Drugs 2002; 62 (2): 309-317
0012-6667/02/0002-0309/$27.50/0

Intravenous/Oral Sequential Therapy in Patients Hospitalised with Community-Acquired Pneumonia

Which Patients, When and What Agents?

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Abstract

Cost and pharmacoeconomic aspects are becoming more and more important in antibacterial therapy. Nevertheless, antibacterial therapy is curative and initial use of the right antibacterial with high activity and low resistance rates against the relevant pathogens can help to save costs. A new trend in antibacterial therapy is sequential therapy (intravenous/oral) in hospitalised patients with moderate to severe infections.

Large studies comparing intravenous therapy with sequential therapy (intravenous/oral) have shown equivalence in clinical and bacteriological outcome. One main indication investigated is community-acquired pneumonia (CAP). CAP requires prompt and effective antibacterial treatment and conventional therapy for patients hospitalised with CAP has typically been parenteral antibacterial therapy for 7 to 10 days. However, clinical evidence shows that in most patients the objective and subjective indicators of infection are substantially improved within the first 2 to 3 days of treatment. Today a large number of clinical trials in patients with CAP have been undertaken and sequential therapy with appropriate antibacterials used in suitable patients has been proven as a treatment option. This demonstrates pharmacoeconomic benefits without compromising

antibacterial efficacy. Recommended antibacterials for intravenous/oral sequential therapy in patients with CAP are second- and third- generation cephalosporins, aminopenicillins plus a β-lactamase inhibitor, and new fluoroquinolones.

Community-acquired pneumonia (CAP) requires prompt and effective antibacterial treatment. Conventional therapy for patients hospitalised with lower respiratory tract infections such as pneumonia has typically been parenteral antibacterial therapy for 7 to 10 days. However, clinical evidence shows that in most patients the objective and subjective indicators of infection are substantially improved within the first 2 to 3 days of treatment. At the end of the 1980s and the beginning of the 1990s, McCracken[1] posed the question of whether patients could be switched to oral antibacterials after 2 to 3 days of parenteral therapy without compromising treatment efficacy. The postulated benefits for this new treatment regimen were substantial savings in terms of cost of care and length of hospital stay. However, at that time there were many concerns about use of short periods of intravenous treatment because of lack of clinical data to support the concept. There was a clear need for large-scale comparative clinical trials to validate the efficacy of this treatment approach. Several investigators addressed this issue and the following main questions posed in the clinical studies were:

- which patients should not be switched to oral therapy?
- which patients could be treated with a short intravenous course followed by oral treatment?
- which indications were appropriate for switch therapy?
- what initial antibacterial doses?
- what agents are useful and effective?
- is it possible to use two different antibacterials?
- could the intravenous and oral antibacterial components of the regimen be different?

Today a large number of clinical trials have been undertaken and reported using intravenous/oral therapy, and sequential therapy with appropriate antibacterials used in suitable patients has been proven as a treatment option demonstrating pharmacoeconomic benefits without compromising antibacterial efficacy.

1. Which Patients Can Be Treated?

In recently published guidelines for initial empirical antibacterial therapy in patients with CAP, oral treatment alone is sometimes recommended because modern highly bactericidal agents are available that cover the most frequently encountered pathogens.[2] Nevertheless, clinical experience shows the limitations of oral treatment alone which has been mainly investigated in CAP in outpatients with mild to moderately severe infections.[3]

Therefore, initial intravenous therapy of CAP is recommended in most hospitalised patients, patients after surgery, older patients, and patients with underlying chronic diseases, problems with enteral absorption or insufficient compliance because these patients need to be stabilised quickly with intravenous therapy. Both clinical and microbiological evidence support initial use of intravenous antibacterial therapy to ensure relatively rapid delivery of high concentrations of drug to the infection site because pathogens are likely to be present in greater numbers during the early stages of infection.

After intravenous treatment for 2 to 3 days, patients often respond quickly and are well enough to be switched to oral treatment.

