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Original Article

Epidemiology and clinical outcomes of monomicrobial carbapenem-resistant *Enterobacteriaceae* (CRE) from a metropolitan area of Kerala, India

Sanjeev K Singh[1], Sangita Sudhir[1], Vidya Menon[2], Anup R Warrier[3], Arya R V[4], Fabia Edathadathil[1], Dipu T Sathyapalan[1], Sivaprasad PS[4], Sabu Thomas[5]

[1] Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, India -682041
[2] New York City Health and Hospitals/Lincoln, New York City, New York 10451, United States
[3] Aster Medcity, Kochi, Kerala – 682027, India
[4] Ernakulam General Hospital, Kochi, Kerala - 682011, India
[5] Sabu Thomas, Rajiv Gandhi Centre for Biotechnology, Trivandrum, Kerala – 695 014, India

Abstract

Introduction: The emergence of Carbapenem-resistant *Enterobacteriaceae* (CRE) is a major public health threat in India posing challenges in infection management. Our study aims to address the regional incidence of monomicrobial CRE in a metropolitan area of Kerala and characterize prescriptions in relation to clinical management.

Methodology: The multicentre, prospective observational study was conducted in secondary and tertiary care centres jointly following public-private partnership model in Ernakulam district of Kerala, India from October 2018 to October 2019.

Results: The overall incidence of monomicrobial CRE-positive cases from the study hospital network was found to be 0.855 per 1000 patient-days. Among the available data in the cohort, 77 % (312/405) were observed to attain clinical cure and in-hospital all-cause mortality was at 20% (83/410). The proportion of patients with clinical cure to treatment was found to be significantly higher than clinical failure among patients with urinary tract infections ($p < 0.001$, OR 2.88, 95% CI 1.73 – 4.79) and pneumonia ($p < 0.001$, OR 0.36, 95% CI 0.21 - 0.6) at 87% and 61% respectively in comparison to other infections. The prevalence of colistin resistance among the total number of patients recruited with isolated monomicrobial CRE was found to be at 3%.

Conclusions: Our prospective study on the regional epidemiology of monomicrobial CRE has revealed notable incidence and all-cause mortality. The antimicrobial regimens for clinical management detailed in the study and the assessment of focus of infection-based clinical cure status rates indicate the need of optimized antimicrobial therapy to improve treatment practices in CRE infections.

Key words: Carbapenem-resistant *Enterobacteriaceae* (CRE); antimicrobial resistance (AMR); colistin resistance.

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Introduction

The emergence of Carbapenem-resistant Enterobacteriaceae (CRE) is a major public health concern since it was first identified in 1990. As per the CDC data, around 13,000 patients admitted in US health care setting was isolated with CRE between 2013 and 2017. Out of which, there was 1100 deaths and the estimated health care cost was around $130 million [1].

Recent ICMR (Indian Council of Medical Research) report in India has noted an increase in resistance to Imipenem among Escherichia coli from 14% in 2016 to 36% in 2021 [2]. With high population density, India is one of the major countries with high antibiotic consumption with an estimated rise of 39% in the last decade as per CDDEP – World Antibiotic report 2021 [3]. Furthermore, the demonstrated non-judicious antimicrobial prescription practices in the country further act as a favourable breeding ground for the emergence of CRE and its various phenotypic variants [4]. The lack of phenotypic identification as part of routine antimicrobial susceptibility testing among healthcare sectors poses challenges in optimizing antimicrobial therapy to appropriately target the CRE type and contain the infection [5]. Studies demonstrated New Delhi metallo-β–lactamase (NDM) and coproduction of NDM with Oxacillinase-48 like (OXA-48–like) enzymes are the most predominant mechanisms of CRE infections in India [6,7]. Hence, with the increased incidence of infection due to CRE, consumption of polymyxins is increasing. Inappropriate use of last-line antibiotics being the major driving factors for emergence of resistance, becomes imperative to understand the pattern of antimicrobial prescription in CRE infections [8]. Moreover, there are

