Inappropriate Use of Antibiotics and the Risk for Delayed Admission and Masked Diagnosis of Infectious Diseases

A Lesson From Taiwan

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Background: Antibiotic resistance is a serious problem worldwide. It is particularly alarming in Taiwan and other countries of the Pacific Rim, where antimicrobial drugs are used excessively.

Objective: To determine whether use of antimicrobial drugs before coming to an emergency department was associated with delayed admission or masked or missed diagnoses at a large general hospital in Taiwan.

Methods: Antimicrobial activity in urine (AAU) was determined in all patients seen in the emergency department during a 3-month study. A physician, unaware of the results of the urine tests, reviewed the medical charts of patients who were admitted to the hospital to determine whether admission was delayed for at least 7 days or the diagnosis was masked or missed.

Results: Of the 1182 patients, 444 were admitted to the hospital. In 220 patients (49.5%), AAU was detected. There was no significant difference in AAU between patients with or without an infectious disease (53.0% vs 46.3%, respectively; \( P = .41 \)). For patients with infection, 34.8% of those with AAU had a delayed admission, compared with only 21.6% without AAU (relative risk [RR], 1.61; 95% confidence interval [CI], 1.03-2.52; \( P = .03 \)). For patients without infection, 36.2% of those with AAU had a delayed admission compared with 31.1% without AAU (RR, 1.16; 95% CI, 0.81-1.68; \( P = .64 \)). For patients with infection, 48.7% of those with AAU had a masked or missed diagnosis, compared with 25.5% without AAU (RR, 1.91; 95% CI, 1.30-2.80; \( P < .001 \)). For patients without infection, 27.6% of those with AAU had a masked or missed diagnosis compared with 14.8% without AAU (RR, 1.87; 95% CI, 1.11-3.17; \( P = .02 \)).

Conclusion: Use of antimicrobial drugs before coming to an emergency department was associated with a significantly increased risk for delayed and masked or missed diagnoses of infectious diseases and missed diagnosis of noninfectious diseases.

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SUBJECTS AND METHODS

STUDY POPULATION

All patients who came to the ED of the Kaohsiung Veterans General Hospital during the 3 months from January to April 1997, were asked whether they had recently received antimicrobial drugs and to submit a urine specimen. The ED records were reviewed to obtain the initial diagnosis and demographic information and to determine whether the patient had been admitted to the hospital or discharged. The study population consisted of patients who came directly to the ED for care or were referred from the clinic within 3 days and admitted to the hospital. Patients who were transferred from another medical facility were not included. One of us (Y.-C.L.) from the Section of Infectious Diseases reviewed the records while unaware of the results of the urine tests. He determined whether the patient had an infectious disease, the admission had been delayed for 7 or more days before coming to the ED, and the presumed diagnosis on admission was incorrect or masked because of obscure signs or symptoms (eg, absence of fever, leukocytosis, or localized signs of infection). The analysis was conducted on a case-by-case study without preset definitions. The evaluation was based on chart review of the clinical, laboratory, and radiological findings and the discharge diagnosis. The information was coded and kept confidential. The hospital’s institutional review board did not require review of protocols or informed consent for the urine tests or medical chart review. The investigators complied with the principles outlined in the Declaration of Helsinki.

DETERMINATION OF AAU

The urine specimens were immediately refrigerated and frozen within 24 hours. Assays for AAU were performed within 1 week with strains of *B. stearothermophilus* ATCC 7953, *E. coli* ATCC 25922, and 5 *pyogenes* ATCC 19165 (American Type Culture Collection, Manassas, Va), as previously described. The presence of a zone of inhibition of at least 10 mm with any of the 3 assay strains was considered evidence of receipt of antimicrobial drugs within the previous 48 hours.

