Staphylococcus aureus as a paradigm of a persistent problem of bacterial multiple antibiotic resistance in Abha, Saudi Arabia

N.E. Bilal [1] and M. Gedebou [1]

العنقوديات الذهبية كنموذج لمشكلة مستمرة تمثلها الجراثيم المقاومة لمضادات حيوية متعددة في أبها بالمملكة العربية السعودية

نصر الدين بلال ومسل جدبو

خلاصة: راجعنا سجلات مختبر الأحياء الدقيقة في مستشفى أبها للولادة بالمملكة العربية السعودية في العامين 1996 و1998 وذلك لتقدير مدى مقاومة المضادات الحيوية المتعددة، مع أخذ العنقوديات الذهبية كنموذج. لقد تم استنراد (عزل) 587 و485 ذرية في العامين 1996 و1998 على التوالي. وفي سنة 1996 وُجد أن أكثر من 60% من الذراري كانت مقاومة لخمسة من المضادات الحيوية التسعة التي اختُبرت. وفي سنة 1998 كان 55% منها مقاومة لستة مضادات حيوية. وفي كلتا السنتين كان 71% من الجراثيم عنقوديات ذهبية مقاومة للمثيسلين. وكان أكثر من 85.0% من جميع الذراري متعددة المقاومة. ورغم اكتشاف أكثر من مئة نمط من أنماط المقاومة، فإن أكثر من نصف الذراري أظهرت أقل من 15 نمطاً. وكانت الذراري التي استفردت (عزلت) أكثر من غيرها هي التي تعتبر من ذراري المستشفيات، والتي سبّبت معظم حالات العدوى.

ABSTRACT We reviewed the microbiology laboratory records of Abha Maternity Hospital, Saudi Arabia for 1996 and 1998 to assess multiple antibiotic resistance, using *Staphylococcus aureus* as a paradigm. A total of 587 and 485 strains were isolated in 1996 and 1998 respectively. In 1996, over 60.0% were resistant to five of the nine antibiotics tested; in 1998, over 55.0% were resistant to six antibiotics. In both years, 71.0% were methicillin-resistant *S. aureus*. Over 85.0% of all strains were multiresistant. Although over 100 types of resistance patterns were detected, more than half of the strains displayed fewer than 15 types. The strains most frequently isolated were considered hospital strains, which accounted for most infections.

***Staphylococcus aureus* comme paradigme d'un problème persistant de multirésistance bactérienne aux antibiotiques en Abha en Arabie saoudite**

RESUME Nous avons passé en revue les dossiers du laboratoire de microbiologie de la Maternité d'Abha (Arabie saoudite) pour les années 1996 et 1998 afin d'évaluer la multirésistance aux antibiotiques, en utilisant *Staphylococcus aureus* comme paradigme. Au total, 587 et 485 souches ont été isolées en 1996 et 1998 respectivement. En 1996, plus de 60,0% étaient résistantes à cinq des neuf antibiotiques testés; en 1998, plus de 55,0% étaient résistantes à six antibiotiques. Dans les deux années, 71,0% étaient des *S. aureus* résistantes à la méthicilline. Plus de 85,0% de toutes les souches étaient multirésistantes. Bien qu'on ait trouvé plus de 100 types de tableaux de résistance, plus de la moitié des souches présentaient moins de 15 types. Les souches les plus fréquemment isolées étaient considérées comme des souches hospitalières, qui étaient responsables de la plupart des infections.

[1]*Department of Clinical Microbiology and Parasitology, Abha College of Medicine, King Khalid University, Abha, Saudi Arabia.*

Received: 25/08/99; accepted: 07/03/00

Introduction

Staphylococcus aureus is one of the most frequently isolated pathogens in a clinical microbiology laboratory of any hospital. It is a common etiological agent of hospital-acquired infections, which are a constant therapeutic problem to clinicians [*1*]. A variety of human infections are caused by *S. aureus*, including infections of the skin, respiratory tract, bone and joints, cardiovascular system and metastatic infections. *S. aureus* infections are often difficult to treat because many methicillin-resistant strains are multiresistant [*2–4*]. In some cases, vancomycin or teichoplanin are the only effective drugs for treatment of infections. Methicillin-resistant *S. aureus* (MRSA) has caused several hospital outbreaks throughout the world and remains endemic in many hospitals worldwide [*5*]. Strains resistant to multiple antibiotics are prevalent in the hospital environment where the selective pressure from therapeutic and prophylactic use of antibiotics favours their proliferation and transmission.

