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The Positive Impact of an Antimicrobial Prescribing Protocol on the Healthcare Costs of Community-Acquired Pneumonia, Stratified by Infection Severity

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Abstract: The objective of the present study was to assess the impact of an antimicrobial prescribing protocol on clinical and economic outcome measures in hospitalized patients with community-acquired pneumonia (CAP). The study was performed as a prospective controlled clinical trial within the medical wards at Antrim Area Hospital. All hospitalized adult patients with a primary diagnosis of CAP during the period December 1994 to February 1995 (control group; n = 112). After a CAP management protocol had been developed, all hospitalized adult patients with a primary diagnosis of CAP over the period December 1995 to February 1996 formed the intervention group (treated according to the protocol; n = 115). The results showed a statistically significant impact of the protocol in terms of clinical and economic outcome measures. Patients treated using the prescribing protocol had significant reductions in length of hospital stay (geometric mean 4.5 versus 9.2 days), iv drug administration (34.8% versus 61.6%), duration of iv therapy (geometric mean 2.1 versus 5.7 days) and treatment failures (7.8% versus 31.3%). The use of the protocol was a major factor in streamlining the prescribing of antimicrobial therapy for CAP and led to more cost-effective patient management.

Key words: Community-acquired pneumonia · Healthcare cost · Antimicrobial protocol

INTRODUCTION

Prospective population studies have reported that the incidence of Community-Acquired Pneumonia (CAP) ranges from 5 to 11% per 1000 of the adult population [1-4] and is associated with high rates of hospitalization, morbidity and mortality [1, 5]. The incidence is more prevalent in patients aged 70-79 years of age than those aged 16-19 years. [6]. In the United Kingdom, 22-42% of adult patients diagnosed with CAP are admitted to hospital [1, 7]. The disease diagnostic features are important determinants in guiding decisions about hospital admission and management of its progression. The presence of two or more the following three factors: [1] Respiratory rate >30/min; [2] Diastolic blood pressure <60 mm Hg; [3] serum urea > 7 mmol/L are associated with a 21-fold increase in the risk of death or the need for intensive care management [7-11].

CAP and Associated Costs: CAP associated costs account for a substantial proportion of total health care costs, of which hospitalization is one important factor. The healthcare costs associated with treating CAP may be decreased by reducing hospital admissions, [7, 12] length of treatment, diagnostic test frequency and therapeutic interventions undertaken [13, 14]. Length of hospitalization is the main cost factor, so identifying patients who are suitable for early conversion from parenteral to oral antimicrobial therapy can shorten hospital stay and reduce healthcare cost per patient. However, while early therapeutic intervention may reduce the number of diagnostic tests performed, it may increase drug costs because of the use of broad-spectrum antimicrobials to cover all possible causative organisms [15].

The aim of the present study is to develop an antimicrobial prescribing protocol for the management of hospitalized patients with CAP stratified by infection severity. A further goal was to assess the economic impact of the introduction of the prescribing protocol.

Study Methods

Control Group: All adult patients in the medical wards of Antrim Area Hospital with a primary diagnosis of CAP

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admitted during the period December 1994 to February 1995 formed the control group on which baseline data was collected. Diagnoses were made on clinical grounds, with or without radiological evidence. These patients received empirical treatment for their condition, i.e. before the development of the prescribing protocol. The severity of pneumonia in this group was assessed using the scoring system detailed below.

Intervention Group: All consecutively admitted adult patients with a primary diagnosis of CAP (see above) over the following period from December 1995 to February 1996 formed the intervention group, i.e. they were treated according to an agreed protocol (Table 1), which was developed through collaboration between clinicians, physicians, microbiologists and clinical pharmacists. The protocol was introduced in November 1995 and considered the severity of the infection, with a score of one point given for each of the following if present: age >60 years; respiratory rate >30 breaths/min; diastolic blood pressure <60 mm Hg; WBC >20 or $<4 \times 10^9$ cells/L; new confusion; new atrial fibrillation; multiple lobe involvement on X-ray [16]. The CAP was deemed moderate if the overall score was two or less, severe if the score was three or more and very severe if the score was three or more and the patient also suffering from hypoxaemia ($pO_2 < 8$ kPa on 28% oxygen). In the protocol group, treatment depended on infection which stratified by severity.

