**ANTIBIOTIC USAGE IN COMMUNITY-ACQUIRED INFECTIONS IN HOSPITALS IN TAIWAN**

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**Background and Purpose:** Using an epidemiologically meaningful in-hospital population with community-acquired infections, we evaluated antibiotic therapy in terms of indication and choice of antibiotic and microbiologic work-up.

**Methods:** Infectious disease specialists evaluated charts of 436 patients from 9 hospitals and selected those who received antibiotics within 3 days of admission. Each antibiotic prescribed was ranked for appropriateness of indication and choice. Microbiologic isolates were evaluated for their clinical significance.

**Results:** The most common infections were in the lower respiratory tract (46.1%). Each patient received a mean of 2.25 antibiotics for 8.1 ± 6.4 days. Of the 975 courses of antibiotics given in the study period, indication and choice were correct in 37.4% and unsatisfactory in 14.5%. The vast majority of antibiotics used (79.2%) were first-line antibiotics — usually first-generation cephalosporins, aminoglycosides, and aminopenicillins. Most patients (66%) had a microbiology laboratory work-up, but only 37.4% were judged by evaluators to have a meaningful microbiologic diagnosis. Among the 201 patients with lower respiratory tract infections, 105 (52.2%) had a diagnosis of pneumonia. A positive isolate was recovered in 30 (28.6%) patients, and most of these isolates (20, 68.7%) were aerobic gram-negative rods. There were three positive blood cultures but none grew *Streptococcus pneumoniae*.

**Conclusions:** Antibiotics were used excessively in number and duration. The microbiologic work-up had little effect on the indication and choice of antibiotics. Community-acquired pneumonia differed markedly from that in Western countries in that only 3.3% were caused by *S. pneumoniae*.

Antibiotic resistance is a global problem that is particularly serious in Taiwan [1–4]. The development of resistance is a result of excessive and inappropriate use of antibiotics. However, it is believed that, if antibiotics were used more stringently, the resistance problem might not disappear but it would be substantially reduced [5]. This generality alone is inadequate to influence the practice patterns of individual physicians. They should have more specific data that will relate to their practice. The availability of current data on in-hospital infections and the appropriateness of antibiotic usage would be extremely useful.

In 1973, Kunin et al described a method of evaluating the appropriate use of antibiotics for therapy and prophylaxis in hospital practice that had been practiced by expert physicians [5]. The result of their first such study showed that “more than half of the antibiotics used were not needed, or that an inappropriate agent was chosen, or the dose was incorrect”. Jones et al elaborated further by evaluating the use of antibiotics before and after an educational campaign [6]. Since then, many investigators have used this method to evaluate antibiotic use in hospitals in many countries [7, 8].
We adopted Kunin's basic idea [5] and modified it with the assistance of experienced physicians. The disadvantage of this system is that it is largely subjective. However, we made important additions. First, we chose to evaluate an epidemiologically meaningful sample of community-acquired infections. Secondly, we evaluated performance and use of the microbiology laboratory for each antibiotic used. While most evaluations of antibiotic use focus on one hospital or a group of hospitals (5–8), this study had a nationwide focus.

In theory, the hospital microbiology laboratory plays an important role in the guidance and usage of appropriate antibiotics. The laboratory can identify the etiologic pathogen and can provide antibiotic susceptibility and resistance data. However, in practice it is less clear to what extent hospital laboratories accomplish these tasks, and to what extent they contribute to the practicing patterns of antibiotic usage. Therefore, it is important to study these practicing patterns in order to improve laboratory practice and make it more practical.

Our study used a cohort of unselected patients, chosen so that they would represent hospital practice throughout Taiwan. We focused on community-acquired infections by restricting patient inclusion to those who received antibiotics within 72 hours of admission. Information regarding the circumstances under which antibiotics were given was also collected. The study intended to identify possible corrective measures with the aim of rectifying them.

**Methods**

**Hospitals**

Three medical center hospitals and six regional hospitals from the populous northern (6), northeastern (1), middle (1), and southern (1) parts of Taiwan were chosen. These hospitals had a total of 6,671 beds (mean, ±302 beds; range, 440–1359 beds) and a mean of 56 ± 36 intensive care unit (ICU) beds (range, 17–113 beds).

**Chart review, data and evaluations**

Chart review was undertaken in each hospital by an infectious disease internist or pediatrician who was board certified by the Infectious Diseases Society of the Republic of China and who had graduated from the Infectious Disease Training Program of the Republic of China (1993–2001).

