

Longitudinal surveillance of antibiotic use in the hospital

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Received 19 September 2000 and in revised form 30 November 2000

Summary

We evaluated antimicrobial use in our hospital by department, including indications for use, source of infections, use of the microbiology laboratory, and appropriateness of prescribing, in a prospective, comparative, non-interventional study of all patients receiving antimicrobial agents. We excluded departments where antimicrobial use was negligible. The other 19 departments were followed for 3 ($n=4$) or 4 ($n=15$) months, including 2 consecutive months in the spring-summer and either 1 or 2 in the autumn-winter. Antimicrobial therapy was followed from initiation, through possible adaptations, and possible change from intravenous to oral therapy, until discontinuation of treatment. Overall, 6376 antibiotics were given to 2306 patients. Of the surveyed hospitalized patients, $62\% \pm 22\%$ received antibiotics, with a range of 4–100% per department. Antibiotics were prescribed for infections acquired in the community (3037 instances, 47%), in the hospital (2182, 34%), in a nursing home (575, 9%), and for prophylaxis continued post-operatively (582, 9%). The most common indications for antimicrobial use were: respiratory tract infection (1729, 27%), urinary tract infection (955, 15%), sepsis (701, 11%), intra-abdominal infections (663, 10%),

prophylaxis 582 (9%), soft-tissue infection (572, 9%), and surgical site infection (319, 5%). Univariate indicators for appropriateness of treatment were: age, department, site of infection, source of infection, antimicrobial drug and serum creatinine (all $p < 0.001$). Forty-nine antimicrobials were prescribed in 279 combinations, 58% as single agent and 42% as drug combinations. Half of all antimicrobial use consisted of four agents: cefuroxime (19.1%), metronidazole (11.3%), gentamicin (10.6%) and ampicillin (10.2%), which together accounted for 20% of expenditure on antibiotics. Although use of as many as 53% of antimicrobials (26/49) surveyed was restricted, use in this category accounted for only 29% of all antimicrobial courses. Of 6376 antibiotic courses, 4101 (64%) were given intravenously and 2275 (36%) orally. Appropriateness of use of restricted drugs was lower (70%) than of unrestricted ones (84%, $p < 0.001$). Of 24 571 defined daily doses (DDD) given orally, 4587 (19%) were restricted, compared to 7264 (34%) of 21 602 DDDs given intravenously ($p < 0.001$). Antibiotic treatment in our hospital appears to be substantial and increasing, justifying efforts to improve appropriateness of therapy and improve clinical and financial results.

Introduction

Many infectious diseases have been brought under control in the 20th century, by improved living conditions, public health measures, vaccinations

and antimicrobial agents. Early optimism about the approaching end of all bacterial infections was premature, and in the last two decades there has

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been an increase in infectious disease morbidity and mortality.¹ In addition, many organisms have developed resistance to antibiotics to which they used to be susceptible, prompting the development of more broad-spectrum—and expensive—agents.^{2,3} With the growing need for broad-spectrum agents, have come reports of inappropriate antimicrobial drug use, which contributes to the development of resistance and wastes resources.^{4–8} Most of these studies are point-prevalence studies and pharmaceutical reviews.^{5–12}

The purpose of the current study was to generate up-to-date information on antimicrobial use in our hospital: overall use per department, indications for use, source of infections, utilization of the clinical microbiology laboratory, and appropriateness of use. We used a prospective and longitudinal approach rather than the point-prevalence method. Antimicrobial therapy was followed from initiation, through possible adaptations, possible change from intravenous to oral therapy, until discontinuation of treatment. Each department was followed for 3 or 4 months, including 2 consecutive months in the spring-summer and 1 or 2 in the autumn-winter.

Methods

This study was done in the Shaare Zedek Medical Center, a 528-bed university-affiliated institution. The hospital contains all major services and departments, including medical and surgical subspecialties, haematology-oncology, and neonatal, paediatric, medical and surgical intensive care units. The hospital serves the general population of Jerusalem; a substantial proportion of the patients are elderly, many of whom are referred from nursing homes. The infectious diseases unit has issued protocols for empiric antimicrobial use for the most frequently encountered conditions, including treatment and prophylaxis.¹³ These protocols are based on recommendations published in the literature, as well as on data from the clinical microbiology laboratory and locally available antimicrobial agents.^{14–16} Protocols are concise and arranged in easy-to-use table-format; examples of frequently-used protocols are attached (Appendix). As a matter of policy, aminoglycosides are the drugs of choice for empirical treatment of infections caused by Gram-negative bacilli, e.g. intra-abdominal and urinary tract infections and most nosocomial infections. In instances where organisms other than Gram-negative bacilli are expected to be involved, another agent is added to cover the additional organisms. When the estimated creatinine clearance^{17,18} is below

