Impact of Different Antibiotic Regimens in the Treatment of Carbapenem-Resistant Bacteria on Mortality and Readmission

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Background: Carbapenem-resistant Enterobacteriaceae (CRE) has become an obvious threat, and is associated with an increase in morbidity and mortality. Therefore, evaluation of the following antibiotic regimens: Colistin only antibiotic regimen (COAR), Colistin combination antibiotic regimen (CCAR), and Non-Colistin antibiotic regimen (NCAR) on mortality and readmission is essential to determine the best intervention.

Objective: To evaluate the impact of different antibiotic regimens used in the management of Carbapenem resistant bacteria (CRB) on mortality and readmission.

Design: A Retrospective Cohort Study.

Setting: King Hamad University Hospital, Bahrain.

Result: One hundred nine patients with CRE 37 (33.9%), CRB 36 (33%) and CRPsA 26 (23.9%), and 10 (9.2%) Escherichia coli MDR OXA-48, Calcoaceticus MDR, and Enterobacter cloacae MDR OXA-48 from 1 January 2017 to 31 December 2018 were evaluated. The mean age was 66 (±16) years. Forty-five (41.2%) patients received COAR, 44 (40.3%) received NCAR, and 20 (18.34%) received CCAR. The mortality was higher in COAR 30 (27.5%) compared to 10 (9%) in CCAR and 20 (18.3%) in NCAR (P=0.117). On the other hand, readmission was found to be higher in NCAR 6 (50%) compared to 5 (41.7%) in COAR and one (0.9%) in CCAR (P=0.45).

Conclusion: None of the three different antibiotic regimens (COAR, CCAR, and NCAR) was found to be significantly associated with reduced mortality or readmission; however, COAR had the worst negative impact on mortality or readmission.

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There has been an increase in the number of carbapenem resistant bacteria (CRB) in the world. Enterobacteriaceae (especially Klebsiella pneumonia) and other gram-negative bacteria, such as Acinetobacter baumannii and Pseudomonas aeruginosa have been associated with a significant increase in morbidity and mortality[1]. The Intensive Care Unit (ICU) is considered a critical challenge in the prevalence of multidrug-resistant gram-negative bacteria[2]. The Centers for Disease Control and Prevention (CDC) reported that carbapenem-resistant Enterobacteriaceae rose from 1% to 4% between 2001 and 2011, carbapenem-resistant K. pneumonia (CRKP) rose from 2% to 10%, and in 2011 there was a wave of CRKP. Eleven out of 18 CRKP patients died according to the National Institutes of Health (NIH)[3]. CRKP patients accounted for 8.1% among European countries' populations[4]. Managing CRB depends on three main factors: the micro-organism, the host and the antibiotic itself.

Carbapenem and Colistin usage should be evidence-based, as it was found that inappropriate initiation or usage of these agents were linked to treatment failure and increase of Carbapenem-resistant Enterobacteriaceae (CRE) mainly Carbapenem-resistant K. pneumonia (CRKP), Carbapenem-resistant P. aeruginosa (CRPsA), and Carbapenem-resistant Acinetobacter baumannii (CRAB)[5].

Polymyxins (Colistin) is the most effective antibiotic for treating CRB infections. Colistin may work in combination with other antibiotics such as Meropenam and Tigecycline[6,7]. Several studies showed that Carbapenem combination therapy has lower mortality rates than other combinations[8,9]. In Acinetobacter baumannii infections (carbapenem-non-susceptible Gram-negative bacteria), Colistin plus Meropenam was not superior to Colistin alone as monotherapy[10]. Studies of CRB are limited and there are conflicting results on whether monotherapy or combinations are more effective[11].

The aim of this study is to evaluate the effect of COAR, CCAR, and NCAR antibiotic regimens on mortality and readmission.

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METHOD

Between 1 January 2017 and 31 December 2018, medical records of 175 patients with a reported CRB were reviewed. Sixty-six patients' cultures were undefined and the results were unclear; therefore, they were excluded from the study; 109 patients had a culture confirming CRB infection and were included in the study.

The following were documented: personal characteristics, laboratory culture results, clinical diagnosis, causative micro-organisms [CRKP, CRPsA, CRAB], prescribed antibiotics and duration of prescribed antibiotics.

Mortality was defined as death due to infection after culture and initiation of the antibiotic regimen; readmission was defined as readmission within 45 days after discharge with a recurrent CRB infection. Data were analyzed using SPSS (Chi-squared test and t-test were utilized for the analysis) and Microsoft Office Excel. A P-value of less than 0.05 was considered significant.

RESULT

Medical records of 175 patients with CRB infection from 1 January 2017 to 31 December 2018 were reviewed. One hundred nine patients with positive CRB culture were included in the study; 66 patients with unclear culture results were excluded from the study, see figure 1.

