Antimicrobial practice

Indications for antibiotic use in ICU patients: a one-year prospective surveillance

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The high prevalence of nosocomial infections in critically ill ICU patients is associated with high antibiotic consumption. Besides its economic impact, there is the constant threat of selection and induction of antibiotic resistance. Surveillance studies recording the incidence of infections, antibiotic use, and antimicrobial susceptibilities of pathogens supply vital information regarding infection control and prevention of antibiotic resistance. In order to analyse antibiotic consumption we recorded antibiotic use in a general ICU during one year by categorizing the indications for antibiotic use into three groups; (i) prophylaxis; (ii) therapy for a bacteriologically proven infection (BPI); (iii) therapy for a non-bacteriologically proven infection (non-BPI). Bronchoscopic techniques were used to diagnose pneumonia. In practice, BPI must be treated, but a proportion of antibiotics prescribed for non-BPI may be unnecessary. The subdivision in BPI and non-BPI may help to identify these cases. In all, 515 patients were admitted to ICU and 36% of these had at least one infection. Of all infections, 53% were ICU-acquired and 99% of these occurred in intubated patients. Antibiotics were prescribed in 61% of admissions. Of all antibiotics prescribed for therapy, 49% were for respiratory tract infections, 19% for abdominal infections and 13% for sepsis eci. Categorized by indication, 59% of all antibiotic prescriptions were for BPI, 28% for non-BPI and 13% for prophylaxis. A theoretical reduction of 25% in the number of non-BPI prescriptions would result only in a 7% decrease of total antibiotic use. We conclude that almost all antibiotics prescribed were for intubated patients and for BPI. Respiratory infections were the single most common infection and accounted for 49% of all antibiotics used. Therefore, in our setting, prevention of respiratory tract infections is probably the most effective mode to reduce antibiotic use.

Introduction

The last decade has witnessed the increasing problem of antibiotic resistance as a consequence of excessive or inappropriate antibiotic use. Indeed, contemporary literature has addressed the doom scenario of the 'post-antimicrobial era'.[1] Collecting data on motives for anti-biotic use is the first step in managing this problem. Therefore, surveillance studies regarding the incidence of infections, antibiotic prescription policies and knowledge about antimicrobial susceptibilities of pathogens are crucial.[1–5]

Critically ill patients treated in ICUs frequently have an infection or are prone to develop new infections. As a corollary, the total antibiotic consumption is approximately ten times greater in ICU wards than in general hospital wards.[6] A considerable part of total hospital antibiotic consumption and cost are for antibiotic use in ICU.[3,4] Data from the National Nosocomial Infection Surveillance System (NNISS) describe 'rough' changes in epidemiology and antibiotic susceptibility of pathogens in US hospitals over a 20 year period, while the European Prevalence of Infection in Intensive Care study (EPIC)

determined prevalence of infections, antibiotic use and susceptibilities of isolated pathogens in a continent-wide point-prevalence study.[5] Only few detailed longitudinal surveillance studies exist on infections and antibiotic use in ICUs.[6,7] As a result, little is known about the indications for and costs of antibiotic therapy for different patient populations within a general ICU. We, therefore, prospectively analysed antibiotic use and related costs in a general ICU ward over a 1-year period. Special emphasis was given to the indications for antibiotic use, which were divided into bacteriologically proven infections, non-bacteriologically proven infections, and prophylactic use.

Patients and methods

Setting

The University Hospital in Maastricht is a 700-bed facility. Critically ill medical, surgical, neurological/neuro-surgical and trauma patients requiring haemodynamic monitoring and/or mechanical ventilation are admitted to one of two similar general ICUs. The total capacity is 15 beds of which two are reserved for paediatric patients. Coronary-care patients and patients recovering from cardiac surgery are cared for in other separate units as are neonates. The ICU is managed by a multidisciplinary staff (internal medicine, surgery, anaesthesiology), with daily assistance from the departments of medical microbiology, pulmonology and radiology. During the study period no changes in the composition of the medical staff occurred.