Protocol: According to the agreed protocol, moderate infection was treated using oral amoxycillin/ clavulanic acid 375 mg every 8 h, while severe infection was treated with iv cefuroxime 1.5 g every 8 h and very severe infection was treated using IV cefuroxime 1.5 g every 8 h and iv erythromycin 1 g every 6 h. Erythromycin was also recommended when atypical infection was considered likely or if the patient was allergic to penicillin (clarithromycin was an alternative if erythromycin was poorly tolerated). In severe and very severe cases the

Table 1: Prescribing protocol for CAP

Assessment of Severity: On admission score 1 for each of these present:		
- Age >60 years old		
- Respiratory rate>30/min		
- Multiple lope involvement on X-ray		
- WBC>20 or <4x10^9/L		
- New confusion		
- New atrial fibrillation		
- Diastolic BP<60mm-Hg		
Mild: score two or lesss	Oral Co-amoxiclav	
Severe: score3 or more	IV Cefuroxime	Switch to oral co-amoxiclav or cefuroxime once patient met these criteria: 1) cough, sputum and respiratory distress improving; 2)afebrile; 3) normal functioning GIT; 4) WBC is normalizing
Very severe: score3 or more	IV Cefuroxime and	
With hypoxaemia (PO_2<8 kPa On28% O_2)	IV Erythromycin	

Table 2: Patient demography

	Control	Protocol	*P* value
Number of patients	112	115	
Allergy (penicillin)	6 (5.3%)	4 (3.5%)	0.542[a]
Out-patient status			
Domiciliary residence	104(92.9%)	104(90.4%)	0.683[a]
Nursing home	8 (7.1)	11 (9.6%)	Age (years)
Mean (± SD)	69.3(±21.3)	66.4(±16.8)	0.232[b]
Gender			
Female	57(50.9%)	62(53.9%)	0.750[a]
Male	55(49.1%)	53(46.1%)	Onset (days)[c]
Mean (± SD)	4.96(±1.4)	4.93(±1.3)	0.890[b]
Severity			
Very severe	0	0	0.674[a]
Severe	35 (31.2%)	40 (34.8%)	
Moderate	77 (68.8%)	75(65.2%)	

[a]X^2 test, [b]*t* test, [c]Number of days of illness before admission

following criteria were applied to switch patients from IV to oral therapy: patient able to tolerate oral preparations; cough, sputum and respiratory distress improving; patient afebrile; WBC count normalizing [17-19]. The number of factors to be improved and the extent of the improvement before switching were left to clinical judgment.

Data Collection and Outcome Measures: Control and intervention patients (Table 2) were followed during their complete hospital stay allowing therapeutic and economic comparisons to be made between the two groups. Details were recorded for each patient as follows: age, gender, allergic status, out-patient status (admission from nursing home or community), length of time between onset of illness and admission to hospital, length of hospital stay, treatment duration and modalities, treatment success, signs and symptoms of infection (as per outlined scoring system), severity of illness. Biochemistry, haematology, microbiology and radiology reports during the hospital stay were also recorded. In respect of radiology, reports were available within a few hours for interpretation by clinicians. A customized data collection form was used to record this information.

In assessing therapeutic outcomes, the following definitions were agreed by the research team: [1] treatment success-major improvement or complete resolution of all signs and symptoms; [2] 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. All costs were calculated for the total hospital stay.

Statistical Analysis: Excel spreadsheet software was used for data entry whereas statistical analyses were performed using SPSS. Differences between control and protocol groups were analysed using the χ^2 test and Fisher's exact test for categorical variables as appropriate. Student's t test was used for continuous variables. A logarithmic transformation to base 10 was performed to normalize the outcome measures data (length of hospital stay, duration of IV administration, duration of treatment in hospital and elements of healthcare costs) and to calculate confidence intervals for means [20]. Results are reported as statistically significant at $P< 0.05$.

