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In Vitro Activities of Mupirocin, Tigecycline, Ceftaroline, Vancomycin, Linezolid and Daptomycin in Clinical Isolates of Methicillin-Resistant *Staphylococcus aureus* by E-Test Methodology

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Abstract

Introduction: In 2013, the Center for Disease Control (CDC) designated methicillin-resistant *Staphylococcus aureus* (MRSA) as a serious threat. In addition to its intrinsic virulence, MRSA has become resistant to numerous antibacterial agents. In many instances, mupirocin is used empirically to decolonize patients harboring MRSA to decrease the possibility of progression to disease. *In vitro* susceptibility information is critical to identify patients who would benefit from use of mupirocin for decolonization and treatment of infections caused by MRSA. Methods: One-hundred and sixty-three recent MRSA single patient clinical isolates were collected from the Clinical Microbiology Laboratory. *In-vitro* susceptibility testing was performed using E-test methodology for tigecycline, ceftaroline, daptomycin, vancomycin, linezolid, and mupirocin. Results: Of the 163 MRSA isolates tested, >99% demonstrated susceptibility to tigecycline, ceftaroline, daptomycin, vancomycin, and linezolid. Seventy (43%) had vancomycin MICs ≥ 1.5 μg/ml, twenty-four isolates (15%) were resistant to mupirocin, and three appeared to express mupirocin hetero-resistance. Conclusion: While antibiotic susceptibility to mupirocin is not routinely performed in clinical microbiology laboratories, the level of resistance to mupirocin identified in this surveillance study suggests that susceptibility testing should be added to routine MRSA panels.

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Keywords

Methicillin-Resistant *Staphylococcus aureus*, Mupirocin Resistance, Antibiotic Susceptibility, MIC Creep

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a ubiquitous, virulent pathogen found in a variety of hospital, long-term care facility and community settings [1] [2]. It has been recognized as a serious threat by the Center for Disease Control and Prevention (CDC) in 2013 [3]. A recent survey from the CDC on antimicrobial-resistant pathogens associated with healthcare-associated infections (HAIs) found MRSA to be associated with 54.6% of central line-associated bloodstream infections (CLABSI), 58.7% of catheter-associated urinary tract infections (CAUTI), 48.4% of ventilator-associated pneumonia (VAP), and 43.7% of surgical site infections (SSI) [4]. Active intravenous agents include vancomycin, tigecycline, ceftaroline, linezolid, and daptomycin. Mupirocin is a topical agent used to eradicate nasal carriage with MRSA as well as topical treatment for MRSA associated wound infections and impetigo in adult patients and health care personnel. As mupirocin susceptibility is not routinely performed in most clinical microbiology laboratories, it is assumed to be an active agent when used. This *in vitro* susceptibility surveillance study using E-test methodology was undertaken to determine mupirocin susceptibility along with comparator antibiotics against recent MRSA isolated from a variety of clinical patient specimens.

2. Materials and Methods

The Clinical Microbiology Laboratory at New York Hospital Queens identifies MRSA using Vitek-2 panels. Single-patient clinical MRSA isolates from April 2013 to July 2014 were included. Isolates were stored on columbia naladixic acid agar (CNA) plates at 4˚C until ready for use. Isolates were re-streaked onto new CNA plates to ensure purity before conducting susceptibility studies.

Minimal inhibitory concentrations (MICs) were determined for mupirocin, vancomycin, tigecycline, ceftaroline, linezolid, and daptomycin by E-test according to manufacturer's specifications (bioMérieux, France). The Clinical Laboratory Standards Institute (CLSI) guidelines were used for susceptibility interpretation for vancomycin, daptomycin, ceftaroline, and linezolid [5]. Tigecycline susceptibility was determined using FDA breakpoints. ATCC 43300 was used as a methicillin resistant *Staphylococcus aureus* quality control strain. Definition of mupirocin susceptibility based on MICs was as follows: mupirocin susceptible ≤ 4 μg/ml; low-level resistance 8 - 256 μg/ml and high-level ≥ 512 μg/ml [6]. The study was reviewed and approved by The New York Hospital Queens Institutional Review Board.

3. Results

3.1. Patient and Isolate Characteristics

Of the 163 patients, 88 (54%) were female, with mean age of 66 years (range 2 - 102 years). Anatomic locations of the isolates were as follows: 42 (26%) blood, 78 (48%) wounds, 15 (9%) urine, 3 (2%) nose, 3 (2%) nares, and 22 (13%) sputum (**Table 1**).