Data collection

Study population. From January 1, 1994 to December 31, 1994 all adult patients (age > 15 years), ventilated or non-ventilated, who had been admitted to ICU were studied prospectively. On admission the following data were recorded: age, sex, medical speciality, pre-existent diseases, APACHE II score[8] and length of hospital stay before admission to the ICU. Subsequently, the number of days in ICU, number of days on mechanical ventilation, surgical procedures, type of nutrition and mortality were monitored. During ICU stay, parameters of infection (temperature, leucocyte count and differentiation, X-ray results, culture results) and types and doses of prescribed antibiotics, with the exception of topical applications, were registered daily. Selective decontamination of the digestive tract (SDD) was not used during the study period.

Microbiology. Semi-quantitative and quantitative microbiological analysis of samples collected for culture were performed according to standard microbiological methods.[9,10] Besides the cultures performed of samples that were collected on indication, all patients had routine urine and sputum cultures taken twice weekly. Antibiotic susceptibility was determined by means of a microbroth dilution method according to the NCCLS guidelines. *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922 and ATCC 35218, *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were used as reference strains. The criteria for susceptibility and resistance, according to the NCCLS guidelines, were used to determine the percentages of strains susceptible to the most frequently used agents.

Data analysis

All collected data were analysed by one investigator according to the definitions described below. The multidisciplinary staff of the ICU wards were not informed of the study to prevent bias.

Definitions

Infections. The Centers for Disease Control definitions for surveillance of nosocomial infections were used.[11] However, an additional classification was made based upon the culture results as described below in order to categorize infections and associated antibiotic use in groups in which a clinical suspicion of infections was or was not microbiologically confirmed. More detailed criteria were used for pneumonia (see below). Infections occurring within 48 h of admission to ICU were considered non-ICU-acquired (i.e. community or hospital acquired). Infections that were clinically suspected and diagnosed more than 48 h after admission to ICU were considered to be ICU-acquired.

A clinical suspicion of infection was based on the following infection parameters: (i) temperature of > 38°C or < 35.5°C; (ii) leucocytosis of > 10×10^3/mm^3 with or without left-shift in differential count or leucopaenia < 3×10^3/mm^3. In addition, clinical findings such as a new or progressive infiltrate on chest X-ray, cloudy urine, purulent sputum or phlebitis in the absence of above mentioned criteria were considered indicative of possible infection. If a clinical suspicion of infection was present, samples of the suspected site of infection (urinary tract, respiratory tract, blood, wound drainage, ascites, cerebrospinal fluid, catheters, etc.), were taken for culture. Depending on the culture results, the infections were divided into two groups: (i) non-bacteriologically proven infection (non-BPI): all cases of clinical suspicion of infection, with negative or non-significant bacterial culture results, but necessitating antibiotic therapy in view of the clinical condition of the patient; (ii) bacteriologically proven infection (BPI): all cases of clinical suspicion of infection with significant culture results from samples collected from the suspected infection site that were treated with antibiotics.

Decisions regarding the presence of a clinical suspicion of infection, the orders to take samples for culture, the

Table I. Criteria used in the diagnosis of pneumonia

	Criterion
A	At least three of the following four positive: rectal temperature above 38.0°C or below 35.5°C blood leucocytosis ($>10 \times 10^3$/mm^3) and/or left shift or blood leucopenia ($<3 \times 10^3$/mm^3) >10 leucocytes per high-power field in Gram stain of tracheal aspirate positive culture from tracheal aspirate
B	New, persistent or progressive infiltrate on chest radiograph
C	At least one of the following three positive: positive quantitative culture of a sample obtained by broncheolar lavage (cut-off $\geqslant 10^4$ cfu/mL) or protected specimen brush (cut-off point $\geqslant 10^3$ cfu/mL) positive blood culture unrelated to another source and obtained within 48 h before and after respiratory sampling positive pleural fluid culture in the absence of previous pleural instrumentation

A + B + C = bacteriologically proven pneumonia; A + B = non-bacteriologically proven pneumonia.

interpretation of culture results, and the institution of antibiotic therapy were made by the primary care team assisted by the department of medical microbiology.

