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Retro-respective Evaluation of New Fixed Dose Combination of Antibiotics in Management of Severe Skin and Soft Tissue Infections – A Comparative Pharmacoeconomic Study

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Authors' contributions

This work was carried out in collaboration between both authors. Author PB designed the study and wrote the protocol. Author MAM performed the statistical analysis and wrote the first draft of the manuscript and managed literature searches. Author PB managed the review of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Study Background: Skin and soft tissue infections (SSTIs) are the second most common infection encountered in hospitals. Present study aims to comparatively analyze efficacy of new fixed dose combination (FDC) with teicoplanin in treating severe SSTI patients and to assess the costs associated with respective therapies.
Materials and Methods: During this retrospective study, case sheets of patients who were treated for severe SSTIs / Sepsis with teicoplanin or fixed dose combination of Vancomycin +Ceftriaxone+ adjuvant (FDC) between March 2009 and August 2012 at tertiary care hospitals were analyzed. Various demographic features, antibiotic therapy, length of treatment duration and the resulting efficacy were evaluated. Microbiological correlation was done with clinical success monitored in terms of complete omission of systemic signs and symptoms and evaluation of % failure in each

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case or need of concomitant therapy to treat sepsis. Overall cost involved in the infections management was estimated in INR.

Results: A total of 314 confirmed SSTI cases out of 538 patients who met other study entrance criteria were further analyzed. Out of these 314 patients, empirical treatment with teicoplanin was received by 186 patients and 128 patients were treated with FDC empirically. Amidst all the patients, 132 (70.96%) of 186 from teicoplanin group and 102 (79.68%) of 128 from FDC group achieved clinical success. 26 / 128 (in FDC group) and 54 /186 (in Teicoplanin group) patients whose MIC falls in intermediate range failed to respond and tigecycline was added to ongoing therapy. Comparative cost expenditure analysis of the two drug treatment groups revealed that, the overall treatment cost for patients cured with empirical teicoplanin group was 92.83% more than that of FDC therapy. The strongest predictor of the increase in treatment costs was clinical failure. Similar trends were maintained for the patients cured with tigecycline additional therapy, with teicoplanin group accounting 56.63% more expenditure than FDC group.

Conclusion: For the treatment of different types of SSTIs, the empirical intravenous FDC therapy was safe, well tolerated with higher efficacy including in infections caused by multidrug resistant strains (VRSA and GISA) than teicoplanin. Pharmacoeconomic analysis clearly shows that starting appropriate empirical antibiotic therapy has a large impact on the cost of treatment in management of SSTIs and preferring FDC empirically both as mono/combination therapy, can significantly reduce the cost involved in the treatment. Empirical use of FDC followed by correlating it with MIC values can prevent failure and SSTI turning in sepsis.

Keywords: Ceftriaxone; MRSA; multi-drug resistant bacteria; sepsis; teicoplanin; vancomycin.

1. INTRODUCTION

Skin and soft tissue infections (SSTIs) can be defined as a suppurative microbial invasion of the epidermis and subcutaneous tissues that induce either a local or systemic host response. SSTIs are characterized by induration, erythema, warmth and pain or tenderness [1]. SSTIs have been classified as complicated or uncomplicated [2], with a range of severity from simple subcutaneous abscesses to severe necrotizing infections. Uncomplicated infections are superficial, often self-limiting, and can usually be treated successfully by incision and drainage alone or in combination with oral antibiotics [3]. The complicated SSTIs (cSSTIs) extend to subcutaneous tissue, fascia, or muscle [4] and require complex treatment, combining careful selection of antimicrobials with expeditious surgical intervention. The main etiological agents implicated in SSTIs are the Gram-positive organisms, *Staphylococcus aureus* (*S. aureus*), and the beta-hemolytic streptococci (Groups A, B, C and G). Methicillin-resistant *S. aureus* (MRSA) infections have risen in prominence over the last 20 years, comprising 59% of *S. aureus* isolates in a recent study in the USA [5] and > 10% of isolates in 19 out of the 28 countries in the 2009 European Antimicrobial Resistance Survey [6].

Cellulitis is an acute, spreading, pyogenic inflammation of the lower dermis and associated subcutaneous tissue. It is a skin and soft tissue infection that results in high morbidity and severe financial costs to health-care providers worldwide [7]. Myositis or Idiopathic inflammatory myopathies are an important type of SSTIs present with muscle weakness [8]. Necrotizing myopathy (NM) has a multifactorial etiology; it may have an acute or subacute onset, can be severe, may have a seasonal variation or cancer association, and may be triggered by statins [9]. Necrotizing fasciitis (NF) is relatively uncommon, but life-threatening type of SSTIs, which tend to progress rapidly through the fascia planes, causing gradual destruction of the fascia at a rate reaching 2–3 cm/h. The infection progresses rapidly, and septic shock may ensue; hence, the mortality rate is high (median mortality 32.2%) [10].

