An Outbreak of *Staphylococcus aureus* Strains with Reduced Susceptibility to Glycopeptides in a French General Hospital

We describe the isolation of *Staphylococcus aureus* isolates with glycopeptide heteroresistant subpopulation from 15 patients (11 with colonizations and 4 with infections) in a French hospital. Non of the patients were previously treated with glycopeptides. The 15 isolates belonged to 2 different pulsotypes unrelated to other methicillin-resistant *S. aureus* isolates from the same hospital.

Vancomycin-intermediate *Staphylococcus aureus* are strains intermittently resistant to vancomycin that have...
minimum inhibitory concentrations (MICs) of vancomycin >4 µg/mL, as defined by the National Committee for Laboratory Standards (NCCLS) [1]. *S. aureus* strains with reduced susceptibility to vancomycin and/or teicoplanin (for glycopeptide-intermediate *S. aureus* [GISA]) have now been reported from Japan [2], the United States [3], and Europe [4]. All cases involved patients who had undergone prolonged therapy with a glycopeptide for infection with methicillin-resistant *S. aureus* (MRSA). However, there have not been reports of outbreaks of nosocomial infections caused by GISA, or of colonization by GISA of patients and/or staff in hospitals or other institutions, until very recently [5].

We describe the isolation of GISA from 15 patients in 1 hospital. The institution has 822 beds in 2 independent buildings; patients were frequently transferred between the buildings. Because MRSA were endemic in the hospital, patients from the long-term care facility and the intensive care unit were all screened on admission and then weekly for nasal colonization by MRSA and GISA (by use of Mueller-Hinton agar plates containing 4 µg/mL teicoplanin). Seventy-six MRSA strains were isolated in 1998 from 833 patient admissions to these units, for a rate of MRSA colonization of 9%. In June 1998, a GISA isolate was recovered from a specimen from the nose of a patient 3 months after admission. MRSA had not previously been isolated from this patient, and he had received no glycopeptide before the GISA isolate was detected. Subsequently, from January 4th to April 4th 1999, 14 GISA isolates were cultured from specimens from 14 patients. Ten isolates came from nasal specimens from elderly patients living in the long-term care facility; 1 isolate came from a urine sample and was responsible for a urinary tract infection in a 82-year-old patient, and 3 isolates came from protected tracheal aspirates (>10⁴ cfu/mL) that were associated with pulmonary infection in patients in the intensive care unit. None of the patients had been treated with glycopeptide before the isolation of a GISA strain.

We determined MICs for vancomycin and teicoplanin using Etest strips (AB Biodisk, Solna, Sweden). We used a heavy inoculum (≥10⁴ CFU/mL) in brain-heart infusion agar, which we incubated for 48 h at 35°C [6]. The low break point for vancomycin was 4 µg/mL and for teicoplanin 8 µg/mL, as defined by the NCCLS [1]. Vancomycin MICs for the GISA isolates ranged from 6 to 8 µg/mL, and teicoplanin MICs ranged from 16 to 32 µg/mL; all had a sharp break point. Control GISA isolates (*S. aureus* Mu50 [2] and LIM2 [4]) were correctly detected, and had MICs of vancomycin and teicoplanin of 8 µg/mL and 24 µg/mL, respectively; the glycopeptide MIC for the *S. aureus* susceptible strain ATCC29213 was 2 µg/mL, as expected [6].

When we used a conventional inoculum (i.e., 5 × 10⁸ CFU/mL), resistance was not detected, especially for vancomycin, whatever the technique applied: vancomycin MICs for the GISA isolates ranged from 1 to 4 µg/mL, and teicoplanin MICs ranged from 2 to 16 µg/mL (results were obtained with use of the Etest, broth microdilution, and agar dilution MIC techniques). Eight representative GISA isolates were tested for the presence of heteroresistant subpopulations, as described elsewhere [7]. All GISA isolates that we tested had resistant subpopulations that grew in the presence of 6 µg/mL vancomycin, in contrast to *S. aureus* ATCC29213, which had no subpopulation that grew in the presence of >3 µg/mL vancomycin. The mupirocin MICs for the GISA isolates ranged from 0.125 to 0.5 µg/mL, which corresponds to susceptible isolates [8].

All GISA-infected patients and carriers were isolated in a single room and control measures (hand washing, gloving, protective clothing, etc.) recommended for controlling the spread of MRSA were instituted. Infected patients received nasal mupirocin cream and chlorhexidine baths and were treated by vancomycin for 10 days; all were cured of infection. Since May 1999, no new patients have been colonized or infected by a GISA strain. Thirteen of the 15 patients from whom a GISA strain was isolated either were discharged from the hospital or died from unrelated causes; 2 patients were still present in the hospital in October 1999.

![Figure 1. Pulsed field gel electrophoresis banding patterns of representative isolates of *Staphylococcus aureus* that are intermediately susceptible to vancomycin and/or teicoplanin (glycopeptide-intermediate *S. aureus* [GISA]) and banding patterns for isolates of non-GISA methicillin-resistant *S. aureus* (MRSA). The length (in kb) of the *SmaI* restriction fragments of *S. aureus* NCTC 8325 is indicated. GISA-A, isolate with pulsotype A; GISA-B, isolate with pulsotype B; MRSA, non-GISA MRSA isolate; NCTC 8325, control strain.](image-url)
long-term care facility unit in November 1999. Nasal eradication of the GISA strain was achieved for 1 patient; the other became a chronic carrier.

Pulsed field gel electrophoresis (PFGE) was performed on the 15 GISA isolates and on the 6 MRSA isolates that had colonized 6 of the 15 patients before they were colonized with GISA (figure 1). Two major clones were recognized: pulsotype A in 11 patients, including the patient from 1998 and the first 10 patients in whom GISA was detected in January and February 1999, and pulsotype B (differing by >5 bands from pulsotype A) in 4 patients in whom GISA was detected in March and April 1999. Pulsotypes A and B were observed in isolates from patients hospitalized in both of the hospital buildings. The MRSA isolates susceptible to glycopeptides (non-GISA MRSA) produced distinct PFGE types, unrelated to pulsotypes A and B (figure 1). GISA-MRSA and non-GISA MRSA isolates from a single geographical area usually have closely related PFGE types, and glycopeptide selective pressure is considered to be responsible for the emergence of resistance among the resident clones [7]. In our case, it is likely that both GISA clones were brought into the hospital and then transmitted from patient to patient.

Therefore, GISA can be epidemic in a hospital setting, as has been observed for other epidemic strains of MRSA. They need to be detected by systematic screening, including the screening of patients who are not receiving glycopeptide antibiotics. GISA can be responsible for both colonization and infections. Fortunately, in our cases, the low level of resistance observed (MIC of vancomycin, 6–8 μg/mL) allowed successful treatment.

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References