"A RETROSPECTIVE STUDY TO EVALUATE THE EFFICACY OF TRIMETHOPRIM/SULFAMETHOXAZOLE (TMP/SMX) COMPARED TO DAPTOMYCIN OR LINEZOLID FOR THE TREATMENT OF INFECTIONS DUE TO METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)"

By
Aparna Lakshmi Poona Murari,
E00897767
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Thesis Committee:
Dr. Stephen Sonstein PhD., Chair
Director, Clinical Research Administration,
Eastern Michigan University
and
Dr. Keith S. Kaye, MD, MPH
Corporate Director, Division of Infectious Diseases,
Detroit Medical Center and Wayne State University
December 4, 2011,
Ypsilanti, Michigan

Thesis Committee:
Stephen Sonstein, Ph.D
Keith S. Kaye, MD, MPHS

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ABSTRACT

Background: *Staphylococcus aureus* is still considered as one of the most significant human pathogens in terms of morbidity, mortality, and costs. Vancomycin should be avoided if possible for the treatment of MRSA when the Minimum Inhibiting Concentration (MIC) to Vancomycin is 2µg/mL, as it poses a therapeutic challenge. Main therapeutic options include Daptomycin and Linezolid, two new, expensive drugs; and trimethoprim/sulfamethoxazole(TMP/SMX), an old, inexpensive agent. Study aims were to compare the clinical efficacy and potential cost savings associated with TMP/SMX use.

Methods: A retrospective study was conducted at Detroit Medical Center. For calendar year 2009, unique adult patients (>18 years) with infections due to MRSA with MIC to Vancomycin of 2 µg/mL were included if they received ≥2 doses of TMP/SMX and/or Daptomycin and/or Linezolid. Data were abstracted from patient charts and pharmacy records.

Results: There were 328 patients included in study cohort, 143 received TMP/SMX alone, 89 received Daptomycin alone, 75 received Linezolid alone, and 21 patients received a combination therapy. In bivariate analysis, patients on TMP/SMX had significantly better outcomes, including in-hospital ($p=0.003$) and 90-day mortality ($p<0.001$). Patients on TMP/SMX were also younger ($p<0.001$), with less co-morbidities ($p<0.001$), less severe disease states ($p<0.001$), and lower intervals to initiation of appropriate therapy ($p=0.001$). In multivariate models, both with/without the use of a propensity score, the association between TMP/SMX treatment and mortality was no longer significant, but ORs remained lower than 1. Cost savings of using TMP/SMX averaged $2,067 per patient. The susceptibility rate to TMP/SMX had significantly increased from 2005 to 2009, despite increased usage.

Conclusions: TMP/SMX compared favorably with Linezolid and Daptomycin in terms of efficacy and mortality. Cost saving were enormous. TMP/SMX use should be considered, particularly for skin and soft-tissue infections, and even in severe disease states due to MRSA with elevated vancomycin MICs.

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CHAPTER 1: INTRODUCTION AND BACKGROUND

Introduction

Methicillin-resistant *Staphyloccus aureus* (MRSA) is a deadly human pathogen[25], and Vancomycin is considered the therapeutic option of choice[27]. In recent years, the minimal inhibitory concentrations (MIC) to Vancomycin have been increasing in MRSA isolates[11,29,39]. Recent data demonstrated higher rates of clinical and bacteriological failures with Vancomycin treatment against MRSA strains, which have Vancomycin MIC $\geq$ 2 μg/mL[11,15,18,27,29,39,44,45]. The options to treat MRSA infections when the vancomycin MIC are $\geq$ 2 μg/mL include "new" and expensive agents that were extensively studied for the treatment of MRSA infections, like daptomycin or linezolid, or "older", generic, inexpensive agents like trimethoprim/sulfamethoxazole (TMP/SMX), clindamycin or fusidic acid. There are scant clinical data comparing the "new" widely used agents to the "old" agents; therefore, management decisions are not based on solid scientific data. Clindamycin is a bacteriostatic agent which has strong correlation to *Clostridium difficile* infections[25], and therefore prescribes are reluctant to use it as a single agent for severe invasive MRSA infections, particularly for prolonged courses[25]. Fusidic acid has recently become available in the US, clinical efficacy data are lacking[16] and rapid emergence of resistance when given as monotherapy is a major concern[20]. TMP/SMX, despite being used against *S. aureus* for many years, has not been extensively studied in controlled trials for this indication[26].

Background

The emergence of antibiotic resistance is an evolutionary process that is based on selection for organisms that have enhanced ability to survive doses of antibiotics that would have previously been lethal[3]. The primary causes of antimicrobial resistance include:

- The widespread use of antibiotics both inside and outside of medicine; and
- The misuse and overuse of antibiotics by doctors, other health personnel and patients.

