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Outcomes of Patients with Carbapenem-Resistant Enterobacteriaceae

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Abstract

Background: In an era of increasing antibiotic resistance, the emergence of Carbapenem-Resistant Enterobacteriaceae (CRE) poses a serious threat to public health given the limited treatment options and high mortality rate.

Methods: This is a single center, retrospective, cohort study that evaluated characteristics and outcomes of adult patients hospitalized from July 1, 2010 through June 30, 2013 with their first diagnosis of CRE as confirmed via the Modified Hodge Test.

Results: 27 cases of CRE were identified during the study period. 18 were deemed to have a true infection while 9 were asymptomatic colonizers. *Klebsiella pneumoniae* was the causative organism in all but one case of *Klebsiella oxytoca*. The mean time to CRE diagnosis was 18 days and the mean length of hospital stay was 37 days. 41% of patients were admitted from home, 37% from an outside hospital (OSH), and 22% from a long term care facility. Patients transferred from an OSH had an increased mortality (p 0.0269). Of those admitted from home, 45% were diagnosed with early infection (positive culture in the first 48 hours). Of those with early infection admitted from home, 80% had been hospitalized during the 90 days before CRE diagnosis. Infection was most common in the urine and respiratory tract. Overall mortality rate for patients with an active infection was 44.4%. A higher mortality rate was seen in patients with pulmonary infections (p 0.0003) and patients who had isolation of MDR *Pseudomonas* 6 months prior to CRE (p 0.0172). 81.4% of patients received antibiotics within 90 days prior to CRE diagnosis. The most common antibiotics with activity against gram negatives that patients were exposed to were: piperacillin/tazobactam (37%), fluroquinolones (33.3%), and carbapenems (29.6%). For patients with true infection, 33.3% were given combination therapy with at least 2 of the following: amikacin, colistin, tigecycline, and a carbapenem. 83% of patients who received combination therapy died (p 0.0037). 76.2% of tested isolates were susceptible to colistin, 62.5% to tigecycline, 59.3% to amikacin, and 11.1% to gentamicin.

Conclusion: Infections due to CRE are associated with a prolonged length of stay and result in significant mortality in spite of combination therapy. We observed a particularly high mortality in patients with CRE pneumonia.

Introduction

The emergence and rise of CRE in the U.S. poses a serious threat to public health. Carbapenems have been the antimicrobials of choice for the treatment of extended-spectrum beta-lactamase (ESBL) producing bacteria. In response to the increasing prevalence of ESBL infections, carbapenem use has increased, resulting in resistance.[1] In the U.S., carbapenem resistance is primarily linked to Klebsiella pneumoniae carbapenemase. This hydrolyzing enzyme is transmissible via plasmids, which carry genetic elements that can be spread to other genera or from person to person.[2] The first reported case of CRE was in North Carolina in 2001.[3] Since then, notable outbreaks have occurred.[4] Risk factors for developing CRE include exposure to antimicrobials, exposure to healthcare with poor functional status, stay in the ICU and mechanical ventilation.[9] CRE infections are particularly concerning because they are difficult to treat and have the potential to rapidly spread within healthcare facilities.[6] Antibiotic options are limited and include aminoglycosides, polymixins, tigecycline, fosfomycin, and temocillin. CRE infections are associated with a mortality rate as high as 50%.[2] According to the CDC, the percentage of enterobacteriaceae that were carbapenem-resistant increased from 1.2% in 2001 to 4.2% in 2011.[2]

Methods

Study Design: This single center, retrospective chart review was performed on hospitalized individuals infected with CRE at Georgetown University Hospital between July 1, 2010 and June 30, 2013. A list of all patients diagnosed with CRE was generated by the Microbiology laboratory. All CRE infections were confirmed by the Modified Hodge Test. Inclusion criteria were age ≥ 18 and first diagnosis of CRE. In total, 27 patients fulfilled the inclusion criteria.

