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Original Research Paper

Enterobacter Bacteremia – A Retrospective Study in A Teaching Hospital

Medical Science

KEYWORDS : Bacteremia, *Enterobacter*, Underlying Disease, Intravascular Catheter

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ABSTRACT

Objective: *To evaluate the microbiological, clinical and therapeutic factors associated with bacteremia caused by Enterobacter species.*

Methods: *One hundred and twenty-seven cases of bacteremia caused by Enterobacter species over a period of ten years from January 2006- December 2015 in a teaching hospital in Kuwait were enrolled in a retrospective study. Organisms detected by blood culture (BACTEC) were identified by commercial identification systems (API 20E, Vitek 2). Antimicrobial susceptibility was determined by disc diffusion method and Vitek 2. Medical records of the cases were reviewed to study the clinical and therapeutic factors related to the bacteremia.*

Results: *Enterobacter bacteremia accounted for 1.78% of all bacteremias during this period of study, E. cloacae being the leading species (84.25%). The incidence rate in 2006 was 1.19/1000 bacteremic cases ,and 1.88/1000 cases in 2015. One hundred and ten (86.61%) cases were hospital acquired.*

Underlying diseases were detected in 92.12%, the most common being renal disease (59.09%). The most common source of bacteremia was the intravascular catheter (50.39%). Antimicrobial resistance was as follows: third generation cephalosporins 29.92%. ESBL producers were 16.53%. AmpC beta lactamase production was observed in 89.76% of the isolates. Resistance to cefepime , piperacillin –tazobactam, trimethoprim sulfamethoxazole and cefoxitin was 16.53% , 16.53% , 7% and 89.76% respectively. All were sensitive to carbapenems, aminoglycosides and ciprofloxacin except for one strain that was resistant to carbapenems. The response to therapy was 90.55%.

Conclusions: *Enterobacter bacteremia is mostly nosocomial in origin. Intravascular device related bacteremia is a significant clinical problem. AmpC beta lactamase production is a major factor in deciding antimicrobial therapy in Enterobacter bacteremia. In serious infections, carbapenems, ciprofloxacin and aminoglycosides may be the antibiotics of choice with colistin being the only choice if the strain is multidrug resistant.*

Introduction

Enterobacter species are ubiquitous in nature and are frequent colonizers of hospitalized patients. With increasing use of medical support and indwelling devices, nosocomial bacteremia [1,2,3]due to *Enterobacter* species has become more frequent in those with prolonged hospitalisation. *Enterobacter* species which commonly colonise or infect humans are *E. cloacae*, *E. aerogenes*, *E. sakazakii*, *E. gergoviae*, *E. taylorae*,. and *E. amnigenus* [4].

Methods

Case analysis

The microbiological records at Al-Amiri hospital, a 500 bedded teaching hospital in Kuwait, were screened to identify patients with *Enterobacter* bacteremia over a ten year period from January 2006 to December 2015.

A total number of 84,895 blood samples for culture and sensitivity were received during this period of study of which 7100 samples were confirmed positive for various organisms. Out of the positive blood cultures, 127 were found to harbour different species of *Enterobacter*.

Organism identification and antibiotic susceptibility tests

Blood culture samples were processed by BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems, Spark , MD, USA) and positive samples were sub-cultured on blood agar, chocolate agar and MacConkey agar and the plates incubated at 37 ºC for 24 hrs. The organisms were identified by commercial identification systems for Gram negative rods (API 20E; bio Merieux SA, France and Vitek 2). Antimicrobial susceptibility was determined by Vitek 2 and disc diffusion method using Clinical and Laboratory Standards Institute (CLSI)[5]) to the following antibiotics : cefotaxime,

cefepime, cefoxitin, gentamicin, amikacin, ciprofloxacin, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, imipenem and meropenem. Double disc antagonism method was used for the detection of AmpC beta lactamase. Double disc synergy test and E –test (AB Biodisk, Solna, Sweden) were used for the detection of extended spectrum beta lactamases (ESBLs).

The medical records of 127 patients with *Enterobacter* bacteremia were retrospectively reviewed. The bacteremia was labelled as *Enterobacter* bacteremia if the blood culture collected at the stage of acute infection in the patient (eg. high grade fever) turned positive for one of the species of *Enterobacter*. The infection was termed nosocomial if it occurred more than 48 hours after hospitalization. Patients who were not hospitalized but developed bacteremia due to their frequent regular visits to the hospital for peritoneal or haemo dialysis were also grouped under those with nosocomial bacteremia.

