Management of CNS and VAP Infections with a New Ready to use Combination: A Retrospective Study

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ABSTRACT

Introduction: The present retrospective study was aimed to analyze the efficacy of ready to use combination (RTUC) of (ceftriaxone + vancomycin) along with metronidazole compared to other drug combinations for management of ICU patients suffering from post-operative central nervous system (POCNS) and ventilator associated pneumonia (VAP) infections due to multi-drug resistant (MDR) gram-positive bacteria.

Material and Methods: This study analyzed the data of 208 patients treated at a tertiary-care hospital. Patient demographic characteristics, infection type, co-morbidities, antibiotic therapy, dosage, treatment duration have been studied. Microbiological success was measured in terms of bacterial eradication, while clinical success was monitored in terms of complete omission of systemic signs and symptoms.

Results: Among 208 patients analyzed, 150 cases were found to be suffering from POCNS infections and 58 patients were of VAP. Out of these 208 patients, 79 cases were treated with empirical use of Meropenem-Vancomycin (MER-VAN), 55 cases were treated with empirical use of Piperacillin Tazobactam-Tigecycline (PTZ-TIG) and the remaining 74 cases were treated with empirical use of Ready to Use Combination of Vancomycin and Ceftriaxone along with Metronidazole (RTUC-Metro). The clinical cure rates reported in MER-VAN, PTZ-TIG and RTUC-Metro groups were 77.2%, 72.7%, and 81.1% respectively.

Conclusion: Infections with MDR gram-positive bacteria are frequent in ICU patients and the current study demonstrates that RTUC in combination with metronidazole has comparatively equivalent efficacy to MER-VAN and better than PTZ-TIG combinations. The results of this retrospective study favors the use of RTUC as a safer alternative to any other available drugs to treat ICU patients with infections caused due to MDR gram-positive bacteria. However more data from other centers on different indications needs to collected in favor of this new combination.

Keywords: MRSA, Intensive Care Units, Post-Operative CNS Infections, VAP, Multi-Drug Resistant.

INTRODUCTION

The development of resistance to antimicrobial agents has been an ongoing and evolving process since antibiotics were introduced a half-century ago. Anti-microbial resistant pathogens are becoming a prevalent cause of hospital-acquired infections, particularly in Intensive Care Units (ICU).[1,2] Severity of infections in critically-ill patients increases with rise in antibiotic resistance and pose a major health care challenge to treating physician. Such cases are reported to have higher morbidity and mortality in the ICUs.[3] Among others, POCNS and VAP infections are dreadful and necessitate immediate and effective medical intervention. Post-operative CNS infections include epidural abscess, subdural empyema, cerebral abscess, meningitis, and extra-axial infections. Over the past 30 years, the advent of different diagnostic imaging modalities, prolonged patient life span, and increased prevalence of solid organ transplantation have contributed to the increasing number of wound infections after intracranial neurosurgery.[4] VAP is a common infection that occurs 48 hours after intubation and mechanical ventilation and occurs in 8-38% of patients undergoing mechanical ventilation.[5] The incidence of pneumonia is known to be higher in ICU patients than in general ward patients, and even several folds higher in patients undergoing mechanical ventilation.[6-9] In addition, the mortality of VAP has been reported to be higher among all hospital-acquired infections.[10]

The microbiology in the ICU has changed in the last 2 to 3 decades with gram-positive bacteria now representing one of the dominant species in some centres in India like west. A recent survey on gram positive infections showed *Staphylococcus aureus (S. aureus)* (16%) being the most predominating causative pathogen.[11] *S. aureus* is the major gram-positive bacteria responsible for POCNS infections and VAP.[12,13] The major concern with this predominant pathogen is the increasing emergence of methicillin resistant *Staphylococcus aureus* (MRSA) strain. More than 50% of nosocomial infections are reported to be caused by MRSA, leading to increase in ICU length of stay, post operational complications, and mortality.[14] Hence, it is very essential to rightly assess infection type and start with appropriate antimicrobial therapy empirically. However, there are only few therapeutic options for the treatment of patients with MRSA infections. The only antibiotic therapy available for the treatment of MRSA sepsis is intravenous vancomycin therapy as all other antimicrobials including the fluoroquinolones and third generation cephalosporins are reported to be ineffective against MRSA.[15]

