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Original Article

Gut Colonization with Carbapenem-resistant Enterobacteriaceae Adversely Impacts the Outcome in Patients with Hematological Malignancies: Results of A Prospective Surveillance Study

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Abstract. ***Background:*** **Gut colonisation with carbapenem-resistant enterobacteriaceae (CRE) is a risk factor for CRE bacteremia and patients with haematological malignancies (HM) are at the highest risk of mortality.**
Methods: **We conducted a prospective surveillance study of gut colonisation with CRE and its impact on the outcome of 225 consecutive patients of HM over 28 months.**
Results: **The median age of the cohort was 46 years, the majority with acute leukaemia. 48 (21%) patients were colonised with CRE on admission (CAD). Another 46 patients were colonised with CRE in the hospital (CIH). The risk factors for CAD and CIH were a diagnosis of acute leukaemia and duration of hospital stay respectively. CRE accounted for 77% of infection-related mortality (IRM). The incidence of CRE bacteremia in CRE positive patients was 18% (17/94), and mortality in those with CRE bacteremia was 100%. IRM was 35.3% in CIH group compared to 10.5% in the CAD group (p=0.0001). IRM was highest in those with acute myeloid leukaemia (AML) and CIH (54.9% p=0.0001). On multivariate analysis, CIH was the most important risk factor for IRM (HR-7.2).**
Conclusion: **Our data demonstrate that a substantial proportion of patients with HM are colonised with CRE without prior hospitalisation, but those with nosocomial colonisation have the highest risk of mortality, particularly in those with AML.**

Keywords: Carbapenem-resistant enterobacteriaceae, Haematological malignancies, Acute myeloid leukemia, Colonization, Mortality.

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Introduction. The smallest of the organisms have always evolved mechanisms of survival amidst all odds. This concept is exemplified by the way pathogenic bacteria have developed resistance to each generation of antibiotics, which humans have designed to combat them. Gram-negative Enterobacteriaceae (GNE) have been most prolific in this regard.[1] Development of carbapenems was hoped to provide a lasting solution to the menace of antibiotics resistance. However, true to its

survival algorithm, GNE developed several pathways of resistance to carbapenems within a decade of their arrival.

Carbapenem resistance is due to either carbapenem-hydrolysing enzymes, which is the most common mechanism or changes in the outer membrane porins combined with overproduction of AmpC β lactamases.[2] The increasing incidence of infection by carbapenem-resistant enterobacteriaceae (CRE) is a significant public health challenge worldwide, especially in the developing countries.[3-5] It has acutely exposed the limitations of our antibiotics armamentarium.[6] Patients with haematological malignancies (HM) and the recipients of hematopoietic stem cell transplantation (HSCT) are particularly vulnerable to infections with CRE. Although precise data is scant, mortality associated with CRE is 60-100% in such patients.[2,7] The Centers for Disease Control and Prevention (CDC) has reported increased CRE infections in parts of the United States and Europeans countries.[2,8] India and other developing countries are worst affected by this emerging population of multidrug-resistant bacteria.[9] Despite the looming threat of a global epidemic, few studies[10,11] have evaluated the incidence and impact of CRE in the most vulnerable population of patients, i.e., those with HM.

We conducted a prospective longitudinal study over 28 months to evaluate the prevalence of colonisation with CRE in patients with haematological malignancies and its impact on the outcome of the patients undergoing treatment for these disorders.

Materials and Methods. This was a prospective observational study of gut colonisation with CRE in 225 consecutive patients with newly diagnosed HM admitted to our institution from October 2013 to January 2016, who underwent active treatment. Patients previously treated for the same condition or those with relapsed disease were not included in the study. The study was approved by the Institutional Review Board, and informed consent was obtained from patients.

Surveillance for CRE. Rectal swabs of all patients were collected in an aseptic manner at the bedside, during the first day of admission and repeated subsequently on a weekly basis for a continuous hospital stay or in subsequent entries. The duration of surveillance continued through the entire period of active treatment. However, efforts were made to collect samples on a weekly basis for the first four weeks on all patients whose therapies were scheduled at 3-4-week intervals.