Pneumonia. When pneumonia was clinically suspected, bronchoscopy with protected specimen brush and broncho-alveolar lavage were performed as described elsewhere.[12] The diagnosis of pneumonia was established according to the criteria listed in Table I. When criteria A and B were met it was considered a non-bacteriologically proven pneumonia and the infection regarded as non-BPI. When criteria A, B and C were met, pneumonia was bacteriologically proven and the infection considered to be a BPI.

Antibiotic use. Antibiotic use was analysed either in prescriptions or in courses. The term 'prescription' was used to describe the uninterrupted use of a single antibiotic. A 'course' was defined as an episode of clinical or suspected infection in which antibiotics, either consecutively or in combination, were prescribed. Antibiotic consumption was analysed in prescribed daily doses (PDD) or as PDD per 100 bed days.[6] The costs of antibiotic therapy were calculated using the prices per PDD paid by the hospital pharmacy, including the costs of monitoring serum antibiotic concentrations for aminoglycosides and vancomycin (average three times weekly).

The indications for antibiotic use were categorized into three groups: (i) prophylaxis, either for a surgical procedure or endocarditis; (ii) therapy for a BPI; (iii) therapy for a non-BPI.

Statistical analysis

Data are expressed as absolute numbers with or without percentages, as means with standard deviation or as medians with ranges. Antibiotic costs are expressed in Dutch florins (Dfl) (100 Dfl approximately equals 60 US$ and £40 sterling). Frequency comparisons were performed by chi-square test or Fisher's exact test. A probability value less than 0.05 was considered to denote statistical significance.

Results

Patient characteristics

During 1994, 469 patients were admitted to ICU. Since 30 patients were admitted twice and eight patients three times, the total number of admissions was 515 (Table II).

Infections

Of all patients admitted to ICU, 36% had at least one infection during ICU stay: 19% had $\geqslant 1$ BPI, 13% had $\geqslant 1$ non-BPI and 4% had both BPI and non-BPI. In all, 179 BPI were observed in 121 patients: 77 (43%) of these originated in the respiratory tract, 29 (16%) were of abdominal origin and 73 (41%) originated from other sites. Of all BPI, 164 (92%) occurred in intubated patients and the majority of these infections ($n = 116$, 71%) were ICU-acquired. Among non-intubated patients, 15 BPI were diagnosed of which one was ICU-acquired (Table III).

A non-BPI emerged 95 times in 86 patients: in 64 (67%) cases this related to the respiratory tract, in 16 (17%) cases to the abdomen. There were nine (10%) cases of clinical sepsis and six (6%) cases originated from other sites. As with BPI, the majority of non-BPI were seen in intubated patients ($n = 81$, 85%), and 29 (36%) of these were ICU-acquired (Table III). All non-BPI ($n = 14$) seen in non-intubated patients were non-ICU-acquired.

Table II. Characteristics of the patients

	All (n = 515)	Intubated (n = 276)	Non-intubated (n = 239)
Median age (range)[a]	61 (16–93)	63 (16–90)	56 (19–93)
Male/female[a]	279/190	166/88	113/102
Median APACHE II score (range)[b]	15 (0–50)	18 (2–50)	9 (0–40)
Days on ICU; median (range)	3 (1–75)	7 (1–75)	2 (1–12)
Number of patient bed-days (%)	4091	3434 (84%)	657 (16%)
Medical speciality			
medical[c]	209	107	102
surgery[d]	259	137	122
trauma	47	32	15
Surgical procedures			
abdominal surgery	110	90	20
thoracic surgery	26	23	3
neurosurgery	97	21	76
Mortality in ICU (%)[a]	102 (22%)	92 (33%)	10 (4%)
Mortality after ICU discharge (%)[a,e]	32 (9%)	20 (11%)	12 (5%)

[a] Second and third admissions not analysed (first admissions, n = 469).
[b] APACHE II score was determined for 386 admissions.
[c] Including pulmonology, cardiology, neurology and anaesthesiology.
[d] Including neurosurgery, ENT, cardiopulmonary surgery, gynaecology and urology.
[e] Percentage of patients that died after discharge from ICU to hospital ward.