Staphylococcus aureus is recognized as a cause of a wide range of infections, from minor skin infections and chronic bone infections to devastating septicemia and endocarditis[1,37]. Significant events in the evolution of *S. aureus* have included the development of community strains of *S. aureus* that are methicillin resistant (Methicillin-Resistant *S. aureus*, MRSA) but also harbor genes associated with increased virulence[13]. MRSA alone (which probably accounts for fewer than one-third of all *S. aureus* infections) caused more deaths in the United States in 2005 than human immunodeficiency virus infection (estimated MRSA mortality rate in 2005 of 6.3 per 100,000 individuals) and caused more invasive infections (estimated MRSA incidence in 2005 of 31.8 per 100,000 individuals) than other important bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides*[7,50]. Vancomycin was the 'therapy of choice' for treating MRSA. However, the emergence of Vancomycin-resistant *Enterococcus* (VRE), Vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) in several countries[13] further reduced the treatment options.

The Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) defined breakpoints for MIC and disc diffusion testing of vancomycin against *S. aureus* over 20 years ago[10]. In 2006, the CLSI redefined vancomycin breakpoints as follows: susceptible at a vancomycin broth MIC of $\leq$ 2µg/mL, intermediate at a vancomycin broth MIC of $\geq$16µg/mL.

In recent years, the minimum inhibiting concentrations (MICs) to vancomycin have been increasing in MRSA isolates, as reflected by increments in MIC_{50} and MIC_{90} reported on antibiograms from various centers around the world, with the main mechanism being heteroresistant vancomycin-intermediate Staphylococus aureus (hVISA)[11]. This "MIC creep" has

been validated by showing how the fraction of hVISA isolates increase with increasing vancomycin MICs[40]. As mentioned earlier, accumulated data demonstrates higher rates of clinical and bacteriological failures with vancomycin treatment against MRSA strains, which have vancomycin MIC ≥ 2 μg/mL[11,15,18,29,39,44,45]. Therefore, whenever prescribers are confronted with MRSA with vancomycin MIC of 2 μg/mL, they are placed in a crucial junction in terms of management decision: they can choose to use new and expensive agents that were extensively studied for the treatment of MRSA infections, like daptomycing or linezolid, or they can choose to use older, generic, inexpensive agents like trimethoprim/sulfamethoxazole (TMP/SMX) or clindamycin that were less studied against MRSA infections. There are scant clinical data comparing the "new" agents to the "old" agents, and therefore prescribers cannot base their decision on solid scientific data, and are also reluctant to use Clindamycin as a single agent for severe MRSA infections, particularly for prolonged periods[25]. TMP/SMX, despite being used against S. aureus for many years, had not been extensively studied in controlled scientific set-ups for this indication. A recent comparative retrospective trial of clindamycin versus TMP/SMX for the treatment of mild skin and soft-tissue infections (SSTI) had demonstrated the importance of incision and drainage in these syndromes but did not show any differences in terms of efficacy of the agents being used[21]. A different trial found TMP/SMX to be non-inferior to vancomycin for the treatment of MRSA bacteremia in a region where most strains has a vancomycin MIC ≤ 1 μg/mL[22].

The Detroit Medical Center (DMC), is located in the Southeast Michigan, which is an endemic region for *Acinetobacter baumannii (AB)*, carbapenem-resistant *enterobacteriaceae* (CRE) and hetero-resistant vancomycin-intermediate *Staphylococcus aureus* (hVISA), Methicillin-resistant *Staphylococcus aureus* (MRSA) and VISA infections, with rates reported being amongst the

highest in the country. And 10 out of the 12 cases ever reported of vancomycin-resistant S. aureus (VRSA) in the US were from this region[18].

Study Objectives

Study aims were to:

1) To conduct a retrospective comparative trial of TMP/SMX versus Daptomycin or Linezolid for the treatment of MRSA infections in Southeast Michigan, when the strain has a Vancomycin minimum inhibiting concentration (MIC) of 2 μg/mL (including all infectious clinical syndromes)

2) Analyze potential costs savings by using TMP/SMX instead of Daptomycin or Linezolid when possible; and

3) Monitor the levels of drug susceptibilities in MRSA in light of the usage of these study drugs in the past 5 years.

Study Hypotheses

- Trimethorpim/Sulfamethoxazole (TMP/SMX) treatment for hVISA will not be associated with enhanced in-hospital mortality compared to Daptomycin or Linezolid.

- The trend of resistance rate of hVISA to TMP/SMX over the past years, do not significantly differ from the trend of resistance rate to Daptomycin or Linezolid.

- The costs associated with the use of TMP/SMX for treating hVISA will be significantly lower than the costs associated with the use of Daptomycin and/or Linezolid.

CHAPTER 2: REVIEW OF LITERATURE

Co-trimoxazole, (trimethoprim/sulfamethoxazole, TMP/SMX), an antibiotic in use for several decades, has been shown to be active against *S. aureus* (including MRSA) *in vitro*[24]. Its components have synergistic bactericidal activity against *S. auerus*[19]. The susceptibility of MRSA isolates to co-trimoxazole increased from 73% in 1994-98 to 95% in 2001-04 in the USA[14].

