Trimethoprim-sulfamethoxazole vs. vancomycin for severe infections caused by methicillin-resistant Staphylococcus aureus: randomized controlled trial

Journal:	*BMJ*
Manuscript ID:	BMJ.2014.022885.R1
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	01-Oct-2014
Complete List of Authors:	Paul, Mical; Rambam Health Care Campus, Division of Infectious Diseases Bishara, Jihad; Rabin Medical Center, Infectious Diseases Yahav, Dafna; Rabin Medical Center, Infectious Diseases Goldberg, Elad; Rabin Medical Center, Infectious Diseases Neuberger, Ami; Rambam Health Care Campus, Division of Infectious Diseases Ghanem-Zoubi, Nesrin; Rambam Health Care Campus, Division of Infectious Diseases Nseir, William; The NAZARETH Hospital, Internal Medicine Dan, Michael; Wolfson Hospital, Leibovici, Leonard; Beilinson Campus Rabin Medical Center, Medicine E
Keywords:	MRSA, Bacteremia, Sepsis, Infection, Antibiotic resistance

Trimethoprim-sulfamethoxazole vs. vancomycin for severe infections caused by methicillin-resistant *Staphylococcus aureus*: randomized controlled trial

Mical Paul[1]*†, Jihad Bishara[2]*, Dafna Yahav[3], Elad Goldberg[4], Ami Neuberger[5], Nesrin Ghanem-Zoubi[6], Yaakov Dickstein[7], William Nseir[8], Michael Dan[9], Leonard Leibovici[10]

* Equal contribution

[1] Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Current address: Division of Infectious Diseases, Rambam Health Care Campus, Haifa. Israel

[2] Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Israel

[3] Unit of Infectious Diseases; Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Israel

[4] Unit of Infectious Diseases; Medicine F, Rabin Medical Center, Beilinson Hospital, Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Israel

[5] Division of Infectious Diseases; Medicine B, Rambam Health Care Campus and The Technion-Israel Institute of Technology and the Ruth & Bruce Rappaport Faculty of Medicine, Haifa. Israel

[6] Division of Infectious Diseases; Rambam Health Care Campus, Haifa. Israel.

[7] Division of Infectious Diseases; Medicine A, Rambam Health Care Campus and The Technion-Israel Institute of Technology and the Ruth & Bruce Rappaport Faculty of Medicine, Haifa. Israel

[8] Internal Medicine Department, Holy Family Hospital, Nazareth, Faculty of Medicine in the Galilee, Bar-Ilan Univesity, Safed, Israel. Current address Internal Medicine Department, E.M.M.S. Nazareth.The NAZARETH Hospital and Faculty of Medicine in the Galilee, Bar-Ilan Univesity, Safed. Israel

[9] Infectious Diseases Unit, E. Wolfson Hospital, Holon and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Israel

[10] Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv. Israel

† Contact author: Mical Paul, MD. Division of Infectious Diseases, Rambam Health Care Campus, Haifa, 31096, Israel. Email: paulm@post.tau.ac.il; Tel. +972-4-7772291; Fax. +972-4-7771620

Abstract

Objectives: To show non-inferiority of trimpehoprim-sulfamethoxazole (TMP-SMZ) vs. vancomycin for the treatment of severe infections due to methicillin-resistant *Staphylococcus aureus* (MRSA).

Design: Parallel, open-labeled, randomized controlled trial

Setting: Four acute-care hospitals in Israel

Participants: Adults with severe infections caused by MRSA susceptible to TMP-SMZ and vancomycin. Patients with left-sided endocarditis, meningitis, chronic hemodialysis and prolonged neutropenia were excluded.

Interventions: TMP-SMZ 320 mg/ 1600 mg B.I.D vs. vancomycin 1gr B.I.D for a minimum of 7 days and then by indication.

Main outcome measures: The primary efficacy outcome was treatment failure assessed at day 7 consisting of: death, persistence of hemodynamic instability or fever, stable or worsening Sequential Organ Failure Assessment score and bacteremia persistence. The primary safety outcome was all-cause mortality at day 30. Non-inferiority was defined by a difference <15% for treatment failure.

Results: 252 patients were included in the trial, of whom 91 (31.1%) had bacteremia. Treatment failure was non-significantly higher with TMP-SMZ (51/135, 37.8%) vs. vancomycin (32/117, 27.4%), risk ratio 1.38 (95% confidence interval 0.96-1.99). TMP-SMZ did not meet criteria for non-inferiority vs. vancomycin. For patients with bacteremia, the risk ratio was 1.4 (95% CI 0.91-2.16). In a multivariable logistic regression analysis, TMP-SMZ was significantly associated with treatment failure (adjusted odds ratio 2.00. 95% CI 1.09-3.65). The 30-day mortality rate was 32/252 (12.7%) and there was no statistically

significant difference between arms. Among patients with bacteremia, 14/41 (34.1%) with TMP-SMZ vs. 9/50 (18%) with vancomycin died (RR 1.9, 95% CI 0.92-3.93).

Conclusions: High-dose TMP-SMZ did not achieve non-inferiority criteria to vancomycin in the treatment of severe MRSA infections. The difference was particularly marked for patients with bacteremia.

