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Place of Parenteral Cephalosporins in the Ambulatory Setting

Clinical Evidence

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Abstract

During the last decade, 6 parenteral third generation cephalosporins have been introduced into clinical practice. The three most frequently used agents are cefotaxime, ceftazidime and ceftriaxone. Although primarily used in hospitals, these agents are increasingly employed in the ambulatory setting. In particular, ceftriaxone, because of its favourable pharmacokinetic profile allowing once-daily administration by a bolus injection, has demonstrated both tolerability and efficacy in the ambulatory setting during extensive worldwide use. Sophisticated parenteral infusion systems enable cephalosporins that require more frequent administration to be delivered in this setting.

In noncomparative studies involving a range of patient populations and serious infections (mostly bone, joint and soft tissue, and pneumonia and febrile episodes in neutropenia), these cephalosporins achieved equivalent efficacy and tolerability, and considerable cost savings, since patients were able to receive all or part of their treatment in the home or outpatient setting. However, more comparative studies of ambulatory parenteral therapy in the inpatient setting or ambulatory oral therapy are necessary to further clarify the true cost effectiveness of this type of healthcare delivery. This is increasingly relevant in countries where parenteral antimicrobials are not the 'standard of care' in managing many serious infections.

Published experience to date confirms that third generation cephalosporins, particularly ceftriaxone, should have an essential place in the therapeutic formulary of any ambulatory parenteral antibiotic programme.

1. Ambulatory Use of Parenteral Antibacterials: Contemporary Perspectives

In the US, the cost of medical care has progressively increased to more than 12% of the Gross National Product (GNP). Similarly, during the past 20 years, the cost of healthcare represents the fastest growing segment of Western European government spending, with an annual increase of 0.6 to 0.7 GNP percentage points annually. Concern regarding these healthcare costs has led to prioritising cost-efficient systems of delivering healthcare.

Expenditure on antibiotic agents accounts for the largest proportion (up to 30%) of a hospital's drug budget,[1] with broad spectrum intravenous antibiotics – particularly third generation cephalosporins – being the most expensive on a cost-per-day basis.[2] Over the years, a number of factors,[3] particularly in the US, promoted the increasing use of intravenous antibiotics in the inpatient hospital

setting, to the extent that a medical culture was created in which treatment of any but the most trivial infection by any other route became almost unacceptable.[4] Indeed, until very recently, inpatient intravenous therapy was the 'standard of care' in the US.[4] This philosophy is also prevalent in certain European countries such as Germany and France, while in Italy the intramuscular route is preferred.[5] However, in Britain the use of oral drugs remains high,[5] and intravenous drugs are preferred either for short courses or for well defined conditions such as bacterial meningitis and endocarditis.

In the US, until the early 1970s many patients were admitted to hospital primarily to receive intravenous antimicrobials. Therefore, home healthcare was originally conceived as a means to facilitate hospital discharge. However, the remit is now wider and allows patients in the community or from emergency centres direct access to intravenous antimicrobials on an outpatient basis without prior hospitalisation.[6,7] Ultimately, the prevention of hospitalisation remains the more cost-effective option. The main stimulus in the US for intravenous therapy in the outpatient or home setting is a desire to reduce costs associated with hospital stay[8] and to return the patient to home/work as soon as possible,[9] with a resultant improvement in quality of life,[10,11] but without compromising outcome.[12]

1.1 Outpatient and Home Parenteral Antibiotic Therapy (OHPAT)

The availability of new potent parenteral antibiotics with favourable pharmacokinetic profiles, better catheters for vascular access, and improved infusion devices has allowed the development of effective and safe programmes by highly motivated, well trained multidisciplinary members (physicians, nurses, pharmacists etc.) of Outpatient and Home Parenteral Antibiotic Therapy (OHPAT) teams.[6,7,13]

