ORIGINAL ARTICLE

An Outbreak of Heterogeneous Glycopeptide-Intermediate *Staphylococcus aureus* Related to a Device Source in an Intensive Care Unit

Sylvie Parer, MD;[1,2] Anne Lotthé, MD;[1,2] Patrick Chardon, MD;[3] Rosie Poncet, MD;[4] Hélène Jean-Pierre, MD;[2,5] Estelle Jumas-Bilak, PhD, PharmD[1,2]

OBJECTIVE. The emergence of *Staphylococcus aureus* with reduced susceptibility to glycopeptides (glycopeptide-intermediate *S. aureus* [GISA] and heterogeneous GISA [h-GISA]) leads to intensive care unit (ICU) outbreaks that frequently result in ward closure. We investigated the role of hospital hygiene in the transmission and eradication of an h-GISA outbreak.

DESIGN. The study is a description of an original environmental investigation around a series of 12 cases.

SETTING AND PATIENTS. The outbreak occurred in a 20-bed polyvalent/trauma ICU in a 2,800-bed tertiary care university hospital in France.

INTERVENTIONS. Specimens were obtained for surveillance and diagnostic cultures from all patients in the unit. Surface sampling was also performed. Geographic cohorting, contact isolation, emphasis on adherence to infection control practices, and environmental cleaning were implemented.

RESULTS. Twelve patients with h-GISA infection ($n = 5$) or colonization ($n = 7$) were identified. The mean interval between admission and h-GISA detection was 23.6 days (range, 10–89 days), with a median of 16.5 days. Environmental investigation identified an unexpected reservoir, namely, SpO_2 sensors. The outbreak was controlled by a combination of measures, including eradication of this reservoir, avoiding total ward closure.

CONCLUSIONS. Targeted surface sampling helps to secure the environment through active investigation of various reservoirs while maintaining normal activity on the ward. In our study, this method led to the detection of an unsuspected reservoir, the eradication of which helped control the h-GISA epidemic. Further applications of this original investigative procedure should allow confirmation of its relevance and efficiency.

Infect Control Hosp Epidemiol 2012;33(2):167-174

Outbreaks caused by multidrug-resistant bacteria (MDRB) in intensive care units (ICUs) can be difficult to control,[1] and eradication of the epidemic strain often requires radical measures, such as closure of the ICU.[2,3] Over the past decades, methicillin-resistant *Staphylococcus aureus* (MRSA) strains have become endemic in hospitals worldwide, leading to an increase in empirical vancomycin use and possibly selective pressure.[4] In 1997, the first strain of *S. aureus* with reduced susceptibility to vancomycin and teicoplanin was reported from Japan.[5-7] Soon after, cases and outbreaks of glycopeptide-intermediate *S. aureus* (GISA) were reported from the United States[8] and later from Europe,[9] particularly in France.[10-13] GISA display homogeneous resistance in the presence of vancomycin or teicoplanin at concentrations of at least 4 μg/mL, whereas for heterogeneous GISA (h-GISA) a subpopulation grows in the presence of vancomycin or teicoplanin at such concentrations.[11] Patients with GISA had a history of glycopeptide treatment,[13] unlike patients with h-GISA,[14] suggesting a role of antibiotic selective pressure in the emergence of GISA strains from a precursor h-GISA phenotype.[12] Both GISA and h-GISA could confer reduced clinical response to glycopeptides.[15,16]

Several outbreaks of GISA and h-GISA infections have been described that underline the role of hospital hygiene in the

Affiliations: 1. Département d'Hygiène Hospitalière, Centre Hospitalier Régional Universitaire de Montpellier, Montpellier, France; 2. Unité Mixte de Recherche 5119 (Université Montpellier 2, Centre National de la Recherche Scientifique [CNRS], Institut de Recherche pour le Développement [IRD], Institut Français de Recherche pour l'Exploitation de la Mer [IFREMER], Université Montpellier 1), équipe Pathogènes et Environnements, Université Montpellier 1, Montpellier, France; 3. Département d'Anesthésie et Réanimation A, Centre Hospitalier Régional Universitaire de Montpellier, Montpellier, France; 4. Service de Médecine du Travail, Centre Hospitalier Régional Universitaire de Montpellier, Montpellier, France; 5. Laboratoire de Bactériologie, Hôpital Arnaud de Villeneuve, Centre Hospitalier Régional Universitaire de Montpellier, Montpellier, France.

Received May 16, 2011; accepted October 11, 2011; electronically published January 3, 2012.