Determining when to change from intravenous to oral therapy requires clinical judgement and is likely to depend on the individual patient. In general, the following parameters would be taken into account in deciding to change to oral treatment:

- no clinical indication to continue intravenous antibacterial therapy
- decrease in C-reactive protein levels, returning to normal
- decrease in leucocyte numbers, returning to normal

Table I. Clinical criteria for parenteral to oral switch

No clinical indication for continuing intravenous therapy
Presence of normal gastrointestinal absorption
Temperature returning to normal
Signs and symptoms related to infection (cough, respiratory distress) improving or resolved
WBC and differential counts returning to normal
C-reactive protein levels returning to normal
Ability to swallow tablets

WBC = white blood cell count.

- normal gastrointestinal absorption; no diarrhoea
- improved or resolving signs and symptoms of infection
- temperature returning to normal (patient is afebrile or almost afebrile)
- oral medication is feasible for the patient.

Especially in patients with CAP, laboratory measurements such as white blood cell count (WBC), differential count and C-reactive protein measures may be useful indicators and can support clinical observations (table I). This is supported by results of a nonblind clinical study in 87 paediatric patients with CAP. Inclusion criteria were temperature ≥38.5°C, WBC >15,000/mm^3 and lobar infiltration on chest radiograph. WBC, temperature, and chest radiographic findings were used as clinical markers to switch to oral antibacterial therapy. All children were febrile initially and had significantly elevated WBC. By day two of intravenous antibiotic therapy with the second-generation cephalosporin cefuroxime, more than 90% of patients had become afebrile, and mean WBC had fallen dramatically. These patients were switched to oral cefuroxime axetil treatment with high clinical success rates (cure or improvement) of 97.8% post-treatment. Patients were continued on intravenous treatment only if the clinical response was not satisfactory, for example if their temperature did not return to normal or almost normal. In this study, chest radiography was not considered sufficiently sensitive to serve as a determinant of when to switch to oral therapy.[4]

Ramirez et al.[5] investigated clinical outcome with an early switch from intravenous to oral third-generation cephalosporins. Patients were switched to oral cefixime 400 mg/day as soon as they met the following criteria:

- resolution of fever
- improvement of cough and respiratory distress
- improvement of leucocytosis and
- presence of normal gastrointestinal absorption.

Long-term follow-up of the 75 clinically evaluable patients showed that 74 were cured; only one patient required readmission for further intravenous therapy.

2. Limits of Intravenous/Oral Sequential Therapy

A switch to oral antibacterial treatment in patients with CAP is not recommended in patients who are neutropenic or have other high-risk immunocompromise, in those in intensive-care, or if multiresistant pathogens are expected (table II). If problems with gastrointestinal absorption cannot be excluded or if patients are not able to swallow tablets, intravenous therapy should be continued. Unsatisfactory clinical response or worsening of symptoms are both further reasons.

3. Duration of Intravenous Therapy: When to Switch?

Siegel et al.[6] investigated three regimens in 73 elderly patients with CAP. Group 1 received 2 days of intravenous and 8 days of oral therapy, group 2 received 5 days of intravenous and 5 days of oral treatment, and group 3 received 10 days of intravenous treatment. Antibiotics used were intravenous cefuroxime 750mg three times daily and oral

Table II. Limits for parenteral/oral switch therapy in patients with community-acquired pneumonia

Patients with neutropenia
Highly immunocompromised patients
Patients in intensive care unit
Multi-resistant pathogens
Problems with gastrointestinal absorption
Fever >38°C
Unexplained tachycardia
Persisting signs and symptoms of infection

cefuroxime axetil 500mg twice daily. No difference was found in the clinical course, cure rates, or resolution of chest radiographic abnormalities among the three groups. A significant difference was found in the length of hospital stay in favour of group 1.

In some patients, the reasons for a later switch to oral therapy, that is, after more than 2 to 3 days, could be the severity of the disease. However, in many cases physicians are not familiar with the wealth of clinical data supporting sequential therapy and are consequently reluctant to change their normal practice and discontinue intravenous treatment.

The study conducted by Shalit et al.[4] demonstrated that in most cases patients respond after 2 days of intravenous therapy. This is supported by other published clinical trials (table III), so 48 to 72 hours appear to be the preferred timing for switching from intravenous to oral treatment.[4,7-12] Oral antibacterial therapy should be continued for at least 5 days.