In order to include patients admitted for community-acquired infections and exclude those with hospital-acquired infections, each hospital was asked to collect data from charts of 50 patients admitted during a period of 2 months, beginning in March 2000, for whom antibiotics were prescribed within 3 days of admission. Those who received prophylactic antibiotics for surgery and for the treatment of tuberculosis were excluded from the study.

Each chart was reviewed by filling out a form that collected the following data from the patient's chart: demographic information, discharge diagnoses, the discharge diagnosis for which antibiotics were prescribed, procedures such as surgery, and other underlying medical conditions. The reviewer also designated the organ system to which the infection was related. Microbiologic studies were described by the source of specimens (blood, sputum, urine, etc) and microbes that were identified. An evaluation was made as to whether the culture result helped identify the microbiologic agent, was unrelated to the infection, or whether it was a contaminant. This evaluation was based on the types of organisms isolated, the quantity of organisms (where available, as in urine), the laboratory reports, and the suspected clinical diagnoses. A copy of the reports of microbial identifications and susceptibility results was appended to the review form. In addition, a record was made if a microbial work-up was performed but a meaningful microbial diagnosis was not made, or if no microbial work-up was performed.

A course of antibiotic treatment was defined for each antibiotic prescribed. Two or more antibiotics could have been given to a patient, not necessarily simultaneously. Evaluation of a course included whether the dose and duration was appropriate and by assigning marks (described below).

**Marking system**

The indication and choice of each antibiotic prescribed was graded using one of three marks. A1 meant the antibiotic was "indicated and the choice was correct"; A3, the antibiotic was "not indicated or choice was incorrect"; and A2, an intermediate mark, given when the criteria of neither A1 nor A3 was met.

Evaluation of the performance and use of microbiology laboratories was also made for each antibiotic course prescribed. An LS mark was given when the infection event was defined bacteriologically, antibiotic susceptibility tests were done, and the antibiotic used was consistent with susceptibility results. The LU mark was given when the antibiotic used was not consistent with susceptibility findings.

**Analysis**

Standardized data were entered in a relational database with Access 97 (Microsoft, Redland, WA, USA) and analyzed with Epi (version 6.04; Centres for Disease Control and Prevention, Atlanta, GA, USA) The
statistical method used tested the difference between a proportion of a group and the proportion in the remaining groups using chi-square with Yates' correction.

Results

The nine hospitals contributed a total of 442 patient charts, a mean of 49.1 ± 2.7 charts per hospital. Males comprised 62.6% and females 37.4% of the study population. The mean age was 46 ± 29 years with a range of less than 1 year to 99 years. Children were less than 15 years of age.

We excluded six patients who had no infection related to the prescription of antibiotics. Two of these patients had used antibiotics for surgical prophylaxis, and four were probably cases where there was no infection. Thus, of 442 charts, 436 were used for analysis. A total of 992 courses of antibiotics were recorded. After excluding those courses prescribed for the excluded patients, 982 courses remained for the analysis.

Distribution of infections by site

The type of infection in each case was specified by two designations: the diagnosis on the patient's chart and the anatomic site of infection as determined by the reviewer. Table 1 lists the sites of infection and the evaluation of antibiotic usage. There were 436 presumed infections in 436 patients, involving 341 adults (78.2%) and 95 children (21.8%). The most common site of infection was the lower respiratory tract, followed by the genitourinary tract, the gastrointestinal tract, and soft tissue.

The site distribution of infections in each individual hospital was analyzed and compared with others for differences (data not shown). While the frequency of infections of the lower respiratory tract varied from 28% to 63%, they were the most prevalent type of infection in every hospital.

Description of major infections

The 201 lower respiratory tract infections consisted of 105 cases of pneumonia and 96 non-pneumonia cases. There were 157 (78.1%) adults and 44 (21.9%) children. Among the 96 patients in the non-pneumonia group, there were 80 (83.3%) adults and 16 (16.7%) children. Thirty had chronic obstructive pulmonary disease (COPD) (31.3%), 16 had bronchitis (16.7%), nine had bronchiolitis (9.4%), eight had asthma (8.3%), and seven had bronchiectasis (7.3%). There were four deaths (4.2%) in this group.