Table III. Bacteriologically proven and non-bacteriologically proven infections

Sites	Category	Intubated (n = 276)		Non-intubated (n = 239)		All admissions (n = 515)
		non-ICU-acquired	ICU-acquired	non-ICU-acquired	ICU-acquired	
Respiratory tract	BPI	17	58	2	–	77
	non-BPI	32	23	9	–	64
Abdominal	BPI	12	15	2	–	29
	non-BPI	12	2	2	–	16
Sepsis eci	BPI	5	10	2	–	17
	non-BPI	6	2	1	–	9
Tissue (wound, bone, etc.)	BPI	9	7	3	–	19
	non-BPI	–	1	1	–	2
IV-line-related sepsis	BPI	–	11	–	–	11
	non-BPI	–	–	–	–	–
Central nervous system	BPI	3	1	3	–	7
	non-BPI	–	1	1	–	2
Urosepsis	BPI	1	5	–	–	6
	non-BPI	2	–	–	–	2
Urinary tract	BPI	1	4	1	–	6
	non-BPI	–	–	–	–	–
Bacteraemia	BPI	–	5	–	1	6
	non-BPI	–	–	–	–	–
Endocarditis	BPI	–	–	1	–	1
	non-BPI	–	–	–	–	–
All	BPI	48	116	14	1	179
	non-BPI	52	29	14	–	95

BPI, bacteriologically proven infection; non-BPI, non-bacteriologically proven infection.

All diagnoses of BPI of the respiratory tract were established on positive quantitative culture results of samples obtained by protected specimen brush and/or bronchoalveolar lavage. Twenty-two patients were treated for pneumonia despite non-significant culture results from bronchoscopy. These cases, therefore, did not fulfil the criteria for BPI. Although bronchoscopy is not recommended within 48 h after institution or change of antibiotic therapy, this procedure was, in fact, performed within this time period in nine patients. Despite negative culture results, new antibiotics were prescribed for these patients. Although the remaining 13 patients had not received antibiotics before bronchoscopy and had negative or non-significant culture results, their clinical condition necessitated antibiotic therapy in the opinion of the physician in charge. In 42 (66%) cases of a non-BPI of the respiratory tract no bronchoscopy was performed, either because of logistical problems ($n = 12$), or because the infection was considered to be community- or hospital-acquired (non-ventilator-associated) in which cases we do not routinely perform bronchoscopy ($n = 30$). Moreover, a number of these patients were not intubated. During the study period, another 48 bronchoscopies were performed when pneumonia was suspected, but culture results were negative and no antibiotic treatment was instituted. These episodes were not labelled as non-BPI.

Microorganisms and antibiotic susceptibility

Among the isolated microorganisms considered as the causative agent of infection (Table IV), Gram-negative bacteria were isolated most frequently (mainly Pseudomonadaceae and *E. coli*).

All isolates cultured during 1994 from samples from both ICUs were analysed to determine the percentage of isolates of *P. aeruginosa*, *E. coli*, *S. aureus* and *E. faecalis* that were susceptible to the tested antibiotics. All strains of *S. aureus* were susceptible to methicillin and flucloxacillin, and all isolates of *E. faecalis* were susceptible to amoxycillin and vancomycin. Of the Gram-negative microorganisms, all isolates of *E. coli* were susceptible to ceftazidime, ciprofloxacin and gentamicin and >90% were susceptible to cefuroxime and co-amoxiclav. More than 95% of *P. aeruginosa* isolates were susceptible to gentamicin, piperacillin, ceftazidime and ciprofloxacin; all isolates were susceptible to imipenem.

Indications for antibiotics

Antimicrobial therapy was prescribed in 312 (61%) of 515 admissions. Among intubated patients, 74% received antibiotics as compared with 45% of non-intubated patients (chi-square test, $P < 0.00001$).

