Increasing Prevalence of Methicillin-Resistant *Staphylococcus aureus* Causing Nosocomial Infections at a University Hospital in Taiwan from 1986 to 2001

Po-Ren Hsueh,1,2,3* Lee-Jene Teng,4 Wen-Hwei Chen,3 Huei-Ju Pan,1,3 Mei-Lin Chen,1,3 Shan-Chwen Chang,2,3 Kwen-Tay Luh,1,2 and Fang-Yue Lin3

Departments of Laboratory Medicine1 and Internal Medicine2 and Committee of Infection Control,3 National Taiwan University Hospital, and School of Medical Technology, National Taiwan University College of Medicine,4 Taipei, Taiwan

Received 3 June 2003/Returned for modification 1 September 2003/Accepted 30 December 2003

A rapid emergence of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection (from 26.3% in 1986 to 77% in 2001) was found. The susceptibility of 200 nonduplicate blood isolates of MRSA and 100 MRSA isolates causing refractory bacteremia to 22 antimicrobial agents disclosed that glycopeptides, quinupristin-dalfopristin, and linezolid remained the most active agents.

Antimicrobial drug resistance has become a great public health problem worldwide (15, 25). Among the resistant pathogens, methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) is of great concern because of the predominance of this organism that causes various clinical infections, including those acquired in the community or hospitals (2, 3, 5, 8, 22). Recently, MRSA strains with reduced susceptibility to vancomycin, i.e., vancomycin resistant, vancomycin intermediate (VISA), or heterogeneously resistant (hetero-VISA), have been reported (1, 6, 10, 24).

In Taiwan, the prevalence of MRSA in the hospitals has been steadily increasing in the past decade (11, 13, 14). Hospitals in Taiwan continue to have high selective pressure of glycopeptides and extended-spectrum cephalosporins (12, 13). Moreover, overuse and abuse of surgical antibiotic prophylaxis in hospitals are common (18). The purpose of this study is to point out the high resistance of isolates of *S. aureus* to many available antibiotics at the National Taiwan University Hospital (NTUH) and to determine the potential roles of some newly developed agents against infections caused by this resistant pathogen.

The NTUH is a 1,800-bed university hospital located in northern Taiwan. The Nosocomial Infection Control Committee of the hospital was established in 1980. Definitions for nosocomial infection followed the National Nosocomial Infections Surveillance guidelines (9). The annual patient-days of the hospital increased from 360,210 in 1991 to 631,410 in 2001. To determine the secular trend of antimicrobial resistance patterns of *S. aureus* causing nosocomial infections at the NTUH, data on the disk diffusion susceptibilities to oxacillin, erythromycin, clindamycin, gentamicin, and vancomycin of this organism recovered from 1986 to 2001 were retrieved from the annual summary documents.

The annual consumption of extended-spectrum cephalosporins (third- and fourth-generation cephalosporins: cefotaxime, ceftriaxone, ceftazidime, cefepime, and cefpirome), carbapenems (imipenem and meropenem), ciprofloxacin (parenteral form), and glycopeptides (vancomycin and teicoplanin) expressed as defined daily dose per 1,000 patient-days from 1991 to 2001 was also analyzed. All of these drugs were introduced into the hospital before 1991, except for cefepime, which became available only in 1997; meropenem, available since 1998 only; and cefpirome, available since 2000.

From January 1999 to June 2002, all of the isolates of MRSA recovered from various specimens from the patients treated at the NTUH were routinely subjected to screening for their susceptibility to vancomycin by a method described previously (10). Briefly, overnight cultures of MRSA isolates were adjusted to 0.5 U of McFarland turbidity and 10 μl of the cell suspension was inoculated onto a brain-heart infusion agar (BBL Microbiology Systems, Cockeysville, Md.) plate containing >4 μg of vancomycin (Eli Lilly & Co., Indianapolis, Ind.)/ml. The plate contents were incubated at 37°C for 48 h. If confluent growth was seen within 24 h, the isolate was considered possibly vancomycin-resistant *S. aureus* or VISA. If a countable number of colonies were found within 48 h, the isolate was considered possibly hetero-VISA (10).

A total of 300 consecutive and nonduplicate blood isolates of *S. aureus*, including 200 isolates of MRSA and 100 of oxacillin (methicillin)-susceptible *S. aureus* (MSSA), from 300 patients who had bloodstream infections and who were treated at the NTUH from January 2000 to July 2002, were collected for this study. An additional 100 isolates of MRSA were also collected from 30 patients with MRSA bacteremia (infective endocarditis, osteomyelitis, and center venous catheter-related sepsis) who failed glycopeptide therapy (persistent fever and breakthrough MRSA bacteremia). These patients were seen at the hospital between January 2001 and June 2002. Each patient had to four MRSA isolates, with intervals of 7 to 28 days, recovered from blood specimens. The isolates were stored at −70°C in Trypticase soy broth (Difco Laboratories, Detroit, Mich.) supplemented with 15% glycerol before being tested.

*Corresponding author. Mailing address: Department of Laboratory Medicine, National Taiwan University Hospital, No 7, Chung-Shan South Rd., Taipei, Taiwan. Phone: 886-2-23123456, ext. 5363. Fax: 886-2-23224263. E-mail: hsporen@ha.mc.ntu.edu.tw.
of MRSA from patients with refractory bacteremia, only five agents (oxacillin, vancomycin, teicoplanin, fusidic acid, and linezolid) were tested.