Glycopeptides including teicoplanin and Vancomycin remains the most frequently prescribed treatment options for severe SSTIs especially for serious MRSA infections and are now the second most common antibiotic group used in hospitals to treat cephalosporin resistant gram positive infections [11]. Unfortunately, the cure rate for glycopeptides has been disappointing [12-14] with high mortality rates [12]. However, comparatively decreased mortality cases were reported by Wunderink et al. [15] in a clinical trial study and attributed the decreased mortality rates to the optimized glycopeptide dosing and overall improvement in the quality of care in patients with MRSA

infections. The decreased cure rates with glycopeptides may be due to any previously reported reasons [16-20], which can limit the usefulness of teicoplanin/vancomycin mono therapy. All these aspects accentuates the need for new antibiotics. A new FDC of ceftriaxone + vancomycin + adjuvant (Vancoplus) is increasingly being used in Indian hospitals. Various reports of the *in-vitro* susceptibility studies [21-25] hints the possibility of this new FDC to overcome the hurdles of infections caused by MRSA, GISA and GRSA strains clinically. If effective *in-vivo* clinical success is achieved by this new FDC, it can be a potent alternative to mono therapy of either teicoplanin/vancomycin to treat infections caused by these multi-drug resistant strains. Therefore, current study was planned with objective to analyze if MIC correlates with clinical success and can empiric right choice of therapy prevent SSTI turning into sepsis. Further, the study also retrospectively evaluated cost of two therapies and cost driving factors.

2. MATERIALS AND METHODS

2.1 Study Design Overview

The present study was a retrospective, observational analysis of the data collected from different tertiary care hospitals for the patients treated between March 2009 and August 2012. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and to the current norm for observational studies. Due to the retrospective nature of the design, informed consent was not taken.

2.2 Patient Selection

The patients were selected by going through their case history sheets of the hospitals. Hospitalized adult patients aged above 18 years, who were admitted between March 2009 and August 2012 were considered for the study. The other criteria for patients inclusion were; 1) patients with the primary diagnosis of SSTIs based on the clinical investigations and relevant signs and symptoms, 2) patients with identified baseline / super infection culture 3) patients in whom either FDC or teicoplanin were used at least for a period of >3 days 4) patients in whom adequate doses of the above said drugs were used and 5) patients who were hospitalized for more than 5 days.

2.3 Patient Analysis

Case history sheets of all the patients were reviewed and relevant information like patient age, gender, co-morbidities, culture identification tests, MIC values, antibiotic therapy, dose and duration, considering additional cover, the reasons for the additional cover and length of the hospital stay were recorded. Among all the case sheets analyzed, 314 patients which were given either FDC or teicoplanin and fulfilled the other above mentioned inclusion criteria were included for the analysis. The FDC dose used in the therapy was 3 g / 12 hrs, whereas for teicoplanin, an initial 3 loading doses of 400 mg / 12 hrs followed a maintenance dose of 400 mg every day. For tigecycline (used as additional cover), an initial loading dose of 100 mg was used followed by 50 mg / 12 hrs were used (Fig. 1).

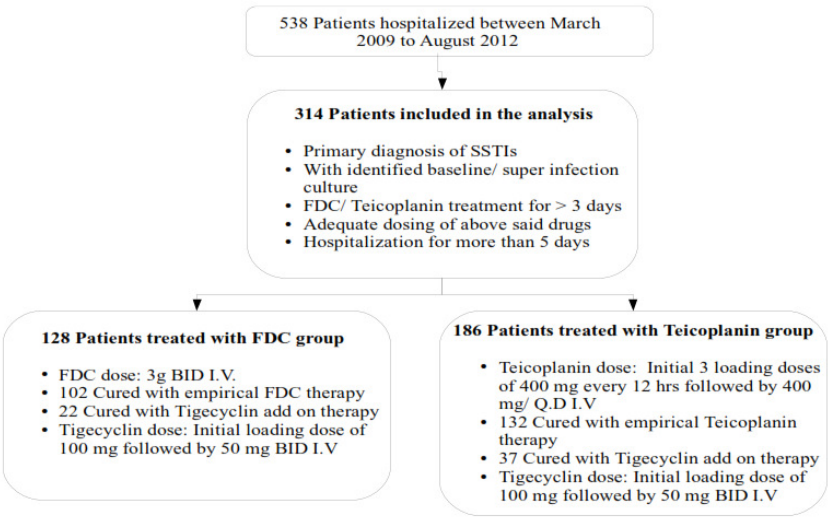

Fig. 1. Flow chart of the study design

2.4 Initial Antibiotic Treatment and Outcomes

For better presentation and easy understanding, the patients analyzed retrospectively were broadly divided in to two groups; FDC group – patients [128 (40.74%)] to whom FDC was administered empirically and Teicoplanin group – patients [186 (59.24%)] which were on empirical teicoplanin therapy. The progress of the therapy was measured in terms of clinical improvement in signs and symptoms. After the initial microbiological assessment (after 3 days) and clinical progress (signs of improvement), the decision on whether to consider tigecycline additional cover was taken. The patients from both the groups, showing improvement with the empirical therapy were continued with the same regime and the patients with intermediate susceptibility and who failed to show significant clinical improvement (deteriorated) with mono therapy were given an additional cover of tigecycline.