 0899-823X/2012/3302-0010$15.00. DOI: 10.1086/663703

eradication of environmental reservoirs.[14,17,18] We report an outbreak of h-GISA involving 12 ICU patients. An original method of targeted investigation led to identification of an environmental reservoir while avoiding total ward closure.

METHODS

Setting

The outbreak occurred in a 20-bed polyvalent/trauma ICU of the Montpellier Hospital (France), a 2,800-bed split-site tertiary care University Hospital. The ICU is divided in 5 areas of 4 single rooms. Healthcare workers (HCWs) are dedicated to a single unit. Patients are admitted from the outside for trauma or transferred from other hospitals or wards within the hospital. For MDRB surveillance, samples from the anterior nares, rectum, and upper respiratory tract are collected from all patients expected to stay longer than 48 hours, on admission and once a week thereafter. Contact precautions are implemented for the care of patients colonized or infected with MDRB: donning of aprons (or gowns) and gloves when entering the room, hand disinfection with hydroalcoholic rub or antiseptic scrub when leaving the room and during patient care, cohorting of colonized/infected patients with designated nurses, signaling of MDRB-carrier status on the room door, and intensified cleaning (wash, rinse, disinfection) of all surfaces, equipment, and walls in the room upon patient discharge. Infected patients are generally hospitalized in or transferred to areas 4 and 5. Horizontal surfaces of the rooms, bed rails, and high-touch surfaces are routinely cleaned twice a day for all patients.

Hospital MDRB Surveillance System

Real-time surveillance is implemented through a daily account of all patients newly colonized or infected with MDRB, using an antibiotic resistance information system (Sirscan, i2a). Surveillance data are transmitted to the hospital infection control team via the electronic hospital network. When a colonized or infected patient is notified, the referent infection control nurse informs HCWs on the ward and ensures that adequate precaution measures are implemented.

Microbiology

For screening of *S. aureus* carriage in patients and HCWs, nasal swabs were plated onto chromogenic medium (SAID, bioMérieux). Routine environmental microbial assessment was based on growth (at 37°C for 48 hours) on Count-tact (AES) medium. Irregular surfaces were sampled with a cotton swab, which was used to inoculate trypticase-soy and Chapman agar plates (bioMérieux).

Antimicrobial susceptibility was tested by disk diffusion assay.[19] Decreased susceptibility to glycopeptides is suggested by an inhibition zone of less than 17 mm around a teicoplanin disk associated with a difference of at least 3 mm between vancomycin and teicoplanin inhibition-zone diameters. Associated resistances to gentamycin and/or rifampicin gave additional insights into h-GISA/GISA phenotype.[13] Vancomycin minimal inhibitory concentration (MIC) was evaluated with Etest (AB Biodisk) on Mueller-Hinton agar with an inoculum concentration of 0.5 McFarland standards. The population analysis profile–area under the curve (PAP-AUC) reference method for h-GISA/GISA phenotype confirmation was performed at the French National Reference Center for Staphylococci according to the method described by Hiramatsu et al.[6] Purification of genomic DNA, *Sma*I (New England Biolabs) restriction, and pulsed-field gel electrophoresis (PFGE) were performed as described by Corne et al.[20]

Environmental Investigation

A targeted method for surface sampling assessed the adequacy of ward cleaning by systematically testing vacated rooms after thorough cleaning and surface disinfection. Sampling of about 15 sites per room focused on equipment and devices that could come into contact with patients and/or HCWs. Swabs were inoculated onto Chapman agar plates and Mueller-Hinton agar with 4-mg/L gentamycin agar plates targeting gentamycin-resistant staphylococci. Culture results were returned within 36–48 hours. Admission of a new patient was permitted only if all targeted cultures were negative. In the event of a positive screening, the room was cleaned again without waiting for complete microbial identification.

Case Definition

A clinical case was defined as a patient admitted to the ICU after June 18, 2007, showing positive culture of h-GISA in a clinical or screening sample, regardless of location at the time of diagnosis. For the first strain isolated in the case series, h-GISA character was confirmed by the PAP-AUC method. A microbiological case met all the following criteria: (1) presence of MRSA in a clinical sample, (2) reduced inhibition diameters around vancomycin and teicoplanin disks, (3) vancomycin MIC > 2 μg/mL, (4) resistance to gentamycin and rifampin, and (5) a pulsotype identical to that of the h-GISA isolate confirmed by PAP-AUC.

