A study of antimicrobial misuse in a university hospital

DENNIS G. MAKI
ARTHUR A. SCHUNA

Abstract: We undertook a prospective study to determine patterns and sequelae of antimicrobial misuse and factors associated with inappropriate antimicrobial therapy in a teaching hospital. Over an eight-week period, 144 (26.2%) of 549 hospitalized medical and surgical patients received one or more courses of antimicrobial therapy. An average course comprised 1.4 drugs. Presumptive infection was the reason for 70% of courses and prophylaxis, 30%. Therapy was judged appropriate in 59% of courses overall. Unnecessary therapy, poor drug choice (bacteriologically, pharmacologically, or both), or misguided prophylaxis most frequently underlay inappropriate therapy. Adverse reactions (17% overall) were twice as frequent and the cost of therapy was 56% greater in inappropriate courses. Performance of pretherapy cultures (p<0.05), obtaining gram-stained smears of sputum in presumed respiratory tract infections (p<0.001), and notation in the record that antimicrobial therapy had been instituted (p<0.001) were strongly associated with appropriate therapy. This study underscores the need for more effective programs of postgraduate education which stress basic principles of infectious disease and antimicrobial pharmacology and guidelines for prophylaxis. Antimicrobial utilization review should figure heavily in hospital programs of medical self-evaluation. Additional measures to upgrade the use of antibiotics are discussed.

KEY INDEXING TERMS
Antibiotic misuse
Antibiotic overuse
Antimicrobial prophylaxis
Antimicrobial therapy

Recent reports suggest a substantial degree of overuse and misuse of antibiotics* in this country.1-4 Comprising 35% of the national expenditure for drugs,3-4 over 180 million prescriptions for antibiotics are filled in the United States every year.4 Approximately 30% of all hospitalized patients receive one or more antimicrobial agents during their confinement, yet up to two thirds

*The terms antibiotic, antimicrobial, and antimicrobial are used interchangeably in this paper.

From the Infection Control Unit, Department of Medicine and the Department of Pharmacy, University of Wisconsin Hospitals, Center for Health Sciences, Madison.
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Requests for reprints should be addressed to Dennis G. Maki, M.D., Infectious Disease Unit, University of Wisconsin Hospitals, 1300 University Avenue, Madison, Wisconsin 53706.
of these have no evidence of infection.\textsuperscript{1-6}

Despite liberal use of an ever-increasing antimicrobial armamentarium now exceeding 40 generic forms and over 200 proprietary preparations in this country alone, bacterial infec-
tion continues to be a major cause of mo: idiety and mortality.\textsuperscript{7} The incidence of
some life-threatening infections, such as gram-negative rod bacteremia, may actually be rising.\textsuperscript{7,8} Furthermore, emergence of clinically important drug resistance in previously
highly sensitive species such as \textit{Neisseria meningitis} (sulfonamide),\textsuperscript{9} \textit{Staphylococcus aureus} (penicillin and recently methicillin),\textsuperscript{10}
the gonococcus (progressively increasing levels of penicillin),\textsuperscript{9} \textit{Pseudomonas aerugi-
nosa} (gentamicin and carbenicillin),\textsuperscript{11,12} \textit{Shigella} (ampicillin),\textsuperscript{13} \textit{Hemophilus influenzae} (ampicillin),\textsuperscript{14}
and most recently the pneumococcus (penicillin),\textsuperscript{15} is now an unwelcome consequence of an era of heavy use of antibiotics. Superinfections by multiply resis-
tant bacteria or by fungi, often lethal,\textsuperscript{16,17} or toxic or hypersensitivity reactions\textsuperscript{18,19} com-
plicate up to 20\% of courses of therapy in hospitalized patients. Of added concern,
outbreaks within intensive care units of infections caused by multiply resistant gram-
negative bacilli have recently been linked to heavy use of broad spectrum antibiotics,
primarily for prophylaxis.\textsuperscript{20-24} In two instances, epidemic infections could not be
controlled until prophylactic antimicrobial therapy was sharply curtailed.\textsuperscript{23,24} In several
outbreaks, the multiply resistant epidemic pathogen,\textsuperscript{26,27} and in one, the “epidemic
episome” mediating drug resistance,\textsuperscript{28} spread to family members of colonized pa-
tients following discharge from the hospital, affirming far-reaching sequelae of antibiotic over-utilization.

