A PROFILE AND SPECTRUM OF FOUR CASES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN A BURNS INTENSIVE CARE UNIT

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SUMMARY. This report describes and evaluates four patients with hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* infections at the Burns and Plastic Surgery Hospital, in Libya, between August 1999 and August 2002. Neither rifampicin nor vancomycin was used to treat these patients. Inhalation injury with major burns (> 60% total body surface area), a major degree of burns (3rd degree), and septicaemia caused by both MRSA and multi-resistant *P. aeruginosa* invariably proved fatal. One patient responded well to antibiotic therapy, but the other three died in spite of similar therapy. Vancomycin and rifampicin should be established as the first choice to treat MRSA infection, and infected wounds need aggressive management with antibiotics prior to skin grafting.

Introduction

Cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were detected soon after the introduction of methicillin in 1960[1] and increased in number in the following few years. MRSA then diminished in frequency in some European countries, possibly because of increased prescribing of aminoglycosides.[2] By 1988, MRSA strains had become increasingly prevalent as a pathogen, especially in burn wounds with an associated mortality of 20-40%. It has been suggested that burn wound infections due to MRSA are caused by endogenous flora present at the time of injury[3] and recognized as a major therapeutic problem - they remain the main cause of cross-infection in hospital, and also contribute in some cases to increased length of hospital stay and higher health care costs.[4] Vancomycin is a frequently used therapy for MRSA multidrug-resistant strains.[5]

The increase in vancomycin utilization for these serious infections has recently led to a new concern. The United States, Japan, and Europe have documented the existence of MRSA strains with decreased sensitivity to vancomycin.[6-8] Risk factors for developing post-operative infections caused by MRSA include previous antimicrobial therapy, prolonged hospitalization, severe underlying disease, old age, and multiple invasive procedures. Extensive burn injuries are particularly susceptible to infection as a result of the disruption of the normal skin barrier, and the accompanying depression of immune responses has been identified as an additional risk factor. Colonization of surface burn wounds with staphylococci can cause septicaemia.[9] It has been shown that the risk of acquiring MRSA infection is 45%,[10] - it has therefore become widespread in the hospital environment, particularly in burn units.[11-14]

Multidrug-resistant *Pseudomonas* has frequently been reported as the cause of nosocomial outbreaks of infection in burn units or as colonizers of the wounds of burn patients.[15-17] Despite advances in surgical care and the introduction of a wide variety of antimicrobial agents with anti-pseudomonal activities, life-threatening infections caused by *P. aeruginosa* continue to be a common complication in burn patients, contributing substantially to burn-related morbidity and mortality worldwide.[15-19] This study describes the type of organisms responsible for septicaemia and the factors that might have contributed to the death of three out of a group of four burn patients admitted to our burn intensive care unit.

Patients and methods

Four cases were selected from a previous study[20] carried out at the intensive care unit in the Burns and Plastic Surgery Hospital, Tripoli, Libya, between August 1999 and August 2002. Each of these patients had a simultaneous infection with both MRSA and *Pseudomonas* isolates. The average age was 21 years and the average total body surface area (TBSA) burned was 70%. MRSA and *Pseudomonas* were identified in the patients by blood, urine, and swab cultures. Methicillin-resistance was assessed using oxacillin (1 mg) disks on a medium containing NaCl (5% w/v), and the cultures were incubated at 37 ºC for 24 h. All the isolates were sensitive to vancomycin with a minimum inhibition concentration of less than or equal to 1.0 mg. The antibiotic susceptibility of each isolate was

tested manually according to the National Committee for Clinical Laboratory Standards recommendations for disc diffusion.[21] The antibiotic sensitivity patterns of all isolates positive for MRSA were individually analysed; all MRSA and *P. aeruginosa* isolates were tested against a minimum of eight antibiotics. All patients received immediate care and resuscitation therapy with the application of broad-spectrum intravenous antibiotics, followed by appropriate supportive treatment.

Results

The cases are summarized in *Table I*, and the pattern of antibiotic sensitivity of the bacterial isolates in *Table II*.

