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Excessive use of antibiotics in the community associated with delayed admission and masked diagnosis of infectious diseases

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Resistance to antimicrobial drugs is becoming more serious throughout the world, and is a major problem in Taiwan. The selective pressure of antibiotic use makes some degree of antibiotic resistance inevitable, but extraordinarily high rates of resistance suggest excessive use. This report reviews collaborative studies undertaken in the southern city of Kaohsiung to better define the use of antibiotics in the community and to determine whether recent use of antibiotics results in delayed admission and missed or masked diagnoses of infectious diseases among patients presented at an emergency department. Because of the unreliability in the patients' medical history, antibiotic activity was determined in the urine. These studies demonstrated that (1) detection of antibiotics in the urine offers a simple and inexpensive means to determine antibiotic use when a history of drug use is unreliable; (2) the high frequency of antibiotics use among patients presenting at emergency departments, clinics, and in the community may account for the extraordinarily high rates of antimicrobial drug resistance in Taiwan; and (3) recent use of antimicrobial drugs before visiting an emergency department was associated with a significantly increased risk of delayed and masked or missed diagnoses of infectious diseases, and missed diagnosis of noninfectious diseases. These findings reflect inherent social, economic, and cultural problems and constraints in the medical care system in Taiwan. The issue of inappropriate use of antibiotics in the community, hospitals, and agriculture is now being addressed at a national level.

Key words: Antibiotics, medical care, resistance, urine assay

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Resistance to antimicrobial drugs is becoming more serious throughout the world [1-4]. Resistance is an inevitable result of the selective pressure of intensive use of antibiotics, the adaptive plasticity of the microorganisms, and the increasing ease of international travel [5,6]. This problem is particularly serious in developing countries where antimicrobial drugs are excessively prescribed or are available without prescription. The high rate of antimicrobial drug resistance in these countries appears to be due to a combination of the heavy burden of bacterial infectious diseases, inappropriate use of the available antimicrobial drugs, and rapid spread of resistant strains through crowding, poor sanitation, and unsafe sexual practices. As a consequence, it is becoming more difficult and costly to select appropriate drugs for life-threatening infectious diseases.

Antibiotic resistance is a major problem in Taiwan, a developed nation with about 23 million people. It has one of the highest rates of antibiotic-resistant microorganisms in the world [7-9]. The extremely high prevalence of antibiotic-resistant *Streptococcus pneumoniae* in the community appears to be related to the dissemination of high-level penicillin-resistant, extended-spectrum cephalosporin- and erythromycin-resistant clones, and the selective pressure of antibiotic use [10,11]. It is reasonable to assume that high rates of resistance in community-acquired pathogens are the result of the selective pressure of intensive use of antibiotics in the general population. A series of questions were formulated to address these issues (Table 1).

Community use of antimicrobial drugs can be readily determined in western countries by measuring sales and prescriptions, and conducting surveys of

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Table 1. Relation between antibiotic resistance and use of antibiotics in the community in Taiwan

1) Taiwan has one of the highest rates of antibiotic-resistant microorganisms in the world.
2) Does excess use of antibiotics account for the heavy burden of resistance?
3) How can the magnitude of antibiotic use be determined when consumers are often unaware of drugs prescribed and physicians and pharmacists would not tell?
4) Does inappropriate use delay admission to hospitals and mask the diagnosis of infectious diseases?
5) What are the special conditions in Taiwan that lead physicians to prescribe antibiotics when they are not needed?
6) Why do people seek antibiotics?
7) Can effective measures be devised to improve the appropriate use of antibiotics and decrease the burden of resistance?

physician prescribing practices [12,13]. It is much more difficult to measure use in countries such as Taiwan, where consumers are often unaware of the drugs that were self-purchased, prescribed by physicians, or injected by a local pharmacist. Physician and pharmacy records are largely unavailable [14]. Wide range of available products and mixtures, potential adulteration, and inadequate labeling of antibiotic drugs make the task even more difficult. Antibiotics dispensed in pharmacies without prescription are often irrational, inappropriate, and the dosage are inadequate [15-18]. Understanding the social, behavioral, and economic factors in the community is of critical importance in investigating and combating the problem [19,20].