Against the background of an 'intravenous antibiotic culture', this form of therapy has been well accepted by patients, payers and providers,[14] and has made the provision of home/outpatient intravenous antimicrobials the premier growth industry in the US, surpassing parenteral nutrition and chemotherapy.[15] Indeed, the development of these services is now regarded as a critical opportunity for US infectious diseases clinicians working within the managed-care setting.[16] Despite the enthusiasm and generalised acceptance of this mode of therapy in the US and, more recently, in Canada,[17] many countries are still in the infancy of developing and implementing such programmes.[6]

However, in many societies, hospitalisation for intravenous therapy remains the gold standard for delivering such therapy. In contrast, outpatient intramuscular therapy for an array of infections of variable severity is considered acceptable in Italy.[6]

Nevertheless, in the UK for example, many clinicians remain unconvinced about the necessity of continuing or initiating intravenous antibiotic therapy at home when potent new oral antibiotics with superior pharmacokinetic profiles may obviate the underlying risk and cost of intravenous therapy.[5,18] Indeed, in the UK, because intravenous administration of antibiotics is not the 'standard of care' for many infections, the fear of potential liability from not using intravenous therapy is less important.

Moreover, there is increasing evidence from *in vitro* as well as clinical studies supporting the efficacy of oral antibiotics in many infections. This subject has recently been reviewed.[3] However, other comparative studies from Europe have suggested that in countries such as the UK, where oral therapy is preferred, there appears to be a higher rate of initial treatment failure.[5] Similarly, the predominant use of oral therapy for common conditions (such as lower respiratory tract infection) has also recently been associated with higher rates of initial treatment failure and hospitalisation when compared with the more frequent use of initial parenteral therapy.[19] The reasons for this are unclear and need further investigation.

The extensive use of parenteral second and third generation cephalosporins in hospitals has led

to the emergence of resistance and superinfection.[20,21] Whether this pattern of resistance will emerge in ambulatory therapy programmes primarily using popular third generation cephalosporins, such as ceftriaxone, is as yet uncertain.

The intravenous route has been viewed by the majority of clinicians as the most effective, best tolerated, and quickest method of initiating therapy.[3] Increasingly, contemporary literature indicates that oral therapy with new antimicrobials is as efficacious as, and more cost effective than, intravenous therapy in the hospital or at home.[3,18,22,23] However, a number of key considerations support the continuing use of ambulatory parenteral antibiotic therapy for many infections and healthcare systems. These are summarised in table I.

Table I. Key considerations supporting the continuing use of ambulatory parenteral antibiotic therapy

Drug factors
Lack of available oral drug/formulation to treat specific infection
Failure of previous trial of oral therapy
Oral antibiotic less efficacious
Poor oral bioavailability or adverse pharmacokinetic/pharmacodynamic properties
Host factors that may render some oral antimicrobials less effective
Achlorhydria
Neutropenia
Immunosuppression
Gastrointestinal tract dysfunction
Patient factors
Inability to tolerate oral medication
Poor patient compliance with self-medication
Patient preference for parenteral therapy
Socioeconomic or cultural factors
Potential legal liability because of perception that oral therapy is not standard of care for sick patient
Cultural preference for parenteral therapy
Insistence by payers
Religious (e.g. Ramadan)
Infection factors
Severe lower respiratory tract infection
Endocarditis, especially early part of therapy
Meningitis
Certain types of osteomyelitis/septic arthritis
Vascular infections
Some soft tissue infections
Others

1.2 Infections Amenable to OHPAT

Among the variety of infections amenable to OHPAT,[6,7,14] those due to Gram-positive organisms clearly predominate.[24,25] However, a significant proportion of the infections amenable to OHPAT are due to Gram-negative bacilli, anaerobes, viruses and other pathogens such as *Borrelia*. The range of infections due to Gram-negative aerobic bacilli continues to increase and many are now being treated in the community setting.[7,26] For example, there is increasing evidence for treating complicated pulmonary and urinary tract infections with outpatient therapy, often after initial assessment in emergency centres.[27] Furthermore, the types of infections treated in the OHPAT setting are dependent on many factors, such as their prevalence, as well as the speciality of the unit, geographical considerations and cultural attitudes of the patients towards ambulatory therapy.

