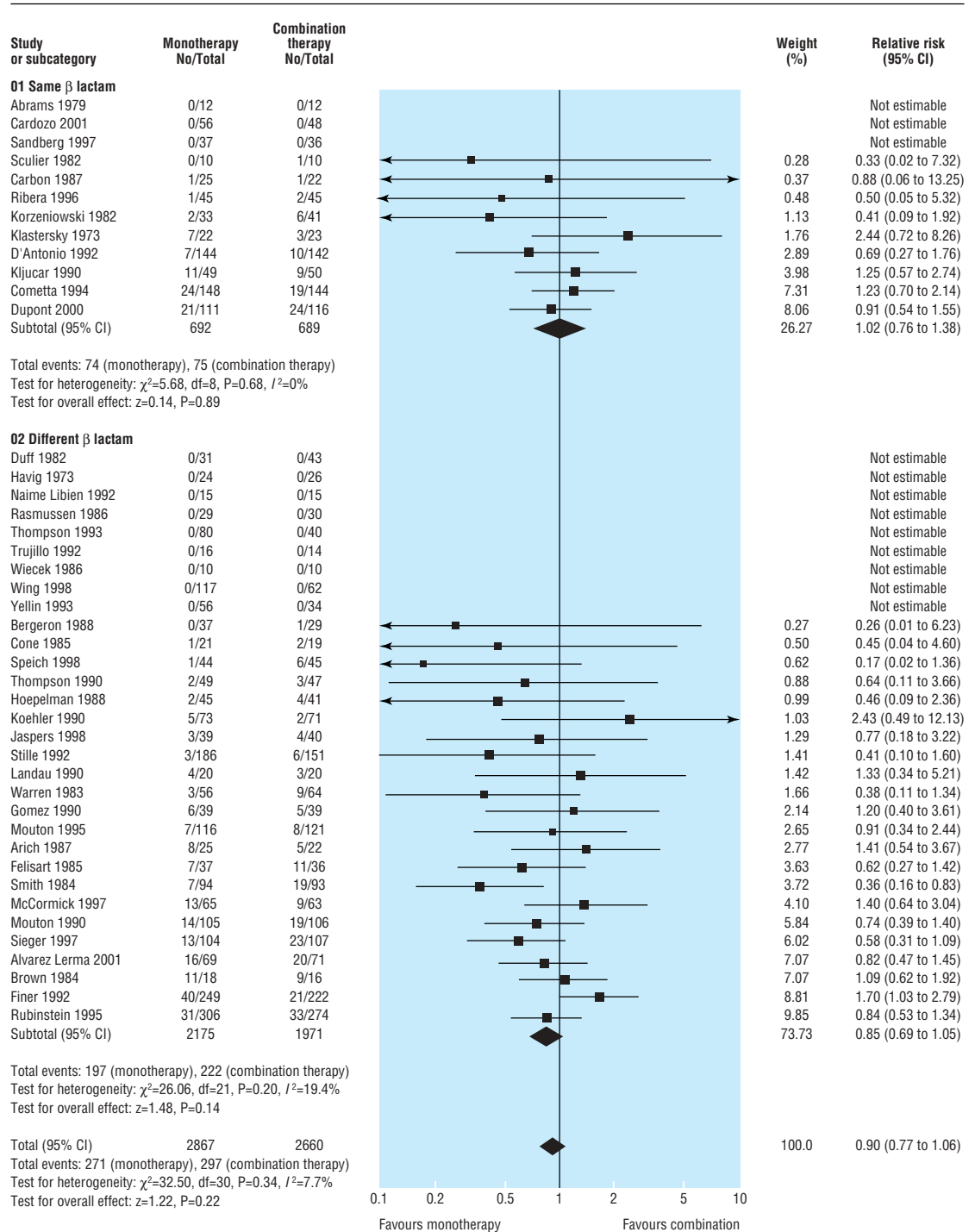


Fig 1 All cause fatality in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

similar when reported. Fatality was not significantly different. Failures were significantly more common with combination therapy. Among all trials, we found no evidence for any potential prevention of infection by resistant isolates with combination therapy.