Antimicrobial Activity in the Urine as a Surrogate Maker for Recent Use

A study was undertaken to determine whether patients visiting the emergency department of Veterans General Hospital-Kaohsiung had received antibiotics prior to their visit. Because most patients were unaware of the nature of the drugs that had been prescribed, and not much information on antibiotic use can be retrieved from physicians because of missing records, antimicrobial activity in the urine was thus used as a surrogate marker. The study first determined whether commonly used oral antibiotics can be detected in the urine of volunteers who had not recently received antimicrobial drugs [21]. The sensitivity and specificity of the method was then tested by obtaining urine from hospitalized patients who were or were not receiving antimicrobial therapy.

Healthy volunteers were given single oral dose of each of the oral antimicrobial drugs listed in Table 2. The drugs were taken before breakfast shortly after a baseline urine specimen was obtained. Urine was collected in each subsequent, spontaneous void for 3 days. A 15-mL aliquot was stored at –20°C until assayed. Urine was also collected on 2 consecutive mornings from 117 inpatients receiving cardiac and gastrointestinal services. Their medical charts were reviewed to determine whether they had received antimicrobial drugs the day before. Results showed that 39 patients were receiving antimicrobial drugs and 78 were not. Most of the patients receiving antimicrobial drugs were on regularly scheduled doses. Urine was collected from most patients about 6 h after the last dose.

Antimicrobial activity was determined by the disk diffusion method using 3 different bacterial assay strains. *Bacillus stearothermophilus* ATCC 7953 provided a highly sensitive marker of most antibacterial drugs; *Escherichia coli* ATCC 25922 was used to detect drugs that are active against most gram-negative bacteria; and *Streptococcus pyogenes* ATCC 19165 was used to detect drugs that are active against most gram-positive bacteria.

Antimicrobial activity was not detected in the baseline urine specimen. It was readily detected in about

Table 2. Detection of antimicrobial activity in urine of volunteers following a single oral dose of commonly used antimicrobial drugs [21]

Ability to detect antimicrobial activity			
12-24 h		>48 h	
Drug	Dose (mg)	Drug	Dose (mg)
Ampicillin	1000	Clindamycin	600
Amoxicillin	250	Tetracycline	1000
Amox/clav	750	TMP/SMZ	160/800
Cefaclor	1000	Ciprofloxacin	250
Carbenicillin	500	Norfloxacin	400
Erythromycin	1000		

Abbreviations: Amox/clav = amoxicillin/clavulanate; TMP/SMZ = trimethoprim/sulfamethoxazole

12 to 24 h following a single oral dose of β-lactam antibiotics and erythromycin and clindamycin. It was detected in 48 to 72 h following a single oral dose of tetracycline, trimethoprim/sulfamethoxazole, and ciprofloxacin. *B. stearothermophilus* produced the largest zones of inhibition and detected activity for the longest periods of time (Table 2).

In hospitalized patients receiving multiple drugs, the sensitivity and specificity of antimicrobial drugs were: *B. stearothermophilus* 100% and 85.9%; *S. pyogenes* 94.9 % and 94.9 %, and *E. coli* 71.8 % and 98.7 %, respectively. Thus, detection of antimicrobial activity in the urine appeared to be a good surrogate marker of antimicrobial drug use within 12 to 48 h.

High Usage of Antibiotics Revealed by Antimicrobial Activity in Urine

To determine the usage of antibiotics in the community, urine was collected from a variety of populations [22]. These include patients admitted to the emergency department at Veterans General Hospital-Kaohsiung during a 3-month period, patients queuing to see physicians in the internal medicine outpatient department, students at a local high school, and senior citizens attending a day care center. Demographic characteristics and medical history were recorded. The participants were asked whether they had recently received antimicrobial drugs and to submit a urine specimen. The specimens were immediately refrigerated and frozen within 24 h. Assays were performed within 1 week. A 100% compliance was achieved. The findings are shown in Fig. 1.