STATISTICAL ANALYSIS

The data were entered into a commercially available computer program (Microsoft Excel; Microsoft Corp, Redmond, Wash) and analyzed by means of statistical software (Epi Info Version 6; Centers for Disease Control and Prevention, Atlanta, Ga) using the χ² method (Mantel-Haenszel) and relative risk with 95% confidence intervals.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Four hundred forty-four of the 1182 patients who were seen in the ED met the criteria for entry into the study (Figure). The age and sex distribution of patients with infection (n=217; mean [±SD] age, 55±21 years; range, 1-90 years; male-female ratio, 1.2:1) was not significantly different from those without infection (n=227; mean [±SD] age, 51±21 years; range, 1-85 years; male/female ratio, 1.1:1). We detected AAU in 220 of the 444 patients (49.5%). There was no significant difference in the proportion with AAU in patients with (53.0%) and without (46.3%) an infection (P=.41) (Figure and Table).
Patients Seen in the ED (N=1182)

Medical Charts Reviewed
1177 (99.6%)

Admitted
572 (48.6%)

Discharged
505 (51.4%)

Information Available
563/572 (98.4%)

Came Directly to ED (n=391) or From Clinic (n=53)

Infection 217/444 (48.9%)

No Infection 227/444 (51.1%)

Antibacterial Activity in Urine

Infection 115/217 (53.0%)

No Infection 105/227 (46.3%)

Flow diagram showing how the patients were selected to enter the study. ED indicates emergency department.

### Effect of Recent Antibiotic Use on Delayed Admission or Masked or Missed Diagnosis

<table>
<thead>
<tr>
<th>Infection (n = 217)</th>
<th>No Infection (n = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Delayed Admission</td>
<td></td>
</tr>
<tr>
<td>AAU</td>
<td>40</td>
</tr>
<tr>
<td>No AAU</td>
<td>22</td>
</tr>
<tr>
<td>Total†</td>
<td>62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Masked or Missed Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAU</td>
</tr>
<tr>
<td>No AAU</td>
</tr>
<tr>
<td>Total‡</td>
</tr>
</tbody>
</table>

*AAU indicates antimicrobial activity in urine, determined by a zone of inhibition with any of the following microorganisms: Bacillus stearothermophilus, Escherichia coli, and Streptococcus pyogenes. Patients were referred from the clinic or came directly to the emergency department of a general hospital in Kaohsiung, Taiwan.
†For patients with infection, relative risk was 1.61 (95% confidence interval [CI], 1.03-2.52; P = .03); patients with no infection, 1.16 (95% CI, 0.81-1.68; P = .64).
‡For patients with infection, relative risk was 1.91 (95% CI, 1.30-2.80; P < .001); for patients with no infection, 1.87 (95% CI, 1.11-3.17; P = .02).

### ILLUSTRATIVE CASES

The following cases illustrate the decision process that was used for classification. The reviewer was unaware of the results of the urine tests.

#### Category 1

**Infection (+), urine test (+), delayed admission (+), and masked diagnosis (+).**

A 2-year-old boy was seen in the ED because of fever for 1 week, vomiting for 1 day, and shortness of breath. An outside clinic considered him to have bronchiolitis and treated him with unknown drugs. He improved temporarily, but dyspnea developed. The final diagnosis was bronchopneumonia and acute otitis media.

Results of testing for AAU were positive. It appears that this child was given antibiotics without supporting information from results of an adequate physical examination, a chest x-ray film, or laboratory tests, leading to delayed admission and masked diagnosis.

#### Category 2

**Infection (+), urine test (+), delayed admission (−), and masked diagnosis (+).**

A 77-year-old man sought medical care at a local hospital because of 3 days of generalized abdominal pain and 4 days of constipation. He was thought to have gastritis or peptic ulcer disease and was treated with unknown drugs. Symptoms recurred after initial improvement. When seen in the ED, he was found to have an acute abdomen and underwent a laparotomy. The final diagnosis was perforated gastric ulcer with peritonitis.