How should these findings be interpreted?

It can be debated which design appropriately examines the clinical interpretation of synergism, studies comparing same or different β lactams. Synergism has been defined as a 2 log₁₀ or greater reduction in bacte-

rial count with the combination versus that with each of the agents alone.¹³ In studies comparing the same β lactam this is directly tested, but the effect of increasing the antibiotic spectrum cannot be separated from a synergistic effect. In studies comparing different β lactams the spectrum of coverage was similar in both arms. However, synergism can be examined only indirectly. If we assume that the aminoglycoside offers more than its additional coverage, the combination arm should perform as well, or better, than the broader

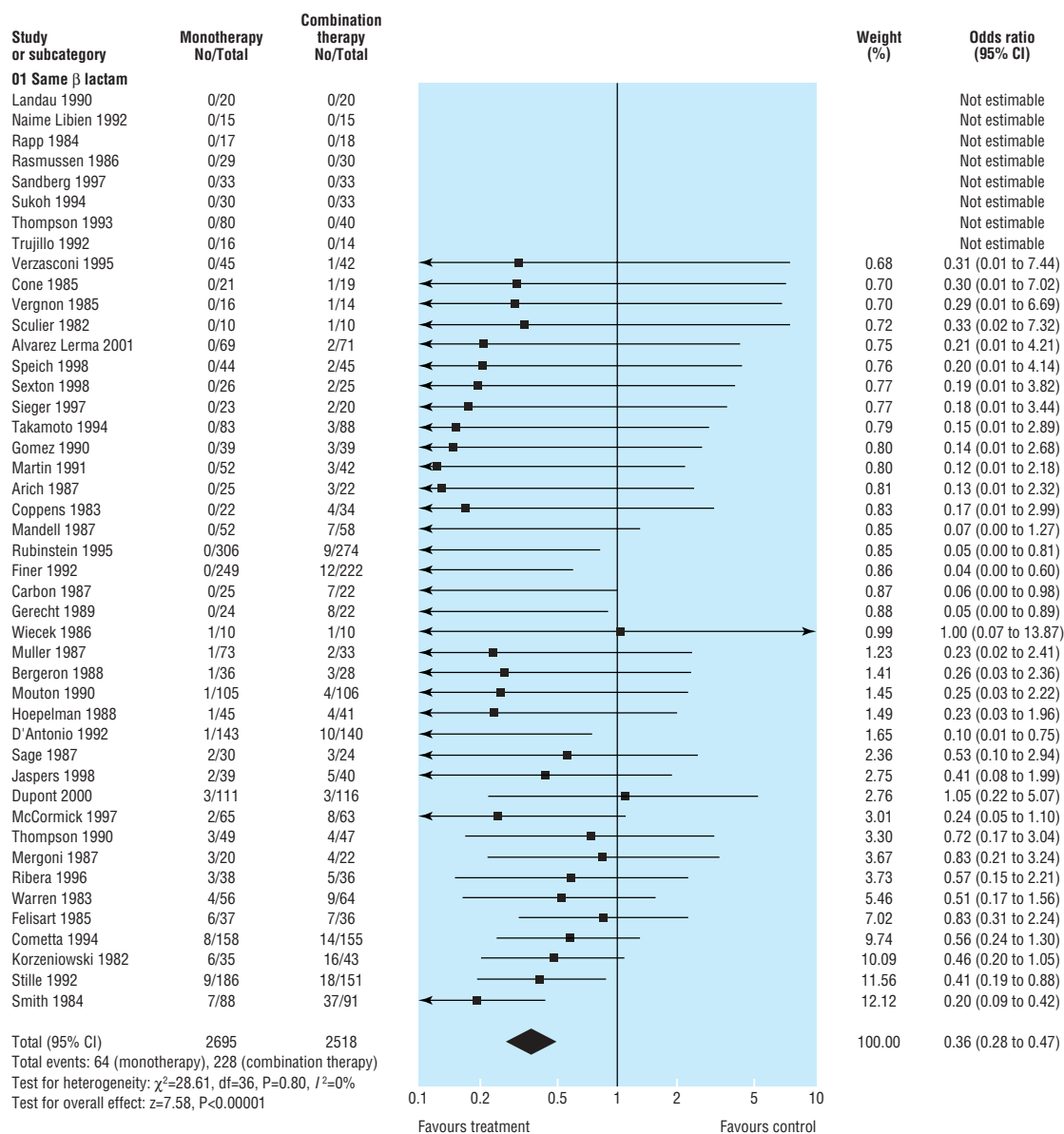


Fig 2 Adverse events: nephrotoxicity in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

spectrum β lactam monotherapy. With the former design we did not detect an advantage to the combination, while with the latter we found an advantage to monotherapy.

Weaknesses of the study

The quality of included studies was poor overall. We did not detect bias induced by any of the measures assessed. We could not obtain data on all cause fatality for 33% of studies. It is unlikely that missing results would shift the results for studies comparing the same β lactam, but it is of concern that studies comparing different β lactams may not detect important harm to patients.

Our assessment of treatment effects for patients with *P aeruginosa*, Gram negative, and blood infections relies on subgroup analysis. We did not detect an advantage for combination therapy among these patients. Only few patients with documented *P aerugi-*

nosa infections could be evaluated. The types of infections addressed by included studies suggest that further infections were caused by this pathogen.

Does further evidence support our findings?

Suggestions for an advantage for combination treatment for *P aeruginosa* rely mostly on a prospective observational study.¹⁴ A similar study focusing on *Klebsiella* bacteraemia found an advantage for combination therapy only among patients with hypotension,¹⁵ while other studies have not found such an advantage.^{16–19}

In a comparison of β lactam monotherapy with β lactam-aminoglycoside combination therapy restricted to patients with neutropenia we found no advantage to combination treatment.²⁰ Although the approach to the management of patients with and without neutropenia is separated in clinical practice, this similarity supports a biological basis underlying our results.