Table IV. Microorganisms isolated according to type and site of infection

Microorganisms	Type of infection		Site of infection		
	BPI	non-BPI	respiratory	abdominal	other
E. faecalis	27	2	6/29	10/29	13/29
S. aureus	33	11	26/44	1/44	17/44
Other *Staphylococcus* spp.	19	–	–	4/19	15/19
Streptococcus pneumoniae	8	11	18/19	–	1/19
Other *Streptococcus* spp.	18	2	7/20	4/20	9/20
E. coli	41	10	27/51	15/51	9/51
Other facultative aerobic					
Gram-negative species	44	7	25/51	11/51	15/51
Pseudomonadaceae	45	14	45/59	4/59	10/59
Others					
Anaerobes	8	–	–	6/8	2/8
Bacillus cereus	1	–	1/1	–	–
Corynebacterium sp.	1	–	–	–	1/1
Cytomegalovirus	1	–	1/1	–	–
Fungi	6	2	4/8	1/8	3/8
Haemophilus influenzae	9	10	19/19	–	–
Legionella sp.	2	–	2/2	–	–
Neisseria meningitides	5	–	2/5	–	3/5
No microorganisms isolated	–	45	16/45	15/45	14/45
Number of isolates/total					
number of isolates	268/337	69/337	183/337	56/337	98/337

BPI, bacteriologically proven infection; non-BPI, non-bacteriologically proven infection.

In all, 710 prescriptions of antibiotics were recorded; 574 (81%) prescriptions for intubated and 136 (19%) for non-intubated patients. In the intubated patients, 51% of antibiotic prescriptions were used for BPI, as compared with 31% for non-BPI and 18% for prophylaxis. For non-intubated patients these percentages were 19%, 15% and 66% respectively. Moreover, intubated patients, when compared with non-intubated patients, were treated with more prescriptions (means of 3 and 1 per patient, respectively), more courses of antibiotics (means of 2 and 1 per patient, respectively) and for a longer period (means of 11 and 3 days, respectively).

Patients were treated with antibiotics for 2430 of 4091 patient days (59%). Intubated patients received antibiotics for 2145 of 3434 patient days (63%), and non-intubated patients for 285 of 657 patient days (43%) (chi-square test, $P < 0.00001$).

Of all prescriptions of antibiotics indicated for therapy, 49% were administered for respiratory tract infections, 19% for abdominal infections and 13% for sepsis eci.

Respiratory tract infections, the most important site of infections in ICU patients, accounted for 41% of total antibiotic use for BPI and for 63% of antibiotic use for non-BPI.

Types of antibiotics

The five most frequently used antibiotics in BPI (expressed as percentage of total number of prescriptions used) were: co-amoxiclav (26%), aminoglycosides (24%), piperacillin (8%), ciprofloxacin (8%) and glycopeptide antibiotics (6%). For the group of non-BPI the most frequently used antibiotics were quite similar: co-amoxiclav (38%), aminoglycosides (23%), piperacillin (10%), ciprofloxacin (5%) and metronidazole (4%). The five most frequently used antibiotics for prophylaxis were: flucloxacillin (43%), cefuroxime (17%), aminoglycoside antibiotics (14%), co-amoxiclav (13%) and metronidazole (9%). The frequent use of flucloxacillin in this group is due to the routine prophylaxis with this agent in neurosurgical patients.

Total consumption in PDD and costs of antibiotic therapy

Altogether, 3767 PDD were prescribed for a total amount of Dfl 212,823. In intubated patients, 3387 (90%) PDD were prescribed corresponding to Dfl 200,195 (94% of total cost). In non-intubated patients 380 (10%) PDD were prescribed thus accounting for Dfl 12,629 (6% of total cost).

The largest proportion of PDD (58%) was used for BPI, accounting for 68% of all costs for antibiotic use. Approximately 29% of total PDD was prescribed for non-BPI which represented 25% of the total costs.

Finally, only 13% of all PDD (7% of all costs) was administered for prophylactic use.

Overall, β-lactam antibiotics accounted for 56% of the usage in PDD, corresponding to 56% of the total cost. The aminoglycoside antibiotics accounted for 21% of the usage in PDD, but corresponded to only 12% of the total cost (Table V).

