

Treatment of sepsis in an intensive care unit

C. C. Smith

Department of Medicine, Aberdeen Royal Infirmary and The Infection Unit, City Hospital, Aberdeen, Scotland

Abstract. The management of severe bacterial sepsis is an integral part of intensive care medicine. Early and appropriate treatment with antimicrobials positively affects mortality and significantly reduces the time spent in both intensive care and the hospital. Drug choice is usually made on a “best guess” basis and instituted prior to receipt of appropriate blood, sputum, urine or drainage culture results. Bactericidal drugs should be given in combination, delivered by intravenous bolus and directed towards broad cover of all likely pathogens. Aminoglycoside/ureidopenicillin combinations are synergistic and widely used – often combined with metronidazole. Aminoglycoside toxicity can be reduced by giving the drug once daily (OD) rather than by traditional multiple daily dosing (MDD) and by measuring peak and trough serum levels. Efficacy is increased by attention to the peak serum level/MIC ratio which determines the response to treatment. Several newer agents have been more recently introduced. These drugs include ceftazidime, imipenem/cilastatin, the quinolones and clavulanic acid/semisynthetic penicillin combinations. Other newer drugs currently under evaluation include aztreonam, teicoplanin, the penems and carbapenems.

Key words: Severe infection – ITU setting – “best guess” choice – Bactericidal antimicrobials – Combinations vs. monotherapy – Prevention of nosocomial infection

Infection is not infrequently the precipitant of admission to an intensive care unit from both the community and other services within the hospital. Septicaemic shock is most appropriately dealt with by the multidisciplinary team approach in that environment. Most patients come to intensive care after surgery – usually after major abdominal and notably colorectal surgery. Others are admitted following trauma or cardiopulmonary resuscitation. All age groups are represented in intensive care – but the elderly with background disease and septic shock

have a significantly higher mortality than do younger patients [1]. This largely reflects an increased incidence of cardiovascular or pulmonary disease and major nutritional problems. The condition of the patient prior to admission greatly influences the outcome following intensive care management. Protracted shock with disseminated intravascular coagulation (DIC) and renal failure with acidaemia and hypoxaemia are associated with a high mortality or protracted stay in ITU if they survive. Early intervention is accompanied by an improved prognosis [2, 3].

Once the patient is admitted to intensive care the risk of developing nosocomial infection there will progressively increase the longer the patient remains in that environment [4]. Oropharyngeal colonisation with potential (usually aerobic Gram-negative enteric derived) pathogens is followed in a significant proportion of patients by the development of pneumonia [5]. This may be complicated by bacteraemia and septic shock. These events are particularly common in patients who require protracted ventilation (IPPV) [6]. Infection is therefore an important limiting factor in the success of treatment delivered in intensive care units and a frequent cause of the patient's demise. For this reason early instigation of “best guess” intravenous bolus antimicrobial chemotherapy is widely implemented [7]. Bactericidal drugs are delivered in combination – and generally involve an aminoglycoside with a ureidopenicillin – often combined with metronidazole. Antifungal and antiviral chemotherapy is occasionally also necessary, for example in immunocompromised patients with systemic Candidiasis or CMV pneumonia.

Newer drugs are coming forward for potential use in intensive care, notably those which are broad-spectrum or safer than established antimicrobials. Ceftazidime [8] and imipenem/cilastatin [9] have proved especially useful following investigation and have been used as monotherapy. Other drugs currently under evaluation include aztreonam [10], the quinolones [11], penems and carbapenems. Aztreonam needs to be combined with an antimicrobial directed against Gram-positive pathogens

because of its narrow Gram-negative spectrum of activity [12]. Vancomycin remains a useful and widely employed drug while teicoplanin [13] is currently being assessed as a possible replacement for vancomycin and for potential use in "methicillin resistant" *S. aureus* (MRSA) infections – which may become a problem in ITU's. Flucloxacillin, clavulanic acid/semisynthetic penicillin combinations and several newer cephalosporins are used or are being evaluated in ITU's. The potential future usage of these drugs will be briefly developed in this overview of contemporary management of sepsis in intensive care.