Despite the predominance of infections due to Gram-positive pathogens, cephalosporins (particularly ceftriaxone) and vancomycin are the two most commonly used agents in OHPAT programmes in the US.[7,28] In Europe, a similar situation exists, although teicoplanin, rather than vancomycin, is mainly used for ambulatory therapy.[14,24,25]

1.3 Parenteral Third Generation Cephalosporins

Although many parenteral cephalosporins are available for use in clinical practice, the most widely used agents within this group are the third generation cephalosporins.[20,21] Of the 6 parenteral third generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefoperazone, ceftizoxime and latamoxef) that have been introduced into clinical use, the three most frequently used are cefotaxime, ceftriaxone and ceftazidime.[21] This predominance is reflected in hospital as well as OHPAT programmes. The only exception is in the ambulatory setting in the US, where cefazolin, a

second generation cephalosporin, is commonly used.

The third generation agents are characterised by a broad spectrum of activity and increased stability in the presence of β-lactamases compared with the first and second generation cephalosporins. They are most active against the Enterobacteriaceae but generally less active against staphylococci and streptococci. However, their relative broad spectrum of activity allows them to be effective for treating a range of infections, particularly when empirical therapy is required or when no organism is isolated. The various microbiological and pharmacokinetic properties, including drug stability in the ambulatory setting, of selected parenteral cephalosporins have been summarised elsewhere in this supplement.

2. Place of Cephalosporins in the Ambulatory Setting: Clinical Evidence

The remainder of this review summarises the available data regarding (i) the comparative clinical efficacy of parenteral cephalosporins, especially the third generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime), in the treatment of serious bacterial infections in the ambulatory setting, and (ii) their efficacy in treating infections in specific patient subgroups.

Rules of scientific evidence that can be used to evaluate published data have been developed and recently applied to assessing sequential antibiotic therapy trials.[22] The critical issue associated with ambulatory parenteral therapy is whether it can perform as well as standard therapy in the inpatient setting. Ideally, any study should be randomised and comparative – i.e. it should involve the same treatment delivered to similar patient populations in the two different settings. Unfortunately, currently available studies regarding the use of cephalosporins in the ambulatory setting have set out primarily to show equivalent efficacy and tolerability, and have compared their findings with data from previous studies performed in hospital or with historical data.

Furthermore, the emphasis in these studies was on the attendant pharmacoeconomic advantages. The majority of these were open-labelled non-comparative trials and confirmed that parenteral cephalosporins are clinically and microbiologically effective in treating a broad range of serious bacterial infections in the ambulatory setting. These results compared favourably with similar outcome parameters from studies of hospitalised patients. In the studies in the ambulatory setting, many patients were begun on parenteral therapy in hospital, and therapy was continued in the ambulatory setting once they were judged to be clinically stable. However, a significant majority of carefully selected patients received all their therapy in the ambulatory setting.

Random assignment of patients reduces bias associated with nonrandomised clinical trials. Regardless of the setting in which the treatment was initiated, in the studies reviewed in this paper there was often introduction of a high degree of selection bias, since only patients showing a high likelihood of therapeutic response were recruited for either initiation or continuation of therapy in the outpatient setting. These studies are summarised in tables II and III.[29-53]

2.1 Experience with Ceftriaxone

The wealth of published experience in the ambulatory setting is with ceftriaxone[29-45] (table II), which has been successfully used to treat a range of serious infections in all age groups and in patients who were either immunocompetent or immunocompromised and/or neutropenic. In addition to these trials, many other[54,55] authors have summarised their experience of the efficacy and tolerability of OHPAT programmes that primarily used ceftriaxone, thereby indirectly supporting the data from clinical trials.