30 ml/min, clinicians are advised to use an alternative agent to aminoglycosides, such as quinolones, third or fourth generation cephalosporins, or β -lactams (piperacillin-tazobactam, aztreonam, or a carbapenem). Our hospital has changed aminoglycoside therapy from three-times-daily to once-daily dosing in 1996. Although this reliance on aminoglycosides as a matter of policy is not universally applied, it was intended to decrease use of β -lactam antimicrobials and delay associated emergence of extended-spectrum β -lactamase-producing Gram-negative bacilli.^{32,34}

The study was prospective and observational (i.e. non-interventional), and was conducted throughout 1998. Each department was enrolled for review of all antimicrobial usage for two consecutive months in the summer and one or two in the winter, for a total of four months. Enrolled were: three medical departments, three geriatric departments, the emergency department, paediatrics, paediatric surgery, general surgery, vascular surgery, urology, orthopedics, chest and cardiac surgery, plastic surgery, gynaecology, the general intensive care unit, the neonatal intensive care unit, and the paediatric intensive care unit. Excluded from this study were the following departments, where antimicrobial use was deemed negligible: otorhinolaryngology and ophthalmology (together 25 beds), cardiology (35 beds) and the coronary intensive care unit (six beds), and outpatient institutes. Enrolled departments accounted for a total of 310/376 acute care beds (82%). Also excluded from this study was the maternity service, a facility including a ten-bed delivery suite, 76 beds for mothers for up to 48 h postpartum, and 76 infant cribs.

One of the investigators, a clinical pharmacist, visited the departments at least five times a week and reviewed the patients' drug records. On each visit, the number of admitted patients was recorded as well as the number and percentage of patients receiving antimicrobial agents. The clinical records of patients receiving an antimicrobial agent were reviewed for pertinent demographic and clinical data, which were extracted and entered into a patient-specific form. Obtained data included: age; sex; date of admission and duration of admission; the diagnosis for which the drugs were given; whether the infection was acquired in the community, hospital or nursing home; the kind of antimicrobial(s) prescribed; changes in antimicrobial management; baseline serum creatinine; use of relevant cultures and response to laboratory results; oral vs. parenteral therapy; and duration of treatment. Patients were followed until all antimicrobial treatment was discontinued. If, subsequently, antibiotic treatment was resumed,

the patient was recorded as a new patient if at least 3 days had lapsed between discontinuation of the previous and initiation of the new antibiotic course, and the indication for the new course differed from that of the previous antibiotic course. No attempt was made to verify data from the medical record by examining patients or interviewing the medical or nursing staff. Additional sources of information were computerized records from the hospital's pharmacy on antimicrobial usage, and reports from the clinical microbiology laboratory.

Infections were considered to have been acquired in the community unless the patient was admitted from a nursing home because of an infection. A hospital-acquired infection was defined as one that was diagnosed 72 h or more after admission, where there was no obvious relation between the specific infection and the original reason for admission.^{19,20} Appropriateness of antibiotic treatment was determined according to compliance with protocols issued by the hospital's infectious disease unit as previously described.¹³ Whenever there was doubt regarding appropriateness of the employed antimicrobial regimen, this was discussed by at least two investigators and mostly condoned.

Data were entered into a computer program (Epi Info 6.04c, Centers for Disease Control and Prevention); statistical analysis was carried out with tools provided by the same program, mainly Student's *t* test, Fischer's exact test, and χ^2 analysis. Univariate regression analysis was done to determine possible indicators for inappropriateness of antimicrobial treatment.

Results

Of the 19 enrolled departments, four departments were observed for 3 months each, while the remaining 15 departments were observed for 4 months each, making a total of 72 department-study months. In these study periods, a total of 6376 antibiotics were given for 2951 infections to 2306 patients, of whom 1075 (47%) were female and 1231 (53%) male. In addition, there were 44 patients who received antimicrobial treatment but who were not included because their records were unretrievable. Of the surveyed hospitalized patients, 62% \pm 22% received antimicrobial therapy, with a range of 4% to 100% per department (Table 1). Of the patients receiving antibiotics, 58% were \geq 61 years old, 21% were 21–60 years and 21% were \leq 20 years. Antibiotics were given for infections acquired in the community (3037 instances, 48%), in the hospital (2182, 34%), in nursing homes (575, 9%),

and for prophylaxis continued post-operatively (582, 9%) (Table 2). Indications for antimicrobial treatment are presented in the same table. Overall appropriateness of treatment was 80% \pm 9%, with a range of 62–94% per department ($p < 0.001$).