Evidence for clinical efficacy of co-trimoxazole in *S. aureus* infections is limited. Only one randomized controlled trial has assessed co-trimoxazole for treatment of *S. aureus* infections, and was limited to an intravenous drug user population[26]. In this study, inferiority of co-trimoxazole to vancomycin was seen only for MRSA, while cure rate and other clinical and microbiological outcomes were similar for both drugs against the MRSA group.

Other evidence for the efficacy of co-trimoxazole in *S. aureus* infections is limited to small non-randomized studies, animal studies and case reports. Successful treatment of *S. aureus* endocarditis, meningitis and other osteomyelitis with co-trimoxazole has been reported[8,9,12,26,30,31,33,] and a few cases of right-sided MRSA endocarditis were included in the randomized trial. However, co-trimoxazole treatment was inferior to cloxacillin, teicoplanin and vancomycin in an animal model of *S. aureus* aortic endocarditis[17]. Two reviews attempting to summarize the data concerning co-trimoxazole treatment for *S. aureus* infections emphasize the need for further clinical studies comparing this drug with other available options, specifically vancomycin[5,6].

In 2001, Fridkin reviewed the U.S. experience with VISA (defined at the time as MRSA clinical isolates with vancomycin MICs of 8 to 16µg/mL). Six patients were discussed, some previously reported. Five patients died, but only one died directly from MRSA sepsis, and this patient was a

dialysis patient with line sepsis. Of the other patients, one patient treated with surgical drainage plus linezolid, trimethoprim-sulfamethoxazole (TMP/SMX), and doxycycline survived. The remaining 4 patients either refused surgical treatment or were cured of MRSA before death from another cause[4]. For the survivor, weekly serum vancomycin levels were in the range of 2.7 to 4.9 µg/mL during the 10 weeks prior to the detection of VISA in peritoneal fluid[49].

Khosrovaneh et al. described 22 patients with recurrent or persistent MRSA bacteremia in Detroit, MI[48]. Patient isolates were specifically examined for hVISA using a PAP/AUC ratio of $\geq$ 0.9. Khosrovaneh et al., while observing that isolates with higher initial MICs (in the vicinity of 4 µg/mL) were more likely to produce subcolonies with even higher MICs, detected definite hVISA in only 3 of their 22 patients and concluded that hVISA defined in this way was uncommon and that treatment failure could be explained by other factors without the need to invoke the presence of resistant subpopulations *per se* [48].

In a retrospective cohort study from Texas, Maclayton et al. studied patients undergoing hemodialysis who developed MRSA bacteremia, and these researchers also attempted to relate outcomes to initial MICs. In the univariate analysis, MICs of <0.5 µg/mL predicted improved survival, but recent surgery and ICU admission were also risk factors for having MRSA isolates with MICs of 2 µg/mL. The MIC method was not defined. In a multivariate analysis that included cost modeling, patients with high-MIC isolates had increased lengths of stay and increased hospital costs compared with patients with low-MIC isolates and uninfected control patients, but mortality was not increased[42]. A further recent report suggested that prior glycopeptides exposure is associated with increased MICs and reduced in vitro vancomycin killing in patients who subsequently developed MRSA sepsis[47].

In another retrospective cohort study conducted in February 2010 from Israel, Elad Goldberg et al. studied the efficacy and safety of co-trimethoxazole to Vancomycin in adult patients with MRSA bacteremia. The outcomes collected were 30-day mortality, persistent bacteremia (defined as positive blood culture (BC) > 14 days after the first positive BC, but within 30 days), relapse (defined as recurrence of the same phenotype > 30 days after the first positive BC within 12 months) and adverse events. And within the limitations of a small retrospective study, the study concluded that co-trimoxazole had a safety and efficacy profile similar to that of vancomycin and may offer an attractive additional therapeutic option for MRSA bacteremia. The data from these clinical studies show that Co-trimoxazole is comparatively effective and safe to treat *S. aureus* infections compared to the treatment methods available on market.

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

Setting

This study was conducted at Detroit Medical Center, an 8-hospital healthcare system with >2,200 inpatient beds, located in Southeast Michigan. The dedicated departments involved in the study include, Division of Infectious Diseases, Department of Pharmacy Services, Department of Clinical Microbiology, and Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit Medical Center and Wayne State University, Detroit, MI.

Study Design

This was an unblinded, retrospective study analyzing existing hospital medical records to extract data of adult patients infected with hVISA/MRSA who have received TMP/SMX and/or Daptomycin or Linezolid, seen at Detroit Medical Center (DMC). Prior to initiation of this study, approvals were obtained from Institutional Review Board of DMC, Human Investigation Committee, Wayne State University and later this project' proposal was approved by Eastern

Michigan University's Human Subjects Review Committee. A waiver of the consent was granted for this study.

Study Population

Three hundred and twenty eight patients were identified over a one-year period (January 1, 2009, through December 31, 2009) and were included in a retrospective cohort study of outcomes associated with infections caused by MRSA with vancomycin MIC of 2µg/mL. Of those, 143 received TMP/SMX alone, 89 received Daptomycin alone, 75 received Linezolid alone, and 21 patients received a combination therapy.