Unfortunately, the cure rate for vancomycin has been disappointing.[16] Oxazolidinone (Linezolid) is an alternate antibiotic therapy in vancomycin-resistant cases especially having impaired renal function or poor intravenous access. However, Linezolid treatment is associated with severe adverse events including thrombocytopenia and myelosuppression.[17] Considering these clinical challenges, necessity was felt to find alternative effective empirical solutions for management

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of MRSA infections and/or mixed infections. Thus, the present retrospective study was planned to analyze the best performing therapies in patients suffering with CNS and VAP infections in ICU who were treated with different antibiotic combinations between period of 2012 to 2015.

MATERIAL AND METHODS

This retrospective, observational study has been conducted at tertiary care hospital in north India. The data of patients suffering from different POCNS or VAP infections who were treated between September 2012 to February 2015 were collected and analyzed for the antibiotic regimes used, microbiological outcome and clinical outcomes of the therapy.

Patient selection and treatment regime

Case history sheets of all the patients were reviewed and relevant information like patient age, gender, co-morbidities, culture identification tests, antibiotic therapy, dose and duration and length of the hospital stay were recorded. All the patients who were suffering from POCNS infections and VAP and were managed with antibiotic regime consisting either of intravenous Meropenem- Vancomycin (MER-VAN) or Piperacillin Tazobactam-Tigecycline (PTZ-TIG) or RTUC- Metro (RTUC-Metro) were included in the study. The patients who were cured with more than 2 therapies or who were given the above drugs for a period of less than 3 days were excluded from the study. Among 270 case sheets analyzed, 208 subjects fulfilled the above-mentioned inclusion criteria and were included in the analysis.

Initial antibiotic treatment

For better presentation and easy understanding, the patients analyzed retrospectively were broadly divided in to three groups: MER-VAN group [79 (37.98%)] – patients to whom Meropenem- Vancomycin was administered empirically as first line of therapy, PTZ-TIG group [55 (26.44%)] – patients in whom Piperacillin Tazobactam- Tigecycline were given as first line of therapy and third RTUC-Metro group [74 (35.57)]- patients to whom RTUC- Metro was administered. The progress of the therapy was measured in terms of clinical improvement in signs and symptoms. After the initial assessment (after 5 days) of the clinical progress (signs of improvement), the decision on whether to consider the shift of therapy was taken. The patients from the three groups, showing improvement with the ongoing therapy were continued with the same regime and the patients who failed to show any improvement (deteriorated) were shifted to next line of therapy. However, such patients who were shifted to other drug regimens (other than three considered in study) were considered as clinical failures and were excluded from the study.

Dosage of antibiotic

The dosages for the antibiotic combinations used to manage the infections were as follows. Meropenem: 2g/8 hrs; Vancomycin: 1g/12 hrs; piperacillin tazobactam: 4.5g/8 hrs; Tigecycline: an initial loading doses of 100 mg followed a maintenance dose of 50 mg/12 hrs; RTUC: 3g /12 hrs, whereas for metronidazole, 500 mg/8 hrs was used (Figure-1).

Microbial evaluations

Culture reports of the patients were assessed at the baseline and at the end of the therapy. Minimum inhibitory concentrations (MICs) and antimicrobial susceptibility of test antibiotics were determined in accordance to Clinical and Laboratory Standards Institute (CLSI) (2012).[18] Assessment of microbiological response at patient level was based on the results of the pre-therapy isolation and identification of isolates, susceptibilities of the isolated pathogens and clinical outcome of the patients. The microbiological response was considered satisfactory/ success when the original causative pathogen was completely eradicated or presumed to be eradicated (i.e. when further

