selecting optimal treatment based on the understanding of pathophysiological mechanisms. Because of discrepancies between population groups, further studies are needed, with larger sample sizes that include a range of ages in both men and women. The demonstration of the effect of these common vitamin D receptor genotypes on bone mineral density in a second, geographically distinct population of older and postmenopausal women opens the way to a wide range of studies to provide novel approaches to the prevention and treatment of osteoporosis.

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Oral versus intravenous antibiotics for community acquired lower respiratory tract infection in a general hospital: open, randomised controlled trial

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Abstract

Objective—To see whether there is a difference in outcome between patients treated with oral and intravenous antibiotics for lower respiratory tract infection.

Design—Open controlled trial in patients admitted consecutively and randomised to treatment with either oral co-amoxiclav, intravenous followed by oral co-amoxiclav, or intravenous followed by oral cephalosporins.

Setting—Large general hospital in Dublin.

Patients—541 patients admitted for lower respiratory tract infection during one year. Patients represented 87% of admissions with the diagnosis and excluded those who were immunocompromised and patients with severe life threatening infection.

Main outcome measures—Cure, partial cure, extended antibiotic treatment, change of antibiotic, death, and cost and duration of hospital stay.

Results—There were no significant differences between the groups in clinical outcome or mortality (6%). However, patients randomised to oral co-amoxiclav had a significantly shorter hospital stay than the two groups given intravenous antibiotic (median 6 *v* 7 and 9 days respectively). In addition, oral antibiotics were cheaper, easier to administer, and if used routinely in the 800 or so patients admitted annually would lead to savings of around £176 000 a year.

Conclusions—Oral antibiotics in community acquired lower respiratory tract infection are at least as efficacious as intravenous therapy. Their use reduces labour and equipment costs and may lead to earlier discharge from hospital.

Introduction

Community acquired lower respiratory tract infection is a common cause of hospital admission, and intravenous antibiotics including cephalosporins are frequently used as first line treatment.[1] The increasing use of intravenous access initiated routinely on admission for giving drugs, particularly antibiotics,[2] has increased drug costs substantially. Moreover, this route is largely "clinical choice" rather than selected because of the unavailability of or the patient's inability to tolerate an oral formulation of the preferred antibiotic.[3] This practice has been questioned,[1 3-7] and up to 65% of such treatment may be judged inappropriate in some respects.[4-9] It may also increase the duration and cost of hospitalisation.[9]

Oral antimicrobial agents are promoted particularly for general practice and parenteral antimicrobial agents for hospital practice.[10] If it was feasible to treat many uncomplicated infections with oral agents without compromising patient care there would be substantial benefits in terms of comfort and convenience. We conducted an open, randomised study to see if there is a difference in outcome for patients with lower respiratory tract infections treated with the same

antibiotic by mouth and intravenously or with cephalosporins.

Subjects and methods

Eleven of 14 physicians concerned with emergency admissions participated in the study, which was approved by the ethics and medical committees. Consecutive patients over 14 years of age with a clinical diagnosis of community acquired lower respiratory tract infection admitted through the accident and emergency department were entered on the basis of the following criteria.

Inclusion criteria were a clinical diagnosis of lower respiratory tract infection as defined by (*a*) a new or increasing cough productive of sputum and associated with other symptoms or signs of chest infection, including shortness of breath, wheeze, chest pain, or focal or diffuse signs on chest examination or radiography, and (*b*) one or more constitutional symptoms, including fever, sweating, headache, and aches and pains.

Exclusion criteria—We excluded patients who were immunocompromised—for example, those with HIV infection or neutropenia; patients allergic to penicillin or cephalosporins; critically ill patients requiring admission to intensive care or requiring either inotropic or respiratory support; patients with clinical or laboratory evidence of septicaemia; patients unable to tolerate oral medicines; acutely confused patients; patients with multilobar disease seen on chest radiography; and pregnant or lactating women.

Prior use of antibiotics for the illness did not exclude patients from the study. At entry details of relevant symptoms, signs, and laboratory findings were noted (including radiological and microbiological findings when available). By means of simple randomisation (drawing a sealed envelope) patients were assigned to one of the following three treatment groups.

Group 1 received co-amoxiclav 375 mg by mouth three times a day for seven days.

Group 2 received co-amoxiclav 1·2 g intravenously three times a day for three days followed by 375 mg by mouth three times a day for four days.

Group 3 received cefotaxime 1 g intravenously three times a day for three days followed by cefuroxime axetil 500 mg by mouth twice daily.