After collection, the samples were immediately transported to the microbiology department, and subsequently cultured. Records of Identification and antibiotic sensitivity pattern of microorganism were maintained for all the patients. Enterobacteriaceae was identified based on standard laboratory protocols. All clinical specimens were inoculated on MacConkey agar and blood agar for isolation of gram-negative bacteria. After 18-24 hrs of incubation, the Mac-Conkey agar plates were examined for both lactose-fermenting (pink) colonies as well as non-lactose fermenting (pale) colonies. More than one colony morphology may represent distinct species. Wherever there was a difference in the colony morphology, colonies of each were sub-cultured in nutrient agar media (non-selective media). Isolates were subjected to a series of biochemical tests for identification, both manually or using automated identification system, Vitek2® (BioMérieux, France), if necessary. These colonies were identified up to species level using standard protocol.[12] Susceptibility testing was performed by disc diffusion (Kirby-Bauer) method following CLSI guidelines version 2016. Isolates showing positive disc screen test with ertapenem (10µg) and meropenem (10µg) or imipenem (10µg) were suspected as possible CRE, and they were further subjected to Modified Hodge Test (MHT) for detecting carbapenemases with ZnSO4 supplementation of culture media to increase the detection rate of NDM1.[13,14] Reference strains used as controls were E. coli ATCC 25922, Klebsiella pneumonia 700603 and Pseudomonas aeruginosa 27853. CRE was defined as non-susceptibility to anyone out of the three antibiotics tested. Since breakpoints of colistin and tigecycline were not mentioned for Enterobacteriaceae in CLSI guidelines, EUCAST guideline was followed. Aminoglycosides used were Amikacin and Gentamycin

Monitoring and management of patients with CRE colonization. Patients with a positive rectal swab screening on the first sample, without any sign or symptoms of infection, were defined as Colonised at Admission (CAD). Horizontal transmission

during the current hospitalisation was hypothesised for CRE positive patients who had a negative screening at admission and were labelled as Colonized in Hospital (CIH).

CRE-positive patients were put under barrier nursing care precautions as per CDC guidelines. Patients were kept in isolation rooms whenever available or cohorted in double-occupancy rooms. Dedicated nurse and housekeeping staff were assigned to CRE positive patients in single or cohort allocation at each shift. The patients themselves were advised for regular sitz bath and cleaning with chlorhexidine-based cleansing solutions

CRE infections and therapy. All patients received levofloxacin as antibacterial prophylaxis on admission unless they were initiated on empirical or definitive antibiotics for febrile or infective episodes. Paired blood and urine samples were sent for culture before starting of empirical antibiotics for patients developing clinical pictures suggesting an infection. All patients were assessed on the basis of age, comorbidities, performance status, duration and severity of neutropenia, previous infections and exposure to broad-spectrum antibiotics (i.e., beta-lactams, quinolones, and aminoglycosides), and duration of central venous catheter placement. Patients with known CRE colonisation were started on a high dose of anti-pseudomonas carbapenems along with aminoglycosides. Antibiotics were escalated as per sensitivity report and the clinical status of patients. However, those with CRE colonisation had colistin and tigecycline added if there were signs of progression of sepsis or if there was a lack of response within 24-48 hours.

Statistics. Binary variables were compared between the two groups using chi-square test, and the continuous variables were analysed using independent sample t-test considering the Levenes test for equality of variances. Probabilities of survival were estimated using the Kaplan-Meier product-limit method. CRE – related mortality (CRE-RM) was defined as death attributable to microbiologically documented bacteremia caused by CRE, in the absence of other confounding factors. Infection-related mortality (IRM) was defined as death due to infectious causes verified on culture of blood or sterile body fluids, in the absence of other confounding factors. The cumulative incidence rates of IRM and CRE-RM were computed to take account of the presence of competing risks such as disease-progression or relapse. Multivariate analysis was carried out using Cox Regression analysis. The data were censored if a patient was treated with hematopoietic stem cell transplantation (HSCT) at the time of admission for the same. An outcome was determined to be significantly different if the observed P value was <0.05. All analyses were performed using statistical software IBM SPSS Statistics Version 22.

Results.