The various sources of bacteremia were grouped as intra-abdominal, urine, intravascular catheter, bed-sore, sputum/endotracheal secretion, surgical wound, or un-

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known, if no source identified. The source of bacteremia was confirmed if the organism isolated from the same was a similar species of *Enterobacter* and had a similar antibiogram to that isolated from blood.

Diverse factors like age, sex, and risk factors like underlying disease, bladder catheterization, intravenous catheterisation, previous antibiotic therapy especially with third generation cephalosporins and the period of stay in hospital prior to bacteremia were assessed.

Temperature, vital signs and inflammatory markers of the patient after starting antibiotic therapy was evaluated and this gave a measure of the clinical response in the patient .

Statistical analysis of data was done using SPSS statistical package.

Results

In this study, 7100 positive blood cultures were obtained during the study period, of which 127 were positive for *Enterobacter*. *Enterobacter* bacteremia, therefore, accounted for about 1.78% of all bacteremias.

Microbiological and therapeutic factors *E. cloacae* 107 (84.25 %) was the leading species followed by *E. aerogenes* 19 (14.96%) and *E. sakazakii* 1(0.78%).

Of the 127 isolates of *Enterobacter*, 38 (29.92%) were resistant to the third generation cephalosporins, 21(16.53 %) being ESBL producers, 13 (61.90%) by *E.cloacae* and 8 (38.09%) by *E.aerogenes*. AmpC beta lactamase production was observed in 114 (89.76% of the isolates (table 4). Isolates with combined Amp C and ESBL was observed in 15 (11.81%). Resistance to cefepime (4th generation cephalosporin) was at 16.5%. Resistance to piperacillin-tazobactam, co-trimoxazole and cefoxitin were at 16.5%, 7% and 89.7% respectively (Table 1). All the isolates were susceptible to carbapenems, aminoglycosides and ciprofloxacin except one strain which was resistant to the carbapenems and intermediate to ciprofloxacin. The strain of *E . sakazakii* isolated was found to be sensitive to all the above mentioned antibiotics. The MIC (minimum inhibitory concentration) range in µg/ml for the ESBL and the non-ESBL producers of *Enterobacter* species is summarized in Table 2.

The MIC values for the single carbapenem resistant strain of *E. cloacae* were as follows: cefotaxime >64 µg/ml, cefotaxime-clavulanic acid > 1 µg/ml ,cefepime 6µg/ml, imipenem 32 µg/ml, meropenem 32µg/ml, ciprofloxacin 1.5µg/ml. The isolate was sensitive to aminoglycosides, cotrimoxazole and colistin (MIC 0.38 µg/ml).

Clinical and therapeutic factors

Out of the 127 cases of *Enterobacter* bacteremia, 69(54.3%) were males and 58(45.6%) were females. The age groups affected ranged from a 12 day old neonate to an 89 year old male. Maximum prevalence of *Enterobacter* bacteremia was seen in the age group 40-79 yrs (71.6%).

The bacteremia was nosocomially acquired in 110 (86.6%).

The risk factors observed were as follows: underlying disease 117(92.12%), intravascular catheterisation 64(50.39%),bladder catheterisation50 (39.3%), hospital stay > 2 weeks 55 (43.3%), treatment with antibiotics in the past 1 month 56 (44.09%), post-surgical 12(9.4%) (Table 3).

The most common underlying disease observed was renal disease 75 (59.05%), followed by diabetes 51 (40.15%) and cardiovascular disease 24 (18.89%). An underlying gastrointestinal pathology was seen in 19 (14.96%) cases. Other diseases collectively contributed to 14 (11.02%) cases which include tuberculosis, carcinoma, auto immune disorders and neurovascular pathology (Figure 1).

The source of infection could be identified in 97 (76.3%) and in 30 (23.6%), the source was unknown. Intravascular device/site was the main source in 64 (50.39%) cases followed by respiratory (sputum, endotracheal) 12(9.4%) urine 11 (8.6%), intra-abdominal (bile, ascitic fluid, drain fluids) 6 (4.7%) and sources like bed sore and synovial fluid in 4 (3.14%) cases. (Table 4).