Adult patients (>18 years) who received ≥2 doses of either TMP/SMX or daptomycin or linezolid from 3 days prior to 14 days after their culture date were included. Colonization cases (based of absence of SIRS criteria[18] or of attending physician clinical discretion) were excluded, and only unique patient infectious episodes were analyzed.

Data Collection

Variables collected for each patient included: 1) demographics; 2) co-morbidities (including Charlson's scores[34]); 3) microbiologic data; 4) acute illness indices (including McCabe score[36]); 5) time to initiation of appropriate therapy per *in-vitro* susceptibility results and 6) outcomes: in-hospital and 30-days mortality, length of hospital stay (LOS), functional status deterioration in ≥1 activities of daily living[41], discharge to a long-term care facility (LTCF) after being admitted from home, additional hospitalization in the following 6 months, additional isolations of the same organism in the following 3 months (i.e. "bacteriologic failures"), and costs of the antibiotic regimen prescribed. Antimicrobial costs and usage of study drugs within the health system, in defined daily doses (DDD) for the years 2005-2009, were obtained from pharmacy records.

DMC central microbiology laboratory processes on average 500,000 samples annually. Bacteria were identified to the species level, and susceptibilities were determined to pre-defined antimicrobials, based on an automated broth microdilution system (MicroScan™; Siemens AG; Germany), and in accordance to Clinical and Laboratory Standard Institutions (CLSI) criteria and breakpoints[2]. Daptomycin susceptibility was added to the automated system panel in 2008. Prior to 2008, E-tests (bioMérieux, France) were used to determine daptomycin susceptibility, and were done inconsistently upon specific requests. MRSA antibiograms for the years 2005-2009 were conducted according to the revised CLSI criteria issued in 2007[2].

Data Analysis

Statistical analyses were performed by using IBM-SPSS 19 (2011) and Epi Info™ (version 6.0). Conditional logistic regression tests were used for multivariate analyses. Chi-square test for trend and Spearman correlation test were used to analyze trends of MRSA prevalence, incidence (per 1,000 patient days), susceptibility rate to study drugs, drug usage, and correlation between drug usage and the prevalence and incidence of MRSA isolation and the susceptibility rates to study drugs, all for the years 2005-2009.

CHAPTER 4: RESULTS

There were overall 328 patients infected with MRSA with vancomycin MIC of 2 µg/mL during 2009, who received one of the study drugs and met all inclusion criteria. Twenty-two of the patients had a catheter-related bloodstream infection (BSI), 42 had BSI without an identifiable source, 90 had pneumonia, 11 had urinary tract infection, and 145 had skin and soft-tissue infection (SSTI). Overall, 143 received TMP/SMX alone, 89 received daptomycin alone, 75 received linezolid alone, and 21 patients received a combination of TMP/SMX with either

daptomycin or linezolid. Of the entire cohort, 5 (1.5%) isolates were non-susceptible to TMP/SMX. All isolates were susceptible to daptomycin (mean MIC=0.5 ±0.4 μg/mL) and linezolid (mean MIC=2.5 ±0.9 μg/mL). The univariate analysis between patients based on the anti-MRSA regimen is displayed in Table I. TMP/SMX was associated with significant favorable outcomes (including *all* outcomes captured) compared to the other regimens prescribed (bottom of Table I). However, TMP/SMX was also prescribed to an entirely different population, which consisted of younger individuals (48±5 vs. 56.3 years, $p<0.001$), with lower Charlson's scores ($p<0.001$), with better McCabe scores ($p<0.001$), who had more commonly SSTIs ($p<0.001$), less commonly BSI ($p<0.001$), and who had lower severity of sepsis levels ($p<0.001$)[5]. Moreover, patients who received TMP/SMX had significantly shorter intervals to initiation of appropriate therapy (62±71.7 vs. 93.3±62.8 hours, $p<0.001$), which is considered the strongest modifiable factor associated with reduced mortality in severe sepsis[46]. Multivariate analysis was conducted for in-hospital mortality, with parameters inserted into the model included 1) age (dichotomized to > 55 and ≤ 55 years), 2) Charlson's combined condition score (dichotomized to > 4 and ≤ 4 co-morbidities), 3) the infectious clinical syndrome (dichotomized to SSTI vs. other clinical syndromes), 4) level of sepsis (dichotomized to sepsis syndrome vs. severe sepsis / septic shock / multi-organ failure), 5) time to initiation of appropriate therapy (dichotomized to > 80 and ≤ 80 hours), and 6) the anti-MRSA therapy administered (dichotomized to patients receiving TMP/SMX vs. those who did not). TMP/SMX was not associated with in-hospital mortality in multivariate analysis (OR=0.6, CI-95%=0.2-1.7, p=0.34). Six other multivariate models were constructed for each of the other outcomes: 1) 3-months mortality; 2) LOS from infection to discharge of > 10 days (excluding the patients who died); 3) functional status deterioration; 4) discharged to LTCF after being admitted from home; 5)

additional hospitalization; and 6) bacteriologic failures. For each model, the same parameters as displayed for the in-hospital mortality model were incorporated. TMP/SMX was no longer significantly associated with anyone of these outcomes, although all odds ratios (OR) remained < 1 (data not shown).