RESULTS

General: A total of two-hundred and twenty seven patients were assessed during the study (112 control patients and 115 protocol patients). Details of the patients in the two groups are included in Table 2. The vast majority of patients in both groups were admitted from their domiciliary residence (92.9% and 90.4% respectively in the control and protocol groups) and the remaining patients were admitted from nursing or residential homes. There was no significant difference in the patients' living arrangements before admission ($P > 0.05$). Furthermore, there were no significant differences ($P > 0.05$) between the two groups regarding patient age and gender. The mean onset time (i.e. the number of days of illness before admission) was almost identical between the two groups at approximately 5 days (Table 2). Signs and symptoms on admission (fever, cough, sputum, tachypnoea and tachycardia) did not differ between the two groups ($P > 0.05$). The severity of disease also did not differ significantly ($P > 0.05$) between the two groups. The proportion of patients who scored three or more was 31% in the control group and 35% in the protocol group. Although the mortality rate appeared higher in the control group (8.0% versus 3.5%) this was not significantly different ($P > 0.05$).

Laboratory: A range of laboratory tests were used in both control and protocol patients (Table 3). The only statistically significant test difference between the groups was the fact that a higher percentage of patients in the protocol group had a sputum culture ordered ($P < 0.05$). The results obtained from these tests were, however, not significantly different ($P > 0.05$). The most frequently isolated organism was Streptococcus pneumoniae, which was isolated in approximately 35% of patients. No significant growth in the sputum cultures was observed in about 42% of cases. Less commonly isolated organisms were Haemophilus influenzae, Moraxella catarrhalis and Staphylococcus aureus and in two cases in the protocol group, Haemophilus parainfluenzae was isolated. Chest X-ray data obtained for both groups of patients was also very similar and did not differ significantly ($P > 0.05$). White blood cell counts, serum creatinine and blood urea were also similar ($P > 0.05$) in the two groups (Table 3). There were no changes in reporting of sensitivities from the microbiological laboratory during the study periods.

Table 3: Laboratory Findings

	Control	Protocol	*P* value
Biochemistry and Haematology (on admission)			
Blood Urea (mmol/L) mean (± 95% CI)	7.1 (± 1.1)	7.0 (±1.3)	0.96[a]
Serum Creatinine (mmol/L) mean (± 95% CI)	113.8 (± 6.2)	114.8 (± 5.8)	0.89[a]
White Blood Cells (WBC) mean (± 95% CI)	12.9 (±1.5)	13.0 (± 1.8)	0.93[a]
Microbiology			
Sputum Culture			<0.001[b]
Not ordered	51 (45.5%)	2 (1.7%)	
Sputum Cultured	61 (54.4%)	113 (98.3%)	
Pathogen isolated (sputum culture)			
No significant growth	23 (37.8%)	47 (41.5%)	
S. Pneumoniae	22 (36.1%)	40 (35.4%)	
H. Influenza	9 (14.7%)	17 (15.1%)	
M. Catarrhalis	3 (4.9%)	5 (4.4%)	
S. Aureus	4 (6.5%)	2 (1.8%)	
H. Parainfluenzae	-	2 (1.8%)	
Chest X-ray			0.62[b]
Number of Patients	111 (99.1%)	112 (99.1%)	
Consolidation	75 (67%)	72 (63%)	
Shadow Patchy	46 (41.1%)	48 (43%)	
Effusion	4 (3.6%)	5 (4.3%)	
Cavitation	3 (2.7%)	2 (1.8%)	
pre-Existing Disease	29 (25.9%)	26 (22.6%)	

