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ORIGINAL ARTICLE

Optimizing antibiotic therapy—the Aberdeen experience

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Objective To study the quality and continuity of treatment in the Acute Medicines Assessment Unit (AMAU) with regard to empirical prescription of antibiotics, mode of administration, adherence to ward antibiotic policy, as well as collection, awareness and utilization of microbiological investigations.

Methods A prospective study over a 3-month period at the AMAU, Aberdeen Royal Infirmary (ARI), a teaching hospital in north-eastern Scotland, was performed. The study included all patients started on empirical antibiotics on admission to the AMAU and followed up until their discharge.

Results Of 1303 patients admitted, 221 (17%) were started on empirical antibiotics. This was in accordance with hospital antibiotic policy in 52% of cases. Appropriate specimens were taken from 77% of patients. Culture results showed that 29% ($n = 65$) of the patients had clinically significant growth of organisms. Of the 65 patients with clinically significant culture results, 49% ($n = 32$) were on an inappropriate empirical regimen. In 55%, the medication was not changed to a more appropriate antibiotic. In 72% of the patients with a negative culture, the culture report had no obvious effect on the duration or type of antibiotic being administered. Intravenous antibiotics were used in 60% of patients.

Conclusion This study demonstrates a significant overuse of antibiotics, especially intravenous forms, despite a paucity of positive sepsis parameters and chest X-ray findings in these patients The duration of treatment could be shortened and an early switch policy introduced if culture results and sepsis profiles were taken into consideration, as there was a large number of unproven infections. Suggestions are made about how these improvements in prescribing could be made within the current administrative set-up of AMAUs.

Keywords Antibiotic, antibiotic resistance, intravenous antibiotic, drug utilization review, medical audit, Acute Medicines Assessment Unit

Accepted 31 July 2002

Clin Microbiol Infect 2003; 9: 406–411

INTRODUCTION

The successful and efficient treatment of infectious diseases with antimicrobial agents continues to present problems in modern medicine, with many studies showing a significant increase in the incidence of resistance worldwide [1–3]. This is responsible for increased global healthcare costs, because of the lack of efficacy of many first-line drugs, and the consequent need to use more expensive second- and third-line drugs, prolonged periods during which individuals are infectious, increased morbidity, increased length of hospital stay, and even, in some cases, increased mortality [1,4].

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In modern medicine, most antibiotic therapy is empirical [1]. However, inappropriate empirical therapy is associated with poor outcomes and excess mortality, in addition to increased antibiotic resistance [2,4]. One of the key issues in the empirical usage of antibiotics lies in the drug selection. This is complicated by the ever-increasing range of antibiotics available today. Keeping this in mind, the Grampian formulary was prepared for both hospital and general practice as a guideline for rational prescribing in the Grampian region [5,6].

Another key issue is the mode of administration of antibiotics. Published studies have shown that an early switch from intravenous to oral antibiotics is beneficial in terms of reducing drug costs, patient stay and hospital-related morbidity [7,8].

The Accident and Emergency (A&E) department offers care to patients who arrive with urgent problems and who have usually not been seen by a general practitioner (GP). It is an initial point of triage, where patients may be admitted for further treatment if deemed necessary. Currently, UK hospitals are undergoing yet another phase of administrative reorganization. Most major hospitals now utilize an Acute Medicines Assessment Unit (AMAU), where patients are admitted directly or after initial triage in the A&E department. In the AMAU, the medical emergency admissions are assessed, stabilized, and then sent to appropriate wards [9]. There are concerns with this type of system with regard to the maintenance and continuity of good quality of care, which may be further compromised by the implementation of the European Working Time Directive and reorganization of trainees' working time [10,11].

This study looked at the quality of treatment in the AMAU with regard to empirical prescription of antibiotics, type of antibiotic used, mode of administration, degree of adherence to ward antibiotic policy, duration of treatment, as well as collection, awareness and utilization of microbiological investigations.

MATERIALS AND METHODS

The prospective study was conducted over a 3-month period, from 16 April 2000 to 16 July 2000. All patients admitted to the AMAU of the Aberdeen Royal Infirmary (ARI) who were started on antibiotic therapy were included in the study.

The patients were identified on a daily basis by examination of the medical and nursing notes as well as their drug record. Patients were followed up by one of us throughout their antibiotic treatment in the hospital. There were no specific exclusion criteria. Apart from the head of the unit, staff were informed only in general terms about the purpose of the audit.

