Journal of Hospital Infection (2007) **65**(S2) 73–81

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The role of microbiology and pharmacy departments in the stewardship of antibiotic prescribing in European hospitals

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KEYWORDS
Microbiology;
Pharmacy;
Antibiotic Stewardship;
Europe

Summary This observational, cross-sectional study describes the role played by clinical microbiology and pharmacy departments in the stewardship of antibiotic prescribing in European hospitals. A total of 170 acute care hospitals from 32 European countries returned a questionnaire on antibiotic policies and practices implemented in 2001. Data on antibiotic use, expressed as Defined Daily Doses per 100 occupied bed-days (DDD/100 BD) were provided by 139 hospitals from 30 countries. A total of 124 hospitals provided both datasets. 121 (71%) of Clinical Microbiology departments and 66 (41%) of Pharmacy departments provided out of hours clinical advice. 70 (41%) of microbiology/infectious disease specialists and 28 (16%) of pharmacists visited wards on a daily basis. The majority of laboratories provided monitoring of blood cultures more than once per day and summary data of antibiotic susceptibility testing (AST) for empiric prescribing (86% and 73% respectively). Most of the key laboratory and pharmacy-led initiatives examined did not vary significantly by geographical location. Hospitals from the North and West of Europe were more likely to examine blood cultures more than once daily compared with other regions ($p < 0.01$). Hospitals in the North were least likely routinely to report susceptibility results for restricted antibiotics compared to those in the South-East and Central/Eastern Europe ($p < 0.01$). Hospital wards in the North were more likely to hold antibiotic stocks (100%) compared with hospitals

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in the South-East which were least likely (39%) ($p < 0.001$). Conversely, hospital pharmacies in the North were least likely to dispense antibiotics on an individual patient basis (16%) compared with hospital pharmacies from Southern Europe (60%) ($p = 0.01$). Hospitals that routinely reported susceptibility results for restricted antibiotics had significantly lower median total antibiotic use in 2001 ($p < 0.01$). Hospitals that provided prescribing advice outside normal working hours had significantly higher antibiotic use compared with institutions that did not provide this service ($p = 0.01$). A wide range of antibiotic stewardship measures was practised in the participating hospitals in 2001, although there remains great scope for expansion of those overseen by pharmacy departments. Most hospitals had active antibiotic stewardship programmes led by specialists in infection, although there is no evidence that these were associated with reduced antibiotic consumption. There was also no evidence that pharmacy services reduced the amount of antibiotics prescribed.

Introduction

In the battle against the closely related problems of antibiotic resistance and excessive antibiotic prescribing in the hospital setting, the microbiology laboratory and pharmacy departments are uniquely placed to provide information and leadership in a collaborative atmosphere.[1,2] Indeed, there have been recent calls for the formation of multidisciplinary teams[3] with pharmacists and infection specialists providing the backbone to improved stewardship in European hospitals.[4,5]

The ARPAC (Antibiotic Resistance: Prevention and Control) study was established with the aim of laying the foundations for a better understanding of the emergence and epidemiology of antibiotic resistance in human bacterial pathogens. The project was conducted by four study groups belonging to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). It collated and analysed data on antimicrobial susceptibility testing, antimicrobial resistance prevalence, typing methods, antimicrobial consumption, infection control polices and antibiotic prescribing policies from European hospitals. The ESCMID Study Group on Antibiotic Policies (ESGAP) was responsible for investigating the roles played by Clinical Microbiology and Pharmacy departments in the stewardship of antibiotic prescribing in European hospitals and to establish any association between such activities and antibiotic use. Its findings are presented in this paper.

Materials and methods

Hospital recruitment

This was an observational, cross-sectional study and was part of a Concerted Action project (ARPAC) funded by the European Commission (project number QLK2-CT-2001-00915). This part of the project was carried out under the auspices of ESGAP. All full members of ESCMID (approximately 2500) were invited to participate in the ARPAC study during 2002 and to provide data relating to 2001; a total of 263 hospitals from European regions participated in the study.

Data collection

Roles of Clinical Microbiology and Pharmacy departments

A detailed postal questionnaire was designed to capture the policies on practices governing antibiotic prescribing during 2001. The questionnaire, to be completed by a medical microbiologist, infectious-disease physician, ICU physician, pharmacist or other appropriate person, included questions on committees, antibiotic availability, antibiotic policies, audit of antibiotic use, the role of the laboratory (13 questions) and the role of the pharmacy (13 questions) in influencing antibiotic prescribing. The questionnaire was developed, piloted and revised by the ARPAC Steering Group before it was circulated to the 263 recruited hospitals in 2003.