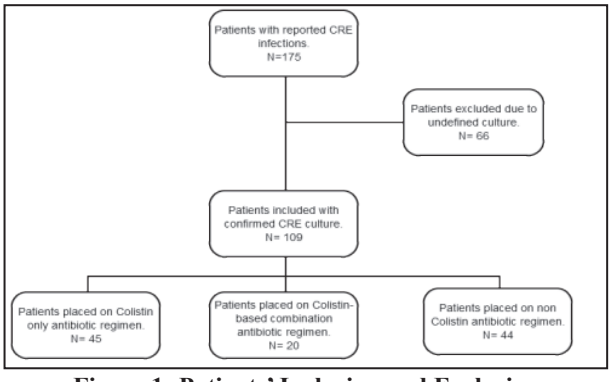

Figure 1: Patients' Inclusion and Exclusion

One hundred nine patients with CRE 37 (33.9%), CRB 36 (33%), CRPsA 26 (23.9%), and 10 (9.2%) Escherichia coli MDR OXA-48, Calcoaceticus MDR, and Enterobacter cloacae MDR OXA-48 were evaluated. Patients received antibiotic therapy as a result of the positive infection with CRB according to microbiological culture sensitivity. The mean age was 66 (±16) years with almost equal distribution between the two genders: 55 (50.5%) males and 54 (49.5%) females. CRB infection increased by 59.5% from 1 January 2017 to 31 December 2018; positive CRB culture increased from 42 to 67 patients. Sixty (55%) patients died and 49 (45%) survived; 12 (11%) of the survivors were readmitted due to reinfection, see table 1.

CRB infections were mainly due to Acinetobacter Baumannii MDR, 37 (33.9%) followed by Klebsiella pneumonia MDR OXA-48, 36 (33%), and Pseudomonas aeruginosa MDR, 26 (23.9%). Other microorganisms such as Escherichia coli MDR OXA-48, Calcoaceticus MDR, and Enterobacter cloacae MDR OXA-48 have been isolated in 10 (9.2%) samples, see figure 2.

Table 1: Characteristics and Clinical Outcomes

Age "mean (±S.D.)"		66 (±16)
Gender	Male	55 (50.5%)
	Female	54 (49.5%)
Isolation Year	2017	42 (38.5%)
	2018	67 (61.5%)
Clinical Outcomes		
Mortality	Yes	60 (55%)
	No	49 (44.9%)
Re-admission	Readmitted	12 (11%)
	No readmission	37 (33.9%)

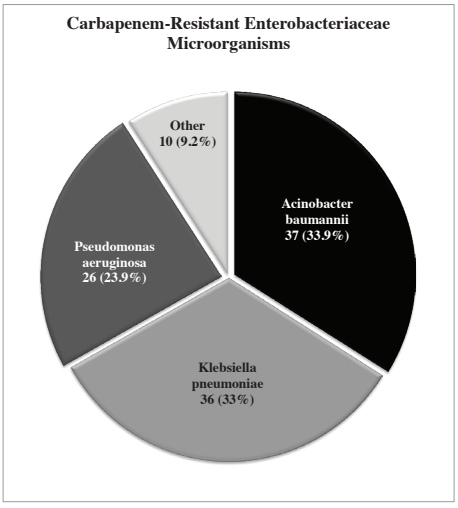

Figure 2: CRKP, CRPsA, CRAB and Others

Forty-five (41.3%) patients were on COAR, 44 (40.4%) were on NCAR and 20 (18.3%) were on CCAR. Patients were classified and analyzed according to the initiation of the treatment following the culture and duration of therapy, see table 2. Thirty-one (28.4%) patients of the COAR group started their antibiotic course within 5 days of the culture where the remaining 14 (12.8%) started after 5 days. Twenty-seven (24.8%) patients in that group required more than 14 days therapy compared to 18 (16.5%) patients that required less than 14 days therapy. In the CCAR group, 14 (12.8%) patients received their treatment within 5 days of culture result

Table 2: Antibiotic Regimens

		COAR (N=45)	CCAR (N=20)	NCAR (N=44)	**Total (N=109)**
Therapy initiation following the culture.	≤ 5 days	31 (28.4%)	14 (12.8%)	17 (15.6%)	**62 (56.8%)**
	< 5 days	14 (12.8%)	6 (5.5%)	27 (24.8%)	**47 (43.1%)**
Total		**45 (41.3%)**	**20 (18.3%)**	**44 (40.4%)**	**109 (100%)**
Therapy duration.	≤ 14 days	18 (16.5%)	5 (4.5%)	24 (22%)	**47 (43.1%)**
	<14 days	27 (24.8%)	15 (13.8%)	20 (18.3%)	**62 (56.8%)**
Total		**45 (41.3%)**	**20 (18.3%)**	**44 (40.4%)**	**109 (100%)**

COAR = Colistin only antibiotic regimen
CCAR = Colistin based combination antibiotic regimen
NCAR = Non-Colistin antibiotic regimen