***Data Collection/Anaylsis*:** Patients selected underwent medical chart abstraction to determine demographic factors, mortality, hospital length of stay, infection characteristics, co-pathogens, and antibiotic treatment. Outcomes were determined by clinical documentation. Infection eradication was determined when there was either proven or presumed pathogen eradication. Survival was determined when the patient was able to be discharged from the hospital. Subset analyses of outcomes based on pathogen, infection site, co-pathogens, and administered regimens were assessed for statistical significance using fishers exact test and chi-squared test.

Results

Table 1. Patient Information

			Mortality	
Total CRE cases (number of patients)	27	%	Rate	P Value
True CRE infection	18		**44.4%**	
Asymptomatic CRE colonizer	9		0%	
Sex				
Male	12	44.4%	41.6%	
Female	15	55.6%	20%	
Average Age (years)[a]	57			
Mean Length of Hospitalization (days)[b]	37			
Mean time to diagnosis of CRE	18			
Unit of Diagnosis: ICU	12	44.4%	66.7%	0.003
Unit of Diagnosis: Med/Surgery Floor	15	55.6%	0%	
Causative organism				
Klebsiella *pneumonia*	26			
Klebsiella *oxytoca*	1			
Admission Type				
Home	11	40.7%	18%	
Outside Hospital	10	37.1%	60%	0.0269
Long Term Care Facility	6	22.2%	0%	

Table 1. Demographic characteristics of patients diagnosed with CRE. The data reported are number, percent, or mean. Overall mortality for patients with true infection 44.4%. Patients transferred from an OSH had a statistically significant increased mortality with mortality rates of 60% (p 0.0269) as did patient diagnosed with CRE while in the ICU (0.003).

Table 2. Antibiotic Exposure 90 Days Prior to CRE Diagnosis

Antibiotic	Number of Patients	Mean Days Used	% of Patients
Zosyn	10	6.6	37%
Fluroquinolones	9	10.125	33.3%
Carbapenems	8	10	29.6%
3rd Generation Cephalosporin	5	5.2	18.5%
Aminoglycoside	4	11.5	14.8%
Colistin	2	10	7.4%
Tigecycline	2	17.5	7.4%

Table. 2. Antibiotic Exposure 90 Days prior to CRE Diagnosis. 81.4% (n=22) of patients received antibiotics within 90 days prior to CRE diagnosis. 18.6% (n=5) had no known antibiotic exposure, but all of those patients had a hospitalization within the 90 days prior to CRE diagnosis.

Table 3. Patient Characteristics of Patients Admitted from Home

	No. of Patients	% of Patients	Hospitalized within 90 days prior to CRE
Patients Admitted From Home	11		8 (72%)
Early Infection[a]	5	45%	4 (80%)
Infection >48 hours	6	55%	4 (66.6%)

Table 3. Of those admitted from home, 45% were diagnosed with early CRE infection. 80% of the patients admitted from home with early CRE infection had been hospitalized within the 90 days preceding the CRE diagnosis.

[a]Early Infection: Positive culture was drawn within 48 hours of admission

Table 4. Patient Outcomes

	Survivors	Non Survivors	Total
Total CRE Cases	19	8	27
Co-pathogen isolated within 72 hours CRE culture (patients)	11 (57.9%)	6 (75%)	17 (63%)
Mean Time to Appropriate Antibiotics (days)	3.8	5.1	
Microbiologic Cure	7 (36.8%)	1 (16.6%)	8 (29.6%)
90 Day Re-admission Rate	9 (47.4%)	N/A	19

Table 4. Clinical outcomes of patients with CRE. Microbiologic outcomes were based on results of subsequent bacterial cultures and clinical notes.