2.5 Patient Evaluations and Definitions

All the patients enrolled into the study were thoroughly evaluated by examining the systemic signs of infection such as temperature >38°C, tachycardia (heart rate >90 beats per minute), tachypnea (respiratory rate >24 breaths per minute) or abnormal white blood cell count (>12 000 or <400 cells / µL), culture and sensitivity reports from the specimen sampled from the affected site, hematology and biochemistry including the levels of albumin, C-reactive protein (CRP), creatinine, alanine aminotransferase, hemoglobin, the leukocytes count, the platelet count and other relevant investigations on case to case basis. All the evaluations were done to derive a co-relation of lab results with clinical parameters. The lab parameters were also evaluated to rule out nephro-toxicity during course of treatment. Minimum inhibitory concentrations (MICs) of antibiotics for clinical isolates were determined by micro-broth dilution method according to the Clinical and Laboratory Standards Institute (CLSI). The assessment of microbiological response at patient level was based on the results of susceptibilities of the isolated pathogens and clinical outcome of the patients.

2.6 Definitions

2.6.1 Clinical success

The patient's response was considered as clinical success when, the patient recovered with either first line empiric antibiotic therapy or a step down from the initial therapy.

2.6.2 Clinical failure

An individual case was defined as clinical failure when either the treatment was given an additional cover or when the death of patients occurred.

2.6.3 First line / empiric antibiotic therapy

It is defined as the regime started at the beginning before the availability of any culture data.

2.6.4 Second-line antibiotic therapy

It is defined as the addition of one or more antibiotics to the initial regime or as a complete or partial shift of the initial antibiotic with another parenteral antibiotic regime.

2.6.5 Susceptible

A MIC of ≤ 2 mg/L for teicoplanin and ≤ 8 mg/L for FDC was defined as susceptible.

2.7 Antibiotic Therapy Cost Analysis

An assessment of the direct cost of antibiotics was performed by multiplying the number of days of antibiotic therapy by the unit price of respective individual antibiotic and by the number doses per day, whereas the overall cost of antibiotic treatment for each patient was the sum of costs calculated for all parenteral antibiotics received by the patient during the hospitalization period. The unit price of antibiotics was based on maximum retail price (MRP) per unit of antibiotics. Hospitalization charges, laboratory tests, instrumental charges and overhead charges were calculated based on the average rate card of different hospitals in the vicinity. Costs incurred towards prior treatment procedures carried out and prior antibiotic therapies used before FDC and teicoplanin treatment were not included in analysis, as we assume they were independent of the adopted antibiotic therapy. Costs were expressed in Indian rupees (INR).

3. RESULTS

3.1 Patients and Demographic Characteristics

During the study period 538 patients were admitted out of which 314 patients were

confirmed with SSTIs who met other study entrance criteria were further analyzed (Fig. 1). The baseline and demographic characteristics of the patients which were given either FDC (n=128) or teicoplanin (n=186) empirically are given in Table 1. Most of the baseline characteristics among the patients from both the groups were comparable. Male population was more when compared to their counter parts in both the groups with male: female ratio of 79:49 and 109:77 for FDC and teicoplanin groups respectively. The mean age of patients in FDC was 62.56 ± 11.54 and the same in patients belonging to teicoplanin group was 61.00 ± 10.05. The analysis of the disease severity data measured in terms of APACHE II score reveals that irrespective of the groups, majority of patients were having a score of <15. 86 (67.18%) out of 128 patients from FDC group were having APACHE II score of <15, whereas 123 (66.12%) patient out of 186 from teicoplanin group were having the severity score of <15. Among different types of SSTIs, there were 163 cases of cellulites (69 in FDC; 94 in teicoplanin group), 89 cases of myositis (38 in FDC; 51 in teicoplanin group) acardiovascular diseases nd 62 cases of necrotizing fasciitis (21 in FDC; 41 in teicoplanin group). Diabetes mellitus was the most common co-morbidity observed in patients from both the groups (49 in FDC; 76 in teicoplanin group) followed by chronic obstructive pulmonary disease (COPD) (31 in FDC; 41 in teicoplanin group), (24 in FDC; 31 in teicoplanin group), cirrhosis (25 in FDC; 24 in teicoplanin group), cancer (14 in FDC; 26 in teicoplanin group), chronic kidney disease (CKD) (12 in FDC; 20 in teicoplanin group) and least number of cases were observed with cerebrovascular diseases (08 in FDC; 09 in teicoplanin group) (Table 1).

3.2 Bacteriological Response

Out of total 314 SSTI cases, 26 / 128 (in FDC group) and 54 /186 (in Teicoplanin group) were found to have MIC in intermediate range of respective therapies. *Staphylococcus aureus* (*S. aureus*) was the predominant Gram positive pathogen in both the groups causing SSTIs (72 in FDC; 99 in teicoplanin group) followed by *Staphylococcus epidermidis* (*S. epidermidis*) (13 in FDC; 29 in teicoplanin group), *Streptococcus pyogenes* (14 in FDC; 22 in teicoplanin group), Glycopeptide Intermediate *S. aureus* (GISA) (06 in FDC; 18 in teicoplanin group) and the least number of patients had infections with Glycopeptide Resistant *S. aureus* (GRSA) (05 in FDC; 10 in teicoplanin group). Mixed culture infections were also significantly contributed to the SSTI infections (18 in FDC; 14 in teicoplanin group) (Table 1).