Although a number of studies, mainly in community and municipal hospitals,\textsuperscript{5,28,27}
have documented heavy use of antibiotics, few\textsuperscript{5,28,29} have specifically examined patterns
of misuse, particularly possible causes of irrational therapy.

This prospective study in a university hospital was designed to: (1) determine in this
type of hospital the patterns of antimicrobial usage in hospitalized adult medical and
surgical patients, especially the magnitude and profile of inappropriate therapy, (2)
quantitate the adverse clinical effects of misuse and economic costs of overuse, and (3)
gain further understanding of the possible causes of inappropriate therapy.

\textbf{Methods}

\textbf{Background}

The University of Wisconsin Hospitals is a 420-bed, acute care, referral institution and
serves as the major teaching hospital of the University of Wisconsin Center for Health
Sciences. The Infection Control Unit conducts periodic prevalence surveys of noso-
comial infection and antimicrobial usage.\textsuperscript{29} Most patients with complex infections are
seen by consultants from the Infectious Disease Service. Use of cephalixin, indanyl
carbenicillin, tobramycin, and amikacin is restricted; physicians wishing to use any of
these drugs must justify the need to a physician member of the Infection Control
Committee before the second dose can be given.\textsuperscript{30} Certain policies of the hospital's
clinical microbiology laboratory also are designed to influence the use of antibiotics,\textsuperscript{31}
such as susceptibility to carbenicillin is routinely tested only with isolates of \textit{Pseudomonas aeruginosa} and urinary isolates of \textit{Enterobacter} and indole-positive \textit{Proteus}, and the
results of chloramphenicol and clindamycin testing against aerobic isolates are provided
only on specific request. The Pharmacy and Therapeutics Committee has also attempted
to upgrade usage of antibiotics in the hospital by control of the formulary,\textsuperscript{32} primarily by
limiting the number of drugs carried. Since 1971, registered pharmacists have been as-
signed to most patient care units to administer medications and provide pharmacologic monitoring and consultation.

\textbf{Study Population}

The neurosurgical ward, urology ward, a
general surgical ward, and two general medical wards were selected for study. All adult patients admitted to these units between Feb 1 and March 8, and between June 2 and June 22, 1975, were followed for their entire hospitalization. Ward physicians were not aware of the study during its tenure.

Data Collected

All primary data were collected by the co-investigator who is a clinical pharmacist (A.S.). Information obtained from each treated patient included major medical diagnoses, allergies—especially to drugs—surgical operations, clinical signs and symptoms of infection, results of all gram-stained smears, bacteriologic cultures and antimicrobial susceptibility testing, pertinent laboratory data (hemogram, platelet count, urinalysis, roentgenograms, radionuclear scans, serum creatinine, bilirubin, and glutamic oxaloacetic transaminase), and all systemic antibiotics received during the study, including the dose, route, and duration of each. Only the use of antibacterial drugs administered systemically was studied.

From the patient’s chart it was determined whether therapy was intended for prophylaxis or for treatment of presumed infection. Antimicrobial therapy without clinical evidence of infection and without a statement in the record indicating a specific suspected infection was considered prophylaxis.

Whether the physician stated in the patient’s record (1) that antibiotics had been started, and (2) the clinical rationale for antimicrobial therapy (ie, for a specific presumed infection or for prophylaxis) were recorded.

Nursing notes, the narrative record, and laboratory data were regularly reviewed for evidence of temporally related adverse reactions that might have been related to antimicrobial therapy. The methods and criteria of Cluff et al were employed for monitoring and defining adverse effects. During each course, other concurrent drug therapy was also reviewed to identify adverse drug inter-

actions involving the antimicrobial agent or agents. The cost of each patient’s antimicrobial therapy was obtained from Central Pharmacy billing records.

Criteria and Definitions

Definitions of infection employed in the study were those published by the National Nosocomial Infection Surveillance Study of the Center for Disease Control. Appropriateness of antimicrobial therapy in each course was not determined until after all of the antibiotics had been discontinued. In every case, appropriateness was determined jointly by both investigators.