4. What Antibacterials for Sequential Therapy in Community-Acquired Pneumonia?

Recommendations for antibacterial treatment in patients with CAP are published in the guidelines of the American Thoracic Society and the European Medical Scientific Society.[13,14]

With current diagnostic tools it may take up to several days before the causative pathogen is identified and frequently the causative agent is never isolated at all. Empirical antibacterial therapy, covering the most important pathogens, is therefore recommended (figure 1).[3] Results of microbiological surveillance concerning local epidemiology and development of resistance are important criteria for local decision making. Besides the antibacterial spectrum of different agents, it is of great importance to be aware of the actual resistance status regarding the most important pathogens, which can differ tremendously when comparing different hospitals, regions or countries.

Main pathogens that have to be covered by initial therapy in CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and in atypical pneumonia *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. Guidelines recommend second- (or third-) generation cephalosporins, aminopenicillins plus a β-lactamase inhibitor and newer fluoroquinolones with improved activity against *S. pneumoniae*.[14] In less severe infections, macrolides are recommended because of their good activity against atypical bacteria. However, macrolides have only weak to moderate activity against *H. influenzae* and resistance in pneumococci, streptococci and staphylococci has increased up to 20% or more during recent years, and therefore, combination with an oral cephalosporin would be appropriate.

5. Efficacy in Clinical Trials

5.1 β-Lactam Antibiotics

The efficacy of sequential therapy has been demonstrated in a large number of studies and β-

Table III. Time point for parenteral to oral switch in patients with community-acquired pneumonia

Drug	Study	Duration of therapy	
		initial IV	oral sequential therapy
Amoxicillin/clavulanic acid *vs* cefuroxime + cefuroxime axetil	Brambilla et al.[8]	2-3 days	5 days
Amoxicillin/clavulanic acid *vs* cefuroxime + cefuroxime axetil	Britton[9]	2-3 days	5 days minimum
Ceftriaxone IV cefixime or amoxicillin/clavulanic acid (oral)	Amir et al.[10]	2 days	8 days
Cefuroxime + cefuroxime axetil	Shalit et al.[4]	2-3 days	5 days
Cefuroxime IV (full IV course 10 days) cefuroxime + cefuroxime axetil	Stille et al.[11]	3 days	7 days
Cefuroxime + cefuroxime axetil	Van den Brande et al. [12]	2-3 days	7 days

IV = intravenous.

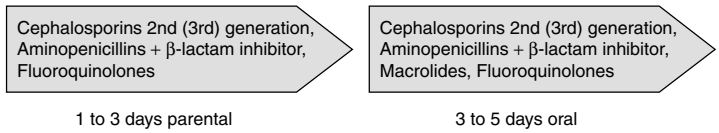

Fig. 1. Switch from initial parental antibacterial treatment to oral antibacterial therapy.

lactam antibiotics have been among the most widely used oral antibacterials in sequential therapy trials. In most cases a second-generation cephalosporin or an aminopenicillin in combination with a β-lactamase inhibitor has been used. The results obtained with intravenous second-generation cephalosporins (cefuroxime or cefotiam) followed by oral cefuroxime axetil are shown in table IV.[4,6,8,11,12] In most of these trials success rates are above 90%.

In one controlled, randomised clinical study, 154 clinically evaluable patients with CAP were treated with either cefuroxime 1.5g 3 times daily over a 10-day period or with sequential therapy of intravenous cefuroxime 1.5g 3 times daily for 3 days followed by 7 days of oral cefuroxime axetil 500mg twice daily. The positive treatment response was 98.8% in the intravenous group and 98.6% in the sequential therapy group. Clear, or reduction in purulence of, sputum was found in 90% in the intravenous group and in 87.8% in the sequentially treated group. The chest radiograph had returned to normal in a higher percentage of patients in the sequential therapy group, as well as the decrease in the initial infection signs and symptoms such as cough, sputum production, thoracic pain and dyspnoea.[11] Comparable results were demonstrated in a study of patients with lower respiratory tract infection (LRTI) with complete intravenous treatment with the second-generation cephalosporin cefotiam versus sequential therapy with cefuroxime then cefuroxime axetil therapy.[15]