RESULTS

Outbreak Description

The microbiology laboratory gave an alert on June 30, 2007, when 3 patients (numbered 1, 2 and 3 in Table 1) received diagnoses of infections caused by MRSA resistant to gentamycin and rifampin. The diameter around vancomycin and teicoplanin disks and associated resistance led to suspicion of h-GISA/GISA strains.[21,22] The h-GISA phenotype was confirmed by PAP-AUC for the strain of patient 1. PFGE indicated that the strains of the 3 patients were identical (Figure 1). None had carried MDRB on admission or before h-GISA identification.

Despite barrier precautions and mask wearing by all HCWs

https://doi.org/10.1086/663703 Published online by Cambridge University Press

TABLE 1. Characteristics of h-GISA-Colonized or Infected Patients

Patient	Sex; age, years	Initial diagnosis; admission date	Clinical sample;[a] date of first h-GISA detection	Nasal carriage; date of first culture-positive sample	Contamination delay, days	Anti-infection treatment	Length of ICU stay, days	Area[b]
1	Male; 44	Trauma; May 31	Sputum (i); Jun 18	MRSA, h-GISA; Jun 19[c]	18	Vancomycin[d] (Jun 18–28)	36	4
2	Male; 16	Trauma; Jun 14	Catheter (c); Jun 25	MSSA; Jun 15	11	Vancomycin, rifampin	20	2
3	Male; 26	Trauma; Jun 9	Sputum (c); Jun 26	MRSA, h-GISA; Jul 6[c]	19	None	39	1, 2
4	Male; 47	Trauma; Jul 2	External fixator (c); Jul 7	MRSA, h-GISA; Jul 16[c]	15	None	25	2
5	Male; 68	Cardiac arrest; Jul 22	Urine (i); Aug 20	None ($n = 4$)	29	Trimethoprim-sulfamethoxazole,[d] amoxicillin	32	2
6	Male; 63	Trauma; Jul 28	Catheter (c); Sept 6	None ($n = 4$)	40	Vancomycin	47	2
7	Male; 29	Trauma; Aug 24	Sputum (c); Sept 7	MRSA, h-GISA; Sept 11[c]	14	None	28	1, 3
8	Female; 65	Trauma; Aug 23	Sputum (i); Sept 10	MRSA, h-GISA; Sept 11	18	Linezolid[d] (nasal mupirocin)	42	2
9	Male; 33	Trauma; Aug 31	Wound (c); Sept 28	MRSA, h-GISA; Sept 10	10	None	11	2
10	Male; 76	Gangrene; Sept 12	Abcess (i); Sept 22	None ($n = 2$)	10	Clindamycin,[d] metronidazole, imipenen, fluconazole	15	2
11	Female; 38	Trauma; Sept 14	Sputum (i); Sept 24	None ($n = 5$)	10	Trimethoprim-sulfamethoxazole,[d] pristinamycin,[d] linezolid[d]	38	1, 4
12	Male; 74	COPD; May 31	Sputum (c); Aug 28	None ($n = 5$)	89 (after discharge)	None (nasal mupirocin)	34	5, 4

NOTE. All dates are in 2007. COPD, chronic obstructive pulmonary disease; h-GISA, heterogeneous glycopeptide-intermediate *Staphyloccoccus aurea*; MRSA, methicillin-resistant *S. aurea*; MSSA, methicillin-susceptible *S. aureus*.

[a] i, infected site; c, colonized site.

[b] Location of patient within the intensive care unit at time of diagnosis.

[c] After 1–4 negative samples.

[d] Treatment related to h-GISA infection.

