

Staphylococcus aureus urinary tract bacteriuria: single-institutional antibiotic susceptibility trends over a decade

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Competing interests: The authors have declared that no competing interests exist.

Abbreviations used: MRSA, methicillin resistant *Staphylococcus aureus*; SA, *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCR, polymerase chain reaction; UTI, urinary tract infections

Received January 3, 2017; Revision received June 13, 2017; Accepted July 21, 2017; Published September 28, 2017

ABSTRACT

OBJECTIVES: Methicillin resistant *Staphylococcus aureus* (MRSA) is a troublesome pathogen which is difficult for clinicians to treat. The purpose of this surveillance program is to assess the prevalence of MRSA urinary tract infections and determine risk factors for methicillin resistance in adults amongst urinary isolates of SA and to describe the antibiotic susceptibilities to guide empirical therapy.

METHODS: From 2005 through to 2014, we retrospectively reviewed urine cultures recorded in a laboratory database at a university hospital in Cambridge, UK. Susceptibility testing was performed by BSAC (British Society of Antimicrobial Chemotherapy) disc diffusion testing and reported for fluoroquinolones, gentamicin, nitrofurantoin, linezolid, trimethoprim and vancomycin. Samples were denoted "MRSA" if they were resistant to oxacillin or ceftioxin.

RESULTS: In total, 690 cultures were positive for SA, of which 293 (42.5%) were methicillin resistant. The number of SA bacteriuria decreased from around 100 per year to 40 per year. The proportion demonstrating methicillin resistance decreased from around 60% to around 20%. Both methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA isolates were susceptible to vancomycin and nitrofurantoin. MRSA isolates demonstrated some increased resistance to trimethoprim and gentamicin and greatly increased resistance to fluoroquinolones. Urinary catheterization and increasing age were risk factors for methicillin resistance.

CONCLUSION: The incidence of SA and MRSA bacteriuria decreased during the study period. A high degree of resistance to fluoroquinolones was observed in MRSA compared to MSSA. Analysis of antibiotic susceptibility profiles suggests nitrofurantoin and trimethoprim may be useful in treating uncomplicated MSSA and MRSA urinary tract infections without concurrent bacteremia.

Keywords: bacteria, antibiotics, urinary tract infection, drug resistance, *staphylococcus aureus*, trimethoprim

INTRODUCTION

Globally, up to 150 million episodes of urinary tract infections (UTI) occur each year and results in a significant socio-economic impact [1]. UTIs account for a large proportion of the global antibiotic consumption and may contribute to progressive bacterial resistance [2]. Of the known causative pathogens, *Staphylococcus aureus* (SA) is a

nosocomial bacterial pathogen and is a relatively uncommon cause of UTI, resulting in up to 7% of such cases [3]. SA bacteriuria can result from an ascending infection precipitated by urinary catheterization or from a hematogenous route of infection, often resulting from intravascular device exposure, and may represent an undetected bacteremia [4,5]. SA bacteriuria might be a measure of bacteremia severity as it has been linked to a three-fold increase in mortality amongst patients with SA

How to cite this article: Toner L, Papa N, Perera M, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. *Staphylococcus aureus* urinary tract bacteriuria: single-institutional antibiotic susceptibility trends over a decade. *Bladder* 2017;4(3):e30. DOI: 10.14440/bladder.2017.478

bacteremia [6,7].

The incidence of methicillin resistant *Staphylococcus aureus* (MRSA) UTI is increasing, with reports of a doubling of incidence over the past decade [8]. Outcomes in MRSA bacteriuria has been observed to be worse than methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteriuria [9,10]. A prospective study demonstrated that invasive disease and symptomatic disease results from urinary tract colonization with SA [11] which suggests that such colonization may benefit from antimicrobial therapy. Additionally, SA bacteriuria could be indicative of more sinister pathology even in the apparent absence of bacteremia [12].

This study aims to demonstrate any changes in the incidence of MRSA bacteriuria at our institution over the past decade and to review the antibiotic susceptibility profile of staphylococcal bacteriuria in order to guide empirical antimicrobial therapy.

PATIENTS AND METHODS

Patient population

This study was deemed surveillance by the Health Research Authority. Therefore, formal ethical review or National Health Service (NHS) Research and Development (R&D) approval was waived. A computerized laboratory results database (Meditech®, Westwood, Massachusetts, USA) was searched for urinary isolates of all pathogens including SA for the period of 1 January 2005 to 31 October 2014. The database included patient and sample identifiers, gender, date of birth, location and date of collection, specimen type, causative organism and antibiotic susceptibility. Urinary samples from outside our institution (including community isolates) were excluded from analysis.