In order to try and further explore the potential impact of TMP/SMX on mortality, compared to the "newer" agents, a propensity score analysis was conducted. Patients who received TMP/SMX alone or in combination (n=164) were compared to patients who have not received TMP/SMX (n=164). The probability of receiving TMP/SMX ("propensity") was estimated using a multivariate logistic regression model. Based on the β-coefficients of the final model, a propensity score was developed: 1) Charlson's combined condition score > 4 and hours to effective therapy > 80 were assigned 2 points each; 2) high level of sepsis (severe sepsis / septic shock / multi-organ failure) was assigned 2.5 points; and 3) SSTI was assigned 3 points. The propensity score of receiving TMP/SMX was calculated for each patient. In multivariate analysis for in-hospital mortality, the impact of the anti-MRSA therapy (dichotomized to patients receiving TMP/SMX vs. those who did not) on mortality was controlled for the propensity score. TMP/SMX was again not significantly associated with in-hospital mortality (OR=0.62, CI-95%=0.26-1.5, p=0.3).

One of the potential clinical niches for TMP/SMX treatment is SSTIs. In the sub-group of 145 SSTI cases, TMP/SMX alone was prescribed to 95 patients, daptomycin alone to 33 patients, linezolid alone to 12 patients, and 5 patients with SSTI had received TMP/SMX with either daptomycin or linezolid. In the univariate analysis, TMP/SMX was again associated with favorable outcomes including in-hospital mortality (none of the patients who received TMP/SMX had died, vs. 4 in the daptomycin group, OR=0.9, CI-95%= 0.83-0.99, p=0.002), 3-

months mortality (OR=0.89, CI-95%= 0.81-0.99, p=0.002), LOS from culture to discharge after excluding the patients who died (4.2±5.6 vs. 10.2±9.6 days, p<0.001), discharge to LTCF after being admitted from home (OR=0.3, CI-95%= 0.07-0.9, p=0.03), and bacteriologic failures (p<0.001). However, as in the general cohort, among the SSTI group of patients; TMP/SMX was prescribed to younger individuals (p<0.001), with lower Charlson's scores (p<0.001), with better McCabe scores (p=0.003), with lower indices of acute sepsis levels (p<0.001), and shorter intervals to initiation of appropriate therapy (p=0.004). No multivariate analyses for mortality could have been conducted to control for these confounders (none of the patients who received TMP/SMX had died). In the multivariate models of the other outcomes that were significant in the univariate analysis, with the same variables as mentioned for the general cohort entered into the models, TMP/SMX was no longer significantly associated with any of the outcomes, though all OR remained < 1 (data not shown).

Figure 1 displays the prevalence of MRSA, the usage in DDD of all study drugs, and the susceptibility rates (in percents) of MRSA to all study drugs, for the years 2005 to 2009. The incidence of MRSA isolations had remained stable during the study years (7.5±0.23 cases per 1,000 patient days, p for trend=0.7), along with insignificant increments in TMP/SMX usage (14,630±5,135 DDD per year, p for trend=0.7), daptomycin usage (4,620±3,595 DDD per year, p for trend=0.2), and linezolid usage (4,416±2,486 DDD per year, p for trend=0.9). The susceptibility rate to linezolid (mean of 99.9±0.05% per year, p for trend=0.08) and daptomycin (mean of 99.8±0.07% per year, p for trend=0.3) had insignificant increments, and the susceptibility rate to TMP/SMX had a significant increment during the 5-years study period (mean susceptibility rate of 98.3±0.3% per year, p for trend=0.048).

The antibiotic course in the daptomycin (n=89) and linezolid (n=75) groups of patients had cost $2,486±2,576 and $1,670±1,414 per patient, respectively (mean number of treatment days with daptomycin was 12.3±11.5 days and with linezolid 9.6±8.3 days). In the group who received TMP/SMX (n=143), the antibiotic course had cost $27±44 per patient (mean number of treatment days was 5.5±5.8). The difference between the groups was statistically significant ($p<0.001$). There were 161 patients (49% of the entire cohort) who had an isolate that was susceptible to TMP/SMX but instead were treated with daptomycin or with linezolid. If these patients had been treated instead with TMP/SMX for the same number of treatment days that they received daptomycin or linezolid, the total cost savings would have been $332,844.20, for an average of $2,067.40 per patient.