Case 1

A 19-yr-old female was admitted with 60% TBSA 3rd-4th degree burns in the face, trunk, and both upper and lower limbs. She also had severe inhalation injury. The patient was transferred from Benghazi hospital 6 days after the injury. She was in a serious condition owing to large areas of infected burn wounds, toxaemia, suspected septicaemia, anaemia, and high fever. She received gentamicin and vitamin C. Debridement of both upper and lower limbs was carried out two days after admission. Initially, *P. aeruginosa* was isolated from the blood culture and the patient was put on meropenem intravenously. X-ray revealed bilateral bronchitis. Gastrointestinal bleeding started seven days after admission and fresh blood was given. The patient deteriorated 10 days after admission with hypotension and suspected septic shock. Mono-skingrafts were carried out - initially she received 20% in both lower limbs. A nasotracheal tube was inserted, and she was put on rocefin. In the third week, she received auto-skingrafts on 12% of both thighs and the chest. She had another auto-skingraft on 8% of the thighs, chest, and neck 15 days following admission and made a good recovery. The nasotracheal tube was removed and she received a final auto-skingraft on 10% of the left thigh, abdomen, neck, and left arm. She then deteriorated with vomiting and hypokalaemia. After six weeks another blood culture identified both MRSA and multi-resistant *Pseudomonas*, and *Candida* was isolated from her urine. Her temperature increased to 40.5 ºC and she had vomiting. Rocefin was commenced twice daily in conjunction with amphocil (fungizone) and nystatin. She continued to deteriorate and developed severe allergic reactions and oedema of the face, hands, and trunk due to amphocil. Broncholavage was performed, but she died on day 52. The causes of death were multi-system organ failure and cardiac arrest.

Case 2

A 9-yr-old girl presented to the emergency room 4 h after suffering a fire burn covering 60% TBSA (third-degree burns in the face, trunk, and both upper and lower limbs). She also had severe inhalation injury. In the first three days she was treated according to the Evans formula: plasma protein (5% v/v), Ringer's lactate solution, penicillin, and Nebcin, plus dressing with betadine. On day 2 she had sequential excision in both lower limbs and the right arm; on day 7 she received a homo-skingraft on 25% of both lower limbs; on day 11 she was put on tienam, and received homo-skingrafts on 16% both upper limbs. After two weeks she received auto-skingrafts on 15% of both lower limbs. Meronem was given after 22 days and an X-ray showed bilateral bronchitis. On day 25 she received auto-skingrafts on 7% of both lower limbs. Her condition then deteriorated; she had fever and respiratory failure with right-side pleuropneumonia and pleural effusion. The blood culture identified MRSA and *P. aeruginosa*, and the patient was treated with rocefine. After six days her condition improved. On day 31 she received auto-skingrafts on 10% of her left upper limbs and on residual wounds in both lower limbs; the operation was re-

Table I - Factors possibly contributing to death of patient

Factor	Case 1	Case 2	Case 3	Case 4
Age (yr)	19	9	25	31
Degree of burn	3-4	3	2-3	2-3
TBSA (%)	60	60	90	70
Inhalation injury	+	+	+	+
Type of organisms isolated	MRSA and *P. aeruginosa*	MRSA and *P. aeruginosa*	MRSA and *P. aeruginosa*	MRSA and *P. aeruginosa*
Cause of death	Cardiac arrest and multi-system organ failure	Patient survived	Cardiac arrest and multi-system organ failure	Cardiac arrest
Hospitalization (days)	52	42	10	35

Table II - Pattern of antibiotic sensitivity (R = resistant; I = intermediate; S = sensitive; - = not done)

Type of antibiotic	Case 1		Case 2		Case 3		Case 4	
	M*	P†	M*	P†	M*	P†	M*	P†
Augmantin	R	R	R	S	R	I	R	R
Ciprofloxacillin	R	S	R	S	R	R	R	R
Cephtriaxone	I	S	I	S	R	R	I	S
Cephotaxim	R	R	R	R	R	R	R	R
Impeniem	R	R	R	S	R	R	R	S
Vancomycin	S	-	S	-	S	-	S	-
Rifampicin	S	-	S	-	S	-	S	-
Deoxyfloxacillin	I	R	I	R	R	S	R	R
Amikacin	R	R	R	R	R	S	R	R
Oxacillin	R	-	R	-	R	-	R	-
Meropenum	R	S	R	R	R	R	R	R

* MRSA
† *P. aeruginosa*

peated on day 36 for the right upper limbs (5%). In week 6, she was transferred to the paediatric department for rehabilitation, and a course of intravenous ciprofloxacin was commenced. The patient went on to make an excellent recovery with no further septic episodes. One week later, the patient was found to be MRSA-negative and consequently she was discharged.

