Antimicrobial practice

Sequential antimicrobial therapy: treatment of severe lower respiratory tract infections in children

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Although there have been a number of studies in adults, to date there has been little research into sequential antimicrobial therapy (SAT) in paediatric populations. The present study evaluates the impact of a SAT protocol for the treatment of severe lower respiratory tract infection in paediatric patients. The study involved 89 paediatric patients (44 control and 45 SAT). The SAT patients had a shorter length of hospital stay (4.0 versus 8.3 days), shorter duration of inpatient antimicrobial therapy (4.0 versus 7.9 days) with the period of iv therapy being reduced from a mean of 5.6 to 1.7 days. The total healthcare costs were reduced by 52%. The resolution of severe lower respiratory tract infection with a short course of iv antimicrobials, followed by conversion to oral therapy yielded clinical outcomes comparable to those achieved using longer term iv therapy. SAT proved to be an important cost-minimizing tool for realizing substantial healthcare costs savings.

Introduction

Severe lower respiratory tract infections, such as community-acquired pneumonia, are a common reason for hospitalization of children. Intravenous administration of antimicrobials is usually used to help ensure that high serum and tissue antimicrobial concentrations are achieved rapidly. It is the route of choice in acutely ill children with lower respiratory tract infection and is essential for children unable to tolerate oral medication. In today’s era of cost-containment, it has become common practice to streamline the empirical regimen to a more cost-effective one, when the patient’s clinical condition has been identified. Sequential (i.e. iv followed by oral administration) antimicrobial therapy (SAT) is a cost-minimization strategy in reducing healthcare costs while maintaining patient care.

The concept that a full course of iv antimicrobial therapy is needed to treat hospitalized patients with infectious diseases is no longer valid. It has been suggested that iv antimicrobials can often be discontinued when patients show clinical improvement with initial therapy. An important factor in determining the length of hospital stay in patients with lower respiratory tract infection is the duration of iv therapy. Unnecessarily prolonged iv administration of antimicrobials leads to increased costs associated with iv drug acquisition costs, labour, iv fluids and with the associated expenses of administration apparatus. In addition, iv therapy can lead to increased morbidity, particularly thrombophlebitis and exposure to nosocomial pathogens, both of which can also prolong the length of hospital stay.

Although some clinicians are hesitant to initiate an early transition to oral antimicrobial therapy, even in patients who are demonstrating signs of improvement, there is increasing evidence to support the early use of oral agents in the treatment of several infections. Several studies have assessed the efficacy of oral antimicrobial therapy in
various infections including respiratory tract, skin and soft tissue, and bone and joint infections. These have provided considerable evidence to suggest that the use of oral agents is both safe and cost-effective. Louie has reviewed a number of clinical trials comparing iv with oral therapy. With the exception of patients with infections in areas into which antimicrobial penetration is poor (e.g. meningitis and infective endocarditis), the majority of hospitalized patients do not require prolonged courses of iv therapy.

The aim of the study was to examine the impact of the introduction of a SAT prescribing protocol on the clinical and economic outcomes of hospitalized children with severe lower respiratory tract infection.

Materials and methods

Study site

The study was carried out in the paediatric wards of Antrim Area Hospital, a 378-bed teaching hospital.

Baseline data collection

Data were collected on a standard custom-designed form to record the patient history, physical examination, treatment and laboratory data. Data collection was divided into two phases, baseline data and intervention data (SAT). Baseline data were collected retrospectively before the implementation of the SAT protocol to assess current practice and for comparative purposes, covering the period from December 1994 to February 1995.

Introduction of SAT

A major aim of the introduction of SAT was to minimize the duration of hospital stay for acute illness in children. It was agreed by the paediatric wards’ team that any paediatric patient with a severe lower respiratory tract infection, diagnosed on clinical grounds, with or without radiological changes, should be included in the study. The team also agreed the following as part of the SAT programme:

(a) Empirical antimicrobial treatment
   (i) Intravenous cefotaxime or co-amoxiclav.
   (ii) Oral cefixime or co-amoxiclav to be prescribed following the empirical iv treatment as soon as the patient is clinically stable.
   (iii) Azithromycin should also be used when atypical infection is considered likely.