3.3 Clinical Response

Overall clinical response along with success among the subgroups is depicted in Table 2. Statistically significant difference was observed in overall clinical response among FDC and teicoplanin groups. Empirical FDC treatment with successful clinical response was observed in 102 (79.686%) patients out of 128 patients from FDC group. The mean treatment duration among these 102 patients was 7.64 days ± 0.69 (SD). For the remaining 26 patients, tigecycline additional cover was given to which 22 patients responded positively. The mean treatment duration for the 26 patients with tigecycline cover was 9.88 days ± 0.71 (SD). On the other hand, 132 patients out of 186 who were on teicoplanin empirically achieved clinical success with mean treatment duration 13.69 days ± 1.69 (SD). Out of the remaining 54 patients who were given tigecycline additional cover, only 37 patients achieved clinical success. The mean treatment duration for the 54 failure patients from teicoplanin group was 14.18 days ± 1.45 (SD).

Clinical response among the subgroups is depicted in Table 2. The clinical response in all the sub groups followed a similar pattern as that of a overall clinical response. Both the groups had lower cure rates in patients with higher APACHE II scores (FDC – 73.80%; teicoplanin – 63.49%) as compared to patients with APACHE II score of <15 (FDC – 82.55%; teicoplanin – 74.79%). FDC therapy had highest cure rates in cellulites (82.60%) followed by myositis (78.94%) and the least success was observed in necrotizing fasciitis (71.42%). However, teicoplanin had highest cure rates in myositis (72.54%), followed by almost similar cure rates for cellulites (70.21) and necrotizing fasciitis (70.73%). Even though, no noted difference among the groups was observed for *S. aureus*, *Streptococcus pyogens* and *S. epidermidis* caused SSTIs, significant differences were observed with GRSA and GISA caused SSTIs. Teicoplanin therapy failed completely in patients with GRSA and GISA infections where MIC values were ≥2 mcg/ml, where as FDC had a statistically significant higher clinical cure rates among GRSA (P value 0.0082) and GISA (P value 0.0018). SSTIs where MIC value was ≤8 mcg/ml. Co-morbidities did not have any

significant difference among the clinical cure rates of both the groups except diabetes mellitus where FDC showed higher clinical efficacy. Clinical success among the FDC group patients with tigecycline additional cover had higher cure rates as compared with that of teicoplanin + tigecycline group. The detailed clinical response in all the subgroups with tigecycline additional cover is given in Table 2.

3.4 Antibiotic Therapy Cost Analysis

The cost expenditure for the patients considered in the study is depicted in Table 3. The average cost of the empirical drug used to treat the patients in FDC group [11256.47 ± 1028.35 (SD)] was significantly lower (P<0.001; or 10449.59, 95% CI 9985.06 – 10914.11) as compared to the cost of teicoplanin group empirical drug [21706.06 ± 2202.07 (SD)]. Significant difference (P<0.001; or 60499.11, 95% CI 56982.86 – 64015.35) of cost towards hospitalization and overhead charges (diagnosis and instrumentations) was also observed. The average overall treatment charges for teicoplanin group [158675.75 ± 19141.09 (SD)] was significantly (P<0.001; or 70948, 95% CI 66968.28 – 74929.11) higher than that of FDC group charges [87727.08 ± 8014.49 (SD)]. Similar pattern of costs were observed for the patients cured with tigecycline additional cover antibiotic therapy. There was a considerable difference (P<0.001; or 24132.75, 95% CI 20725.52 – 27539.97) between the average cost of drugs in FDC group and teicoplanin group (42611.69 ± 3750.73 (SD) and 66744.44 ± 7418.70 (SD) respectively). The average overall treatment charges in the teicoplanin group [208596.29 ± 21965.19 (SD)] was (P<0.001; or 67138.45, 95% CI 57078.40 – 77198.49) higher than that of FDC group charges [14157.84 ± 10865.18 (SD)].