Trial registration: NCT00427076

Background

Trimethoprim-sulfamethoxazole (TMP-SMZ) is an old antibiotic active against *Staphylococcus aureus*. Trimethoprim is the main active component and bactericidal in itself, but the combination is highly synergistic. (1) With increasing rates of methicillin-resistant *S. aureus* (MRSA) infections in healthcare settings and in the community, TMP-SMZ has been suggested as a convenient treatment option. (2-4)

MRSA isolates have retained susceptibility to TMP-SMZ in many locations worldwide despite several decades of exposure to the antibiotic. Coverage rates >90% are described in contemporary reports for community-associated (CA-MRSA) and nosocomial isolates in the United States, (5-7) Canada, (8-10) Japan, (11), Europe, Israel and Turkey. (12-14) Resistance is described in Australia, where 30% of nosocomial and 10% of community-associated MRSA isolates were resistant to TMP-SMZ in 2012, but a significant trend for decreasing resistance from 2005 was observed, unlike other antibiotics. (15) From sub-Saharan Africa, 19% resistance has been recently documented, due to high rates of trimethoprim resistance. (16) In India, more than 85% of MRSA isolates were TMP-SMZ-resistant between 2009 and 2011. (17, 18)

TMP-SMZ is recommended for the treatment of uncomplicated skin/ soft tissue infections (SSTIs), but not for MRSA bacteremia or pneumonia. (19) Vancomycin is the primary treatment recommendation for the latter infections. Alternatives to vancomycin are sought since vancomycin is probably not a very effective drug, given its inferiority to beta-lactams in methicillin-susceptible *S. aureus* (MSSA) infections, (20, 21) and since resistance to vancomycin is becoming a significant problem. (22) A single randomized controlled trial compared TMP-SMZ vs. vancomycin for bacteremia, finding no significant difference in

outcomes and shorter hospital-stay with TMP-SMZ, among 54 intravenous drug users (IVDUs) who had MRSA bacteremia. (21)

We conducted a RCT to assess whether TMP-SMZ is non-inferior to vancomycin for the treatment of inpatients with severe MRSA infections, including bacteremia.

Methods

Open-label, parallel, 1:1 RCT, conducted in four acute-care hospitals (listed in the appendix) in Israel, between July 2007 to April 2014. The trial was approved by the ethics committees in each study center and informed consent was obtained from all patients or their legal guardian. The trial was internally funded and was registered before start (NCT00427076).

We included adult inpatients with severe infections caused by MRSA including bacteremia or patients with highly-probable MRSA infections. Bacteremia was defined as the isolation MRSA in more than one blood culture bottle or if isolated in a single bottle accompanied by fever >38˚C, chills or systolic blood pressure <90 mmHg. Other microbiologically-documented MRSA infections were defined using predefined criteria adapted from surveillance definitions of healthcare-associated infections (23) plus isolation of MRSA from a sterile sample from the source of infection. Patients with SSTIs could be included only if fulfilling the sepsis inflammatory response syndrome criteria. (24) Patients with polymicrobial infections could be included, except those involving MSSA or mandating treatment with vancomycin or TMP-SMZ. The highly-probable group included patients with ventilator-associated pneumonia with prior antibiotic treatment; central catheter-related infections or surgical site infections in the presence of a foreign body, all without microbiological documentation. (25) We excluded patients receiving TMP-SMZ or vancomycin for more than 48 hours; patients with MRSA resistant to TMP-SMZ or vancomycin; highly suspected or confirmed left-sided endocarditis or meningitis; patients with chronic renal failure (creatinine clearance <15 ml/min) and chronic hemodialysis (those with severe acute renal failure, including acute hemodialysis, could be included); known allergy to either study drug; treatment with methotrexate; pregnancy, lactation; previous

enrollment in this study or concurrent participation in another trial; and neutropenic patients with acute leukemia or bone marrow transplantation.

Patients were randomized to treatment with TMP-SMZ vs. vancomycin. TMP-SMZ was started intravenously at a dose of 320 mg trimethoprim/ 1600 mg sulfamethoxazole twice daily and could be switched to oral treatment using the same dose at the discretion of the treating physician. The vancomycin starting dose was 1gr twice daily. In both arms treatment was adjusted to renal function and in the vancomycin arm directed by serum levels to obtain drug trough levels between 10-20 mg/dl. The complete study protocol is available on request. Treatment had to be administered for a minimum of 7 days, following which the duration depended on the indication. Concomitant antibiotics, other than the combination of vancomycin and cotrimoxazole, could be administered.

The primary efficacy outcome was defined as clinical failure at 7 days and was a composite of: death, persistence of fever (<38˚C for two consecutive days and no increase above 38 following the resolution was required to rule out persistence), persistence of hypotension <90 mmHg systolic or need for vasopressor support, non-improving Sequential Organ Failure Assessment (SOFA) score (for baseline SOFA ≥ 3 a decrease of at least 30% was required and for baseline SOFA <3 a stable or decreased SOFA score was required to rule out failure), or persistent bacteremia on day 7. Blood cultures were repeated daily for patients with persistent fever or other signs infection. We also defined a primary safety outcome of all-cause mortality at 30 days.

