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Ambulatory Use of Parenteral Antibacterials

Contemporary Perspectives

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Abstract

Outpatient parenteral antimicrobial therapy (OPAT) offers increased patient comfort and convenience in appropriately selected patients who require parenteral antibacterial therapy, as well as opportunity for cost savings. Home-based programmes, with drugs being administered by the patient or the caregiver, have become the norm in the USA. Choice of drugs for OPAT is based on antimicrobial spectrum, dosage regimen, drug stability, toxicity profile, and cost. Over the past decade, availability of sophisticated programmable pumps has allowed a wider range of antimicrobial agents to be used in the ambulatory setting. The most popular antibacterial agents in OPAT programmes in the USA are vancomycin and β-lactams.

1. Rationale for Ambulatory Use of Parenteral Antibacterials

Containing the costs associated with antimicrobial therapy has been the focus of much interest during recent years. One approach to cost containment is use of outpatient parenteral antimicrobial therapy (OPAT). It is now well recognised that hospitalising patients solely for parenteral antimicrobial therapy is neither cost efficient nor capable of profiting from many potential advantages of treating patients at home.

The advantages of OPAT can be summarised as follows (fig. 1):

- Increased convenience and comfort for patients and relatives. Patients experience considerably less disruption to their personal and family life and sleeping pattern, and may be able to continue working or attending school. Being treated at home may be particularly psychologically advantageous for children.
- Avoidance of the costs associated with hospitalisation. Hospitalisation is usually the most costly component of patient care. Whether this cost saving benefits the patient, third-party payer or hospital depends on individual circumstances. The freeing-up of hospital beds may also benefit the institution.

Oral administration of drugs is usually preferred when pharmacologically feasible, as it obviates the costs and risks associated with parenteral access, as well as being more comfortable and convenient for the patient.[1] However, intravenous or intramuscular administration produces higher and more predictable serum and tissue concentrations for many drugs with less than optimal oral bioavailability. Moreover, some patients are unable to take oral medications, or oral formulations of the most suitable antimicrobial agent may not be available (e.g. aminoglycosides, carbapenems and glycopeptides). There are additional considerations in the USA. Most third-party payers will not accept the cost of acute inpatient care for patients who can be

treated by the oral route, or who are otherwise ambulatory and able to self-administer antibiotics parenterally.[2] Furthermore, potential legal liability exists when oral treatment is not perceived as the standard of care for a particular illness.[3]

Patients may receive OPAT as a hospital-based outpatient programme, a physician office-based or infusion centre outpatient programme, or a home-based programme serviced by an independent infusion company. Home-based programmes, which involve administration of drugs by the patient or the caregiver, are the most commonly used approach in the USA, representing a major growth industry in the 1990s. In Europe, drugs are usually administered by a nurse or physician, typically in a hospital outpatient setting, although home-based treatment is popular in Italy. Initially, most patients received OPAT after early discharge from the hospital. Increasingly, OPAT is initiated without hospitalisation, and patients are frequently referred directly from the emergency room or a physician's office.[4] This is an efficient approach which avoids the inconvenience and expense of hospital admission.

2. Factors Influencing Antibacterial Selection for Ambulatory Use

The suitability of a drug for OPAT depends on several factors. These include antibacterial spectrum and profile of activity, dosage regimen, mode of administration, duration of therapy, tolerability profile, drug stability and costs.[5]

2.1 Pharmacodynamic Factors

Antibacterial agents can be classified into 3 groups depending on their pattern of bactericidal activity and whether they exert persistent inhibitory effects [postantibiotic effects, postantibiotic leucocyte enhancement or postantibiotic subminimum inhibitory concentration (MIC) effects][6-9] (table I).

