The Detection of Mupirocin Resistance and the Distribution of Methicillin-resistant *Staphylococcus aureus* at the University Hospital of the West Indies, Jamaica

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ABSTRACT

Objectives: *The objectives of this study were to determine the susceptibility of Methicillin Resistant* Staphylococcus aureus *(MRSA) isolates to Mupirocin and other antimicrobial agents and to record the prevalence and distribution of this organism at the University Hospital of the West Indies (UHWI).*

Methods: *MRSA isolates collected between January 1, 2008 and December 31, 2008, were tested for low and high level resistance to Mupirocin. Susceptibility testing to other antibiotics including co-trimoxazole, minocycline, tetracycline, clindamycin, erythromycin, gentamicin and vancomycin was also done. Laboratory records for all patients from whom MRSA was recovered were reviewed and data on type and source of isolates, clinical diagnosis, history of previous hospitalization and use of mupirocin were extracted. In addition, the laboratory records for 2004 and 2005 were also reviewed to determine prevalence during these periods.*

Results: *Seven per cent of* Staphylococcus aureus *isolates were resistant to methicillin (MRSA) and of these, 30% and 24% showed low level and high level resistance to mupirocin, respectively. Ninety-four per cent of MRSA strains were resistant to erythromycin while 52% showed resistance to clindamycin. Resistance to tetracycline, co-trimoxazole and minocycline was 27%, 12% and 6%, respectively, while about one-third of the isolates were resistant to gentamicin. There was no resistance to vancomycin. More than half (58%) of the isolates were from skin and soft tissue specimens while isolates from respiratory and urinary tracts and the bloodstream accounted for 19%, 13% and 4%, respectively. There has been a steady increase in prevalence from 4% in 2004 to 5% in 2007 and 7% in 2008.*

Conclusion: *Resistance of MRSA to mupirocin appears to be an emerging problem at the UHWI and must be monitored carefully. There is also significant resistance to commonly used antimicrobial agents and strict adherence to antibiotic policy is required to preserve the usefulness of these agents.*

Keywords: Methicillin-resistant *Staphylococcus aureus,* Mupirocin, Resistant

Detección de la Resistencia a la Mupirocina y Distribución de *Staphylococcus aureus* Resistente a la Meticilina en el Hospital Universitario de West Indies, Jamaica

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RESUMEN

Objetivos: *Los objetivos de este estudio fueron determinar la susceptibilidad de aislados de* Staphylococcus aureus *resistentes (MRSA) frente a la mupirocina y otros agentes antimicrobianos, y grabar la prevalencia y distribución de este organismo en el Hospital Universitario de West Indies (UHWI).*

Métodos: *Aislados de MRSA recogidos entre el 1ero. de enero de 2008 y el 31 de diciembre de 2008, fueron sometidos a prueba a fin de determinar sus niveles bajo y alto de resistencia a la mupirocina. También se investigó la susceptibilidad frente a otros antibióticos tales como co-trimoxazol, minociclina, tetraciclina, clindamicina, eritromicina, gentamicina y vancomicina. Se revisaron las historias de laboratorio de todos los pacientes de quienes de recobró MRSA, y se extrajeron datos sobre el tipo y fuente de los aislados, el diagnóstico clínico, la historia de hospitalización previa, y el uso de mupirocina. Además, se revisaron las historias clínicas de laboratorio de 2004 y 2005 a fin de deter-*

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minar la prevalencia durante estos periodos.

Resultados: *Setenta por ciento de los ailados de estafilococo dorado era resistente a la meticilina (MRSA) y de éstos, 30% y 24% mostraron un bajo nivel y un alto nivel de resistencia a la mupirocina, respectivamente. Noventa y cuatro por ciento de las cepas de MRSA eran resistentes a la eritromicina, mientras que el 52% mostró resistencia a la clindamicina. La resistencia a la tetraciclina, el co-trimoxazol, y la minociclina fue de 27%, 12% y 6%, respectivamente, mientras que aproximadamente un tercio de los aislados eran resistentes a la gentamicina. No hubo resistencia a la vancomicina. Más de la mitad (58%) de los aislados procedían de especimenes de tejido blando y de la piel, mientras que los aislados de las vías respiratorias y urinarias así como del torrente sanguíneo constituyeron el 19%, 13% y 4%, respectivamente. Ha habido un aumento constante de la prevalencia de 4% en 2004 a 5% en 2007 y 7% en 2008.*

Conclusión: *La resistencia de MRSA a la mupirocina parece ser un problema emergente en el HUWI y debe monitorearse cuidadosamente. Hay también una resistencia significativa a los agentes antimicrobianos normalmente usados y se requiere una adhesión estricta a la política antibiótica a fin de preservar la utilidad de estos agentes.*

Palabras claves: *Staphylococcus aureus* resistente a la meticilina, mupirocina, resistente