no adequate CPE (Carbapenemase-Producing Enterobacterales) screenings or comprehensive and mandatory CRE monitoring or surveillance networks. The inadequate Infection Prevention and Control practices focusing on the containment of CRE including immediate alerting system, contact isolation practices are uncommon in India [9,10]. Numerous studies in India have reported the prevalence of CRE in tertiary care centres, however there is a dearth of regional data in this respect from Kerala [11-13]. A study among sepsis patients identified hospital stay and antibiotic exposure as significant risk factors [14]. This study aims to address the regional incidence of CRE in a metropolitan area of Kerala and to characterize antimicrobial prescriptions in relation to clinical management.

Methodology

Study design and setting

The multicentre, prospective observational study was conducted in the district of Ernakulam, Kerala, India at private super specialty quaternary care centres comprising of 1300-bedded Amrita Institute of Medical Sciences and 670-bedded Aster DM Healthcare, as well as at 783-bedded General Hospital, a state owned – public health hospital by Government of Kerala. Ethical approval for this study was taken from the Institutional Ethics Committee at Amrita Institute of Medical Sciences, with due permission from Health &Family Welfare Department, Government of Kerala for the conduct of the study in public hospital.

Study population

In the study, all the patients with culture positivity to Carbapenem-resistant *Klebsiella* species and *E coli* from anybody fluid (blood, urine, ascetic fluid, pus, BAL) were selected from each healthcare centre of the study during the time period from October 2018 to October 2019. Patients with polymicrobial infections, post solid organ/bone marrow transplantation and pregnant women were excluded.

Methodology

A single site of the hospital network involved in the study served as a data repository centre for case review, data collation and processing. The workflow from one of the study sites included an alert system wherein the microbiologist notified the clinical pharmacist upon isolation of a CRE from any body fluids. Patient identifiers were shared through an email and clinical pharmacist reviewed cases. The clinical data of patients whose specimens were isolated with carbapenem-resistant *Klebsiella* species and *E. coli* were reviewed through patient medical charts and electronic health records.

Baseline demographic characteristics, SOFA (Sequential Organ Failure Assessment) score at diagnosis of carbapenem-resistant bacterial infection, Charlson's comorbidity index, the details of common site of infections including pneumonia, bloodstream infection, urine, skin and soft tissue infections, meningitis, and sepsis were captured. The therapy/regimen for treatment of the infection was at the discretion of primary care physician. Characteristics of treatment including choice of drug, single or combination therapy, and antibiotic prescriptions according to culture, and susceptibility were reviewed. The patients were followed up for clinical cure status (clinical cure and failure) and in hospital all-cause mortality (Supplementary Table 1). Complex medical cases were reviewed with Infectious Disease physicians of the hospital Antimicrobial Stewardship team.

Microbiological studies

All the isolates which were reported as "colistin-resistant" on the automated AST system were analyzed by broth micro dilution (BMD) method as per CLSI M07 A-9 to confirm colistin resistance [15]. In brief, pure bacterial culture inoculum and recommended twofold dilutions of antibiotic stock solution were added to untreated 96-well polystyrene microwell-plates containing cation-adjusted Mueller Hinton Broth and incubated overnight at 37 °C. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *E. coli* NCTC 13846 were used as quality control strains. Colistin susceptibility for *Enterobacteriaceae* was interpreted using EUCAST 2018 breakpoints (susceptible $\leq$ 2mg/L, resistant > 2mg/L) [16].

Statistical analysis

Based on normality of distribution, continuous variables were analyzed for its association with outcomes by student-t test or Mann-Whitney U test and Chi-square test was used for categorical variables. Significant variables at $p < 0.15$ from univariate analysis was utilized for multivariate binary logistic regression analysis. IBM SPSS Statistics for Windows, version 28.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analysis. A $p < 0.05$ was considered to be significant.