The highest rates of antibiotic use were found in patients visiting the emergency department, followed by internal medicine outpatients. The rates in high school students and the elderly were virtually identical,

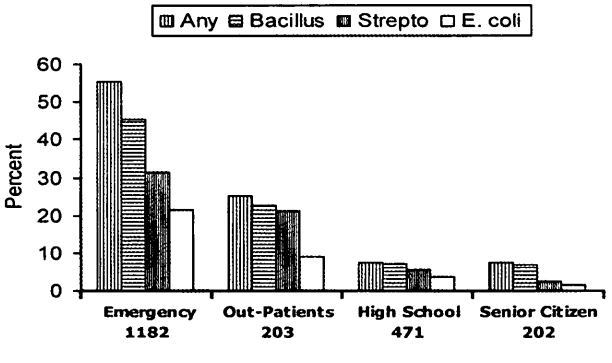

Fig. 1. Antimicrobial activity in the urine as detected by any of the assay strains or by a single assay strain consisting of *Bacillus stearothermophilus*, *Streptococcus pyogenes* and *Escherichia coli* [22].

and the rates between males and females in any group were not significantly different. Among the emergency department patients, antimicrobial activity was detected in 58.8% of 541 medical, 51.3% of 604 surgical, 65.7% of 35 pediatric, and 100% of 2 obstetrics patients (medicine vs surgery, p=0.01; adults vs pediatrics, p=0.27).

The largest zones of inhibition were obtained with *B. stearothermophilus*. This species independently detected 83.4% of all positive urine samples. *S. pyogenes* independently detected 74.3% and *E. coli* independently detected 40.4% of all positive urine sample. *B. stearothermophilus* together with *S. pyogenes* accounted for 98.9% of all positives. *E. coli* added only 1.1%.

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

The emergency department records of patients who participated in the study were reviewed [23]. Information on the initial diagnosis, demographic characteristics, and whether the patient had been admitted to the hospital or discharged was obtained. The studied population consists of those who directly visited the emergency department, and those referred from the clinic and admitted to the hospital. Patients who were referred from another medical facility were not included. The author who reviewed the medical records was blinded to the results of the urine tests. He determined whether the patient had an infectious disease, whether the admission had been delayed for 7 or more days before visiting the emergency department, and whether 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 basis without preset definitions. The evaluation was based on chart review of the clinical, laboratory, and radiologic findings and the discharge diagnosis. The information was coded and kept confidential. A flow diagram that describes this process is shown in Figure 2.

Four hundred and forty four of the 1182 patients seen in the emergency department met the entry criteria of the study (Fig. 2). The age and sex distribution of infected patients (mean age, 55 ± 21 years; range, 1-90 years; male/female ratio, 1:1.2) was not significantly different from those without infection (mean age, 51 ± 21 years; range, 1-85 years; male/female ratio, 1:1.1). Antimicrobial activity was detected in the urine of 220 (49.5%) of the 444 patients. There was no significant

difference in the proportion of patient with antimicrobial activity in the urine between infected and uninfected patients (53% vs 46.3%; p=41) (Fig. 2).

The effect of recent antibiotic use on delayed admission or masked diagnosis among the 444 patients is summarized in Figs. 3 and 4. Patients with infection and antimicrobial activity in the urine were more likely to have had a delayed admission and a masked diagnosis than those without antimicrobial activity in the urine (p=0.03 and 0.0004, respectively). The differences between these 2 groups in Fig. 3 were 13.2% and 23.2%, respectively. Patients without infection and antimicrobial activity in the urine were no more likely to have had a delayed admission (p=0.64), but more likely to have had a missed diagnosis (p= 0.02) than those without antimicrobial activity in the urine. The differences between these groups in Fig. 4 were 5.1% and 10.3%.

Discussion

The above studies demonstrates that: (1) detection of antibiotics in the urine offers a simple and inexpensive means to correlate antibiotic use and resistance with socioeconomic and behavioral factors in populations when a history of drug use is unreliable; (2) the high frequency of antibiotic use among patients presenting at emergency departments, clinics, and the community may account for the extraordinarily high rates of antimicrobial drug resistance in Taiwan; and (3) recent use of antimicrobial drugs before visiting an emergency department was associated with a significantly increased risk of delayed and masked or missed diagnoses of infectious diseases, and missed diagnosis of noninfectious diseases.