(b) SAT criteria
   As soon as the following criteria are met, the patient should be switched from iv to oral therapy:
   - Cough, sputum and respiratory distress are improving
   - Patient is afebrile
   - WBC count and/or C-reactive protein is/are decreasing
   - Patient tolerating oral preparation

(c) Protocol implementation
Before the implementation of the protocol, three techniques were employed to promote its use:

(i) Presentation to the medical staff: this brief dialogue described the aims of the protocol and highlighted the potential cost saving.
(ii) Distribution of the SAT protocol to the medical staff.
(iii) Preparation of an algorithm (Figure) and display of this on each paediatric ward.

Prospective data collection was initiated concurrently with implementation of the SAT protocol, covering the period from December 1995 to February 1996.

Patient inclusion criteria

All patients admitted to the paediatric wards of Antrim Area Hospital, during the period from December 1994 to February 1995 (control group) and the period from December 1995 to February 1996 (SAT group) and diagnosed with severe lower respiratory tract infection were included in the study. A lower respiratory tract infection

MANAGEMENT OF SEVERE LOWER RESPIRATORY TRACT INFECTION IN CHILDREN

<table>
<thead>
<tr>
<th>Empirical antimicrobial therapy</th>
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<tbody>
<tr>
<td>Intravenous cefotaxime or co-amoxiclav</td>
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</table>

Switch therapy criteria

- Cough, sputum and respiratory distress are improving
- Patient is afebrile
- WBC is normalizing
- Functioning GIT

Oral therapy

- Cefixime
- Co-amoxiclav

Observation

Routine Labs
- FBP
- CRP
- U + E
- Chest X-ray
- Sputum and blood culture 'if clinically indicated'

Discharge within 48h if satisfactory

A typical infection suspected

Azithromycin can be used

Figure. A algorithm for SAT protocol.
Treatment of severe LRTI in children

was defined as an acute infection of the lower respiratory tract (or bronchial tree) resulting in acute bronchitis or pneumonia. All patients were adjudged to have severe illness by the clinician responsible on the basis of clinical and chest X-ray features.

The following definitions were used in assessing therapeutic outcome:

(i) Treatment success—major improvement or complete resolution of all signs and symptoms.
(ii) Treatment failure—persistence or progression of signs and symptoms; development of new clinical findings consistent with active infection or death from primary diagnosis; presence of adverse reaction to the prescribed medication leading to its discontinuation.

Pharmacoeconomic analysis

The economic analysis was limited to three main healthcare costs i.e. total antimicrobial costs (antimicrobial acquisition costs and hidden costs, including cost of consumable materials, staff time and waste disposal); diagnostic test costs and hospital bed costs.

Patient follow-up

All parents of SAT-treated patients were given a letter regarding their child’s clinical progress after discharge. Within 4–6 weeks after the discharge, patients’ parents were contacted by telephone and asked whether there had been a return of symptoms of the infection.

Statistical analysis

Data were entered on to a desktop computer using Paradox (version 3.5; Corel Corporation Ltd., Dublin, Republic of Ireland) software and analysed using SPSS (version 7) software. Differences in variables between patient groups, i.e. baseline and protocol groups, were analysed using the chi-squared test and Fisher’s exact test for categorical variables. A logarithmic transformation to base 10 was performed to normalize some outcome measures’ data (length of hospital stay, duration of iv administration, duration of oral treatment, duration of treatment in hospital and elements of healthcare cost) and to calculate confidence intervals for the mean data. Results were reported as statistically significant at \( P < 0.05 \).

Results

Patient characteristics

From December 1995 through to February 1996, 45 patients were recruited for the SAT group while 44 patients admitted from December 1994 to February 1995 formed the control group.