Brambilla et al.[8] investigated the efficacy of intravenous/oral sequential therapy with amoxicillin/clavulanic acid (1.2g intravenously three times daily followed by 625 orally twice daily) in a large multicentre, randomised controlled study in 512 patients with LRTI. Clinical and bacteriological efficacy was compared with cefuroxime 750mg three times daily followed by cefuroxime axetil 500mg twice daily. The parenteral antibiotics were given for 2 to 3 days and were followed by 5 days of oral therapy. Of the 512 patients entered in the study, 225 were diagnosed as having CAP.[8] The response in the two regimens was similar. Clinical response at follow-up assessment was 87 versus 86.3%. Altogether 88.8% (104 of 117) of the amoxicillin/clavulanic acid-treated patients had a complete resolution or improvement in the infiltrate observed on the pre-treatment chest radiograph compared with 85.2% (115 of 135) of the cefuroxime then cefuroxime axetil-treated patients. The difference was not significant.

Results of further clinical trials investigating aminopenicillins with a β-lactam inhibitor are shown in table IV.[9,10] Further studies investigated the effectiveness of third-generation cephalosporins intravenous (cefotaxime or ceftriaxone) followed by oral third-generation cephalosporins with comparable good results of complete intravenous or intravenous/oral therapy (table IV).[5,10,16]

5.2 New Fluoroquinolones

Whereas older fluoroquinolones like ciprofloxacin and ofloxacin with only moderate activity against pneumococci are not drugs of first choice in CAP, newer quinolones with improved activity against Gram-positive organisms, especially pneumococci, are now further options for intravenous/oral sequential therapy in CAP. Clinical trials with successful results have been completed.[17,18] An open, randomised, multicentre study in hospitalised patients with pneumonia compared

Table IV. Results of sequential therapy with β-lactam antibiotics and new fluoroquinolones in patients with community-acquired pneumonia

Drug	No. pts	Dosage	Duration	Clinical success (%)	Reference
Cefuroxime + cefuroxime axetil	84	75 mg/kg/day 30 mg/kg/day	2-3 days 5 days	97.6	4
	137	750g tid IV 500mg bid PO	2-3 days 5 days	98.6[a]	8
	210	1.2g tid IV 500mg bid PO	2-3 days 7 days	86, 96[a,b]	11
	73	750mg tid IV 500mg bid PO	2 days 8 days	90	6
	636	1.2g bid IV 500mg bid PO	2-3 days 7 days	87	12
Ceftriaxone + cefuroxime axetil	44	1g 500mg bid PO	once 5 days	91	19
Ceftriaxone + cefixime	62	1 g/day 400 mg/day	2 days 8 days	97	10
Ceftizoxime or ceftriaxone + cefixime	120[c]	1g per day IV 400 mg/day PO	1-6 days 10 days	99	5
Ceftriaxone + cefetamet pivoxil	62	50 mg/kg/day IM 20 mg/kg/day PO	1 day 6 days	96	16
Amoxicillin/clavulanic acid	134	1.2g tid IV 625mg tid PO	2-3 days 5 days	87, 98[a,b]	8
	62	1g ceftriaxone IV 625mg tid PO	2 days 8 days	94	10
	181[d]	1.2g tid IV 625mg tid PO	2-3 days ≥5 days	96	9
Levofloxacin IV/PO ceftriaxone IV	266	500mg bid 4g once daily	8 days	87, 86[b]	17

a Evaluable patients.

b First value is for IV therapy and second is for oral.

c Noncomparative clinical trial.

d Lower respiratory tract infection, including pneumonia.

bid = twice daily; **IM** = intramuscular; **IV** = intravenous; **PO** = orally; **tid** = three times daily.

levofloxacin 500mg twice daily with ceftriaxone 4g intravenously once daily. Levofloxacin patients were treated intravenously and were switched to oral therapy on day 3 to 5 if signs and symptoms had improved. The minimum treatment duration was 5 days, except for treatment failure, and the median duration 8 days. At the clinical endpoint, 2 to 5 days after the end of treatment, the cure rates for levofloxacin (n = 127) and ceftriaxone (n = 139) regarding the per-protocol population were 87 and 86%, respectively [intention to treat population (n = 619): 76 and 75%]. Again intravenous/oral therapy was as good as a complete course of intravenous therapy (table IV).[17]

6. Initial Dose Administration

Recommendations for antibacterial dose administration, obtained in early dose-ranging studies, are given in the prescribing information sheets and sometimes differ between different indications depending on severity or expected severity of the infection. For CAP, an initial high dosage is usually recommended.