Diagnosis of sepsis

Early clinical diagnosis of "the sepsis syndrome" [3] and rapid institution of appropriate antimicrobial and supportive treatment has long been known to significantly influence outcome [2]. The mortality from bacteraemia – both Gram-negative and Gram-positive, remains unacceptably high at over 20% in spite of the ready availability of a wide range of effective drugs and access to intensive care in most major hospitals. If shock supervenes the mortality rises to over 50% [14]. It is therefore crucial that the clinical recognition of "the sepsis syndrome" be followed by early administration of bactericidal antimicrobials and appropriate supportive therapy to positively influence progression of the condition [7]. The longer the patient is bacteraemic or in shock the worse the outcome. Development of the adult respiratory distress syndrome (ARDS) necessitating ventilation is associated with an increased stay in ITU and the potential for development of nosocomial infection – notably Gram-negative pneumonia [15]. Long intravascular lines, indwelling bladder catheters and abdominal or thoracic drains further increase the potential for secondary infection, often with "multi-resistant" Gram-negative bacteria and staphylococci [16, 17]. Septicaemia, hypovolaemia, hypoxaemia, acidaemia and DIC with renal failure creates problems with drug handling, especially if the patient is oliguric or receiving haemodialysis. This is especially important with aminoglycoside therapy [18, 19]. The potential for deleterious drug-induced sequelae is obvious and, without regular measurement of peak and trough levels, underdosing may result with significant decrease in the likelihood of successful treatment [20].

Objective bacteriological diagnosis should be attempted in all patients prior to instigation of treatment by the taking of appropriate pre-treatment source cultures in addition to aerobic and anaerobic blood cultures [21]. Close liaison with a clinical microbiologist is crucial if sepsis patients are to be successfully managed in intensive care, as elsewhere. This can be particularly helpful in differentiating colonisation from actual infection – notably in the diagnosis of nosocomial pneumonia in its early stages or in assessing the clinical relevance of fungal isolates. The chest X-ray and white cell count may, for example, both be normal in seriously ill patients with clinical pneumonia – and fever may have connotations other than sepsis, notably drug hypersensitivity.

The patients in ITU

A wide range of infections may precipitate septic shock and necessitate admission to an intensive care unit. Those infections which are community-acquired include pneumonia caused by *S. pneumoniae* (notably type 3) and *Kl. pneumoniae* with septicaemia, *L. pneumophila* infection or post-influenzal *S. aureus* pneumonia in addition to streptococcal and meningococcal infections with DIC. In-hospital transfer to the ITU is frequent after Gram-negative septicaemia – notably that due to *E. coli*, *B. proteus*, *Enterobacter* spp. or *Ps. aeruginosa*, especially when arising in elderly or compromised patients.

Once patients have been admitted to the ITU environment they become liable to the development of secondary nosocomial infection [22], especially if they are being ventilated and their ITU stay exceeds four days. Most of the patients admitted have had recent surgery – notably abdominal surgery, especially for colorectal disease, gastroduodenal or hepatobiliary problems, or major trauma, and performed as an emergency with minimal pre-operative preparation. These patients have a particularly high incidence of Gram-negative and polymicrobial sepsis and can only be appropriately managed in an ITU setting. The likelihood of developing nosocomial pneumonia increases the longer the patient is there and receiving ventilation. These secondary infections may indeed lead to their demise. Preventive ploys are therefore being widely investigated and implemented to address this problem, the most effective of which is selective decontamination of the gut [23], sometimes combined with parenteral antimicrobial chemotherapy [24].