Among the 105 cases of pneumonia, 57 were uncomplicated (without comorbidities) and 48 were complicated by comorbidities. Among patients with uncomplicated pneumonia, the mean age was 33.4 ± 33.9 years, there were 28 (49.1%) children, 19 (33.3%) females, 36 males and 2 with unknown gender. Three patients died (5.3%). There were no children among the 48 cases of complicated pneumonia. The mean age was 64.4 years, with 34 males (70.8%) and 14 females (29.2%). The comorbidities were: COPD in 13 (27.1%); diabetes mellitus in 12 (25.0%); cardiovascular disease in 12 (22.9%); cancer in nine (18.8%, 5 cancers of lung); hepatitis in six (12.5%); renal insufficiency in four (8.3%); and stroke in four (8.3%). The mortality for cases of complicated pneumonia was 22.9% (11), and in the whole cohort of 105 pneumonia patients was 13.5% (14).

Of the 65 cases of genitourinary tract infection, 55 (84.6%) occurred in adults and 10 (15.4%) in children. Urinary tract infection was diagnosed in 46 (70.8%) and acute pyelonephritis in 11 (16.9%), giving a total of 57 (87.7%) for the two conditions. The comorbidities in these 57 cases were: diabetes mellitus in 12 (21.1%); stroke in nine (15.8%); hypertension and cardiovascular disease in eight (14.0%); cancer in four (7.0%); hepatitis in four (7.0%); benign prostatic hypertrophy in three (5.3%); and renal insufficiency in two (3.5%).

Antibiotic appropriateness by infection site

The total number of antibiotic courses (982) and their distribution among the 436 cases by infection site and the number of days during which patients received antibiotics are shown in Table 1. Each patient received a mean of 2.25 antibiotic courses. The upper range of the number of courses varied widely. As many as 14 courses were used for lower respiratory tract infections. For other infections, the maximum number of courses was 5 or 6. A total of 365 (37.4%) courses had correct indications and choice, while 141 (14.5%) were incorrect (A1 and A3 categories). These were also the respective proportions of patients with correct and incorrect indications and choice for lower respiratory tract infections, the predominant infection in this study. Genitourinary tract infections and gastrointestinal tract infections had significantly more patients with correct indications and choice marks, while soft tissue and upper respiratory tract infections had significantly fewer patients with correct indications and choice marks. Upper respiratory tract infections also had significantly more incorrect indications and choice marks. The antibiotic treatment in these patients was least satisfactory.

Antibiotics used for categories of infection

Table 2 shows the type of antibiotics used for each category of infection. The number of patients and
Antibiotics in Infections in Taiwan Hospitals

Details concerning combinations of antibiotics are given for lower respiratory tract infection and pneumonias as an example. First-generation cephalosporins were used singly or in combination with one to five other antibiotics in 107 patients (53.2%). Aminoglycosides were used singly and in combination in 66 patients (32.8%). Aminopenicillins were used singly and in combination in 33 patients (16.4%). Macrolides were used in 21 patients singly or in combination (10.4%). Altogether, 65.2% received two or more antibiotics and 34.8% received monotherapy. Monotherapies were also led by first-generation cephalosporins.