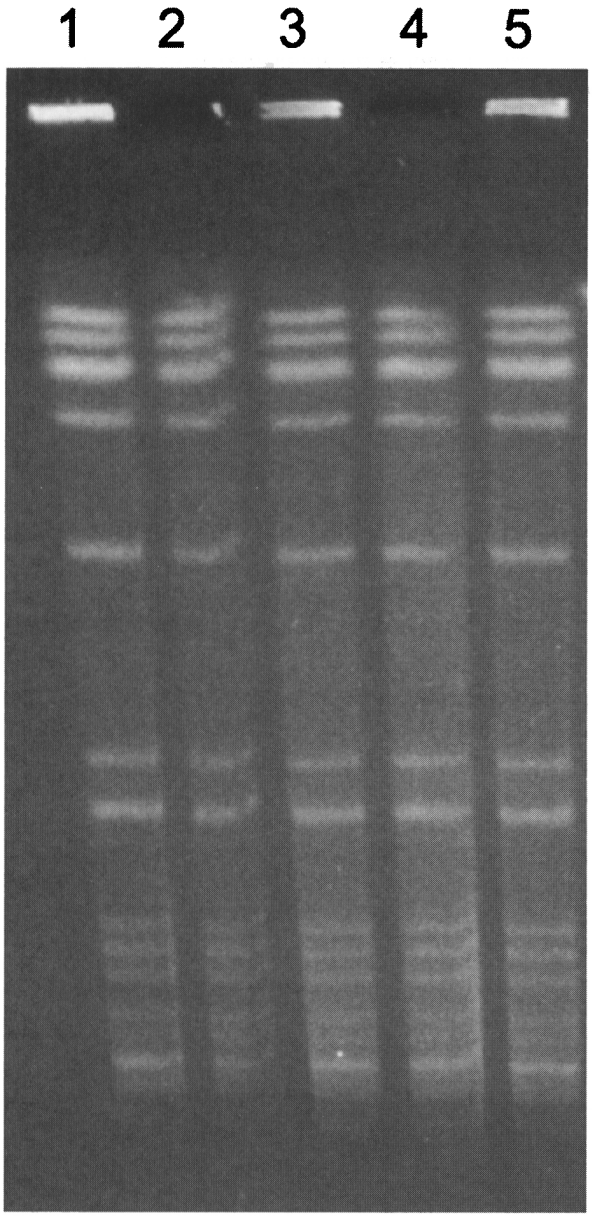

FIGURE 1. Pulsed-field gel electrophoresis banding patterns of *Sma*I-digested chromosomal DNA of 5 heterogeneous glycopeptide-intermediate *Staphylococcus aureus* (h-GISA) strains isolated from the first 5 patients identified as colonized or infected by h-GISA strains during the intensive care unit outbreak period. Lanes 1–5 show the h-GISA strains isolated in patients 1–5, respectively.

attending the h-GISA patients, cohorting, enhanced cleaning, and staff information, the outbreak continued, and a total of 12 patients became colonized or infected with the epidemic strain between June 16 and September 24. The 12 epidemic isolates shared the same antibiotype and the same PFGE fingerprint (Figure 1). The epidemic curve and case synopses are presented in Figure 2. Relevant patient and epidemic features are summarized in Table 1. The synopsis of interventions and investigations for infection control is presented in Table 2.

Only 6 of the 12 case-patients showed h-GISA nasal carriage; for patient 9 alone was the epidemic strain first isolated from a screening sample, and this occurred only 18 days later from a cutaneous wound. For the other patients, the strain was isolated from a clinical sample before (2 cases) or simultaneously with (3 cases) anterior-nares carriage. The other 6 patients never showed nasal carriage of h-GISA, in spite of colonization and/or infection of clinical sites. None of the patients had received glycopeptide therapy prior to acquiring h-GISA. The mean interval between admission and h-GISA detection was 23.6 days (range, 10–89 days), with a median of 16.5 days. All patients were eventually discharged from the ICU, except 2 who died for reasons unrelated to h-GISA infection.

Retrospective Microbiological Investigation

Surveillance data from the ICU indicated that in 2006 the incidence of MRSA in clinical samples was 1.89/1,000 patient-days. MRSA strains isolated from January 2003 to December 2006 were retrospectively surveyed via SIR software archives in search of h-GISA strains. Only 6 MRSA strains isolated in 2004 and 2005 showed resistance to rifampin and gentamycin, and this particular antibiotype was not found thereafter until the outbreak presented here. Reduced susceptibility to glycopeptides was not detected at the time of isolation. These strains were unavailable for further investigation.

In calendar 2007, 842 anterior-nares samples were obtained for routine surveillance of MRSA carriage in the ICU. All 24 MRSA strains thus detected were assayed for gentamycin and rifampin resistance. No gentamycin- and rifampin-resistant strain, other than those involved in the epidemic discussed here, was detected.

HCWs and Environmental Microbiological Investigations

Of the current 114 HCWs of the ICU, 111 (97.4%) were screened for nares carriage of *S. aureus*. Twelve (10.8%) had positive results, of whom 3 (2.7%) carried MRSA strains susceptible to vancomycin, gentamycin, and rifampicin. The epidemic clone was not detected among HCWs.

Environmental investigation was initially performed by repeated sampling of surfaces in patients' rooms, the admission room, and units where h-GISA carriers had been staying. Specimens were also sampled from medical equipment (electrocardiograph, fiber-optic bronchoscope, mobile ultrasonograph apparatus). On July 11, the h-GISA epidemic strain was detected on a strap of the patient scales, which were meticulously cleaned. When a new case emerged in area 2, surface specimens sampled in this area did not reveal the epidemic strain; neither was it detected after complete cleaning of that particular unit.

