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Underlying Characteristics and Outcome of Extensively Resistant *Acinetobacter baumannii* Infection and Colonization in a Saudi Neonatal Intensive Care Unit

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Abstract

Extensively drug-resistant *Acinetobacter baumannii* (XDRAB) is a rapidly emerging pathogen causing threat to health care settings. The resultant morbidity and mortality rates are high due to limited therapeutic options. The present study demonstrates the characteristics of neonates, infected or colonized with XDRAB, antibiotic susceptibility patterns of the isolates, and neonatal outcomes. This retrospective study was conducted in the neonatal intensive care unit (NICU) of Dallah hospital, Riyadh, Saudi Arabia during the period January 2015 to December 2017. All neonates with positive XDRAB cultures from any location in the body were included, infected and colonized cases were compared. XDRAB was isolated from 16 neonates. Seventy-five percent of the affected neonates were preterm, with a median gestational age and birth weight of 32.5 weeks and 1,675 g, respectively. The median time to XDRAB infection/colonization for all cases was 14 days. Seventy-five percent of the cases had central venous catheters and 50 percent had surgery/procedure performed during stay in NICU. Half of the affected neonates had underlying congenital anomalies and chronic medical conditions. Fourteen affected neonates (87%) received prior courses of cefotaxime. In 15 of 16 cases, XDRAB infection manifested clinically as late-onset sepsis with bacteremia and ventilator-associated pneumonia (VAP). XDRAB isolates were resistant to all β-lactams and carbapenems. Resistance rate to other antibiotics was 93% for gentamicin and 50% for ciprofloxacin. All XDRAB isolates were susceptible to colistin. Seventy-five percent of the infected neonates died due to XDRAB sepsis, while 37% of the colonized group died of other underlying diseases. Fifty percent of the infected neonates died within 4 days of XDRAB infection. Prematurity, low birth weight, the use

Keywords
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- extensively drug resistance

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of vascular devices, and prior use of cefotaxime played a major role in XDRAB infection/colonization in our unit. It is crucial to consider early start of colistin, either alone or in combination therapy, especially for the neonates at high risk, for example, those with certain underlying chronic conditions who manifest with late-onset sepsis and/or VAP.

Introduction

Extensively drug-resistant (XDR) gram-negative bacteria *Acinetobacter baumannii* is an escalating global public health threat. The morbidity and mortality rates are high due to limited therapeutic alternatives because the isolates are resistant to carbapenems the "last-line" antibiotics, particularly for managing those with multidrug-resistant gram-negative infections.[1] Among critically ill neonates, infection with XRD *A. baumannii* (XDRAB) has emerged over the past few years as a serious threat. These infections vary in presentation, and in neonates tend to be associated with preterm birth and low birth weight. XDRAB causes life-threatening infections in neonates hospitalized in neonatal intensive care units (NICUs), including pneumonia, meningitis, bacteremia and have been related to increased duration of hospitalization and substantial health care expense.[2,3] The organism's exceptional survival characteristics, along with its diverse clinical spectrum of disease and multiple resistance mechanisms, make it a challenging pathogen in the health care environment. In neonates, the prevalence of *A. baumannii* infection has been reported to be 0.2 to 6.9%.[4,5] *A. baumannii* has been reported as a causative pathogen in 14% of the cases of early onset sepsis and in 9% of the late-onset sepsis in newborns.[6] The reported prevalence of neonatal XDRAB infection has varied from 33.3 to 62% in South Asia, mainly in the outbreak reports.[7] There have been limited reports of characteristics and outcomes of XDRAB infection in the NICU in non-outbreak settings. In this study, we present the underlying characteristics of neonates, either infected or colonized with XDRAB, the antibiotic susceptibility patterns of the isolates, and neonatal outcomes at our center.

Patients and Methods

Between January 1, 2015 and December 31, 2017, all neonates with *Acinetobacter* were identified retrospectively through both infection control surveillance data and computerized microbiology laboratory databases; all neonates who had developed either an infection or colonization with XDRAB were included.

The NICU at Dallah hospital is a level III private hospital with 36 beds (including 18 intensive care beds and 3 isolation rooms) in Riyadh, Saudi Arabia. Dallah hospital is a tertiary care, Joint Commission International-accredited hospital with 400 beds with separate pediatric, neonatal, adult, and cardiac intensive care units. It is a major birthing center in Riyadh, with approximately 3,000 deliveries performed annually. The NICU is supervised by two consultant neonatologists and three pediatricians. The unit policy for neonatal sepsis is to obtain cultures and to start empiric antibiotics. Ampicillin and gentamicin were used for early-onset sepsis (EOS). For late-onset sepsis vancomycin and cefotaxime or meropenem are used.

Modification of antibiotic regimens is then based on the results of antibiotic susceptibility or when the neonate's clinical condition does not improve after 48 hours as judged by the treating physician. The hospital has an Infection Prevention and Control Department, consisting of an infectious disease consultant and three infection control nurses. They run a surveillance program for health care-associated infections.

Data were recorded using a predesigned procedure. Information about neonates including demographic characteristics, gestational age, birth weight, mode of delivery was recorded. The admission and discharge dates, use of central vascular catheters, duration of mechanical ventilation, parenteral nutrition, signs and symptoms of sepsis, microbiologic culture result, prior antibiotics use, and timing of appropriate antibiotic treatment were abstracted from the patient chart. We included neonates who were admitted in the NICU during the study period, had a duration of stay of at least 24 hours, and who had either positive XDRAB culture from clinical specimen or a positive surveillance culture (swabs of the nose, throat, Eustachian tube, axilla, groin, stool, or rectum).