**Table 1.** Infection by site and evaluation of antibiotic usage

<table>
<thead>
<tr>
<th>Infection site</th>
<th>Cases, n (%)</th>
<th>Antibiotic courses, mean ± SD antibiotic (range)</th>
<th>Duration of antibiotic courses, mean ± SD (range)</th>
<th>Evaluation of antibiotic usage, n (%)</th>
<th>A1</th>
<th>A3</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract</td>
<td>201 (46.1)</td>
<td>474, 2.3 ± 1.5 (1-14)</td>
<td>8.7 ± 6.6 (1-53)</td>
<td>176 (37.4) NS</td>
<td>68 (14.5)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>65 (14.9)</td>
<td>141, 2.2 ± 1.0 (1-6)</td>
<td>9.3 ± 6.2 (1-38)</td>
<td>65 (46.4) &lt; 0.05</td>
<td>19 (13.6)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>60 (13.8)</td>
<td>132, 2.2 ± 1.0 (1-6)</td>
<td>9.1 ± 7.5 (1-37)</td>
<td>36 (27.3) &lt; 0.05</td>
<td>17 (12.9)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>50 (11.5)</td>
<td>117, 2.3 ± 1.1 (1-5)</td>
<td>6.6 ± 6.3 (1-34)</td>
<td>63 (54.8) &lt; 0.01</td>
<td>7 (6.1) &lt; 0.01</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>33 (7.6)</td>
<td>68, 2.1 ± 0.9 (1-5)</td>
<td>5.7 ± 3.1 (1-15)</td>
<td>11 (16.2) &lt; 0.01</td>
<td>20 (29.4)</td>
<td>&lt; 0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Blood and sepsis</td>
<td>16 (3.7)</td>
<td>29, 1.8 ± 0.4 (1-2)</td>
<td>4.4 ± 3.2 (1-11)</td>
<td>9 (31.0) NS</td>
<td>3 (10.3) NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>5 (1.1)</td>
<td>8, 2.0 ± 0.7 (1-3)</td>
<td>5.5 ± 2.6 (1-7)</td>
<td>3 (37.5) NS</td>
<td>1 (12.5) NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6 (3.0)</td>
<td>13, 2.2 ± 0.4 (2-3)</td>
<td>3.2 ± 1.8 (1-5)</td>
<td>2 (15.4) NS</td>
<td>6 (46.2) &lt; 0.01</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
**All sites**                   | 436 (100.0)  | 982, 2.3 ± 1.2 (1-14)                               | 8.1 ± 6.4 (1-53)                                   | 365 (37.4) 141 (14.5)              | NS | NS | NS |

*Proportion of A1 scores compared with remainder of A1 scores for significance of difference by chi-square test. A1 = correct antibiotic usage and choice; A3 = incorrect antibiotic usage and choice. The total number of A scores (975) does not equal the number of courses because some were not scored.

**Table 2.** Types of antibiotics used for infections at different sites

<table>
<thead>
<tr>
<th></th>
<th>LRT 201/474*</th>
<th>UT 65/141</th>
<th>Soft tissue 60/132</th>
<th>GI 50/117</th>
<th>URT 33/68</th>
<th>Blood and sepsis 16/29</th>
<th>CNS 5/8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>145 30.6</td>
<td>63 44.7</td>
<td>58 43.9</td>
<td>55 47.0</td>
<td>17 25.0</td>
<td>5 17.2</td>
<td>1 12.5</td>
</tr>
<tr>
<td>2nd generation</td>
<td>35 7.4</td>
<td>6 4.3</td>
<td>1 0.8</td>
<td>1 0.9</td>
<td>5 7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd generation</td>
<td>13 2.7</td>
<td>5 3.5</td>
<td>4 3.4</td>
<td></td>
<td>2 6.9</td>
<td>4 50.0</td>
<td></td>
</tr>
<tr>
<td>4th generation</td>
<td>1 0.2</td>
<td></td>
<td>1 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>82 17.3</td>
<td>33 23.4</td>
<td>36 27.3</td>
<td>31 26.5</td>
<td>11 16.2</td>
<td>12 41.4</td>
<td>1 12.5</td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>37 7.8</td>
<td>7 5.0</td>
<td>1 0.8</td>
<td>6 5.1</td>
<td>19 27.9</td>
<td>9 31.0</td>
<td>1 12.5</td>
</tr>
<tr>
<td>Aminopenicillin inhibitor</td>
<td>35 7.4</td>
<td>4 2.8</td>
<td>4 3.0</td>
<td>1 0.9</td>
<td>7 10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>26 5.5</td>
<td>3 2.1</td>
<td>6 4.5</td>
<td>1 0.9</td>
<td>4 5.9</td>
<td>1 3.4</td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>5 1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-spectrum penicillins</td>
<td>2 0.4</td>
<td></td>
<td>1 0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillinase-resistant penicillins</td>
<td>2 0.4</td>
<td></td>
<td>13 9.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>53 11.2</td>
<td>1 0.7</td>
<td>2 1.7</td>
<td>2 2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincosamide</td>
<td>15 3.2</td>
<td></td>
<td>6 4.5</td>
<td>7 6.0</td>
<td>3 4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>16 3.4</td>
<td>6 4.3</td>
<td>2 1.5</td>
<td>1 0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>4 0.8</td>
<td>12 8.5</td>
<td>2 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1 0.2</td>
<td>1 0.7</td>
<td>1 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glycopeptide</td>
<td>2 0.4</td>
<td></td>
<td>2 1.5</td>
<td></td>
<td></td>
<td></td>
<td>1 12.5</td>
</tr>
<tr>
<td>Imidazole</td>
<td>1 0.8</td>
<td></td>
<td>5 4.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of patients/number of courses of antibiotics. LRT = lower respiratory tract; UT = urinary tract; GI = gastrointestinal tract; URT = upper respiratory tract; CNS = central nervous system; No. = number of courses of antibiotics.
(41, 20.4%), followed by aminopenicillins (9, 4.5%). Other antibiotics were used less than 4.5% each.