Forty-nine antimicrobials were prescribed in 279 combinations, 58% as single agent, and 42% as drug combinations. The 20 most frequently prescribed antimicrobial courses are shown in Table 3. Fifty percent of all antimicrobial use consisted of four agents: cefuroxime (19.1%), metronidazole (11.3%), gentamicin (10.6%) and ampicillin (10.2%). These four antimicrobial agents, whose use is unrestricted in our hospital, as in most others, together accounted for 20% of total expenditure on antibiotics (Table 4). Although as many as 53% of antimicrobials (26/49) surveyed in this study were restricted, use in this category accounted for only 29% of all antimicrobial courses. Of the total of 6376 antimicrobial drug courses, 2275 (36%) were entirely provided by the oral route, 4101 (64%) intravenously. Restricted antimicrobials were more often given intravenously (61%) than unrestricted ones (42%, $p < 0.001$), and appropriateness of use of restricted drugs was lower (70%) than that of unrestricted drugs (84%, $p < 0.001$). This study involves 37 283 patient days; a total of 24 571 defined daily doses (DDD) were given orally (i.e. 66 DDD/100 bed days), and 21 602 DDD were given intravenously (i.e. 58 DDD/100 bed days). Of 66 DDD/100 bed days given orally, 12 (18%) were restricted; of 58 DDD/100 bed days given intravenously, 19 (33%) were restricted ($p < 0.001$). The mean duration of treatment was 5.8 \pm 5 days, with a median of 4 days and a range of 1–87 days. Reasons for discontinuation of treatment were, in order of decreasing frequency: discharge from hospital (1976 courses, 31%); completion of treatment (1896, 29.7%); change to another intravenous antimicrobial (849, 13.3%); change from an intravenous to an oral drug (710, 11.1%); change from one to another oral antimicrobial (660, 10.4%); death (208, 3.3%); change from an oral to an intravenous drug (77, 1.2%).

Univariate analysis of indicators for appropriate antimicrobial therapy revealed that male and female patients received appropriate treatment at the same rates (80%). Six indicators were identified with which appropriateness of therapy could be determined: age, serum creatinine, department, source of infection, antimicrobial drug, and site of infection. Of patients 10 years old or younger, 87% received appropriate therapy, compared to 78% of patients 11–20 years old, 63% of patients 21–60 years old, and 79% of patients 61–100 years old ($p < 0.001$). Of patients with normal serum

Table 1 Number of patients receiving antimicrobial agents during the study periods, by department

Department	No. of patients hospitalized in department (\pm SD) ^a	Percentage of patients receiving antibiotics (\pm SD) ^b	No. of patients receiving antibiotics	DDD ^c per 100 bed-days	Appropriate antibiotic treatment (%)
Medicine ^d	65 \pm 2	64 \pm 13	532	173 \pm 32	83 \pm 2
Geriatrics ^d	40 \pm 2	66 \pm 14	263	128 \pm 35	81 \pm 1
Emergency ^e	11 \pm 2	68 \pm 15	92	NA	94
Paediatrics	22 \pm 4	72 \pm 12	282	65	92
Surgery	35 \pm 4	49 \pm 13	246	149 \pm 39	80 \pm 3
Subspecialties ^f	101 \pm 5	52 \pm 13	740	68 \pm 32	71 \pm 10
ICU + PICU ^g	9 \pm 1	85 \pm 14	56	232 ^h	83 \pm 1
NICU ^g	20 \pm 3	35 \pm 14	95	15	94
Total	303 \pm 7	62 \pm 22	2306	124 ⁱ	80 \pm 9 ^j

^aNumber of patients admitted to the particular ward on survey days. ^bPercent of admitted patients receiving antibiotics on survey days. ^cDDD, defined daily dose, see Methods for definition. ^dThree medical departments combined, three geriatric departments combined. ^eEmergency: patients receiving antibiotic treatment before being admitted to a hospital department. ^fSurgical subspecialties. Includes: paediatric surgery (16 \pm 3 admitted patients), cardiac surgery (20 \pm 5), plastic surgery (11 \pm 2), urology (12 \pm 3), gynaecology (23 \pm 5), orthopedics (19 \pm 3). ^gICU, intensive care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit. ^hDDDs/100 bed-days for ICU 232, for PICU 25. ⁱTotal DDD/100 bed-days = 100 \times (46173 DDD/37283 bed-days). ^jThe differences between rates of appropriateness was highly significant ($p < 0.001$).