For each patient, the following data were collected prospectively: gender, age, provisional diagnosis, major system affected, sepsis parameters [13], antibiotic(s) used, dose and route of administration, frequency/dosing interval, time delay between admission and commencement of therapy, the types and dates of specimens collected, whether the specimens were collected with appropriate precautions, dates of the report being viewable at ward level, dates on which the report was noted and acted upon, and patient outcomes. Data on chest X-ray (CXR) were collected from 1 May 2000 to 16 July 2000.

The data were analyzed using both Excel and SPSS software packages. For analysis of two variables, a contingency table was constructed. Cross-tabulation and chi-square analysis were used to ascertain whether there were any significant relationships between the variables.

The antibiotic policy [6] gives guidelines on route, dose and duration of administration and choice if the patient is allergic to penicillin. Advice on investigation is also given.

Definitions and criteria used

Empirical therapy: The initial use of antibiotics before the pathogen was identified.

Inappropriate antimicrobial treatment: The bacterial isolate was resistant to the antibiotic being used or the antibiotic was not indicated in the susceptibility results.

Appropriate antimicrobial treatment: The empirical therapy instituted complied with the sensitivity data.

Appropriate specimens: The specimens taken for laboratory examination were pertinent to the working diagnosis.

Sepsis parameters [13]: Considered as a positive sepsis profile if two or more of the following were present: temperature >38 °C or <36 °C; heart rate >90 beats/min; respiratory rate >20 breaths/min or $PaCO_2$ <4.3 kPa; white cell count >12 000/mm^3 or <4000/mm^3.

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Severe sepsis: Sepsis associated with hypotension or organ hypoperfusion.

RESULTS

In total, 26 consultants admitted patients to the AMAU. During the period of the study, 1303 patients (652 female, 651 male) were admitted to the AMAU, of whom 221 (128 female, 93 male) (17%) were started on empirical antibiotics. Besides the 221 started on antibiotics in the hospital, there were 16 patients already on antibiotics prescribed by their GP who were not considered in the analysis.

The majority of cases started on empirical antibiotics had respiratory (48%, $n = 107$) or genitourinary (25%, $n = 55$) diseases. Bacteremia accounted for about 3% ($n = 7$) of the cases. The mean delay from time of admission until receipt of first dose of antibiotics, when indicated, was 7.2 h (SD = ± 6.2 h).

In 52% ($n = 115$) of the patients, empirical therapy was in accordance with the antibiotic policy. Of 221 patients, only 77% ($n = 170$) had appropriate laboratory samples taken, of whom 38% ($n = 65$) had clinically significant growth of organisms (Table 1). In 30% ($n = 51$), the specimens were taken after administration of the first dose of antibiotics. Two of the 65 clinically significant cases had fungal infections, and were not further considered in the analysis. Only 29% ($n = 63$) of the 221 patients had culture results that merited antibiotic treatment.

In the study of the 133 patients started on empirical intravenous antibiotics, 72% ($n = 96$) of the patients had negative culture results, and 69% ($n = 92$) had negative sepsis profiles (Table 2). Almost half (48%, $n = 64$) of the patients started on intravenous antibiotics had both negative sepsis profiles and negative culture results. The relative risk of being on an intravenous antibiotic in spite of a negative culture was 72%, implying an odds ratio of 2.6. There was a trend to a positive sepsis profile in patients treated with intravenous antibiotics, but this was not statistically significant ($P = 0.178$).

In a subset study ($n = 95$), the results of CXR were compared with culture and sepsis results: 43% ($n = 41$) of patients with no clinically significant CXR findings also had negative culture results, and 41% ($n = 39$) also had negative sepsis profiles (Table 3). There was a trend to negative sepsis profiles and culture results in those with clear CXR, but this was not statistically significant ($P = 0.375$).