Table 1. Demographic characteristics of the patients treated during the study period

Characteristic	Treatment groups		P value
	FDC group	Teicoplanin group	
Evaluable patients (n)	128	186	
Sex ratio – male:female [*n* (%)]	79:49 (61.71%: 38.29%)	109:77 (58.60%: 41.40%)	0.5812
Age, mean year SD	62.56 ± 11.54	61.00 ± 10.05	0.2044
APACHE II score			
<15	86 (67.18%)	123 (66.12%)	0.8451
≥15	42 (32.82 %)	63 (33.88%)	0.8451
Type of SSTIs (%)			
Cellulitis	69 (53.90 %)	94 (50.53%)	0.5576
Myositis	38 (29.68 %)	51 (27.41%)	0.6614
Necrotizing Fasciitis	21 (16.40 %)	41 (22.04%)	0.2180
Causative pathogens			
S. aureus	72 (56.25%)	99 (53.22%)	0.5968
	(23 – 31.94%) *	(27 – 37.50%) *	0.4535
Streptococcus pyogenes	14 (10.93%)	22 (11.82%)	0.8081
S. epidermidis	13 (10.15%)	29 (15.59%)	0.1647
GRSA	05 (03.90%)	10 (05.37%)	0.5488
GISA	06 (04.68%)	12 (06.45%)	0.5079
Mixed cultures	18 (14.06%)	14 (07.52%)	0.0601
Comorbidities			
Diabetes mellitus	49 (38.28%)	76 (40.86%)	0.6468
Chronic obstructive pulmonary disease (COPD)	31 (24.21%)	41 (22.04%)	0.6536
Chronic kidney disease (CKD)	12 (09.37%)	20 (10.75%)	0.6916
Cardiovascular diseases	24 (18.75%)	31 (16.66%)	0.6326
Cirrhosis	25 (19.53%)	24 (12.90%)	0.1122
Cancer	14 (10.93%)	26 (13.97%)	0.4278
Cerebrovascular disease	08 (06.25%)	09 (04.83%)	0.5852

*Note: * MSRA isolates and their percentile share in total number of S. aureus isolates in the group*

Table 2. Clinical success rates among the treatment groups

Sub group	Success rate [no. of successes/total no. (%)] for:			
	FDC group		Teicoplanin group	
	FDC therapy	FDC + tigecycline add on therapy	Teicoplanin therapy	Teicoplanin + tigecycline add on therapy
Evaluable patients for efficacy analysis	128	26	186	54
Overall clinical success	124/128 (96.87)		169/186 (90.86)	
Treatment regime-wise	102/128 (79.68)	22/26 (84.61)	132/186 (70.96)	37/54 (68.51)
APACHE II score				
<15	71/86 (82.55)	14/15 (93.33)	92/123 (74.79)	25/31 (80.64)
≥15	31/42 (73.80)	08/11 (72.72)	40/43 (63.49)	12/23 (52.17)
Type of SSTIs (%)				
Cellulitis	57/69 (82.60)	10/12 (83.33)	66/94 (70.21)	19/28 (67.85)
Myositis	30/38 (78.94)	7/8 (87.50)	37/51 (72.54)	10/14 (71.42)
Necrotizing fasciitis	15/21 (71.42)	5/6 (83.33)	29/41 (70.73)	08/12 (66.66)
Causative pathogens				
S. aureus	60/72 (83.33)	11/12 (91.66)	81/99 (81.81)	14/18 (77.77)
Streptococcus pyogenes	10/14 (71.42)	03/04 (75.00)	16/22 (72.72)	05/06 (83.33)
S. epidermidis	10/13 (76.92)	03/03 (100.00)	26/29 (89.65)	03/03 (100.00)
GRSA	03/05 (60.00)	01/02 (50.00)	00/10 (00.00)	05/05 (50.00)
GISA	04/06 (66.66)	02/02 (100.00)	00/12 (00.00)	08/12 (66.66)
Mixed cultures	15/18 (83.33)	02/03 (66.66)	09/14 (64.28)	02/05 (40.00)
Comorbidities				
Diabetes mellitus	38/49 (77.55)	10/11 (90.90)	48/76 (63.15)	23/28 (82.14)
Chronic obstructive pulmonary disease (COPD)	24/31 (77.41)	06/07 (85.71)	25/41 (60.97)	14/16 (87.50)
Chronic kidney disease (CKD)	09/12 (75.00)	03/03 (100)	14/20 (70.00)	05/06 (83.33)
Cardiovascular diseases	19/24 (79.16)	04/05 (80.00)	22/31 (70.96)	06/09 (66.66)
Cirrhosis	18/25 (72.00)	05/07 (71.42)	18/24 (75.00)	03/06 (50.00)
Cancer	09/14 (64.28)	04/05 (80.00)	17/26 (65.38)	07/09 (77.77)
Cerebrovascular disease	06/08 (75.00)	02/02 (100.00)	07/09 (77.77)	01/02 (50.00)

4. DISCUSSION

Skin and soft-tissue infections (SSTIs) encompass a broad set of conditions encountered frequently in clinical practice [3]. Among Gram positive pathogens, *S. aureus* continues to cause SSTIs in the community as well as invasive infections in the hospitalized patients [26]. Because many episodes of SSTIs are not cultured, the most common causes of SSTIs in general remain uncertain, although *S. aureus* and betahemolytic *streptococci* (BHS) are often suggested as being the most important causes [1,27,28]. In a recent Europe-wide survey, the most common organisms in SSTIs were *S. aureus* (71% cases) with 22.5 per cent being MRSA [26]. The antibiotic treatment choice for SSTIs mainly depends on clinical presentation of the patients and the type of the pathogens causing the infection. In probable Gram-positive infection where MRSA is suspected, treatment may include b-lactam/glycopeptide combinations, fluoroquinolones with enhanced Gram-positive activity such as moxifloxacin, co-trimoxazole or tigecycline [27,29]. However, the mainstay of treatment for serious MRSA infections has been the glycopeptides vancomycin and teicoplanin [30,31]. The present study comparatively analyzes the case history sheets of 314 patients diagnosed with different SSTIs and treated with either FDC or teicoplanin empirically.