We reviewed 2 years of microbiology laboratory records at Abha Maternity Hospital, a small 120-bed teaching hospital in the south-west region of Saudi Arabia. We assessed the problem of antibiotic resistance and, in particular, resistance to multiple antibiotics. It has been the experience of laboratory staff in various hospitals in the region that multiresistant strains of *S. aureus* and various Gram-negative organisms are frequently isolated. Therefore, we chose *S. aureus* as a paradigm to elucidate the magnitude of such a problem.

Materials and methods

Strains of *S. aureus* were isolated from various clinical specimens submitted to the bacteriology laboratory for diagnosis of suspected bacterial infections. Specimens were processed and isolates were characterized and identified as *S. aureus* following conventional procedures [*6*]. Specimens were inoculated on blood agar plates and incubated aerobically for 24 hours. The following colonies were considered to be *S. aureus*: β-haemolytic or non-haemolytic, morphologically typical, large pigmented or non-pigmented, catalase- and coagulase-positive colonies.

The susceptibility of strains to antibacterial agents was determined by the standard agar disc diffusion method [*7*]. Every strain was tested using the following panel of antibiotic discs: cephalothin (30 μg), clindamycin (2 μg), erythromycin (15 μg), gentamicin (10 μg), oxacillin (1 μg), penicillin (10 μg), tetracycline (30 μg), trimethoprim-sulfamethoxazole (25 μg) and vancomycin (30 μg). The standard sensitive strain of *S. aureus* ATCC 25923 was routinely included as a control for reproducibility of results with every batch of antibiotic sensitivity test.

Susceptibility or resistance of strains to each antibiotic was determined on the basis of the size of the zone of growth inhibition, according to the chart of interpretive standards for disc diffusion susceptibility testing [*7*]. The few strains with intermediate susceptibility to the various antibiotics were arbitrarily included with the susceptible strains for the assessment.

Methicillin-resistant strains were tested by using 1 μg of oxacillin disc. A strain showing a growth inhibition zone diameter of > 10 mm after incubation at 35 °C for 24 hours was considered MRSA [*7,8*].

Rates of resistance to each antibacterial agent and the antibiogram of each strain were determined for the *S. aureus* isolates. These were studied to assess the problem and prevalence of multiresistant strains.

We reviewed the medical charts of 21 patients with MRSA bacteraemia to check the therapy they received in relation to the antibiograms of the etiologic agents and the outcome of their treatment.

Results

In 1996, culture requests were received for 6878 miscellaneous specimens of which 30.7% were positive. In 1998, there were 7738 requests with 31.1% positive cultures. In both years, over 95.0% of the *S. aureus* strains were isolated from fewer than 10 types of specimen: high vaginal swabs, urine, blood, eye or ear swabs, wound or pus swabs, sputum or endotracheal tubes and umbilical cords. *S. aureus* isolates in 1996 comprised 27.8% of all the positive cultures while in 1998, the rate was 20.2%. A total of 587 and 485 strains were isolated in 1996 and 1998 respectively.

Resistance rates of *S. aureus* to the antibiotics tested for both years are shown in Table 1. No strain resistant to vancomycin was detected in either year. The majority of the strains were resistant to five or six of the nine antibiotics tested. Resistance rates of strains to seven of the nine antibiotics tested increased between 1996 and 1998. Resistance increased significantly to the drugs clindamycin, penicillin and trimethoprim-sulfamethoxazole (Table 1). Multiple resistance (resistance to three or more antibiotics) was 85.5% and 88.0% in 1996 and 1998 respectively. The isolated strains in both years showed more than 100 different types of resistance pattern or antibiogram: 122 types in 1996 and 105 in 1998. These types varied from resistance to only one antibiotic, to resistance to eight of the nine antibiotics tested. More than half of the strains (50.9% and 56.1%) displayed 14 and 10 types of antibiogram, if we considered just those antibiogram types shown by

Table 1 **Antibiotic resistance of *Staphylococcus aureus* isolates**

Antibiotic	Zone diameter[a] (mm)	Resistance of isolates of 1996 (587 strains) No.	%	Resistance of isolates of 1998 (485 strains) No.	%	χ^2
Cephalothin	≤14	132	22.5	130	26.8	2.68
Clindamycin	≤14	266	45.3	265	54.6	9.24[b]
Erythromycin	≤13	376	64.1	328	67.6	1.51
Gentamicin	≤12	240	40.9	214	44.1	1.14
Oxacillin	≤10	420	71.6	345	71.1	0.02
Penicillin	≤28	496	84.5	432	89.1	4.78[c]
Tetracycline	≤14	444	75.6	388	80.0	2.91
Trimethoprim-sulfamethoxazole	≤10	425	72.4	398	82.1	13.90[b]
Vancomycin	≤14	0	0	0	0	

[a] *Growth inhibition zone diameter for resistance [7].*
[b] *P = 0.01.*
[c] *P = 0.05.*

10 or more strains (Table 2). The rate of resistance of *S. aureus* to eight of the nine antibiotics increased from 3.4% in 1996 to 16.5% in 1998 ($\chi^2 = 53.78$, $P < 0.001$). Among those strains with a greater number of antibiogram type, MRSA comprised 242 out of the total 299 strains (80.9%) in 1996 and 236 out of 249 strains (94.8%) in 1998 ($\chi^2 = 23.36$, $P < 0.001$).