3.2. Susceptibility Results

For vancomycin, 92 (56%) of isolates had MICs of ≤1.0 μg/ml, 70 (43%) had MICs ≥ 1.5 μg/ml. Of the 42 blood isolates, 22 (52%) had MICs ≥ 1.5 μg/ml. For ceftaroline, 162 (99%) of isolates had MICs of ≤1.0 μg/ml and one isolate had MIC of 1.5 μg/ml. For daptomycin, 162 (99%) of the isolates had MICs of ≤1.0 μg/ml and one isolate had MIC of 1.5 μg/ml. For linezolid, all isolates (100%) had MICs of ≤4 μg/ml. For tigecycline, 162 (99%) of the isolates had MICs of ≤0.5 μg/ml and one isolate had MIC of 0.75 μg/ml. For mupirocin, 139 (85%) of the isolates were susceptible with 24 (15%) demonstrating high level resistance MIC ≥ 512 μg/ml (**Table 2**). Three of the isolates displayed mupirocin heteroresistance (colony growth within the ellipse). Colonies taken

Table 1. Source of isolates and mupirocin resistant strains.

Source of Isolate	Number of Isolates	Number and Mupirocin Resistance (%)
Blood	42	10 (26)
Wounds	78	12 (15)
Urine	15	0
Sputum	22	0
Nares	3	1 (33)
Nose	3	1 (33)
TOTAL	163	24

Table 2. Antibiotic susceptibility of 163 methicillin-resistant *Staphylococcus aureus* by E-test.

		µg/ml	
Antimicrobial Agent	MIC_{50}	MIC_{90}	MIC Range
Mupirocin	0.094	>1024	0.064 - >1024
Vancomycin	1.0	1.5	0.19 - 3.0
Linezolid	0.5	1.5	0.047 - 4.0
Ceftaroline	0.5	1.0	0.023 - 1.5
Daptomycin	0.25	0.75	0.032 - 1.5
Tigecycline	0.125	0.38	0.047 - 0.75

from within this area demonstrated the same phenomenon when repeated. All other results with the remaining 160 isolates demonstrated clear and sharp margins with all of the other antibiotics tested by E-test.

4. Discussion

A recent meta-analysis of health-care-associated infections evaluated financial impact on the US health-care system. The total annual costs for CLABSI, VAP, SSI, *Clostridium difficile* associated infection and CAUTI was estimated at 9.8 billion US dollars [7]. MRSA was the major contributor of CLABSI and SSI in their investigation and led to the highest attributable length of stay [7]. In another study, the direct cost of HAIs in the United States was more than triple this amount [8]. As a result of the serious morbidity and mortality associated with MRSA, the CDC targeted this multi-drug resistant organism in 2013 as a serious threat [3].

In this investigation, we found that over 99% of our isolates were susceptible to tigecycline, daptomycin, ceftaroline and all were susceptible to linezolid. Results from vancomycin susceptibility data should be of concern since 43% of isolates from all sources had MICs ≥ 1.5 µg/ml and of these, one-half were from bloodstream isolates. A prior investigation from our facility documented the majority of MRSA clinical isolates to have vancomycin MICs ≤ 1 µg/ml [9]. The increase in MIC (now documented with E-test methodology) is in accordance to other reports of increasing vancomycin MICs among MRSA isolates and suggests consideration of alternate therapeutic modalities for these patients due to increased risk of treatment failure and/or mortality when vancomycin MICs are ≥ 1.0 µg/ml [10]-[13].

Former investigations showed varying susceptibility levels to mupirocin ranging from 0% to 38% while our study documented 15% high level resistance [14]-[17]. However, in our investigation, we had the unexpected finding of mupirocin hetero-resistance. Etiology of this finding may be due to simultaneous expression of single amino acid changes in the inherent isoleucyl-tRNA synthetase (IleRS) gene and acquisition of a new IleRS gene, or other possibilities yet to be determined [18]. Hetero-resistance has been demonstrated with vancomycin among *Staphylococcus aureus* isolates [1].

Limitations of this study include lack of correlation with patient clinical data and small number of isolates. Further studies of interest would be the clinical impact of mupirocin hetero-resistance as well as further investigation into the nature of this mechanism.

Administration of intranasal mupirocin to intensive care unit patients and to those undergoing surgery can reduce SSIs, be cost effective, and improve patient outcomes [19]-[24]. Prevention of even 20% of HAIs can save 5.7 - 6.8 billion US dollars [8]. As MRSA is associated with such a large proportion of these, screening and decolonization of MRSA using mupirocin can make a significant impact. In conclusion, while antibiotic susceptibility to mupirocin is not routinely performed in clinical microbiology laboratories, the level of resistance to mupirocin identified in this surveillance study suggests that susceptibility testing should be added to routine MRSA panels [25].