Secondary outcomes included treatment failure or modification, comprising of treatment failure (as defined) or treatment modification; bacteriological failure, defined as bacteremia persistence after 48 hours and 7 days of therapy; hospitalization duration; and resistance

development defined as acquisition of TMP-SMZ or vancomycin-resistant *S. aureus* or vancomycin-resistant Enterococci. Adverse events included renal failure defined using RIFLE criteria, (26) rash, leukopenia, any and clostridium-difficile-associated diarrhea and other adverse events.

To establish non-inferiority we allowed a difference of up to 15% in the primary outcome. Assuming a 30% treatment failure rate for both treatment groups, a sample of 128 patients per arm was calculated for a one-sided test to rule out the pre-specified difference in the 95% confidence interval of the difference between groups, allowing for 10% non-evaluable patients (α=0.05, β=0.8). We performed interim analyses of the primary safety outcome following recruitment of 1/3 and 2/3 of patients, with stopping boundaries (two-sided alpha level, <0.01).

Patients were randomized using a central computer generated random number list. Allocation was concealed in sealed, opaque numbered envelopes that were opened consecutively after obtaining informed consent. Following randomization no blinding was performed, but adjudication of outcomes was performed blinded to allocation.

The primary analysis was conducted by intention to treat (ITT). Per-protocol (PP) analysis was conducted for patients without exclusion criteria after randomization, who received allocated treatment for a minimum of 7 days. Subgroup analysis was performed for patients with MRSA bacteremia. Categorical outcomes were compared using the Chi square or Fisher exact tests and continuous outcomes using a T-test or the Mann-Whittney U test, as appropriate. Multivariable analyses were conducted for the primary efficacy and safety outcomes, including the treatment arm as independent variable. All variables significantly associated with the outcome on univariate analysis ($p<0.05$) were entered into a logistic regression analysis. Risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) are presented.

Results

We evaluated 782 patients, of whom 252 were included. The main reasons for exclusion were prior treatment with TMP-SMZ or vancomycin for more than 48 hrs. or inability to provide informed consent (Figure 1). Inclusion was based on microbiologically-documented inclusion criteria in 245 (97.2%) patients: 91 (31.1%) with bacteremia and 154 (61.1%) with MRSA isolated from other clinical samples. Mean patients' age was 65.8±17 years and all infections were healthcare-associated; 218 (86.5%) hospital-acquired. Patient and infection characteristics were mostly balanced between groups, with the exception of bacteremia that was more common in the vancomycin group (Table 1). Appropriate empirical antibiotic treatment was infrequent, as empirical vancomycin was discouraged in the study centers. Surgical interventions and catheter extraction when indicated were similarly performed in the study groups. Vancomycin trough levels were available for 97/117 (82.9%) patients in the vancomycin arm and were ≥ 10 µg/mL in 80 patients (82.5%). Isolates' MIC to vancomycin was 2 µg/mL in 12/77 (15.6%) of patients in the vancomycin arm and lower in the remaining. All isolates were susceptible to TMP-SMZ (disk zone <=10mm).

Treatment failure at day 7 was more common in patients receiving TMP-SMZ, although the difference was not statistically significant (RR 1.38, 95% CI 0.96-1.99) for the ITT population. The failure rate with TMP-SMZ was 51/135 (37.8%) vs. 32/117 (27.4%) with vancomycin and the 95% CI for the difference fell outside of the lower limit of the 15% predefined for non-inferiority (-1.2% to 21.5%). Of the components comprising the composite outcome, the advantage to vancomycin emerged from higher bacteremia persistence at day 7 and lack of improvement in SOFA score at day 7 with TMP-SMZ. Similar results were observed in the PP population of patients completing 7 treatment days (RR 1.24, 95% CI 0.82-1.89), absolute

difference 9.9% (95% CI -3.1% to 22.5%) and for patients with bacteremia (Table 2). Among patients without bacteremia the RR was 1.66 (95% CI 0.91-3.03). Restricting the analysis to patients in the vancomycin group whose isolates' MICs were <2 μg/mL resulted in an advantage to vancomycin (RR 1.64, 95% CI 0.99-2.68).

All-cause 30-day mortality was not significantly different between groups, but among patients with bacteremia a clinically-significant difference was observed with 14/41 (34.1%) vs. 9/50 (18%) deaths for TMP-SMZ vs. vancomycin (RR 1.90, 95% CI 0.92-3.93) by ITT and 9/33 (27.3%) vs. 6/42 (14.3%) per-protocol (RR 1.91, 95% CI 0.76-4.82). Among non-bacteremic patients, mortality rates were low (5/94 [5.4%] vs. 4/67 [6%], respectively) and not significantly different (RR 0.89, 95% CI 0.25-3.2).

No significant differences were observed with regard to the pre-defined secondary outcomes (Table 2). Bacteremia persistence was slightly more common with vancomycin at 48 hours, and with TMP-SMZ at 7 days. Duration of hospitalization for patients discharged alive was non-significantly shorter with TMP-SMZ. Adverse events were observed with similar frequency. Renal failure at day 7 and day 30, slightly more common with vancomycin, was not clinically or statistically different.