Targeted environmental screening (169 samples) of 12 cleaned vacated rooms was implemented starting October 7

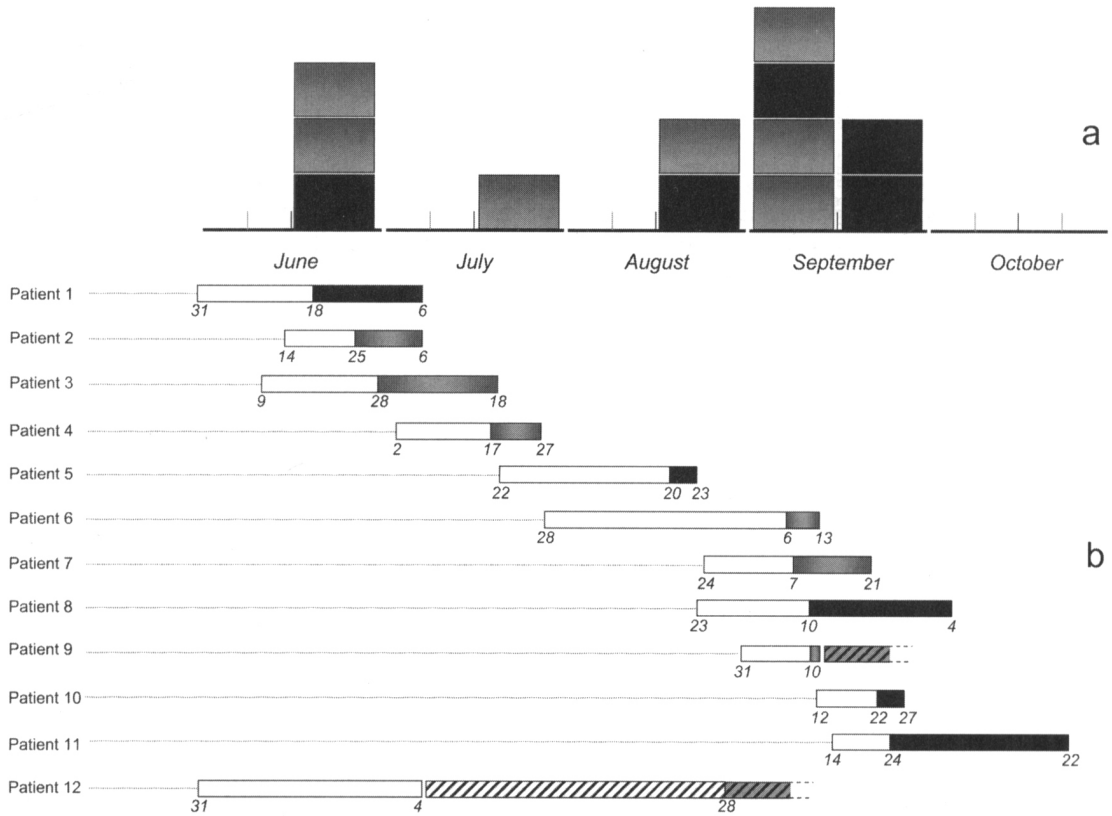

FIGURE 2. Epidemic curve (*a*) and time course (*b*) of the outbreak of heterogeneous glycopeptide-intermediate *Staphylococcus aureus* infection and colonization. *a*, Each square represents a case of colonization (gray) or infection (black). *b*, Open bars, intensive care unit (ICU) stays; gray bars, period from the first recovery of the epidemic strain to ICU discharge for colonized patients; black bars, period from the first recovery of the epidemic strain to ICU discharge for infected patients; hatched bars, hospitalization outside the ICU. Italicized numbers below the bars indicate dates (eg, May 31, June 18, and July 6 for patient 1).

in order to secure the environment for newly admitted patients. On October 10, a culture from the inner lining of an SpO_2 rubber sensor from area 2 was found to be positive for h-GISA. All other samples obtained from cleaned rooms yielded negative results. Targeted screening was maintained after the last case-patient was discharged to ascertain that there was no persistent reservoir.

