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Author manuscript

*J Hosp Infect.* Author manuscript; available in PMC 2014 November 01.

Published in final edited form as:

*J Hosp Infect.* 2013 November ; 85(3): 183–188. doi:10.1016/j.jhin.2013.07.007.

## Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria\*

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### Summary

**Background**—Infections with vancomycin-resistant enterococci (VRE) are a growing concern in hospitals. The impact of vancomycin resistance in enterococcal urinary tract infection is not well-defined.

**Aim**—To describe the epidemiology of enterococcal bacteriuria in a hospital and compare the clinical picture and patient outcomes depending on vancomycin resistance.

**Methods**—This was a 6-month prospective cohort study of hospital patients who were admitted with or who developed enterococcal bacteriuria in a 1250-bed tertiary care hospital. We examined clinical presentation, diagnostic work-up, management, and outcomes.

**Findings**—We included 254 patients with enterococcal bacteriuria; 160 (63%) were female and median age was 65 years (range: 17–96). A total of 116 (46%) bacteriurias were hospital-acquired and 145 (57%) catheter-associated. Most patients presented with asymptomatic bacteriuria (ASB) (119;47%) or pyelonephritis (64; 25%); 51 (20%) had unclassifiable bacteriuria and 20 (8%) had cystitis. Secondary bloodstream infection was detected in 8 (3%) patients. Seventy of 119 (59%) with ASB received antibiotics (mostly vancomycin). There were 74 (29%) VRE bacteriurias. VRE and vancomycin-susceptible enterococci (VSE) produced similar rates of pyelonephritis [19 (25%) vs 45 (25%);  $P = 0.2$ ], cystitis, and ASB. Outcomes such as ICU transfer [10 (14%) VRE vs 17 (9%) VSE;  $P = 0.3$ ], hospital length of stay (6.8 vs 5.0 days;  $P = 0.08$ ), and mortality [10 (14%) vs 13 (7%);  $P = 0.1$ ] did not vary with vancomycin susceptibility.

\*This study was presented at IDweek 2012 in San Diego, California, USA (abstract #725).

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**Conflict of interest statement:** All other authors have no conflicts of interest to declare.

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**Conclusions**—Vancomycin resistance did not affect the clinical presentation nor did it impact patient outcomes in this cohort of inpatients with enterococcal bacteriuria. Almost half of our cohort had enterococcal ASB; more than 50% of these asymptomatic patients received unnecessary antibiotics. Antimicrobial stewardship efforts should address overtreatment of enterococcal bacteriurias.

### Keywords

Asymptomatic disease; *Enterococcus*; Outcomes research; Urinary tract infection; Vancomycin

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## Introduction

Enterococci are the third most frequent cause of urinary tract infections in hospitalized patients.<sup>1</sup> These bacteria have been associated with cystitis, pyelonephritis, catheter-associated urinary tract infections (UTIs) and asymptomatic bacteriuria, a condition which generally does not require antimicrobial treatment. There are limited data on the optimal treatment of symptomatic enterococcal UTI. Various antibiotics have been used, from low-cost agents, such as amoxicillin and nitrofurantoin, to expensive drugs such as linezolid and daptomycin.<sup>2</sup>

Over the past two decades vancomycin-resistant enterococci (VRE) have become a common nosocomial pathogen. About 17% of all enterococcal isolates in the USA are vancomycin resistant and are primarily *Enterococcus faecium* and *E. faecalis*.<sup>3</sup> VRE is perceived as a difficult-to-treat pathogen. It has been hypothesized that *E. faecium* maintains vancomycin resistance at the expense of being less virulent than *E. faecalis*.<sup>4</sup> However, studies have reported that VRE bacteraemia results in poorer outcomes than vancomycin-susceptible enterococci (VSE) bacteraemias.<sup>5,6</sup> Because vancomycin is a frequent empiric treatment in patients with sepsis of unclear aetiology, appropriate treatment of VRE bacteraemia may be delayed and result in worse patient outcomes. It is unclear whether this scenario is also true for UTIs, where vancomycin is not a typical empiric treatment.