*Patient Characteristics (**Table 1**).* A total of 2263 samples from 225 patients with HM were evaluated. We further analysed them in two cohorts as per their rectal swab surveillance results as CRE positive and CRE negative. CRE positive subgroup was also categorised as colonised at admission (CAD) and colonised in the hospital (CIH) as described above.

The details of patients are mentioned in the **Table 1**. The median age of the entire study group was 46 years with a male predominance (61%). Acute leukaemia (45%) accounted for the majority, followed by lymphoma (33.8%), myeloma (8.9%) and the rest. The median duration of follow-up was 16 months (range 12 days-26 months). All patients were newly diagnosed at our institution had active disease at presentation. Patients with prior treatment and those with relapsed diseases were not included in the study.

Colonisation with CRE and Risk Factors. Out of 225 patients, 48 (21%) patients were colonised with CRE at admission. Another 46 patients with the prolonged hospital stay or on subsequent treatment had a positive CRE on surveillance, accounting for 26% of patients with CIH. The median time to acquisition of CRE amongst the CIH group was 3 weeks (range 2-13). Amongst the CRE positive cohort, the majority (n=56, 59.7%) were diagnosed with acute leukaemia and 37 (66%) of those had acute myeloid leukaemia (AML). The median duration of continuous hospital stay was higher amongst CIH (26 days, range 1-64) compared to non-CIH group (5 days, range 1-28), [p=0.0001].

Both univariate and multivariate analyses were carried out to ascertain the risk factors for CAD and CIH as detailed in **Table 2**. CAD tended to be

Table 1. Characteristics of patients with CAD, CIH and without CRE colonization.

	CRE negative (N=131)	CAD (N=48)	CIH (N=46)	p values
Age : years (median, range)	45 (2-84)	49 (2-75)	46.5(2-74)	0.9
Gender (Male /Female)	83/48	35/13	33/13	0.4
Diagnosis ALL AML LYMPHOMA MM OTHERS	 25 21 54 14 17	 11 17 12 05 03	 08 20 10 03 05	0.02
ECOG- PS (median, range)	2 (0-4)	2 (1-4)	2 (0-4)	0.2
CCI (median, range)	3 (0-5)	3.5 (0-5)	3 (0-4)	0.1
Hospital stay (median, range)	5 (1-25)	8 (1-28)	26 (1-64)	0.001
CRE -RM	0	3	14	0.0001
IRM	0	5	17	0.0001

Abbreviations: AL: Acute Leukemia; ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, CRE: Carbapenem-resistant Enterobacteriaceae; CCI: Charlson Comorbidity Index; CRE: Carbapenem Resistant Enterobacteriaceae; CAD: CRE at diagnosis; CIH-CRE in hospital; CRE-RM: CRE related mortality; ECOG-PS: Eastern Cooperative Oncology Group- Performance Status, IRM: Infection related mortality; MM: Multiple Myeloma.

Table 2. Univariate and Multivariate Analysis of Risk Factors for CRE Colonization and Mortality.

Variables	CAD HR(95% CI)/pvalue	CIH HR(95% CI)/p value	CRE-RM HR(95% CI)/ p value	IRM HR(95% CI)/p value
Age	0.99(0.98-1.01) /0.94	0.99(0.98-1.01) / 0.94	1.0(0.98-1.04) / 0.20	1.0(0.98-1.03) / 0.40
Gender	0.73(0.36-1.3)/ 0.39	0.76(0.37-1.5) / 0.45	0.41(0.11-1.4) / 0.17	0.57(0.20-1.6) / 0.3
AL	1.85(1-3.5) /0.05	2.2(1.1-4.3) / 0.02 **0.60 (0.17-2.12)/ 0.43*	2.3(0.84-6.6) / 0.1	2.8(1.1-7.3) / 0.03 *1.08 (0.23-4.9)/ 0.92*
AML	1.89(0.95-3.78)/0.07	2.85(1.4-5.6)/ 0.003 **0.31 (0.07-1.35) /0.11*	2.80(1.0-7.7)/0.04 *1.48(0.42-5.17)/ 0.54*	4.0(1.6-10.0)/ 0.002 *2.23(0.47-10.74)/0.31*
CCI	1.26(0.94-1.7)/0.11	0.81(0.62-1.0)/0.15	1(0.64-1.52)/0.97	1.01(0.69-1.48)/0.94
PS	1.23(0.89-1.71)/0.22	0.79(0.56-1.1)/ 0.16	1.42(0.85-2.39)/0.18	1.4(0.88-2.20)/0.15
Hospital stay	-	1.23(1.16-1.31)/0.0001 **4.3(2.5-8.9) / 0.0001*	1.06(1.03-1.1)/0.0001 *1.0(0.96-1.04) / 0.88*	1.07(1.04-.10)/0.0001 *1.01(0.97-1.05) / 0.61*
CAD	-	-	0.79(0.22-2.9) / 0.73	1.12(0.4-3.2) / 0.82
CIH	-	-	25.6(6.9-94.4) / 0.0001 **22(4.58-106.0) / 0.0001*	20.4(6.8-50.5) / 0.0001 *13.9(3.43-56) / 0.0001*