Results

Among a total of 449 patients with CRE positive culture specimens included from the 3 study sites

during the study period, 464 monomicrobial cultures were isolated. The overall incidence of monomicrobial CRE positive cases from the study hospital network was found to be 0.855 per 1000 patient-days with individual CRE incidence rates at the 3 study sites estimated to be ranging between 0.827 – 1.314 per 1000 patient-days.

Demographic and epidemiological characteristics

Demographic details of the patients and clinical profile are depicted in the Table 1. Of the 449 patients recruited based on the inclusion criteria, 199 (44%) patients belonged to the age group of 61-80 years followed by 153 (34%) patients in the age group of 41-60 years. Patients in the medical specialties 256 (60%) were isolated with more CRE compared to surgical specialties 171 (40%). Similarly, the prevalence of CRE was more in ward when compared to ICU. Among the common sources of infection among the cohort, 199 (44%) were diagnosed with Urinary Tract Infections followed by 127 (28%) patients with skin and soft tissue infections and 92 patients with pneumonia (20%). Out of the 2 organisms focused, *Klebsiella* sp. were more common 356 (79%). None of the hospitals had a CRE surveillance and screening being carried out on admission as part of the Infection Prevention and Control Practices.

Table 1. Baseline characteristics of cohort.

Baseline characteristics of cohort	n (%)
Number of patients recruited with monomicrobial CRE cultures	449
Age distribution (N- 449)	
< 18 years	18 (4%)
18-40	44 (10%)
41-60	153 (34%)
61-80	199 (44%)
> 80	35 (8%)
Department (N- 427)	
Medical	256 (60%)
Surgical	171 (40%)
Location during infection (N- 449)	
ICU	157 (35%)
Ward	292 (65%)
Focus of infection (N- 449)	
Urinary Tract Infections	199 (44%)
Skin and Soft tissue infections	127 (28%)
Pneumonia	92 (20%)
Bacteremia	33 (7%)
Sepsis	25 (5%)
Abdominal	7 (1%)
Other (Febrile neutropenia, meningitis, brain abscess, unknown focus)	7 (1%)
Organism (N- 449)	
Klebsiella sp	356 (79%)
E. coli	93 (21%)
Mortality rate	
14 days (n- 432)	54 (13%)
30 days (n-410)	83 (20%)
Outcome	
Clinical cure (n-404)	312 (77%)
Clinical failure (n-404)	92 (23%)
Other patient characteristics	**Mean ± SD**
qSOFA	0.984 ± 0.976
Length of stay	21.57 ± 18.76

*Clinical cure/failure data & mortality data is not available from all centres and therefore denominator varies.

Clinical outcomes

Clinical cure status and 30-day mortality data were available from 405 and 410 patients respectively from the study sites. Among the available data in the cohort, 77 % (312/405) of patients were observed to attain clinical cure and in-hospital all-cause mortality was found to be 20% (83/410). The inpatient all-cause mortality was observed to be significantly high at 74% among patients with clinical failure when compared to the mortality rate among patients who attained clinical cure (26%) ($p < 0.00001$, OR 23.28, 95% CI 12.53-43.25) (Table 2).

The proportion of patients with clinical cure to treatment was found to be significantly higher than clinical failure among patients with urinary tract infections ($p < 0.001$, OR 2.88, 95% CI 1.73 – 4.79) and pneumonia ($p < 0.001$, OR 0.36, 95% CI 0.21 - 0.6) at 87% and 61% respectively in comparison to other infections. The clinical failure rates were significantly higher among patients with sepsis ($p < 0.001$, OR 11.38, 95% CI 0.4.61 – 28.08), abdominal ($p = 0.001$, OR 8.94, 95% CI 1.7 – 46.86) and other focus of infections (febrile neutropenia, meningitis, brain abscess and unknown focus of infection) ($p = 0.028$, OR 4.7, 95% CI 1.03 – 21.38) at 73%, 71% and 57 % respectively

Table 2. Distribution of characteristics based on clinical cure and failure.