Antibiotic use data

The European ARPAC participating hospitals were asked to provide antibiotic use data for J01 antibacterial agents of the World Health Organisation classification, categorised using the Anatomical Therapeutic Chemical (ATC) classification index and measured using the WHO recommended unit of DDD per 100 occupied bed-days (DDD/100 BD).[6]

Table 1
ARPAC hospitals that provided data on antibiotic prescribing (n = 170)

Northern Europe n = 19 (11%)	Western Europe n = 55 (32%)	Centre/East + Baltic States n = 43 (25%)	South-Eastern Europe n = 13 (8%)	Southern Europe + Israel n = 40 (24%)
Denmark (n = 5)	Austria (n = 5)	Bulgaria (n = 7)	Bosnia (n = 2)	Greece (n = 7)
Netherlands (n = 7)	Belgium (n = 18)	Czech Republic (n = 3)	Croatia (n = 6)	Israel(n = 2)
Norway (n = 3)	France (n = 6)	Estonia (n = 2)	Macedonia (n = 1)	Italy (n = 9)
Sweden (n = 4)	Germany (n = 10)	Hungary (n = 7)	Yugoslavia (n = 4)	Malta (n = 1)
	Switzerland (n = 5)	Latvia (n = 2)		Portugal (n = 2)
	UK (n = 11)	Lithuania (n = 3)		Spain (n = 9)
		Poland (n = 6)		Turkey (n = 10)
		Romania (n = 2)		
		Russia (n = 1)		
		Slovakia (n = 5)		
		Slovenia (n = 5)		

Statistical analysis

Data were analysed by European region using a modified version of a standard European reference system[7] with hospitals from the UK categorised as part of Western rather than Northern Europe (Table 1).

Data were entered into Microsoft Access 2000, and an independent validation check was made on a 10% sample of data entered. Statistical analysis was conducted using SPSS for Windows (version 12.0). Associations between key stewardship variables with geographic/hospital factors[8] and total antibiotic use (J01) were analysed using the Chi-squared test for categorical variables and the Mann–Whitney U test for antibiotic use. P-values of less than 0.01 were considered statistically significant.

Results

Sample characteristics

A total of 263 hospitals from Europe and Israel expressed an interest in participating in the study. Hospitals from Israel were eligible for inclusion because of a bilateral scientific co-operation agreement for EC-funded studies. Of these, 204 hospitals subsequently submitted at least one further dataset and are described elsewhere.[8] Completed questionnaires on antibiotic prescribing were received from 170 (65%) of 263 ARPAC hospitals across 32 European countries (Table 1). Comparisons were made between these 170 hospitals and the 93 recruited ARPAC hospitals that failed to provide antibiotic prescribing data. Responding hospitals were more likely to have teaching status ($p = 0.05$), but there were no differences by geographical region ($p = 0.54$), hospital size ($p = 0.64$), presence or size of ICU ($p = 0.27$). Of the 170 hospitals that provided antibiotic prescribing data, 130 (76%) had teaching status, 159 (94%) had an ICU and the median hospital size was 669 beds (IQR 408, 1022). Antibiotic consumption data were provided by 139 hospitals from 30 countries and are described elsewhere.[6] 124 hospitals provided both antibiotic prescribing and antibiotic use data.

Microbiology laboratory service

Hospital microbiology laboratory practice is presented in Table 2. There did appear to be some variation in practice across geographical regions. Evidence of variation in the frequency of examination of blood cultures was found ($p < 0.01$), with more hospitals in the North and West of Europe examining blood cultures more than once per day compared to other regions. Fewer hospitals in the North routinely reported susceptibility results for restricted antibiotics than those in the South-East and Central/Eastern Europe.

The majority of hospitals provided an emergency microbiology laboratory service (75%) and prescribing advice (71%) outside normal working hours (Table 2). The majority also examined blood cultures more than once a day (86%), provided antibiotic susceptibility test (AST) data to physicians to assist with empiric therapy (73%) and reported AST results for non-formulary antibiotics when organisms were resistant to formulary agents (67%). Only 52% routinely reported AST results for restricted antibiotics. Less than half (41%) of the clinical microbiologists/ID specialists conducted daily ward rounds to advise on therapy.