The reusable SpO_2 rubber sensor (EnviteC-Denmark ApS) is generally located on the patient's first finger. Standard hospital procedure requires cleaning it daily with a detergent disinfectant solution, in accordance with manufacturer's recommendations. On October 12 and October 18, all SpO_2 sensors in the ICU were sampled, and another one (from area 1) was found to have a culture positive for h-GISA. It is noteworthy that a total of 6 *S. aureus* strains were isolated from SpO_2 sensors, suggesting that this device is a convenient niche for *S. aureus*.

DISCUSSION

This is the first report of an h-GISA outbreak for which an environmental reservoir was identified, namely, SpO_2 sensors. The outbreak was controlled by a combination of measures, including eradication of this reservoir. Bacterial persistence on SpO_2 sensors has been previously described in an outbreak of *Klebsiella pneumoniae* in a neonate ICU.[23]

This outbreak presented unusual features. First, in almost all cases, the epidemic h-GISA strain led to infection in the absence of previous nares colonization. However, we did not search for oropharyngeal or multiple-site colonization, which might have improved screening sensitivity in this epidemic context.[24,25] Second, the median time to h-GISA acquisition (16.5 days) was longer than that usually reported for MRSA colonization and infection (8–12 days).[26] We hypothesized that both characteristics are related to the reservoir: trauma patients are sedated and motionless during the first days after admission, with an SpO_2 sensor placed on a finger. On recovering mobility, they often lose the sensor and have many occasions for self-contact, allowing dissemination of the h-GISA strain to clinical sites.

In this outbreak, the microbiology laboratory gave immediate warning of a clinical MRSA strain with an unusual resistance pattern but may have missed h-GISA carriage in

https://doi.org/10.1086/663703 Published online by Cambridge University Press

TABLE 2. Synopsis of Control Interventions

Interventions	Before outbreak (baseline)	Jun 30 (3 cases)	Jul 18–Aug 20 (4 cases)	Aug 21–Oct 31 (12 cases)	End of outbreak
Precautions during health care	Contact precautions for patients colonized or infected with MDRBs	Mask-wearing for care to h-GISA-positive patients			Cleaning and disinfection of all SpO_2 sensors
Patient management	Cohorting; dedicated equipment (stethoscope, glucometer)		Closure and cleaning of area 2 (Jul 18–22); patients discharged only if screening results negative	Closure of area 2 (Sept 27–Oct 1)	
Education and information to HCWs	MDRB surveillance system	Information on standard precautions: hand disinfection and environmental cleaning; information on patient status at discharge; information for high-risk situations (patient transport)			Notification of National Health authorities; information about cleaning of SpO_2 sensors
Microbiological investigation	MDRB screening: nares, respiratory tract, rectum	Multiple surface sampling (h-GISA found on patient scale)	Screening of all HCWs working in the ICU	Targeted environmental screening (Oct 7)	Absence of h-GISA in area 4 after thorough cleaning
Objectives of intervention	Control of MDRB diffusion	Control of h-GISA diffusion in the unit and in the hospital	Control of HCW source; eradication of suspected environmental reservoir in area 2	Avoid total ward closure; ensure environmental safety for incoming patients	

NOTE. HCWs, healthcare workers; h-GISA, heterogeneous glycopeptide-intermediate *Staphyloccoccus aurea*; ICU, intensive care unit; MDRB, multidrug-resistant bacteria.

asymptomatic patients, since in our hospital routine surveillance samples are tested only for methicillin resistance. The retrospective database search over the past 4 years, as well as retrospective assays on carriage strains isolated in the previous year, identified only 2 possible strains outside this outbreak, none of which occurred after 2005. Thus, our hospital could be considered free of h-GISA, this outbreak occurring as an epidemic onset without endemic background. In a review of studies published between 1997 and 2001, Liu and Chambers[27] found a gross worldwide prevalence of h-GISA strains of 1.67%, with reported statistics varying from 0% to 73%. These reports occurred before susceptibility breakpoint values and h-GISA detection techniques were revised.[22] For some authors, the growing incidence of h-GISA strains involved in persistent bacteremic MRSA infections warrants systematic detection of glycopeptide susceptibility by the Etest macromethod.[28] In our hospital, h-GISA does not appear to be a clinical problem; however, we believe that active surveillance cultures for MRSA should be tested for associated antibiotic resistances when an epidemic occurs.