References

[1] Stryjewski, M.E. and Corey G.R. (2014) Methicillin-Resistant *Staphylococcus*: An Evolving Pathogen. *Clinical Infectious Diseases*, **58**, S10-S19. http://dx.doi.org/10.1093/cid/cit613

[2] Greenlee-Wacker, M., DeLeo, F.R. and Nauseef W.M. (in Press) How Methicillin-Resistant *Staphylococcus aureus* Evade Neutrophil Killing. *Current Opinion in Hematology*.

[3] CDC. http://www.cdc.gov/drugresistance/threat-report-2013/pdf

[4] Sievert, D.M., Ricks, P., Edwards, J.R., Schneider, A., Patel, J., Srinivasan, A., Kallen, A., Limbago, B. and Fridkin, S. (2013) Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-1020. *Infection Control Hospital Epidemiology*, **34**, 1-14. http://dx.doi.org/10.1086/668770

[5] Clinical and Laboratory Standards Institute (2013) Performance Standards for Antimicrobial Susceptibility Testing; 23rd Informational Supplement. CLSI Document M100-S23, Clinical and Laboratory Standards Institute, Wayne.

[6] Cookson, B.D. (1998) The Emergence of Mupirocin Resistance: A Challenge to Infection Control and Antibiotic Prescribing Practice. *Journal of antimicrobial Chemotherapy*, **41**, 11-18. http://dx.doi.org/10.1093/jac/41.1.11

[7] Zimlichman, E., Henderson, D., Tamir, O., Franz, C., Song, P., Yamin, C.K., Keohane, C., Denham, C.R. and Bates, D.W. (2013) Healthcare-Associated Infections: A Meta-Analysis of Costs and Financial Impact on the US Health Care System. *JAMA Internal Medicine*, **173**, 2039-2046. http://dx.doi.org/10.1001/jamainternmed.2013.9763

[8] Scott, R.D. (2009) The Direct Medical Costs of Healthcare-Associated Infections in US Hospitals and the Benefits of Prevention. http://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf

[9] Sader, H.S., Fey, P.D., Fish, D.N., Limaye, A.P., Pankey, G., Rahal, J., Rybak, M.J., Snydman, D.R., Steed, L.L., Waites, K. and Jones, R.N. (2009) Evaluation of Vancomycin and Daptomycin Potency Trends (MIC Creep) against Methicillin-Resistant *Staphylococcus aureus* Isolates Collected in Nine US Medical Centers from 2002 to 2006. *Antimicrobial Agents and Chemotherapy*, **53**, 4127-4132. http://dx.doi.org/10.1128/AAC.00616-09

[10] Jacob, J.T. and DiazGranados, C.A. (2013) High Vancomycin Minimum Inhibitory Concentration and Clinical Outcomes in Adults with Methicillin-Resistant *Staphylococcus aureus* Infections: A Meta-Analysis. *International Journal of Infectious Diseases*, **17**, e93-e100.

[11] Sakoulas, G., Moise-Broder, P.A., Schentag, J., Forrest, A., Moellering Jr., R.C. and Eliopoulos, G.M. (2004) Relationship of MIC and Bactericidal Activity to Efficacy of Vancomycin for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *Journal of Clinical Microbiology*, **42**, 2398-2402. http://dx.doi.org/10.1128/JCM.42.6.2398-2402.2004

[12] Brink, A.J. (2012) Does Resistance in Severe Infections Caused by Methicillin-Resistant *Staphylococcus aureus* Give You the "Creeps"? *Current Opinion in Critical Care*, **18**, 451-459. http://dx.doi.org/10.1097/MCC.0b013e3283578968

[13] Bland, C.M., Porr, W.H., Davis, K.A. and Mansell, K.B. (2010) Vancomycin MIC Susceptibility Testing of Methicillin-Susceptible and Methicillin-Resistant *Staphylococcus aureus* Isolates: A Comparison between Etest® and an Automated Testing Method. *Southern Medical Journal*, **103**, 1124-1128. http://dx.doi.org/10.1097/SMJ.0b013e3181efb5b1

[14] Arunava, K., Selvaraj, S., Sivaraman, U., Shailesh, K., Noyal, M.J. and Sreenivasan, S. (2013) Changing Trends in Resistance Pattern of Methicillin Resistant *Staphylococcus aureus*. *Journal of Clinical and Diagnostic Research*, **7**, 1979-1982.