Commonly used antibacterial drugs can be readily detected in human urine, with considerable sensitivity and specificity, and with minimal interference by the large variety of other drugs commonly used in hospitalized patients. It seems reasonable to use all 3 strains in field studies. *B. stearothermophilus* offers the advantage of detecting low levels of drug for the longest period of time. *E. coli* and *S. pyogenes* provide helpful clues regarding the type of drug that was administered.

The urine test is inexpensive and can be used at sites that lack sophisticated equipment. It may serendipitously detect unexpected antimicrobial activity of other drugs, local remedies, or special diets. The method can be used for detecting adulterated or counterfeit products [24]. Absence of antimicrobial activity in urine may explain why a patient failed to respond to putative antimicrobial therapy. The disadvantages are dependence on renal excretion, inability to identify specific drugs and their metabolites, and inability to detect use beyond 1 to 3 days. These problems can be addressed by using more sensitive and specific high-pressure liquid chromatography and other methods.

The test is particularly useful in developing countries where antimicrobial drugs are often self-prescribed and the patient's medical history is unreliable, and in developed countries where antibiotics are often given unnecessarily for respiratory infections. Assay of antimicrobial activity in urine in conjunction with surveillance cultures provides useful information about the impact of antimicrobial drug on the resistance

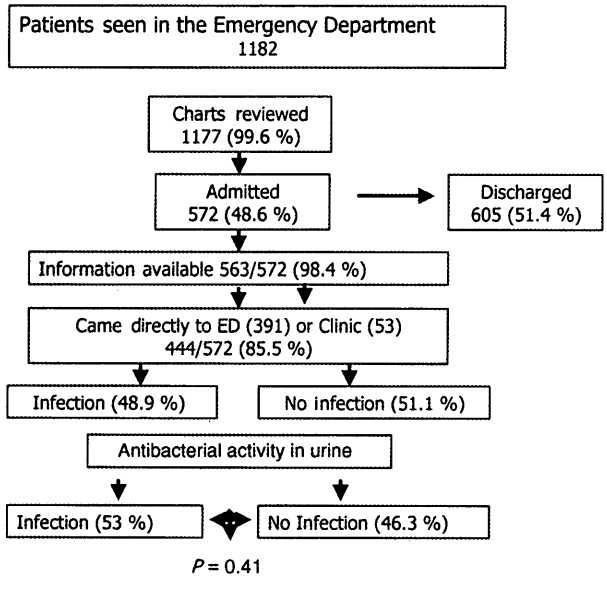

Fig. 2. A flow diagram showing how the patients were selected to enter the study. ED = emergency department [23].

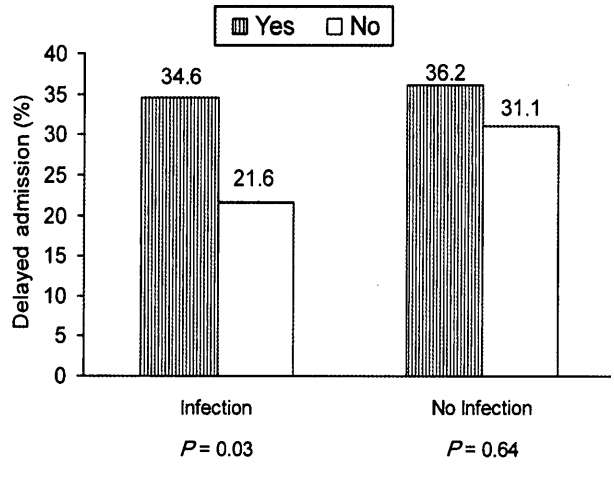

Fig. 3. Determination of the effect of recent antibiotic use on delayed admission [23].

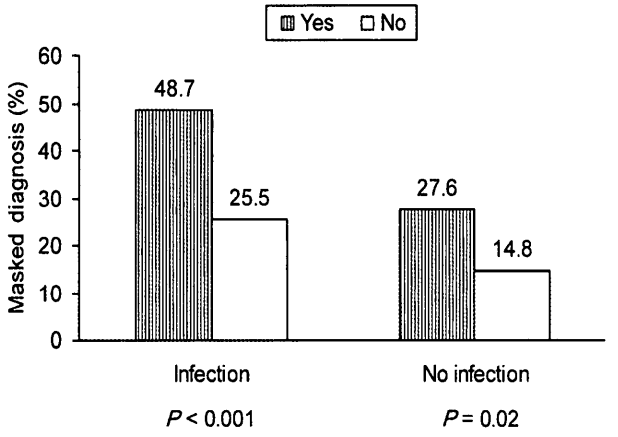

Fig. 4. Determination of the effect of recent antibiotic use on masked or missed diagnosis [23].

in defined populations. It would be of great interest to compare the resistant rates with similar populations in other developing and developed countries.