The therapy of pneumonias was similar to that of lower respiratory tract infection, except that there was less use of first-generation cephalosporins alone (15.8%), aminoglycosides (21.1%), and aminopenicillins (7.0%), and more of macrolides (17.5%) and second- and third-generation cephalosporins (21.1%). However, none of the differences with the remainder of patients with lower respiratory tract infections reached significance.

**Evaluation of individual antibiotics prescribed**

The distribution of types of antibiotics used among 436 patients and 982 courses of antibiotics is shown in Table 3. First-generation cephalosporins were the most frequently used antibiotics (43.6%), followed by aminoglycosides (21.4%) and the penicillins (19.9%). The vast majority of courses of antibiotics were first-line antibiotics, consisting of first-generation cephalosporins, penicillin, aminopenicillin, oxacillin, erythromycin, and trimethoprim–sulfamethoxazole (778, 79.2%, data not shown).

Table 3 also lists the best and worst L and A marks for each of the major classes of antibiotics prescribed. Overall, 16.2% of all antibiotics were prescribed according to “bacteriologically defined events, and antibiotic used was consistent with susceptibility result” (LS), and 37.4% of antibiotics were indicated and chosen correctly (A1). Cephalosporins as a group had more LS and A1 marks, although the difference from the mean was not great (< 5%). Third-generation cephalosporins had more LS marks, suggesting that their use was better guided by laboratory data than other antibiotics. Marks for the use of aminoglycosides were worse than the others, with more LU and A3 and fewer A1 marks.

**Microbiology laboratory use**

From the review of each of the 436 cases, we could determine: 1) whether the patient had a microbiology laboratory work-up; 2) whether the work-up resulted in a meaningful microbiologic diagnosis that helped make the diagnosis of the infection event; and 3) whether antibiotic susceptibility testing was performed. All patients were divided into four groups according to these three criteria: Group I (criterion 1 yes, criterion 2 yes, criterion 3 yes) and Group II (criterion 1 yes, criterion 2 yes, criterion 3 no) represented patients who had a meaningful microbiologic diagnosis (163, 37.4%). Group III (criterion 1 yes, criterion 2 and 3 no) and Group IV (criteria 1, 2 and 3 no) represented patients who did not have meaningful microbiologic diagnoses (273, 62.6%). Groups I, II, and III had a microbiologic work-up (332, 76.2%) and Group IV had no microbiologic work-up (104, 23.8%).