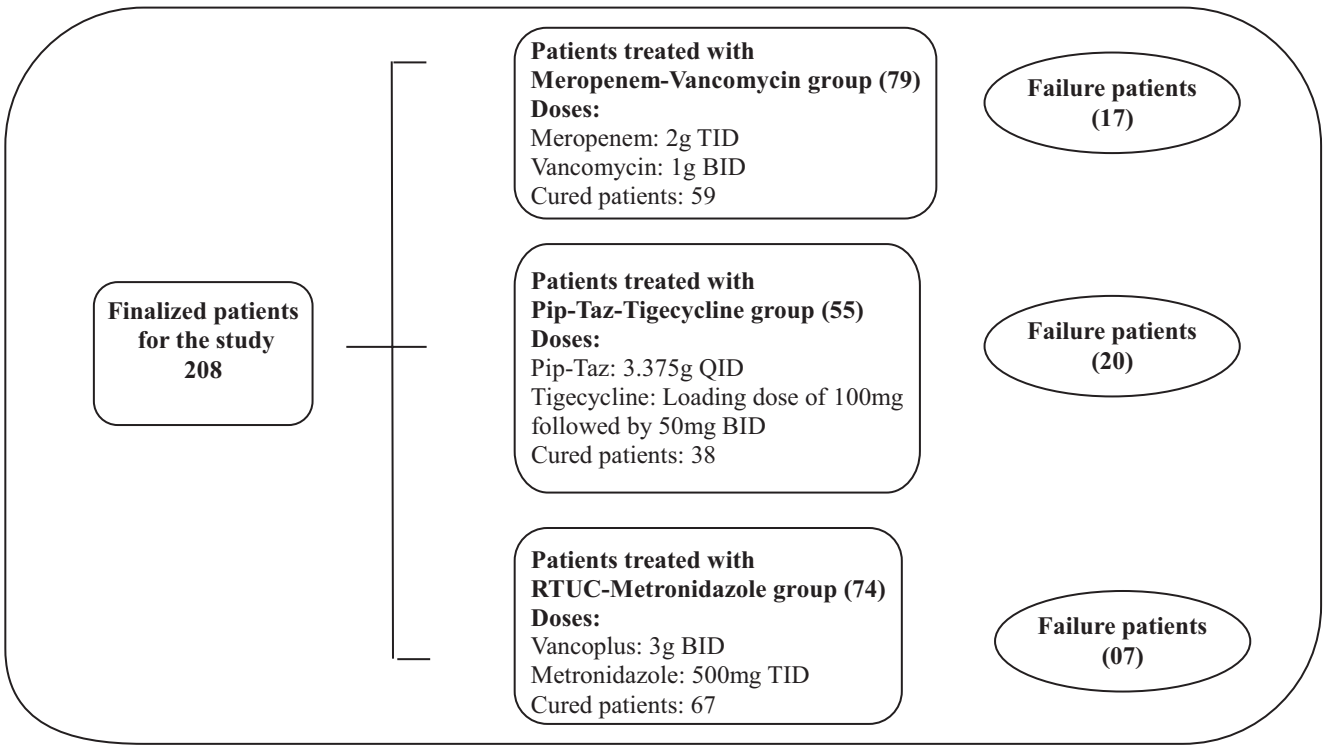

Figure-1: Schematic representation of the study design.

sampling for culture was not considered significant because of clinical cure/improvement). The response was considered unsuccessful/failure if the diagnosed pathogen persisted or a new pathogen was isolated from the original site of infection during the study (super-infection).

Clinical evaluations

The patient's response was considered as clinical success when, the patient recovered with either first line of antibiotic therapy or in view of clinical improvement, antibiotics were step down from the initial therapy i.e. instead of two antibiotics only one was continued and other antibiotics was stopped.[19]

An individual case was defined as clinical failure when either the ongoing treatment failed and additional antibiotics were used for management or in case of patient death.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the statistical analysis. Descriptive statistics like mean and percentages were used for the statistical analysis.

RESULTS

Demographic and clinical characteristics of subjects

Out of 270 ICU patients considered for the retrospective analysis, 208 patients confirmed with POCNS and VAP infections, and meeting all inclusion criteria were analyzed (Figure-1). The baseline and demographic characteristics of the three group of patients who were treated with MER-VAN (n=79), PTZ-TIG (n=55) or RTUC-Metro (n=74) empirically are given in (Table-1). Most of the baseline characteristics of the patients from all the treatment groups were comparable. Male population was more in all the groups with male: female ratio of 47:32, 34:21 and 46:28. The mean age of patients in MER-VAN, PTZ-TIG and RTUC-Metro groups were 61.27± 12.63, 62.50 ± 13.59 and 62.31 ± 11.97 respectively. The analysis of the disease severity data measured in terms of APACHE II score revealed that majority of patients in all the groups were having a score of <15. 54 (68.35%) of MER-VAN group were having APACHE II score of <15, 36 (65.45%) patient of PTZ-TIG group and 52 (70.27%) from RTUC-Metro group were having the severity score of <15.