One group of antibacterial agents (aminoglycosides, fluoroquinolones and metronidazole) displays concentration-dependent killing and prolonged persistent effects. Increasing the drug concentration increases the rate and extent of bacterial killing; thus, peak drug concentrations and the area under the drug concentration-time curve (AUC) in relation to the MIC are important determinants of the clinical efficacy of these drugs. Also, the persistent effects allow wide dosage intervals.[10] With respect to aminoglycosides, Moore et al.[11] found that peak drug concentration : MIC ratios of at least 8 to 10 were required to achieve an optimal clinical response in 90% of patients treated for infection. Forrest et al.[12] noted that, in patients treated with ciprofloxacin for serious infections, clinical and bacteriological response rates of <50% were achieved when the AUC : MIC ratio was <125. When a higher AUC : MIC ratio was obtained, the response rate rose to approximately 80%. These findings have been replicated for bacterial infections of the respiratory tract, skin, or urinary tract treated with levofloxacin.[13]

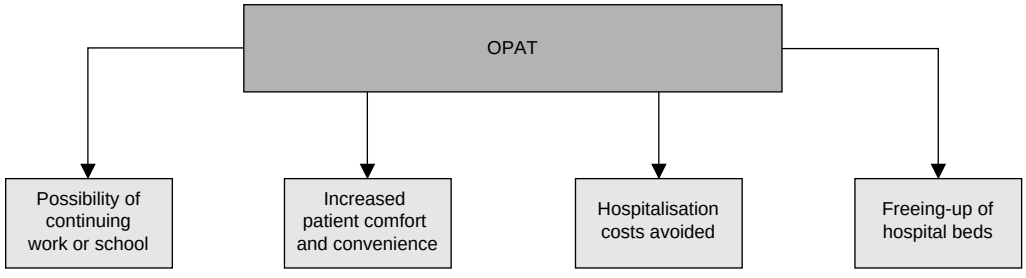

Fig. 1. Advantages of outpatient parenteral antibacterial therapy (OPAT).

Table I. Influence of pharmacodynamic properties of antibacterial agents on dosage regimen and parameters correlating with clinical efficacy (adapted from Craig,[9] with permission)

Antibacterials	Goal of dosage regimen	Parameters that correlate with clinical efficacy
Agents with concentration-dependent killing and prolonged PAE		
Aminoglycosides	Maximise drug concentrations	Peak concentration : MIC ratio; 24-hour AUC : MIC ratio
Fluoroquinolones		
Metronidazole		
Agents with time-dependent killing and short or no PAE		
Aztreonam	Maximise exposure time	t>MIC/MBC
Carbapenems		
Cephalosporins		
Clindamycin		
Macrolides		
Penicillins		
Agents with time-dependent killing and prolonged PAE		
Azithromycin	Maximise daily amount of drug	t>MIC/MBC
Tetracyclines		
Vancomycin		

AUC = area under the drug concentration-time curve; **MBC** = minimum bactericidal concentration; **MIC** = minimum inhibitory concentration; **PAE** = postantibiotic effect; **t>MIC/MBC** = time that serum concentrations exceed MIC or MBC.

The second group of antibacterial agents (aztreonam, carbapenems, clindamycin, cephalosporins, macrolides, penicillins) shows time-dependent killing and short or no persistent effects. The bacterial killing rate reaches a ceiling at serum concentrations about 4 to 5 times the MIC, and bacterial regrowth begins promptly after serum and tissue concentrations fall below the MIC. The length of time that serum drug concentrations exceed the MIC or the minimum bactericidal concentration (MBC) is the important determinant of efficacy for this group. Suprainhibitory serum concentrations for 40% of the dosage interval provide a minimum threshold for these antimicrobial agents in otitis media.[14,15] Schentag et al.[16] reported that, in patients with nosocomial pneumonia, the number of days of cefmenoxime therapy required to eradicate pathogens from sputum was inversely correlated with the proportion of time during which serum drug concentrations exceeded the MIC: 10 to 13 days' treatment was required if concentrations exceeded the MIC for less than 50% of the dosage interval. However, this time was reduced to between 1 and 6 days when drug concentrations exceeded the MIC for all or most of the dosage interval. Syndman et al.[17] noted that clinical response of *Bacteroides fragilis* infections to cefoxitin therapy was dependent on the proportion of time that serum concentrations were above the MIC. Weinstein et al.[18] found that all patients with osteomyelitis who failed treatment with β-lactam agents had undetectable serum antibacterial drug concentrations at trough.