No patient was excluded because of non-functioning of their gastrointestinal tract or inability to tolerate oral therapy. A iso no patient was found to be hypersensitive to penicillin or cephalosporin at the time of entry into the study. Characteristics of patients entering the SAT and control groups were as follows: the mean age (\( \pm \text{s.d.} \)) of the SAT group was 3.3 years (\( \pm 1.4 \)), ranging from 1 to 6.5 years compared with 3.2 (\( \pm 1.9 \)), ranging from 10 months to 7.5 years in the control group (\( P = 0.809 \)). Twenty-two (48.0%) patients were male in the SAT group compared with 21 (47.7%) patients in the control group (\( P = 0.920 \)). The mean duration of symptoms (\( \pm \text{s.d.} \)) before hospital treatment commencement was 4.7 days (\( \pm 1.3 \)) for the SAT group compared with 4.8 (\( \pm 1.1 \)) for the control group (\( P = 0.674 \)).

There were also no statistically significant differences between the two groups at baseline in the following variables: mean temperature at the time of hospital admission (\( P = 0.119 \)); the number of patients with fever (\( P = 1.00 \)); blood urea (\( P = 0.452 \)); serum creatinine (\( P = 0.198 \)); WBC (\( P = 0.979 \)). By the second day of iv therapy in both groups, 95% or more of patients had normal body temperatures. The mean (\( \pm \text{s.d.} \)) time to resolution of fever was 1.7 days (\( \pm 0.8 \)) ranging from 1 to 3 days in the SAT group compared with 1.6 days (\( \pm 0.9 \)) ranging from 1 to 4 days in the control group (\( P = 0.79 \)).

Clinical outcome measures

The rates of therapeutic response were identical in both study groups, with no patient failing to respond to therapy. All SAT-treated patients were assessed 4–6 weeks after discharge and no return of the signs and symptoms of the infection or re-admission had occurred. No adverse effects, severe enough to lead to discontinuation of antimicrobial therapy including rash, nausea, vomiting or diarrhoea, occurred in either arm of the study.

Summary outcome measures are presented in the Table. There were statistical differences as follows: decreased length of hospital stay, decreased duration of iv antimicrobial therapy, decreased duration of total antimicrobial therapy and decreased total healthcare costs for the SAT group. The mean decrease in hospital stay amounted to 4.3 days.

In the initial phase of antimicrobial therapy, all patients in both SAT and control groups were treated with iv therapy. Thirty-four (75.5%) patients were administered one agent and 11 (24.5%) patients received two agents in the SAT group; while 23 (52%) patients were given one agent, 19 (43%) patients received two agents and two patients were treated with three agents in the control group (\( P = 0.044 \)).

Antimicrobial therapy used included cefotaxime in 34 (75.5%) patients and co-amoxiclav in 11 (24.5%) patients.
while flucloxacillin was also included in 11 (24.5%) patients treated with cefotaxime in the SAT group. The antimicrobial agents used in the control group were cefotaxime in 24 patients, ceftriaxone in seven, co-amoxiclav in 10, ampicillin in one, penicillin G in one, flucloxacillin in 20 and cefuroxime in four patients.

The antimicrobial agents that were used following the iv therapy in the SAT group were cefixime in 34 (75.5%) patients and co-amoxiclav in 11 (24.5%) patients, as recommended by the SAT protocol; while in the control group the corresponding agents were co-amoxiclav in eight patients, cefuroxime in three, azithromycin in three, cephradine in four and ampicillin in one patient.

Because SAT and conventional (control) therapy demonstrated equal clinical effectiveness, a cost-minimization analysis was used to calculate the saving associated with the implementation of the SAT protocol.

(i) Antimicrobial cost
Costs related to antimicrobial acquisition costs and hidden costs while patients were hospitalized were calculated, for both SAT and control groups, based on the actual prices to the Department of Pharmacy (1995/96 contract prices). The geometric mean (± 95% CI) antimicrobial acquisition cost was £10.3 (± 2.0) ranging from £6.9 to £19.0, and the related hidden costs were £6.7 (± 0.6) ranging from £4.0 to £11.8 for the SAT group. Equivalent costs in the control group were £26.0 (± 2.1) ranging from £9 to £95, and £17.4 (± 1.9) ranging from £8.5 to £38 for the control group, respectively. These differences were statistically significant (P < 0.001).