Ninety one (71.6%) cases were on empirical antibiotic treatment. The treatment in these cases was modified according to the results of the antibiotic sensitivity tests (Figure 2). Seventy (55.11%) were treated with meropenem, 22 (17.32%) with piperacillin-tazobactam, 17 (13.38%) with ciprofloxacin and 8 (6.2%) with cefepime.

Aminoglycosides were used in combination with the above antibiotics in 25 (19.6%) cases. Amikacin courses were for short duration usually extending for 3-5 days. Of the ten (7.87%) cases that were initially on ceftriaxone, five were changed to meropenem due to lack of clinical progress. The remaining five, however responded to ceftriaxone , probably because these isolates were not ESBL or Amp C producers and perhaps due to the added effect of amikacin.

Overall response to therapy was observed in 115 (90.55%) cases. The cause of death in the remaining cases was not related to the bacteremia but were due to cardio-pulmonary arrest in 4 cases, end stage renal failure in 5 and wide spread carcinomatous metastases in 3.

ANOVA test revealed that the values for the age groups 40-49, 50-59,60-69 and 70-79 years were significantly higher than those compared to age groups 0-9, 10-19, 20-29,30-39 and 80-89years.

p-value<0.05. We are currently unable to offer any scientific explanation for the difference in the values observed in these age groups.

Discussion

In this study, *E . cloacae* accounted for the majority of bacteremic episodes caused by Enterobacter species. This is in accordance with most of the previous studies on *Enterobacter* bacteremias [6,7,8] with the exception of one study [9] where *E. aerogenes* was the leading species.

The bacteremia was nosocomially acquired in 110 (86.6%) cases [10,11,12,13].

Of the 76.3% cases, where the source of bacteremia was known, the intravascular cannula was the most common source (50.39%), thereby suggesting that intravascular device related blood stream infection is a signifi-

cant clinical problem[14]. The source of bacteremia was unknown in 23.6 % cases.

Underlying disease was observed in 92.12% with renal disease being the predominant disease (59.05%) in these patients.

Among the diverse risk factors observed in this study , 44.09% cases were exposed to broad spectrum antibiotics in the past 30 days prior to the onset of bacteremia and 43.3% had a stay in hospital for more than 2 weeks before the bacteremic episode. A 12 day old neonate with *Enterobacter* bacteremia was a preterm baby with vesicoureteric reflux Grade 4 and a small right kidney and was empirically treated with cefotaxime.

The antibiotic resistance pattern showed 30% of the species to be resistant to the third generation cephalosporins. ESBL production was seen in 16.5% and combined ESBL with AmpC in 11%. All isolates had MICs in the susceptible range for carbapenems except one strain which was carbapenem resistant (imipenem MIC 32µg/ml, meropenem MIC 32µg/ml). This strain showed intermediate susceptibility to ciprofloxacin (MIC 1.5µg/ml). Colistin MIC was 0.38µg/ml and the patient, a post surgical case, was treated with colistin (intravenous and nebulisation) successfully. The patient underwent tracheostomy and prolonged mechanical ventilation and a prolonged hospital stay of more than 2 months before the onset of bacteremia. The sources of infection in this case was the intravenous cannula and the sputum/ endotracheal secretion.

Enterobacter species have an inducible chromosomally encoded cephalosporinase (Amp C β lactamase) the induction of which, on exposure to third generation cephalosporins, results in resistance to these antibiotics [15,16]. Broad spectrum cephalosporin resistance has been shown to complicate the treatment of *Enterobacter* bacteremias in several studies [15,17].

The fourth generation cephalosporin (cefepime) [16] is relatively stable to Amp C β lactamase and has moderate activity against *Enterobacter* species.

Carbapenems, although being strong inducers of Amp C β lactamase, remain stable to the action of these enzymes, and are therefore most reliable antibiotics to treat *Enterobacter* bacteremias. The other drugs indicated are aminoglycosides and fluoroquinolones, with cefepime being a distant choice [18].

In the treatment of carbapenem resistant *Enterobacter* isolates, ciprofloxacin can be used ,if susceptible. Otherwise, colistin becomes the ultimate drug of choice .