A fourfold increase in the annual prevalence of MRSA causing nosocomial infection was noted from 1990 (8.9 per 100,000 discharges) to 2000 (32.6 per 100,000 discharges) (Fig. 1). There was a 2.9-fold increase in the prevalence of MRSA from 26.7% in 1990 to 77% in 2001.

The annual prevalence of oxacillin resistance in S. aureus, particularly the prevalence of MRSA causing nosocomial bloodstream infection rose remarkably and reached 60 to 80% in the last 5 years. In 2001, isolates from surgical-site infection had a slightly higher level of resistance than did isolates from three other infection sites. The rapid increase in nosocomial bloodstream MRSA isolates from 1990 to 1996, followed by a plateau beginning in 1997, correlated with extended-spectrum β-lactamase and carbapenem consumption more than with consumption of other agents, although hospital consumption of glycopeptidase and ciprofloxacin (intravenous and oral forms) also rose in the last 12 years (Fig. 2).

From January 1999 to June 2002, a total of 5,500 clinical isolates of MRSA were routinely screened for their susceptibility to vancomycin. However, isolates with reduced susceptibility to vancomycin were not found.

For the 100 MSSA isolates, >90% of isolates were susceptible to agents tested except for penicillin (13% susceptible), azithromycin (57% susceptible), clindamycin (87% susceptible), and chloramphenicol (87% susceptible) (Table 1). All the penicillin-susceptible isolates were negative for β-lactamase by means of the nitrocefin-based test (Cefinase disk; BBL Microbiology Systems). One isolate was intermediate to quinupristin-dalfopristin. Among the fluoroquinolones tested, garenoxacin and sitafloxacin were the most active agents (MICs at which 90% of the isolates tested were inhibited were 0.03 μg/ml for both agents). Of the carbapenem group, imipenem was over eight times more active than meropenem or ertapenem.

For the MRSA isolates, all were susceptible to glycopeptidase and linezolid. Less than 5% were nonsusceptible to quinupristin-dalfopristin or fusidic acid. For more than 90% of isolates, azithromycin MICs were >128 μg/ml, and all of the isolates were also resistant to clindamycin (constitutively resistant). Sitafloxacin was most active, followed by gatifloxacin, moxifloxacin, and garenoxacin, which all had similar activities against ciprofloxacin-resistant isolates. Activity levels of teicoplanin and azithromycin were similar, and were both very poor. Multidrug-resistant MRSA, defined as isolates with resistance to three or more drug classes other than β-lactam antibiotics, accounted for 95% of all MRSA isolates.

For the 100 isolates, the MIC ranges of the five agents were as follows: oxacillin, 32 to >128 μg/ml; vancomycin, 1 to 2 μg/ml; teicoplanin, 1 to 4 μg/ml; fusidic acid, 0.06 to >32 μg/ml; and linezolid, 0.5 to 2 μg/ml. Multiple isolates from one patient had nearly identical MICs (within one twofold dilution) for the five antimicrobial agents tested. Two patients had isolates for which vancomycin MICs changed from 1 to 2 μg/ml. For four MRSA isolates that were recovered from two patients (two in each) suffering from refractory bacteremia treated with linezolid, linezolid MICs were identical (1 μg/ml).

Two important points were clearly demonstrated in this study.
study. First, the rapid emergence of MRSA in the recent 10 years paralleled the increasing consumption of extended-spectrum cephalosporins, carbapenems, ciprofloxacin, and glycopeptides in the hospitals. These observations partly support previous findings (7, 15, 25). Fortunately, no vancomycin-intermediate or -resistant isolates were found even among MRSA isolates causing refractory bacteremia where glycopeptide therapy failed. Second, newer fluoroquinolones, such as sitafloxacin, moxifloxacin, and gatifloxacin, had better activities than did ciprofloxacin or levofloxacin against MRSA. These results were in agreement with previous findings (16, 21, 23). Telithromycin activity was similar to that of azithromycin. Glycopeptides, fusidic acid, quinupristin-dalfopristin, and linezolid remain the most active agents in vitro against MRSA in Taiwan.

Previous studies showed that telithromycin, a ketolide, had excellent activities against erythromycin-susceptible or -inducibly resistant MSSA. However, its activity against erythromycin-resistant MRSA was poor (4, 17). In this study, the activity of telithromycin was over 256 times lower against MRSA than

FIG. 1. Incidence of nosocomial bloodstream infections caused by \textit{S. aureus} and distribution of \textit{S. aureus} among all pathogens causing nosocomial bloodstream infections at the NTUH, 1981 to 2001.

FIG. 2. Association between the prevalence of oxacillin-resistant \textit{S. aureus} (MRSA) causing nosocomial infections and annual consumption (defined daily dose [DDD] per 1,000 patient-days) of extended-spectrum cephalosporins (ceftaxime, ceftriaxone, cefazidime, cefepime, and ceftipirome), carbapenems (imipenem and meropenem), ciprofloxacin, and glycopeptides (vancomycin and teicoplanin) at the NTUH, 1986 to 2001.
its activity against MSSA. Both azithromycin and telithromycin lack activity against MRSA with probable constitutive expression of erm methylase. Our results were in line with their findings (4, 17).

In summary, there are both a rapid emergence of nosocomial \textit{S. aureus} infection and increasing prevalence of MRSA in the hospital. Minimizing the antibiotic pressure that favors the selection of MRSA is essential to controlling the emergence of these resistant strains in the hospitals.

REFERENCES