Organism	N	Clinical cure (N = 312)	Clinical failure (N = 92)	*p*
Klebsiella sp	316	233 (74%)	83 (26%)	0.002
E. coli	88	79 (90%)	9 (10%)	
Department				
Medical department	241	184 (76%)	57 (24%)	0.58
Surgical department	164	129 (79%)	35 (21%)	
Mortality				
All cause mortality*	76	20 (26%)	56 (74%)	< 0.001
Alive	306	276 (90%)	30 (10%)	
Clinical characteristics				
Length of stay *		20.98 ± 18.29	28.39 ± 20.84	0.0016
qSOFA*		0.85 ± 0.878	1.34 ± 1.03	< 0.001

* As per the availability of both the clinical cure status and the variable among patients.

compared to the rest of the infections. In patients with urinary tract infections, skin soft tissue infections, bacteremia and pneumonia as focus of infection, the clinical cure to treatment for CRE was higher than clinical failure rates when compared to infections like sepsis, abdominal, febrile neutropenia, meningitis, brain abscess and infections with unknown focus (Figure 1).

Clinical cure rates were found to be significantly higher at 84.9% among patient with CR *E. coli* isolates in comparison to 65.4% patients with CR *Klebsiella* isolates ($p < 0.001$, OR 2.98, 95% 1.62 – 5.48). The mean qSOFA was also noted to be significantly higher for patients infected with CR *Klebsiella* isolates at 1.06 ± 0.981 in comparison to patients with CR *E. coli* at 0.69 ± 0.907 ($p = 0.0013$, mean difference -0.37, 95% CI -0.59 to -0.144) (Figure 2). The clinical cure rate was noted to be similar for patients who were treated according to the culture results and antimicrobial susceptibility reports and patients who were not treated accordingly at 75% and 80% respectively ($p = 0.23$). Clinical cure rates were found to be highest among patients treated with an aminoglycoside (95%) ($p = 0.02$) and lowest among patients treated with tigecycline (46%) ($p < 0.001$) (Figure 3).

In our study, similar clinical cure rates were observed for colistin monotherapy and combination therapy at 81% (47) and 80% (106) respectively ($p = 0.47$). Carbapenem combination therapy exhibited a significantly lower clinical cure rate at 69% (61) relative to the rest of the antimicrobial therapy in the cohort ($p = 0.02$, OR 0.56, 95% CI 0.33-0.94). For 22 (54%) patients, colistin was administered as monotherapy for Urinary Tract Infections followed by 12 (29%) as local administration for skin and soft tissue infections.

Colistin resistance

The prevalence of colistin resistance among the total number of patients recruited with isolated monomicrobial CRE was found to be at 3% (n = 15). Table 3 demonstrates the distribution of Minimum Inhibitory Concentration (MIC) values of colistin

Table 3. Distribution of Minimum Inhibitory Concentration of colistin resistant isolates (performed by Microbroth Dilution Method).

Minimum Inhibitory Concentration	N = 15
4µg/mL	2
16µg/mL	6
32µg/mL	1
64µg/mL	2
≥128µg/mL	1

*Microbroth dilution was not done in 3 patients.

Figure 1. Clinical cure and failure based on focus of infection.

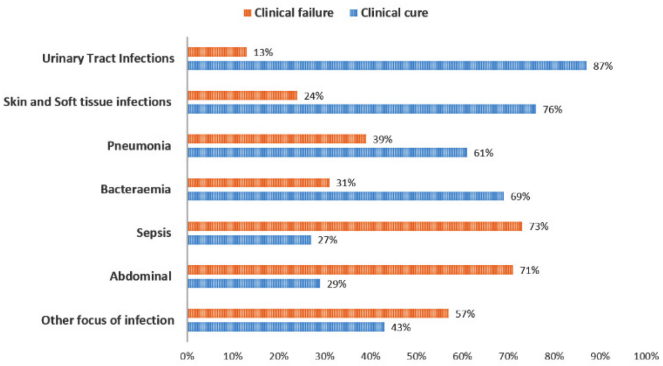


Figure 2. Distribution of qSOFA among patients with CR Klebsiella and CR E. coli isolates.