The antibiotic consumption was 92.1 PDD/100 bed days accounting for 52 Dfl/bed day. Comparison of these ratios for the three groups of patients yielded the following results: 84.9 PDD/100 bed days and 47 Dfl/bed day for medical patients, 100.5 PDD/100 bed days and 56 Dfl/bed day for surgical patients and 80.5 PDD/100 bed days and 52 Dfl/bed day for trauma patients.

Discussion

The results of this one-year longitudinal surveillance show that 36% of patients admitted to a general ICU had at least one infection during their ICU stay. Of all ICU-acquired infections, 99% occurred in intubated patients. As a result, 90% of total antibiotic use and 95% of the costs for antibiotics were spent in this group. Furthermore, the respiratory tract was by far the most important site of infection, accounting for 43% of BPI and 67% of non-BPI. Under the circumstances tested, reduction of antibiotic use may be achieved most successfully by shortening duration of therapy for respiratory tract infections or reducing prescriptions for BPI by means of infection prevention.

The methods used in the present study provide a simple way to analyse incidence and prevalence of infection and the amount of antibiotic use. We feel that this method of registration would be suitable for others to use, both in other intensive care wards, and in general hospital wards. The most important aspect in this regard is, in our opinion, the distinction between BPI and non-BPI. In addition, by using predefined criteria for infection, the impact of different types of infection on antibiotic use and costs can be easily calculated and flaws such as the variations in interpretation of diagnostic criteria for infection, inevitable in large multi-centre studies, are avoided. The EPIC study was performed by questionnaire and the investigators had to rely on the correct use of the CDC definitions for nosocomial infections by physicians of the 1417 participating ICUs.[5,13] Difficulties in diagnosis of infection in critically ill patients pertain, in particular to respiratory tract infections.[14] Moreover, differences between centres regarding antibiotic susceptibilities weaken the relevance of resistance data obtained from a continent-wide study. This is clearly demonstrated by the antibiotic susceptibilities of the pathogens in our ICU: all *S. aureus* strains were methicillin-sensitive, 97% of *P. aeruginosa* strains were susceptible to gentamicin and 100% to imipenem, and all enterococci were susceptible

Table V. Antibiotic use in prescribed daily doses and cost according to indication

Antibiotics	Prescribed daily doses				Costs in Dutch florins[a]			
	total	prophylactic	BPI	non-BPI	total	prophylactic	BPI	non-BPI
Aminoglycoside antibiotics[b]	774	67	460	238	26,208	2339	16,544	7325
β-Lactam antibiotics								
penicillin	50	–	47	3	1601	–	1505	96
flucloxacillin	283	167	97	19	4687	2766	1606	315
amoxycillin	61	6	33	22	554	54	300	200
co-amoxiclav	1094[c]	79	585	426	37,021[c]	2673	19,796	14,416
piperacillin	314	6	184	124	35,457	678	20,777	14,002
co-ticarclav	105	–	72	33	19,963	–	13,689	6274
cephalosporins	211	61	115	35	17,680	2381	12,428	2871
aztreonam/imipenem	6	–	6	–	1253	–	1253	–
Ciprofloxacin	273	–	215	58	19,262	–	15,170	4092
Chloramphenicol	35	–	28	7	275	–	220	55
Clindamycin	23	–	18	5	1536	–	1202	334
Co-trimoxazole	31	–	10	21	264	–	85	179
Erythromycin	76	–	30	46	332	–	131	201
Glycopeptide antibiotics[b]	196	19	173	4	35,065	2403	32,156	506
Metronidazole	104	51	34	19	749	367	245	137
Rifampicin	31	–	29	2	763	–	714	49
Other antimicrobial agents	100	15	60	25	10,153	1530	5814	2809
Total PDD and cost	3767	480	2196	1087	212,823	15,191	143,635	53,861

[a] 100 Dutch florins approximately equals US$60 and £40 sterling.
[b] The costs for routine serum-antibiotic titre (3/week) were taken into account.
[c] Co-amoxiclav was prescribed once for unknown reason for 4 days.

to amoxycillin and vancomycin. The relationship between antibiotic use and the emergence of antibiotic resistance has been demonstrated frequently.[15,16] Our data, therefore, suggest that the relative lack of significant resistance in nosocomial pathogens in our ICU is a result of restrictive antibiotic policy in our hospital for many years.