The patients were observed by two investigators on alternate days until discharge or death. Their management, which included all decisions about treatment (change of antibiotic or duration of use) and discharge (based on the usual clinical grounds, radiographs, etc), was the sole responsibility of the relevant admitting consultant and his or her team, who on discharge classified patients into one of the following categories.

Cured—Patients were classified as cured when there was total resolution of the symptoms and signs which were present at diagnosis.

Partial cure was recorded when there was resolution in some but not all of the symptoms or signs present at diagnosis but the patient did not require any extension or change from the initial antibiotic regimen and was regarded as fit for discharge.

Antibiotic extended referred to patients who required an extension in the duration of antibiotic beyond that stated in the protocol.

Antibiotic changed was recorded when the patient required a change in the type or route of antibiotic from that in the protocol as a result of adverse drug reactions, clinical deterioration, or microbiological sensitivity reports.

Death was recorded when the patient died in hospital irrespective of cause.

The total duration of hospital stay and the above categories were considered as the final outcome measures.

Statistical analysis—We calculated that a minimum of 160 patients were required, based on the assumption of a combined cure and partial cure rate of 80% to achieve a power of 90% ($\alpha = 5\%$; two sided test with a difference of more than 15% taken as significant between the groups). The three groups were compared for various demographic and medical characteristics by analysis of variance, the χ^2 test, and the Kruskal-Wallis test. The groups were compared for outcome measures by χ^2 analysis in the case of the five category classification measures described above and by the Kruskal-Wallis test for the duration of stay in hospital. Costs of antibiotics were derived from prices quoted in the *Monthly Index of Medical Specialities*[11] and are expressed in Irish pounds (£Ir; sterling equivalent roughly 95p).

Results

Of the 541 patients recruited, 181 were randomised to group 1, 181 to group 2, and 179 to group 3. Some 88 patients were excluded, largely because of the severity of infection, inability to tolerate oral medicines, or concomitant disease. The mean (SD) age of patients in the study was 64 (5) years, 281 (52%) were female, and the duration of symptoms before presentation was 7·4 (6·4) days. One third of the patients had received antibiotics in the previous two weeks. Details regarding clinical features, laboratory data (arterial blood gas pressure values available in 433 (80%) patients), and radiological data are given in table I. The three groups were comparable.

Table II shows the distribution of outcome categories among patients in the three groups. On discharge 142 (78·5%) patients in group 1 were either completely or partially cured compared with 129 (71·3%) and 122 (68·2%) in groups 2 and 3. There was no significant difference in final outcome based on the five category classification between the three groups ($\chi^2 = 8·7$; df=8; P=0·36). There was also no significant difference in mortality ($\chi^2 = 0·77$; df=2; P=0·67), roughly half of all deaths being due to pneumonia and respiratory failure. The median durations of hospital

TABLE I—*Demographic and laboratory details of patients on admission to hospital and outcome (duration of stay and cost of antibiotics)* *

	Group 1	Group 2	Group 3
No of patients	181	181	179
No with prior exposure to antibiotics	50	56	67
Mean temperature (SD) (°C)	37·1 (0·8)	37·0 (0·9)	37·1 (0·9)
Mean pulse (SD) (beats/min)	98·7 (16·7)	98·8 (17·0)	101·2 (17·2)
Mean respiratory rate (SD) (breaths/min)	27·0 (6·5)	27·6 (5·6)	27·3 (6·1)
Mean white cell count (SD) ($\times 10^9$/l)	12·1 (4·7)	12·6 (4·7)	12·6 (4·2)
Mean blood urea (SD) (mmol/l)	7·2 (4·7)	7·9 (5·2)	7·4 (4·4)
Mean pH (SD)	7·4 (0·3)	7·4 (0·1)	7·4 (0·2)
Mean oxygen pressure (SD) (kPa)	8·3 (2·0)	8·1 (1·8)	8·0 (1·9)
Mean carbon dioxide pressure (SD) (kPa)	5·7 (1·4)	5·7 (1·5)	5·7 (1·4)
Radiographs (506 patients) (% showing acute infective changes)	44·1	44·8	37·4
Sputum samples (301 patients) (% positive)	30·7	32·3	31
Duration of hospital stays (days):			
Median	6*	7	9
Interquartile range	3-6	4-10	6-12
No discharged within three days	36*	11	10
Ingredient cost per patient (£Ir)	7·8	32	51

*Group 1 significantly different (P<0·05) from groups 2 and 3.