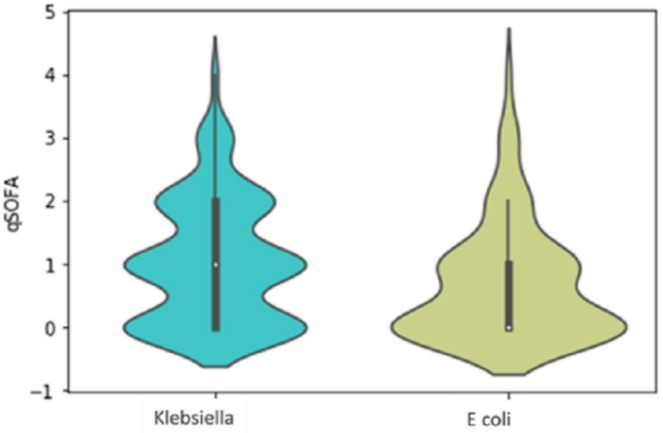
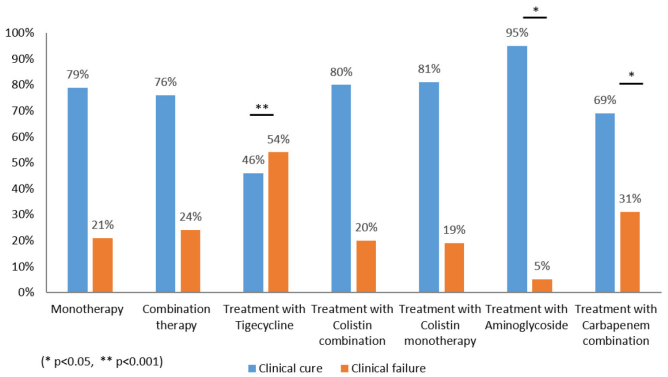


Figure 3. Distribution of clinical cure and failure based on treatment.



resistant isolates performed by Microbroth Dilution Method except for 3 patients for which data was not available. Among patients administered with colistin, colistin resistance rate was observed to be 2.6%. Clinical failure rates were observed to be significantly associated with colistin resistance with higher clinical failure rate at 75% among patients with colistin resistant isolates in comparison to 21% among patients without colistin resistant isolates ($p < 0.001$, OR 0.09, 95% CI 0.02-0.34). Similarly, all-cause mortality was also significantly high among patients with colistin resistance at 50% (6/12) when compared to patients without colistin resistance at 18% (70/390) ($p = 0.005$, OR 4.57, 95% CI 1.43-14.59).

Predictors of clinical cure

Multivariable analysis revealed combination therapy ($p < 0.001$, OR 2.14, 95% CI 1.34-3.40), CR *E. coli* isolate ($p = 0.033$, OR 2.04, 95% CI 1.06-3.95), UTI ($p < 0.001$, OR 2.52, 95% CI 1.56-4.08), sepsis ($p = 0.001$, OR 0.185, 95% CI 0.07-0.486), ICU stay ($p < 0.001$, OR 0.344, 95% CI 0.218-0.541) to be significantly associated with clinical cure status (Hosmer and Lemeshow goodness of fit, $p = 0.386$). Patients who received combination therapy were observed to be 2.14 times more likely to attain clinical cure. Patients who were diagnosed with UTI were 2.52 times more likely to attain clinical cure in comparison with other focus of infections. Patients harboring CR *E. coli* are 2.04 times more likely to achieve clinical cure in comparison to patients with CR *Klebsiella*. Patients diagnosed with sepsis (OR 0.185) and with ICU stay (OR 0.344) were less likely to attain clinical cure status.