The geometric mean (± 95% confidence intervals) total antimicrobial cost (antimicrobial acquisition plus hidden costs) was £17.0 (± 3.1) ranging from £12.3 to £30.4 for the SAT group compared with £43.4 (± 5.5) ranging from £17.5 to £129.0 for the control group (P < 0.001).

(ii) Laboratory tests costs
Costs related to the laboratory tests performed for individual patients during the hospitalization were calculated, based on individual laboratory costs from the individual hospital departments, in both SAT and control groups. The geometric mean (± 95% CI) costs of haematology, microbiology and radiology tests performed were, respectively, £4.7 (± 0.4) ranging from £4.4 to £8.4; £17.2 (± 1.4) ranging from £10.6 to £32.0; and £16.2 (± 0.0) ranging from £13 to £32.4 in the SAT group. The corresponding data for the control group were £5.5 (± 0.6) ranging from £4.4 to £8.8; £23.6 (± 1.7) ranging from £20.6 to £32.8; and £18.7 (± 2.0) ranging from £16.2 to £32.4. There were statistically significant differences in tests costs for haematology (P = 0.012), microbiology (P = 0.001) and radiology (P = 0.001). The geometric mean (± 95% CI) costs for biochemistry tests performed was £6.9 (± 1.3) ranging from £3.4 to £13.5 in the SAT group compared with £5.8 (± 1.5) ranging from £3.4 to £13.5 in the control group. This difference did not reach statistical significance (P = 0.242). The geometric mean (± 95% CI) costs for all laboratory tests performed was £45.0 (± 3.1) ranging from £34.6 to £66.1 in the SAT group compared with £53.6 (± 2.9) ranging from £44.6 to £70.9 in the control group. This difference was found to be statistically significant (P < 0.001).

(iii) Hospital bed costs
Costs related to hospital bed occupancy were calculated based on the daily cost to Antrim Area Hospital for a

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**Table.** Comparisons of outcome measures between the control and SAT groups

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Control (geometric mean)</th>
<th>Protocol (geometric mean)</th>
<th>Ratio control/protocol</th>
<th>95% CI* of the ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td>8.3 (7.7–9.0)</td>
<td>4.0 (3.5–4.6)</td>
<td>2.1 (1.8–2.5)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>IV antimicrobial therapy (days)</td>
<td>5.6 (5.1–6.2)</td>
<td>1.7 (1.5–1.9)</td>
<td>3.3 (2.8–3.9)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Oral antimicrobial therapy (days)</td>
<td>2.0 (1.7–2.5)</td>
<td>2.2 (1.8–2.6)</td>
<td>0.9 (0.7–1.2)</td>
<td>0.597&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Duration of antimicrobial therapy (days)</td>
<td>7.9 (7.2–8.7)</td>
<td>4.0 (3.5–4.6)</td>
<td>1.9 (1.6–2.3)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Total healthcare costs (£)</td>
<td>2463 (2271–2707)</td>
<td>1167 (1007–1370)</td>
<td>2.1 (1.8–2.5)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*CI, confidence interval.
*bStudent's t-test.

Healthcare cost, summation of antimicrobial acquisition costs, hidden costs (associated with drug administration), laboratory test costs and bed costs.

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patient admitted to the medical paediatric service (M arch 1996 prices). The geometric mean (± 95% CI) hospital bed cost based on the length of hospital stay was £1105 (± 95) ranging from £285 to £2850 for the SAT group, compared with £2366 (± 200) ranging from £1425 to £4560 for the control group. This difference was statistically significant (P < 0.001).

(iv) Overall healthcare cost
Mean data have already been presented in the Table. The approximate mean potential savings per patient using the SAT protocol are as follows: antimicrobial costs £26.4; laboratory costs £8.6; hospital bed costs £1261.0, giving an overall saving of £1296 (52%). Using these data the estimated saving for the 45 patients who entered the SAT protocol was in excess of £58,000.

Discussion

Patient characteristics

The patient characteristics in the control (retrospective) and SAT (prospective) groups were almost identical. In the control group, several different oral antimicrobial agents were selected by the physicians when therapy was changed from iv to oral, including co-amoxiclav, cefuroxime, azithromycin, cephradine and ampicillin. In the SAT group, according to the agreed protocol, all patients were switched to either cefixime (75.5%) or co-amoxiclav (24.5%) before being discharged to complete the remainder of their oral course at home.