[a]*t* test, [b]x^2 test

Table 4: Treatment Failures and Causes

	Control (n=112)	Protocol (n=115)	*P*value
Total no. of Treatment Failures	35 (31.3%)	9 (7.8%)	<0.001[a]
Resistant organism	2	None	
Adverse reaction	5	2	
No improvement	19	3	
Death	9	4	

[a]x^2 test

Table 5: Outcome measures

Outcome measures	Control (geometric mean)	Protocol (geometric mean)	*P*value
Length of stay (days) (95% CI)	9.2 (8.5-10.0)	4.5 (4.0-5.1)	<0.001[a]
Iv duration (day) (95% CI)	5.7 (5.2-6.2)		<0.001[a]
Treatment duration in hospital (days) (95% CI)	8.8 (8.2-9.4)	4.5 (4.0-5.0)	<0.001[a]
Antimicrobial acquisition costs (£) (95% CI)	36.4 (27.7-43.5)	5.8 (4.1-6.7)	<0.001[b]
Hidden costs (£) (95% CI)	17.3 (14.2-18.5)	4.9 (4.2-5.7)	<0.001[b]
Total antimicrobial cost (£) (95% CI)	53.7 (44.9-64.2)	10.7 (8.8-13.1)	<0.001[b]
Biochemistry(£) (95% CI)	6.2 (5.6-6.8)	4.2 (3.9-4.5)	<0.001[b]
Haematology(£) (95% CI)	5.7 (5.3-6.2)	4.7 (4.4-5.0)	<0.001[b]
Microbiology(£) (95% CI)	32.2 (27.5-36.3)	52.5 (43.6-63.2)	<0.001[b]
Radiology (£) (95% CI)	21.9 (20.5-23.4)	16.2 (0)	<0.001[b]
Total laboratory cost (£) (95% CI)	66.0 (56.5-77.2)	77.6 (68.5-88.0)	<0.001[b]
Bed cost (£) (95% CI)	1904 (1754-2070)	932 (830-1049)	<0.001[b]
Total healthcare cost (£) (95% CI)	2024 (1878-2220)	1020 (933-1175)	<0.001[b]

[a]Student's *t*test, [b]*t* test

Antimicrobials: A wide range of antimicrobials were used in the control group (cefuroxime, cefotaxime, erythromycin, co-amoxiclav, ampicillin, amoxycillin, penicillin, clarithromycin, ofloxacin, flucloxacillin, ciprofloxacin and tetracycline) whereas only three agents (cefuroxime, erythromycin and co-amoxiclav) were used in the protocol group. Intravenous cefuroxime was given to all patients who were considered to have a severe infection (Table 1) whereas erythromycin (oral) was given to those patients who were considered to have an atypical

pneumonia, on clinical grounds. All usage of co-amoxiclav was via the oral route. The number of initial treatment failures was much lower in the protocol group (7.8% versus 31.3%; 95% confidence interval (CI) of the difference, 13.6-33.4%; P < 0.001; Table 4).

Hospital Duration: There were also highly significant differences in the treatment duration in hospital, with the number of days (geometric mean) almost doubled in the control group (8.8 days versus 4.5 days; P < 0.001; Table 5). This decreased length of treatment was largely due to the initial use of oral antimicrobial and patients being 'switched' early from IV to oral therapy as per the protocol, therefore permitting earlier discharge of patients. Patients' length of hospital stay (geometric mean) in the protocol group was 4.5 days compared with 9.2 days in the control group (P < 0.001). The number of patients receiving IV antimicrobials was also reduced in the protocol group (40% versus 69%; P < 0.001), as was the duration (geometric mean) of IV therapy (2.1 versus 5.7 days; P < 0.001). All patients in the protocol group were followed up at 28 days to ensure that early discharge did not have a detrimental effect on their clinical outcome. No treatment failures were identified.

Cost Decrease: Economic data is presented in Table 5. The decreased length of hospital stay contributed to substantial decreases in the overall cost (geometric mean) of hospitalization per patient (£1020 versus £2024; P < 0.001). Laboratory test costs were slightly higher, but not statistically so, in the protocol group. This was due largely to appropriate requests for sputum cultures. The costs of antimicrobials (including hidden costs, e.g. consumable materials used in drug preparation and delivery) were approximately five times higher in the control group (geometric mean; £53.7 versus £10.7; P < 0.001).