### Table 3. Types of antibiotics used and marks

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. of courses</th>
<th>%</th>
<th>% L marks</th>
<th>% A1</th>
<th>% A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antibiotics</td>
<td>982</td>
<td>100.0</td>
<td>16.2</td>
<td>9.2</td>
<td>37.4</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>428</td>
<td>43.6</td>
<td>18.5*</td>
<td>7.4</td>
<td>41.6*</td>
</tr>
<tr>
<td>1st generation</td>
<td>349</td>
<td>35.5</td>
<td>17.7</td>
<td>8.0</td>
<td>40.4</td>
</tr>
<tr>
<td>2nd generation</td>
<td>48</td>
<td>4.9</td>
<td>8.3</td>
<td>6.3</td>
<td>50.0</td>
</tr>
<tr>
<td>3rd generation</td>
<td>29</td>
<td>3.0</td>
<td>44.8*</td>
<td>3.4</td>
<td>48.3</td>
</tr>
<tr>
<td>4th generation</td>
<td>2</td>
<td>0.2</td>
<td>50.0</td>
<td>0.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>210</td>
<td>21.4</td>
<td>15.0</td>
<td>15.0*</td>
<td>27.1*</td>
</tr>
<tr>
<td>All penicillins</td>
<td>195</td>
<td>19.9</td>
<td>10.7*</td>
<td>8.7</td>
<td>34.7</td>
</tr>
<tr>
<td>Natural penicillin</td>
<td>39</td>
<td>4.0</td>
<td>5.1</td>
<td>20.5*</td>
<td>30.8</td>
</tr>
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<td>Aminopenicillins</td>
<td>80</td>
<td>8.1</td>
<td>3.8*</td>
<td>5.0</td>
<td>16.3*</td>
</tr>
<tr>
<td>Aminopenicillin β-lactamase inhibitor combination</td>
<td>49</td>
<td>5.0</td>
<td>14.3</td>
<td>6.1</td>
<td>55.1*</td>
</tr>
<tr>
<td>Penicillinase-resistant penicillins</td>
<td>16</td>
<td>1.6</td>
<td>17.6</td>
<td>11.8</td>
<td>47.1</td>
</tr>
<tr>
<td>Extended-spectrum penicillins</td>
<td>9</td>
<td>0.9</td>
<td>55.6*</td>
<td>0.0</td>
<td>77.8*</td>
</tr>
<tr>
<td>Macrolides</td>
<td>58</td>
<td>5.9</td>
<td>6.9</td>
<td>5.2</td>
<td>39.7</td>
</tr>
<tr>
<td>Lincosamide</td>
<td>32</td>
<td>3.3</td>
<td>18.8</td>
<td>3.1</td>
<td>40.6</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>25</td>
<td>2.5</td>
<td>32.0*</td>
<td>4.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>18</td>
<td>1.8</td>
<td>0.0</td>
<td>5.6</td>
<td>11.1*</td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p < 0.05 when compared with the remainder of other antibiotics. LS = laboratory justification satisfactory; LU = laboratory justification unsatisfactory; A1 = correct antibiotic indication and choice; A3 = incorrect antibiotic indication and choice.
Antibiotics in Infections in Taiwan Hospitals

**Microbiologic determinations in major infections**
The results of microbiologic determinations undertaken in patients with the five most frequent infections by site are presented in Table 4. The proportion of patients for whom any culture was obtained ranged from 46.0% in patients with gastrointestinal infections to 85.6% in patients with lower respiratory tract infections. The proportion of cultures for which the result was helpful in making a microbiologic diagnosis ranged from 6.1% of upper respiratory tract infections to 38.5% of urinary tract infections. Although cultures were available for 84.6% of patients with suspected urinary tract infections, 61.5% of cases of urinary tract infections had no meaningful microbiologic diagnosis; most urine cultures were negative. In reviewing data from five random hospitals in this study, the proportions of negative urine cultures in patients with a diagnosis of urinary tract infection were 16.7%, 54.5%, 60.0%, 57.1%, and 73.7%.

Table 5 shows 30 agents identified from 105 cases of pneumonia (30, 28.6%). There were eight isolates from sterile sites (7.6%), three from blood, and five from pleural fluid. Others were from screened sputum cultures (18, 17.1%). The identified pathogens were largely aerobic gram-negative rods (AGNR; 20/30, 66.7%). There was only one isolate of *Streptococcus pneumoniae* and no cases of pneumococcal bacteremia. The frequency of identification of significant pathogens was 12.5% (12) among patients with non-pneumonia lower respiratory tract infections, significantly lower than the frequency of identifying pneumonia pathogens (28.6%, p < 0.05). No isolates from blood, pleural fluid, or tissues were obtained from patients without pneumonia.

**Effect of microbiologic work-up on antibiotic choices**
Antibiotics were prescribed in 384 courses when a microbiologic diagnosis was made and in 591 courses when it was not. When a diagnosis was made, LS marks were significantly more frequent (p < 0.01, 38.7% vs 1.5%). Conversely, LU scores were significantly higher when there was no microbiologic diagnosis (p < 0.01, 19.5% vs 2.6%). Apparently, the data required for giving these two differentiated marks were more readily available when there was a meaningful microbiologic diagnosis.

In terms of the indication and choice of antibiotic marks, whether there was a meaningful microbiologic diagnosis or not made no significant difference. Thus, the proportions of A1 scores (40.4% vs 35.5%, p = NS) were not significantly different. The frequencies of A3 scores were also close in both groups (14.5% vs 14.4%). While significant laboratory work-up had a significant effect on the L or laboratory marks, as might be expected, it had no effect on the A marks.

**Effect of dose and duration of antibiotics on evaluations**
Among 963 (98.1%) courses of antibiotics for which data was available, 58.5% (563) were administered correctly in terms of dose and duration. The dosage was correct but the duration of administration was incorrect in 31.8% (307). The dosage was incorrect but the duration was correct in 3.7% (36). Both dose and duration were incorrect in 5.9% (57).