Established drugs

The *aminoglycosides* are time-tested bactericidal antimicrobials which continue to occupy a central role in the treatment of patients with severe bacterial infection [25]. There are, however, gaps in their spectrum of activity (*B. fragilis*, *Strep. pyogenes* for example) and they therefore are used as part of combination therapy. The potential for nephrotoxicity and ototoxicity is considerable and the safety margin between efficacy and toxicity narrow [26]. Wide variation occurs in the half life of the aminoglycosides in elderly patients, those with renal dysfunction and even there where is apparently normal renal function [26, 27]. In some of these latter patients the half life may be as long as 6–8 h. Regular monitoring of serum peak and trough levels is therefore mandatory [28, 29]. The peak serum level should be taken one hour after IV dosing and the trough immediately prior to the next dose. The peak level for gentamicin should be in the range 6–10 mg/l and that for netilmicin in the range 12–15 mg/l. Trough levels should not exceed 1.5 to 2 mg/l and 2 to 3 mg/l respectively. Initial dosage for gentamicin should be 2.5–5 mg/kg and netilmicin 5–7.5 mg/kg daily. Hidden costs clearly exist in the laboratory measurement of the serum levels and the cost for measuring netilmicin is greater than that for gentamicin.

It has long been established that high peak serum levels are crucial for successful therapy, and the ratio of

peak level to MIC (of the causative bacteria) largely determines outcome of therapy [29]. Low dosing from fear of inducing toxicity may lead to treatment failure [29, 30].

Netilmicin is generally regarded as less intrinsically nephrotoxic than gentamicin, but gentamicin remains widely used. Once daily (OD) dosing with gentamicin and netilmicin is regarded as equally effective but less hazardous than conventional multiple daily (MDD) dosing and this therapeutic ploy is now being increasingly used [31]. To provide comprehensive broad-spectrum cover aminoglycosides are combined with semi-synthetic penicillins – notably amoxicillin and piperacillin. Metronidazole is added to provide anti-anaerobic cover and flucloxacillin where there is *S. aureus* infection. These combinations are widely employed in intensive care and usually prove efficacious. Gentamicin-resistant strains of the nosocomial opportunistic Gram-negative bacteria have appeared, however, but are generally sensitive to netilmicin or amikacin. Gentamicin is removed by haemodialysis and the drug should be given post-dialysis in a dose of 1.5–2 mg/kg body weight with close monitoring of serum level. Patients with hepatic disease are particularly prone to develop gentamicin nephrotoxicity. Drug interactions need to be borne in mind – notably with diuretics, and aminoglycosides should never be mixed with other antimicrobials but always given individually. Hypersensitivity reactions are uncommon but neuromuscular blockade and neurological sequelae occasionally arise.

The semi-synthetic penicillins are widely used in intensive care – usually as part of combination therapy with aminoglycosides [32]. Ampicillin, amoxicillin, piperacillin and flucloxacillin are most commonly prescribed. Piperacillin gives cover against *Ps. aeruginosa* and *B. fragilis* while flucloxacillin provides additional cover against *S. aureus* infection. When given with an aminoglycoside these drug combinations generally prove successful in treating severe sepsis in compromised or neutropenic patients in addition to those in intensive care. Amoxicillin is being preferred to ampicillin because of its low protein binding and infrequent induction of hypersensitivity reactions, overgrowth syndromes and pseudomembranous colitis. Many strains of *E. coli* are, however, now resistant to amoxicillin. The drug is, nevertheless, used in the combinations with aminoglycosides to provide cover against *Strep. pyogenes*, *Strep. pneumoniae* and the *Strep. viridans* together with *Strep. faecalis* [32].

Cephalosporins are widely used in the management of severe sepsis because of their broad-spectrum of activity and safety profile. Cefuroxime and cefotaxime may be combined with aminoglycosides or metronidazole but are seldom used alone except when directed against a single sensitive isolate [32]. Cefoxitin, a cephamycin, provides some anti-anaerobic cover, is relatively stable to beta-lactamases and is active against ampicillin-resistant coliforms, but the drug has not found broad favour in Europe. The newer cephalosporins are not nephrotoxic but their half life is stretched by renal dysfunction. Hypersensitivity and haemolysis are relatively uncommon but a bleeding diathesis does sometimes arise during treatment.