For therapy of presumed infection to be designated as appropriate required: (1) clinical signs and symptoms suggesting infection at the outset of therapy, (2) rational drug choice (considering the probable or known pathogens, the patient’s overall clinical status, and the clinical pharmacology of the drug or drugs), and (3) modification of therapy when indicated by the clinical course and results of bacteriologic studies. Failure to obtain cultures before therapy was not considered grounds to designate therapy as inappropriate; one of the goals of the study was to determine whether performance of cultures correlated with the quality of antimicrobial usage.

General guidelines for nonsurgical antimicrobial prophylaxis have been published; only those indications published in the Medical Letter were considered as appropriate in this study.

In the past decade, prospective, carefully controlled studies such as Polk and Lopez-Mayor’s have demonstrated conclusively that systemic antibiotics chosen for efficacy against anticipated intraoperative bacterial contaminants, begun preoperatively and continued for only one or a few days, can augment surgical asepsis and significantly reduce the rate of wound infection, primarily in operations associated with a high risk of intraoperative contamination and infection. Recent studies have also shown that prophylactic
antibiotics are effective in clean hip surgery, however, no studies in other types of clean surgery have demonstrated clear-cut efficacy. In our study, which did not include any orthopedic patients, antimicrobial prophylaxis was considered inappropriate if employed for clean surgical procedures (as defined by the National Research Council Study). Both animal experiments and clinical studies have shown that prophylaxis begun postoperatively is of little, if any, value. Thus, overall, in our study surgical prophylaxis was considered appropriate: (1) when utilized for potentially contaminated operations, (2) if begun preoperatively, (3) if the drug or drugs were likely to be effective against anticipated microbial contaminants, and (4) if not continued beyond 72 hours postoperatively. Prophylaxis during prostatic resection was considered acceptable if consonant with criteria 2 through 4 above.

Results

Incidence of Antimicrobial Use

Overall, 26.2% of the 549 study patients received one or more systemic antibiotics during hospitalization (Table I). Usage was greatest in urology patients (32.1%) and lowest on neurosurgery (12.7%). The mean number of drugs comprising a course of therapy ranged from 1.3 in medical patients to 2.2 in neurosurgical patients and 1.4 overall.

Four drugs or groups of drugs, ampicillin (33%), cephalosporins (26%), penicillins G and V (17%), and gentamicin (17%) comprised part or all of over 90% of antimicrobial regimens (Table II). Parenteral cephalosporins were employed in 64% of courses for prophylaxis, but the oral cephalosporin cephalaxin was used only twice during the entire period of study.

Apparent or suspected infection prompted antimicrobial therapy in 70% of instances, whereas prophylaxis was the specifically stated or presumed therapeutic goal in 30% of courses (Table I). Infection, when suspected, was confirmed in 68 (65%) of 104 instances overall, 72% of the time in surgical patients but in only 41% of suspected infections in patients on medicine.