The medical charts of the 21 patients with MRSA bacteraemia showed that they were all given an empirical treatment of ampicillin and gentamicin. Some were also given a third antibiotic, which was either metronidazole, ceftriaxone or cefotaxime. In all, 10 patients responded favourably to the treatments, while 3 patients did so only after receiving vancomycin treatment following the laboratory reports of the etiologic agents and their sensitivity to the antibiotics. Also, 4 patients were transferred to another hospital because they were not responding to the combined empirical therapy. The remaining 4 patients left the hospital against medical advice and the charts did not indicate the outcome of the empirical treatment.

Table 2 **Resistance antibiogram types shown by 10 or more strains of *Staphylococcus aureus***

Antibiotic resistance pattern	**1996 (597 strains)**		**1998 (485 strains)**	
	No.	**%**	**No.**	**%**
ClinEryOxaPenTetTri-sul	39	6.6	47	9.7
ClinEryGenOxaPenTetTri-sul	39	6.6	52	10.7
CephEryGenOxaPenTetTri-sul	29	4.9	–	–
ClinOxaPenTetTri-sul	26	4.4	13	2.7
EryGenOxaPenTetTri-sul	25	4.3	14	2.9
EryOxaPenTetTri-sul	21	3.6	17	3.5
CephClinEryGenOxaPenTetTri-sul	20	3.4	80	16.5
Pen	17	2.9	13	2.7
EryOxaPenTet	17	2.9	–	–
EryPenTetTri-sul	15	2.6	–	–
PenTri-sul	–	–	11	2.3
ClinEryGenPenTetTri-sul	11	1.9	–	–
EryGenPenTetTri-sul	14	2.4	–	–
OxaPenTetTri-sul	13	2.2	–	–
CephClinEryOxaPenTetTri-sul	13	2.2	13	2.7
PenTet	–	–	12	2.5
Total	299	50.9	272	56.1

Clin = clindamycin; Ery = erythromycin; Oxa = oxacillin; Pen = penicillin; Tet = tetracycline; Tri-sul = trimethoprim-sulfamethoxazole; Ceph = cephalothin; and Gen = gentamicin.

– = antibiograms shown by fewer than 10 strains.

Discussion

Resistance rates to every antibiotic tested increased in the 2-year period, except to oxacillin and vancomycin, to which resistance and susceptibility rates remained unchanged (Table 1). The rates of resistance to oxacillin in both years indicated a very high prevalence of MRSA, among the highest rates reported worldwide [*5*]. MRSA infections accounted for 71.0% of the total *S. aureus* infections in both years. Despite such a high endemic rate, there was no outbreak of MRSA strains in the hospital in either year. Many of our MRSA strains were susceptible *in vitro* to cephalothin, clindamycin or gentamicin, as reflected by the lower rates of resistance to these antibiotics, in contrast to what is generally reported [*4,9,10*]. However, Mulligan et al. have reported that despite such *in vitro* activity against MRSA, treatment with cephalosporins has not been successful [*8*].

Over 85% of the isolates in both 1996 and 1998 were multiresistant, with a slight increase in 1998. Such a high rate of *S. aureus* resistance to multiple antibiotics should raise concern as it limits the choice of effective antibiotics. In some cases only vancomycin was effective. The concern is manifested in our study by the significant increase of resistance rates to eight antibiotics from 3.4% to 16.5% in the 2-year period (Table 2). Vancomycin was the only effective antibiotic for these strains. The spectre of vancomycin-resistant *S. aureus* is a serious health threat. The fear that MRSA strains will also become fully resistant to vancomycin is becoming real following recent reports from Japan [*11*] and the United States of America of MRSA strains with intermediate resistance to vancomycin [*12,13*].

Considering the patterns of antibiotic resistance of the isolates in both years, there was a decrease in the number of antibiogram types from 122 in 1996 to 105 in 1998. Although not statistically significant ($P > 0.05$), this indicates that some strains of certain antibiogram type are increasing in prevalence in the hospital. Despite the large number of antibiogram types, the strains showed that over half of all the infections by *S. aureus* were by 14 types in 1996 and 10 types in 1998 (Table 2). This indicates that these strains are more prevalent in the hospital. In 1996, 80.9% of the strains with the 14 more common antibiogram type were MRSA strains. Similarly in 1998, 94.8% of the strains with the 10 more common antibiogram type were MRSA strains, indicating a significantly increased prevalence of the more common MRSA strains in the hospital.