Abbreviations: AL: Acute Leukemia; AML: Acute Myeloid Leukemia, CCI: Charlson Comorbidity Index; CRE: Carbapenem Resistant Enterobacteriaceae; CAD: CRE at diagnosis; CIH-CRE in hospital; CRE-RM: CRE related mortality; IRM-Infection related mortality; PS-performance status. * indicates multivariate analysis.

higher in those with acute leukaemia (27/102 vs 20/123 without acute leukaemia, HR 1.85 95%CI 1.0-3.5, p=0.05) Duration of hospitalisation was a risk factor for CIH (HR 4.3 (95%CI 2.5-8.9). A diagnosis of AML was the strongest risk factor for overall CRE colonisation (37/58 vs 57/157 without AML, HR-2.5, 95%CI 1.1-5.6, p=0.03).

Microbiology of CRE colonisation. Klebsiella pneumoniae (KP) was the predominant microorganism isolated from the rectal swab sample of the patients as CRE pathogen amongst both CAD (53%) and CIH (83%) groups. Escherichia Coli was the other isolated organism accounting for the rest. Both pathogens were detected in 6% and 8% in the CAD and CIH groups respectively. Thus, Klebsiella species accounted for significantly higher colonisers amongst those with CIH (p=0.02). All isolates were positive by susceptibility testing as well as MHT.

All CRE isolates were resistant to all the carbapenems tested. Twelve out of 17 patients who died of CRE had Klebsiella species isolated from their blood culture (**Table 3**). Although all the species isolated were sensitive to colistin, seven were sensitive to tigecycline, and only one isolate was sensitive to aminoglycosides. Among five patients who were infected with E.Coli, four were resistant to aminoglycosides, and one was

Table 3. Antibiotic sensitivity of the CRE isolated on blood culture.

Organisms	Colistin	Tigecycline	Aminoglycosides
Klebsiella			
• Sensitive	12	7	1
• Resistant	0	5	11
E.Coli			
• Sensitive	5	4	1
• Resistant	0	1	4

resistant to Tigecycline. Amongst those with CIH, 12 had documented CRE bacteremia, ten were Klebsiella species, and two were E.coli. Six of the isolates were sensitive to colistin alone. All but one patient had received meropenem or Imipenem in combination with aminoglycosides, tigecycline and colistin for over 48 hours before they succumbed to the CRE infection.

Infection-Related Mortality (IRM) And CRE-Related Mortality (CRE-RM). The overall IRM over a period of 26 months was 9.5% (22 patients). CRE-RM accounted for 17 of the 22 deaths. The other five patients succumbed to gram-negative sepsis (n=4, Pseudomonas aureginosa-2, Enterobacter-1, Acinetobacter Baumanii-1) and sudden cardiac death (n=1) while on treatment for CRE. No IRM or CRE-RM was noted in patients who were CRE negative throughout the study period. Thus, all IRM occurred exclusively in patients colonised with CRE. IRM and CRE-RM in CRE positive group were 24.7% (n=22/94, 95% CI 20-29.4) and 18.8% (17/94, 95% CI 14.7-22.9) respectively.
Those with acute leukaemia had a higher IRM