Very few studies have scrutinized enterococcal UTIs in the age of widespread vancomycin resistance.<sup>7–10</sup> In this study, we describe the clinical presentation, management, and outcomes of enterococcal bacteriuria in a tertiary care hospital in the midwestern USA. Our goals were: (i) to determine the frequency of enterococcal symptomatic UTIs and asymptomatic bacteriuria; (ii) to determine how often enterococcal asymptomatic bacteriuria is treated; (iii) to identify the antibiotics most commonly used in treatment; and (iv) to determine how management and outcomes vary between VRE and VSE bacteriuria.

## Methods

### Study design and setting

We conducted a prospective cohort study of patients with enterococcal bacteriuria admitted to Barnes–Jewish Hospital (BJH) between 1 July 2011 and 31 December 2011. BJH, a 1250-bed teaching hospital, is the largest hospital in Missouri, and has a referral base that

includes the St Louis metropolitan area, eastern Missouri and western Illinois. It houses all medical specialties. BJH is affiliated with Washington University School of Medicine.

### Inclusion and exclusion criteria

Patients with enterococcal bacteriuria were identified by means of a daily query of the hospital medical informatics system by one of the authors (H.K.). We included all adult inpatients with enterococcal bacteriuria (aged  $\geq 17$  years) and excluded outpatients or patients discharged home directly from the emergency department and those with concurrent non-enterococcal bacteraemia within 3 days of enterococcal bacteriuria. Polymicrobial bacteriurias were not excluded; they were defined as detection of two or more microbial species in the same urine culture.

### Clinical data collection and laboratory work-up

Upon inclusion, one of the authors (H.K.) reviewed the patients' medical records to identify signs and symptoms associated with the bacteriuria. Demographic and clinical data were also collected plus pertinent laboratory and radiological findings. Both antibiotic management (including antibiotic prescriptions upon discharge) and urinary catheter management were recorded. Enrolled patients' medical records were reviewed daily during admission and the following outcomes were evaluated: (i) symptom resolution within 3 days of the start of treatment (or at the time of discharge if discharged within 3 days of the positive culture); (ii) secondary bloodstream infection; (iii) length of hospital stay; (iv) transfer to the intensive care unit (ICU); and (v) crude in-hospital mortality. Post-discharge outcomes of interest were readmission to the hospital within 30 days with recurrent bacteriuria and/or bacteraemia.

Routine microbiological work-up on the specimens was performed by the BJH Clinical Microbiology Laboratory, including speciation (into *E. faecalis*, *E. faecium*, or other enterococcal species) and testing for antimicrobial susceptibilities. The latter was done with disc diffusion methodology, using cut-offs proposed by the Clinical and Laboratory Standards Institute (<http://www.clsi.org>). The cut-off for significant bacteriuria employed in our hospital microbiology laboratory was  $5 \times 10^4$  colony-forming units (CFU)/mL in non-catheterized and  $5 \times 10^3$  CFU in catheterized patients.

### Definitions

Symptomatic UTI was defined as the presence of bacteriuria and one or more bladder symptoms (dysuria, hesitancy, frequency, suprapubic pain), flank pain and/or fever. Cystitis was defined as the presence of bladder symptoms, including dysuria, hesitancy, frequency, and suprapubic pain. Pyelonephritis was defined as the presence of fever and/or flank pain in a bacteriuric patient. Asymptomatic bacteriuria (ASB) denoted the absence of any of the above-mentioned symptoms.<sup>11</sup> Patients unable to report symptoms were considered unclassifiable. Bacteriuria was considered to be catheter-associated if a urinary catheter was present within 48 h before the positive urine culture. Pyuria was defined as  $>10$  white blood cells per high-power field in urine microscopy.

