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EVALUATION OF VANCOMYCIN POTENCY TRENDS ("CREEP") AGAINST METHICILLIN-RESISTANT *S. AUREUS* COLLECTED IN 9 UNITED STATES HOSPITALS OVER FIVE YEARS (2002- 2006)

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ABSTRACT

Background: Vancomycin MIC creep has been reported by some institutions but not proven in large surveillance studies. We evaluated the possible MIC creep occurrence when testing vancomycin and daptomycin against MRSA by precise CLSI methods.

Methods: 9 hospitals (1 / CDC region) randomly selected bloodstream MRSA strains (target, 40/year) from 2002-2006. MICs were determined by CLSI broth microdilution (BMD) using incremental dilutions (up to 7 between each log2 dilutions). Isolates with vancomycin MIC >1 μg/ml were typed by PFGE.

Results: Vancomycin MIC mode was 0.625 μg/ml in all centers and 73% (69-77%) of strains had vancomycin MIC between 0.563 and 0.688 μg/ml. No yearly variation on the central tendency of vancomycin MIC of the wild-type population was observed in any medical center; however, when analyzed by geometric mean, vancomycin MIC showed increases in 3 and decline in 3 centers. Daptomycin MIC mode varied from 0.156 (2003-2005) to 0.219 μg/ml (2002 and 2006) and 83% (80-89%) had MIC between these values. Among PFGE typed strains, 43 of 55 (78%; 7 hospitals) showed a pattern similar to USA100; which represented all strains from 2 hospitals and 64-88% of strains from 5 other hospitals; only 1 strain (2%) was USA300.

Year (no.)	% of strains at vancomycin MIC (μg/ml) value of:						
	≤0.375	0.406-0.5	0.563	0.625	0.688	0.75-1	>1
2002 (342)	2.6	6.7	8.5	36.8	24.0	18.1	3.2
2003 (365)	1.1	6.6	9.6	45.2	22.5	13.1	1.6
2004 (347)	2.9	6.1	8.9	39.8	19.9	18.7	3.7
2005 (380)	2.4	7.9	10.8	41.6	22.1	11.6	3.7
2006 (366)	1.1	4.1	9.3	44.0	21.0	15.8	3.0

Conclusions: Perception of vancomycin MIC creep may vary according to the methods used to analyze the data. Geometric mean MIC data revealed 3 of 9 sites had an MIC Creep over the 5 year period which was not evident using modal MIC values. Prevalence of strains with vancomycin >1 μg/ml was very low, with no increase trend but related to clonal occurrence (USA100).

INTRODUCTION

Vancomycin resistance remains extremely rare among *Staphylococcus aureus*. However, vancomycin treatment failure is not uncommon in methicillin-resistant *S. aureus* (MRSA) infections, even when the strain is considered fully susceptible to vancomycin (MIC, ≤2 μg/ml). A reduction in the efficacy of vancomycin against MRSA with elevated vancomycin MIC (1-2 μg/ml) has been widely described, suggesting that recent changes in the MIC may explain clinical failures.

Studies reporting vancomycin "MIC creep" with MRSA have produced conflicting results. While some institutions have reported MIC creep, large multicenter surveillance studies have not demonstrated trends towards higher vancomycin MIC results. Several factors can be responsible for these discrepancies, including the sensitivity of the susceptibility method for detecting MIC variations and the statistical method used to analyze the MIC data. It is also important to clearly distinguish "MIC creep" (which should be defined as a gradual increase in the central tendency of the vancomycin MIC of the wild-type population) from an increase in the occurrence of individual strains with elevated vancomycin MIC.

In this study, we evaluated the possible MIC creep occurrence when testing vancomycin and daptomycin against MRSA in a large comprehensive multicenter study using precise reference broth microdilution methods.

METHODS

Bacterial isolates:

Nine hospitals located in large urban areas (one from each of the United States census regions) and with established vancomycin use, were selected to participate in the study. Each medical center was requested to send randomly selected MRSA strains (target, 40) from bloodstream infections per year from 2002 through 2006 - total of 200 strains per medical center.