The last group of antibacterial agents (azithromycin, tetracyclines and vancomycin) exhibits time-dependent killing and prolonged persistent effects. Although the duration of antibacterial exposure is important with respect to these agents, because of their persistent effects, clinical efficacy is not compromised if concentrations fall below the MIC for a considerable portion of the dosage interval.

2.2 Pharmacokinetic Factors

As already mentioned, for the β-lactams it is important to maintain drug concentrations above the MIC against the infecting pathogen over much of the dosage interval. Thus, agents with long half-lives can be given less frequently (table II). Dosage

Table II. Dosage intervals for parenteral antibacterial agents in the treatment of serious infections

Drugs that can be given once daily
Aminoglycosides
Vancomycin
Ceftriaxone
Teicoplanin
Pefloxacin
Fleroxacin
Drugs that can be given twice daily
Cefazolin
Cefotetan
Cefonicid
Meropenem
Drugs usually given 3 times daily or more frequently
Cefazolin[a]
Cefotaxime
Ceftazidime
Aztreonam
Carbapenems[a]
Most penicillins
Drugs that can be given by continuous infusion
β-Lactams

a Less frequent administration of cefazolin and meropenem has been found to be effective.[19,20]

intervals for drugs excreted by the renal route can be extended in patients with impaired renal function. Ceftriaxone has the longest half-life of the β-lactams (approximately 8 to 10 hours) and can be given once daily. Cefotetan and cefonicid have half-lives of >2 hours and can be given twice daily; cefazolin, cefotaxime, ceftazidime and aztreonam have short half-lives of only 1 to 2 hours and generally need to be given 3 times daily. Other cephalosporins and most of the penicillins have half-lives of only 0.5 to 1 hour and generally require 4-times-daily, or more frequent, administration.

The carbapenems (imipenem/cilastatin, meropenem) also have very short half-lives of approximately 1 hour; thus, 3-times-daily administration would not provide concentrations above the MIC throughout the dosage interval. However, the persistent effects of these agents may allow a longer dosage interval. Indeed, twice-daily administration of meropenem has been shown to be as effective as 3-times-daily administration in patients with urinary tract or respiratory infections,[19] as has twice-daily cefazolin for cellulitis.[20]

Vancomycin has a long half-life of approximately 6 hours and, against susceptible pathogens, doses of 15 mg/kg produce serum concentrations above the MIC for 12 to 24 hours.

Because the aminoglycosides have half-lives of approximately 2 to 3 hours, it may be difficult to obtain peak concentration : MIC ratios of ≥8 to 10 without excessively toxic exposure with 8-hourly administration. Moreover, these ratios are also important in preventing the emergence of resistance.[21] Thus, there is an increasing trend towards once-daily administration of these agents. This has been shown to be more effective and possibly less toxic than traditional 8-hourly administration.[22-25]

Fluoroquinolones have excellent oral bioavailability; therefore, they would generally be used in OPAT programmes only for patients with impaired gastrointestinal absorption.

Antibacterial drugs with prolonged half-lives, allowing a once-daily dosage regimen, have generally been preferred for OPAT programmes. A once-daily regimen results in minimal disruption of daily activities for the patient, reduces costs of ancillary items (syringes, needles, sterile gloves) and minimises handling of the intravenous line, thus limiting the potential for intravenous site infections. Examples of such drugs include teicoplanin, aminoglycosides, ceftriaxone, and the fluoroquinolones fleroxacin and pefloxacin. Teicoplanin has even been administered on a 3-times-weekly basis in the management of osteomyelitis.[26]