Variables significantly associated with day-7 treatment failure on univariate analysis and included in the multivariable analysis are listed in Table 3. The McCabe score, presence of nasogastric tube or urine catheter at infection onset, WBC and albumin levels were correlated with other included variables and were thus excluded from the regression analysis. On multivariable analysis, allocation to TMP-SMZ was significantly associated with treatment failure, adjusted OR 2.02 (1.1-3.7). Other independent risk factors were bacteremia and mechanical ventilation at infection onset, while surgery in the 30 days prior to infection was

inversely associated with treatment failure. Risk factors for 30-day mortality were similar on univariate analysis, with the addition of dementia, congestive heart failure and shock at onset that were significantly associated with mortality. Due to the paucity of outcomes, only variables remaining significant in the regression analysis were retained in the final model. Adjusted to these variables, treatment with TMP-SMZ was associated with an OR of 1.96 (95% CI 0.83-4.63) for mortality (Table 3).

Discussion

In a RCT including 252 patients with invasive MRSA infections, TMP-SMZ did not fulfill criteria for non-inferiority to vancomycin. The absolute difference in treatment failure rates at day 7, comprising of clinical/ hemodynamic stability and bacteremia clearance, was 10.4% in favor of vancomycin (95% CI -1.2% to 21.5%), crossing the upper limit of 15% difference defined for non-inferiority. Adjusting for differences between groups, treatment with TMP-SMZ was significantly associated with treatment failure (OR 2.00, 95% CI 1.09-3.65). Thirty day mortality was not significantly different between groups (RR 1.27, 95% 0.65-2.45), but among patients with bacteremia (N=91), the difference between arms seemed clinically significant with 14/41 (34.1%) deaths with TMP-TMZ vs. 9/50 (18%) with vancomycin, RR 1.9 (95% CI 0.92-3.93). Results were similar in a per protocol analysis. Bacteriological cure and adverse event rates were not significantly different between groups.

Our trial was pragmatic, targeting all patients treated with vancomycin in clinical practice. We defined no exclusion criteria related to severity of background illness or sepsis. Exclusions were based only on contra-indications for TMP-SMZ (e.g. chronic hemodialysis) or prior evidence suggesting inferiority to TMP-SMZ. Thus, left-sided endocarditis was excluded due to an in-vivo study of endocariditis in rabbits showing lower survival, vegetation sterilization and higher bacterial load on vegetations with TMP-SMZ compared to vancomycin and other antibiotics. (27) We excluded patients with MRSA meningitis due to inferiority of TMP-SMZ vs. nafcillin in an experimental model of MSSA meningitis (28) and lack of evidence with MRSA, despite good penetration of TMP-SMZ to the brain. (29) We originally intended to recruit patients with non-microbiologically documented, highly-probable MRSA infections. But in practice we found it difficult to identify such patients prospectively and practically the trial

included only patients with microbiologically-confirmed MRSA infections. The main reason precluding patient inclusion was inability to obtain informed consent at the time of acute sepsis. In Israel, regulations allow only legal guardians to replace patients' informed consent and with acute conditions most patients did not have an appointed legal guardian.

Few RCTs have assessed the effectiveness of TMP-SMZ for the treatment of staphylococcal infections. In the only RCT comparing TMP-SMZ vs. vancomycin, among 54 IVDUs with MRSA bacteremia no difference in cure rates, fever and bacteremia duration were noted. (21) Hospital stay was non-significantly shorter with TMP-SMZ (mean 19.3 vs. 27.8 days), as in our study, reflecting the possibility to provide TMP-SMZ orally. A single death was reported in the trial, reflecting the characteristics of S. aureus bacteremia among IVDUs, unlike the mortality rate in our trial (25.3%). In a recent RCT, TMP-SMZ combined with rifampin was compared to linezolid in the treatment of MRSA infections, showing no differences in failure/ relapse rates or mortality. (14) In comparison with our study, the cohort include less ill patients (bacteremia in 18/150, 12%, and mortality in 14/150, 9.3%). Among 50 patients with chronic MSSA osteomyelitis randomized to TMP-SMZ-rifampin vs. oxacillin, long-term outcomes were similar and patients allocated TMP-SMZ-rifampin had a significantly shorter hospital-stay (median 51 vs. 31 days). (30) Finally, TMP-SMZ was not significantly different from doxycycline for uncomplicated SSTIs in a small RCT assessing 22 patients with MRSA. (31).