Participant centers:

1. New England Medical Center (Boston, MA).
2. New York Hospital Queens (New York, NY).
3. Ochsner Clinic Foundation (New Orleans, LA).
4. University of Colorado Health Science Center (Denver, CO).
5. University of Nebraska Medical Center (Omaha, NE).
6. University of Washington (Seattle, WA).
7. University of Alabama at Birmingham (Birmingham, AL).
8. Wayne State University (Detroit, MI).
9. Medical University of South Carolina (Charleston, SC).

Susceptibility testing:

Minimum inhibitory concentration (MIC) values were determined by broth microdilution method (BMD) for daptomycin, vancomycin and oxacillin with appropriate medium variations (50 mg/L of calcium for testing daptomycin). Twenty dilutions between 16 and 0.06 μg/ml were tested for daptomycin and 36 dilutions between 64 and 0.06 μg/ml were tested for vancomycin.

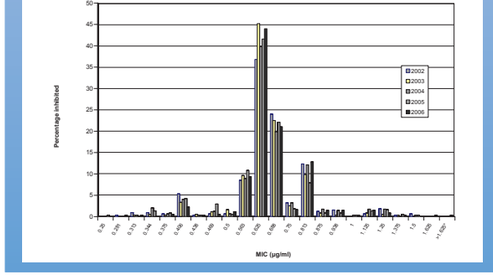
Molecular Typing:

Isolates with vancomycin MIC at >1 μg/ml were epidemiologic typed by pulsed-field gel electrophoresis (PFGE). Gel pattern analysis was carried out using the GelCompar II software (Applied Math, Kortrijk, Belgium) and the PFGE patterns obtained during this study were compared to the USA clones, such as the USA100, USA300-0114, USA700 and USA1100. Percent similarities were identified on a dendogram derived from the unweighted pair group method using arithmetic averages and based on Dice coefficients. Band position tolerance and optimization were set at 2.3% and 0.5%, respectively.

RESULTS

- Vancomycin MIC mode was 0.625 μg/ml in all centers and 73% (69-77% by site) of strains had vancomycin MIC between 0.563 and 0.688 μg/ml (**Figure 1**).

Figure 1: Vancomycin broth MIC (incremental) by year



RESULTS

- No yearly variation on the central tendency of vancomycin MIC of the wild-type population was observed in any medical center; however, when analyzed by the geometric mean statistic, vancomycin MIC showed increases in 3 medical centers but a decline in 3 other sites. Furthermore, results on geometric mean MIC may change if rounded $\log_2$ MIC was applied instead of precise incremental MIC (**Figures 2 and 3**).
- Medical center number 3 showed the most prominent "MIC Creep" when yearly geometric mean results were analyzed. However, the geometric mean only increased 0.12 μg/ml in 5 years, from 0.90 μg/ml in 2002 to 1.02 μg/ml in 2006 (**Figure 2**).

Figure 2: Vancomycin broth MIC (incremental) by year - Site #3

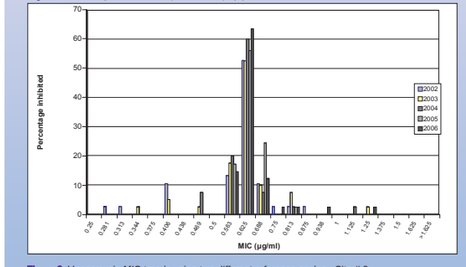
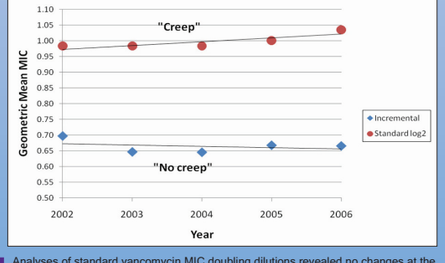


Figure 3 Vancomycin MIC trends using two different reference scales - Site # 8:



- Analyses of standard vancomycin MIC doubling dilutions revealed no changes at the studied medical centers over the tested interval (2002-2006): all modes and MIC90 values are 1 μg/ml. The overall frequency (all years together) of MRSA isolates with vancomycin MIC >1 μg/ml varied from ≤1.5% in the University of South Carolina (0.5%), New York Hospital Queens (1.0%) and Ochsner Clinic Foundation (1.5%) to the highest rate of 5.0% in the New England Medical Center and the University of Alabama at Birmingham. Only one strain with a vancomycin MIC result at >2 μg/ml was identified during the study (**Table 1**).
- When results from all medical centers were analyzed together, the frequency of isolates with vancomycin MIC at >1 μg/ml varied from 1.6% in 2003 to 3.8% in 2004 (3.1% overall; 55 strains), and no trend toward higher resistance was observed during the study period (**Table 2** and **Figure 1**).
- Daptomycin MIC mode varied from 0.156 (2003-2005) to 0.219 μg/ml (2002 and 2006) and 83% (80-89%) had MIC results between these values (**Tables 1** and **2**).
- Analyses of standard daptomycin MIC doubling dilutions showed a mode of 0.25 μg/ml for all years and all medical centers evaluated (**Table 2**). The percentage of strains with daptomycin standard doubling MIC value of 0.25 μg/ml (0.156-0.25 μg/ml) varied from 78.5% in the New York Hospital Queens to 94.5% at the University of Colorado (**Table 1**).

Table 1. Trends in vancomycin and daptomycin susceptibility of MRSA over a five year period in nine medical centers (1,800 isolates) when tested by broth microdilution methods.

Medical center/ year (no. tested)	No. at vancomycin MIC (μg/ml)*					No. at daptomycin MIC (μg/ml) *				
	0.25	0.5	1	2	4	0.12	0.25	0.5	1	2
Site #1 (200)										
2002 (40)	0	1	36	3	0	0	35	5	0	0
2003 (40)	0	0	36	4	0	1	37	2	0	0
2004 (40)	0	1	37	2	0	0	35	4	0	1
2005 (40)	0	1	39	0	0	0	34	6	0	0
2006 (40)	0	0	39	1	0	1	37	1	1	0
Site #2 (200)										
2002 (40)	0	4	36	0	0	3	35	2	0	0
2003 (40)	0	3	37	0	0	3	36	1	0	0
2004 (40)	0	6	34	0	0	4	30	6	0	0
2005 (40)	0	15	23	2	0	8	27	5	0	0
2006 (40)	0	5	35	0	0	11	29	0	0	0
Site #3 (200)										
2002 (38)	0	6	32	0	0	1	35	2	0	0
2003 (40)	0	4	35	1	0	0	39	1	0	0
2004 (40)	0	3	36	1	0	4	36	0	0	0
2005 (41)	0	0	41	0	0	0	41	0	0	0
2006 (41)	0	0	40	1	0	0	39	2	0	0
Site #4 (200)										
2002 (40)	0	5	34	1	0	0	39	1	0	0
2003 (40)	0	1	39	0	0	1	37	2	0	0
2004 (40)	0	1	36	3	0	0	38	2	0	0
2005 (40)	0	0	39	1	0	0	39	1	0	0
2006 (40)	0	0	38	1	1	0	36	2	2	0
Site #5 (200)										
2002 (40)	0	0	40	0	0	1	39	0	0	0
2003 (40)	0	2	38	0	0	0	39	1	0	0
2004 (40)	0	3	37	0	0	3	37	0	0	0
2005 (40)	0	0	36	4	0	1	34	5	0	0
2006 (40)	0	1	38	1	0	0	37	3	0	0
Site #6 (200)										
2002 (21)	0	1	20	0	0	0	18	3	0	0
2003 (45)	0	2	43	0	0	0	40	5	0	0
2004 (45)	0	1	41	3	0	1	41	3	0	0
2005 (45)	0	3	39	3	0	0	40	5	0	0
2006 (44)	0	2	39	3	0	1	37	6	0	0
Site #7 (200)										
2002 (43)	0	3	35	5	0	1	37	5	0	0
2003 (40)	0	3	36	1	0	2	37	1	0	0
2004 (22)	0	1	19	2	0	0	22	0	0	0
2005 (52)	0	6	45	1	0	0	49	3	0	0
2006 (43)	0	4	38	1	0	1	40	2	0	0
Site #8 (200)										
2002 (40)	0	3	35	2	0	2	37	1	0	0
2003 (40)	0	1	39	0	0	0	39	1	0	0
2004 (40)	0	3	35	2	0	0	37	2	1	0
2005 (40)	0	3	34	3	0	0	33	6	0	1
2006 (40)	0	0	38	2	0	0	36	2	2	0
Site #9 (200)										
2002 (40)	0	9	31	0	0	0	29	11	0	0
2003 (40)	0	12	28	0	0	1	38	1	0	0
2004 (40)	0	12	28	0	0	0	39	1	0	0
2005 (42)	1	10	31	0	0	3	35	4	0	0
2006 (38)	0	7	31	1	0	1	32	5	0	0

* MIC values reported in standardized $\log_2$ dilutions (0.12, 0.25, 0.5, 1, 2, 4, etc.)