Nevertheless, a dose-ranging study investigating initial intravenous therapy dose administration has been completed in 636 adults with the diagnosis CAP requiring hospitalisation and initial intravenous treatment. Patients were randomised to two different treatment groups; cefuroxime 1.5g intravenously three times daily or twice daily for 48 to 72 hours followed by oral cefuroxime axetil 500mg twice daily for 7 days in both groups. For clinically evaluable patients, the clinical response rates were equivalent for cefuroxime three times daily and twice daily groups post-treatment (cure/improvement 79 and 84%, respectively) and at follow-up (maintained cure 87 and 82%, respectively). All signs and symptoms of pneumonia were improved at the time of switch from intravenous to oral antibiotics. The main pathogens were S. *pneumoniae* (23%), *H. influenzae* (18%) and Enterobacteriaceae. In total, 111 pathogens were isolated. Both regimens were well tolerated. The study demonstrated that twice-daily intravenous cefuroxime followed by oral cefuroxime axetil is an effective sequential therapy regimen for the treatment of CAP. It can replace the initial intravenous three times daily regimen in this indication. In addition,

dose-ranging studies of initial intravenous treatment in sequential therapy have shown it offers potential cost savings.[12]

7. Is it Possible to Use Two Different Antibacterials for Intravenous and Oral Treatment?

Several studies have been completed to clarify whether it is possible to use two different agents for intravenous and oral treatment.[5,10,16,19]

As discussed in section 4, CAP is caused predominantly by *S. pneumoniae*, *H. influenzae*, *S. aureus*, *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae*. Older oral cephalosporins (cephalexin, cefadroxil, cefaclor) have good activity against Gram-positive organisms but only minor to moderate (cefaclor) activity against *H. influenzae*. Second-generation cephalosporins like cefuroxime axetil have improved activity against Gram-negative organisms including *H. influenzae* and improved β-lactamase stability, thus maintaining high activity against Gram-positive organisms. Oral third-generation cephalosporins (cefetamet pivoxil, cefixime, ceftibuten, cefpodoxime proxetil) have high *in vitro* activity against Gram-negative enterobacteria but lack activity against staphylococci or possess only weak-to-moderate activity (cefpodoxime proxetil).[20]

Regarding typical causative pathogens of CAP, second-generation cephalosporins are mainly recommended for this indication.[14] No oral form of any intravenous third-generation cephalosporin has been developed, so sequential clinical trials investigating oral third-generation cephalosporins have to be done with two different compounds. Initial intravenous therapy was mainly started with cefotaxime, ceftizoxime or ceftriaxone, followed by a different oral third-generation cephalosporin (cefixime, cefpodoxime proxetil, cefetamet pivoxil) [table IV]. One drawback is that third-generation cephalosporins differ in their activity from intravenous agents. *S. pneumoniae* is the most frequently isolated causative pathogen in this indication but ceftibuten demonstrates only weak-to-moderate activity.[14]

It is possible to use two different antibacterials for intravenous and oral treatment, but it is important that both compounds have a comparable antibacterial spectrum and cover the most frequently isolated and important pathogens. In CAP, the causative pathogen is relatively rarely isolated and so the choice of third-generation agent needs to be guided by the physician's judgement of whether *S. pneumoniae* or *S. aureus* is present or whether Gram-negative organisms are more likely (table V).

Therefore, there is no basis for saying that there should always be a preference in sequential therapy for the same class of drugs to be used for intravenous and oral administration. There are undoubted advantages, however, such as knowing that the patient has had no serious adverse reaction to the intravenous formulation and so is unlikely to have a reaction to the oral formulation.[21]

Table V. Antibacterial agents used in sequential therapy in patients with community-acquired pneumonia

Same antibacterial IV/PO	Different antibacterial IV/PO
Cefuroxime + cefuroxime axetil	Cefotaxime + cefuroxime axetil
Amoxicillin/clavulanic acid	Cefotiam + cefuroxime axetil
Ampicillin/sulbactam	Cefotaxime + cefixime
Levofloxacin	Ceftriaxone + cefetamet pivoxil
Erythromycin	Ampicillin/sulbactam + amoxicillin/clavulanic acid
Clarithromycin	

IV = intravenous; **PO** = orally.