What is already known on this topic

Early appropriate antibiotic treatment for severe infections decreases mortality

In vitro studies have shown that the bactericidal activity of a β lactam may be enhanced by the addition of an aminoglycoside

Prospective studies have suggested that the combination also has a clinical advantage

What this study adds

There is no difference in mortality when β lactam-aminoglycoside combination therapy is compared with β lactam monotherapy

Clinical failure and renal toxicity are more common with combination therapy

β lactam-aminoglycoside combination therapy does not improve clinical outcomes in patients with severe infections

Implications for practice

Antibiotic treatment is nearly always instituted empirically and is often continued with no isolate to direct specific treatment. Most trials assessed this scenario and do not support a benefit for combination therapy. Clinicians may still opt for combination empirical treatment to increase the probability of appropriate empirical treatment, which has indeed been shown to improve survival.^{21 22} Current evidence suggests that aminoglycoside monotherapy may be inadequate for infections outside the urinary tract.^{16 23 24} Thus, for the purpose of enhancing antimicrobial spectrum, aminoglycosides may constitute a poor choice.

Implications for further research

Novel β lactams should not be compared with older generation β lactams or penicillins combined with aminoglycosides. The reason for further trials assessing the addition of an aminoglycoside to a β lactam seems dubious as well.

We included in our review a small subset of trials that assessed the value of addition of an aminoglycoside in Gram positive infections. β lactam-aminoglycoside treatment is well ingrained in existing guidelines and clinical practice with these infections,²⁵ yet our results do not point to a clinical benefit with combination therapy. With these infections, further studies should assess whether the addition of an aminoglycoside is justified.

We thank the Cochrane Infectious Diseases Group for their support, review process, and help in obtaining papers; all the authors who responded for our requests for additional data; and Rika Fujiya, who translated the Japanese studies. The protocol for this review with the detailed search strategy and methods is published in the Cochrane Library.²⁶ The complete review will be published in the forthcoming issue of the Cochrane Library. Contributors: See bmj.com

Funding: This work was supported by an EU 5th framework grant (TREAT project, grant No 1999-11459).