The development of sophisticated delivery devices has allowed a wider range of antibacterials to be considered for home use, although this can increase drug delivery costs. These include computerised intravenous pumps capable of accurate delivery of prescribed doses intermittently or continuously over a 24-hour period[5,27,28] and portable pumps for continuous infusion.[29] Continuous infusion is the most efficient method of administration for β-lactam agents with short half-lives,

providing efficacy similar to that of intermittent therapy with a lower drug dosage. For ceftazidime, continuous infusion of 1g over 24 hours maintains serum concentrations of approximately 5 mg/L, but a 1g dose every 8 hours produces serum concentrations of approximately 2 mg/L over the dosage interval.[8,30] For benzylpenicillin (penicillin G), continuous infusion allows sufficiently high serum concentrations to treat even penicillin-resistant *Streptococcus pneumoniae* non-meningeal infections.[31] A pilot study suggests that an 8 g/day continuous infusion of oxacillin provides suprainhibitory concentrations against *Staphylococcus aureus* 100% of the dosage interval, versus 62% for intermittent (2g every 4 hours) administration.[32]

Administration of β-lactam agents by the intramuscular route slows their absorption and extends by several hours the time during which serum concentrations exceed the MIC. In OPAT programmes, this approach has been used principally with ceftriaxone, since a single 1g intramuscular dose produces inhibitory serum concentrations against susceptible organisms for at least 24 hours. Once-daily administration has been successfully used to treat a range of infections in geriatric patients.[33]

2.3 Stability Issues

The stability at room temperature of the drug chosen is of particular importance when using continuous infusion or programmable pumps. Prolonged exposure of the prepared drug solution to room temperature may lead to formation of degradation products, which may increase the risk of adverse effects. This has been demonstrated with penicillin.[34,35]

Drugs that are stable for fewer than 12 hours in solution are best administered intermittently. If such drugs are given by continuous infusion, it is important that solutions are changed regularly, which makes home administration difficult.

Most antibacterial drugs are stable for at least 24 hours at room temperature and for 3 to 10 days if refrigerated.[5,7] Ceftriaxone and mezlocillin are stable for longer periods. In contrast, imipenem/cilastatin and ampicillin solutions are stable at room temperature for only 4 and 8 hours, respectively, while cefradine and cefalothin solutions are stable for only 10 to 12 hours (table III).[5]

2.4 Tolerability Issues

General and local tolerability is an important issue when drugs are administered away from the closely supervised hospital setting. The aminoglycosides are ototoxic and nephrotoxic, and their serum concentrations may need to be monitored in order to minimise toxicity. On the other hand, cephalosporins are very well tolerated, with few serious adverse effects. Nevertheless, with respect to associated adverse effects, it appears that OPAT has as many as or more than parenteral antimicrobial therapy has in hospitalised patients.[36]

Erythromycin, tetracycline, doxycycline, oxacillin, vancomycin and amphotericin B all tend to cause phlebitis, which limits their potential for use in OPAT programmes unless central venous catheters are employed. In contrast, most cephalosporins and the aminoglycosides have a low potential for causing phlebitis.

3. Selection of Patients for Ambulatory Parenteral Antibacterial Therapy

OPAT can be considered when patients are medically stable and no longer require close observation and daily nursing/supportive care. Patients must be carefully selected.[37] Factors to consider include the following: type, severity and aetiology of infection; the patient's general condition and presence of concomitant conditions, such as diabetes, renal impairment, cardiac disease and immunosuppression; and the ability and motivation of the patient (or of the caregiver) to look after him-/herself adequately and comply with an OPAT programme. Facilities at home, including access to telephone and transport, are also an important consideration. Practice guidelines for OPAT have been formulated in several countries.[38,39]

Table III. Stability of selected antimicrobial drugs for outpatient parenteral therapy (Data from Gilbert et al.,[5] with permission. Copyright© 1997 Massachusetts Medical Society. All rights reserved.)