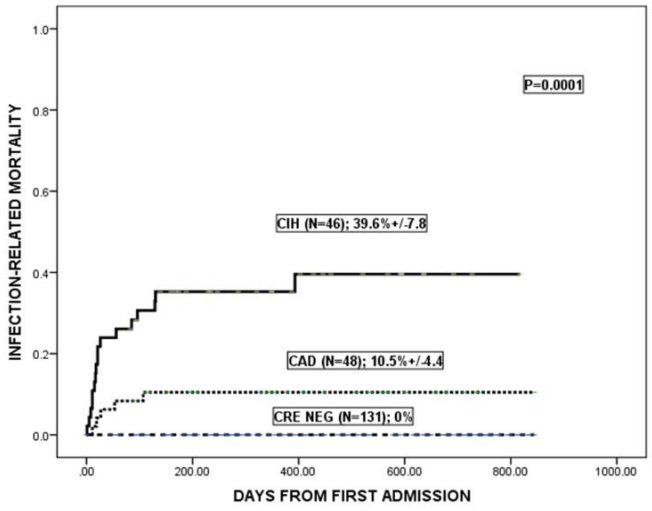

Figure 1. Cumulative Incidences of Infection-Related Mortality. The solid line **(__)** represents CIH (CRE acquired in the hospital stay). The dotted line (…….) represents CAD (CRE at the time of diagnosis and the broken line **(- - - -)** represents CRE negative group. The log rank p value is 0.0001.

(15/102, [14%; 95%CI 10.5-17.5] compared to 7/123, [5.8 %; 95%CI 3.7-7.9] in those without AL, log rank p=0.01). On subgroup analysis, 12 out of 58 with AML had IRM (22.9% 95%CI 16.8-29.0) compared to 10 out of 167 of those without AML (10/167, 5.5; 95%CI 3.7-7.3) (log rank p=0.0001).

On further analysis, IRM was significantly higher in the CIH group compared to CAD group (17/46, [39.6%] vs 5/48 [10.5%], p=0.0001, **Figure 1**). CRE-RM was also significantly higher in the CIH group (14/46, [31.4% (95%CI 24.4-38.4%)] vs 3/48, [6.6% (95%CI 2.9- 10.3%)] p=0.0001) compared to CAD group. This trend for mortality in patients with CIH was similar in patients with and without AL. However, the incidence of IRM was highest in those with AML and CIH (10/20) [54.9%; 95%CI 32.4-67.4%] compared to 2/17 in those with AML and CAD (11.8; 95%CI 4-18.6; p=0.0001).

CRE bacteremia occurred exclusively in those colonised with CRE. Thus, CRE colonisation was the most significant risk factor for CRE bacteremia (p=0.0001). No patient with CRE infection in the above cohort survived. Therefore, the incidence of CRE bacteremia in CRE positive patients was 18% (17/94), and mortality in those with CRE bacteremia was 100%. All the patients were neutropenic at the time of CRE bacteremia. The median time to the detection of bacteremia from diagnosis of CRE colonisation was 19 days (0-41). The median time to death from the onset of the febrile neutropenic episode was six days (1-14) and from the beginning of severe neutropenia was four days (1-8). On multivariate analysis, CIH was the single most important risk factor for both CRE-RM and IRM in patients with haematological malignancies (**Table 2**).

Discussion. CRE, particularly the NDM-1 strain was reported to be highly prevalent in various parts of India in 2011.[4] This was confirmed by another study from South India, highlighting the prevalence of NDM as well as OXA-48 like strains.[15] However, few studies have emerged from the subcontinent highlighting the burden and the impact of CRE.[5,16,17] Despite recognition of CRE as a global public health threat, the study on the acquisition and the natural history of colonisation with CRE in patients with various HM remain sparse. A review in 2014 by Satlin et al. identified six studies reporting 35 patients of

HM and HSCT in total, with a mortality rate of 50-100%.[2] While a few studies since then have studied the incidence CRE bacteremia and its risk factors in both adults and children, any longitudinal research on the incidence of colonisation and its long-term impact is lacking.[8,18-24]

We studied a cohort of 225 patients over a 28 months period with a minimum follow-up of 6 months. 21% of the patients were colonised with CRE at their first visit. Due to the use of non-selective media and in the absence of molecular typing, it is possible that we might have under-reported the incidence of colonisation. It is not possible to ascertain if such cases of CAD are genuinely community-acquired or these were acquired during infrequent hospital visits before reaching a tertiary care centre.[25] Patients with acute leukaemia are more prone to colonisation as is evident from our data. This could be due to multiple visits to health care set-ups before arrival at the tertiary care centre. This is augmented by the disease-induced neutropenia for prolonged periods in such patients.