Ceftazidime, a third-generation parenteral cephalosporin with broad-spectrum activity – notably against *Ps. aeruginosa* and “multi-resistant” Gram-negative opportunistic and nosocomial pathogens, does not provide anti-anaerobic cover. The MIC against *S. aureus* is high (MIC 2–8 mg/l) but the drug has been widely researched in patients with severe sepsis, where it has proved efficacious as monotherapy [8]. It has also been successfully employed as monotherapy in the ITU setting [32, 33]. Side effects are few and the drug can be safely combined with metronidazole, flucloxacillin or aminoglycosides. It is not nephrotoxic and side effects are few. Bleeding does not occur with the drug and pseudomembranous colitis and overgrowth syndromes are uncommon. In-treatment resistance can develop, notably to *Enterobacter* spp. The low protein binding of the drug makes for excellent tissue penetration and ceftazidime in a dose of 2 g t.i.d. is regarded as an important tool in the treatment of severe infections in hospitalised patients [7].

Imipenem/Cilastatin, a parenteral carbapenem, has high activity against both aerobic and anaerobic bacteria [9]. The drug is widely distributed in the body after administration and it is therefore well suited for potential use in ITU. The drug shows high stability to beta-lactamases and binding to all the penicillin-binding proteins (PBP's) but with great affinity for PB2 and 1, the transpeptidases implicated in elongation of the bacterial cell walls. The drug is venotoxic and nausea is a common problem, often with vomiting. Slowing of the IV infusion may reduce this side effect. The drug can cause diarrhoea, and development of in-treatment resistance has been described with *Ps. aeruginosa*. Neutropenia may occasionally arise but hypersensitivity reactions are uncommon although they may arise in penicillin-allergic patients. Confusion or seizures are well described – usually on a background of neurological disease or renal insufficiency. The drug is not nephrotoxic but in patients with renal failure the dose should be reduced, indeed by 50% where the GFR is less than 30 ml/min. The drug has been successfully used as monotherapy in the management of serious infection, including infections in ITU in doses of 2 g i.v. t.i.d. [9, 34].

The clavulanate/beta-lactam antibiotics have been developed to combat destruction by the beta-lactamase enzymes – notably of Gram-negative bacteria, the main reason for development of bacterial resistance to this group of drugs [35]. Clavulanate is a potent inhibitor of many plasma-mediated beta-lactamases of Gram-negative bacteria, including the widely distributed TEM-type enzymes [36].

Amoxicillin/clavulanate is widely used in its parenteral form to treat serious infections, but is seldom used in the ITU setting. Ticarcillin/clavulanate has been developed to give broad antibacterial cover, including activity against *B. fragilis*, and has proved effective and safe as monotherapy in the treatment of severe abdominal-derived infection.

The antistaphylococcal agents employed in ITU include *Flucloxacillin*, *Clindamycin* and *Fucidin*. The former can be safely combined with gentamicin or ceftazidime and gives excellent cover. Although tightly pro-

tein bound, i.v. flucloxacillin achieves prolonged and high serum and tissue levels which can be enhanced by concurrent administration of probenecid. The drug is predominantly employed in the treatment of *S. aureus* infection. Clindamycin is effective against *B. fragilis* in addition to *S. aureus* infection, but is prone to induce *Cl. difficile*-associated colitis. Fucidin is active against *S. aureus* – including beta-lactamase producing strains and is relatively non-toxic save for its venotoxicity. It is safe in penicillin-allergic patients and can be given for prolonged periods where there is no hepatic disease.

Vancomycin is highly effective against Gram-positive cocci, notably *S. aureus*, *S. epidermidis*, *Strep. pyogenes*, *S. pneumoniae* and the *Strep. viridans*. It is venotoxic and must be given by slow IV infusion because of flushing (“the red man syndrome”). Fast IV infusion may also induce hypotension. The drug should therefore be given by slow infusion over 1 hr. Given orally vancomycin is non-absorbable and is the most effective therapy for *Cl. difficile*-associated pseudomembranous colitis. Its current use in ITU is mainly in the management of long-line-associated *S. epidermidis* and *S. aureus* infection and in Gram-positive infections in penicillin-allergic patients.