Drug	Recommended diluent	Concentration (g/L)[a]
Adequate stability[b]		
Nafcillin	Water or normal saline	80
Oxacillin	Water	50 or 100
Ticarcillin-clavulanate	Water or normal saline	10-100
Cefazolin	Water	73.2
Cefuroxime	Water	≤30
Cefoxitin	Water	40
Ceftriaxone	Normal saline	40
Ceftazidime	Water	30 or 60
Vancomycin	Water or normal saline	10
Amikacin	5% dextrose in water	20
Gentamicin	5% dextrose in water	5.45
Tobramycin	5% dextrose in water	3.2
Pentamidine	Normal saline or 5% dextrose in water	3
Ganciclovir	Normal saline or 5% dextrose in water	5
Amphotericin B[c]	5% dextrose in water	0.1
Intermediate stability[d]		
Aciclovir[e]	Normal saline or 5% dextrose in water	5
Erythromycin	Water or normal saline	20
Benzylpenicillin	Water	180 000 U/ml
Poor stability[f]		
Ampicillin	Water or normal saline	60
Imipenem-cilastatin	Normal saline	5
Doxycycline	Normal saline	2
Trimethoprim-sulfamethoxazole[e]	5% dextrose in water	0.8-4

a The concentrations listed are those frequently used in outpatient infusion devices and those for which data on stability are available.

b Adequate stability refers to a drug that retains ≥90% of its original concentration for a minimum of 24 hours at room temperature (25°C) and 4 to 7 days under refrigeration (3 to 5°C).

c Light protection is required if the drug will be exposed to light for more than 24 hours.

d Intermediate stability refers to a drug that retains ≥90% of its original concentration for a minimum of 24 hours at room temperature (25°C) and less than 4 days under refrigeration (3 to 5°C) or is not recommended for refrigeration.

e Storage of this preparation in a refrigerator (3 to 5°C) may result in the formation of a precipitate.

f Poor stability refers to a drug that retains ≥90% of its original concentration for less than 24 hours at room temperature (25°C).

4. Clinical Experience

Most of the early published experience with OPAT related to the treatment of septic arthritis and osteomyelitis.[40-42] However, a wide range of infections has since been treated, including pneumonia,[43,44] neutropenic infections in cancer patients,[45-49] pulmonary exacerbations of cystic fibrosis,[50-52] skin and soft tissue infections,[9,53] endocarditis,[54-57] and secondary bacterial infections in HIV-infected patients.[58] A recent review summarises the use of OPAT in these and other infections.[59]

In the USA, the most commonly used antibacterial agents in OPAT programmes have been third generation cephalosporins, particularly ceftriaxone, and vancomycin.[9,60] In our OPAT programme, in which we treat approximately 1000 patients per year, penicillins, cephalosporins, and vancomycin each account for 25 to 30% of all antimicrobials used. In Europe, teicoplanin is favoured over vancomycin.[61,62]

Estimated savings of approximately $US200 per patient per day (based on actual costs) have been achieved in US OPAT programmes. Patients were treated for various infections, including osteomyelitis, other bone/joint infections, skin and soft tissue infections, endocarditis and pulmonary exacerbations of cystic fibrosis.[63-69]

5. Conclusions

OPAT exemplifies the shift from inpatient to ambulatory care that has occurred during the last decade or so. Hospitalisation generally represents the most costly aspect of patient care. Thus, this approach offers considerable opportunities for cost savings in carefully selected patients who require parenteral antibacterial therapy. Moreover, there are benefits to the patient in terms of increased comfort and convenience.

Selection of a drug for OPAT is based on pharmacodynamic, pharmacokinetic and stability issues, although the development of sophisticated delivery devices has expanded the range of antibacterials that can be considered for home use.