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INTRODUCTION

Staphylococcus aureus continues to be an important nosocomial pathogen and in recent years has also become an important community-acquired pathogen (1). Infections caused by this pathogen are often acute and pyogenic and range from skin and soft tissue infections to life-threatening complications including pneumonia, foreign body infection, osteomyelitis, endocarditis and general sepsis (1–5**)**. Methicillin resistance in *Staphylococcus aureus* was first described in England in 1961, soon after its introduction for clinical use (6). Since then, MRSA has been detected in many countries with prevalence increasing dramatically throughout the world, 50% in the USA, 40% in the UK and 30-40% in France (7). Increased prevalence in India, from 12% in 1992 to 81% in 1999, points to the seriousness of MRSA in the developing world (8). MRSA infections are associated with significant morbidity and mortality and these strains are thought to be more pathogenic than methicillin-sensitive (MSSA) strains especially in the immunocompromised and seriously ill patients (8). Locally, the first case of MRSA was identified at the University Hospital of the West Indies (UHWI) in 1988 (9).

Treatment of these infections is a growing problem because of the organism's resistance to many antimicrobial agents (10–12). Resistance to methicillin automatically implies resistance to all β-lactam antibiotics such as the penicillins, cephalosporins and carbapenems and is often associated with resistance to other classes of antibiotics such as the aminoglycosides and quinolones.

At the UHWI, serious infections with MRSA are treated with vancomycin since other agents active against MRSA such as linezolid, quinupristin-dalfopristin and daptomycin are not available in Jamaica. The treatment of mild or moderate infections is guided by the susceptibility report of the isolate. On the other hand, nasal carriage of the organism in a patient or healthcare worker (HCW) and superficial wounds may be treated with mupirocin ointment (Pseudomonic acid A). This is one of only a few topical antimicrobial agents clinically shown to be safe and effective against MRSA.

Mupirocin acts by inhibiting protein synthesis in bacteria by binding competitively to bacterial isoleucyl-tRNA synthetase [IRS] (13). It was first introduced in the UK in 1985 and was used to treat staphylococcal and streptococcal wound infections and to eradicate nasal carriage of *Staphylococcus aureus* including MRSA. (14). Within two years after its introduction, mupirocin resistance among MRSA isolates emerged in the UK (15) and since then in Ireland, 2% (16), New Zealand, 12.4% (13), the USA, 24**%** (17) and in Trinidad and Tobago, 44.1% **(**18).

Most resistance to mupirocin may be associated with over prescribing of the drug. In one hospital in Brazil where there was heavy usage of mupirocin, 50% of the isolates in 1994–1995 showed resistance to mupirocin compared to 6% in a nearby hospital where mupirocin use was infrequent (19). Low level resistance to mupirocin (LMR) and high level mupirocin resistance (HMR) have been identified. Low level mupirocin resistance is thought to result from mutation in the ileS-2 (mupA) gene and tends to occur in *Staphylococcus aureus* isolates exposed to progressively higher concentrations of mupirocin *in vitro* while HMR is thought to be due to acquisition of a transferable plasmid containing the ileS-2 gene encoding an additional IRS enzyme (13).

This is the first study to determine the existence of resistance to mupirocin at the UHWI. In addition, this study seeks to determine the susceptibility profile of MRSA to other antibiotics as well as to record the prevalence of MRSA and the source and distribution of these isolates at the UHWI in 2008. The prevalence of MRSA for 2004 and 2005 is also

determined and compared with that of 2008. The results of this study will provide local data to guide the treatment of MRSA infections as well as shape the infection control policies necessary to effectively control spread of infection at the UHWI.

MATERIALS AND METHODS

Between January 1, 2008 and December 31, 2008, all non-duplicate clinical isolates of *Staphylococcus aureus* were collected from bloodstream, skin and soft tissue, urine and respiratory tract specimens at the UHWI. *Staphylococcus aureus* was identified by conventional laboratory methods. Strains were tested for methicillin resistance on Mueller-Hinton agar with 1µg oxacillin disks using the Kirby-Bauer disk diffusion method according to the Clinical Laboratory Standards Institute (CLSI) guidelines (20). The MRSA isolates were then tested for susceptibility to a range of antimicrobial agents.

The laboratory records for 2004 and 2005 were also reviewed to determine the prevalence of MRSA during these periods.

Methicillin-Resistant *Staphylococcus aureus* isolates were tested against the following antimicrobial agents (concentrations in brackets) using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (20): co-trimoxazole (25µg), minocycline (30µg), tetracycline (30µg), clindamycin (10µg), erythromycin (15µg), gentamicin (10 µg) and vancomycin (30µg**)**. Mupirocin disks (5 µg and 200 µg) were used to determine low level and high level resistance, respectively. Zone diameter breakpoints for MRSA susceptibility and resistance to mupirocin were set at ≥ 14 mm and ≤ 13 mm, respectively, as recommended by Finlay *et al* (21). *Staphylococcus aureus* ATCC strain 25923 was used as the control organism.