The main treatment options for MRSA infections other than vancomycin or teicoplanin and TMP-SMZ include linezolid, daptomycin, tigecycline, telavancin and more recently ceftaroline. (22) RCTs have demonstrated higher clinical and microbiological cure rates for linezolid compared to vancomycin in SSTIs. (32) Mortality was rarely assessed in these trials and when reported was very low (overall 1.5%). Similar efficacy and safety for was demonstrated for

linezolid and vancomycin in nosocomial pneumonia and the mortality rate in these trials was 14.3%. (33) Daptomycin was non-inferior to vancomycin in a RCT including 245 patients with *S. aureus* bacteremia, of whom 89 had MRSA bacteremia. (34) The overall mortality was 11.1%. Tigecycline was non-inferior to vancomycin in a RCT including 156 patients with invasive MRSA infections, mostly SSTIs (mortality rate 5.1%). (35) Telavancin was non-inferior to vancomycin for SSTIs (579 patients with MRSA, overall mortality in the study 0.08%) (4) and hospital-acquired pneumonia (293 patients with MRSA, overall mortality in the study 19.3%). (36) Ceftaroline was non-inferior to vancomycin/ aztreonam for SSTIs (330 patients with MRSA infections, 9 with MRSA bacteremia, overall mortality in study 0.2%). Compared to these trials, our trial included a larger group of patients with MRSA bacteremia and overall a sicker cohort as evidenced by the mortality rates, more closely reflecting patients treated with MRSA infections in clinical practice.

The main limitation of our trial is the small sample size of patients with bacteremia, in whom results suggest an important advantage to vancomycin. No statistically significant differences were observed between groups at baseline for nearly all variables. However, a subtle difference did exist for important prognostic variables and more patients allocated to vancomycin were bacteremic. Multivariable analysis of the entire study cohort, increased the advantage to vancomycin with regard to treatment failure (reaching statistical significance) and mortality. Patients with polymicrobial infections and receiving additional antibiotics were included in the study, reflecting the pragmatic nature of the study. However, treatment against MRSA was based on the allocated treatment which was started in all randomized patients.

In summary, TMP-SMZ did not fulfill non-inferiority compared to vancomycin among patients with invasive MRSA infections. In the subgroup of patients with bacteremia the

difference in treatment failure and all-cause mortality was high and clinically-important. TMP-SMZ should not be used for the treatment of severe MRSA infections. We propose a further RCT to examine the feasibility of step-down from vancomycin to TMP-SMZ, allowing early discharge of MRSA patients responding to treatment.

Conflicts of interests: all authors, none declared

Participating centers:

Rabin Medical Center, Petah-Tikva (192 patients)

Rambam Health Care Campus (38 patients)

Holy Family Hospital Nazareth (7 patients)

Wolfson Medical Center (6 patients)

Acknowledgments:

Study conception and design: Mical Paul, Jihad Bishara, Leonard Leibovici

Data collection: Maria Raskin, Ynon Lischinski, Morad Wattad, Olga Talker, Rawi Hazan, Laura Farbman, Vered Shani, Vered Zaretsky (Rabin Medical Center); Yaakov Dickstein, Roni Bitterman, Ami Neuberger, Nesrin Ghanem-Zoubi, Anat Stern, Yael Dishon-Benattar, Fidi Koppel (Rambam Health Care Campus), all authors.

Data analysis: Mical Paul, Jihad Bishara, Leonard Leibovici

Data interpretation and final manuscript: all authors

Funding: The study was partially funded by The Sima Lior scholarship 2008 (Mical Paul) and Rabin Medical Center Young Investigator scholarship 2009 (Dafna Yahav). The funders had no role in trial design, data collection, analysis, interpretation or manuscript preparation.

Data sharing: Case report forms, dataset and statistical code available from the corresponding author.

Licence to BMJ Publishing Group Limited ("BMJ Group") for Publication: I Mical Paul The Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs within and any related or stand alone film submitted (the Contribution") has the right to grant on behalf of all authors and does grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence set out at: http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse."

✓ I am one author signing on behalf of all co-owners of the Contribution

References

1. Elwell LP, Wilson HR, Knick VB, Keith BR. In vitro and in vivo efficacy of the combination trimethoprim-sulfamethoxazole against clinical isolates of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 1986 Jun; 29(6):1092-4.

2. Nathwani D, Davey PG, Marwick CA. MRSA: treating people with infection. Clin Evid (Online). 2010 2010(

3. Pappas G, Athanasoulia AP, Matthaiou DK, Falagas ME. Trimethoprim-sulfamethoxazole for methicillin-resistant Staphylococcus aureus: a forgotten alternative? J Chemother. 2009 Apr; 21(2):115-26.

4. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2008 Jun 1; 46 Suppl 5(S368-77.

5. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Costello AJ, Kroeger JS et al. Activity of ceftaroline and epidemiologic trends in Staphylococcus aureus isolates collected from 43 medical centers in the United States in 2009. Antimicrob Agents Chemother. 2011 Sep; 55(9):4154-60.

6. Wackett A, Nazdryn A, Spitzer E, Singer AJ. MRSA rates and antibiotic susceptibilities from skin and soft tissue cultures in a suburban ED. J Emerg Med. 2012 Oct; 43(4):754-7.

7. Wood JB, Smith DB, Baker EH, Brecher SM, Gupta K. Has the emergence of community-associated methicillin-resistant Staphylococcus aureus increased trimethoprim-sulfamethoxazole use and resistance?: a 10-year time series analysis. Antimicrob Agents Chemother. 2012 Nov; 56(11):5655-60.

8. Muileboom J, Hamilton M, Parent K, Makahnouk D, Kirlew M, Saginur R et al. Community-associated methicillin-resistant Staphylococcus aureus in northwest Ontario: A five-year report

of incidence and antibiotic resistance. Can J Infect Dis Med Microbiol. 2013 Summer; 24(2):e42-4.