A total of 124 (73%) of hospitals provided summary antibiotic susceptibility data to guide empiric therapy. This was sent to individual physicians in 54 (32%), individual units in 64 (38%) and to the whole hospital in 59 (35%) hospitals. No evidence of variation by geographical region, hospital size

Table 2
Hospital microbiology laboratory practice by European region (n = 170 hospitals)

	All regions n = 170 (%)	Missing (%)	North n = 19 (%)	West n = 55 (%)	CE n = 43 (%)	SE n = 13 (%)	South n = 40 (%)	p value*
Hospital laboratory provided an emergency service outside routine working hours	127 (75)	3 (2)	15 (79)	47 (85)	30 (70)	8 (62)	27 (68)	0.16
Laboratory examined blood cultures >1 daily	147 (86)	3 (2)	19 (100)	54 (98)	34 (79)	10 (77)	30 (75)	<0.01
Microbiology department provided antibiotic sensitivity test data to physicians to assist with empiric treatment	124 (73)	5 (3)	11 (58)	37 (67)	33 (78)	11 (85)	32 (80)	0.16
Susceptibility results routinely reported for restricted antibiotics	88 (52)	15 (9)	3 (16)	25 (45)	31 (72)	9 (69)	20 (50)	<0.01
Susceptibility results reported for non-formulary antibiotics when organisms resistant to formulary agents	114 (67)	13 (8)	15 (79)	31 (56)	31 (72)	8 (62)	29 (73)	0.02
Prescribing advice was available out with normal working hours	121 (71)	4 (2)	18 (95)	43 (78)	27 (63)	9 (60)	24 (60)	0.05
Clinical microbiologist/ID specialist conducted daily ward round to advise on therapy	70 (41)	7 (4)	11 (58)	27 (49)	13 (30)	4 (31)	15 (38)	0.13

[a] *Chi-squared test.

Table 3
Hospital pharmacy practice by European region (n = 170)

	All regions n = 170 (%)	Missing (%)	North n = 19 (%)	West n = 55 (%)	CE n = 43 (%)	SE n = 13 (%)	South n = 40 (%)	p value*
Prescribing advice available from pharmacist during normal working hours	138 (81)	7 (4)	17 (90)	52 (95)	28 (65)	9 (69)	32 (80)	0.05
Prescribing advice available outside of working hours, including weekends	66 (41)	10 (6)	9 (47)	30 (55)	12 (28)	2 (15)	13 (33)	0.03
Daily ward visits by pharmacist to advise on therapy	28 (16)	6 (4)	1 (5)	12 (22)	7 (10)	1 (8)	7 (18)	0.55
Antibiotics dispensed directly from pharmacy per patient	66 (41)	8 (5)	3 (16)	20 (36)	14 (33)	5 (38)	24 (60)	0.01
Wards held stocks of antibiotics	119 (70)	9 (5)	19 (100)	46 (84)	27 (63)	5 (39)	22 (55)	<0.001

*Chi-squared test.

or teaching status was found (data not shown). Summaries of susceptibility data were fedback to users at varying intervals: 86 (51%) fedback annually, 37 (22%) twice or more per year and 13 (8%) less than once yearly. 34 (20%) of hospitals failed to provide information on the frequency of feedback of summary susceptibility data.

Only 89 (52%) of laboratories routinely reported MIC values and only 20 (12%) of hospitals detailed cost information within the laboratory report.

Role of the pharmacy

Some variation in key pharmacy initiatives across geographical region was found (Table 3). Variation in holding antibiotic stocks on the ward ranged from 100% of hospitals in the North to only 39% of hospitals in the South-East. Conversely, only 16% of hospital pharmacies in the North dispensed antibiotics on an individual patient basis compared with 60% of hospital pharmacies in the South.

Overall, the majority of hospital pharmacies offered prescribing advice during normal working hours (81%) and held antibiotic stocks at ward level (70%) (Table 3). 41% offered prescribing advice outside normal working hours and 41% of pharmacy departments dispensed antibiotics on an individual patient basis (Table 3). Most notably, only 16% of hospitals operated a system whereby

Table 4
Total antibiotic use in 2001 by key laboratory practice variables (n = 124)