TABLE II—*Final outcomes of treatment groups (expressed as numbers (percentages) of patients)*

Outcome	Group 1	Group 2	Group 3
Cure	74 (40·9)	63 (34·8)	69 (38·6)
Partial cure	68 (37·6)	66 (36·5)	53 (29·6)
Antibiotic extended	16 (8·8)	21 (11·6)	30 (16·8)
Antibiotic changed	14 (7·7)	18 (9·9)	16 (8·9)
Death	9 (5·0)	13 (7·2)	11 (6·1)
Total	181 (100·0)	181 (100·0)	179 (100·0)

<table>
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Key messages

● The vast majority of patients admitted to hospital with community acquired lower respiratory tract infection receive antibiotics, usually intravenously, irrespective of the aetiology of the infection

● In patients who are not immunocompromised and do not have severe life threatening infections —that is, most—co-amoxiclav by the oral route is as effective as intravenous co-amoxiclav or third generation cephalosporins

● Oral treatment is easier to administer, cheaper, and associated with earlier discharge from hospital

● The continued routine use of intravenous antibiotics in these patients cannot be justified

stay were 6, 7, and 9 days in groups 1, 2, and 3 and there was a significant difference between the groups (H=16·9; df=2; P<0·001). There was no difference between groups 2 and 3. Further analysis showed that 36 patients (20%) who were randomised to group 1 were discharged within the first three days compared with 21 (6%) in the remaining two groups.

Sputum microbiology—At least one sputum sample was received by the laboratory for culture and sensitivity tests for 301 patients. A potential bacterial pathogen was grown in 93 (31%) cases, streptococcal pneumonia, *Haemophillus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* representing 78% of the microorganisms isolated. There was no significant difference in the frequency of organisms isolated and their antibiotic sensitivities among the three groups (table I).

Radiological investigations—Results of chest radiography were obtained either from the official report or from the notes of the admitting doctor for 506 patients (35 radiographs missing); 212 (41·9%) radiographs showed acute infective changes. There was no significant difference in the frequency of acute changes among the three groups (table I).

Discussion

Increasingly, expensive intravenous antibiotics—in particular, third generation cephalosporins—are being used as drug of first choice in uncomplicated respiratory tract infections[1][12] with few data to suggest that they are more efficacious.[13] This study of the outcome and economics of common antibiotic regimens evaluated current practice in our and, we believe, many other hospitals.[12] Other than in choice of initial treatment, we did not intervene in the patient's management or the decision to discharge from hospital. Though an open design may have predisposed the study to bias, we believe this was outweighed by the independence of the treating clinician's decision. As we studied 87% of patients admitted during one year under the care of participating consultants (that is, 70% of all admissions with the appropriate diagnosis), the sample was highly representative. The severity of illness among patients in the three groups was comparable (table I) and the outcome consonant with that in other studies of respiratory tract infection.[14][15]

There are factors that may explain the earlier discharge of patients given oral antibiotics, which are largely related to the convenience of oral administration. The increasing use of the intravenous route associated with inadequate formal training for junior hospital doctors[16] has resulted in difficulty in ensuring that drugs are given at the correct times.[17] In this study roughly two thirds of the intravenous administration of antibiotics was by junior hospital doctors and the remainder by nurses. Oral administration, which requires less time and labour, improves compliance and accuracy of the timing of administration, which may have contributed to the results.

Roughly one fifth of patients randomised to oral treatment were discharged within three days compared with 6% in the other (intravenous) groups. This demonstrates a disadvantage of intravenous treatment which confines patients to hospital for that part of their treatment. Furthermore, there is reluctance to discharge a patient immediately after he or she is switched from intravenous to oral treatment without ensuring that the patient will not relapse or be intolerant of the drug.

These results have important economic implications and support several other studies showing savings on equipment, ingredient, and labour costs by using the oral route. From a recent audit three quarters of all patients admitted annually to our hospital with lower respiratory tract infections are started on intravenous antibiotics, mainly cephalosporins or co-amoxiclav. If all eligible patients were started on oral co-amoxiclav, with a consequential reduction in hospital stay, savings of £176 000 a year could be achieved. This calculation is based on the costs of ingredient (table I), equipment (estimated as £1.30),[3] labour, and an average patient bed day of £250. Some patients may even return to work earlier.

Our results suggest that oral administration of appropriate antibiotics confers significant advantages over the intravenous route. These include earlier discharge from hospital, reduction in labour requirements for preparation and administration of the drug, and significant savings on ingredient costs. Furthermore, the trend (table II) for patients treated with oral antibiotics to have higher cure and partial cure rates at the time of discharge, less requirement for extension of antibiotic treatment, and a death rate comparable to that of the intravenous treatment groups is reassuring. We believe that the continued "routine" use of the intravenous route to administer antibiotics to patients with community acquired lower respiratory tract infections can no longer be justified.

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