CHAPTER 5: CONCLUSIONS

In the past 2 years, two pivotal clinical practice guidelines have been published by the Infectious Diseases Society of America (IDSA) and other related professional societies: 1) treatment guidelines for MRSA infections[25], and 2) therapeutic guidelines for vancomycin usage[27]. Both guidelines pointed to a commonly encountered gap in current scientific knowledge, pertaining to the preferred management of MRSA infections when the isolate's vancomycin MIC is of 2 μg/mL or above. A recent publication even questioned whether vancomycin might still be an option to treat these pathogens[23]. This study analyzed a large cohort of infected patients during a 1-year period from an endemic US location. The main finding was that prescribers are reluctant to use TMP/SMX for severe MRSA infections, and prefer to use drugs which are much more expensive, even though their superiority over TMP/SMX has never been established or even investigated. Despite the retrospective nature of the study, with all its inherent biases, the data

suggest non-inferiority of TMP/SMX compared to daptomycin or linezolid. Multivariate models, with and without propensity scores, controlling in different ways for possible confounders that might bias the true impact of the anti-MRSA therapy on outcomes, revealed that TMP/SMX is at least as effective as the "newer" agents. Not just in-hospital mortality was analyzed, but 6 additional outcomes were captured, with all multivariate models displaying the same trend of results. Since the possibility of conducting a prospective comparative randomized controlled clinical trial in the near future between these 'on-patent' drugs and TMP/SMX seems low, due to reluctance of pharmaceutical companies to invest in such a trial, this study provides the most controlled data that could be obtained. Use of a propensity score, enabled to theoretically overcome inherited biases, which are inevitable in this type of comparative retrospective study design.

These analyses provide data pertaining to a commonly encountered clinical scenario in many parts around the country and worldwide. Non-inferiority of TMP/SMX compared to daptomycin or linezolid for the treatment of MRSA infections when the vancomycin MIC is 2 μg/mL, means that the latter agents can be preserved for severe systemic infections. This will hopefully translate into reductions in emergence of resistance to these 2 agents, which has already been described when these drugs were extensively used in certain locations[28,32]. The potential costs reductions associated with the use of the generic TMP/SMX proved to be enormous. Just for calendar year 2009 at DMC, if patients infected with a susceptible isolate would have been treated with TMP/SMX instead of one of the other agents, this would have save the healthcare system over $330,000 just in antibiotic costs.

The fact that the susceptibility rates to all study drugs had increased at DMC for the past 5 years (only the susceptibility to TMP/SMX had a significant increment), averaging over 98% for all

drugs, is reassuring (figure 1). This is particularly important in light of the fact that DMC's antibiotic stewardship committee issued practice guidelines back in 2007, recommending to avoid the use of vancomycin for MRSA infections when the MIC to the drug is ≥2 μg/mL. Still, despite this practice being applied for almost 3 years, and despite the increase usages of TMP/SMX, daptomycin, and linezolid in the past years (figure 1), the drugs remain extremely active versus the vast majority of MRSA strains. This is in accordance to a recent comprehensive systematic review that reported prolonged TMP/SMX use was not associated with increments in antibiotic resistance[35].

The sub-analysis of the group of patients with SSTIs, points to a special niche where TMP/SMX should be promoted, even in severe infections and in inpatients with higher levels of acute illness indices. SSTI is the most common infectious clinical syndrome caused by MRSA, and therefore using it for this indication will reduce the burden of usage of the other expensive on-patent agents. In addition, the availability of both parenteral and oral TMP/SMX preparations enables a natural step-down in treatment and early hospital discharge when the patient stabilizes, i.e. an important factor in the management of this infectious clinical syndrome. The unavailability in many locations around the US and abroad in the past year of the parenteral preparation should be addressed, so that when prescribers do want to use TMP/SMX, the parenteral drug should be easily available.

The true significance of TMP/SMX nephrotoxicity (not the false elevations in serum creatinine), along with the increased drug-drug interaction recently reported with warfarin[38], and other adverse events such as hyperkalemia[43], should all be further explored and studied, particularly when the drug is being prescribed for prolonged courses. Nevertheless, the drug is effective,

cheap, and should be considered even in severe disease states, in order to try and reduce the emergence of resistance and the costs associated with over usage of daptomycin or linezolid.

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CONFLICTS OF INTEREST

No potential conflicts of interest

CHAPTER 6: LIMITATIONS OF THE STUDY

Limitations of this study included the following: (a) incomplete medical records excluded some subjects from contributing to this study; (b) the possibility of observer bias during data abstraction due to the unblinded nature of the study although the data was analyzed by a statistician after data collection; (c) findings in this study may not be generalizable to other community hospitals; (d) study findings were not designed to evaluate the patient's needs for hospitalization or intensive monitoring or to evaluate other medical conditions that may need further attention.