Culture analysis

Urine was processed by calibrated loop sampling on to chromogenic clear media (Oxoid Ltd, Basingstoke, UK). A positive culture was defined as $\geq 10^5$ CFU/ml except for samples of pregnant women where a cut-off value of $> 10^3$ CFU/ml was used. Susceptibility testing was performed by BSAC (British Society of Antimicrobial Chemotherapy) disc diffusion testing and reported for fluoroquinolones (norfloxacin

from 2005–2010 and ciprofloxacin from 2011–2014) gentamicin, nitrofurantoin, linezolid, trimethoprim and vancomycin. Susceptibilities that were classified as “intermediate resistance” were re-designated as “sensitive”. SA Samples were denoted “MRSA” if they were resistant to oxacillin or ceftiofloxacin from 2011 onwards as per BSAC guidelines [13]. In the 20 cases where both were tested, the oxacillin finding was taken as indicative of sensitivity or resistance.

Exclusion criteria included the growth of more than two organisms (heavy mixed growth) as this likely represented a contaminated sample, missing gender, age or antibiotic susceptibility, age < 16 years and an unusual specimen type such as an ileal conduit, nephrostomy, extraprostatic secretion, suprapubic aspirate or a bag specimen. We also excluded samples if they were ordered less than 30 d after a previous sample (unless a different organism was isolated) as this would skew our data by analyzing the same infection multiple times.

Statistical analysis

Data management and analysis were performed using Stata SE v.12.0 (StataCorp, College Station, TX). We compared the numbers of MRSA vs. MSSA and MRSA by oxacillin vs. MRSA by ceftiofloxacin isolates sensitive to various antibiotics with the Fisher exact test. We examined differences in incidence by gender, catheterization and age greater or less than 65 with the chi-square test. All tests were two sided with significance set at 0.05.

RESULTS

From 1 January 2005 to 31 October 2014, we retrospectively reviewed 37538 positive urine cultures from 28604 unique patients. Prior to this 12326 isolates were excluded for reasons as above (Table 1). In total, 690 cultures (1.84% of all pathogens) were positive for SA, of which 293 (42.5%) were methicillin resistant. MRSA as a proportion of all *Staph aureus* bacteriurias was observed to decrease from around 60% at the start of the study period to 20% in 2014 (Fig. 1). Additionally, the absolute number of SA isolates also decreased from over 100 to around 40 per year in 2012–2014.

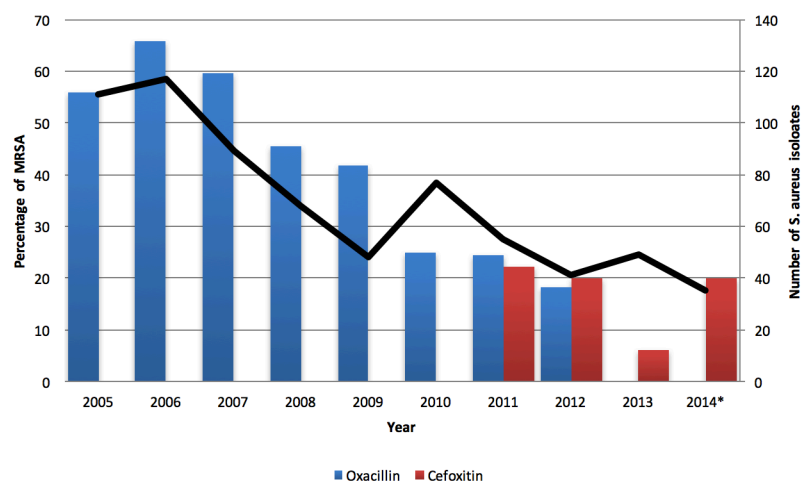


Figure 1. Percentage of MRSA isolates per year, split according to the method of determination. Black line is the number of SA bacteriuria per year. *denotes incomplete collection for the calendar year.

Table 1. Details of the isolates excluded from analysis.

49864 isolates recorded in electronic database
Exclusion criteria applied
37538 isolates remaining
873 heavy mixed growth
2197 missing age, gender or antibiotic susceptibility
3094 aged < 16 years
693 unusual specimen type
5469 samples repeated within 30 d
690 <i>Staphylococcus aureus</i>
397 MSSA
293 MRSA

As shown in **Table 2**, both MRSA and MSSA isolates were uniformly susceptible to vancomycin and nitrofurantoin with susceptibility rates exceeding 99%. Of note, 97% of MRSA isolates demonstrated resistance to fluoroquinolones, compared to only 28% of MSSA isolates. MRSA isolates demonstrated very small increased resistance to trimethoprim (5% to 9%) and gentamicin (1% to 4%). Differences between oxacillin and cefoxitin defined MRSA were detected for these two antibiotics. However, the small number of resistant isolates precludes meaningful time-trend analysis.