There were 150 cases of neuro-surgical infections (57 in MER-VAN; 38 in PTZ-TIG; 55 in RTUC-Metro) and 58 cases of VAP infections (22 in MER-VAN; 17 in PTZ-TIG; 19 in RTUC-Metro). Chronic obstructive pulmonary disease (COPD) was the most common co-morbidity observed in patients from all the groups (28 in MER-VAN; 21 in PTZ-TIG; 31 in RTUC-Metro group) followed by Diabetes mellitus (24; 17; 30), Cardiovascular diseases (25; 20; 25), cancer (13; 15; 23), chronic kidney disease (14; 12; 17) and least number of cases were observed with cirrhosis (04;04;07) (Table-1).

The most predominant gram-positive pathogen in all the three groups was MRSA (21 in MER-VAN; 17 in PTZ-TIG; 28 in RTUC-Metro) followed by *streptococcus s pneumoniae* (16; 12; 13), *Staphylococcus aureus* (12; 10; 10), Glycopeptide intermediate *S. aureus* (GISA) and/ or Glycopeptide resistant *S. aureus* (GRSA) (10; 09; 12), mixed pathogens contributed to 14 in MER-VAN, 06 in PTZ-TIG; 10 in RTUC-Metro group and other gram positive pathogens contributed to the least number

Characteristic	Data of patients who received		
	Mero-Van Group	PTZ-TIG Group	RTUC-Metro Group
Studied patients	79	55	74
Sex ratio – male: female [n (%)]	47:32 (59.49%: 40.50%)	34:21 (61.81%: 38.18%)	46:28 (62.12%: 37.83%)
Age, mean year SD	61.27 ± 12.63	62.50 ± 13.59	62.31 ± 11.97
APACHE II score			
<15	54 (68.35%)	36 (65.45%)	52 (70.27%)
≥15	25 (31.65%)	19 (34.55%)	22 (29.73%)
Prior antibiotic use	75 (94.93%)	52 (94.54%)	71 (95.94%)
Types of infections			
Postoperative central nervous system infections			
Epidural/ subdural abscess	20 (25.31%)	14 (25.45%)	21 (28.37%)
Brain abscess	19 (24.05%)	10 (18.18%)	16 (21.62%)
Bacterial Meningitis	18 (22.78%)	14 (25.45%)	18 (24.32%)
Ventilator associated pneumonia	22 (27.84%)	17 (30.90%)	19 (25.67%)
Co-morbidities			
Diabetes mellitus	24 (34.78%)	17 (30.90%)	30 (40.54%)
Chronic obstructive pulmonary disease (COPD)	28 (40.57%)	21 (38.18%)	31 (41.89%)
Chronic kidney disease (CKD)	14 (20.28%)	12 (21.81%)	17 (22.97%)
Cardiovascular diseases	25 (36.23%)	20 (36.36%)	25 (33.78%)
Cirrhosis	04 (05.79%)	04 (7.27%)	07 (09.45%)
Cancer	13 (18.84%)	15 (27.27%)	23 (31.08%)
Causative pathogens			
S.aureus	12 (15.18%)	10 (18.18%)	10 (13.51%)
MRSA	21 (26.58%)	17 (30.90%)	19 (37.83%)
S. pneumoniae	16 (20.25%)	12 (21.81%)	13 (17.56%)
GRSA/GISA	10 (12.65%)	09 (16.36%)	12 (16.21%)
Other Gram positive pathogens	06 (7.59%)	04 (07.27%)	05 (06.75%)
Mixed cultures	14 (17.7%)	6 (10.90%)	10 (13.51%)

Table-1: Demographic and clinical features of ICU patients managed with different antibiotic combinations.

of cases (06; 02; 01) (Table-1).