References

1. MacGregor RR, Graziani A. Oral administration of antibiotics: a rational alternative to parenteral route. Clin Infect Dis 1997; 24: 457-67
2. Poretz DM. Evolution of outpatient parenteral antibiotic therapy. Infect Dis Clin North Am 1998; 12: 827-34
3. Bartlett JG. Impact of new oral antibiotics on the treatment of infectious diseases. Infect Dis Clin Pract 1993; 2: 405-13
4. Tice AD. Experience with a physician-directed, clinic-based program for outpatient parenteral antibiotic therapy in the USA. Eur J Clin Microbiol Infect Dis 1995; 14: 655-61
5. Gilbert DN, Dworkin RJ, Raber SR, et al. Outpatient parenteral antimicrobial-drug therapy. N Engl J Med 1997; 337: 829-38
6. McDonald PJ, Wetherall BL, Pruul H. Postantibiotic leukocyte enhancement: increased susceptibility of bacteria pretreated with antibiotics to activity of leukocytes. Rev Infect Dis 1981; 3: 38-44
7. Craig WA. Selecting the antibiotic. Hosp Pract 1993; 28 Suppl. 1: 16-20
8. Andes D, Craig WA. Pharmacokinetics and pharmacodynamics of outpatient intravenous antimicrobial therapy. Infect Dis Clin North Am 1998; 12: 849-60
9. Craig WA. Antibiotic selection factors and description of a hospital-based outpatient antibiotic therapy program in the USA. Eur J Clin Microbiol Infect Dis 1995; 14: 636-42
10. Craig WA. Postantibiotic effects in experimental infection models: relationship to *in vitro* phenomena and to treatment of infection in man. J Antimicrob Chemother 1993; 31 Suppl. D: 149-58
11. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of peak concentration to minimal inhibitory concentration. J Infect Dis 1987; 155: 93-9
12. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993; 37: 1073-81
13. Preston SL, Drusano GL, Berman AL, et al. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 1998; 279: 125-9
14. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996; 15: 255-9
15. Craig WA. Choosing an antibiotic on the basis of pharmacodynamics. Ear Nose Throat J 1998; 77 (6 Suppl.): 7-11
16. Schentag JJ, Smith IL, Swanson DJ, et al. Role for dual individualization with cefmenoxime. Am J Med 1984; 77 Suppl. 6A: 43-50
17. Syndman DR, Cuchural GJ, McDermott L, et al. Correlation of various *in vitro* testing methods with clinical outcomes in patients with *Bacteroides fragilis* group infections treated with cefoxitin: a retrospective analysis. Antimicrob Agents Chemother 1992; 36: 540-4
18. Weinstein MP, Stratton CW, Hawley HB, et al. Multicenter collaborative evaluation of a standardized serum bactericidal test as a predictor of therapeutic efficacy in acute and chronic osteomyelitis. Am J Med 1987; 83: 218-26
19. Romanelli G, Cravarezza P, and the Italian Intramuscular Meropenem Study Group. Intramuscular meropenem in the treatment of bacterial infections of the urinary and lower respiratory tracts. J Antimicrob Chemother 1995; 36 (Suppl. A): 109-19
20. Leder K, Turnidge JD, Grayson JL. Home-based treatment of cellulitis with twice-daily cefazolin. Med J Aust 1998; 169: 519-22
21. Blaser J, Stone BB, Groner MC, et al. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bacterial activity and emergence of resistance. Antimicrob Agents Chemother 1987; 31: 1054-60
22. Kale-Pradhan PB, Habowski SR, Chase HC. Once daily aminoglycosides: a meta-analysis of nonneutropenic and neutropenic adults. J Pharm Technol 1988; 14: 22-9
23. Craig WA. Once-daily dosing of aminoglycosides. Can J Infect Dis 1994; Suppl. C: 28-33
24. Mattie H, Craig WA, Pechere JC. Determinants of efficacy and toxicity of aminoglycosides. J Antimicrob Chemother 1989; 24: 281-93
25. Gilbert DN, Lee BL, Dworkin RJ, et al. A randomized comparison of the safety and efficacy of once-daily gentamicin or thrice-daily gentamicin in combination with ticarcillin-clavulanate. Am J Med 1998; 105: 182-91
26. Graninger W, Wenisch C, Wiesenger E, et al. Experience with outpatient intravenous teicoplanin therapy for chronic osteomyelitis. Eur J Clin Microbiol Infect Dis 1995; 14: 11-5
27. New PB, Swanson GF, Bulich RG, et al. Ambulatory antibiotic infusion devices: extending the spectrum of outpatient therapies. Am J Med 1991; 91: 455-61
28. Williams DN, Gibson JA, Bosch D. Home intravenous antibiotic therapy using a programmable infusion pump. Arch Intern Med 1989; 149: 1157-60
29. Kravitz GR. Advances in IV delivery. Hosp Pract 1993; 28 Suppl. 1: 21-7
30. Craig WA, Ebert SC. Continuous infusion of beta-lactam antibiotics. Antimicrob Agents Chemother 1992; 36: 2577-83
31. Bryan CS, Talwani R, Stinson MS. Penicillin dosing for pneumococcal pneumonia. Chest 1997; 112: 1657-64
32. Turnidge JD. The pharmacodynamics of β-lactams. Clin Infect Dis 1998; 27: 10-22
33. Russo TA, Cook S, Gorbach SL. Intramuscular ceftriaxone in home parenteral therapy. Antimicrob Agents Chemother 1988; 32: 1439-40