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Figure 1. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) isolations, coupled with the rate of susceptibility and level of usage (in defined daily doses) to trimethoprim / sulfamethoxazole, daptomycin and linezolid, Detroit Medical Center, 2005-2009

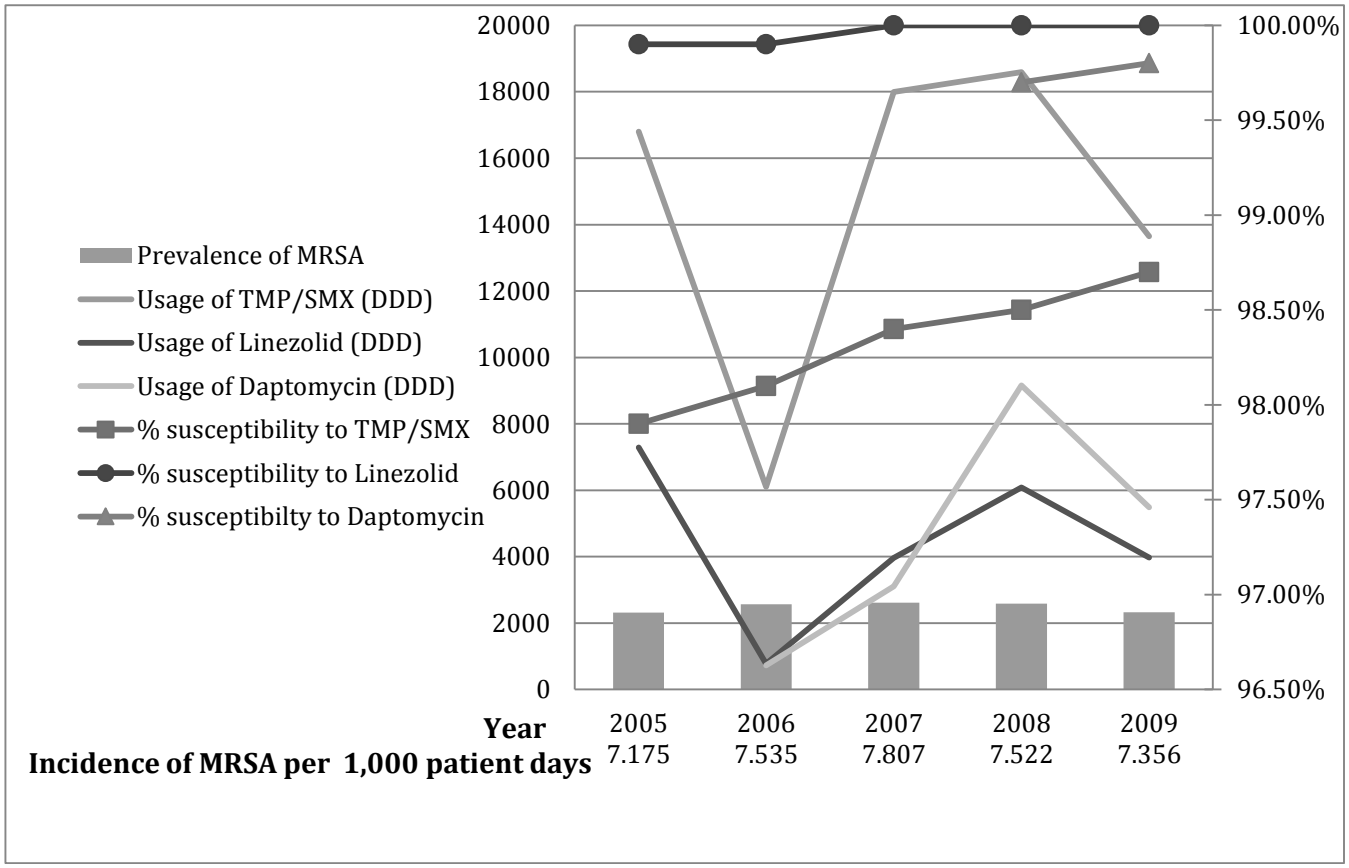

Table I: Bivariate analysis of patients treated with trimethoprim/sulfamethoxazole (TMP/SMX), daptomycin, linezolid, or combination of TMP/SMX with either daptomycin or with linezolid, for infections caused by methicillin-resistant *Staphylococcus aureus* with MIC of 2 µg/mL to vancomycin, Detroit Medical Center, 2009

Parameter	TMP/SMX therapy (n=143)	Daptomycin therapy (n=89)	Linezolid therapy (n=75)	Combination of TMP/SMX plus daptomycin or linezolid (n=21)	P value
Demographics					
Male sex	86 (60%)	56 (63%)	40 (53%)	11 (52%)	0.57
Age, years (mean ± SD)	47.6±18	57±17	56±16	55±14	<0.001
Elderly (≥65 years)	26 (18%)	26 (29%)	18 (24%)	4 (19%)	0.3
African American	102 (71%)	57 (64%)	42 (56%)	16 (76%)	0.08
LTCF permanent residence	16 (11%)	29 (33%)	16 (21%)	3 (14%)	0.001
Background Chronic conditions					
Hemodialysis	2 (1.4%)	27 (30%)	4 (5%)	3 (14%)	<0.001
Ischemic heart disease	16 (11%)	23 (26%)	26 (35%)	3 (14%)	<0.001
Congestive heart failure	19 (13%)	31 (35%)	25 (33%)	7 (33%)	<0.001
Peripheral vascular disease	15 (11%)	23 (26%)	14 (19%)	4 (19%)	0.02
Diabetes Mellitus	34 (24%)	35 (39%)	29 (39%)	8 (38%)	0.04
Chronic renal failure [A]	17 (12%)	49 (55%)	25 (33%)	6 (29%)	<0.001
Chronic lung disease [B]	38 (27%)	31 (35%)	52 (69%)	9 (43%)	<0.001
Peptic ulcer disease	15 (11%)	28 (32%)	28 (37%)	3 (14%)	<0.001
Neurovascular disease [C]	10 (7%)	14 (16%)	18 (24%)	5 (24%)	0.003
Dementia	8 (6%)	8 (9%)	13 (17%)	1 (5%)	0.03
Malignancy [D]	9 (6%)	18 (20%)	14 (19%)	1 (5%)	0.002
HIV positive	10 (7%)	1 (1%)	1 (1%)	1 (5%)	0.08
Charlson's [19] weighted index co morbidity	2.2±2.6	4.3±3.3	4.9±3.6	3.1±3	<0.001
Charlson's [19] combined condition score	3.1±3.1	5.8±3.9	6.4±3.9	4.4±3	<0.001