## Sample size

In 2010, 28% of enterococci recovered from clinical urine cultures at BJH were vancomycin resistant. We hypothesized that a 15% difference in successful clinical treatment (i.e. resolution of symptoms at day 3 or at discharge) between VRE and VSE would be clinically significant. Assuming that symptom resolution is achieved in 80% of VRE bacteriurias vs 95% of VSE bacteriurias it was estimated that 55 vs 141 patients (or total, 196) would be required to make a statistically significant statement (given  $\alpha = 0.05$  and power = 80%).

## Statistical analysis

We used the statistical package SPSS (SPSS Inc., version 18, Chicago, IL, USA) to perform analyses. Univariate analyses included chi-square test or Fisher's exact test for categorical variables, as appropriate, and Student's *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate.  $P < 0.05$  was considered statistically significant. Variables with  $P > 0.1$  were included in a multivariate model. Outcomes were compared between VRE and VSE bacteriurias by means of the chi-square test. The project was approved by the Human Research Protection Office at Washington University (which waived informed consent due to the observational nature of the study) on 25 May 2011. The submission number was 201104218.

## Results

### Epidemiology of enterococcal bacteriuria in hospitalized patients

In all, 254 patients with enterococcal bacteriuria were enrolled, of whom 160 (63%) were female and 171 (67%) white. The median age was 65 years (range: 17–96 years). The body mass index (BMI) was 26.3 kg/m<sup>2</sup> (range: 15.7–79.6). The clinical manifestations ranged from ASB (119; 47%), to pyelonephritis (64; 25%), cystitis (20; 8%), and unclassified bacteriuria (51; 20%); 116 (46%) had hospital-acquired bacteriurias, and 145 (57%) were catheter-associated bacteriurias. Table I summarizes the baseline demographic characteristics and comorbidities of these patients, depending on vancomycin susceptibility. Seventy-four (29%) urine isolates were vancomycin resistant (VRE). Compared to those with VSE bacteriuria, patients with VRE bacteriuria were more likely to be non-white ( $P = 0.02$ ), to have renal insufficiency ( $P = 0.001$ ), and to be receiving immunosuppressive treatment (corticosteroids, other immunosuppressants, chemotherapy). In multivariate analysis, non-white race [odds ratio (OR): 1.96; 95% confidence interval (CI): 1.05–3.70] and renal insufficiency (OR: 2.37; 95% CI: 1.27–4.41) were independent predictors of vancomycin resistance. Otherwise the two groups were similar in their demographics and comorbidities. A total of 177 (70%) patients received pathogen-directed antibiotic treatment.

Out of 254 isolates, 243 were available for speciation (96%). The majority of these were *E. faecalis* (176; 69%), followed by *E. faecium* (62; 24%), and other *Enterococci* spp. (5; 2%). *E. faecalis* were resistant to vancomycin in 32% of cases, whereas 79% of *E. faecium* were VRE. There were 61 (24%) polymicrobial bacteriurias. Polymicrobial bacteriurias were associated with functional or anatomical urinary tract abnormality ( $P = 0.01$ ) and with pyuria ( $P = 0.03$ ), but did not result in worse outcomes than monomicrobial infections (data not shown).

### Asymptomatic bacteriuria with enterococci

A significant number of patients had ASB (119; 47%), of which 70 (59%) received antibiotic treatment. Of the 70 who received antibiotic treatment, 24 (34%) had a concomitant diagnosis of infection at another site that could have led to antibiotic usage. Based on the medical record, we could not determine whether antibiotics were given to treat the bacteriuria or for the alternative indication in these patients; 46 (39%) of 119 ASB patients received antibiotics exclusively for ASB. The presence of pyuria in patients with ASB did not affect the likelihood of antibiotic administration [35/54 (65%) with pyuria vs 33/65 (51%) without pyuria;  $P = 0.1$ ]. Among antibiotics used for ASB, vancomycin (14/70; 20%), ampicillin, and linezolid (each 13/70; 19%) were the most common. Vancomycin resistance was not associated with increased antibiotic use in ASB [15/28 (54%) in VRE vs 55/91 (60%) in VSE;  $P = 0.5$ ].