In one study, a health economics model[56] with a hypothetical decision-tree analysis has also been used as a means of estimating the most effective clinical and cost-effective strategy for managing febrile infants at risk of serious bacterial infections. This study showed that combining all available

Table II. Noncomparative trials of parenteral ceftriaxone administered once daily as monotherapy or in combination in selected outpatients with serious bacterial infections (adapted from Davis & Bryson[26]). These evaluated patients received most or all of their ceftriaxone regimen in the outpatient setting

Infection	Clinical success[a] (%)	References
Adults		
Bone/joint	83 to 94	Jauregui et al.;[29] Eron et al.[30]
Skin/soft tissue	93 to 96	Jauregui et al.;[29] Eron et al.[30]
Streptococcal endocarditis[b]	87.5 to 100	Stamboulian et al.;[31] Francioli et al.[32,33]
Serious bacterial infections[c]	86 to 100	Jauregui et al.;[29] Karachalios et al.;[34] Russo et al.[35]
Children		
Febrile episodes	93	Bass et al.[36]
Febrile episodes in the immunocompromised neutropenic child	67 to 95[d]	Preis et al.;[37] Martino et al.;[38] Kaplinsky et al.;[39] Mustafa et al.[40]
Pneumonia	97	Leibovitz et al.[41]
Serious bacterial infections[e]	96 to 100	Bradley et al.;[42] Dagan et al.[43]
Infants		
Febrile episodes	100	McCarthy et al.;[44] Baskin et al.[45]

a Clinical success was defined as complete or partial improvement in signs and symptoms of infection.

b Ceftriaxone was given in addition to once-daily amikacin.

c Serious bacterial infections included infections in the abdomen, respiratory tract, blood, urinary tract, cerebrospinal fluid and endometrium.

d In the study of Martino et al.,[38] amikacin was given in combination with ceftriaxone; addition of teicoplanin or vancomycin to a nonresolving fever improved clinical success rate to 92%.

e Includes infections in the meninges, skin and soft tissue, and renal tract, and abscesses, septic arthritis, bacteraemia and pneumonia.

diagnostic tests for sepsis with empirical ambulatory intramuscular ceftriaxone prevented 76% of all potential sequelae and incurred the fewest hospitalisations of any strategy.

2.2 Experience with Cefotaxime and Ceftazidime

Many of the published studies with cefotaxime[46-53] in the ambulatory setting have limitations similar to those for studies with ceftriaxone, and many have been published in the proceedings of a single symposium.[46,48-53] In these studies, cefotaxime was usually given as an infusion, often by sophisticated computerised delivery systems, and was efficacious in treating many infections (table III). The authors of these studies emphasised the mean reductions in hospital stay that were gained, compared with allotted inpatient days for a specific diagnosis-related group (DRG), and the attendant direct and indirect fiscal and quality-of-life advantages to the patient and caregivers.[46,48-53]

As these studies were primarily performed in North America and relied on a payment system related to DRG allotments to justify the economic savings, such findings may be less relevant to other healthcare systems. Finally, little information exists regarding the role of ceftazidime in the ambulatory setting, except for its established role in the management of pulmonary infective exacerbations in cystic fibrosis.[57] In this study, outpatient ceftazidime delivered continuously by infusion pump was well tolerated and effective in treating a small group of children with cystic fibrosis. However, patient selection was believed to be of paramount importance if undue anxiety of patients and parents was to be avoided.

2.3 Study Limitations

A recent study[58] has attempted to address the limitations of the studies summarised in sections 2.1 and 2.2. The authors questioned whether a combination of initial parenteral cephalosporin therapy followed by oral antibiotic therapy in the outpatient setting was comparable to a similar

Table III. Noncomparative clinical trials of cefotaxime administered in the ambulatory setting to patients with a range of serious bacterial infections