34. Neftel KA. Effect of storage of penicillin-G solutions on sensitization to penicillin-G after intravenous administration. Lancet 1982; 1: 986-8
35. Neftel KA, Walti M, Schulthess HK, et al. Adverse reactions following intravenous penicillin-G relate to degradation of the drugs *in vitro*. Klin Wochenschr 1984; 62: 25-9
36. Williams DN. Home intravenous anti-infective therapy (HIVAT) – do the benefits outweigh the risks. Drug Saf 1996; 14: 1-7
37. Nolet BR. Patient selection in outpatient parenteral antimicrobial therapy. Infect Dis Clin North Am 1998; 12: 835-47
38. Williams DN, Rehm SJ, Tice AD, et al. Practice guidelines for community-based parenteral anti-infective therapy. IDSA Practice Guidelines Committee. Clin Infect Dis 1997; 25: 787-801
39. Williams DN, Raymond JL. Practice guidelines for community-based parenteral anti-infective therapy. Infect Dis Clin North Am 1998; 12: 1009-21
40. Eron LJ, Goldenberg RI, Poretz DM. Combined ceftriaxone and surgical therapy for osteomyelitis in hospital and outpatient setting. Am J Surg 1984; 148 (4): 1-4
41. Poretz DM, Eron LJ, Goldenberg RI, et al. Intravenous antibiotic therapy in an outpatient setting. JAMA 1982; 248: 336-9
42. Kunkel MJ, Iannini PB. Cefonicid in a once-daily regimen for treatment of osteomyelitis in an ambulatory setting. Rev Infect Dis 1984; 4: 865-9
43. Williams DN. Reducing costs and hospital stay for pneumonia with home intravenous cefotaxime treatment: results with a computerized ambulatory drug delivery system. Am J Med 1994; 97 Suppl. 2A: 50-5
44. Morales JO, Snead H. Efficacy and safety of intravenous cefotaxime for treating pneumonia in outpatients. Am J Med 1994; 97 Suppl. 2A: 28-33
45. Escalante CP, Rubenstein EB, Rolston KVI. Outpatient antibiotic therapy for febrile episodes in low-risk neutropenic patients with cancer. Cancer Invest 1997; 15 (3): 237-42
46. Girmenia C, Moleti ML, Cartoni C, et al. Management of infective complications in patients with advanced hematologic malignancies in home care. Leukemia 1997; 11: 1807-12
47. Sahu S, Bapna A, Pai SK, et al. Outpatient antimicrobial protocol for febrile neutropenia: a nonrandomized prospective trial using ceftriaxone, amikacin, and oral adjuvant agents. Pediatr Hematol Oncol 1997; 14: 205-11
48. Kaplinsky C, Drucker M, Goshen J, et al. Ambulatory treatment with ceftriaxone in febrile neutropenic children. Isr J Med Sci 1994; 30: 649-51
49. Mustafa MM, Aquino VM, Pappo A, et al. A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. J Pediatr 1996; 128: 847-9
50. Vinks AATMM, Brimicombe RW, Heijerman HGM, et al. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. J Antimicrob Chemother 1997; 40: 125-33
51. Wolter JM, Bowler SD, Nolan PJ, et al. Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects. Eur Respir J 1997; 10: 896-900