RESULTS

There was an increase in the prevalence of MRSA isolates in 2008 (7%) compared to 2005 (5%) and 2004 (4%). Skin and soft tissue specimens accounted for 58% of the isolates while 19% came from respiratory tract specimens and 13% from the urinary tract. Bloodstream specimens accounted for only 4% of isolates (Fig. 1).

Sixty per cent of cases were from the surgery wards, 18% from dermatology and 14% from the other medical wards while paediatric and obstetric/gynaecology wards accounted for 4% each (Fig. 2).

MRSA showed a 12% resistance to co-trimoxazole and 6% to minocycline while the resistance to tetracycline was 27% and gentamicin 33%. Resistance to clindamycin was 52 % while resistance to erythromycin was 94%. Low level resistance to mupirocin was found to be 30% and high level resistance was 24% (Table 1).

There was no resistance to vancomycin.

Of the mupirocin-resistant MRSA isolates, 88% and 63% also showed resistance to erythromycin and clindamycin, respectively, while tetracycline, rifampicin and co-trimoxazole each had 12% resistance (Table 2). One hundred per cent and 58% of the mupirocin-sensitive MRSA isolates showed resistance to erythromycin and clindamycin respectively while there was 33% resistance to tetracycline, 56% resistance to rifampicin and only 12% resistance to co-trimoxazole (Table 2).

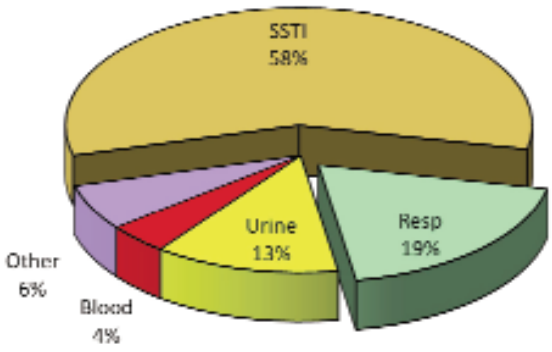

Fig. 1: Source of isolates (UHWI)

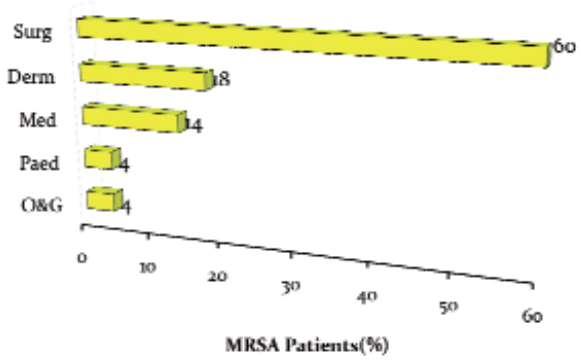

Fig. 2: Service distribution, Jan – Dec 2008

Table 1: Antimicrobial resistance profile of 33 MRSA isolates to mupirocin and selected antimicrobial agents at the UHWI, January – December, 2008.

Antibiotics Tested	No	(%)	Resistant
Co-trimoxazole	4	12%	
Tetracycline	9	27%	
Minocycline	2	6%	
Erythromycin	31	94%	
Clindamycin	17	52%	
Mupirocin **(5µg)**	10	**30%**	
Mupirocin **(200 µg)**	8	**24%**	
Gentamicin	11	33%	
Vancomycin	0	0%	
Total no of isolates tested	**33**		

Table 2: Antimicrobial susceptibilities of mupirocin-susceptible and mupirocin-resistant MRSA isolates

Antimicrobial agent	Mupirocin suscep. MRSA (% resistant)	Mupirocin resist. MRSA (% resistant)	p value
Tetracycline	33%	12%	
Co-trimoxazole	12%	12%	
Rifampicin	56%	12%	
Clindamycin	58%	63%	
Erythromycin	100%	88%	

DISCUSSION

Mupirocin is the drug of choice used to eradicate nasal carriage of MRSA in hospital. The use of this drug at the UHWI has always been empiric as susceptibility testing has never been done. This study found a 30% low-level resistance and 24% high-level resistance to mupirocin. This is high when compared to reports in the literature of 1–13% for low-level and 2.4–14% for high-level resistance (17). However, the rates at the UHWI are lower than those in Trinidad and Tobago (18). The use of mupirocin in Trinidad and Tobago was increased by over 58% from 2005 to 2006. The increased prevalence of MRSA at the UHWI from 5% in 2005 to 7% in 2008 has resulted in increased surveillance for nasal carriage of MRSA resulting in increased use of mupirocin to eradicate nasal carriage of the organism. This has contributed to an increase in the use of topical mupirocin ointment from 68 tubes per month in 2006, 76 tubes per month in 2007 to 122 tubes per month in 2008. Mupirocin ointment is widely used at the UHWI in eradication of nasal carriage of MRSA and in the treatment of superficial wound infections. Studies have shown an association between high level mupirocin resistance and increased usage of the drug (13).