Clinical response

The clinical response among the subgroups is summarized in (Table-2). Overall clinical success among the patients treated in MER-VAN, PTZ-TIG and RTUC-Metro was comparable. However, highest clinical success with and cure rate (81.1%) was observed in RTUC-Metro-group followed by MER-VAN (77.2%) and PTZ-TIG (72.7%). Further sub-group analysis (table 2) has shown that the clinical response in all the sub groups followed a similar pattern. All the treatment groups had lower cure rates in patients with higher APACHE II scores (≥15) (80.00%-MER-VAN; 63.15%-PTZ-TIG; 86.36%-RTUC-Metro) as compared to patients with APACHE II score of <15 (87.03%- MER-VAN; 72.22%-PTZ-TIG; 92.30%-RTUC-Metro-group). Even though RTUC-Metro therapy has comparatively slightly higher cure rates compared to other two regimes, there is no marked difference between the cure rates of patients with varying APACHE II scores. In line with the overall clinical response, the clinical cure rates among patients with different infections in MER-VAN, PTZ-TIG and RTUC-Metro groups were comparable. However, careful evaluation of the data-sheets revealed that, RTUC-Metro group proved to have higher clinical cure rates in all infection types.

Similarly, RTUC-Metro combination was effective treatment against all the causative pathogens. The highest cure rate was observed in patients infected with *S.aureus* and other gram-positive bacteria (100%), followed by *S. pneumoniae* (92.30%), MRSA (89.28%) and the least with GISA/GRSA and mixed culture infections (83.33%). An important point to note here is the competitively higher clinical cure rates among MRSA and GRSA/GISA patients treated with RTUC-Metro therapy. Co-morbidities did not have any significant influence on the clinical cure rates among the different empirical therapy groups. However, in line with the overall therapy, cure rates with RTUC-Metro therapy was comparatively high among all the co-morbidity groups. The detailed clinical response in all the subgroups is given in (Table-2).

DISCUSSION

The ICU often is called the epicentre of infections, due to its extremely vulnerable population (reduced host defences deregulating the immune responses) and increased risk of becoming infected through multiple procedures and use of invasive devices distorting the anatomical integrity-protective barriers of patients (intubation, mechanical ventilation, vascular access, etc.). Among all others, VAP and POCNS in patients undergoing neurosurgical procedures represents a serious problem that requires immediate attention.[12,20,21] The present retrospective study analysed the clinical data sheets of 270 patients with VAP or POCNS bacterial infections managed in ICUs.

Review of the literature indicates a consistent source for POCNS. Pathogens identified in gram-positive are cocci, specifically *Staphylococcus aureus*, *Staphylococcus epidermidis,* and β-hemolytic *Streptococc* us with *S aureus* being the most common organism[13,22-24] whereas the common causative pathogens of gram-negative bacteria such as *P. aeruginosa, E. coli, S. pneumonia*e, and *Acinetobacter* species.[25-27] In agreement to these reports, the present study revealed that gram-

Characteristic	Data for patients who received		
	MER-VAN Group	PTZ-TIG Group	RTUC-Metro Group
Total studied patients	79	55	74
Overall clinical success	61 (77.2%)	40 (72.7%)	60 (81.1%)
APACHE II score			
<15	47/54 (87.03%)	26/36 (72.22%)	48/52 (92.30%)
≥15	20/25 (80.00%)	12/19 (63.15%)	19/22 (86.36%)
Prior antibiotic use	64/75 (85.33%)	35/52 (67.30%)	64/71 (90.14%)
Types of infections			
Postoperative central nervous system infections			
Epidural/ subdural abscess	17/20 (85.00%)	09/14 (64.28%)	18/21 (85.71%)
Brain abscess	17/19 (89.47%)	07/10 (70.00%)	15/16 (93.75%)
Bacterial Meningitis	16/18 (88.88%)	10/14 (71.42%)	16/18 (88.88%)
Ventilator associated pneumonia	19/22 (89.47%)	12/17 (70.58%)	18/19 (94.73%)
Co-morbidities			
Diabetes mellitus	18/24 (75.00%)	10/17 (58.82%)	26/30 (86.66%)
Chronic obstructive pulmonary disease (COPD)	24/28 (85.71%)	16/76.19 (38.18%)	28/31 (90.32%)
Chronic kidney disease (CKD)	11/14 (78.57%)	07/12 (58.33%)	15/17 (88.23%)
Cardiovascular diseases	20/25 (80.00%)	13/20 (65.00%)	21/25 (84.00%)
Cirrhosis	01/04 (75.00%)	02/04 (50.00%)	06/07 (85.71%)
Cancer	10/13 (76.92%)	10/15 (66.66%)	20/23 (86.95%)
Causative pathogens			
S. aureus (MSSA)	12/12 (100.00%)	09/10 (90.00%)	10/10 (100.00%)
MRSA	16/21 (76.19%)	09/17 (52.94%)	25/28 (89.28%)
S. pneumonia	15/16 (93.75%)	10/12 (83.33%)	12/13 (92.30%)
GRSA/GISA	06/10 (60.00%)	05/09 (55.55%)	10/12 (83.33%)
Other Gram positive pathogens	06/06 (100.00%)	03/04 (75.00%)	05/05 (100.00%)
Mixed cultures	04/04 (100.00%)	02/03 (66.66%)	05/06 (83.33%)