### Impact of vancomycin resistance on clinical presentation

Of the 254 urine isolates tested, 74 (29%) were VRE. Overall, symptoms were not significantly more likely to be reported in VRE vs VSE infections [46/137 (34%) vs 28/121 (24%);  $P = 0.06$ ]. The two groups were also similar with regard to the subsets of cystitis, pyelonephritis, and ASB (Table II).

### Management of enterococcal bacteriuria and patient outcomes

Out of 254 patients, 177 (70%) received pathogen-directed antibiotics. Linezolid was more likely to be used as the first pathogen-directed antibiotic in patients with VRE bacteriuria [25 (51%) vs 9 (7%) in VSE bacteriuria patients;  $P < 0.001$ ]. Also, doxycycline [7 (14%) vs 5 (4%);  $P = 0.02$ ] and daptomycin [4 (8%) vs 0 (0%);  $P = 0.005$ ] were more commonly used in patients with VRE infection. Twenty-four (32%) of VRE isolates were ampicillin susceptible; 7 (29%) were treated with linezolid. There were no significant differences in other antibiotics used. As expected, vancomycin was not used as pathogen-directed antibiotic for VRE. In addition to antibiotic management, catheter management was examined across the two groups: in the VRE group, 23 (55%) patients had catheters removed compared to 47 (45%) in the VSE group ( $P = 0.3$ ).

Vancomycin susceptibility did not significantly alter outcomes such as transfer to ICU [10 (14%) VRE vs 17 (9%) VSE;  $P = 0.3$ ], length of hospital stay [6.8 days (0.1–150.8) vs 5 days (0.2–78.2);  $P = 0.08$ ], and mortality [10 (14%) vs 13 (7%);  $P = 0.1$ ] (Table II). Outcomes were similarly unaffected in the symptomatic subset of patients (data not shown). Bacteraemia was present in 8 (3%) of the bacteriuria cases. Thirty-day post-discharge outcomes were similar independent of vancomycin resistance.

## Discussion

Although enterococcus is the third-most frequent cause of UTI, its optimal treatment is poorly characterized. In addition, treatment has been complicated by widespread vancomycin resistance. In this prospective study of enterococcal bacteriuria at a tertiary care hospital, asymptomatic enterococcal bacteriuria was detected as frequently as symptomatic UTI, antibiotic therapy for asymptomatic enterococcal bacteriuria was frequently used, and

clinical severity was unaffected by enterococcal vancomycin resistance. Patient outcomes did not differ between those with VRE and VSE bacteriuria.

National guidelines state that ASB is, with very few exceptions, not an indication for antibiotic treatment.<sup>12</sup> In spite of this, it is not uncommon for asymptomatic patients with positive urine cultures to receive antibiotics.<sup>13</sup> A recent retrospective analysis of enterococcal bacteriurias in inpatients and outpatients at two centres serving veteran and immunocompromised populations, respectively, reported that approximately one-third of asymptomatic bacteriuric patients were treated with antibiotics.<sup>9</sup> However, the authors did not report alternative indications for antibiotics. In this study of general hospital patients, we found that 59% of our patients with ASB received treatment. Even after accounting for possible alternative indications for treatment, 39% still received unnecessary antibiotics. We focused on hospitalized patients in our investigation for a number of reasons: (i) the complexity of patients seen in an urban, tertiary care hospital, and its impact on treatment decisions; (ii) the importance of antibiotic overtreatment of bacteriuria for antimicrobial stewardship; and (iii) the ability to follow outcomes prospectively during hospitalization. We feel that the lack of guidance on optimal treatment strategies may make enterococcal bacteriuria an ideal target for antimicrobial stewardship measures.