Table 2. Frequency of vancomycin and daptomycin MIC (μg/ml) values by year (broth microdilution method).

Year (no. tested)	No. of strains (%) with vancomycin MIC (μg/ml) of:					No. of strains (%) with daptomycin MIC (μg/ml) of:				
	≤0.25	0.5	1	2	4	≤0.12	0.25	0.5	1	2
2002 (342)	0 (0.0)	32 (9.4)	299 (87.4)	11 (3.2)	0 (0.0)	8 (2.3)	304 (88.9)	30 (8.8)	0 (0.0)	0 (0.0)
2003 (365)	0 (0.0)	28 (7.7)	331 (90.7)	6 (1.6)	0 (0.0)	8 (2.1)	342 (93.7)	15 (4.2)	0 (0.0)	0 (0.0)
2004 (347)	0 (0.0)	31 (8.9)	303 (87.3)	13 (3.8)	0 (0.0)	12 (3.5)	315 (90.8)	18 (5.2)	1 (0.3)	1 (0.3)
2005 (380)	1 (0.2)	49 (12.9)	316 (83.2)	14 (3.7)	0 (0.0)	12 (3.1)	332 (87.3)	35 (9.2)	0 (0.0)	1 (0.3)
2006 (366)	1 (0.3)	19 (5.2)	335 (91.5)	10 (2.7)	1 (0.3)	15 (4.1)	323 (88.3)	23 (6.3)	5 (1.4)	0 (0.0)
Total (1,800)	2 (0.1)	159 (8.8)	1,584 (88.0)	54 (3.0)	1 (<0.1)	55 (3.1)	1,616 (89.8)	121 (6.7)	6 (0.3)	2 (0.1)

- Among 55 MRSA strains with vancomycin MIC at >1 μg/ml, 43 (78.2%) showed a PFGE pattern consistent with USA100, also called New York/Japan clone and designated "A" in the present study. The A pattern isolates were observed in 7 of 8 hospitals with strains showing vancomycin MIC values above the mode (>1 μg/ml) and 24 subtypes were identified (**Table 3**).
- Isolates with PFGE pattern "A" and its subtypes represented all strains from two hospitals and 63.6-87.5% of strains from the other five hospitals where this pattern was detected. The remaining 12 strains (from five medical centers) exhibited eight distinct PFGE patterns (1-2 strains of each group). Only one strain (2%) was related to the community-acquired MRSA USA300 clone (**Table 3**).

Table 3. Summary of molecular typing results of MRSA strains with vancomycin broth microdilution MIC >1 μg/ml

PFGE patterns	No. of strains	Number of subtypes	Medical center(s)
A*	43	24	1, 3, 4, 5, 6, 7 and 8
B	2	1	7
C	1	1	8
D‡	1	1	3
E	2	1	6
F	2	2	7 and 8
G	2	1	2
H	1	1	8
I	1	1	7

* PFGE profile equivalent to the USA100
‡ PFGE profile equivalent to the USA300

CONCLUSIONS

- MIC increases using precise incremental dilutions were not apparent between the years of 2002-2006 for either daptomycin or vancomycin when monitoring 1,800 bacteremic MRSA strains.
- Prevalence of strains with vancomycin >1 μg/ml was very low, with no apparent increase.
- Perception of vancomycin MIC creep may vary according to the methods used to analyze the data. Geometric mean MIC data revealed 3 of 9 sites had a slight MIC Creep (highest increase of 0.12 μg/ml over the 5 year period) which was not evident using modal MIC values.
- The occurrence of MRSA strains with vancomycin MIC at >1 μg/ml was clearly related to clonal occurrences (USA100).
- False perception of vancomycin "MIC Creep" (increase in the MIC of wild-type population) may occur, but it appear to be due to increase occurrence of strains (usually clonal) with an elevated vancomycin MIC (>1 μg/ml).
- Dissemination of MRSA clones with an elevated vancomycin MIC, such as the USA100, is of great concern since infections caused by these strains may not respond well to usual dosing of vancomycin therapy.

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