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Neonatal Gram-negative Sepsis in a Tertiary Hospital in Jordan: When Fever Means Multidrug Resistance!

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Abstract

Objective: Development of multidrug resistance in Gram-negative bacteria affecting neonates is a major challenge. Studying the epidemiology and clinical presentation is crucial to improve preventive and therapeutic measures and helps to decrease morbidity and mortality. This study is the first to report Carbapenems resistant gram negative bacteria in neonates in the Arab world. It will stimulate further research efforts and increase awareness of health decision makers towards this potentially lethal pathogen.

Methodology: This retrospective hospital-based study investigated neonatal sepsis caused by Gram-negative bacteria and identified three groups of microorganisms: Cephalosporin sensitive, Cephalosporin resistant and Carbapenems resistant bacteria (CRB). Clinical presentation, risk factors and outcome were compared.

Results: Gram-negative bacteria isolated from 99 blood cultures were included in the study. The most common Gram negative bacteria were Cephalosporin resistant (47 septic episodes), followed by Carbapenems resistant bacteria (28 septic episodes). Of the cases included, 70% were late septic episodes. Acinetobacter was the only Carbapenems resistant microorganism. Fever was the most common symptom in the Cephalosporin and Carbapenems resistant groups. The mortality rate was 16.2%, with the lowest mortality rate being found in the CRB group. None of the mortalities had fever at presentation.

Conclusion: CRB are a major cause of neonatal sepsis in our hospital. In units where multidrug resistance is an issue, febrile neonates should be managed with great care.

Keywords: Neonate; Sepsis; Gram negative; Multidrug resistance; Fever; Carbapenems resistance; Acinetobacter

Background

Neonatal sepsis is a leading cause of neonatal morbidity and mortality in the Arab countries [1,2]. Gram-negative Bacteria are one of the most important causative agents of neonatal sepsis, resulting in the highest morbidity and mortality rates [3,4]. The treatment of these pathogens has become increasingly difficult, with the surfacing of multidrug resistant Gram-negative bacteria necessitating the use of newer and more expensive agents which in turn has resulted in a significant clinical and economic burden.

Carbapenems have been the last resort for years [5]. The recent occurrence of Carbapenems resistant Gram-negative bacteria in neonatal units in different parts of the world is a cause for great concern [6-8].

This study investigated neonatal sepsis caused by Gram-negative bacteria. We report the microbiological distribution of Carbapenems resistant Gram-negative bacteria, clinical presentation, risk factors and outcome, comparing them to Cephalosporin resistant and Cephalosporin sensitive Gram-negative bacteria.

Methodology

This was a retrospective, descriptive hospital-based study of neonates admitted to the neonatal intensive care unit at the University of Jordan Hospital in Amman, Jordan [9]. This is a level 3 tertiary care unit with an average of 600 admissions per year. The study was approved and funded by the Deanship of Scientific Research at the University of Jordan.

The hospital database was reviewed for all newborns admitted to the NICU during the period August 2009 to December 2011. All newborns that had had blood culture samples taken were included in the study. The laboratory database was reviewed for date of culture, whether positive or negative for bacterial growth, type of microorganisms and antibiotic sensitivity patterns.

The hospital charts of newborns that had positive blood cultures were reviewed for demographic and clinical data by two reviewers. The reason for doing septic work-up (signs at 0 hour) and the outcome were also recorded. The septic episodes due to Gram-negative sepsis were then divided into three groups according to antibiotic sensitivity patterns: Cephalosporin sensitive, Cephalosporin resistant and Carbapenems resistant.

The unit protocol regarding sepsis work up is to draw blood culture and start antibiotics under the following conditions: prematurity caused by spontaneous labour (gestational age <32 weeks), presence of

a major risk factor for sepsis, i.e. prolonged rupture of membranes, and signs of neonatal sepsis.

Early onset sepsis is defined as sepsis occurring in the first 72 hours of life. Late onset sepsis is defined as sepsis occurring after 72 hours of life. Empirical treatment for early onset sepsis consisted of Ampicillin and an Aminoglycoside. Empirical treatment for late onset sepsis consisted of Vancomycin and Imipenem.

Central lines are umbilical venous catheters (UVC) and peripherally inserted central catheters (PICC). In both instances these were inserted using aseptic technique. Duration of UVC use is 5-7 days. PICCs remain in place for as long as the indication for insertion continues.