Results of testing for AAU were positive. It is unclear why this man was treated with antibiotics for apparent gastritis or peptic ulcer disease, masking the final diagnosis. Although the admission was delayed, it did not meet the preset criterion of 7 or more days.

#### Category 3

**Infection (+), urine test (+), delayed admission (+), and masked diagnosis (−).**

A 58-year-old woman noted anal pain and fever for 1 week. She sought advice from several physicians for a presumed inflamed hemorrhoid. She was treated with oral and injected drugs but did not improve. She came to the ED and was immediately admitted. A computed tomographic (CT) scan demonstrated an ischiorectal abscess. She underwent fistulostomy and fasciotomy and recovered. The culture of the abscess yielded E. coli susceptible to all tested antibiotics.

Results of testing for AAU were positive. It appears that her physicians did not perform an adequate rectal examination. Antibiotics had been given because of fever, leading to delayed admission. The diagnosis was readily made in the ED.

#### Category 4

**Infection (+), urine test (−), delayed admission (−), and masked diagnosis (+).**

A 32-year-old man noted generalized discomfort and fever for 5 days. He came directly to the ED because of worsening of symptoms. He was thought to have spondylolisthesis at the space between L4 and L5 and was admitted. A CT scan was performed because of persistent pain and fever and disclosed a paraspinal abscess at L4-5.

The reviewer thought that this patient might have taken antibiotics that masked the diagnosis. Results of testing for AAU were negative, and he had not taken an-
tibiotics. Admission was not delayed, but the diagnosis was delayed until performance of a CT scan.

Category 5

Infection (−), urine test (+), delayed admission (+), and masked diagnosis (+).

A 71-year-old man was seen at several medical centers because of fever and weight loss for several months. He was considered to have acute pharyngitis or a viral infection and was treated with a variety of oral and injected drugs. His symptoms waxed and waned. Finally, he came to the ED and was admitted with the tentative diagnosis of fever of unknown origin. The discharge diagnosis was malignant lymphoma.

Results of testing for AAU were positive. This man had been given antibiotics for symptomatic treatment of fever and weight loss, without the benefit of an adequate differential diagnosis and appropriate studies, leading to delayed admission and missed diagnosis.

Category 6

Infection (−), urine test (−), delayed admission (+), and masked diagnosis (+).

Persistent right upper quadrant abdominal pain and generalized itching developed in a 65-year-old man over several weeks. He visited many clinics, where he was given a variety of drugs for symptomatic pain relief. Finally, a local physician referred him to the ED for presumed gallstones. On admission, he was noted to have jaundice and hepatomegaly. The CT scan revealed a carcinoma at the head of the pancreas with liver metastases.

This man had received a variety of pain medications, which appeared to delay admission and mask the diagnosis. Antibiotics had not been given recently, and results of testing for AAU were negative.

Category 7

Infection (−), urine test (−), delayed admission (+), and masked diagnosis (−).

Severe low back pain developed in a 44-year-old laborer after lifting a heavy machine about 2 weeks before being seen in the ED. He had purchased over-the-counter drugs for pain relief. The symptoms waxed and waned but persisted. He was thought to have severe sciatica and was admitted. Magnetic resonance imaging revealed a herniated intervertebral disc.

This patient elected to treat himself with pain medications and delayed seeking medical advice. Results of testing for AAU were negative.

EFFECT OF RECENT ANTIBIOTIC USE ON DELAY OF ADMISSION OR MASKED DIAGNOSIS

The effect of recent antibiotic use on delayed admission or masked diagnosis among the 444 patients is summarized in the Table. Patients with infection and AAU were more likely to have had a delayed admission and a masked diagnosis than those without AAU (P = .03 and P < .001, respectively). The differences between these groups were 13.2% and 23.2%, respectively. Patients without infection and with AAU were no more likely to have had a delayed admission (P = .64), but were more likely to have had a missed diagnosis (P = .02) than those without AAU. The differences between these groups were 5.1% and 12.8%, respectively. The relative risks are shown in the Table.