Compared with MSSA, MRSA isolates belonged to patients aged over 65 years significantly more frequently (83% vs. 58%, $P < 0.001$) and those with urinary catheters (47% vs. 28%, $P < 0.001$) (**Table 3**). No significant difference was noted in gender distribution ($P = 0.6$). There was no significant difference in these factors when comparing MRSA defined by oxacillin or cefoxitin (all $P > 0.1$). MRSA bacteriuria occurred proportionally more frequently in male, catheterized and older patients than the major uropathogen, *E. coli* and all other uropathogens in aggregate.

DISCUSSION

SA is an uncommon cause of UTI and has been reported as the causative organism in 1%–7% of urine samples [3,14–16]. Despite this, the presence of pathogenic urinary MRSA warrants concern as a result of limited antibiotic selection and poorer outcomes. The results of the current study highlighted the decreasing trend in MRSA diagnosis in absolute and proportional numbers of urinary cultures. Further, this study identified high-risk patients for MRSA bacteriuria and the relative antibiotic sensitivity profiles for MRSA and MSSA in current clinical practice.

While the overall incidence of SA UTI was consistent with previous literature, we observed an absolute decrease in MRSA diagnosis during the study period. Overall, the proportion of MRSA of all SA positive urinary cultures was 42.5%. This finding is in-line with current literature which reports values between 17%–75% [3,4,8,9,17]. The precise rationale for the decline in MRSA incidence is not clear. However, the results of this study identified that MRSA bacteriurias are more likely in male, elderly and catheterized patients. This suggests that MRSA is more likely to be caused by underlying anatomical or functional urinary aberrations. These risk factors for MRSA UTI have

been previously well established [18]. As MRSA is typically a hospital acquired pathogen, compared to *E. coli* which represents commensal gut flora, it is to be expected they would have different mechanisms of infection in the pathogenesis of UTI. The risk factors we have identified are concordant with those for MRSA bacteremia including male gender and instrumentation. Other risk factors beyond the scope of the present study, included chronic kidney disease, diabetes mellitus, previous antibiotic use and prolonged hospital admission [19]. Further, it should be noted that hospital infection control measures such as hand washing and catheter care have been shown to reduce SA bacteremia [20]. It is very likely that increased awareness and hand hygiene campaigns at our institution are predominantly responsible for the observed decline. Robust population-based susceptibility, antibiotic prescription and routine clinical swab testing data were not available for analysis and thus a more in depth assessment of the cause of reduction cannot be drawn.

From our study, distinct variations in antibiotic susceptibility were observed between MRSA and MSSA, particularly in the fluoroquinolone drug class. In our review of the literature (**Table 4**), we identified only one small study considering differences in antibiotic susceptibility between MRSA and MSSA in urinary isolates [17]. To widen our analysis, we included two large studies considering MRSA and MSSA isolates from blood samples. These studies again showed high susceptibility to vancomycin in both MRSA and MSSA isolates [21,22]. Further, these studies suggested that methicillin resistance is associated with increased resistance to fluoroquinolones, as is reflected in our results [23]. *Fluoroquinolones* resistance is a common feature of EMRSA-15, the predominant strain in the UK. One small series [17] suggested the MRSA phenotype is associated with gentamicin resistance which was not observed in our series. At present, Australian and American antibiotic guidelines have no particular recommendation for SA bacteriuria but recommend penicillin or flucloxacillin for MSSA bacteremia and vancomycin or daptomycin for MRSA bacteremia [24,25]. Our results suggest that commonly used antibiotics for UTI such as nitrofurantoin and trimethoprim may be effective for uncomplicated MSSA and MRSA UTIs. Given the low blood concentrations, these two antibiotics achieve; clinicians should be mindful of the clinical circumstances as SA bacteriuria may represent a complicated UTI or an undetected bacteremia. These severe infections require treatment with vancomycin which all MSSA and MRSA isolates in our series were susceptible.