		Median antibiotic use (IQR) DDD/100 BD	p value*
Hospital laboratory provided an emergency service outside routine working hours	Yes n = 98	56.8 (40.3, 72.3)	
	No n = 24	47.4 (38.2, 66.7)	0.19
	Missing n = 2		
Laboratory examined blood cultures >1 daily	Yes n = 111	55.4 (40.9, 71.1)	
	No n = 11	47.5 (24.9, 81.4)	0.63
	Missing n = 2		
Microbiology department provided AST data to physicians to assist with empiric treatment	Yes n = 88	54.2 (38.9, 70.5)	
	No n = 33	59.3 (41.9, 80.2)	0.41
	Missing n = 3		
Susceptibility results routinely reported for restricted antibiotics	Yes n = 67	49.1 (35.9, 68.7)	
	No n = 46	61.1 (46.5, 81.9)	<0.01
	Missing n = 11		
Susceptibility results reported for non-formulary antibiotics when organisms resistant to formulary agents	Yes n = 41	53.2 (39.1, 66.1)	
	No n = 76	57.7 (40.1, 71.9)	0.44
	Missing n = 7		
Prescribing advice was available outside normal working hours	Yes n = 115	55.9 (40.9, 72.2)	
	No n = 7	33.9 (16.3, 45.6)	0.01
	Missing n = 2		
Clinical microbiologist/ID specialist did daily ward round to advise on therapy	Yes n = 95	55.4 (40.8, 71.1)	
	No n = 27	49.4 (33.9, 72.2)	0.49
	Missing n = 2		

*Mann–Whitney U test.

pharmacists carried out daily ward rounds to advise on therapy.

Thirty-three (19%) and 23 (14%) hospitals operated a voluntary system of automatic stop ('auto-stop') dates for prophylaxis and treatment respectively. Only 14 (8%) hospitals operated compulsory automatic stop dates on prophylaxis and 10 (6%) for treatment. Computerised antibiotic prescribing was available in only 25 (15%) hospitals. Regional responses to these questions were too low to test for differences.

Association between antibiotic use and key laboratory practices

Hospitals that routinely reported susceptibility results for restricted antibiotics had significantly lower median total antibiotic use in 2001 (Table 4; 49.1 vs. 61.1 DDDs/100 BD; $p < 0.01$). Hospitals that provided prescribing advice outside normal working hours had significantly higher antibiotic use compared to institutions that did not provide this service (55.9 vs 33.9; $p = 0.01$), although hospital numbers within this latter category were low (Table 4). No statistically significant associations were found between any of the other key laboratory practice variables and antibiotic use (Table 4).

Association between antibiotic use and key pharmacy practices

There was weak evidence to suggest some association between antibiotic use and some of the key pharmacy practices. In fact, antibiotic use in hospitals providing pharmacy advice during normal working hours was almost half that of those hospitals that did not provide such advice ($p = 0.04$) (Table 5).

Discussion

The aim of this study was to describe the contribution made by European hospital-based microbiology and pharmacy departments to antibiotic stewardship and to describe any associations between either policy or practice and antibiotic consumption. Being the first European study of its kind, it is a major contribution to current knowledge. Whilst much is known about antibiotic policies in some individual countries, our study is the first to explore these issues at a European level, to compare differences and look for associations with antibiotic use. The fact that there were higher levels of antibiotic use in hospitals that did have indicators of 'good practice' may indicate that these are very active, acute care hospitals and/or that these stewardship measures were instigated in response to high consumption rather than being the cause of it.

This study was conducted to gain insight into the content of key areas of antibiotic policies across Europe and establish any relationships between policy content and antibiotic use. It was not designed to assess the practice of antibiotic stewardship over time, nor was it designed to establish the relationship between cause and effect or direction of effect.

There are many methodological strengths of the ARPAC study, as well as accepted limitations and these have been discussed elsewhere.[8-10] Other results from the ARPAC study found that antibiotic resistance prevalence, antibiotic use and infection control policies and practice all varied significantly with geographical region.[6,8-10] We, however, found that microbiology and pharmacy-led initiatives to optimise antibiotic prescribing in the hospital did not vary to any great extent across Europe.

A Cochrane review recently cited 66 published studies which described interventions to improve antibiotic prescribing in hospitals.[11] In 22 of these studies the relevant intervention was led by pharmacists and in 17 by infection specialists. The pharmacist-led interventions were predominantly educational, such as reviewing patient charts and recommending changes, and tended to measure outcome only in terms of drug use rather than microbial or clinical outcome. In contrast, the majority of interventions led by infection specialists tended to be restrictive such as controlling access to restricted agents. Of the 66 interventions, a total of 29 were educational, 27 were restrictive, seven were mixed and three structural. Two of the three structural interventions instigated rapid identification and antibiotic susceptibility testing and the third provided a pharmacokinetic service for predicting aminoglycoside serum levels. One of the restrictive and four of the educational interventions were carried out by computer or written feedback. The authors concluded that restrictive interventions were more successful than educational interventions, at least in the short term, but there was little evidence for control of resistance by these interventions. Indeed it is possible that some of the interventions were associated with poorer patient outcome. Much more robust research is needed in this area, particularly to assess the relationship between interventions and relevant clinical outcomes.