Diagnostic Studies Before Therapy

As seen in Tables I and III, pretherapy
### TABLE II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Presumptive Infection (N = 104)</th>
<th>Prophylaxis (N = 45)</th>
<th>Total (N = 149)</th>
<th>Percent Usage Appropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>44 (42%)</td>
<td>5 (11%)</td>
<td>49 (33%)</td>
<td>61%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>10 (10%)</td>
<td>28 (64%)</td>
<td>38 (26%)</td>
<td>74%</td>
</tr>
<tr>
<td>Penicillin G or V</td>
<td>18 (17%)</td>
<td>8 (18%)</td>
<td>26 (17%)</td>
<td>54%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>23 (22%)</td>
<td>3 (7%)</td>
<td>26 (17%)</td>
<td>62%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>12 (11%)</td>
<td>4 (9%)</td>
<td>16 (11%)</td>
<td>43%</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>8 (8%)</td>
<td>8 (5%)</td>
<td>16 (5%)</td>
<td>50%</td>
</tr>
<tr>
<td>Methicillin or cloxacillin</td>
<td>7 (7%)</td>
<td>—</td>
<td>7 (5%)</td>
<td>86%</td>
</tr>
<tr>
<td>Nitrofurant</td>
<td>5 (5%)</td>
<td>1 (2%)</td>
<td>6 (4%)</td>
<td>83%</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>6 (6%)</td>
<td>—</td>
<td>6 (4%)</td>
<td>67%</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>3 (3%)</td>
<td>2 (5%)</td>
<td>5 (3%)</td>
<td>20%</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>—</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>—</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>2 (2%)</td>
<td>—</td>
<td>2 (1%)</td>
<td>50%</td>
</tr>
<tr>
<td>Methenamine mandelate</td>
<td>1 (1%)</td>
<td>—</td>
<td>1 (1%)</td>
<td>—</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>—</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>—</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>1 (1%)</td>
<td>—</td>
<td>1 (1%)</td>
<td>100%</td>
</tr>
<tr>
<td>Total courses</td>
<td>104 (100%)</td>
<td>45 (100%)</td>
<td>149 (100%)</td>
<td>59%</td>
</tr>
<tr>
<td>One Drug</td>
<td>74 (71%)</td>
<td>39 (86%)</td>
<td>113 (76%)</td>
<td>59%</td>
</tr>
<tr>
<td>≥2 Drugs</td>
<td>30 (29%)</td>
<td>6 (14%)</td>
<td>36 (24%)</td>
<td>58%</td>
</tr>
</tbody>
</table>

*Because more than one drug was employed in some courses of therapy, the summation of individual percentages exceeds 100% overall.*

### TABLE III

<table>
<thead>
<tr>
<th>Site</th>
<th>No. Courses</th>
<th>No. with Pretherapy Cultures</th>
<th>No. with Appropriate Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>42</td>
<td>39 (91%)</td>
<td>28 (65%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>27</td>
<td>20 (74%)</td>
<td>16 (59%)</td>
</tr>
<tr>
<td>Wound</td>
<td>19</td>
<td>14 (74%)</td>
<td>13 (68%)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>10</td>
<td>8 (80%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>4 (67%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>All sites</td>
<td>104</td>
<td>85 (83%)</td>
<td>68 (65%)</td>
</tr>
</tbody>
</table>

*Cultures were obtained prior to therapy in 63 of 65 appropriate courses and in 22 of 36 inappropriate courses of therapy (p<0.05).*

*Gram-stained smears of sputum were obtained in 13 of 27 courses of therapy for presumed respiratory tract infection; antimicrobial usage was judged appropriate in 11 (85%) of these instances (p<0.001 by Fisher's exact test).*
cultures were obtained in 82% of presumed infections (81% in surgical patients and 82% on medicine). Gram-stained smears of sputum preceded and guided therapy of presumed respiratory tract infection in 13 (48%) of 27 cases; all were in medical patients.

**Appropriateness of Therapy**

Therapy was judged appropriate in 59% of instances overall, 65% of the time when directed at presumed infection, and in 53% of courses designated for prophylaxis (Table IV). Except for the neurosurgical service where 12 (86%) of 14 courses of therapy were appropriate, appropriateness of therapy was comparable on the other three major specialty services, ranging from 48% to 63%.

The primary bases for inappropriate therapy of presumed infection (Table IV) were poor drug choice (22 of 37 inappropriate courses) and lack of clinical evidence for infection (13 courses). In 14 of the 22 designations of poor drug choice, the drugs selected were unlikely at the outset to be clinically effective considering the pathogens most likely to be encountered; this was affirmed in six instances clinically (ie, by continued infection) and in eight cases by *in vitro* susceptibility testing. Therapy of presumed respiratory tract infection (59%) and sepsis (60%) were least frequently judged appropriate (Table III). In therapy for presumed infection, cultures were obtained in 63 (88%) of 68 appropriate courses, but in only 22 (67%) of 36 inappropriate courses \( (p<0.05) \). Gram-stained smears of sputum preceded therapy in 11 (85%) of 13 appropriately treated respiratory tract infections but in only 2 (14%) of 14 cases subsequently treated inappropriately \( (p<0.001) \).

Prophylaxis was judged inappropriate (Table IV) because of being initiated too late (12 of 24 inappropriate courses, all in surgical patients), not being clinically indicated (eight courses), or being unduly prolonged, ie, greater than 72 hours (11 courses, also all in surgery).