Table 2 The most frequent indications for courses of antimicrobial therapy, breakdown by source of infection

Infection	n (%)	Source of infection (%)			Appropriate ^c (%)
		Community	Hospital	Nursing home	
Respiratory tract	1729 (27)	52	31	17	84
Urinary tract	955 (15)	58	27	15	80
Sepsis	701 (11)	30	66	4	88
Intra-abdominal	663 (10.4)	62	30	8	90
Prophylaxis ^a	582 (9.1)	8 ^b	92	0	53
Soft tissue	572 (9)	78	17	5	80
Surgical site	319 (5)	17	82	1	68
Pelvic infection	148 (2.3)	80	20	0	72
Ear-nose-throat	108 (1.7)	78	22	0	86
Line-associated	100 (1.6)	14	86	0	71
CNS infection	98 (1.5)	61	39	0	94
Fungal	98 (1.5)	9	85	6	99
Gastroenteritis	74 (1.2)	43	43	14	97
Bone and joint	40 (0.6)	43	40	17	88
Endocarditis	38 (0.6)	58	34	8	95
Other	151 (2.4)	72	26	2	83

^aProphylaxis given once only in the operating room prior to surgery was not included in this study. Prophylaxis in this analysis indicates antibiotics provided in the departments subsequent to operation, as well as post-exposure prophylaxis. ^bImmunocompromised hosts, vesiculo-ureteral reflux or recurrent UTI in children. ^cThe differences between rates of appropriateness was highly significant ($p < 0.001$).

creatinine (defined as ≤ 1.3 mg/dl), 80% received appropriate antimicrobial treatment, compared with 83% of patients with creatinine > 1.3 mg/dl ($p < 0.05$). Appropriateness of treatment varied among the departments, with a range of 62% (urology) to 94% (neonatal intensive care unit)

(Table 1, $p < 0.001$). Source of infection appeared to be an indicator of appropriateness of treatment: 87% of community-acquired infections received appropriate antimicrobial therapy, compared to 76% of nosocomial infections and 87% of infections acquired in nursing homes (Table 2,

Table 3 The 20 most frequently prescribed antimicrobial courses (single drugs and/or combinations)

No.	Antimicrobial	<i>n</i> (%)	Appropriate ^a (%)
1	Cefuroxime	726 (16.8)	69
2	Ampicillin and gentamicin	292 (6.7)	96
3	Cefazolin	276 (6.4)	82
4	Amoxicillin-clavulanate	225 (5.9)	58
5	Ciprofloxacin	215 (5)	60
6	Cefuroxime and metronidazole	172 (4)	90
7	Ampicillin and gentamicin and metronidazole	141 (3.3)	91
8	Cephalexin	122 (2.8)	54
9	Cefuroxime and roxithromycin	95 (2.2)	96
10	Cotrimoxazole	95 (2.2)	66
11	Metronidazole	81 (1.9)	93
12	Cloxacillin	73 (1.7)	79
13	Ceftazidime	64 (1.5)	64
14	Ampicillin and ciprofloxacin	63 (1.5)	92
15	Ciprofloxacin and metronidazole	58 (1.3)	74
16	Vancomycin	56 (1.3)	88
17	Amoxicillin	53 (1.2)	89
18	Ampicillin and cipro and metronidazole	52 (1.2)	83
19	Gentamicin	52 (1.2)	90
20	Cefuroxime and gentamicin	51 (1.1)	76

^aThe differences between rates of appropriateness was highly significant ($p < 0.001$).

Table 4 Restriction and appropriateness of antimicrobial use

Characteristic (<i>n</i>)	Restricted use <i>n</i> (%)	Unrestricted use <i>n</i> (%)
No. of antimicrobials (49)	26 (53)	23 (47)
Antimicrobial courses (6376)	1845 (29)	4531 (71)
Defined daily doses/100 bed days		
Intravenous—58	19 (61)	39 (42)
Oral—66	12 (39)	54 (58)
Appropriateness of use (5114, 80%)	1297 (70)	3817 (84)

Of all intravenous antimicrobial use, 19/58 (33%) was in the restricted category. Of all oral antibiotic use, 12/60 (18%) was in the restricted category ($p < 0.001$). The difference between restricted and unrestricted use was highly significant ($p < 0.001$).