Central line-associated bloodstream infection (CLABSI) is defined as sepsis with central line in situ or if central line was present up to 48 hours before the date of a positive blood culture. Abnormal laboratory results include any of the following: leukocytosis, leukopenia, pancytopenia, thrombocytopenia or increased C-reactive protein.

Cephalosporin resistant bacteria are defined as Gram-negative bacteria that are not susceptible to all of the following third-generation Cephalosporins: Ceftazidime, Ceftriaxone and Cefotaxime. Carbapenems resistant bacteria are defined as Gram-negative bacteria that are not susceptible to one of the following Carbapenems: Meropenem or Imipenem, and are resistant to all of the following Cephalosporins: Ceftriaxone, Cefotaxime, and Ceftazidime. Sepsis related Mortality was defined as death within 7 days of the gram negative septic episode. Exposure to an antibiotic was defined as previous treatment with that particular antibiotic.

Results

	Cephalosporin Sensitive (24)	Cephalosporin Resistant (47)	Carbapenems Resistant (28)
Premature <37 week	20 (83.3%)	33 (70.2%)	20 (71.4%)
Birth wt. <2500 g	18 (75.0%)	31 (66.0%)	20 (71.4%)
Late sepsis	21 (87.5)	46 (97.9%)	27 (96.4)
CLABSI	8 (33.3%)	16 (34.0%)	16 (57.0%)
Age of sepsis (Average /days)	15.3	14.2	12.5
Carbapenems exposure	10 (41.7%)	10 (21.3%)	6 (21.4%)
Cephalosporin exposure	2 (8.3%)	15 (31.9%)	5 (17.9%)
Mortality	3 (12.5%)	10 (21.3%)	3 (10.7%)

Table 1: Demographic and clinical data of gram negative neonatal sepsis according to antibiotic sensitivity patterns.

One hundred forty-one blood cultures with Gram-negative bacteria were identified, representing 103 septic episodes in 100 newborns. Four blood cultures were excluded where no sensitivity tests had been carried out. Ninety-nine blood cultures were included in the final analysis after removal of blood culture duplicates. Most of the newborns with Gram-negative sepsis in the three groups were low birth weight (<2500 g) and premature (<37 weeks gestation) infants (69.7% and 73.7%, respectively). Late onset sepsis was the most common in all three groups. CLABSIs were highest in the CRB group (57%). Of 99 newborns with Gram-negative sepsis, 16 died within 7 days of positive culture, giving a mortality rate of 16.2%. The lowest mortality rate was in the CRB group (10.7%).

The most common Gram-negative bacteria according to antibiotic sensitivity pattern were Cephalosporin resistant bacteria (47.5%), followed by Carbapenems resistant bacteria (28.3%). Exposure to Carbapenems was highest in the Cephalosporin sensitive group, while exposure to Cephalosporins was highest in the Cephalosporin resistant group (Table 1). Acinetobacter was the only Carbapenems resistant Gram-negative bacteria identified (Figure 1).

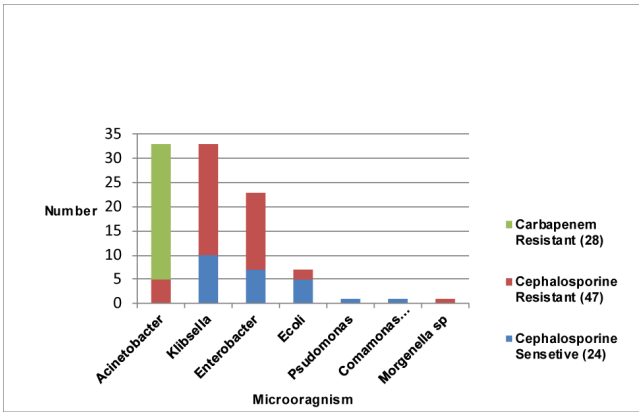

Figure 1: Microbiological distribution of Gram-negative neonatal sepsis according to antibiotic sensitivity patterns.

Fever was the most common presenting symptom in both Cephalosporin resistant and Carbapenems resistant groups. Respiratory symptoms were the most common presentation in the Cephalosporin sensitive group. The laboratory abnormalities in asymptomatic newborns were the third most common presentation of the CRB group (17.9%) (Figure 2). In the Cephalosporin sensitive and CRB groups, none of the infants who died had fever at presentation (Table 2).