The existence of mupirocin resistance among MRSA isolates is cause for concern since there are not many effective alternatives for mupirocin resistant strains. Polysporin triple ointment has been used empirically but no studies on its efficacy have been done. The use of fusidic acid topically is not recommended in order to preserve its usefulness against multi-resistant *Staphylococcus aureus* when administered orally or parenterally (13**)**. In addition, it has been shown that mupirocin resistant isolates were more likely to be resistant to fusidic acid (13, 22). Hydrogen peroxide cream has been recommended as a topical alternative to mupirocin (13).

The results from this study will guide the approach to the management of MRSA carriage and infection. The British guidelines recommend topical mupirocin ointment to the nares two to three times daily for 5–7 days and where there is persistence of carriage, a second course should be given (7). This approach is followed at the UHWI. However, in response to a 15% HMR rate, the Health Department in Western Australia issued guidelines recommending that mupirocin be not used for longer than 10 days and should not be repeated in less than a month of completing one course. This resulted in a reduction of mupirocin resistance from 18% to 0.3% in four years (23). They further recommended that the use of mupirocin in superficially infected skin lesions should be carefully screened and should not be prolonged or interrupted. In light of the relatively high level of resistance encountered at the UHWI, the current approach should be reviewed and adjusted where necessary. It may be necessary to restrict the interval during which mupirocin treatment may be repeated.

In this study, MRSA showed variable susceptibility to the other antimicrobial agents tested, with 12% resistance to co-trimoxazole, 27% resistance to tetracycline and 33% to gentamicin. Over 90% of MRSA isolates were resistant to erythromycin and 52% to clindamycin (Table 1). The D test should be done routinely to determine the existence of inducible resistance to clindamycin (6). These rates are high when compared to a study of MRSA isolates from Southwestern Alaska where there were resistance rates of 0% to co-trimoxazole, 2.5% to gentamicin and 47.5% to both erythromycin and clindamycin (1). Empiric antibiotic choices for mild to moderate MRSA infections should include co-trimoxazole and tetracycline while erythromycin should not be used.

There was some variation in the susceptibility results of mupirocin-susceptible MRSA isolates compared with mupirocin-resistant MRSA isolates in this study. There was increased susceptibility to tetracycline (12% *versus* 33% resistance) and rifampicin (12% *versus* 56%) among mupirocin-resistant isolates compared with mupirocin-susceptible isolates (Table 2). A study done on Canadian MRSA isolates also showed increased susceptibility to tetracycline (7% *vs* 23% resistance) in the mupirocin-resistant isolates compared with the mupirocin-susceptible isolates as well as to co-trimoxazole (10% *versus* 40%) and ciprofloxacin [75% *versus* 90%] (22). Unlike the results of this study, however, resistance to rifampicin was similar in both mupirocin-resistant and mupirocin-susceptible strains. In both studies, resistance to erythromycin and clindamycin was equally high in both mupirocin-resistant and mupirocin-susceptible strains (erythromycin: 94% *versus* 86%; clindamycin 86% *versus* 85%) (22). More studies need to be done to determine the molecular or epidemiological features of resistance.

With the increase in the number of MRSA cases at the UHWI**,** the use of vancomycin must be monitored to prevent the emergence of vancomycin resistance not only in *Staphylococcus aureus* but also among other organisms such as *Enterococcus* spp. One approach used by the UHWI to monitor the use of antimicrobials is to restrict the dispensing of some antibiotics, such as vancomycin, without the counter-signature of a microbiologist. The treatment of less serious MRSA infections should be guided by the antibiogram with vancomycin being reserved for serious infections.

The increased prevalence of MRSA at the UHWI reflects international trends even though the rate still remains relatively low compared to those reported from other

countries such as the USA, UK and France (7). Most of the isolates at the UHWI were from skin and soft tissue specimens and this may reflect the transmission of the organism among patients by healthcare workers (Fig. 1). This was followed by respiratory and urinary tract specimens. The distribution of isolates across the disciplines (Fig. 2) reflects international trends with surgical cases predominating (7).

Methicillin-resistant *Staphylococcus aureus* continues to be an important problem at the UHWI. The level of mupirocin resistance detected is significant and underscores the need for a policy governing mupirocin susceptibility testing as well as mupirocin usage in the management of MRSA carriage and infections. A general review of antibiotic policies using local data should also be undertaken to reduce the contribution of this factor to the emergence and spread of resistance. The role of infection control measures such as barrier nursing and hand-washing is critical in preventing the spread of this organism throughout the hospital (7).

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