Discussion

Our prospective observational study on the incidence and epidemiological characteristics of monomicrobial CRE isolates revealed a notable incidence at 0.855 per 1000 patient days with mortality rates at 20%. The objective assessment of focus of infection based clinical cure prospectively for monomicrobial CRE infections was a unique aspect of our study which recorded an overall clinical cure rate at 77%. The study has also assessed the association of clinical cure status with various antimicrobial drug combinations for treating CRE infections. The study was one of the pioneer multicentric projects in the state on AMR following public private partnership model commissioned by the government.

The CRE incidence was estimated to be 0.3–2.93 infections per 100,000 person-years among the entire US population [17]. The CRE incidence rate in our study is similar to the overall incidence rate reported by Chirag *et al* whereas prevalence of 3.37 to 32.49 per 100,000 population and 18.54% were reported by Daruni *et al* and Namitha *et al* respectively [16,18,19]. Regional studies focusing on CRE prevalence among *Enterobacteriaceae* isolates ranged between 8 to 31% [11-13]. Non-susceptibility to carbapenem drugs was recorded at 15.5% and 24.8% among *E. coli* and *Klebsiella* isolates in a study [20]. However, most of the reported studies included all the CRE cultures whereas our study has only assessed the monomicrobial cultures in order to avoid any potential inclusion of colonizers or contaminants.

Clinical cure rates were observed to be relatively similar between patients with and without treatment based on culture reports and susceptibility patterns in our study. Uncertainty in differentiation of true infection versus colonizer and the use of source control in various infections might be some of the reasons for the similar clinical cure rates. Nonetheless, antimicrobial treatment that was not according to antimicrobial susceptibility and testing reports was high among the cohort at 55% that could further pave way to selection of antimicrobial resistance. Tumberallo *et al* showed association of combination therapy with lower mortality in lieu with other similar studies [21,22]. In the current study, antimicrobial combination and monotherapy showed similar clinical cure rates.

Treatment with aminoglycosides was exhibited to have high rates of clinical cure in our study in lieu with existing studies and recommended regimens as one of the combination drugs for high-risk septic shock cases [23]. Despite being a recommended last resort drug to treat CRE infections, administration of tigecycline have met with significantly low clinical cure rates in our study. This has been consistent with systematic literature reviews on efficacy of tigecycline that revealed increased mortality rates and high clinical failure rates [24,25]. In our study, the lower clinical cure rates could be because tigecycline has been majorly prescribed for Pneumonia and culture negative sepsis and it may not achieve adequate concentration in the lungs with the regular dose and there are possibilities that it may not have achieved adequate serum concentrations. In terms of mortality, our previous study among sepsis patients had revealed the significant association of CRE with mortality at 33% relative to the mortality rate of 24% among non-CRE infections [26]. Our study revealed patients with CRE Klebsiella infections harboring significantly higher qSOFA scores. Ceftazidime-avibactam has demonstrated to have better outcomes for treating K.

pneumoniae carbapenemase–producing CRE infections [27].

In a Low Middle-Income Country (LMIC) like India, lack of uniform and standardized policies in isolation of CRE, diagnosis of a true infection versus colonizer and a standardized management of CRE in both public and private sector are some of the major challenges in obtaining a standardized and uniform data to optimize the treatment and containment strategies [28]. Further studies with more uniform and extensive data variables are warranted to effectively develop a strategic model. Paucity of data on CRE carriers, the risk factors and extent of CRE colonization in the country and the lack of routine CRE screening protocols during hospital admission limits the scope of early identification and management [29,30]. Future investigations should prioritize distinguishing between community-acquired and hospital-acquired CRE infections. Understanding the dynamics and trends of these distinct sources will be critical for enabling clinicians to make evidence-based decisions on initiating empirical therapy especially among critically ill patients. Additionally, this knowledge will support governmental bodies in developing targeted guidelines for primary healthcare providers to suspect and manage resistant infections that do not respond to standard treatments. Molecular studies and identification of phenotypic variants are currently limited to few research studies in the country which is yet another challenge to be addressed to identify the effective antimicrobial drug for the type of CRE resistance and optimize the treatment practice. This would further reduce unnecessary exposure to ineffective antimicrobials and minimize the selection of resistant strains and the transfer of CR mechanisms.