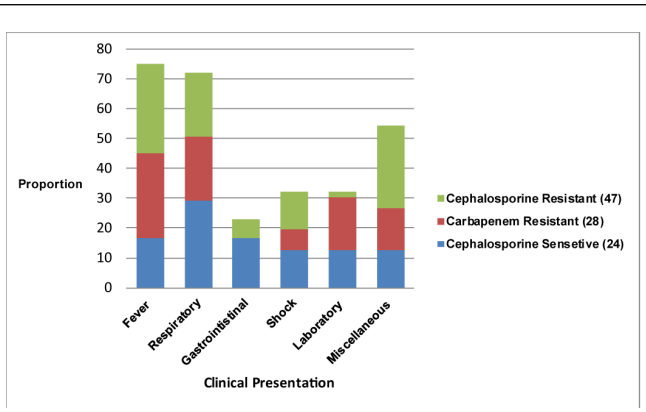

Figure 2: Clinical presentation of Gram-negative neonatal sepsis according to antibiotic sensitivity patterns.

Discussion

Carbapenems resistant bacteria are a threat to our healthcare facilities [10], especially in neonatal units that care for relatively immunocompromised patients for a long period of time. This has now become a worldwide concern [11]. Neonatal units in Jordan experience significant difficulties due to limited resources, cost of prolonged hospitalization and expensive treatment. This constitutes an added obstacle to decreasing neonatal mortality and morbidity, which is relatively high [12].

	Cephalosporin Sensitive (24)		Cephalosporin Resistant (47)		Carbapenems Resistant (28)	
	Survivors (21)	Non-Survivors (3)	Survivors (37)	Non-Survivors (10)	Survivors (25)	Non-Survivors (3)
Average GA (wks)	33	31	33	34.2	34.1	36
male sex	14 (66.7%)	1 (33.3%)	24 (80%)	6 (60%)	18 (72%)	1 (33.3%)
Average Birth Wt. (Kg)	2.14	1.55	1.7	1.88	1.9	2.2
Average Age at sepsis	14.9	18.7	13.7	10	12.4	13.7
CLABSI	8 (38.1%)	1 (33.3%)	12 (32.4%)	4 (40%)	14 (56%)	2 (66.7%)
Shock	0 (0%)	1 (33.3%)	3 (8%)	3 (30%)	1 (4%)	2 (66.7%)
Fever	4 (19%)	0 (0%)	12 (32.4%)	2 (20%)	8 (32%)	0 (0%)

Table 2: Survivors and non-survivors characteristics according to antibiotic sensitivity patterns.

The only Gram-negative bacteria identified in this study as being Carbapenems resistant was Acinetobacter, which has been found in other studies as well [13]. Acinetobacter is an environmental contaminant that can tolerate various temperatures and pH conditions. This enables it to persist in a hospital environment and facilitates transmission of the organism [14].

Infections with CRB occurred more in premature and low birth weight babies, as well as in male newborns, which is a feature of all Gram-negative bacteria identified in this study. Unlike previous reports, most of the newborns with sepsis due to CRB were not exposed to Carbapenems or Cephalosporins. This might be due to the fact that all of the CRB identified in this study were Acinetobacter species, which are influenced more by environmental factors.

Although fever is not a common presentation of neonatal sepsis [15], in our setting it was the most common presenting symptom of multidrug resistant bacteria (Cephalosporin and Carbapenems resistant). In units where multidrug resistant bacteria are a major issue, neonatal fever should be investigated immediately with a view to excluding sepsis.

A total 17.8% of cases of CRB sepsis had presented without clinical signs and were diagnosed by abnormal laboratory results. Thus in outbreaks due to CRB, we suggest that treatment should be initiated on the basis of abnormal laboratory results while awaiting the results of primary blood culture.