Benzylpenicillin is still widely and safely used in the management of pneumococcal, meningococcal and streptococcal infections in ITU, and occasionally for severe gonococcal septicaemia with DIC and multi-organ disease. It is also widely combined with flucloxacillin for the treatment of mixed Gram-positive sepsis for penicillin-sensitive organisms.

New antimicrobials

In treating fungal sepsis, amphotericin B has long been the mainstay of therapy. Its potential for toxicity and need for protracted therapy has led to the development of *Fluconazole* [37]. This drug can be administered i.v. as well as orally, is highly protein bound but excreted unchanged in urine. It has proven to be a safe and effective drug for treating *Candida albicans* infection and may be given in large doses for several days with minimal side effects [38].

Acyclovir, an acyclic purine nucleoside of guanine, is a valuable antiviral agent against the herpes virus infections. It can be safely given i.v. and is effective against severe *H. simplex* and varicella *H. zoster* infections, which occasionally arise in compromised patients in ITU.

Ganciclovir, given by IV infusion, is proving useful in treating severe CMV infections in immunocompromised patients. Its main toxicity is pancytopenia due to bone marrow depression – which especially arises if the drug is used in combination with AZT or co-trimoxazole. The drug is otherwise relatively safe [39].

The 4-fluoroquinolones, notably *Ciprofloxacin*, have been well investigated in a range of serious infections. This drug is active against Gram-positive and Gram-negative bacteria, including *Ps. aeruginosa* and has been shown to have excellent antibacterial activity, pharmacokinetic profile and clinical efficacy. In-treatment development of resistance, notably to *Ps. aeruginosa*, is not uncommon. The major side effects are on the central ner-

vous system, of which the most serious is convulsions. There is a potential drug interaction with theophylline. Ciprofloxacin is effective in treating CAPD-associated peritonitis and systemic *Salmonellosis* but has to date not been widely used in managing infections in ITU [11].

Teicoplanin, a new glycopeptide antibiotic related to vancomycin, is eliminated more slowly, is better tolerated and more potent than vancomycin. Its efficacy against Gram-positive infections is proven and the drug is likely to find a place in the management of severe Gram-positive sepsis including that in neutropenics, and especially in penicillin-allergic patients [13].

Cefmetazole, a new parenteral cephamycin, has been fully investigated and proved to be similar to cefoxitin but effective at lower doses and with less frequent administration than cefoxitin. Prolongation of the prothrombin time has been described and the drug has been shown to be ineffective against *Ps. aeruginosa* infection [40].

Meropenem, a new carbapenem with broad-spectrum activity against Gram-positive and Gram-negative pathogens – including anaerobes, is active against *Ps. aeruginosa*. Early studies suggest that the drug is likely to prove a safe and effective addition to the armamentarium for management of severe infection. It is currently being further investigated and may find a place in ITU therapy of sepsis patients [41]. Other penems are also “on the way” – including FCE 22101, which may prove useful in treating MRSA infections.

Aztreonam, a monobactam beta-lactam with narrow Gram-negative activity, is effective and safe – notably in penicillin and cephalosporin-allergic patients. In “best guess” treatment the drug has to be combined with an appropriate antimicrobial directed against Gram-positive bacteria. It has no activity against *B. fragilis* but has been effectively combined with vancomycin, clindamycin and gentamicin in treatment [12].

Fleroxacin, a newly developed trifluorinated quinolone, is currently under investigation. It has broad-spectrum activity, including activity against *Ps. aeruginosa* and *S. aureus*. The drug has a long half life (10 h) and needs to be administered with caution in patients with renal dysfunction. This may limit its application to therapy in the ITU setting, but other quinolones are under current investigation which may prove useful.