Case 3

A 25-yr-old woman was admitted to the burns unit with 2nd/3rd-degree benzene fire burns in 90% TBSA, severe inhalation injury, and severe burn shock. She was intubated immediately in view of deep burn injury in the face. She was treated according to the Evans formula and with gentamicin, cristapen, Zantac, and daily dressing with betidine. After two days, the patient became hyperkalaemic, with fever and compensative metabolic and respiratory acidosis. After five days the patient was connected to mechanical ventilation. On day 7 a blood culture identified *P. aeruginosa* and MRSA. Cardiovascular signs were suspected and dopamine infusion was initiated. On day 8, she became highly febrile (urea, 76 mg/%), with oligouria, and she continued with dopamine infusion. The following day her condition became critical, with coma, fever, anuria, high urea (205 mg/%), and hyperkalaemia (161 mmol/l). The level of dopamine was increased, and she was treated with amikacin. On day 10, she developed cardiac arrest and multi-system organ failure.

Case 4

A 31-yr-old man was referred to the burns unit three days after suffering 2nd/3rd-degree fire burns. He had large and deep areas of infected burn wounds in 70% TBSA, severe inhalation injury, and toxaemia. He was treated with azactam, and the left arm and leg were debrided; a second operation on day 9 after admission debrided both lower limbs. He then developed bilateral pneumonia and gastrointestinal haemorrhage and became anaemic. The blood culture identified MRSA and *Klebsiella pneumonia*, but the urine culture was negative. He was treated with tienam. Over the course of the next few days, he became stabilized and gradually improved. Three weeks following admission both upper and lower limbs were debrided owing to secondary necrosis and he was given rocefine. A week later, his condition deteriorated. He became acutely unwell, with melaena, vomiting, and gastrointestinal bleeding. The blood culture and wound swabs identified both MRSA and *P. aeruginosa*, and he was treated with tienam. On day 35, he developed cardiac arrest and resuscitation was unsuccessful.

Discussion

Concern about MRSA infection in burn units has been increasing since the late 1980s.[22-27] Previous studies suggested that the selective pressure from antimicrobial agents was a major determinant for the emergence of resistant strains.[16,28,29] The sub-inhibitory antibiotic concentration in burn wounds, due to the administration of an appropriate dosage of a β-lactam, antibiotics, or the regular administration of an aminoglycoside in combination with a β-lactam, provides optimal conditions for selection, subsequent local invasion, and haematogenous dissemination in burn patients.[16,30] This study showed that MRSA isolates were resistant to most commonly used antibiotics in our burn unit; however, they were all sensitive to vancomycin and rifampicin, which have not yet been introduced.

In our previous study[20] MRSA was isolated from 25% of cases of *S. aureus* bacteraemia, which is comparable with studies in the United States (approximately 25%),[31] while in Saudi Arabia MRSA was found in 29% of cases of *S. aureus* bacteraemia.[32] Among cases of *S. aureus* bacteraemia reported in England and Wales,[33,34] the proportion due to MRSA increased significantly from 2% in 1989 to 13% by 1995, 21% in 1996, and 32% in 1997. However, Sanyal et al.,[35] found that 92% of septicaemia episodes in Kuwait were caused by MRSA. Suzuki et al.[36] reported the death of a patient due to multiple brain abscesses, following septicaemia caused by MRSA in spite of aggressive treatment with antibiotics. In other burn unit study,[37] two out of four patients with MRSA septicaemia survived after vancomycin therapy, but the other two did not respond favourably to similar therapy and died. In this study one patient responded well to antibiotic therapy, but the other three died in spite of similar therapy.

The main pathogenic micro-organism in burn wound infection used to be *P. aeruginosa*, but more recently it has been staphylococci.[12,38-40] *Pseudomonas* did not appear in our burn patients until a few weeks after admission, and similar results have been reported by others.[41] Approximately 25-29% of burn patients become colonized with this organism during the course of their stay in hospital, and a quarter of the colonized patients develop invasive infection.[42] When infection caused by *P. aeruginosa* occurs in burn patients, treatment becomes very difficult and the mortality rate among such infected patients is likely to be up to 40-50%.[43,44] Zorgani et al.[20] found that multiresistant *Pseudomonas* was the leading cause (40%) of septicaemia in burns. *P. aeruginosa* isolated from our four cases was resistant to most antibiotics available. All this makes the organism difficult to eradicate from both the patient and the environment.