Competing interests: None declared.

Ethical approval: Not required.

- Giamarellou H, Zissis NP, Tagari G, Bouzos J. In vitro synergistic activities of aminoglycosides and new beta-lactams against multiresistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1984;25:534-6.
- Giamarellou H. Aminoglycosides plus beta-lactams against gram-negative organisms. Evaluation of in vitro synergy and chemical interactions. *Am J Med* 1986;80:126-37.
- Klustersky J, Meunier-Carpentier F, Prevost JM. Significance of antimicrobial synergism for the outcome of gram negative sepsis. *Am J Med Sci* 1977;273:157-67.
- Klustersky J, Zinner SH. Synergistic combinations of antibiotics in gram-negative bacillary infections. *Rev Infect Dis* 1982;4:294-301.
- Den Hollander JG, Horrevorts AM, van Goor ML, Verbrugh HA, Mouton JW. Synergism between tobramycin and ceftazidime against a resistant *Pseudomonas aeruginosa* strain, tested in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother* 1997;41:95-100.
- Mouton JW. Combination therapy as a tool to prevent emergence of bacterial resistance. *Infection* 1999;27:S24-8.
- Wu YL, Scott EM, Po AL, Tariq VN. Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 1999;44:389-92.
- Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163:1730-54.
- Moellering RS. Principles of anti-infective therapy. In: Mandell GL, Bennet JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 5th ed. Philadelphia: Churchill Livingstone, 2000.
- Leone M, Bourgoin A, Cambon S, Dubuc M, Albanese J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. *Crit Care Med* 2003;31:462-7.
- Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992;101:1481-3.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- Levison ME. Pharmacodynamics of antibacterial drugs. *Infect Dis Clin North Am* 2000;14:281-91, vii.
- Hill M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia: outcome correlations in a prospective study of 200 patients. *Am J Med* 1989;87:540-6.
- Korvick JA, Bryan CS, Farber B, Beam TR Jr, Schenfeld L, Muder RR, et al. Prospective observational study of *Klebsiella* bacteraemia in 230 patients: outcome for antibiotic combinations versus monotherapy. *Antimicrob Agents Chemother* 1992;36:2639-44.
- Leibovici L, Paul M, Poznanski O, Drucker M, Samra Z, Konigsberger H, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteraemia: a prospective, observational study. *Antimicrob Agents Chemother* 1997;41:1127-33.
- Siegmán-Igra Y, Ravona R, Primerman H, Giladi M. *Pseudomonas aeruginosa* bacteraemia: an analysis of 123 episodes, with particular emphasis on the effect of antibiotic therapy. *Int J Infect Dis* 1998;2:211-5.
- Crabtree TD, Pelletier SJ, Gleason TG, Pruett TL, Sawyer RG. Analysis of aminoglycosides in the treatment of gram-negative infections in surgical patients. *Arch Surg* 1999;134:1293-9.
- Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. Enterobacter bacteraemia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991;115:585-90.
- Paul M, Soares-Weiser K, Leibovici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003;326:1111.
- Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462-74.
- Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;244:379-86.
- Bailey JA, Virgo KS, DiPiro JJ, Nathens AB, Sawyer RG, Mazuski JE. Aminoglycosides for intra-abdominal infection: equal to the challenge? *Surgical Infections* 2002;3:315-35.
- Bodey GP, Middleman E, Umsawadi T, Rodriguez V. Infections in cancer patients. Results with gentamicin sulfate therapy. *Cancer* 1972;29:1697-701.
- Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-48.
- Paul M, Leibovici L, Grozinsky DG, Silbiger I, Soares-Weiser K. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for treating sepsis (protocol for Cochrane Review). *Cochrane Library*. Issue 2. Oxford: Update Software, 2003.

(Accepted 22 December 2003)

doi 10.1136/bmj.38028.520995.63

Endpiece

Life

The first 40 years of life give you the text; the next 30 years supply the commentary on it.

Arthur Schopenhauer (1788-1860),
German philosopher

Fred Charatan, retired geriatric physician, Florida