L and A marks were given for 963 courses of antibiotics in 436 patients. Of these, 37.4% received an A1 mark and 14.5% received an A3 mark; 16.2% received an LS mark and 9.2% received an LU mark.

Table 4. Microbiologic determinations in different infections

<table>
<thead>
<tr>
<th></th>
<th>LRT</th>
<th>UT</th>
<th>Soft tissue</th>
<th>GI</th>
<th>URT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>201</td>
<td>65</td>
<td>60</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Pathogen identified</td>
<td>41</td>
<td>25</td>
<td>14</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Any culture</td>
<td>172</td>
<td>85.6</td>
<td>35</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Blood culture</td>
<td>111</td>
<td>55.2</td>
<td>13</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>112</td>
<td>55.7</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Urine culture</td>
<td>24</td>
<td>11.9</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other culture</td>
<td>14</td>
<td>7.0</td>
<td>26</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

*% of cases with one or more cultures*
Table 5. Lower respiratory tract pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Pneumonias (n = 105)</th>
<th>Non-pneumonias (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% pathogens</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Identity of pathogens was by meaningful isolates or tests that were considered meaningful by medical evaluators. Of 30 pathogens from pneumonias, 26 were identified by isolates: 18 were from sputum, 3 from blood (1 S. aureus, 1 E. coli, 1 K. rhinoscleromatis), and 5 from pleural fluid (2 S. aureus, 2 S. maltophilia, 1 K. pneumoniae). M. pneumoniae (4) was diagnosed by IgM (3) and by cold agglutinins (1). Eight isolates of Enterobacteriaceae were: 2 K. pneumoniae, 1 K. rhinoscleromatis, 2 Serratia marcescens, 1 Enterobacter aerogenes, 1 E. coli, and 1 Proteus mirabilis. Others included 1 Acinetobacter baumanii, and 1 Group D streptococcus. Altogether, 20 were aerobic gram-negative rods.

Discussion

Cases for this study were successively selected on the basis of patients having received antibiotics within 72 hours of admission. This requirement was intended to exclude biased selection and complex hospital acquired infections, which may be more difficult to evaluate. These 436 cases of presumed community-acquired infection events from nine major hospitals represent a cross-section of community-acquired infectious diseases in Taiwan’s 61 medical centers and regional hospitals. These hospitals were selected because of the availability of board-certified competent infectious disease specialists practicing in them, who evaluated the appropriateness of antibiotic therapy.

The predominant infection was of the lower respiratory tract (46.1%). Pneumonia was the most frequent diagnosis (52.2%). We did not document the roentgenographic and clinical evidence for this diagnosis. Almost all identified pathogens in lower respiratory tract infections were in patients with a diagnosis of pneumonia (70.7%). The pathogens isolated from patients with pneumonia were mostly AGNR (63.3%). There was only one isolate of S. pneumoniae from sputum (3.4%). This is significantly different from a review of the international literature of community-acquired pneumonia (CAP) from 1966 to 1995. In more than 7,000 cases of CAP, where an etiologic agent was diagnosed, the most frequent cause was S. pneumoniae. Two-thirds of bacteremias were caused by S. pneumoniae [9]. There was no S. pneumoniae bacteremia in this study, but there were eight (7.6%) blood culture and pleural fluid isolates with AGNR (5) and Staphylococcus aureus (3). Keeping in mind the difficulty and uncertainty of using sputum cultures for diagnosing pneumonias [10–12], the microbiologic diagnoses we came up with suggest that the primary agents causing CAP in Taiwan may be different from the Western world. This hypothesis should be confirmed by a prospective study with more objective definition of pneumonia, and assurance of optimum microbiologic work-up.

The reason for the preponderance of AGNR in CAP in Taiwan is unclear but several possible hypotheses can be suggested. The development of gram-negative pneumonia is probably preceded by microaspiration of AGNR colonizing the upper respiratory tract [13–15]. Such colonization has been found to be more common in incapacitated hospitalized patients [16], in patients in nursing homes [17], and in patients who have recently been on antibiotics [16, 17]. Gram-negative pneumonia, in particular due to H. influenzae, has been found to be more common in patients with COPD [12], although this has been disputed [18]. On the other hand, the 57 uncomplicated cases of CAP without comorbidities had a similar profile of AGNR (data not shown). Perhaps there is a high rate of colonization by AGNR in healthy subjects in Taiwan. This hypothesis should be directly tested using epidemiologic studies.