In the meantime, repeated audits of antibiotic prescribing[12,13] and analysis of resistance data[14] give great cause for concern about unnecessary

Table 5
Total antibiotic use in 2001 by reported key pharmacy practice variables (n = 124)

		Median antibiotic use (IQR) DDD/100 BD	p value*
Prescribing advice available from pharmacist during normal working hours	Yes n = 103	26.6 (16.3, 36.8)	
	No n = 19	46.5 (38.1, 60.9)	0.04
	Missing n = 2		
Prescribing advice available outside of working hours, including weekends	Yes n = 55	61.6 (40.4, 78.5)	
	No n = 64	51.2 (39.2, 67.9)	0.07
	Missing n = 5		
Daily ward visits by pharmacist to advise on therapy	Yes n = 22	66.8 (34.9, 96.9)	
	No n = 100	54.2 (40.5, 69.5)	0.08
	Missing n = 2		
Antibiotics dispensed directly from pharmacy per patient	Yes n = 48	61.6 (42.2, 79.5)	
	No n = 73	49.6 (39.7, 66.6)	0.05
	Missing n = 3		
Wards held stocks of antibiotics	Yes n = 91	55.9 (42.5, 71.8)	
	No n = 28	55.1 (33.8, 75.2)	0.48
	Missing n = 5		

*Mann–Whitney U test.

and poor quality antibiotic prescribing and major increases in resistance problems in European hospitals. Our findings show that infection specialists are trying to address this by providing frequent out-of-hours services, clinical advice and ward rounds. The activities of pharmacists however, leave room for expansion outside normal working hours. We found similar trends in related educational and audit activities, which will be the subject of another report.

The provision of continuous blood culture monitoring to provide rapid results to guide therapy has been shown to improve both the quality and quantity of antibiotic use, as well as improved patient outcome.[15-17] The provision of antibiotic susceptibility summary data at a local level is the best way to inform local antibiotic policies for the provision of empiric therapy, given the variation in local susceptibility patterns. The limited reporting of non-formulary and restricted agents seems sensible as reporting of agents is often seen by clinicians as a recommendation to treat with these agents.[18] Lastly, the frequent reporting of MIC values is seen as important now that the value of the MIC in defining optimal antibiotic treatment in critically ill patients is known.[19]

The ARPAC study found that relatively few pharmacists carry out ward rounds. There may be staffing issues here but there are increasing moves to create antibiotic/infectious-diseases pharmacists similar to those who have practised in the USA for many years.[5] There is a new MSc in Infection Management for Pharmacists organised by Imperial College, London, UK and some countries have funded development programmes, sometimes in the context of multi-disciplinary teams.

A small number of hospitals encourage voluntary auto-stop of prescriptions; even fewer enforce compulsory auto-stop regimes. Data exist which suggest this is a reasonable method of reducing unnecessarily prolonged prescriptions[20] but there are concerns that it can be unsafe, leading to premature cessation of therapy. Computerised prescribing has many advocates although supportive literature is limited.[21] Computerised prescribing was rarely practised in ARPAC hospitals, probably due to lack of computer facilities. Computerisation can improve both the quality of prescribing and the ability to audit, and there is huge scope for widespread implementation across Europe. It was, however, associated with marginally significant increases in consumption in this study although the low proportions of computerised prescribing decreased the likelihood of detecting an effect. In conclusion, there is ample scope to increase support service activity in antibiotic stewardship in European hospitals. In particular, the role of pharmacists should be expanded as an integral part of multidisciplinary antibiotic teams.

Acknowledgements

The ARPAC study was funded by the European Commission (project QLK2-CT-2001-00915). F.M. MacKenzie was supported by the European Study Group on Antibiotic Policies to write this manuscript.

In addition to the named authors, the ARPAC Steering Group comprised the following members: M.J. Struelens (Belgium), H. Goossens (Belgium), K.J. Towner (UK), P. van den Broek (The Netherlands), L. Dijkshoorn (The Netherlands), J. Vila (Spain), G. Cornaglia (Italy), F. Baquero (Spain), D. Wagner (Belgium), M. van Looveren (Belgium).

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