We have been aware of a high usage of antimicrobial drugs in Taiwan, but the fact that over half of patients who visit an emergency department had taken antibiotics within the previous 12 to 48 h suggests a surprisingly high antibiotics usage. The high rate among internal medicine outpatients, most of whom were older male veterans, may reflect the frequent use of antibiotics in people with chronic obstructive pulmonary disease. Cigarette smoking is a major problem in Taiwan. The similar point prevalence of antibiotic use (about 7.5%) among high school students and the ambulatory elderly suggests that this may be the baseline in the community, but more data are needed from other parts of the country.

The above studies also suggest that the use of antimicrobial drugs before visiting an emergency department is associated with a significant delay in hospital admission and masked diagnoses in infected patients, as well as a significant increase in missed diagnoses among uninfected patients. 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 variation among primary care physicians.

The short comings of this study include the inability to (1) detect use of antimicrobial drugs for more than 1 or 2 days prior to arrival at the emergency department, or drugs such as chloramphenicol that are poorly excreted in the urine; (2) determine the outcome for patients who were discharged from the emergency department; and (3) assess the potential benefits and deficits of antimicrobial therapy among patients who did not visit the emergency department. Furthermore, the high frequency of delayed admissions and masked or missed diagnoses in this population for reasons other than antibiotic use could have partly obscured the effect of prior use of antimicrobial drugs.

There is also potential for systemic bias that cannot be completely addressed in this report. This may occur when patients become acutely ill within a very short period and do not have enough time to see a physician or take any antibiotics. These patients would not be likely to have a positive urine test or a delayed admission. Patients who have been ill for some time are more likely to seek prior medical attention and to have a delayed admission. We did not take into account studies dealing with delayed admission and masked or missed diagnoses other than anecdotal accounts in case reports and conferences. Further studies are needed to confirm findings presented here, 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. The phrase "drugs of fear" was coined a few years ago [25] to characterize the compelling need of physicians to use the latest and best antibiotics to solve a problem and to meet patients' expectations. These fears are compounded each time when a trusted drug becomes less useful because of resistance. The clinical reasoning appears to be straightforward: 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 explain why the promotion of drugs to physicians and the public has been so successful.

Taiwanese are currently covered by universal health insurance. This has increased the number of visits to the physician, while the mean time a physician spend with a patient has increased only from 5.8 to 7.7 min [26]. Simple diagnostic tests are often not performed or deferred until the patient becomes severely ill and is referred to a hospital. The reasons for the short visits are complex and cultural, but are partly related to inadequate compensation for office visits and laboratory tests. Physicians also sell drugs to patients. Often, a patient may seek advice from several physicians and health care providers, and may be given additional drugs.

The problem of inappropriate use of antimicrobial drugs has worsened despite the numerous recommendations and guidelines prepared by eminent organizations and alarming reports in the news media. Attention needs to be focused on the constraints of

medical practice, patient expectation, and promotional practices [19,20]. The research questions are: "Would the use of antimicrobial drugs be more prudent if physicians spend more time and provided more personalized care to their patients?" "Would the availability of low-cost, rapid diagnostic tests improve the situation?" "Can the public be better informed about the risks and benefits of antimicrobial drugs?" "Do current practice guidelines meet the needs of practicing physicians?" "Can we develop more effective methods to help physicians diagnose and manage common infectious diseases?" and "Can the government and nonprofit organizations develop sophisticated methods to counteract exuberant pharmaceutical marketing?".

Nationwide efforts are now underway in Taiwan for better use of antibiotics in the community, hospital, and agriculture. These efforts are supported by the leading professionals in infectious diseases and important government agencies, which will likely improve medical care and reduce the frequency of resistant microbial pathogens.

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