Except for tetracycline (used approximately 43% of the time), of the five drugs used most frequently during the study, appropriateness of usage of each was similar (Table II).

**Physician’s Notes in the Patient Record**

As seen in Table I, the physician indicated in the patient’s chart at the outset of therapy that antibiotic therapy had been started only 34% of the time; a written justification for therapy appeared in only 15% of courses. General surgeons were least likely (35%) to include any mention of antimicrobial therapy in the clinical narrative. Appropriateness of therapy correlated strongly with the comprehensiveness of the physician’s note: medically justifying therapy, 92% of usage appropriate; simply noting institution of antimicrobial therapy, 64% appropriate; and no mention whatsoever of therapy, 48% appropriate \( (\chi^2 = 36.1, 3 \text{ df, } p<0.001) \).

**Adverse Sequelae of Therapy**

Adverse reactions including superinfection (6% of courses), severe gastrointestinal symptoms (5%), and infusion phlebitis (3%), occurred in 17% of patients receiving antimicrobial therapy (Table V). Potentially harmful drug interactions were detected in two patients.

Sixty-two percent of adverse reactions developed in patients receiving inappropriate therapy; inappropriate therapy was associated with an over two-fold increased rate of adverse reactions (26% vs 11% in appropriate courses).

**Cost of Antimicrobial Therapy**

The average cost of an appropriate course of therapy was $55.30 and of an inappropriate course, $84.45. Applying these figures to the 14,650 patients admitted to our hospital in 1975, and considering that based on this study approximately one fourth of patients given antibiotics received them needlessly (Table IV), it can be projected that in our hospital unnecessary antibiotics in 1975 cost $70,465.
### TABLE IV

**OVERALL ASSESSMENT OF ANTIMICROBIAL THERAPY IN 144 PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>Neurosurg (N = 14)</th>
<th>Urology (N = 44)</th>
<th>Gen Surg (N = 51)</th>
<th>Medicine (N = 40)</th>
<th>Total (N = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Therapeutic Courses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Appropriate therapy</strong></td>
<td>12 (86%)</td>
<td>21 (48%)</td>
<td>32 (63%)</td>
<td>23 (58%)</td>
<td>88 (59%)</td>
</tr>
<tr>
<td><strong>Inappropriate therapy</strong></td>
<td>2 (14%)</td>
<td>23 (52%)</td>
<td>19 (37%)</td>
<td>17 (42%)</td>
<td>61 (41%)</td>
</tr>
<tr>
<td>Inapp for presumptive infection</td>
<td>2</td>
<td>17</td>
<td>4</td>
<td>14</td>
<td>37† (25%)</td>
</tr>
<tr>
<td>No evidence of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor drug choice</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>5</td>
<td>22†</td>
</tr>
<tr>
<td>Unlikely to be effective</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Dose</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Route</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Allergic history</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Spectrum unnecessarily broad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Failure to modify</td>
<td>2</td>
<td>6</td>
<td></td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td><strong>Inappropriate prophylaxis</strong></td>
<td></td>
<td>6</td>
<td>15</td>
<td>3</td>
<td>24† (16%)</td>
</tr>
<tr>
<td>Not indicated</td>
<td></td>
<td></td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Poor drug choice‡</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Begin postexposure</td>
<td></td>
<td>5</td>
<td>7</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Duration too long</td>
<td></td>
<td>4</td>
<td>7</td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>

*One hundred forty-four (144) patients received 149 courses of therapy.
†Summation of the contributions from each subcategory exceeds the total for that category; therapy was commonly judged inappropriate for multiple reasons.
‡Subcategories similar to inappropriate for presumptive infection.