In our 201 cases of lower respiratory tract infection, there were 43 (21.4%) cases of COPD. Among our 105 cases of pneumonia, 48 (45.7%) were complicated with comorbidities including 13 with COPD. These patients with complications, vastly different from those without comorbidities, very possibly had prior or repeated
Fluoroquinolones had better L and A marks than other 
tor combinations, extended-spectrum penicillins, and 
J Formos Med Assoc 
Methicillin-resistant 
neither of the two identified cases of pneumonia with 
important cases of omission of treatment. For example, 
appropriate shifting of antibiotics, and duration of adminis-
tration either too long or too short. There were also 
number of antibiotics, inappropriate choice either 
incorrect in terms of indication and choice. Evidence 
courses, including 14.5% that were judged outright 
inappropriate use of antibiotics included excess 
combination, or in tandem in the majority of patients. 
First-generation cephalosporins were used singly, in 
combination, or in tandem in our survey except for central nervous system infections. This is understandable because of the prevalence of gram-negative organisms, but whether it should be used in CAP is debatable, as aminoglycosides are thought to be less effective in the lung because of the low pH of pulmonary secretions [19]. It is clear that once the prevalent organisms have been shown to be different, a new set of empiric therapeutic guidelines should be developed for CAP for Taiwan.

The heavy use of aminoglycosides, especially gentamicin, is a feature of therapy of infection at all sites in our survey except for central nervous system infections. This is understandable because of the prevalence of gram-negative organisms, but whether it should be used in CAP is debatable, as aminoglycosides are thought to be less effective in the lung because of the low pH of pulmonary secretions [19]. It is clear that once the prevalent organisms have been shown to be different, a new set of empiric therapeutic guidelines should be developed for CAP for Taiwan.

The pattern of antibiotic use was similar in infections at other sites. First-generation cephalosporins and aminoglycosides predominated (Table 3). The non-first line antibiotics such as third-generation cephalosporins, aminopenicillin/β-lactamase inhibitor combinations, extended-spectrum penicillins, and fluoroquinolones had better L and A marks than other antibiotics, suggesting that laboratory guidance might have been used. Trimethoprim–sulfamethoxazole had worse marks, probably because physicians are unaware it is no longer effective [1–4].

In our study, about 76.2% of patients had a laboratory work-up, but only 37.4% had a meaningful microbiologic diagnosis. The frequency of fruitful work-ups varied from 6.1 to 38.5% (Table 4). It was 20.4% in the case of lower respiratory tract infections and 38.5% in the case of urinary tract infections. A microbiologic diagnosis was made in 28.6% of cases of pneumonia. This is low but consistent with a review of the North American literature, which showed that even in prospective studies using exhaustive microbiologic methods [10], the etiologic agent was identified only in 40% to 60% of CAPs [11].

A significant problem of negative or inconclusive microbiologic results in Taiwan is administration of antibiotics to patients prior to admission. Liu et al found that 55.2% of patients at arrival in emergency departments and 25.1% of patients in outpatient departments had antimicrobial activity in urine [20]. Twenty-four percent of the patients had no microbiologic laboratory work-up. We have no direct data on the quality of performance of the microbiologic laboratories and whether they were properly and optimally utilized by clinicians.

It is noteworthy that making a microbiologic diagnosis or performing sensitivity tests had no effect on the A mark. Only in 16.2% of cases was the choice of antibiotics guided by a meaningful microbiologic diagnosis and sensitivity test results (LS). This suggests that physicians did not usually use laboratory evidence for choice of antibiotics, which was usually first line and based on empirical judgment.

In conclusion, this study confirms our previous hypothesis that the first-line antibiotics, ie, first-generation cephalosporins, aminopenicillins, gentamicin, and erythromycin, are the primary targets of overuse and misuse in Taiwan [1]. Their use was largely empiric and not usually substantiated or guided by laboratory evidence. Comparatively, the use of non-first line antibiotics relied more on laboratory data. In some cases, they were not used when they should have been. The main problem with microbiologic work-up is that often an etiologic agent is not found, and microbiology laboratory guidance for therapy is not available. As shown by the low efficiency of diagnosing CAP worldwide [9, 11, 12, 18], there is a generic inadequacy of microbiology laboratory practice today.

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References