In our study, the index case was not accounted for: the first detected patient had not been previously hospitalized and presented the epidemic h-GISA strain 18 days after admission, making an imported case unlikely. Fridkin et al. described a case of community-acquired h-GISA,[29] but this remains exceptional. An asymptomatic h-GISA carrier might have cross-transmitted the strain to the first case, remaining undetected because of insufficient sensitivity of screening. Besides, not all contact patients for the first case could be called back and tested. Another possibility is that, prior to the outbreak, an unknown h-GISA carrier contaminated the environment, which thereafter acted as a persisting reservoir. Indeed, prolonged survival of MRSA in the environment has been demonstrated by French et al[30] and was confirmed in our study, the h-GISA strain having been cultured from surface samples even after several thorough cleanings and disinfections. Moreover, a retrospective cohort study of 10,151 ICU patients showed that the odds of acquiring MRSA are significantly increased for patients admitted to a room previously occupied by MRSA-positive patients.[31] Concerning h-GISA, de Lassence et al[17] published an outbreak report with two separate epidemic peaks explained by the ability of the microorganism to survive on inert surfaces. We observed the same epidemic course, which could be related to the persistence of an environmental reservoir acting as a relay.

Targeted microbiological screening is narrowed down to the epidemic microorganism, allowing rapid results and a short period of room vacancy. Sampling targets clinically relevant surfaces, which implies knowledge of specific healthcare activities and repeated exchanges with HCWs. The process increased the commitment of HCWs in charge of environmental hygiene through real-time feedback of surface-sampling results. This method detected a persistent contamination of SpO_2 sensors and showed that exhaustive cleaning is difficult to achieve, particularly in ICUs with complex medical devices and cluttered rooms. The targeted surface sampling guarantees environmental quality by securing a pathogen-free environment for incoming patients while maintaining ICU activity. This could spare the cost of total or partial ward closure, which can occur in up to 10% of *S. aureus* epidemics.[32]

In our study, although the index case remains unexplained, it appears that cross-infection from a patient source occurred for the first 3 cases and that environmental reservoirs perpetuated the epidemic. Targeted investigation led to the detection of an unsuspected reservoir, the eradication of which helped control the h-GISA epidemic. We recommended that this method be implemented early in outbreak management.

ACKNOWLEDGMENTS

Thanks are extended to Fabien Aujoulat and Agnès Masnou for their excellent technical assistance in typing bacterial strains.

Financial support. EA3755 project, Ministère de l'Enseignement Supérieur et de la Recherche, France, and association ADEREMPHA, Sauzet, France.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to Estelle Jumas-Bilak, PhD, PharmD, UMR 5119, Equipe Pathogènes et Environnements, 15 Avenue Charles Flahault, BP 14491, 34093 Montpellier Cedex 5, France (ebilak@univ-montp1.fr).

REFERENCES

1. Gastmeier P, Stamm-Balderjahn S, Hansen S, et al. Where should one search when confronted with outbreaks of nosocomial infection? *Am J Infect Control* 2006;34(9):603–605.
2. Rashid A, Solomon LK, Lewis HG, Khan K. Outbreak of epidemic methicillin-resistant *Staphylococcus aureus* in a regional burns unit: management and implications. *Burns* 2006;32(4): 452–457.
3. Dryden M, Parnaby R, Dailly S, et al. Hydrogen peroxide vapour decontamination in the control of a polyclonal meticillin-resistant *Staphylococcus aureus* outbreak on a surgical ward. *J Hosp Infect* 2008;68(2):190–192.
4. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in *Staphylococcus aureus*. *Emerg Infect Dis* 2001;7(2):327–332.
5. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 1997;40(1):135–136.
6. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet* 1997;350(9092): 1670–1673.
7. Haraga I, Nomura S, Fukamachi S, et al. Emergence of vancomycin resistance during therapy against methicillin-resistant *Staphylococcus aureus* in a burn patient: importance of low-level resistance to vancomycin. *Int J Infect Dis* 2002;6(4):302–308.
8. Center for Disease Control and Prevention. *Staphylococcus au-*