### TABLE V

**ADVERSE REACTIONS TO ANTIMICROBIAL THERAPY**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. (N = 149)</th>
<th>Percent</th>
<th>Drugs Implicated (No. of Instances)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection</td>
<td>9*</td>
<td>6%</td>
<td>Ampicillin (5), Penicillin (2), Penicillin and Gentamicin (1), Penicillin, Oxaclillin, and Gentamicin (1)</td>
</tr>
<tr>
<td>Gastrointestinal (vomiting or diarrhea)</td>
<td>7</td>
<td>5%</td>
<td>Ampicillin (3), Penicillin (1), Tetracycline (2), Trimethoprim-sulfamethoxazole (1)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>5</td>
<td>3%</td>
<td>Cephalothin (4), Ampicillin (1)</td>
</tr>
<tr>
<td>Azotemia</td>
<td>2</td>
<td>1%</td>
<td>Gentamicin (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>1%</td>
<td>Methicillin (1), Ampicillin (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1%</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>All reactions</td>
<td>26</td>
<td>17%</td>
<td>Ampicillin (10), Penicillin (5), Cephalothin (4), Gentamicin (4), Tetracycline (2), Methicillin/Oxacillin (2), Chloramphenicol (1), Trimethoprim-sulfamethoxazole (1)</td>
</tr>
</tbody>
</table>

*Urinary tract, six (14% of 42 treated presumptive urinary tract infections); pneumonia, one (of 27 treated presumptive respiratory infections); Candida vaginitis, one; cutaneous moniliasis, one.*
Discussion

The Joint Commission on Accreditation of Hospitals mandates hospitals to maintain active programs of infection control including surveillance of nosocomial infections and usage of antibiotics. An expert committee under the auspices of the American Medical Association recently recommended that hospitals develop intramural guidelines for antibiotic use and mechanisms for utilization review. The results of our study, the third of its kind in our hospital in the past four years, have been transmitted to the medical and pharmacy staffs as a step toward upgrading use of antibiotics in our institution.

Before comparing rates of antimicrobial usage in different types of hospitals, it is important to be aware of the difference between prevalence and incidence. Most published studies (Table VI), for obvious logistic reasons, have been prevalence surveys\cite{13, 43} which determined the proportion of patients in the hospital on a given day who were receiving antibiotics. Studies of the incidence of usage, such as ours, require collection of data over the entire period of hospitalization, and rates are usually expressed per 100 patients hospitalized. Only if the durations of hospitalization of patients receiving and not receiving antibiotics are identical will the two rates coincide. In that patients receiving antibiotics, on the average, are hospitalized somewhat longer than non-recipients,\cite{4} the prevalence of use will tend to exceed the incidence in similar populations. Thus, the incidence of use in our hospital, 26.2%, and the University of Virginia Hospital,\cite{3} 28.2%, indicate utilization of antibiotics comparable to municipal\cite{26, 27} and most community institutions\cite{13, 43} (Table VI). It may be less valid to compare the percentages of patients receiving antibiotics who have clinical evidence of infection unless uniform criteria are employed. In the various studies, results have ranged widely with no discernable pattern by type of institution; our experience (46%) is the median of the published studies listed in Table VI.
Relatively few studies have examined appropriateness of antimicrobial use. Taking those that did \cite{1,2,8,43} and our study, comparisons are compromised because of variable representation of specialty services and nonuniformity of survey teams, protocols, and criteria for appropriateness. However, based on the limited published data shown in Table VI, the differences are so striking as to possibly circumvent nonuniformity. Antibiotics appear to be used in university hospitals considerably more skillfully (48\% appropriately in the University of Virginia Hospitals, \cite{3} 36\% in the Duke University Medical Center, \cite{43} and 59\% in our institution) than in community hospitals (13\% in Roberts and Visconti's institution).\cite{2} This might be expected, considering the primary emphasis on teaching and the greater availability of consultation in university hospitals. But, misuse one half of the time indicates considerable need for improvement in referral and teaching institutions as well as in community hospitals.

The incidence of adverse reactions to antimicrobial therapy in our study (17\%) is comparable to previous reports.\cite{2,8,19} Nearly two thirds of adverse reactions occurred in patients receiving inappropriate therapy despite the fact that only 41\% of all courses were inappropriate.

This study identified a number of factors associated with inappropriate use of systemic antibiotics in our hospital:

1. Therapy designated for prophylaxis was less likely to be appropriate (47\%) than therapy given for presumed infections (65\%). Misguided prophylaxis, almost solely in surgical patients, and divided between being clinically unwarranted and poorly employed, was responsible for one third of all inappropriate courses. Roberts and Visconti,\cite{2} Kunin et al,\cite{3} and Castle and her co-workers,\cite{43} found misguided prophylaxis accounted for over one half of inappropriate therapy in their hospitals.