DISCUSSION

In can be said with confidence, that healthcare systems around the world are attempting to minimize costs and at the same time improve overall quality of care by developing and implementing the most cost-effective treatment regimens. Following introduction of a treatment protocol for CAP in the study site hospital, the healthcare costs decreased significantly with a concomitant improvement in the outcome measures, e.g. decrease in treatment failures. The success of the protocol method of management of CAP was due to three main contributing factors: [1] the scoring system that stratifying the disease severity adapted from risk factors drawn up by the British Thoracic Society; [16] [2] the introduction of sequential therapy with oral antimicrobials when patient's condition was stabilized or improving according to predetermined criteria; and [3] the clear presentation of the protocol approach to infection management (Table 2). Undoubtedly the care with which hospital physicians were introduced to the protocol (seminar and on-ward discussions) helped ensure full adherence to the protocol. The scoring system, based on identified risk factors, was a useful guide in severity stratification, antimicrobial prescribing and determination of the administration route. This system was able to decrease the incidence of IV administration from 61.6% in the control group, to 34.8% in the protocol group, i.e. a difference of 26.8% (95% CI of the difference was 14.3-39.4%). During this period, no patients were placed in the very severe group. Furthermore, the protocol allowed junior doctors to prescribe, without having to wait for a senior physician. Thus the diagnosis of chest infection could be made by the admitting doctor with the patient being assessed subsequently by a consultant. It is recognized, however, that because of the high percentage of patients scoring two or less in both groups, admission criteria should be reviewed, especially in the light of the success achieved in the present study with oral co-amoxiclav. It is important to note that criteria adapted from Quintiliani *et al*. [17] Allen *et al*. [18] and Ramirez *et al*. [19] assisted the prescribing physicians in converting patients from IV to oral therapy in this study. Although other criteria had to be met, WBC counts were not routinely determined before the sequential therapy was commenced. By using this method, the length of IV therapy and length of hospital stay were significantly reduced (P < 0.001).

From a diagnostic perspective, aetiological organisms involved in control and intervention groups were similar. In both groups S. pneumoniae was responsible for the largest proportion of isolates, accounting for approximately 35% of sputa cultured; this figure is within the range of 30-70% reported by other investigators [21, 22]. The second largest number of isolates was for H. influenzae (15.1%) followed by M. catarrhalis (4.4%), i.e. the proportions of isolated organisms were similar to reports by others [12, 23].

CONCLUSIONS

Length of hospital stay was the most expensive aspect of patient healthcare in this study, as has been reported by others [24, 25]. As expected, there was a general trend of decreased hospital stay in the study site

hospital over time; however, during the period of the study, length of hospital stay fell by only 19%, which is low when compared with the 51% decrease seen after introduction of the protocol. The decreased length of stay led to an average saving per patient treated in the protocol of £1004. The savings resulted from decreased antimicrobial acquisition costs, hidden costs, costs of biochemistry, haematology and radiology tests and hospital bed costs. There was no saving attributed to microbiology tests, as the protocol encouraged treating physicians to perform microbiology tests such as sputum and blood cultures for patients within the group. The availability of these test results is likely to have encouraged adherence to later aspects of the protocol. The present study adds weight to the findings of a study conducted in Dublin [26] in which the researchers concluded that the use of oral antimicrobials is at least as efficacious as IV therapy and led to decreased costs as a result of patients being discharged earlier from hospital.

A further development, which has resulted from the current investigation, is the placement of the algorithm on the hospital intranet with severity scoring being performed automatically in response to questions posed on-screen. In addition, work is continuing on how case-mix variations influence outcomes and on the development of guidelines for use in the primary care setting to facilitate decision- making regarding the need for hospitalization of patients with CAP.

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