Conclusions

Enterobacter bacteremia is common in hospitalized patients with underlying diseases and in those with instrumentation like intravascular catheterization and mechanical ventilation. Cannula related infections are amongst the most important nosocomial infections. Strategies to prevent device related bacteremias should be strictly adhered to. In the wake of emerging carbapenem resistant strains of *Enterobacter* species, clinicians should be alert to the judicious use of antibiotics to curb the growing menace of antibiotic resistance. In the presence of prompt and appropriate antibiotic therapy, *Enterobacter* bacteremia, however, does not adversely affect the outcome in most patients.

Table 1
ANTIMICROBIAL RESISTANCE PERCENTAGE (126/127 *Enterobacter* bacteremia cases)

ANTIBIOTIC	RESISTANCE %
Cefotaxime	29.92
Cefoxitin	89.76
Amikacin,Gentamicin	0
Ciprofloxacin	0
Piperacillin-tazobactam	16.53
Trimethoprim/Sulphamethoxazole	7
Meropenem, Imipenem	0
Cefepime	16.53

Table 2
MIC Range (µg /ml) – 126/127 *Enterobacter* bacteremia cases

Antibiotic	ESBL	Non ESBL
Cefotaxime	16 - > 256	0.047 - 1.0
Cefotaxime-clavulanicacid	0.75 - 1.0	0.032 - 0.5
Ceftazidime	32 - > 32	0.5 - > 1.0
Ceftazidime-clavulanic acid	0.25 - 4.0	0.094 - 1.5
Cefepime	16 - 64	0.023 - 0.094
Gentamicin	0.125 – 0.25	0.064 - 0.25
Amikacin	1.0 – 1.5	0.75 - 1.5
Ciprofloxacin	0.004 - 0.38	0.006 – 0.38
Imipenem	0.19 - 0.38	0.125 - 0.38
Meropenem	0.032 - 0.094	0.012 - 0.064

Table 3
Risk factors associated with the 127 cases of *Enterobacter* bacteremia

Total no.of cases	Bladder catheterization	Intravascular catheterization	Prior antibiotic treatment (within 30 days prior to onset of bacteremia)	Stay in hospital (>2 weeks prior to onset of bacteremia)	Post surgical	Underlying disease
127	50	64	56	55	12	117
%	39.3	50.3	44.1	43.3	9.4	92.1

Table 4
Source of infection in relation to *Enterobacter* bacteremia -127 cases

Source	No.(%) of associated cases of bacteremia
Intravenous cannula	64 (50.3)
Sputum/endotracheal secretion	12 (9.4)
Intra-abdominal	6 (4.7)
Bed-sore	4(3.1)
Urine	11 (8.6)
Unknown	10 (37.03)

Figure -1 Undelying Diseases in relation to *Enterobacter* Bacteremia.

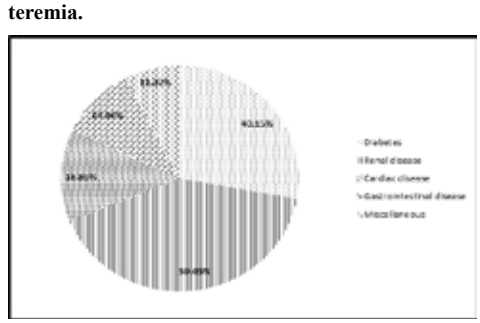

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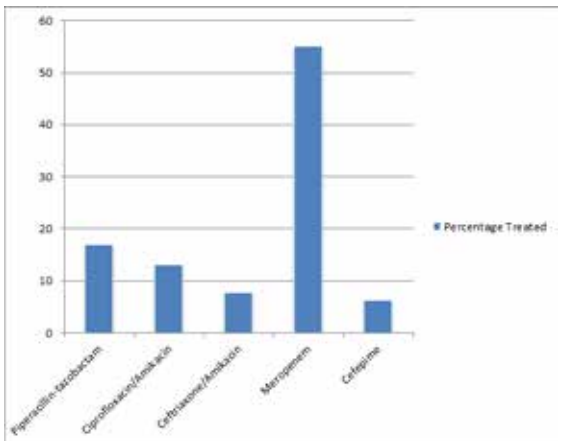
Figure 2 Therapy in relation to *Enterobacter* bacteremia – 126/127 cases



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