$p < 0.001$). Use of certain prescribed drugs carried a low appropriateness rate, e.g. cephalexin (54%) and amoxicillin-clavulanate (58%), others a high appropriateness rate, e.g. ampicillin and gentamicin (96%) (Table 3, $p < 0.001$). Finally, the rate of appropriateness varied according to infection, with a range of 53–99% (Table 2, $p < 0.001$).

Discussion

Much concern has been voiced in the last two decades about the widespread use of antimicrobial agents, including broad-spectrum antibiotics, leading to emergence of multiple-drug-resistant

organisms. In addition, it has been repeatedly demonstrated that 30–60% of use of these agents is inappropriate, with consequent waste of resources. Many hospitals have attempted to modify these worrying trends by supervising use of certain antimicrobial agents, with various degrees of success. Drug use evaluations have been shown to complement these efforts, and may provide valuable information on actual drug use. Cost constraints dictate that most studies on antimicrobial usage are point-prevalence surveys or retrospective analyses.

The purpose of the current study was rather ambitious, namely to generate up-to-date information on antimicrobial use in the hospital: overall

use per department, indications for use, source of infections, utilization of the clinical microbiology laboratory, and appropriateness of use. We therefore used a prospective and longitudinal approach rather than the commonly used point-prevalence method. Upon completion of the first year of the study, the results of which are the subject of this paper, the data were analysed and widely distributed throughout our hospital in order to improve drug use. Subsequent antimicrobial drug use is currently being assessed in a second year, similar in design to the first phase of the study.

The first major finding of this study is that $62\% \pm 22\%$ of the surveyed hospitalized patients received antibiotics, with a range of 4–100% per department. We included all departments except otorhinolaryngology, ophthalmology and cardiology, where antimicrobial use is negligible. The included departments account for 82% of the hospital's acute care beds; therefore, even if there was no antimicrobial use at all in the excluded departments, an overall mean of 52% of admitted patients would still receive antimicrobials. Figures reported from one to two decades ago indicated that up to one third of admitted patients at that time received antimicrobial treatment. A recent study from Raz *et al*¹² using a point-prevalence method to assess seven community hospitals in Northern Israel, found that 30% of admitted patients received an antimicrobial on the particular day of evaluation, with a range of 25–39%. A European study from the early 1990s reported figures closer to ours: 42% (1954 patients) of a German cohort of admitted patients received antibiotics; 44% (1950 patients) of a French cohort; 46% (1597) of an English cohort; 53% (1766) of an Italian cohort; and 55% (1234) of a Spanish cohort.²¹ Case mix may vary considerably among hospitals. Thus, for example, including the large maternity service of our hospital in this study would significantly influence and hence bias the results of our study. We believe it is more relevant to compare interhospital figures per department in the same discipline rather than overall data on antibiotic use. We think our figures are both accurate and reliable, as they derive from a near-daily assessment of all admitted patients in the departments under observation for 30–60 days. To the best of our knowledge, this method has not been previously described. In developing countries, the percent of admitted patients receiving antimicrobials may be much higher, as the principal indication for admission consists of infectious diseases.²² However, it certainly appears from the European study just described, and particularly from the current one, that the percent of admitted patients receiving antimicrobials in developed

countries is much higher than that reported in the 1970s and 1980s. Although, as mentioned, the longitudinal rather than point-prevalence method used could possibly explain part of the differences, we believe that the high percentage of admitted patients receiving antimicrobials found in this study, reflects an important trend, that increasing numbers of admitted patients harbour bacterial infections. Patients in hospitals are nowadays on average older, more severely ill and more immunocompromised than two or three decades ago, and consequently they contract more bacterial infections for which antimicrobial agents are prescribed.