52. Pond MN, Newport M, Joanes D, et al. Home *versus* hospital intravenous antibiotic therapy in the treatment of young adults with cystic fibrosis. Eur Respir J 1994; 7: 1640-4
53. Poretz DM. Treatment of skin and soft-tissue infections utilizing an outpatient parenteral drug delivery device: a multicenter trial. Am J Med 1994; 97 Suppl. 2A: 23-7
54. Stamboulian D. Outpatient treatment of endocarditis in a clinic-based program in Argentina. Eur J Clin Microbiol Infect Dis 1995; 14: 648-54
55. Francioli P, Etienne J, Hoigne R, et al. Treatment of streptococcal endocarditis with single daily dose of ceftriaxone sodium for four weeks. Efficacy and outpatient treatment feasibility. JAMA 1992; 267 (2): 264-7
56. Wilson WR. Ceftriaxone sodium therapy of penicillin G-susceptible streptococcal endocarditis. JAMA 1992; 267: 279
57. Dimayuga E, Brown RB. Outpatient parenteral antibiotic therapy for infective endocarditis. Infect Dis Clin Pract 1995; 4: 468-71
58. Morales JO, Von Behren L. Secondary bacterial infections in HIV-infected patients: an alternative ambulatory outpatient treatment utilizing intravenous cefotaxime. Am J Med 1994; 97 Suppl. 2A: 9-13
59. Tice AD (guest editor). Outpatient parenteral antimicrobial therapy. Infect Dis Clin North Am 1998; 12 (4)
60. Tice AD. Experience with a physician-directed, clinic-based program for outpatient parenteral antibiotic therapy in the USA. Eur J Clin Microbiol Infect Dis 1995; 14: 655-61
61. Nathwani D. Outpatient treatment with teicoplanin. Chemotherapie J 1996; 5 Suppl. 11: 35-8
62. Wilson APR, Gruneberg RN. Use of teicoplanin in community medicine. Eur J Clin Microbiol Infect Dis 1994; 13: 701-10
63. Eron LJ. Intravenous antibiotic administration in outpatient settings. Infect Dis 1982; 14: 4-11
64. Poretz DM, Eron LJ, Goldenberg RI. Intravenous antibiotic therapy in an outpatient setting. JAMA 1982; 248: 336-9
65. Poretz DM, Woolard D, Eron LJ, et al. Outpatient use of ceftriaxone: a cost-benefit analysis. Am J Med 1984; 77: 77-83
66. Kind AC, Williams DN, Gibson J. Outpatient intravenous antibiotic therapy. Ten years' experience. Postgrad Med 1985; 77: 105-8, 111
67. Williams DN, Bosch D, Boots J, et al. Safety, efficacy and cost savings in an outpatient intravenous antibiotic program. Clin Ther 1993; 15 (1): 169-79
68. Tice AD. Patient selection criteria for outpatient parenteral antibiotic therapy – experience with a physician-directed, clinic-based program for outpatient parenteral antibiotic therapy in the USA. Eur J Clin Microbiol Infect Dis 1995; 14: 23-9
69. Hindes R, Winkler C, Kane P, et al. Outpatient intravenous antibiotic therapy in medicare patients: cost-savings analysis. Infect Dis Clin Pract 1995; 4: 211-7

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