A similar analysis was performed using E coli and S pyogenes without B stearothermophilus as the assay strains. Patients with infection and AAU were more likely to have had a delayed admission and a masked diagnosis than those without AAU (P = .14 and P = .005, respectively). Patients without infection and with AAU were no more likely to have had a delayed admission (P = .95), but more likely to have had a masked diagnosis (P = .008) than those without AAU.

COMMENT

The current study sought to determine whether prior antimicrobial drug use would delay admission or mask the diagnosis in patients seen at an ED in Taiwan. It soon became apparent that patients were unaware of the drugs that were prescribed, purchased, or injected by a local pharmacist. Their physicians refused to provide information or stated that it was unavailable. Accordingly, we developed a simple microbiological method to detect AAU and to provide an independent marker of recent antimicrobial drug use.

In the current study, we found that use of antimicrobial drugs before coming to an ED was associated with a significant delay in hospital admission and masked diagnoses in patients with infection. It was also associated with a significant increase in missed diagnoses among patients without infection. The effect of prior antimicrobial drug use appears to be robust in view of the large number of confounding variables. These include the wide range in patient age, high rates of antimicrobial drug use, diverse medical and surgical conditions, and numerous primary care physicians.

The shortcomings of this study include the inability (1) to detect prior use of antimicrobial drugs for more than 1 or 2 days before arrival in the ED or drugs that are not excreted in the urine, (2) to determine the outcome for patients who were discharged from the ED, and (3) to assess the potential benefits and deficits of antimicrobial therapy among patients who did not come to the ED. Furthermore, the high frequency of delayed admissions and masked or missed diagnoses in this population for other reasons could have partly obscured the effect of prior use of antimicrobial drugs. There is also the potential for systemic bias that could not be completely addressed in this report. This bias might occur in patients who suddenly become acutely ill and did not have time to see a physician or take an antibiotic. These patients would not be likely to have had positive results of a urine test or a delayed admission. Patients who had been ill for some time would have been more likely to seek previous medical attention and to have a delayed admission.

There is ample evidence of overuse of antimicrobial drugs in outpatient practices in the United States.17,18 We are unaware of studies dealing with delayed admi-
sion and masked or missed diagnoses, other than anecdotal accounts in case reports and conferences. Further studies are needed to confirm our findings and to determine the impact of inappropriate use of antibiotics on morbidity, mortality, and costs.

The reasons why physicians continue to prescribe antibiotics inappropriately are complex. Some years ago, Kunin et al coined the phrase “drugs of fear” to characterize the compelling need of physicians to use the latest and best antibiotics to solve a problem and to meet patient expectations. These fears are compounded each time a trusted drug becomes less useful because of resistance. The clinical reasoning appears to be quite straightforward, ie, why not use a reasonably safe and effective broad-spectrum drug to prevent an unfavorable outcome for a seemingly trivial but potentially serious illness when the specific diagnosis is not immediately apparent? This perception helps to explain why the promotion of drugs to physicians and the public is so successful.

The problem of inappropriate use of antimicrobial drugs may worsen, despite numerous recommendations and guidelines prepared by eminent organizations and alarming reports in the news media. We believe that attention needs to be focused on the constraints of medical practice, patient expectation, and promotional practices. The research questions are as follows: (1) Would the use of antimicrobial drugs be improved if physicians spent more time and provided more personalized care to their patients? (2) Would the ready availability of low-cost, rapid diagnostic tests improve the situation? (3) Can the public be better informed about the risks and benefits of antimicrobial drugs? (4) Do current practice guidelines meet the needs of practicing physicians? (5) Can more effective methods be developed to help physicians diagnose and manage common infectious diseases? (6) Can government and nonprofit organizations develop sophisticated methods to counteract exuberant pharmaceutical marketing?

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REFERENCES