Bacterial pneumonia is more common in patients aged 6 months to 5 years,7,8 the range within which >95% of the patients in this study lay. In addition, despite the introduction of immunization, H. influenzae infections are more common in this patient population and as this organism is now more frequently resistant to ampicillin,9 cefixime and co-amoxiclav were considered to be appropriate therapy because of their β-lactamase stability.9,10 In addition, cefixime is given od which is a significant benefit to children. It may be the case, however, that cefixime may not be an optimal compound for treatment of lower respiratory tract infections in the future for two reasons: (i) its intestinal absorption is saturable (therefore it is not possible to increase the dose with the hope of increasing blood levels); and (ii) the increasing resistance of Streptococcus pneumoniae.

Only a small percentage of paediatric pneumonia is bacteraemic, and antigen detection is not particularly useful in this context.11,12 These data are in agreement with our findings of only 9% (eight patients) with positive blood cultures. S. pneumoniae and H. influenzae were the two pathogens isolated in our study.

Clinical outcome measures

Clinical protocols and guidelines have been developed to assist the physician with the decision of when to hospitalized patients with lower respiratory tract infections.11 Once the patient is hospitalized, other important medical decisions must be made with regard to the duration of treatment with iv antimicrobials and the duration of hospitalization. Many investigators have suggested a 48 h period to be the preferred timing for converting from iv to oral treatment.14,15

In this study, defined criteria8,20–21 (Figure) were used to determine when an adequate course of iv antimicrobial therapy had been delivered and when the patient was ready to be switched to an oral antimicrobial. The 45 patients were treated for a mean (geometric) of only 1.7 days of iv antimicrobial therapy. Patients were changed to oral therapy as soon as their signs and symptoms improved and they became afebrile (since laboratory tests were generally done on the admission day only). By the second day of iv therapy, 95% of the SAT patients had returned to normal temperatures. Signs and symptoms were favourable in all patients, indicating that the duration of treatment with the iv antimicrobial was adequate. This study shows that the resolution of pneumonia, with a short course of iv antimicrobials and a switch to oral therapy, is comparable to the results achieved in the control group using longer courses of iv therapy. The data therefore support the findings of others.7,8,20,21 This study also demonstrates a significant decrease in the length of hospital stay associated with the use of oral medication following an iv regimen (geometric mean of 4.0 days in SAT versus 8.3 days in control group; P < 0.001). Other authors have obtained similar results.8,22–25 In a paediatric pneumonia study involving 78 children, Shalit and his colleagues7 used WBC count and temperature, together with chest radiographic findings, as clinical markers. They found that these parameters supported the change to oral antimicrobial therapy at approximately 48 h coupled with early discharge from hospital. Reduced length of hospital stay is of benefit to both the hospital and patient, as the longer the patient remains hospitalized, the greater is the risk of iatrogenic events or other medical complications.26–28 In addition hospitalization can be a traumatic experience for both the child and the family, and consequently early discharge is desirable.

The clinical success rates observed in the SAT and control groups were identical. Relapse or failure has been found to be uncommon in patients receiving sequential antimicrobial therapy.29 In this study no treatment failures occurred; furthermore no relapses occurred during the 6-week follow-up period in children from the SAT group.

Pharmacoeconomic analysis

The calculated saving per patient in this controlled study was approximately £1200. Similar savings per patient have
been reported by others. The calculated healthcare costs for treating lower respiratory tract infection in the hospital were 52% less after introduction of the SAT protocol. Early conversion to oral antimicrobials has been shown by others to lead to decreased treatment costs of between 45 and 57%.

From the results of the present investigation it can be concluded that the resolution of lower respiratory tract infection in children with a short course of iv antimicrobials, followed by conversion to oral therapy, yields clinical outcomes comparable to those achieved using longer term iv therapy. Furthermore, SAT is an important cost-minimization tool for realizing substantial healthcare cost savings associated with the treatment of paediatric patients hospitalized with severe respiratory tract infections.

References

Treatment of severe LRTI in children


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