Major burns with inhalation injuries requiring intubation carry a high risk of septicaemia.[45,46] It has been suggested that intravascular devices and endotracheal tubes are the primary foci of infection, in addition to burn wound.[46] This study demonstrates that all the patients with major burns associated with pulmonary complications such

as inhalation injury and intubations developed septicaemia and died. This may have been due to a compromised immune status combined with entry of the organism through the wound surface.

Burn patients are at increased risk of nosocomial infection. Prolonged hospitalization and the performance of one or more surgical procedures may expose burn patients to colonization with multi-resistant organisms.[47] A strong correlation has been determined in burn patients between nosocomial infection and urinary catheters, nasogastric tubes, transfusions, central venous catheters, and percutaneous catheters.[48] TBSA burned is also a major risk factor for nosocomial infection.[49] Parallel to other studies,[48,50] we found that the three patients who died had a combination of several factors, such as 2nd/3rd-degree burns in over 60% TBSA and inhalation injuries. In addition, most of these patients remained for lengthy periods in the intensive care unit, with complications due to mixed infections.

The prevalence of antimicrobial agent-resistant bacteria has dramatically increased in hospitals worldwide during the last few years.[51] The choice of antibiotics should, if possible, depend on susceptibility testing. The use of vancomycin as of other reserve antibiotics has to be prudent.[52] Since 1980 vancomycin has been a uniformly effective antibiotic available for serious staphylococcal infections. If treatment with vancomycin does not show the expected benefit, additional drugs have to be administered.[53] Rifampicin has been successfully used as an adjunct to vancomycin therapy in several clinical conditions of MRSA infections such as endocarditis, ventriculoperitoneal shunts, and septicaemia. The use of linezolid in the treatment of vancomycin-resistant enterococcal septicaemia has been established in patients with burn injuries and may offer an effective alternative treatment.[54,55] The type of treatment depended only on antibiotic susceptibility tests provided by laboratory results: neither vancomycin nor rifampicin was used in this study. Vancomycin should be considered as a first choice in the treatment of cases of MRSA.

Analysis of clinical isolates by molecular techniques can be helpful in studying the epidemiology of outbreak strains and in confirming their clonality.[56] Molecular typing, complemented by conventional methods, provides a sensitive and specific approach for outbreak tracking, and its usefulness in nosocomial epidemiology is very well documented.[57-61] Molecular typing has not been carried out to investigate the relationship of MRSA strains and *Pseudomonas* isolates or to track the source of infection, and no data are available for defining the molecular characteristics of these strains. The determination of toxic shock syndrome toxin for MRSA isolates is also important.

Conclusion

This study suggests that the death of the three patients described was probably due to a combination of several factors: a major degree of burns, inhalation injury, high percentage of TBSA, intubations, multi-resistant organisms, and the non-availability of advanced antibiotic therapy, which remains the foremost concern in the management of our burn patients. Strategies that will improve MRSA treatment and control should also be developed.

RÉSUMÉ. Les Auteurs décrivent et évaluent quatre patients atteints de *Staphylococcus aureus* résistant à la méthicilline acquis dans l'hôpital (MRSA) et d'infections de *Pseudomonas* à l'Hôpital des Brûlures et de Chirurgie Plastique au Liban entre août 1999 et août 2002. Ils n'ont pas utilisé ni la rifampicine ni la vancomycine dans le traitement de ces patients. Les lésions dues à l'inhalation accompagnées de brûlures importantes (> 60% de la surface corporelle totale), les brûlures de degré majeur (3ème degré) et la septicémie causée par la MRSA et par le *P. aeruginosa* multirésistant se sont démontrées invariablement fatales. Un patient a réagi bien à la thérapie antibiotique, mais les trois autres sont décédés malgré une thérapie similaire. Selon les Auteurs, la vancomycine et la rifampicine devraient être le premier choix dans le traitement de l'infection par MRSA; en outre, avant d'effectuer des greffes cutanées, les lésions infectées ont besoin d'une gestion agressive avec des antibiotiques.

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