The second major finding of this study is that of 6376 prescribed antibiotics, 2182 (34%) were given for infections acquired in the hospital. Considering that 52–60% of admitted patients received antimicrobials, as previously mentioned, the fact that 34% of antimicrobial treatments were for nosocomial infections would indicate that 17–20% of admitted patients developed an infection in the hospital. Even if we had included in this analysis the 152-bed maternity facility, 12–15% of all admitted patients would appear to have received an antimicrobial agent for a suspected or proven nosocomial infection. This figure is considerably higher than that reported in Haley's much cited study.²³ In the latter study of American hospitals from 1975–1976, 5.7% of admitted patients developed a nosocomial infection. European studies suggest a nosocomial infection rate in the range of 9–12% in countries such as England (9%), Belgium (10%) and Denmark (12%).^{21,24,25} There may be several explanations for the much higher figure in our study than those reported elsewhere. First, as previously mentioned, there may be considerable differences in case mix between hospitals. Second, although the Centers for Disease Control and Prevention has issued clear definitions of various nosocomial infections,^{19,20} we used a rather simple and pragmatic one: any infection developing ≥ 72 h after admission, in the absence of an obvious association between the cause of admission and ensuing infection.²⁶ This definition may possibly have led to inadvertent inclusions of community-acquired infections, but also to the exclusion of nosocomial infections which only manifest after discharge, such as certain surgical wound infections. Hence, we consider our figure, if anything, to be on the conservative side. Third, we relied on antimicrobial use as an indicator of the presence of an infectious process; even when subtracting antimicrobial use for post-operative prophylaxis, it remains to be seen whether antibiotic prescription indicates presence of infection. A recently published study addressed this issue regarding the use of antibiotics after coronary artery bypass

surgery;²⁷ antibiotic use had a sensitivity of 95% and a specificity of 85% for the presence of wound infection. Many antimicrobials are prescribed when infection is suspected, not necessarily proven. Hence, we believe that up to 17–20% of admitted patients receive antimicrobials for a *proven or suspected* nosocomial infection. Although the real rate of nosocomial infections could be lower or higher than the figure reported here, this study has demonstrated that a substantial percentage of admitted patients do receive antimicrobial treatment for a proven or suspected hospital-acquired infection. This has important implications for the hospital's expenditure on drug use as well as on the development of microbial resistance. It indicates the urgency and necessity of improved infection control and implementation of measures to augment appropriateness of antimicrobial use.

The rate of appropriateness of antimicrobial drug usage in this study was 80% ± 9%, with a range of 62–94% per department. Various studies published in the last three decades indicate that, using disparate criteria and methods, some 40–70% of antibiotic use is inappropriate.^{8–11,28–30} Therefore, the rate of appropriateness in this study appears to be on average much higher than reported elsewhere, in spite of the very high rate of antimicrobial drug use per admitted patient. There may be various reasons for these dissimilar rates. First, the relevant studies employed entirely different methods. In the current study, the diagnosis for which the antimicrobial was prescribed was neither questioned nor reassessed; rather than appropriateness of antimicrobial use, we assessed adherence to the hospitals' published guidelines for antimicrobial usage;¹³ and drug use evaluation was based on the patient's record, and when in doubt, was condoned. Second, the antibiotic policy itself may influence the rate of appropriateness; well organized, detailed, and easy-to-use recommendations, put in table format could possibly enhance appropriate use of antimicrobials. However, we are not aware of any studies that compare rates of appropriate antibiotic use between similar departments, one with well-organized protocols and one without.

Univariate analysis revealed at least six indicators for appropriateness of treatment: age, department, site of infection, source of infection, antimicrobial drug and serum creatinine (all $p < 0.001$, Tables 1–3). These variables may be universal or hospital-specific; hence, the enormous use of antimicrobial agents dictates that each hospital needs to conduct its own audits in order to assess hospital-specific indicators of (in)appropriateness. The obtained information should serve as a teaching tool to improve antimicrobial drug

use by physicians at all levels. In addition, these assessments will provide information on the efficacy of the hospital's infection control program and restricted antibiotic policy. Although the use of as many as 53% of antimicrobials (26/49) surveyed in our hospital were restricted, use in this category accounted for only 29% of all antimicrobial courses. Appropriateness of use of restricted drugs, despite supervision, was lower (70%) than of unrestricted ones (84%, $p < 0.001$). This suggests the importance of continued and possibly improved supervision and ongoing education of physicians pertaining optimal antibiotic use.³¹

In summary, this hospital-wide, longitudinal survey of antimicrobial usage revealed that 62% ± 22% of admitted patients received antibiotics. As ~34% of all antimicrobial use was for hospital-acquired infections, up to 20% of the total admitted patients received antibiotics for a suspected or proven nosocomial infection. Antibiotic treatment in the hospital appears to be substantial and increasing, justifying and warranting efforts to improve appropriateness of therapy in order to optimize treatment, to slow emergence of drug-resistant organisms and to control expenditure. It seems desirable that each hospital conduct surveillance studies of antimicrobial usage, to identify unique indicators of inappropriate drug use, which could be employed as educational tools to improve antibiotic drug use by physicians.