Discussion

Antimicrobial treatment in ITU patients generally has to be instigated on a “best guess” basis without objective microbiological help. Drug hypersensitivity patterns, renal dysfunction, DIC, acidaemia, hypoxaemia, previous administration of antimicrobials, known drug hypersensitivity phenomena, possible drug interactions and known previous interactions have all to be considered in making the drug choice. This also must take into account known sensitivity patterns and the presence or otherwise of “multi-resistant” bacteria or MRSA in the hospital and ITU. Polymicrobial sepsis may also occur.

Combinations of antimicrobials are given and generally include an aminoglycoside with a penicillin plus metronidazole if anaerobes are deemed to be present.

Therapy may need to be changed once bacteriological culture results become available and drug doses (particularly of the aminoglycosides) altered in an environment of changing renal function [42], development of DIC or bleeding diatheses induced by organ disease or the antimicrobials previously given. In this setting few clinicians would use monotherapy. Occasionally monotherapy may be directed against a known sensitive pathogen, e.g., cef-tazidime or imipenem/cilastatin or aztreonam. The various drugs currently used in ITU have, however, been briefly described and some newer agents for potential use in the ITU considered. In current practice, however, antimicrobials with a proven "track-record" continue to be used by clinicians, the search being for safer use in this difficult group of patients.