reus with reduced susceptibility to vancomycin in the United States, 1997. *Morb Mortal Wkly Rep* 1997;46(35):813–815.
9. Bierbaum G, Fuchs K, Lenz W, Szekat C, Sahl H-G. Presence of *Staphylococcus aureus* with reduced susceptibility to vancomycin in Germany. *Eur J Clin Microbiol Infect Dis* 1999;18(10): 691–696.
10. Ploy MC, Grélaud C, Martin C, de Lumley L, Denis F. First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. *Lancet* 1998;351(9110):1212.
11. Garnier F, Chainier D, Walsh T, et al. A 1 year surveillance study of glycopeptide-intermediate *Staphylococcus aureus* strains in a French hospital [published erratum appears in *J Antimicrob Chemother* 2006;57(3):583]. *J Antimicrob Chemother* 2006;57(1): 146–149
12. Howden BP, Davies JK, Johnson PDR, Stinear TP, Grayson L. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev* 2010; 23(1):99–139.
13. Fridkin SK. Vancomycin-intermediate and -resistant *Staphylococcus aureus*: what the infectious disease specialist needs to know. *Clin Infect Dis* 2001;32(1):108–115.
14. Pina P, Marliere C, Vandenesch F, Bedos J-P, Etienne J, Allouch P-Y. An outbreak of *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides in a French general hospital. *Clin Infect Dis* 2000;31(5):1306–1308.
15. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004; 42(6):2398–2402.
16. Neoh H-m, Hori S, Komatsu M, et al. Impact of reduced vancomycin susceptibility on the therapeutic outcome of MRSA bloodstream infections. *Ann Clin Microbiol Antimicrob* 2007;6: 13, doi:10.1186/1476-0711-6-13.
17. de Lassence A, Hidri N, Timsit J-F, et al. Control and outcome of a large outbreak of colonization and infection with glycopeptide-intermediate *Staphylococcus aureus* in an intensive care unit. *Clin Infect Dis* 2006;42(2):170–178.
18. Guerin F, Buu-Hoï A, Mainardi J-L, et al. Outbreak of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to glycopeptides in a Parisian hospital. *J Clin Microbiol* 2000; 38(8):2985–2988.
19. Soussy CJ, Carret G, Cavallo JD, et al. Antibiogram Committee of the French Microbiology Society. Report 2000–2001 [in French]. *Pathol Biol (Paris)* 2000;48(9):832–871.
20. Corne P, Marchandin H, Jonquet O, Campos J, Bañuls A-L. Molecular evidence that nasal carriage of *Staphylococcus aureus* plays a role in respiratory tract infections of critically ill patients. *J Clin Microbiol.* 2005;43(7):3491–3493.
21. Cartolano GL, Cheron M, Benabid D, Leneveu M, Boisivon A, Association of Hospital Bacteriologists Virologists and Hygiene Professionals. Methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to glycopeptides (GISA) in 63 French general hospitals. *Clin Microbiol Infect* 2004;10(5): 448–451.
22. Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents* 2007;30(5):398–408.
23. Macrae MB, Shannon KP, Rayner DM, Kaiser AM, Hoffman PN, French GL. A simultaneous outbreak on a neonatal unit of two strains of multiply antibiotic resistant *Klebsiella pneumoniae* controllable only by ward closure. *J Hosp Infect* 2001;49(3): 183–192.
24. Nilsson P, Ripa T. *Staphylococcus aureus* throat colonization is more frequent than colonization in the anterior nares. *J Clin Microbiol* 2006;44(9):3334–3339.
25. Buehlmann M, Frei R, Fenner L, Dangel M, Fluckiger U, Widmer AF. Highly effective regimen for decolonization of methicillin-resistant *Staphylococcus aureus* carriers. *Infect Control Hosp Epidemiol* 2008;29(6):510–506.
26. Warren D, Guth R, Coopersmith C, Merz L, Zack J, Fraser V. Epidemiology of methicillin-resistant *Staphylococcus aureus* colonization in a surgical intensive care unit. *Infect Control Hosp Epidemiol* 2006;27(10):1032–1040.
27. Liu C, Chambers HF. *Staphylococcus aureus* with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. *Antimicrob Agents Chemother* 2003;47(10):3040–3045.
28. Maor Y, Rahav G, Belausov N, Ben-David D, Smollan G, Keller N. Prevalence and characteristics of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bacteremia in a tertiary care center. *J Clin Microbiol* 2007;45:(5)1511–1514.
29. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities [published erratum appears in *N Engl J Med* 2005;352(22):2362]. *N Engl J Med* 2005;352(14):1436–1444.
30. French GL, Otter JA, Shannon KP, Adams NMT, Watling D, Parks MJ. Tracking contamination of the hospital environment by methicillin-resistant *Staphylococcus aureus* (MRSA): a comparison between conventional terminal cleaning and hydrogen peroxide vapour decontamination. *J Hosp Infect* 2004;57(1): 31–37.
31. Huang SS, Datta R, Platt R. Risk of acquiring antibiotic-resistant bacteria from prior room occupants. *Arch Intern Med* 2006; 166(18):1945–1951.
32. Hansen S, Stamm-Balderjahn S, Zuschneid I, et al. Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. *J Hosp Infect* 2007;65(4): 348–353.