Acknowledgements

This study was supported by the Israeli Health Ministry Grant no. 4013. Presented in part at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 2000.

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Appendix A: The hospital booklet with guidelines for antimicrobial usage consists of the following protocols, all arranged in table form

No	Topic	No	Topic
I.	<i>Introduction to antibiotic use</i>		
	<ul style="list-style-type: none"> ● General guidelines ● List of restricted antibiotics 		
II.	<i>Major antimicrobial categories</i>		
	<ul style="list-style-type: none"> ● Classification of organisms ● Penicillins ● Cephalosporins ● Macrolides ● Vancomycin ● Aminoglycosides ● Empiric treatment of infections caused by Gram negative bacilli ● Antibiotics for anaerobes ● Antifungal agents 		
III.	<i>Treatment of common infections:</i>		
	<ul style="list-style-type: none"> ● Community acquired pneumonia ● Hospital acquired pneumonia ● UTI in young women ● Lower UTI (oral treatment) ● UTI (intravenous treatment) ● Cellulitis and erysipelas ● Antibiotic associated colitis ● Acute/Subacute meningitis ● Aseptic meningitis ● Febrile neutropenia (6 tables) ● Infections due to tunneled central catheters 		
			<ul style="list-style-type: none"> ● Fungal infections ● Intra-abdominal infections ● Pelvic inflammatory disease ● Hospital acquired sepsis ● Surgical wound infection ● Febrile infant (<2 months) ● Febrile child (2–24 months) ● Common infections in the community
		IV.	<i>Antibiotics for prophylaxis:</i>
			1. Surgical prophylaxis:
			<ul style="list-style-type: none"> ● Principles ● Common surgical procedures and recommendations rephylaxis
			2. Invasive procedure prophylaxis:
			<ul style="list-style-type: none"> ● PEG, Pacemaker, ERCP ● Tunneled central line insertion
			3. Infective endocarditis prophylaxis
			4. Perinatal prophylaxis of GBS
		V.	<i>Dosing of antimicrobials:</i>
			<ul style="list-style-type: none"> ● Dosing in adults ● Adaptation for renal function ● Dosing in children ● Pregnancy and lactation
		VI.	<i>Antimicrobial susceptibility tables:</i>
			<ul style="list-style-type: none"> ● Blood culture isolates ● Urine culture isolates

UTI, urinary tract infection; ENT, ear, nose & throat; Ob/Gyn, obstetrics and gynaecology; PEG, percutaneous endoscopic gastrostomy; ERCP, endoscopic retrograde cholangio-pancreatography; GBS, group B Streptococcus.

Appendix B: Selected protocols for frequently used antimicrobial therapy and prophylaxis

1. Empirical treatment of community-acquired pneumonia

No	Disease	Recommended ^a	Alternative ^a
1	Typical pneumococcal pneumonia ^b	IV penicillin 3 million units ×4/day ^c	In case of penicillin allergy, erythromycin ^d 500 mg ×4
2	Atypical pneumonia (e.g., Mycoplasma, Chlamydia, Q fever)	PO erythromycin ^c 500 mg ×4/day	PO Doxycycline 100 mg ×2/day for 1 day, then once daily ^e
3	All other pneumonias, including acute exacerbation of COPD ^f	a) Mild-moderately ill: PO Cefuroxime axetil, or PO Cefaclor b) Moderately ill: IV Cefuroxime 750 mg ×3/day c) Moderately-seriously ill: IV Cefuroxime 750 mg ×3/day + IV Erythromycin 1 gm ×4 + Consult ID	<ul style="list-style-type: none"> • In case of penicillin allergy: Doxy, Clarithro- or Azithromycin • Consult ID
4	In case of significant aspiration	Treat like 3b or 3c, add metronidazole 500 mg ×3, preferable by enteral route	

^aRecommended doses refer to adult dose, per day.

^bThe typical clinical presentation consists of sudden onset, fever >38.5 °C, rigors, productive cough, ± pleuritic chest pain, with signs of consolidation on examination and chest radiogram. The Gram stain of a good sputum specimen may reveal Gram-positive cocci. Many patients with pneumococcal pneumonia may not have such a distinct clinical picture.

^cThis empirical high dose of penicillin is recommended, because in this country only 65% of pneumococcal strains are fully susceptible to penicillin (minimal inhibitory concentration <0.1 µg/ml); 34% are intermediately susceptible, for which cefuroxime or high dose penicillin is efficacious. Once an isolate (from sputum or blood) is shown to be susceptible, a lower dose of penicillin can be safely used.