Table 3: Clinical Outcomes of the Three Regimens and Characteristics

		Mortality			P-value	Readmission			P-value
		Dead (N=60)	Alive (N=49)	Total (N=109)		Readmitted (N=12)	Not readmitted (N=37)	Total (N=49)	
Antibiotic Regimen	COAR	30 (27.5%)	15 (13.8%)	45 (41.3%)	0.117	5 (4.6%)	10 (9%)	15 (13.8%)	0.474
	CCAR	10 (9%)	10 (9%)	20 (18.3%)		1 (0.9%)	9 (8.2%)	10 (9%)	
	NCAR	20 (18.3%)	24 (22%)	44 (40.4%)		6 (5.5%)	18 (16.5%)	24 (22%)	
		60 (55%)	**49 (44.9%)**	**109 (100%)**		**12 (11%)**	**37 (100%)**	**49 (44.9%)**	
Therapy initiation following the culture.	≤ 5 days	37 (61.7%)	25 (22.9%)	62 (56.9%)	0.264	6 (5.5%)	19 (17.4%)	25 (22.9%)	0.935
	> 5 days	23 (38.3%)	24 (22%)	47 (43.1%)		6 (5.5%)	18 (16.5%)	24 (22%)	
		60 (55%)	**49 (44.9%)**	**109 (100%)**		**12 (11%)**	**37 (100%)**	**49 (44.9%)**	
Therapy duration.	≤ 14 days	26 (23.9%)	21 (19.3%)	47 (43.1%)	0.960	5 (4.6%)	16 (14.7%)	21 (19.2%)	0.924
	>14 days	34 (31.2%)	28 (25.7%)	62 (56.8%)		7 (6.4%)	21 (19.3%)	28 (25.7%)	
		60 (55%)	**49 (44.9%)**	**109 (100%)**		**12 (11%)**	**37 (100%)**	**49 (44.9%)**	

COAR = Colistin only antibiotic regimen
CCAR = Colistin based combination antibiotic regimen
NCAR = Non-colistin antibiotic regimen

and 6 (5.5%) received it after 5 days. Fifteen (13.8%) patients required more than 14 days compared to 5 (4.5%) patients who used it for less than 14 days. In addition, the results of NCAR group 17 (15.6%) started their antibiotic course within 5 days of the culture where the remaining 27 (24.8%) started it after 5 days. Twenty-four (22%) patients required prolonged duration therapy, and 20 (18.3%) patients required treatment for less than 14 days.

The mortality was 30 (27.5%) patients among COAR regimen followed by NCAR, 20 (18.3%), and CCAR, 10 (9%), P-value=0.117, see table 3.

Six (5.5%) in the NCAR group were readmitted followed by 5 (4.6%) in COAR group and one (0.9%) among CCAR patients (P=0.474). Regimen's characteristics failed to show significant differences between the three groups.

There was no significant difference in mortality rate among patients who initiated their treatment earlier than 5 days compared to those patients who initiated their treatment later than 5 days 37 (61.7%) vs. 23 (38.3%) respectively (P-value 0.267)

No difference was found in the readmission regarding the initiation of treatment; the readmission for patients who started antibiotics within 5 days were 6 (5.5%) while the readmitted patients who started antibiotics after more than 5 days were 6 (5.5%). Moreover, extended duration therapy was not significant in the reduction of the mortality rate as well as the readmission where 34 (31.2%) of those who received their treatment for more than 14 days died compared to 26 (23.9%) who were treated for less than 14 days (P=0.960); 7 (58.3%) readmitted within 45 days compared to 5 (4.6%) of those who received shorter duration courses (P=0.924).

DISCUSSION

In our study, there was a 59.5% increase in CRB infection rate from 2017 to 2018. This finding is similar to other studies and to the CDC report where carbapenem-resistant and carbapenem-resistant Klebsiella increased by 3% and 8% between 2001 and 2011 respectivly[12]. In the Middle East, the availability of data on Carbapenem-Resistant Enterobacteriaceae is limited. CRB has a resistant rate between 1-86% during 2006-2018[13].

The majority of cases diagnosed with positive CRB infection result in negative clinical outcomes (mortality or readmission). Globally, CRB infection was associated with high risk of mortality compared with other bacterial infections[14]. CRB infection found to prolong significantly the hospitalization (3.7 days, 95% CI 0.3 – 6.9) as well as increase hospital mortality (HR 1.75, 95% CI 1.04–2.94) and reduce the probability of cure (HR 0.61, 95% CI 0.45-0.83)[15].

In general, antibiotic options to treat CRB infection are limited and no regimen showed clear superiority over another, which is similar to our finding as none of the three regimens reported to have superiority in neither the reduction of mortality nor readmission rate[16]. In addition, variation in regimens selection could be due to clinicians' experience and practice, culture susceptibility, medications availability and patient factors.

CONCLUSION

There was no significant association between treatment options and clinical outcomes. Moreover, therapy duration was not significant in mortality reduction. None of the different clinical outcomes was significant with different antibiotic regimens, which might be due to the limited sample size.

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Competing Interest: None.

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