Our primary limitation is the lack of clinical data to correlate with our pathology results, inherently due to the retrospective nature of the study. We were unable to correlate episodes of bacteriuria with concurrent bacteremia, clinical status or symptomatology. However, as infection or invasive disease may arise from earlier urinary tract colonization the susceptibility profile we have reported is still relevant to the management of all these conditions [11]. As our results are, only from a single center they may not reflect the situation at other hospitals. Further, the lack of robust population-based susceptibility data precludes the comparison of our results with the wider population. The laboratory tests for the detection of the MRSA phenotype evolved over the course of our study. Many laboratories in the past decade, including the present study until 2010, relied on oxacillin rather than cefoxitin for the detection of methicillin resistance. The gold standard test for MRSA is detection of the *MecA* gene by PCR, which was not used in the present study or routinely in hospital microbiology laboratories. Compared to this, the reported sensitivity of cefoxitin is > 99% which is superior to oxacillin which has been reported as 78%–95%. Further,

beta-lactamase hyper-production and high NaCl sensitivity results in false positives without clinically significant penicillin resistance when using oxacillin. Ongoing laboratory issues with MRSA detection include the small difference in zone diameter between MSSA and MRSA isolates necessitating precise measurement of the zones [26,27]. It is likely laboratory protocol may account for some regional variations in MRSA prevalence as well as a small part of the decrease in MRSA prevalence we observed.

In conclusion, the incidence of MRSA amongst SA urine cultures decreased at our institution over the past decade. Our series highlights the antibiotic sensitivity patterns of MRSA, with high proportions of resistance to fluoroquinolones compared to MSSA. Further, our antibiotic susceptibility results suggest nitrofurantoin and trimethoprim are useful in treating uncomplicated MSSA and MRSA urinary tract infections without concurrent bacteremia.

Table 2. Antibiotic susceptibility of MRSA and MSSA isolates with MRSA split by the method of determination.

	MSSA (%)	MRSA defined by oxacillin (%)	MRSA defined by ceftioxin (%)	P value for difference MSSA vs. all MRSA	P value for difference MRSA by oxacillin vs. ceftioxin
Vancomycin	277/277 (100)	271/271 (100)	2/2 (100)		
Gentamicin	392/397 (98.7)	263/273 (96.3)	17/20 (85.0)	0.014	0.050
Nitrofurantoin	393/395 (99.5)	271/273 (99.3)	20/20 (100)	> 0.9	> 0.9
Trimethoprim	375/395 (94.9)	251/273 (91.9)	16/20 (80.0)	0.063	0.088
Linezolid	2/2 (100)	1/1 (100)	9/9 (100)		
Nofloxacin/ciprofloxacin	266/370 (71.9)	10/266 (3.76)	1/29 (3.45)	< 0.001	> 0.9

Table 3. Patient demographics of SA compared to *E. coli* and all uropathogens and MRSA compared to MSSA.

	Gender n (%)		Catheter n (%)		Age n (%)		Total
	Female	Male	No	Yes	< 65 years	> 65 years	
<i>S. aureus</i>	232 (34)	458 (66)	441 (64)	249 (36)	218 (32)	472 (68)	690
MSSA	137 (35)	260 (65)	287 (72)	110 (28)	168 (42)	229 (58)	397
MRSA	95 (32)	198 (68)	154 (53)	139 (47)	50 (17)	243 (83)	293
<i>E. coli</i>	15630 (79)	4057 (21)	16580 (84)	3107 (16)	8548 (43)	11139 (57)	19687
All pathogens	25945 (69)	11593 (31)	29533 (79)	8005 (21)	15916 (42)	21622 (58)	37538

Table 4. Relevant studies of MSSA/MRSA incidence and antibiotic susceptibility.

Study (Year)	Isolate	Clinical setting	<i>Staph. aureus</i> (n)	MRSA (n)	MRSA (%)	Susceptible vancomycin (%)	Susceptible gentamicin (%)	Susceptible fluoroquinolones (%)
The present study	Urine	Hospital	690	293	42	100 (MRSA) 100 (MSSA)	96 (MRSA) 99 (MSSA)	3 (MRSA) 72 (MSSA)
Guitguizova <i>et al.</i> (2001) [17]	Urine	Hospital	36	12	33	100 (MRSA) 100 (MSSA)	25 (MRSA) 87.5 (MSSA)	25 (MRSA) ^b 87.5 (MSSA)
Wagelhener <i>et al.</i> (2008) [3]	Urine	Urology unit	200	34	17	100 (SA)	81 (SA)	75 (SA) ^p
Linhares <i>et al.</i> (2013) [14]	Urine	Community	1128	192 ^a	17 ^a	97 (SA)	94 (SA)	82 (SA) ^p
Jones <i>et al.</i> (2013) [22]	Blood	Hospital	1036	522	NR	100 (MRSA) 100 (MSSA)	NR	29 (MRSA) ^c 86 (MSSA)
Mendes <i>et al.</i> (2014) [21]	Blood	Hospital	9115	3448	38	100 (MRSA) 100 (MSSA)	NR	22 (MRSA) ^c 89 (MSSA)

^adefined by resistance to flucloxacillin; ^bdefined by resistance to ciprofloxacin; ^cdefined by resistance to levofloxacin. NR: Not reported.

Acknowledgments

None.

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