Despite major difficulties in study epidemiology we compared several outcome data from our study with those from the EPIC study.[5] In the EPIC study, which was a one-day point-prevalence study, the prevalence of infection was 45%. This probably means that 45% of the patients were treated for infection (at the day of the study). In our study, 36% of the patients had at least one infection during their ICU stay, but were treated for infection on 48% of all patient days, similar to the percentage found in the EPIC study. Infections of the respiratory tract were diagnosed most frequently in both studies, 65% of all infections in the EPIC study and 51% in the present one. Urinary tract infections also are frequently implicated in nosocomial infections.[2,7] This type of infection was seen in 18% of patients in the EPIC study but only 5% of patients in our study. This difference may be explained by our policy to perform routine bladder irrigation with chlorhexidine 0.02% if a bladder catheter is *in situ* and twice-weekly routine replacement of urinary

catheters in case of asymptomatic bacteriuria (i.e. positive urinary cultures without clinical evidence of infection). Antimicrobial therapy is instituted only when urine cultures are persistently positive in spite of the above mentioned regimen and clinical signs of infection develop. Another interesting difference between the EPIC study and ours, is the use of cephalosporins. Forty-four per cent of patients on antibiotics received cephalosporins in the EPIC study as compared with only 8% in the present study. The excellent susceptibility patterns of the isolates cultured in our study partly explain this difference.

Many conditions are known to mimic the signs of infection, especially in critically ill patients.[17] Consequently, antibiotics will often be prescribed unnecessarily. Although it is clear that BPI must be treated, the distinction between BPI and non-BPI, according to the definitions applied in the present study, may help to identify unnecessary antibiotic use. However, due to delay in obtaining culture results and the possibility of false negative results, we accept that in a proportion of the non-BPI treatment should be given anyway. Reduction in antibiotic use in this group of infections may only be achieved by decreasing the prescriptions. In our setting even an estimated reduction of 25% in antibiotic prescriptions for non-BPI would only result in a 7% decrease in the total

number of PDD in ICU and a 6% reduction in total antibiotic costs. Therefore, in our ICU, a significant reduction in antibiotic use could be achieved either by preventing infection or by shortening the duration of antibiotic therapy.

Few data are available on the optimal duration or route of antibiotic therapy for ICU-acquired infections. For example, although the guidelines of the American Thoracic Society advise that community-acquired pneumonia is treated for 7–10 days, no comparative trials on this issue are available.[18] Therefore, future studies evaluating the minimal duration of therapy for nosocomial infections may eventually lead to a decrease in antibiotic use.

Prevention of infections has the highest potential to reduce the enormous antibiotic use in ICUs. Surveillance of infection may help to determine the most prevalent infection and the most important pathogens involved. In our ICU, and in many other European ICUs, respiratory infections have the highest incidence. The use of more specific criteria to diagnose nosocomial pneumonia, for instance with bronchoscopic techniques, may help to rationalize antibiotic use, although a prospective study addressing this question is not yet available.

Implementation of control of infection measures are critical in order to limit the possibility of cross-infections.[19] Many other specific measures have been shown to reduce the incidence of nosocomial pneumonia.[20] However, their true impact and cost-effectiveness are as yet unclear.

In conclusion, surveillance studies on antibiotic use, indications for prescription, incidence of infection and distinguishing between bacteriologically proven and non-bacteriologically proven infections may help to develop local strategies to reduce antibiotic use. The findings of this study suggest that in our setting prevention of respiratory tract infections has the greatest potential to reduce overall antibiotic use and costs. In addition, studies evaluating the optimal duration of antibiotic therapy may help to reduce unnecessary antibiotic use.

Acknowledgement

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