2. Although treatment of presumed infection was more likely than prophylaxis to be appropriate, because of the proportionally larger number of patients receiving antibiotics for this indication, inappropriate therapy of presumed infection made up two thirds of all of our instances of misuse. In the majority of these cases (Table IV), unnecessary therapy or selection of drugs unlikely to be effective against the probable pathogens was implicated.

3. Roberts and Viscontistated that obtaining pretherapy cultures did not influence the likelihood of therapy being rational;\cite{2} however, they included courses of therapy intended for prophylaxis in their evaluation. In general, cultures are not usually performed or necessary prior to administering prophylactic antibiotics. Considering only antimicrobials given for presumed infection, we found obtaining cultures to be significantly associated with appropriate therapy (Table III, p<0.05). Whether this indicates that physicians who regularly obtain cultures are implicitly more skilled at using antibiotics, or the availability of bacteriologic data implicitly facilitates later, clinically indicated alterations of the regimen, or both, is unknown. Our data suggest that both hypotheses may be correct. The diagnostic value of gram-stained smears of sputum is well-established, especially for differentiating bacterial from nonbacterial respiratory infection and for selecting initial antibiotic therapy,\cite{44} and was affirmed in this study. Gram-stained smears of sputum were almost uniformly (85\%) associated with appropriate therapy of presumed respiratory tract infection (p<0.001).

4. The failure of the physician to medically justify, let alone even mention, the institution of antimicrobial therapy in the patient's chart in 51\% of courses and the highly significant association between such a note and the quality of usage point up a major factor under-
ly ing inappropriate therapy: lack of knowledge on the part of physicians of the far-reaching sequelae of overuse and misuse and of basic principles of clinical infectious diseases, particularly use of antibiotics.

Our policy requiring medical justification prior to use of cephalaxin and oral carbenicillin was highly effective in limiting use of these drugs (two courses of cephalaxin in 549 patients). We have found restriction can be accomplished effectively and efficiently without compromising medical care or the prescribing physician’s therapeutic prerogative. Requiring justification before use has been demonstrated by McGowan and Finland, and Ridley et al. to be highly effective in limiting the use of certain drugs. Moreover, several hospitals have shown a substantial drop in the frequency of multiply resistant S. aureus and carbenicillin-resistant Pseudomonas coincident with restrictions on the use of specific drugs. Also outbreaks within intensive care units caused by multiply resistant gram-negative bacilli have been controlled only by stringent restrictions upon usage of broad spectrum antibiotics.

In summary, in regards to measures to upgrade the use of antibiotics in the hospital:
1. This study and others underscore a major need for programs of post-graduate education for physicians which stress basic principles of clinical infectious disease, particularly rational drug selection and guidelines for prophylaxis and antimicrobial pharmacology.
2. Periodic antimicrobial utilization reviews on the order of our and others’ studies should figure heavily in intramural educational programs for physicians and in peer review. Zeman et al. were able to demonstrate a $60,000 savings in expenditures for antibiotics in the first year of a utilization review program in a community hospital. Hospitals ideally should develop their own standards for antimicrobial use, but excellent comprehensive guidelines have recently been published.
3. Greater commitment to infection control, specifically implementing and assuring stringent compliance with proved techniques to prevent hospital-acquired infections can implicitly reduce the use and, in the process, misuse of antibiotics.
4. The hospital’s diagnostic microbiology laboratory can adopt policies that promote more rational use of antibiotics.
5. More active participation by clinical pharmacists in patient care, implicit in their assignment to hospital wards as done in our institution, probably upgrades in-hospital use of antibiotics. Vance, in a controlled study, attributed a 48% reduction in expenditures for antibiotics directly to the surveillance and consultative activities of ward pharmacists.
6. Control of hospital formularies and formation of community-wide formularies are indirect but additional ways to lessen drug costs and improve drug prescribing.
7. Antimicrobial justification programs, even modest ones such as our own, can substantially limit the use of selected drugs and in the process contribute to physician education and improve antimicrobial utilization.

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