Clinical experience with enterococcal bloodstream infections would suggest that vancomycin resistance in enterococcal bacteriuria might be associated with worse outcomes.<sup>5,6</sup> In this study we therefore compared the clinical manifestations between VRE and VSE bacteriurias. The frequencies of patients presenting with either cystitis or pyelonephritis were similar across the two groups. The fact that no difference was observed could be due to similar virulence in the two groups. Because VRE was more commonly encountered in patients with either immunosuppression or renal insufficiency, an alternative explanation might be that less virulent, vancomycin-resistant, enterococci are still able to cause significant clinical disease in vulnerable patients.<sup>14</sup> African-American race was one of the independent predictors of VRE bacteriuria; this association has been reported previously.<sup>15</sup> Renal insufficiency, the other predictor, may be a marker for increased healthcare exposure.<sup>16</sup>

No difference was found in outcomes between VRE and VSE bacteriuria. VRE bacteriurias were more frequently treated with newer agents with extended activity against Gram-positive bacteria such as linezolid or daptomycin (overtreatment with these drugs has recently been described in a retrospective study focusing on VRE bacteriurias).<sup>10</sup> The fact that we did not see worse outcomes in VRE infections may be due to greater clinical effectiveness of these newer antibiotics. Specifically, the role of linezolid in treating enterococcal bacteriuria is unresolved, although it is often an option of last resort for VRE. Alternatively, enterococcal bacteriuria may be a comparatively indolent entity with a low rate of complications regardless of antibiotic administration.<sup>17</sup> Comparative effectiveness studies are needed to best define the treatment for enterococcal bacteriurias.

This study has limitations. Information on the patients' symptoms was collected from the medical records, not by patient interview by the investigators; it is possible that urinary symptoms were underreported by treating physicians. The study focused on hospitalized

patients in a tertiary centre, with many patients having complex comorbidities and occasionally concurrent indications for antibiotic use. Many patients were unable to report symptoms for different reasons (e.g. intubation, coma, psychiatric illness); these patients were analysed as a separate group (i.e. unclassifiable bacteriuria).

In conclusion, it was found that vancomycin resistance did not have a major impact on the clinical presentation and outcomes of enterococcal bacteriuria. This has not been examined before and is in stark contrast to studies on vancomycin resistance in bloodstream infections. The management of VRE bacteriuria was characterized by increased use of broad spectrum antibiotics – even among ampicillin-susceptible strains – and by a substantial proportion of patients treated for asymptomatic bacteriuria. These findings reinforce the need for antimicrobial stewardship in bacteriuria management.

## Acknowledgments

We thank C. Hill and D. Sinclair for their invaluable data management. J. Wu helped with the data collection.

D.W. is a Consultant for 3M Healthcare and Cardinal Health, and has received research funding from Sage Products, Inc., and Cubist Pharmaceuticals.

**Funding sources:** J.M. was supported by the NIH CTSA/NCATS (UL1RR024992) and recipient of a KL2 Career Development Grant (KL2RR024994); he is currently supported by the NIH Office of Research for Women's Health with a BIRCWH award (Building Interdisciplinary Research Careers in Women's Health; grant # 5K12HD001459-13). He is also the section leader for a subproject of the CDC Prevention Epicenters Program grant (U54 CK000162; P.I. Fraser). In addition, J.M. receives support from the Barnes–Jewish Hospital Patient Safety & Quality Fellowship Program, which is funded by The Foundation for Barnes–Jewish Hospital. He also received a research grant from the Barnes–Jewish Hospital Foundation & Washington University's Institute of Clinical and Translational Sciences (ICTS). J.P.H. is the recipient of a Burroughs–Wellcome Career Award for Medical Scientists and is supported by the National Institutes of Health (HD001459-09 and DK064540-09). D.K.W. received a CDC Prevention Epicenters Program grant (U54 CK000162; P.I. Fraser).