Table 3. Cost expenditure summary of treatment groups

	FDC treatment group	Teicoplanin treatment groups	Mean difference (95% CI for mean difference)
Summary of patients responded to empirical therapy therapy			
Number of patients cured with empirical therapy	102/128 (79.68%)	132/186 (70.96%)	8.72 % (1.5445 – 18.4044)
Mean treatment duration	7.64±0.69	13.69±1.69	6.0508* (5.6996 – 6.4004)
Average cost of drugs	11256.47±1028.35	21706.06±2202.07	10449.59* (9985.06 – 10914.11)
Average hospital and overhead charges	76470.58±6986.13	136969.69±16939.01	60499.11* (56982.86 – 64015.35)
Average overall treatment charges (Dugs + hospital and overhead charges)	87727.05±8014.49	158675.75±19141.09	70948.70* (66968.28 – 74929.11)
Summary of patients failed to respond to empirical therapy therapy			
Number of patients	22/26 (84.61%)	37/54 (68.51%)	16.1% (9.7936 – 36.9778)
Mean treatment duration	9.88±0.71	14.18±1.45	4.30* (3.6367 – 4.9633)
Average cost of drugs	42611.69±3750.73	66744.44±7418.70	24132.75* (20725.52 – 27539.97)
Average hospital and overhead charges	98846.15±7114.44	141851.85±14546.48	43005.70* (36352.74 – 49658.65)
Average overall treatment charges (Dugs + hospital and overhead charges)	141457.84±10865.18	208596.29±21965.19	67138.45* (57078.40 – 77198.49)

Note: 95% confidence intervals (CI) are included for the mean differences between the treatment groups.
** - Variables with a P value <0.05*

In present study, the results of the efficacy analysis for the antibiotics revealed that the clinical cure rates are in line with bacteriological findings. For MIC value of ≤ 8 mcg/ml FDC showed susceptibility and MIC values≥ 2 mcg/ml for teicoplanin were indicative of clinical failure of mono therapy with high probability of SSTI converting in sepsis irrespective of pathogen or use of higher drug concentrations. In teicoplanin group cure rate was 70.96% with 54 (29.04%) patients failing to respond to empirical teicoplanin therapy of which 17 patients showed complete treatment failure. Higher failure rates may be attributed to the emergence of teicoplanin resistant Gram positive pathogens including MRSA [32] and/ or members of Coagulase-Negative Staphylococci [33]. Further, the analysis of individual pathogen-wise clinical success rate which clearly demonstrates the inefficiency of teicoplanin to cure patients diagnosed with GRSA and GISA SSTIs. The resistance in GRSA arises intrinsically upon glycopeptide exposure, as the result of multiple mutations and/or alterations in gene expression [34-36], whereas the common GISA resistance features include cell wall thickening, decreased peptidoglycan crosslinking, decreased growth rate and hemolysis, alterations in rates of autolysis, and changes in the structure and/or abundance of cell wall teichoic acids [34,35,37-42].

On the other hand FDC therapy had better efficacy than teicoplanin with cure rates of 79.68%. The higher efficacies of FDC may be attributed to various mechanisms through which FDC target various resistance mechanisms in MRSA strains [21-25]. However, for the remaining 26 patients which did not respond to empiric FDC alone, had MIC values in intermediate range of which 22/26 (84.6%) were successfully cured with addition of tigecycline therapy. The use of FDC as an alternative to the vancomycin makes sense not only because of the proved and/ or proposed mechanisms by which it targets the resistant MRSA, hGISA, GRSA but also because of the lack of safe and efficacious alternative to glycopeptides.

Clinical failure is believed to be the strongest independent predictor of increased hospital costs. Compared to the ones treated

successfully, patients who failed to receive appropriate antibiotic therapy resulted in the increased antibiotic cost by failures. Cost expenditure analysis for FDC and teicoplanin empirical therapy revealed that, clinical failure resulted in significant increase in antibiotic expenditures. Previous reports have shown that hospitalization costs are 1.2 – 1.5 times higher in patients who have failed treatment compared with patients who were treated successfully [43,44]. The present study shows the substantial increase in the hospitalization costs in clinical failure cases in comparison with the patients who achieved clinical success. Average antibiotic costs for patients who achieved clinical success with empirical teicoplanin therapy was 92.83% more than that of FDC cured patients. Similar expenditure trends were observed for patients failed to respond to empirical therapies (cured with tigecycline additional cover) with teicoplanin group spending 56.63% more amount for drugs than that of FDC treated group. The overall treatment cost for successful patients treated with teicoplanin group was 80.87% more than that of FDC treated group. Similarly, the patients cured with tigecycline additional cover also resulted in 47.46% higher expenditure in teicoplanin group as compared to FDC group. Our results are in accordance with previous studies which have shown that antibiotics contribute up to 70% of extra costs associated with severe bacterial infections [44]. This large proportion of clinical failure costs deriving from antibiotic therapy most probably arises from the overlap existing between the failure of antibiotic therapy and clinical failure. Although clinical failure, a widely employed measure of drug effectiveness [44-48], in most instances it is driven by failure of first-line antibiotic therapy. The risk factors such as presence of autoimmune diseases, septic shock, and thrombocytopenia and infection due to MDR pathogen were responsible for un-favorable / failure outcomes in the study.