What was even more striking was that another 26% of patients were colonised during the hospital stay, despite extremely stringent measures for barrier nursing in place. Such high rates of CIH highlight the perennial and obtrusive problem of nosocomial transmission of such microbes. CRE have a high propensity for horizontal transmission, and this has been highlighted in the past.[3] Colonisation in the hospital is not a mere physical event but is contributed by prolonged antibiotic usage, chemotherapy-induced breach of the mucosal barrier of the gut and most importantly both disease and therapy-induced severe and prolonged neutropenia.[18] These factors and their combinations are unique to the patients with HM and not generally witnessed in non-HM patients in intensive care or solid organ transplants. The combination of these factors is probably responsible for the high fatality rate of CRE infections in patients with HM. This was highlighted by a multicenter study from Italy where bloodstream infection with carbapenem-resistant KP was on the rise and was associated with a mortality rate of greater than 50% in patients with HM.[7]

Colonisation with CRE has been postulated to be a risk factor for CRE bacteremia, but the data remains scarce due to the lack of prospective nature of these studies. In a study from Italy, 86% of patients with CRE bacteremia were found to be colonised.[11] However, none of the studies alludes to a longitudinal follow-up in colonised patients. In our study, 42% patients were colonised with CRE in the study period and 18% of those developed CRE bacteremia during a course of therapy-induced neutropenia. CRE bacteremia was associated with 100% mortality, although all patients colonised with CRE were initiated on colistin and tigecycline within 24-48 hours of the onset of febrile neutropenia along with high doses of carbapenems. Thus, a delay in initiation of treatment is unlikely to be responsible for such high mortality. We noted that mortality in patients with CIH was much higher than patients with CAD. Majority of these patients succumbed within a week of the febrile episode and onset of neutropenia. It is possible that the nosocomial strains were more virulent as reflected by the pattern of antibiotic sensitivity.[26,27] Very few isolates were sensitive to aminoglycosides, and the majority of KP were resistant to tigecycline as well. Fosfomycin, another antibiotic which has efficacy against CRE was not available for clinical use during the study period. Resistance to colistin as well as tigecycline is on the rise as reported from both India as well as China.[27-31] Hence, with extreme limitations regarding antibiotic sensitivity, the outcome of such patients is likely to remain extremely poor.[32] However, several newer beta-lactamases such as avibactam, vaborbactam and relebactam in combination with ceftazidime and carbapenems might provide an alternative for CRE infections in the near future.[33,34] In addition, ceftolozane-tazobactam shows promise as a carbapenem-sparing agent against both Pseudomonas as well as enterobacteriaceae.[35]

Further to our study, we have introduced prophylactic granulocyte infusions for all patients colonised with CRE, who are febrile and likely to experience neutropenia over seven days. Given the paucity of effective antibiotics for CRE, it remains to be seen whether this approach benefits patients with CRE colonisation. Our study has addressed the issue of gut colonisation with CRE in patients with HM with reasonable diligence to be able to propose the following. Half of the patients with HM are likely to be colonised with CRE during the first few weeks of treatment despite the best possible preventive measures. With such high

incidence of colonisation, resources are going to be severely challenged to prevent the spread of this organism amongst patients with HM in a busy tertiary care set-up. We are unlikely to save many such CRE infected patients with prolonged neutropenia with a limited array of antibiotics. Those with acute leukaemia, more so with AML remain at the highest risk of early fatality from CRE. Gut sterilisation has stayed unproven in such situations.[36] Rampant and random use of carbapenems is clearly responsible for the current state.[37] Unless a concerted effort at antibiotic stewardship and regulated use of these antibiotics are introduced with all intent and purpose in the healthcare sectors across the globe, the problem of CRE will assume epidemic proportions beyond geographical borders in the near future.

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