9. Levesque S, Bourgault AM, Galarneau LA, Moisan D, Doualla-Bell F, Tremblay C. Molecular epidemiology and antimicrobial susceptibility profiles of methicillin-resistant Staphylococcus aureus blood culture isolates: results of the Quebec Provincial Surveillance Programme. Epidemiol Infect. 2014 Aug 20:1-8.

10. Zhanel GG, Adam HJ, Baxter MR, Fuller J, Nichol KA, Denisuik AJ et al. Antimicrobial susceptibility of 22746 pathogens from Canadian hospitals: results of the CANWARD 2007-11 study. J Antimicrob Chemother. 2013 May; 68 Suppl 1(i7-22.

11. Hanaki H, Cui L, Ikeda-Dantsuji Y, Nakae T, Honda J, Yanagihara K et al. Antibiotic susceptibility survey of blood-borne MRSA isolates in Japan from 2008 through 2011. J Infect Chemother. 2014 Sep; 20(9):527-34.

12. Farrell DJ, Flamm RK, Sader HS, Jones RN. Ceftobiprole Activity against over 60,000 Clinical Bacterial Pathogens Isolated in Europe, Turkey, and Israel from 2005 to 2010. Antimicrob Agents Chemother. 2014 Jul; 58(7):3882-8.

13. Schaumburg F, Idelevich EA, Peters G, Mellmann A, von Eiff C, Becker K. Trends in antimicrobial non-susceptibility in methicillin-resistant Staphylococcus aureus from Germany (2004-2011). Clin Microbiol Infect. 2013 Dec 27;

14. Harbarth S, von Dach E, Pagani L, Macedo-Vinas M, Huttner B, Olearo F et al. Randomized non-inferiority trial to compare trimethoprim/sulfamethoxazole plus rifampicin versus linezolid for the treatment of MRSA infection. J Antimicrob Chemother. 2014 Sep 10;

15. Australian Group on Antimicrobial Resistance: SAP 2011 Antimicrobial Susceptibility Report and SAP 2012 Antimicrobial Susceptibility Report. http://www.agargroup.org/surveys

16. Nurjadi D, Olalekan AO, Layer F, Shittu AO, Alabi A, Ghebremedhin B et al. Emergence of trimethoprim resistance gene dfrG in Staphylococcus aureus causing human infection and colonization in sub-Saharan Africa and its import to Europe. J Antimicrob Chemother. 2014 Sep; 69(9):2361-8.

17. Sharma NK, Garg R, Baliga S, Bhat KG. Nosocomial Infections and Drug Susceptibility Patterns in Methicillin Sensitive and Methicillin Resistant Staphylococcus aureus. J Clin Diagn Res. 2013 Oct; 7(10):2178-80.

18. Kali A, Stephen S, Umadevi S, Kumar S, Joseph NM, Srirangaraj S. Changing Trends in Resistance Pattern of Methicillin Resistant Staphylococcus aureus. J Clin Diagn Res. 2013 Sep; 7(9):1979-82.

19. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1; 52(3):e18-55.

20. Kim SH, Kim KH, Kim HB, Kim NJ, Kim EC, Oh MD et al. Outcome of vancomycin treatment in patients with methicillin-susceptible Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2008 Jan; 52(1):192-7.

21. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann Intern Med. 1992 Sep 1; 117(5):390-8.

22. Rodvold KA, McConeghy KW. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. Clin Infect Dis. 2014 Jan; 58 Suppl 1(S20-7.

23. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008 Jun; 36(5):309-32.

24. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA, Balk RA. Sepsis syndrome: a valid clinical entity. Methylprednisolone Severe Sepsis Study Group. Crit Care Med. 1989 May; 17(5):389-93.

25. Carnicer-Pont D, Bailey KA, Mason BW, Walker AM, Evans MR, Salmon RL. Risk factors for hospital-acquired methicillin-resistant Staphylococcus aureus bacteraemia: a case-control study. Epidemiol Infect. 2006 Dec; 134(6):1167-73.

26. Bellomo R, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Med. 2007 Mar; 33(3):409-13.

27. de Gorgolas M, Aviles P, Verdejo C, Fernandez Guerrero ML. Treatment of experimental endocarditis due to methicillin-susceptible or methicillin-resistant Staphylococcus aureus with trimethoprim-sulfamethoxazole and antibiotics that inhibit cell wall synthesis. Antimicrob Agents Chemother. 1995 Apr; 39(4):953-7.

28. Scheld WM, Keeley JM, Field MR, Brodeur JP. Co-trimoxazole versus nafcillin in the therapy of experimental meningitis due to Staphylococcus aureus. J Antimicrob Chemother. 1987 May; 19(5):647-58.

29. Levitz RE, Quintiliani R. Trimethoprim-sulfamethoxazole for bacterial meningitis. Ann Intern Med. 1984 Jun; 100(6):881-90.

30. Euba G, Murillo O, Fernandez-Sabe N, Mascaro J, Cabo J, Perez A et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. Antimicrob Agents Chemother. 2009 Jun; 53(6):2672-6.