Table VI. Benefits of intravenous to oral sequential antibacterial therapy

Benefits for patients
More convenient
Less local adverse effects related to intravenous administration, such as phlebitis
Earlier mobilisation - lower risk of thrombosis
Reduced hospital stay - lower risk for cross- or nosocomial infections
Pharmocoeconomic benefits
Less infusion equipment, cannula, and infusion bottles required
Less hospital waste to dispose of
Oral antibacterials less expensive than parenteral antibacterials
Reduced storage costs for parenteral therapy
Less hospital staff time required
Reduced length of hospital stay

8. Benefits of Sequential Intravenous/Oral Therapy

The early switch from parenteral to oral antibacterial treatment offers the recovering patient more mobility and avoids infusion-related local adverse effects (e.g. thrombophlebitis). It requires less hospital staff time, reduces the amount of hospital waste as a result of reduced use of infusion equipment, and leads to considerable savings in purchase and administration of antibacterials. A switch to oral antibacterials may also result in a shorter hospital stay and therefore reduces the risk of secondary nosocomial infections (especially in older patients) and saves costs. The workload of hospital wards is reduced because dispensing tablets takes much less time than administration of injectable agents (table VI).[3,22,23]

Ramirez[24] investigated cost savings with an early switch from intravenous to oral antibacterial therapy (figure 2). Total savings were $US801 per patient and the major cost saving was due to reduced length of hospital stay.[24] A 1-day reduction in length of hospital stay might yield substantial cost savings.[25] Comparable results were obtained in a German pharmacoeconomic study in which cost savings of medical treatment, and of nursing, doctor and staff time were analysed.[23] In a prospective, randomised study Siegel et al.[6] investigated sequential therapy in veteran patients. The duration of intravenous treatment differed between the three treatment groups. Groups 1 and 2 received intravenous/oral treatment with cefuroxime then cefuroxime axetil and group 3 received intravenous cefuroxime. No differences were found in cure rates or resolution of chest radiograph abnormalities among the three groups but a significant difference was found in the length of hospital stay (LOS). The mean + SD LOS was 6 + 3 days in group 1 (2 days intravenous, 8 days oral), 8 + 2 days in group 2 (5 days intravenous, 5 days oral) and 11 +1 days in group 3 (10 days intravenous). The shortened LOS could potentially save $US95.5 million for the Department of Veterans Affairs and $US2.9 billion for the US private sector.[6]

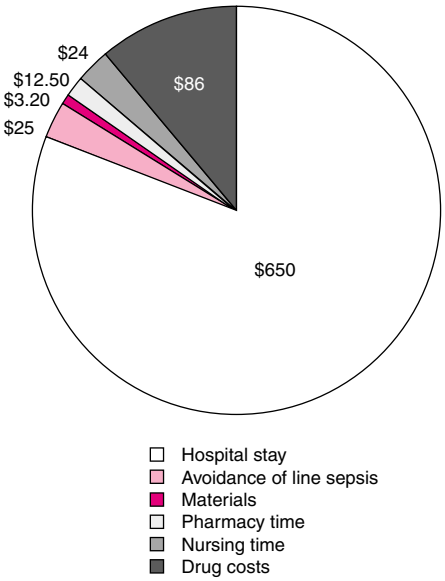

Fig. 2. Breakdown of cost savings associated with early switch from intravenous to oral antibacterial therapy. Savings per patient (total $US801).[24]

9. Conclusion

The findings from numerous clinical studies demonstrate convincingly that sequential antibacterial therapy offers significant benefits to hospitalised patients and provides equivalent efficacy compared with a full course of intravenous antibacterial treatment in appropriate patients. Nevertheless, the decision to switch from intravenous to oral therapy is not predetermined and must reflect the careful clinical observation and judgement of the physician.[25] Sequential therapy with the right antibacterials, with regard for the expected pathogens and actual resistance pattern, used in the appropriate patient, has been proven as a treatment regimen, maintaining a high quality of antibacterial therapy in combination with cost savings and pharmacoeconomic benefits.

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