The mortality rate due to CRB was the lowest for all Gram-negative bacteria. Although the definition of mortality varies amongst studies, in our study the mortality rate due to CRB was lower than in previous reports [16]. This might be attributed to the fact that our unit has experienced considerable multidrug resistance, which has resulted in an aggressive approach to antibiotic treatment. The mortality rate may also be lower due to the patients having a different genetic disposition. Infants who died were more mature, weighed more at birth, and their average age of infection was higher than that of survivors, which is contrary to expectation. We have no explanation for this, but it might be due to a greater tolerance for early signs of sepsis in these babies and a lower index of expectation of serious illness. Further analysis and interpretation were not possible due to the small sample size. None of the mortalities had fever as a presenting sign; this might reflect a decreased immune response in these newborns, or be due to the early initiation of treatment on presentation of this serious clinical symptom.

Conclusions

As far as the authors are aware, this study is the first to report the presence of CRB in neonatal units in Arab countries. It provides significant clinical information regarding the occurrence of Carbapenems resistant bacteria in a neonatal population. This could assist in the development of preventive strategies, including screening methods, and also in the initiation of early treatment so as to achieve a better outcome for these vulnerable hosts. Future research should focus on preventive measures and early diagnostic tools.

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References

1. Al-Shamahy HA, Sabrah AA, Al-Robasi AB, Naser SM (2012) Types of Bacteria associated with Neonatal Sepsis in Al-Thawra University Hospital, Sana'a, Yemen, and their Antimicrobial Profile. Sultan Qaboos Univ Med J 12: 48-54.
2. Tosson AM, Speer CP (2011) Microbial pathogens causative of neonatal sepsis in Arabic countries. J Matern Fetal Neonatal Med 24: 990-994.
3. Al-Hasan MN, Huskins WC, Lahr BD, Eckel-Passow JE, Baddour LM (2011) Epidemiology and outcome of Gram-negative bloodstream infection in children: a population-based study. Epidemiol Infect 139: 791-796.
4. Venkatesh MP, Garcia-Prats JA (2008) Management of neonatal sepsis by Gram-negative pathogens. Expert Rev Anti Infect Ther 6: 929-938.
5. Velaphi S, Wadula J, Nakwa F (2009) Mortality rate in neonates infected with extended-spectrum beta lactamase-producing Klebsiella species and selective empirical use of meropenem. Ann Trop Paediatr 29: 101-110.
6. National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion, Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE), 2012 CRE Toolkit.
7. Lambiase A, Piazza O, Rossano F, Del Pezzo M, Tufano R, et al. (2012) Persistence of Carbapenem resistant Acinetobacter baumannii strains in

an Italian intensive care unit during a forty-six month study period. New Microbiol 35: 199-206.

8. Roy S, Singh AK, Viswanathan R, Nandy RK, Basu S (2011) Transmission of imipenem resistance determinants during the course of an outbreak of NDM-1 Escherichia coli in a sick newborn care unit. J Antimicrob Chemother 66: 2773-2780.
9. Papadimitriou M, Voulgari E, Ranellou K, Koemtzidou E, Lebessi E, et al. (2011) Emergence of VIM-1 metallo-Î²-lactamase-producing Escherichia coli in a neonatal intensive care unit. Microb Drug Resist 17: 105-108.
10. Ageevets VA, Partina IV, Lisitsyna ES, Ilina EN, Lobzin YV, et al. (2014) Emergence of carbapenemase-producing Gram-negative bacteria in Saint Petersburg, Russia. Int J Antimicrob Agents 44: 152-155.
11. Mehar V, Yadav D, Somani P, Bhatambare G, Mulye S, et al. (2013) Neonatal sepsis in a tertiary care center in central India: microbiological profile, antimicrobial sensitivity pattern and outcome. J Neonatal Perinatal Med 6: 165-172.
12. UNICEF report on basic indicators of Jordan.
13. Poirel L, Nordmann P (2006) Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology. Clin Microbiol Infect 12: 826-836.
14. Bergogne-Bérézin E, Towner KJ (1996) Acinetobacter spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin Microbiol Rev 9: 148-165.
15. Hofer N, Müller W, Resch B (2012) Neonates presenting with temperature symptoms: role in the diagnosis of early onset sepsis. Pediatr Int 54: 486-490.
16. Thatrimontrichai A, Apisarnthanarak A, Chanvitan P, Janjindamai W, Dissaneevate S, et al. (2013) Risk factors and outcomes of Carbapenem-resistant Acinetobacter baumannii bacteremia in neonatal intensive care unit: A case- control study. Pediatr Infect Dis J 32: 140-145.