References

- Myers BR, Sherman E, Mendelson MH, Valesquez G, Srulovitch-Chin E, Hubbard M, Hirschmann SZ (1989) Bloodstream infections in the elderly. *Am J Med* 86:379
- Kreger BE, Craven DE, McCabe WR (1980) Gram-negative bacteraemia. The evaluation of clinical features and treatment in 612 patients. *Am J Med* 68:344
- Bone RC, Fisher CJ, Clemmer IP, Stonann GJ, Metz CA, Balh RA (1989) Sepsis syndrome: a valid clinical entity. *Crit Care Med* 12:389
- L'a Force RM (1981) Hospital acquired Gram-negative rod pneumonias: an overview. *Am J Med* 70:664
- Daschner FD, Frey P, Wolff G, Bannann PC, Suter P (1982) Nosocomial infections in intensive care wards: a multicentre prospective study. *Intensive Care Med* 8:5
- Van Uffelen R, Rommes JH, Fidler V, van Saene HK (1987) Preventing lower airway colonisation and infection in mechanically ventilated patients. *Crit Care Med* 15:99
- Smith CC (1986) Initial antibacterial therapy in patients with septicemia. *Res Clin Forums* 8:7-15
- Allan SG, Glover SC, Smith CC, Reid TMS (1983) An open study of ceftazidime in the treatment of serious bacterial infections. *J Antimicrob Chemother* 12:219-227
- Imipenem/Cilastatin; monotherapy of hospital infections (1987) *Scand J Infect Dis [Suppl 52]:5-78*
- Smith G (1988) Use of aztreonam in serious Gram-negative infections. *J Antimicrob Chemother* 21:233-241
- Hawkey PM (1989) Where are we now with Ciprofloxacin? Leading article. *J Antimicrob Chemother* 24:477-479
- Brogden RN, Heel RC (1986) Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 31:96-130
- Williams AH, Grüneberg RN (1988) Teicoplanin revisited: leading article. *J Antimicrob Chemother* 22:392-399
- Bryan CS, Reynolds KL, Brenner ER (1983) Analysis of 1186 episodes of Gram-negative bacteraemia in a non-university hospital: effects of antimicrobial therapy. *Rev Infect Dis* 5:629-638
- Hata JS (1989) Infections in the critical care unit. *Curr Opin Infect Dis* 25:659-662
- Elliott TSJ (1988) Intravascular device infections. *J Med Microbiol* 27:161-167
- Martin MA, Pfaller WA, Wenzel RP (1989) Coagulase-negative staphylococcal bacteraemia: mortality and hospital stay. *Ann Intern Med* 110:9-16
- Moor RD, Smith CR, Wipshy JJ, Mellitis ED, Wietman PS (1984) Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med* 100:352-357
- Keller F, Borner K, Schwartz A, Offerman G, Node H (1987) Therapeutic aminoglycoside monitoring in renal failure patients. *Ther Drug Monit* 9:148-153
- Editorial (1986) Aminoglycoside toxicity. *Lancet* II:670-671
- Chastre J, Fagon JY, Soler P, Bornet M, Domart Y, Tromiket JL, Gibert C, Hance AJ (1988) Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of usefulness of bronchoalveolar lavage and the protected specimen brush. *Am J Med* 85:499-506
- Craven DE, Kunches LM, Lichtenberg DA, Kollisch NR, Barry MA, Heeren TC, McCake WR (1988) Nosocomial infection and fatality in medical and surgical intensive care patients. *Arch Intern Med* 148:1161-1168
- Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF (1984) The effect of selective decontamination of the digestive track on colonisation and infection rate in multiple trauma patients. *Intensive Care Med* 10:185-192
- Ledingham IMcA, Alcock SR, Eastaway AT, McDonald JC, McKay IC, Ramsay G (1988) Triple regimen of selective decontamination of digestive tract, systemic cefotaxime and microbiological surveillance for prevention of acquired infection in intensive care. *Lancet* I:785-790
- Moore RD, Smith CR, Wietman PS (1984) The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteraemia. *J Infect Dis* 149:443-448
- John JF (1988) What price success? The continuing saga of the toxic/therapeutic ratio with aminoglycoside antibiotics. *J Infect Dis* 158:1-6
- Drusano GL (1988) Role of pharmacokinetics in the outcome of infection. *Antimicrob Agents Chemother* 32:289-297
- Moore RD, Wietman PS, Smitz CR (1987) Clinical response to aminoglycoside therapy: importance of ratio of peak concentration to MIC. *J Infect Dis* 155:93-99
- Flint LM, Gott J, Short L, Richardson JD, Polk HC (1985) Serum level monitoring of aminoglycoside antibiotics. *Arch Surg* 120:99-102
- Mattie H, Craig WA, Pechere JC (1989) Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 24:281-293
- Sturm AW (1989) Netilmicin in the treatment of gram-negative bacteraemia - Single dose vs multiple daily dosing. *J Infect Dis* 159:931
- Smith CC (1985) The penicillins and cephalosporins. In: Clinically important adverse drug interactions, vol 3. Elsevier, Amsterdam, pp 111-153
- Richards DM, Brodgen RN (1985) Ceftazidime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 29:105-161
- Graham J (1986) Imipenem in the treatment of severe bacterial infections in serious sick patients. *J Antimicrob Chemother [Suppl E]* 18:131-140
- Robinson GN (1989) β -lactamase induction and resistance to β -lactam antibiotics. *J Antimicrob Chemother* 23:12
- Clavulanate/ β -lactam antibiotics: Further experience (1989). *J Antimicrob Chemother [Suppl B]* 24:1-221
- Warnock DW (1989) Itraconazole and fluconazole: new drugs for deep fungal infection. *J Antimicrob Chemother* 24:275-277
- Van Wout JW, Mattie H, van Furth R (1988) A prospective study of the efficacy of fluconazole against deep seated fungal infections. *J Antimicrob Chemother* 21:665-672
- Cytomegalovirus: the disease and its management (1989). *J Antimicrob Chemother [Suppl E]* 23:1-20
- Cefmetazole: a clinical appraisal (1989). *J Antimicrob Chemother [Suppl D]* 23:1-131
- Meropenem: a new carbapenem (1989). *J Antimicrob Chemother [Suppl A]* 24:1-311
- Zaske DE, Cipolle RJ, Rotschager JC (1982) Gentamicin pharmacokinetics in 1640 patients: method for control of serum concentrations. *Antimicrob Agents Chemother* 30:78

Dr. C. C. Smith
Wards 25/26
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB9 2ZB
Scotland