31. Cenizal MJ, Skiest D, Luber S, Bedimo R, Davis P, Fox P et al. Prospective randomized trial of empiric therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2007 Jul; 51(7):2628-30.

32. Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ. Linezolid versus vancomycin for skin and soft tissue infections. Cochrane Database Syst Rev. 2013 7(CD008056.

33. Kalil AC, Klompas M, Haynatzki G, Rupp ME. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. BMJ Open. 2013 3(10):e003912.

34. Fowler VG, Jr., Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006 Aug 17; 355(7):653-65.

35. Florescu I, Beuran M, Dimov R, Razbadauskas A, Bochan M, Fichev G et al. Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci: a Phase 3, multicentre, double-blind, randomized study. J Antimicrob Chemother. 2008 Sep; 62 Suppl 1(i17-28.

36. Rubinstein E, Lalani T, Corey GR, Kanafani ZA, Nannini EC, Rocha MG et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin Infect Dis. 2011 Jan 1; 52(1):31-40.

Table 1: Patient characteristics

	TMP-SMZ N=135	Vancomycin N=117	P value
Age, years (mean+/-SD)	64.8 +/- 17.0	67 +/- 17.1	0.324
Functional capacity on admission			0.982
Independent	75 (55.6%)	66 (56.4%)	
Dependent	31 (23.0%)	27 (23.1%)	
Bedridden	29 (21.5%)	24 (20.5%)	
Hospital-acquired infection	115 (85.2%)	103 (88.0%)	0.509
McCabe score, no fatal disease	104 (77%)	92 (78.6%)	0.761
Charlson Score (mean+/-SD)	2.59 +/- 2.04	2.65 +/- 2.13	0.829
Diabetes mellitus	67 (49.6%)	54 (46.2%)	0.582
COPD	20 (14.8%)	15 (12.8%)	0.648
Congestive heart failure, NYHA class III-IV	29 (21.5%)	21 (17.9%)	0.483
Chronic renal failure, creatinine >1.3 mg/dl	16 (11.9%)	12 (10.3%)	0.688
Surgery 30 days before	64 (47.4%)	57 (48.7%)	0.835
Source of MRSA infection			0.584
Complicated SSTIs	50 (37%)	38 (32.5%)	
Bone or joint	39 (28.9%)	32 (27.4%)	
Endovascular	10 (7.4%)	16 (13.7%)	
Pneumonia	14 (10.4%)	14 (12%)	
Other	10 (7.4%)	10 (8.5%)	
Primary bacteremia	12 (8.9%)	7 (6.0%)	
Bacteremia	41 (30.4%)	50 (42.7%)	0.042
SOFA score at onset of infection			0.406
0	76 (56.3%)	56 (47.9%)	
1-3	46 (34.1%)	47 (40.2%)	
>3	13 (9.6%)	14 (12%)	

Mechanically ventilated at onset	16 (11.9%)	11 (9.4%)	0.531
Central venous catheter at onset	17 (12.6%)	15 (12.8%)	0.957
Creatinine at onset of infection, mg/dl (mean +/- SD)	1.01 +/- 0.64	1.04 +/- 0.71 (N=116)	0.736
Total leukocytes at onset of infection (K/ml^3, mean +/- SD)	11.6 +/- 6	10.5 +/- 4.6 (N=116)	0.094
Albumin at onset of infection (mg/dl, mean +/- SD)	2.86 +/- 0.76 (N=108)	2.78 +/- 0.63 (N=102)	0.392
Polymicrobial infection	53 (39.3%)	41 (35%)	0.49
Appropriate empirical antibiotic treatment (within 48hr)	13 (9.9%)	14 (12.5%	0.524
Surgery as part of infection management by day 7 [1]	52/71 (73.2)	46/58 (79.3%)	0.422
Foreign body or catheter removal by day 7 [2]	13/63 (20.6%)	15/55 (27.3%)	0.398

[1] The denominator is patients in whom surgery was deemed necessary as part of treatment management. Among all patients rates were 52/135 (38.5%) vs. 46/117 (39.3%), p=0.9.