[15] Richter, S.S., Diekema, D.J., Heilmann, K.P., Dohrn, C.L., Crispell, E.K., Riahi, F., McDanel, J.S., Satola, S.W. and Doern, G.V. (2014) Activities of Vancomycin, Ceftaroline, and Mupirocin against *Staphylococcus aureus* Isolates Collected in a 2011 National Surveillance Study in the United States. *Antimicrobial Agents and Chemotherapy*, **58**, 740-745. http://dx.doi.org/10.1128/AAC.01915-13

[16] Lee, H., Lim, H., Bae, I.K., Yong, D., Jeong, S.H., Lee, K. and Chong, Y. (2013) Co-Existance of Mupirocin and Antiseptic Resistance in Methicillin-Resistant *Staphylococcus aureus* Isolates from Korea. *Diagnostic Microbiology and Infectious Disease*, **75**, 308-312. http://dx.doi.org/10.1016/j.diagmicrobio.2012.11.025

[17] Woodford, N., Afzal-Shah, M., Warner, M. and Livermore, D.M. (2008) *In Vitro* Activity of Retapamulin against *Staphylococcus aureus* Isolates Resistant to Fusidic Acid and Mupirocin. *Journal of Antimicrobial Chemotherapy*, **62**, 766-768. http://dx.doi.org/10.1093/jac/dkn266

[18] Patel, J.B., Gorwitz, R.J. and Jernigan, J.A. (2009) Mupirocin Resistance. *Clinical Infectious Diseases*, **49**, 935-941. http://dx.doi.org/10.1086/605495

[19] Schweizer, M.L. and Herwaldt, L.A. (2012) Surgical Site Infections and Their Prevention. *Current Opinion in Infectious Disease*, **25**, 378-384. http://dx.doi.org/10.1097/QCO.0b013e32835532f7

[20] van Rijen, M.M.L., Bonten, M., Wenzel, R.P. and Kluytmans, J.A.J.W. (2008) Intranasal Mupirocin for Reduction of *Staphylococcus aureus* Infections in Surgical Patients with Nasal Carriage: A Systematic Review. *Journal of Antimicrobial Chemotherapy*, **61**, 254-261. http://dx.doi.org/10.1093/jac/dkm480

[21] Robotham, J.V., Graves, N., Cookson, B.D., Barnett, A.G., Wilson, J.A., Edgeworth, J.D., Batra, R., Cuthbertson, B.H. and Cooper, B.S. (2011) Screening, Isolation, and Decolonization Strategies in the Control of Methicillin Resistant *Staphylococcus aureus* in Intensive Care Units: Cost Effectiveness Evaluation. *British Medical Journal*, **343**, Article ID: d5694. http://dx.doi.org/10.1136/bmj.d5694

[22] Courville, X.F., Tomek, I.M., Kirkland, K.B., Birhle, M., Kantor, S.R. and Finlayson, S.R.G. (2012) Cost-Effectiveness of Preoperative Nasal Mupirocin Treatment in Preventing Surgical Site Infection in Patients Undergoing Total Hip and Knee Arthroplasty: A Cost-Effectiveness Analysis. *Infection Control and Hospital Epidemiology*, **33**, 152-159. http://dx.doi.org/10.1086/663704

[23] Goldsack, J.C., DeRitter, C., Power, M., Spencer, A., Taylor, C.L., Kim, S.F., Kirk, R. and Drees, M. (2014) Clinical, Patient Experience and Cost Impacts of Performing Active Surveillance on Known Methicillin-Resistant *Staphylococcus aureus* Positive Patients Admitted to Medical-Surgical Units. *American Journal of Infection Control*, **42**, 1039-1043. http://dx.doi.org/10.1016/j.ajic.2014.07.011

[24] Huang, S.S., Septimus, E., Avery, T.R., Lee, G.M., Hickok, J., Weinstein, R.A., Moody, J., Hayden, M.K., Perlin, J.B., Platt, R. and Ray, G.T. (2014) Cost Savings of Universal Decolonization to Prevent Intensive Care Unit Infection: Implications of the REDUCE MRSA Trial. *Infection Control Hospital Epidemiology*, **35**, S23-S31. http://dx.doi.org/10.1086/677819

[25] Livermore, D.M. and Pearson, A. (2007) Antibiotic Resistance: Location, Location, Location. *Clinical Microbiology and Infection*, **13**, 7-16. http://dx.doi.org/10.1111/j.1469-0691.2007.01724.x

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