^dAlternatively: Erythromycin as syrup, or roxythromycin.

^eAfter eating, with at least one cup of water.

^fCOPD, chronic obstructive pulmonary disease; PO, per os; IV, intravenous; ID, obtain infectious disease consultation.

2. Empirical treatment of hospital-acquired pneumonia^a

No	Disease	Recommended ^b	Alternative
1	Most patients	IV Cefuroxime 750 mg ×3 + IV Gentamicin ^c	In case of immediate type allergy to β -lactams: IV Clindamycin + Gentamicin ^d
2	If pneumonia develops while on gentamicin or after long admission ^e	Same as above, but use amikacin instead of gentamicin	In case of immediate type allergy β -lactams: IV Clindamycin + Amikacin ^d
3	In case of significant aspiration	Same as above, but add metronidazole, preferably PO or per nasogastric tube	If patient cannot receive metronidazole by enteric route: IV metronidazole <i>or</i> IV amoxi-clav + IV Genta/Amika, <i>or</i> see footnote ^d
4	In case of renal dysfunction ^f	IV Ciprofloxacin. If <i>Strep. pneumoniae</i> is suspected (e.g., by sputum gram stain): add IV penicillin	Cipro is prohibited in pregnancy and children. In these cases consider: IV Ceftazidime, Cefepime <i>or</i> Piperacillin-tazobactam ^d
5	Ventilator-associated pneumonia, especially in ICU setting	IV vancomycin ^g + IV Amikacin. In case of significant aspiration: add metronidazole	In case of renal dysfunction ^f : Vanco + Cipro/Cefepime/Pip-tazo ^h <i>or</i> Vanco + Meropenem

^aNosocomial pneumonia due to *Legionella pneumophila* has never been diagnosed in our hospital. However, if a patient is suspected to harbour this infection, select the appropriate regimen from the table and add IV erythromycin 1 g ×4. If the patient is unable to tolerate the high fluid load required with IV erythromycin, consult ID and consider IV ciprofloxacin 400 mg ×3 and adept the regimen (11).

^bRecommended doses refer to adult dose, per day.

^cFor dosing, see appropriate protocol on aminoglycosides.

^dClindamycin and Gentamicin/Amikacin are also excellent second options for nosocomial pneumonia with significant aspiration, in case of serious allergy to β -lactams. Piperacillin-tazobactam, a β -lactam, also covers anaerobes very well.

^eIndicating either previous exposure to gentamicin or greater likelihood of infection due to multidrug resistant organisms.

^fDefined in our hospital as an estimated creatinine clearance of <30 ml/min (32).

^gIn our hospital, 30% of isolates of *Staphylococcus aureus* are methicillin-resistant, while in the intensive care units the rate is close to 90% (30, 33).

^hCiprofloxacin covers fewer Gram-negative bacilli than cefepime or piperacillin-tazobactam. The latter also covers anaerobes.

3. Empirical treatment of urinary tract infection, requiring intravenous treatment (pyelonephritis, urosepsis or acute prostatitis)

No	Disease	Recommended ^a	Alternative ^a
1	Community-acquired urinary tract infection	IV Ampicillin ^b 1 g ×4, and IV Gentamicin ^c	In case of penicillin allergy, provide only gentamicin ^b
2	Same as above, in case of renal dysfunction ^d	PO Ciprofloxacin 500 mg ×2. If patient cannot receive enteral treatment, give IV Cipro 200 mg ×2	In pregnant or lactating women and children: IV ceftriaxone
3	Same as above, in pregnant women	IV Ampicillin ^b 1 g ×4, and IV Gentamicin ^c	In case of penicillin allergy, provide only gentamicin ^b
4	In pregnant women with renal dysfunction	IV Ceftazidime	In case of β -lactam allergy: aztreonam
5	Hospital-acquired urinary tract infection	IV Ampicillin ^b 1 g ×4, and IV Genta or Amikacin ^c	In case of renal dysfunction: PO cipro (see above 2) or ceftazidime or aztreonam

^aRecommended doses refer to adult dose, per day.

^bAmpicillin for coverage of Enterococcus, the causative pathogen in $\pm 5\%$ of patients. If this organism is isolated in a penicillin-allergic patient, ID should be consulted and vancomycin should be prescribed.

^cDose adapted for estimated creatinine clearance. Aminoglycosides are infused as one daily dose, except in pregnant women where 2–3 divided doses are recommended.

^dDefined in our hospital as an estimated creatinine clearance of < 30 ml/min (32).