5. CONCLUSIONS

Empirical intravenous FDC therapy seems to be safe, well tolerated and has higher efficacy than teicoplanin in treatment of different SSTIs caused by Gram positive pathogens, especially infected with hGISA, GRSA and MRSA. This retrospective study also sheds light on pharmaco-economic benefit associated with right empiric choice of antibiotic therapy and its close association with microbiological findings.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA. Managing skin and soft tissue infections: Expert panel recommendations on key decision points. J Antimicrob Chemother. 2003;52(Suppl 1):i3–i17.
2. Rajan S. Skin and soft-tissue infections: Classifying and treating a spectrum. Cleve Clin J Med. 2012;79:57–66.
3. Barie PS, Wilson SE. Impact of evolving epidemiology on treatments for complicated skin and skin structure infections: The surgical perspective. J Am Coll Surg. 2015;220:105–16.
4. May AK. Skin and soft tissue infections: The new surgical infection society guidelines. Surg Infect. (Larchmt) 2011;12:179–84.
5. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections amongst patients in the emergency department. N Engl J Med. 2006;355(7):666–674.
6. European Center for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2009. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2010.
7. Gokulan P, Das Saroj, Joshi Meera. Diagnosis and management of cellulitis. BMJ. 2012;345:e4955.
8. Carstens PO, Schmidt J. Diagnosis, pathogenesis and treatment of myositis: Recent advances. Clin Exp Immunol. 2014;175:349–358.
9. Dalakas MC. Inflammatory muscle diseases: A critical review on pathogenesis and therapies. Curr Opin Pharmacol. 2010;10:1–7.
10. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. Front Surg. 2014;1:36.
11. Jafari SL, Wilson SE. Telavancin, a new lipoglycopeptide antimicrobial, in complicated skin and soft tissue infections. Infect Drug Resist. 2011;4:87–95.
12. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic

pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis. 1999;29:1171–1177.
13. Keith A. Rodvold, Kevin W. McConeghy. methicillin-resistant *Staphylococcus aureus* therapy: Past, present and future. Clin Infect Dis. 2014;58:S20–27.
14. Bodi M, Ardanuy C, Rello J. Impact of gram-positive resistance on outcome of nosocomial pneumonia. Crit Ical Care Med. 2001;29:82–86.
15. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest. 2003;124:1789–1797.
16. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Reports. 2007; 122:160-166.
17. Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. Lancet. 1997;350:1670–1673.
18. Ariza J, Pujol M, Cabo J, Pena C, Fernandez N, Linares J, et al. Vancomycin in surgical infections to methicillin-resistant *Staphylococcus aureus* with heterogenous resistance to vancomycin. Lancet. 1999; 353:1587–1588.
19. Sieradzki K, Villari P, Tomasz A. Low-level teicoplanin resistance and heteroresistance to vancomycin. Annals Inter Med. 1998;128:245.
20. Sieradzki K, Roberts RB, Haber SW, Tomasz A. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. The New Eng J Med. 1999;340: 517–523.
21. Chaudhary M, Payasi A. Inhibition of in vitro mecA gene transfer among Indian clinical isolates of *Staphylococus aureus*. The J Appl Biochem. Photon. 2013;106:133-139.
22. Chaudhary M, Patnaik SK, Payasi A. Evaluation of different drugs in down-regulation of efflux pumpgenes expression in methicillin-resistant *Staphylococcus aureus* strains. Amer J Infect Dis. 2014A;10:184-189.
23. Chaudhary M, Patnaik SK, Payasi A. Inhibition of panton-valentine leukocidin toxin induced neutrophil cell lysis by vancoplus in methicillin-resistant *Staphylococcus aureus* infections. Amer J Infect Dis. 2014B;10:154-163.
24. Chaudhary M, Payasi A. Taming wall teichoic acid multi drug resistance in gram positive pathogens. J Chem Pharmaceut Res. 2015A;7:18-23.
25. Chaudhary M, Payasi A. Vancoplus kinetic study in vancomycin resistant *Staphylococcus aureus*. Int J Pharmaceut Sci Rev Res. 2015B;31:135-142.
26. Sader HS, Farrell DJ, Jones RN. Antimicrobial susceptibility of Gram-positive cocci isolated from skin and skin-structure infections in European medical centres. Int J Antimicrob Agents. 2010;36:28-32.
27. Dryden MS. Skin and soft tissue infection: Microbiology and epidemiology. Int J Antimicrob Agents. 2009;34(Suppl 1):S2–7.
28. Vinh DC, Embil JM. Rapidly progressive soft tissue infections. Lancet Infect Dis. 2005;5:501–513.
29. Stevens DL, Bisno AL, Chambers H, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41:1373–406.
30. Awad SS, Elhabash SI, Lee L, et al. Increasing incidence of methicillin-resistant *Staphylococcus aureus* skin and soft-issue infections: Reconsideration of empiric antimicrobial therapy. Am J Surg. 2007;194:606–10.
31. Moise-Broder PA, Sakoulas G, Eliopoulos GM, et al. Accessory gene regulator group II polymorphism in methicillin- esistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. Clin Infect Dis. 2004;38:1700–5.
32. Cepeda J, Hayman S, Whitehouse T, et al. Teicoplanin resistance in methicillin-resistant *Staphylococcus aureus* in an intensive care unit. J Antimicrob Chemother. 2003;5:533–534.
33. Cremniter J, Slassi A, Quincampoix JC, et al. Decreased susceptibility to teicoplanin and vancomycin in coagulase-negative Staphylococci isolated from orthopedic-device-associated infections. J Clin Microbiol. 2010;48:1428-1431.