Cephalosporin	No. of patients	MOA	Infection	Age	CS (%)	Mean observed inpatient LOS (days)	Reference DRG inpatient LOS (days)	Reference
Cefotaxime	62	IP	Pneumonia	A	94.8	0.93±2.15	9.3	Morales & Snead[46]
Cefotaxime	56	B	Cellulitis (25%)	A	94.6	5.1	NA	Williams et al.[47]
			Osteomyelitis (18%)					
			Abscesses (9%)					
			Pneumonia (7%)					
			Pyelonephritis (5%)					
			Others (36%)					
Cefotaxime	27	IP	BJI	A	83.3	12.17±11.15[a]	10.4	Mauceri & HIAT group[48]
Cefotaxime	118	IP	SSTI	A	97.5	4.7	7.1	Poretz & HIAT group[49]
Cefotaxime	58	IP	Pneumonia	A	100	0.93±2.15	9.3	Williams[50]
Cefotaxime	211	IP	Pneumonia (26%)	A	93.3	0.93	9.3	Poretz[51]
			BJI (54%)			12.17	10.4	
			SSTI (11.3%)			1.52	7.1	
			Primary bacteraemia (3%)			3.38	7.5	
			Others (5.7%)			5.33	8.0	
Cefotaxime	62	IP	Pneumonia (22.5%)	A	98	1.64	9.3	Angel & HIAT group[52]
			SSTI (40%)			3.60	7.1	
			BJI (9.7%)			15.08	15.08	
			Primary bacteraemia (3%)			5.00	5.00	
			Others (5%)			6.17	6.17	
Cefotaxime	22	IP	SSTI (64%)	A + HIV	98	0.62	7.1	Morales[53]
			Pneumonia (23%)			3.8	9.3	
			Pansinusitis (9%)			10.5	8.0	
			Primary bacteraemia (4.5%)			3.0	7.5	

a 10.3 days if one patient who required 44 days' inpatient treatment is excluded.

A + HIV = adult HIV-infected patients; **B** = bolus; **BJI** = bone and joint infection; **CS** = clinical success; **DRG** = diagnosis-related group; **HIV** = human immunodefiency virus; **IP** = intermittent infusion; **LOS** = length of stay; **MOA** = mode of administration; **NA** = not applicable; **SSTI** = skin and soft tissue infections.

regimen in hospital when treating a specific complicated infection, in this case pyelonephritis. In a randomised comparative controlled trial of pyelonephritis in pregnancy[58] (gestation < 24 weeks), patients were well matched for age, parity and disease severity and the outpatient group received careful follow-up. No difference was noted between the two regimens in terms of efficacy, tolerability or bacteriological cure (table IV).

This is the only randomised comparative controlled trial showing that ambulatory therapy with parenteral cephalosporins combined with continuing oral therapy is as effective as inpatient therapy for a selected population of pregnant women with acute pyelonephritis. Unfortunately, the antibiotic choice differed for the two arms of the study. If we are to convince clinicians of the true efficacy and tolerability of OHPAT programmes, other such comparative studies involving different popula-

tions and using well defined outcome measures are desirable.

2.4 Clinical Rationale for Cephalosporins in the Ambulatory Setting

Many would argue that a substantial number of patients selected for ambulatory parenteral therapy could be adequately treated with oral therapy,[3,18,22,23] which is by far the most cost-efficient means of managing these patients. Despite this, there are many reasons why ambulatory parenteral antibiotic therapy should be considered (table I). For example, in our own study, poor compliance or adverse reactions resulting in failure of oral therapy were the commonest reasons for considering ambulatory therapy.[55] In other situations, such as infections resulting from methicillin-resistant *Staphylococcus aureus* or coagulase-negative pathogens, the lack of an available oral formulation is the principal consideration.[24,25]

In Italy, there are overwhelming cultural pressures to treat many infections with intramuscular drugs, particularly ceftriaxone.[7] Whether the addition of a parenteral antibiotic to a standard oral therapy in the ambulatory setting improves the overall efficacy of, or compliance with, an antibiotic regimen for the treatment of infection has also been examined in terms of non–life-threatening illness. For example, two randomised studies[59,60] have determined the efficacy of single doses of ambulatory parenteral cephalosporin therapy (cefoxitin[59] or ceftriaxone[60]) in combination with oral therapy (doxycycline) compared with standard single (ampicillin-sulbactam[59]) or combination (ciprofloxacin and clindamycin[60]) oral therapy for mild to moderate pelvic inflammatory disease. In both studies, there was no difference in efficacy or tolerability between either regimens, although the cefoxitin-based study showed an overall suboptimal response to treatment in both arms compared with the ceftriaxone-based study (table V). Therefore, when treating mild to moderate pelvic inflammatory disease, single doses of ceftriaxone in combination with oral doxycyline, may be used as an alternative to combined oral ciprofloxacin plus clindamycin, if deemed to be more appropriate for reasons of compliance, culture, logistics or patient preference but not on the grounds of superior efficacy.