The four most commonly used antibiotics in the AMAU were cefotaxime (35%, $n = 78$), clarithromycin (19%, $n = 42$), co-amoxiclav (12%, $n = 27$),

Table 1 Isolates of clinical significance, their percentage distribution relative to each other, and percentage of the total cases on empirical antibiotics

Causative organism	System	No (%) clinically significant	% of the total cases on antibiotics
Haemophilus influenzae	Respiratory	10 (15.4)	4.5
Haemophilus parainfluenzae	Respiratory	2 (3.1)	0.9
Streptococcus pneumoniae	Respiratory	2 (3.1)	0.9
Methicillin-resistant	Respiratory	5 (7.7)	2.3
	Urine	1 (1.5)	0.5
Staphylococcus aureus (MRSA)	Blood	2 (3.1)	0.9
	Soft tissue	8 (12.3)	3.6
Staphylococcus aureus	Respiratory	1 (1.5)	0.5
	Genitourinary	1 (1.5)	0.5
(methicillin sensitive)	Soft tissue	3 (4.6)	1.4
Staphylococcus aureus	Blood	1 (1.5)	0.5
Acinetobacter baumanii	Respiratory	2 (3.1)	0.9
Escherichia coli	Blood	4 (6.2)	1.8
Escherichia coli (0157)	Gastrointestinal	1 (1.5)	0.5
Coliforms	Genitourinary	11 (16.9)	5.0
Pseudomonas aeruginosa	Genitourinary	3 (4.6)	1.4
Enterococcus faecalis	Genitourinary	3 (4.6)	1.4
Proteus spp.	Genitourinary	2 (3.1)	0.9
Candida albicans	Genitourinary	2 (3.1)	0.9
Streptococcus pyogenes	Soft tissue	1 (1.5)	0.5
Total		65 (100)	29.4

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Table 2 The distribution of sepsis profiles and culture results of the patients started on empirical antibiotics

	A Culture and sensitivity (c/s)		B Sepsis profile		Both c/s and sepsis profile Negative
	Positive	Negative	Positive	Negative	
Patients on intravenous antibiotics ($n = 133$)	37 (27.8%)	96 (72.2%)	41 (30.8%)	92 (69.2%)	64 (48.1%)
Patients on oral antibiotics ($n = 88$)	26 (29.5%)	62 (70.5%)	13 (14.8%)	75 (56.3%)	47 (53.4%)
Total ($n = 221$)	63 (28.5%)	158 (71.5%)	54 (24.5%)	167 (75.1%)	111

Table 3 Results of chest X-ray, culture results and sepsis profile for the subset of 95 patients who were started on empirical antibiotics for respiratory ailments

	Culture results		Sepsis profile	
	Positive	Negative	Positive	Negative
X-ray suggests infection	10 (11%)	17 (18%)	12 (13%)	16 (17%)
X-ray does not suggest infection	14 (15)	41 (43%)	15 (16%)	39 (41%)
X-ray not done	5 (5%)	8 (8%)	4 (4%)	9 (9%)
Total ($n = 95$)	29 (31%)	66 (69%)	31 (33%)	64 (67%)

and amoxicillin (8%). Combinations of antibiotics were used in 34% ($n = 77$) of the patients. Of the 77 patients on two or more antibiotics, the three most common combinations used were cefotaxime–clarithromycin (30%, $n = 23$), cefotaxime–metronidazole (21%, $n = 16$), and benzylpenicillin–flucloxacillin (10%, $n = 8$).

Of the 63 patients with clinically significant bacteriologic culture results, 51% ($n = 32$) were on an inappropriate antimicrobial agent, as shown by the sensitivity data. Although 44% ($n = 14$) of these 32 patients had their medication changed to a more suitable antibiotic, 56% ($n = 18$) did not.

Antibiotics were discontinued in 7% ($n = 8$) of the patients with negative culture results, while in 9% ($n = 9$) of the patients, treatment was stopped within 3 days for other reasons, mainly the resolution of clinical signs of infection. In 72% ($n = 158$) of the patients with negative culture results, the culture report had no obvious effect on the duration or type of antibiotic being administered.

The time of switch from intravenous to oral antibiotics ranged from 1 to 11 days (mean = 3.5 - days). The duration of treatment ranged from 1 to 26 days (mean = 8.4 days). Statistical analysis showed no significant relationship between culture results and duration of treatment ($P = 0.392$). Of the patients started on empirical antibiotics, 60% ($n = 133$) received them intravenously, although 83% ($n = 110$) were capable of taking medication orally. Of the patients with negative culture results, 72% ($n = 96$) had been started on intravenous antibiotics.

Documentation of results was found in 86% ($n = 190$) of the case notes. The time interval between the availability of the reports and their documentation in notes was 1 day in 85% of the cases.

Of the 221 cases in the study, 95% ($n = 210$) of the patients recovered, 3.5% ($n = 8$) were still inpatients in a ward when the study was concluded, and 1.8% ($n = 4$) died.