Charlson's [19] 10-year survival probability, percents	65±40	36±39	30±39	50±35	<0.001
Culture body site					
Blood	3 (2%)	62 (70%)	8 (11%)	6 (29%)	<0.001
Respiratory	28 (20%)	3 (3%)	45 (60%)	7 (33%)	<0.001
Urine	17 (12%)	3 (3%)	2 (3%)	0	0.01
Wound	94 (66%)	16 (18%)	18 (24%)	7 (33%)	<0.001
Infectious Clinical Syndrome					
Catheter-related bloodstream infection	0	16 (18%)	3 (4%)	3 (14%)	<0.001
Bacteremia without a determined focus	3 (2%)	28 (32%)	5 (7%)	4 (19%)	<0.001
Pneumonia	24 (17%)	6 (7%)	47 (63%)	8 (38%)	<0.001
Urinary tract infection	15 (11%)	1 (1%)	2 (3%)	2 (10%)	0.002
Skin and soft-tissue infection	95 (66%)	33 (37%)	12 (16%)	5 (24%)	<0.001
Status on admission					
Dependent functional status [E]	33 (23%)	41 (46%)	35 (47%)	5 (24%)	<0.001
Reduced consciousness	22 (15%)	29 (33%)	22 (29%)	4 (19%)	0.012
Permanent/chronic invasive device [F]	35 (25%)	62 (70%)	57 (76%)	14 (67%)	<0.001
Acute illness indices					
McCabe score [20] (mean ± SD)	2.8±0.5	2.5±0.7	2.3±0.7	2.5±0.8	<0.001
Rapidly fatal state per McCabe score [20]	4 (5%)	5 (10%)	6 (13%)	1 (17%)	0.01
High severity of sepsis level [18]	21 (18%)	46 (54%)	33 (48%)	10 (48%)	<0.001
Necessitates transfer to an ICU	18 (14%)	18 (23%)	31 (55%)	9 (47%)	<0.001
Hours to effective therapy [G] (mean ± SD)	61±72	90±58	97±68	76±73	0.001
Outcomes					
In hospital death	5 (3.5%)	9 (10%)	14 (19%)	2 (9.5%)	0.003
Died in 3 months	7 (6%)	10 (13%)	18 (30%)	3 (16%)	<0.001
Functional status deterioration [E]	8 (6%)	17 (19%)	22 (30%)	9 (43%)	<0.001
Discharged to LTCF	14 (11%)	14 (20%)	20 (36%)	8 (50%)	<0.001

[H]					
Additional hospitalizations [I]	51 (36%)	42 (48%)	36 (50%)	15 (75%)	0.005
Bacteriologic failure [J]	5 (3.5%)	11 (13%)	15 (20%)	4 (19%)	<0.001
Total LOS, days (mean ± SD)	7±32	12±42	22±18	19±12	0.006
LOS from culture to discharge, days (mean ± SD)	7±9	12±10	17±13	18±12	<0.001
LOS from culture to discharge, after excluding the dead, days (mean ± SD)	7±9	12±9	17±14	16±11	<0.001

Note. LTCF= long-term care facility; HIV= human immunodeficiency virus; ICU= intensive-care unit; LOS= length of hospital stay;

[A] chronic renal failure was defined as serum creatinine above 1.5mg%.

[B] includes chronic obstructive pulmonary disease (COPD), bronchiectasis, restrictive lung disease, and asthma, among others.

[C] any cerebral stroke in the past (whether with neurologic sequel or not)

[D] includes both active and past malignancy

[E] measured according to Kats criteria, of being or becoming dependent in ≥1 activities of daily living [21].

[F] include permanent devices like tracheotomies, central lines, urinary catheters, external orthopedic devices, gastrostomy, that were in place at least 48 hours prior to MRSA isolation.

[G] effective therapy defined as therapy that the isolate displays susceptibility to per *in-vitro* testing

[H] discharge to a facility after initially being admitted from home

[I] additional hospitalizations in the 6 months following the MRSA isolation

[J] additional MRSA isolations with vancomycin MIC of 2 µg/mL 14 days to 1 year following the index culture