Limitations

The multicentric study design involving the hospital sites as part of public private collaboration posed challenges in terms of objectively assessing clinical cure and related clinical parameters. One of the major limitations of our study would be the exclusion of data on polymicrobial cultures of CRE. Molecular characterization and phenotypic determination of CRE resistance types were beyond the scope of the study.

Conclusions

Our prospective observational study focusing on patients with monomicrobial CRE isolates in the regional metropolitan area has revealed notable incidence and all-cause mortality. The characterization of antimicrobial prescriptions commonly used in regional clinical practice for CRE infections and the focus of infection specific clinical cure and failure assessment for the various antimicrobial regimens resembling real world data would potentially provide clinical insights in optimizing antimicrobial therapy to improve treatment protocols. Future collaborative research in public-private partnership models (PPP) should be strengthened, especially for community-based surveillances on CRE infections and colonization, that could impact antimicrobial policy.

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Corresponding author

Fabia Edathadathil, MSc
Quantitative Researcher
Amrita Institute of Medical Sciences,
Kochi-682041, India.
Tel: 484-2851234
E-mail: fabiaet@gmail.com

Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Table 1. Data dictionary and clinical definitions.

Clinical cure/failure	
Pneumonia	Cure was defined as complete resolution of all clinical signs and symptoms of pneumonia. i.e., objective evidence includes • complete resolution of fever for 48 hours • improvement in tachypnea and respiratory distress • decreased oxygen requirement i.e, (for non-ventilated patients on supplemental oxygen, return to within 10% of pre-morbid baseline. For patients on mechanical ventilation, increase in PaO2/FiO2 ratio • improvement or lack of progression of abnormalities in chest X-ray on serial films
Blood stream infections	Cure was defined as complete resolution of all clinical signs and symptoms of Blood stream infections i.e., objective evidence includes • complete resolution of fever for 48 hours • attainment of hemodynamic stability, if normal before starting treatment • WBC to near normal levels
Urinary tract infections	Cure was defined as complete resolution of all clinical signs and symptoms of Urinary tract infections. i.e., objective evidence includes • complete resolution of fever for 48 hours • resolution of dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain.
Surgical site infections	Cure was defined as complete resolution of all clinical signs and symptoms of surgical site infections i.e, objective evidence includes • complete resolution of fever for 48 hours • resolution of infective symptoms at surgical wound site: redness, delayed healing, fever, pain, tenderness, warmth, or swelling and production of pus (including drains from internal organs or body space)
Carbapenem resistant *Enterobacteriaceae*	Resistant to any carbapenem (i.e., minimum inhibitory concentrations of ≥ 4 mcg/mL for doripenem, meropenem, or imipenem OR ≥ 2 mcg/mL for ertapenem)
Colistin resistance	The European Committee on Antimicrobial Susceptibility Testing (EUCAST) published breakpoints for colistin for Enterobacteriaceae where a susceptible breakpoint of ≤ 2mg/L and resistant breakpoint is > 2mg/L.
Polymicrobial infections	Polymicrobial infections have been defined as the presence of more than one microorganism identified from the site specific cultures.
SOFA score	The SOFA (Sepsisrelated Organ Failure Assessment) score to describe organ dysfunction/failure [17]. SOFA assists health care providers in estimating the risk of morbidity and mortality due to sepsis.
Charleson's co-morbidity index	A prospectively applicable method for classifying comorbid conditions of patients which can estimate the risk of mortality. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.