DISCUSSION

Compared to published data [14,15], the use of empirical antibiotic therapy in the ARI is conservative, with less than 17% of medical admissions receiving antibiotics. The majority of admissions who were started on empirical antibiotic therapy were suffering from respiratory infections, with urinary tract infection being the second most common indication. The collection of appropriate samples seemed reasonable at 77% ($n = 170$), given the difficulty of collecting sputum samples from many patients with respiratory tract infection. However, 30% ($n = 51$) of the specimens were taken after administration of the first dose of antibiotics. This

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is an inherent flaw in the system. A requirement for samples to be taken before antibiotic treatment is commenced should be emphasized, provided that delay in treatment of critically ill patients does not ensue.

The delay of approximately 7.2 h between admission and the administration of the first dose of antibiotics is another area where improvement is desirable, as published studies [16,17] have shown that shorter time delays result in shorter duration of stay and less morbidity. While such delays before commencing empirical therapy do not represent good practice in seriously ill patients, the majority of patients admitted were evidently not in need of urgent antibiotic therapy, and this delay could be best used to collect results of baseline investigations, e.g. measurement of sepsis parameters, Gram stain, and urine microscopy; even results of urine culture with direct susceptibility testing should be available, obviating the need for therapeutic empiricism.

This study demonstrates a significant overuse of antibiotics, which is, of course, well described [18]. There is poor utilization of culture results, particularly negative ones, to streamline or stop treatment. This is also well described in the literature [19,20].

Of the 221 patients started on empirical antibiotics, 60% ($n = 133$) received them in intravenous form, although 83% of these patients were capable of taking medication orally. Of the patients with negative culture results, 72% had been started on intravenous antibiotics, and there was also a paucity of positive sepsis parameters and CXR findings in these patients. Further studies need to be done to evaluate whether this use of intravenous antibiotics is justified, although this seems unlikely. The CXR is the definitive diagnostic test for pneumonia (BTS guidelines), and the overuse of intravenous cephalosporins in this setting is well described [21].

The use of oral forms of antibiotics in empirical therapy would be 'patient-friendly' and would facilitate ease of administration as well as cost-effectiveness. Traditionally, intravenous antibiotics have been employed in order to quickly achieve therapeutic levels. However, studies [7,8] have demonstrated that similar therapeutic levels can be achieved by the use of oral antibiotics if a critical evaluation of each patient is carried out, particularly in the absence of positive sepsis parameters. The switch from an intravenous to an oral antibiotic was usually achieved within 3.5 days, which is similar to results from previous audits in the Grampian region [22–24]. There are no apparent reasons why this period could not be reduced to 24 h.

The duration of antibiotic treatment was 8 days on average, which is similar to the findings of previous studies from Grampian hospitals [22–24]. The duration of treatment could be shortened and an early switch policy could be instituted if culture results and sepsis profiles were taken into consideration, as there are many unproven infections.

Documentation of results in notes, at 86%, was satisfactory compared to published studies [25,26]. However, as the reports were often in the form of a computer printout and tended to get mixed up with older reports, they were frequently not utilized unless the patient was not doing well clinically. It would be beneficial if culture reports were entered into the daily notes, as these are always scrutinized by the clinicians; this could result in a more optimal use of the microbiological results, in particular cessation of unnecessary antibiotics.

COUNTERMEASURES

Inappropriate use of antibiotics is frequently identified as an important driver of high treatment costs, avoidable side effects, treatment failures and antibiotic resistance [27,28].

This study suggests that antibiotic use could be improved via a number of simple steps: (1) increased utilization of microbiological culture reports, microscopy and sepsis profiles; (2) more judicious use of intravenous antibiotics and daily review by a senior doctor, earlier switch to oral medicines, and streamlining or discontinuing treatment in the event of negative sepsis profiles and culture results; (3) more clearly defined ward protocols to guide empirical therapy, as, despite a previous audit [22], compliance with the policy was only 52%; and (4) where sepsis is severe, administration of intravenous antibiotics as soon as possible by authorized nursing staff.

One possible solution for the successful implementation of these recommendations would be the adoption of generic antibiotic policies describing the process of prescribing. These are currently being piloted locally at the ARI. Audit of quality indicators [3,12] will form an increasing part of a

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clinicians' antibiotic-prescribing quality program in the future, in conjunction with the Antibiotic Committee as well as the Clinical Effectiveness, Clinical Governance and Quality Assurance committees of the hospital trust.

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