34. Sieradzki K, Leski T, Dick J, Borio L, Tomasz A. Evolution of a vancomycin-intermediate *Staphylococcus aureus* strain *in vivo*: Multiple changes in the antibiotic resistance phenotypes of a single lineage of methicillin-resistant *S. aureus* under the impact of antibiotics administered for chemotherapy. J Clin Microbiol. 2003A;41:1687–1693.
35. Sieradzki K, Tomasz A. Alterations of cell wall structure and metabolism accompany reduced susceptibility to vancomycin in an isogenic series of clinical isolates of *Staphylococcus aureus*. J Bacteriol. 2003B;185:7103–7110.
36. Singh VK, Schmidt JL, Jayaswal RK, Wilkinson BJ. Impact of sigB mutation on *Staphylococcus aureus* oxacillin and vancomycin resistance varies with parental background and method of assessment. Int. J Antimicrob Agents. 2003;21:256–261.
37. Boyle-Vavra S, Carey RB, Daum RS. Development of vancomycin and lysostaphin resistance in a methicillin-resistant *Staphylococcus aureus* isolate. J Antimicrob Chemother. 2001a;48:617–625.
38. Boyle-Vavra S, Challapalli M, Daum RS. Resistance to autolysis in vancomycin-selected *Staphylococcus aureus* isolates precedes vancomycin- intermediate resistance. Antimicrob Agents Chemother. 2003;47:2036–2039.
39. Boyle-Vavra S, Labischinski H, Ebert CC, Ehlert K, Daum RS. A spectrum of changes occurs in peptidoglycan composition of glycopeptide- intermediate clinical *Staphylococcus aureus* isolates. Antimicrob Agents Chemother. 2001B;45:280–287.
40. Cui L, Ma XX, Sato K, et al. Cell wall thickening is a common feature of vancomycin. J Clin Microbiol. 2003;41:5-14.
41. Peschel A, Vuong C, Otto M, Gotz F. The D-alanine residues of *Staphylococcus aureus* teichoic acids alter the susceptibility to vancomycin and the activity of autolytic enzymes. Antimicrob Agents Chemother. 2000;44:2845–2847.
42. Pfeltz RF, Singh VK, Schmidt JL, Batten MA, Baranyk CS, Nadakavukare MJ, et al. Characterization of passage-selected vancomycin-resistant *Staphylococcus aureus* strains of diverse parental backgrounds. Antimicrob Agents Chemother. 2000;44:294–303.
43. Cattan P, Yin DD, Sarfati E, Lyu R, De Zelicourt M, Fagnani F. Cost of care for inpatients with community-acquired intra-abdominal infections. Eur J Clin Microbiol Infect Dis. 2002;21:787-93.
44. Sturkenboom MC, Goettsch WG, Picelli G, int't Veld B, Yin DD, de Jong RB, et al. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. Br J Clin Pharmacol. 2005;60:438-43.
45. Krobot K, Yin D, Zhang Q, Sen S, Altendorf-Hofmann A, Scheele J, et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community acquired intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis. 2004;23:682-7.
46. Reygaert WC. Antibiotic optimization in the difficult-to-treat patient with complicated intra-abdominal or complicated skin and skin structure infections: Focus on tigecycline. Ther Clin Risk Manag. 2010;6:419-30.
47. Edelsberg J, Berger A, Schell S, Mallick R, Kuznik A, Oster G. Economic consequences of failure of initial antibiotic therapy in hospitalized adults with complicated intra-abdominal infections. Surg Infect. 2008;9:335-47.
48. Dalfino L, Bruno F, Colizza S, Concia E, Novelli A, Rebecchi F, et al. Cost of care and antibiotic prescribing attitudes for community-acquired complicated intra-abdominal infections in Italy: A retrospective study. World J Emerg Surg. 2014;9:39.

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