[2] The denominator is patients with central vascular catheter or foreign body

Table 2: Study outcomes

	All			Bacteremia		
	TMP/ SMZ	Vanco-mycin	RR (95% CI)	TMP/ SMZ	Vanco-mycin	RR (95% CI)
Intention to treat						
Treatment failure, day 7	51/135 (37.8%)	32/117 (27.4%)	1.38 (0.96-1.99)	23/41 (56.1%)	20/50 (40%)	1.4 (0.91-2.16)
All-cause mortality, 30 days	19/135 (14.1%)	13/117 (11.1%)	1.27 (0.65-2.45)	14/41 (34.1%)	9/50 (18%)	1.9 (0.92-3.93)
Treatment failure or modification [1]	59/135 (43.7%)	45/117 (38.5%)	1.14 (0.84-1.53)	24/41 (58.5%)	21/50 (42%)	1.39 (0.92-2.11)
Bacteremia duration >48 hrs.	11/135 (8.1%)	15/117 (12.8%)	0.64 (0.3-1.33)	11/41 (26.8%)	15/50 (30%)	0.89 (0.46-1.73)
Bacteremia duration >7 days	10/135 (7.4%)	4/117 (3.4%)	2.17 (0.7-6.73)	6/41 (14.6%)	4/50 (8%)	1.83 (0.55-6.05)
Hospitalization duration [3]	14 (1-441), N=117	15 (3-241), N=102	0.151	15 (3-98), N=29	18 (3-93), N=39	0.246
Resistance development [5]	5/135 (3.7%)	6/117 (5.1%)	0.72 (0.23-2.31)			
Per protocol						
Primary outcome, day 7	37/110 (33.6%)	26/96 (27.1%)	1.24 (0.82-1.89)	17/33 (51.5%)	15/42 (35.7%)	1.44 (0.85-2.44)
All-cause mortality, 30 days	12/110 (10.9%)	10/96 (10.4%)	1.05 (0.47-2.32)	9/33 (27.3%)	6/42 (14.3%)	1.91 (0.76-4.82)

[1] Failure at day 7 as defined by primary outcome or deviation from the assigned regimen in the first 7 days of treatment

[2] Of 12 and 17 microbiological failures with C and V, 6 and 7 were due to persistent bacteremia at day 7, respectively.

[3] Reported as median (min-max) for patients discharged alive (N). Significance reported as P value for the Mann-Whitney U test.

[4] Reported as median (min-max) for patients with fever at presentation (N). Significance reported as P value for the Mann-Whitney U test.

[5] One patient in each group developed a cotrimoxazole-resistant MRSA isolate, 3C and 5V developed CRE colonization. There were no VISA or VRE isolates.

Table 3: Adverse events

	TMP-SMZ	Vancomycin	RR (95% CI) / p value
Any	39/132 (29.5%)	26/115 (22.6%)	1.31 (0.85-2.01)
Requiring discontinuation	14/132 (10.6%)	8/115 (7%)	1.52 (0.66-3.5)
RIFLE day 7 [1]	N=108	N=100	0.07
None	90 (83.3%)	86 (86%)	
Risk	7 (6.5%)	2 (2%)	
Injury	11 (10.2)	8 (8%)	
Failure	0	4 (4%)	
RIFLE risk, injury or failure, day 7 [1]	18/108 (16.7%)	14/100 (14%)	1.19 (0.63-2.26)
RIFLE day 30 [1]	N=77	N=81	0.157
None	70 (90.9%)	65 (80.2%)	
Risk	2 (2.6%)	4 (4.9%)	
Injury	2 (2.6%)	9 (11.1%)	
Failure	3 (3.9%)	3 (3.7%)	
RIFLE risk, injury or failure, day 30 [1]	7/77 (9.1%)	16/81 (19.8%)	0.46 (0.2-1.06)
Any rash	12/132 (9.1%)	12/115 (10.4%)	0.87 (0.41-1.86)
Diarrhea [2]	12/132 (9.1%)	11/115 (9.6%)	0.95 (0.44-2.07)

[1] Renal failure assessed for patients alive with available measurements at the designated time point

[2] Of those with diarrhea, 3 with C and 4 with V had *Clostridium difficile* infection

Table 4: Multivariate analysis for treatment failure and mortality

	Treatment failure at day 7 OR (95% CI) [1]		**30-day all-cause mortality** OR (95% CI) [2]	
Variable	Univariate	Multivariate	Univariate OR	Multivariate OR
Age	1.02 (1-1.03)	1.01 (0.99-1.03)	1.06 (1.02-1.09)	1.05 (1.01-1.08)
Charlson score	1.24 (1.09-1.42)	1.15 (0.99-1.35)	1.32 (1.12-1.56)	Not included
Bedridden [3]	1.96 (1.06-3.65)	0.80 (0.36-1.76)	3.08 (1.41-6.75)	Not included
COPD	2.16 (1.05-4.45)	0.76 (0.30-1.90)	3.54 (1.51-8.34)	Not included
Previous operation [4]	0.49 (0.28-0.83)	0.52 (0.28-0.96)	0.26 (0.11-0.63)	Not included
Mechanical ventilation [3]	5.98 (2.49-14.3)	5.02 (1.62-15.6)	3.53 (1.39-8.92)	Not included
SOFA score [3]	1.41 (1.2-1.66)	1.15 (0.94-1.40)	1.52 (1.26-1.83)	1.39 (1.13-1.71)
Bacteremia	2.71 (1.57-4.67)	2.24 (1.20-4.18)	5.71 (2.51-13.0)	4.14 (1.71-10.0)
TMP-SMZ arm	1.61 (0.94-2.75)	2.00 (1.09-3.65)	1.31 (0.62-2.78)	1.96 (0.83-4.63)

[1] Hosmer Lemeshow p=0.08, area under ROC 0.75 (95% CI 0.68-0.82)

[2] Hosmer Lemeshow p=0.81, area under ROC 0.83 (95% CI 0.76-0.89)

[3] Variables documented at infection onset. SOFA analysed as continuous variable

[4] Previous operation in the 30 days prior to infection

Figure 1: patient flow