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**Table I**  
**Baseline demographic data and comorbidities for 254 patients with enterococcal bacteriuria, depending on vancomycin susceptibility**

|  | Vancomycin-susceptible<br>enterococci<br>(N = 180) | Vancomycin-resistant<br>enterococci<br>(N = 74) | P-value |
|--|--|---|---------|
| Age  | 67 (17–94)   | 74 (22–96)                                      | 0.9     |
| Female   | 114 (63%)  | 46 (62%)  | 0.9     |
| Body mass index (kg/m <sup>2</sup> , range)        | 26.5 (15.7–67.8)                                   | 26.0 (16.7–79.6)                                | 0.1     |
| White race   | 129 (72%)  | 42 (57%)  | 0.02    |
| Catheter-associated bacteriuria                    | 103 (57%)  | 42 (57%)  | 1.0     |
| Hospital-acquired infection                        | 80 (44%)   | 36 (49%)  | 0.5     |
| Malignancy   | 59 (33%)   | 27 (37%)  | 0.6     |
| Chemotherapy (past 30 days)                        | 7 (4%)   | 8 (11%)   | 0.04    |
| Diabetes mellitus                                  | 49 (27%)   | 21 (28%)  | 0.9     |
| Immunosuppression                                  | 19 (11%)   | 16 (22%)  | 0.02    |
| Steroids   | 28 (16%)   | 20 (27%)  | 0.03    |
| HIV/AIDS   | 4 (2%)   | 1 (1%)  | 0.7     |
| Any transplant                                     | 18 (10%)   | 12 (16%)  | 0.2     |
| Serum creatinine >1.5 mg/dL                        | 43 (24%)   | 33 (45%)  | 0.001   |
| Cerebrovascular insult                             | 37 (21%)   | 13 (18%)  | 0.6     |
| Dementia   | 14 (8%)  | 5 (7%)  | 0.8     |
| Hemiplegia/paraplegia and quadriplegia             | 16 (9%)  | 8 (11%)   | 0.6     |
| Pyuria (WBC >10)                                   | 92 (55%)   | 39 (54%)  | 0.9     |
| Functional or anatomical urinary tract abnormality | 38 (21%)   | 16 (22%)  | 0.9     |
| Urological procedure prior to UTI (this admission) | 13 (7%)  | 11 (15%)  | 0.06    |
| Previous urological procedure                      | 41 (23%)   | 23 (31%)  | 0.2     |
| Previous enterococcal UTI                          | 29 (16%)   | 19 (26%)  | 0.08    |

HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; WBC, white blood cell count; UTI, urinary tract infection.

**Table II**  
**Clinical presentation and patient outcomes in 254 episodes of enterococcal bacteriuria, depending on vancomycin susceptibility**

| Presentation and outcomes  | Vancomycin-susceptible enterococci (N = 180) | Vancomycin-resistant enterococci (N = 74) | P-value |
|--|--|---|---------|
| Clinical presentation  |  |   |         |
| Cystitis   | 11 (6%)                                      | 9 (12%)                                   | 0.1     |
| Pyelonephritis   | 45 (25%)                                     | 19 (25%)                                  | 0.2     |
| Unclassified bacteriuria   | 33 (18%)                                     | 18 (24%)                                  | 0.3     |
| Asymptomatic bacteriuria   | 91 (51%)                                     | 28 (38%)                                  | 0.07    |
| Patient outcomes   |  |   |         |
| Improvement of symptoms (documented)                                       | 47 (26%)                                     | 20 (27%)                                  | 0.9     |
| ICU transfer   | 17 (9%)                                      | 10 (14%)                                  | 0.3     |
| Length of stay after bacteriuria (days)                                    | 5.0 (0.2–78.2)                               | 6.8 (0.1–150.8)                           | 0.08    |
| Hospital all-cause mortality   | 13 (7%)                                      | 10 (14%)                                  | 0.1     |
| Enterococcal bacteraemia (in the first 3 days after bacteriuria)           | 5 (3%)                                       | 3 (4%)                                    | 0.7     |
| Enterococcal bacteraemia within 3–30 days after initial bacteriuria        | 3 (2%)                                       | 4 (6%)                                    | 0.1     |
| Hospital readmission within 30 days from discharge                         | 46 (26%)                                     | 22 (30%)                                  | 0.5     |
| Recurrence of enterococcal bacteriuria within 3–30 days of initial culture | 9 (5%)                                       | 4 (6%)                                    | 0.9     |

ICU, intensive care unit.