Figure 1. Site of CRE Infection

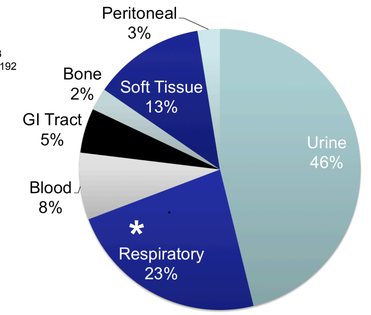

Table 1.
[a]Age Range: 27-93
[b]Length of Stay: 6-192

Figure 1. Site of CRE infections. Infection was most common in the urine (n=18), respiratory tract (n=9), soft tissue (n=5), blood (n=3), GI tract (n=2), and bone (n=1). 25.9% of the patients had more than one documented site of CRE.

*Patients with infections in the respiratory tract had a significant increase in mortality (*P* = .0003)

Figure 2. Mortality by Infection Site

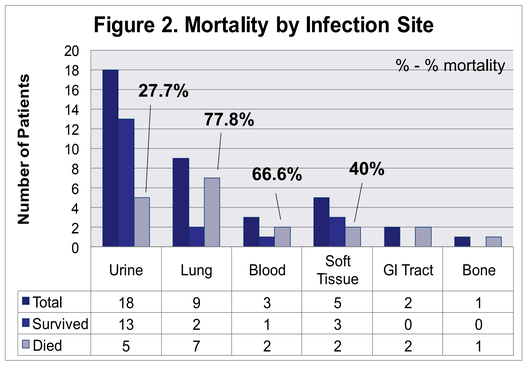

Figure 2. Mortality by Infection Site. Of the patients determined to have an active CRE infection, the mortality rate was 44.4%. Mortality was highest in patients with pulmonary infections (p 0.003) and bacteremias.

Figure 4. Prior MDR Organism

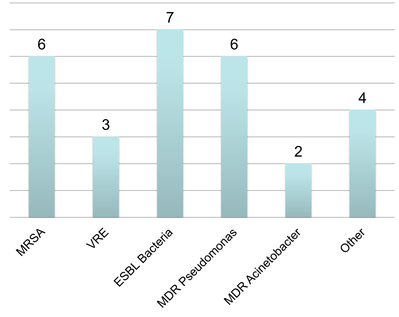

Figure 4. Prevalence of MDR organisms isolated in the past 6 months. MDR organisms were isolated within 6 months before CRE diagnosis in 55.5% of all patients. Patients who had prior isolation of MDR Pseudomonas had an increased mortality rate (p 0.0172).

Figure 5. Antibiotic Regimens

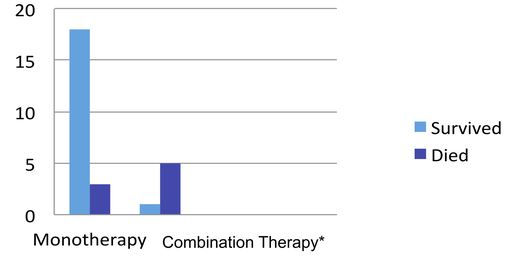

Figure 5. Antibiotic Regimens: 33.3% (n=6) of the patients with true infection were given combination therapy. 83% of patients who received combination therapy died (p 0.0037).

*Combination Therapy: At least 2 of the following: amikacin, colistin, tigecycline, and either imipenem or meropenem.

Conclusions

We observed a prolonged length of stay and a high mortality associated with CRE infections. This is consistent with what has been previously reported in the literature.[8] The ICU had the highest number of infections and it came to no surprise that patients who developed CRE infections while in the ICU had an increased mortality rate. We observed a particularly high mortality in patients with pneumonia due to CRE and with prior history of MDR Pseudomonas. The mean time to infection was 18 days, making most cases hospital acquired. However 45% of the patients admitted from home had infections within the first 48 hours of admission; albeit all of these patients had had prior hospital exposure within the 90 days preceding CRE diagnosis. Despite the use of combination therapy targeted at CRE, poor patient outcomes were still observed. Given the poor outcomes observed with CRE infections, infection prevention practices, antibiotic stewardship as well as industry support for the development of new antibiotics is essential in decreasing the healthcare burden of this infection.

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