Table-2: Clinical cure rates among the sub-groups.

positive bacteria are on rise and is becoming the main causative pathogens isolated from ICU patients suffering with POCNS or VAP infections even in India. Furthermore, among gram-positive bacteria, *S. aureus* (methicillin susceptible *S. aureus* and/or methicillin resistant *S. aureus*) was the most common causative pathogen causing about 47.11% of the infections. Erman et al. (2005)[28] has also reported *S. aureus* to be the most predominant causative agent in POCNS and VAP infections.

The antibiotic treatment of choice indicated for gram-positive infections, where MRSA is not suspected, are penicillins, anti-staphylococcal penicillins, cephalosporins, clindamycin or co-trimoxazole.[29] However, in India where infection is likely to be polymicrobial, treatment with broad range anti-bacterial is recommended. Such treatment may include beta-lactam/ beta-lactamase inhibitor combinations, fluoroquinolones with enhanced gram-positive activity such as moxifloxacin, co-trimoxazole or tigecycline.[30-32] However, the mainstay of treatment for serious MRSA infections has been the glycopeptides, vancomycin and teicoplanin.[33,34] In cases of infections with MDR strains, different combinations of antibiotic regimes are used as demonstrated in the present study. The results of the efficacy analysis for the antibiotics revealed that the clinical cure rate among PTZ-TIG group was 72.7% with 27.3% (15) patients failing to respond to the therapy. Higher failure rates may be attributed to the rise in emergence of tigecycline-resistant gram positive pathogens including MRSA and/ or other members.[35,36] Another major concern with the use of tigecycline in critically ill patients must do with the current dosing which is half of the originally planned dosing. This change was made due to perceived unacceptable nausea and emesis at the higher dose. Several meta-analyses have found the incidence of death to be greater for tigecycline compared to the comparator antibiotics possibly because of dosing issue. The high incidence of death is reported to be most evident in nosocomial pneumonia studies.[37-39] Though, overall clinical cure rate among MER-VAN group was on higher side (77.2%), analysis of individual pathogen-wise clinical success rate revealed significantly low cure rates among patients diagnosed with MRSA, GRSA and GISA infections. The resistance in GRSA arises intrinsically upon glycopeptide exposure, as the result of multiple mutations and/or alterations in gene expression.[40,41] 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.[40-43] The incidences of clinical failures among the discussed drug combinations in developing nations like India hold significance as the incidence of MDR infections are less well-described in critically ill patients in the developing world.[44]

RTUC therapy had higher efficacy than the other two tested drug combinations with cure rates of 81.1%. The higher efficacy of RTUC may be attributed to various mechanisms through which RTUC combats various resistance mechanisms in MRSA strains and other pathogens.[41,45-47] Patients who failed to show response to MER-VAN (n=18) and PTZ-TIG (n=15) groups were shifted to RTUC-Metro and out these 20 (10 from MER-VAN and 10 from PTZ-TIG) patients failed and remaining were cured with RTUC-Metro. In RTUC-Metro group, 7 patients failed to achieve clinical success. Thus, the use of RTUC along with metronidazole appears a good alternative to the existing antimicrobial therapies and makes sense not only because of the proved and/ or proposed mechanisms by which it targets the resistant MRSA, but also because of the lack of safe and efficacious alternative to these therapies.

CONCLUSION

The intravenous RTUC-Metro therapy seems to be safe, well tolerated and has higher efficacy than the other tested drug combinations in management of ICU patients with different infections caused by gram positive pathogens and mixed pathogens with least mortality and failure rate.

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