The high rates of multiple resistance is a direct consequence of hospital and community use of antibiotics and its concurrent selection of resistant strains. In Saudi Arabia, as in many other developing countries, antibiotics are readily available over the counter. A person can buy the antibiotic of their choice or one will be prescribed by the pharmacist just by describing their symptoms. Patients, therefore, treat themselves with the wrong antibiotic or wrong dosage. Thus, patients may then come to the hospital already harbouring resistant strains. These strains may be the cause of endogenous infections or exogenous infections in other patients. Another important cause of resistance is excessive or inappropriate use of antibiotics in hospitals [*14–16*]. The magnitude of the problem of multiresistance is such that clinicians must be familiar with the causes of antibiotic resistance and the measures for preventing or minimizing the emergence of resistance. Our study underscores the need for hospital clinicians to be aware of the common bacterial isolates in their unit and their usual antibiotic sus-

ceptibility. This is imperative in order to make rational decisions for the prudent use of antibiotics, particularly for empirical therapy.

The number of patients' charts reviewed in our study was small. It does, however, highlight some aspects of the pattern of antibiotic usage in the hospital. Therapy was changed after the laboratory report of culture and sensitivity was received for only 4 of the 21 (19.0%) patients. For 6 patients (28.6%), there was no change of therapy upon receipt of the laboratory report, although the patients were not responding to the empirical treatment of combined antibiotics. These were the patients who either were transferred to another hospital or left the hospital against medical advice, one or several days after the laboratory reports were available. It is difficult to explain why treatment was not changed from the records on the charts. Further investigations are warranted to evaluate the pattern of use of antibiotics in the hospital.

Acknowledgement

The authors thank the technical staff of the microbiology laboratory of Abha Maternity Hospital for their contribution to the data analysis.

References

1. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. *Clinical microbiology reviews*, 1993, 6(4):428–42.

2. Speller DCE et al. Resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales, 1989–95. *Lancet*, 1997, 350(9074): 323–5.

3. Lowy FD. *Staphylococcus aureus* infections. *New England journal of medicine*, 1998, 339(8):520–32.

4. Thornsberry C. Emerging resistance in clinically important Gram-positive cocci. *Western journal of medicine*, 1996, 164(1):28–32.

5. Voss A, Doebbeling BN. The worldwide prevalence of methicillin-resistant *Staphylococcus aureus*. *International journal of antimicrobial agents*, 1995, 5: 101–6.

6. Kloos WE, Bannerman TL. Staphylococcus and micrococcus. In: Murray PR et al., eds. *Manual of clinical microbiology*. Washington DC, American Society for Microbiology, 1995:282–98.

7. Woods GL, Washington JA. Antibacterial susceptibility tests: dilution and disk diffusion methods. In: Murray PR et al., eds. *Manual of clinical microbiology*. Washington DC, American Society for Microbiology, 1995:1327–41.

8. Mulligan ME et al. Methicillin-resistant *Staphylococcus aureus*: a consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. *American journal of medicine*, 1993, 94(3):313–28.

9. Ayliffe GAJ. Methicillin-resistant *Staphylococcus aureus* (MRSA) update. *Postgraduate doctor Middle East*. 1998. 21: 98–103.

10. Swartz MN. Hospital-acquired infections: diseases with increasingly limited thera

pies. *Proceedings of the National Academy of Sciences of the United States of America*, 1994, 91(7):2420–7.

11. Hiramatsu K et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet*, 1997, 350(9092): 1670–3.

12. Smith TL et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-intermediate *Staphylococcus aureus* working group. *New England journal of medicine*, 1999, 340(7):493–501.

13. Sioradzki K et al. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. *New England journal of medicine*, 1999, 340(7):517–23.

14. Maki DG, Schuna AA. A study of antimicrobial misuse in a university hospital. *American journal of the medical sciences*, 1978, 275(3):271–82.

15. Visconti JA, Roberts AW. The rational and irrational use of systemic antimicrobial drugs. *American journal of hospital pharmacy*, 1972, 29(10):828–34.

16. Goldmann DA et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *Journal of the American Medical Association*, 1996, 275(3):234–40.

Antimicrobial resistance is a worrying phenomenon since it could have great adverse effects on the control and treatment of diseases such as pneumonia, tuberculosis and malaria. These conditions emphasize the need for health systems to invest in research and development strategies to come up with cost-effective tools to control the remaining threats from infectious diseases.

Source: The World Health Report, 1999. Making a Difference. *Page 22.*