2.5 Delivery of Intravenous Cephalosprins

Minimising the number of daily doses and administration time for cephalosporins reduces costs of labour and disposables, and leads to less handling of the infusion line, thus reducing the risk of line-related sepsis. Therefore, administration of once-daily cephalosporins, such as ceftriaxone, either as a bolus dose or a short infusion is obviously

Table IV. Comparative clinical trial of parenteral cephalosporins in the ambulatory setting versus parenteral therapy in the inpatient setting: acute pyelonephritis in pregnancy[58]

	Inpatient	Outpatient
No. of patients	60	60
Parenteral antibiotic (route; dose; frequency)	Cefazolin (IV; 1g; tid)	Ceftriaxone (IM; 1g; one single dose)
Conditions of study	IV until afebrile for minimum of 48h followed by oral therapy	IM OD dose in the emergency room, observed for 4-24h and followed by oral therapy
Oral antibiotic (dose; frequency; duration given at home)	Cefalexin (500mg; qid; 10 days)	Cefalexin (500mg; qid; 10 days)
No. of patients with:		
bacteriological failure	12/60	11/60
clinical failure		
change in antibiotic	6/60	0/60
recurrence of infection	3/60	3/60
Comment	Equivalent efficacy	

IM = intramuscular; **IV** = intravenous; **OD** = once daily; **qid** = 4 times daily; **tid** = 3 times daily.

Table V. Comparative clinical trials of parenteral cephalosporins combined with oral therapy in the ambulatory setting versus standard single or combination oral therapy[59,60]

	Parenteral cephalosporin	Oral regimen
Acute PID		
No. of patients	37[59]	38[59]
Antibiotic/s (route; dose; frequency; duration)	Cefoxitin (IM; 2g; OD; single dose) with probenecid + doxycycline (PO; 100mg; bid; 10 days)	Ampicillin-sulbactam (PO; 750mg; bid; 10 days)
Outcome – clinical cure	72%	70%
Mild-moderate PID		
No. of patients	64[60]	67[60]
Antibiotic/s (route; dose; frequency; duration)	Ceftriaxone (IM; 250mg; OD; single dose) + doxycyline (PO; 100mg; bid; 14 days) + placebo (PO; 14 days)	Clindamycin (PO; 300mg; tid; 14 days) + ciprofloxacin (PO; 250mg; bid; 14 days) + placebo (IM; single dose)
Outcome – clinical cure	95%	97%

bid = twice daily; **IM** = intramuscular; **OD** = once daily; **PID** = pelvic inflammatory disease; **PO** = oral; **tid** = 3 times daily.

desirable, particularly in areas with minimal resources for developing ambulatory services. However, there now exists a range of devices that allow safe continuous infusion or intermittent bolus administration,[61] although this can further add to the cost of the service.

3. Conclusions

Third generation cephalosporins, particularly ceftriaxone, remain some of the most commonly used parenteral antibiotics in the ambulatory setting. Indeed, experience with ceftriaxone in the OHPAT setting is growing, as highlighted by recent UK experience.[62] A review of the published literature indicates that outpatient or home therapy with cephalosporins is a well tolerated and efficacious alternative to inpatient therapy for a range of infections (such as bone, joint and soft tissue sepsis, endocarditis, pneumonia, pyelonephritis, fever in the neutropenic host, bacteraemia, abscesses and others) and patient populations. However, a multitude of factors need to be examined when considering patients for parenteral ambulatory therapy if the success of this type of healthcare delivery system is to continue and if it is to maintain the trust of patients, clinicians and healthcare managers.

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