Microbiology Identification, and Susceptibility Testing

Blood specimens were cultured using BacT/ALERT pediatric bottle and incubated in the BacT/ALERT 3D automated system (bioMérieux, Durham, North Carolina, United States) for 7 days.

Respiratory cultures used endotracheal tube aspirate specimens obtained from intubated neonates. The active surveillance specimens were inoculated on Mac-Conkey agar plates and incubated at 35°C for 24 to 48 hours. The identification and antimicrobial susceptibility testing of isolates were performed using the Vitek-2 automatized system (bioMérieux, Marcy l'Etoile, France). Classes of tested antibiotics included cephalosporins (ceftazidime, cefepime), extended spectrum penicillin (piperacillin-tazobactam), carbapenems (imipenem and meropenem), aminoglycosides (amikacin and gentamicin), quinolones (ciprofloxacin), and colistin. The minimum inhibitory concentration (MIC) determination and interpretation results were comparable to those of the clinical and laboratory standards institute breakpoints.[8] Colistin MIC was confirmed by E-test (bioMérieux SA, Marcy l'Etoile, France). XDR characteristics were defined as the isolate nonsusceptible to at least one agent in all but

two or fewer in ≥ 6 antimicrobial categories.[9] Nonduplicate XDRAB isolates were selected. Molecular testing of the isolates was not performed due to the unavailability in the hospital. The study was approved by the Hospital Research Ethics Committee.

Definitions

XDRAB infection was defined as any neonate with clinical features of sepsis with apnea, bradycardia, hemodynamic instability, hypoglycemia, reduced activity and skin mottling, along with a positive culture for XDRAB from either blood, urine, cerebrospinal fluid, endotracheal tube, or aseptically fluid. Colonization was defined as the detection of XDRAB from nonsterile body site in the absence of clinical signs of active infection. Prolonged hospitalization is defined as a neonate who required NICU stay after a postconceptional age of 42 weeks. Ventilator-associated pneumonia (VAP) is defined as a progressive respiratory symptom with infiltrates/patches on chest X-ray.[10]

A history of surgery/procedure was considered significant, if the procedure is performed within 7 to 10 days before the result of a positive blood/other site culture.

Death was considered secondary to sepsis if it occurred within 7 days of a positive blood culture or if clinical sepsis was documented in the medical records as the direct cause of death. We considered antimicrobial therapy to be adequate if the regimen included at least one drug showing in vitro activity against the XDRAB isolate, and to be inadequate empiric antimicrobial therapy if the prescribed antibiotic regimen did not cover the resistant *Acinetobacter* isolate for over 48 hours from the day that blood cultures were obtained. Appropriate prompt antibiotic treatment with colistin was defined as the use of colistin either prior to (with clinical manifestations) or notification of positive culture report of XDRAB. The time to XDRAB infection or colonization was calculated from the date of NICU admission.

Data Analysis

Data were analyzed using SPSS software (version 24.00; SPSS Inc., Chicago, Illinois, United States). Descriptive statistics (frequencies, percentages, median, and interquartile range) were used to describe the categorical and skewed quantitative variables.

Fisher's exact test and Mann-Whitney U test were used to observe the statistical significance difference between the infected and colonized patients. A p-value of ≤ 0.05 was considered as statistically significant.

Results

During the study period, 1,453 neonates were admitted to the NICU. Of those, 348 (24%) neonates weighed less than 1,500 g at birth, 872 (60%) neonates were born preterm (prior to 37 weeks gestation), and 727 (50%) were delivered via cesarean section.

Twenty-two neonates (1.5%) had positive culture for *A. baumannii*, of which sixteen were confirmed as XDRAB (1.1%). These manifested as infection in eight neonates (50%) and as colonization in eight neonates (50%). Seventy-five percent of the affected neonates were born preterm, with a median gestational age of 32.5 weeks and median birth weight of 1,675 g. The median time to XDRAB infection/colonization for all cases was 14 days.

Central venous catheters (umbilical lines and/or peripherally inserted central catheters, or PICC) were placed in 12 cases (75%) during their stay in the NICU. Fifty percent of affected neonates had surgery/procedure performed during stay in NICU. These included laparotomies ($n = 2$), tracheostomy ($n = 1$), intraventricular drain insertion ($n = 1$), and intercostal tube insertion ($n = 4$). Fifty percent of the neonates had underlying medical conditions including congenital heart disease (two cases), tracheoesophageal fistula (two cases), intraventricular hemorrhage (two cases), and hypoxic ischemic encephalopathy (two cases). Infected compared with colonized neonates, infected neonates had lower birth weights, shorter durations of hospitalization, and shorter time to XDRAB infection (►**Table 1**); however, this was not statistically significant ($p > 0.05$).

Seven of the eight neonates who developed XDRAB infection presented with late-onset sepsis. The median time from admission to the development of XDRAB infection was 8.5 days (IQR 25.5 days). Seventy-five percent of these infants were under 2 weeks of age at the time of the diagnosis of XDRAB infection. All infected infants developed XDRAB bacteremia and VAP.

In addition, one neonate had meningitis (cerebrospinal fluid culture positive for XDRAB) and another had urinary tract infection (positive urine culture). One neonate had positive XDRAB culture on the second day of admission; maternal high vaginal swab (HVS) cultures as well as labor room swabs (respiratory therapy equipment, sinks, tap water, weighing scales, resus station) were performed but all were negative.

In the colonized group, nasopharyngeal swab and endotracheal tube aspirate were the most common site for colonization ($n = 7$), followed by inguinal ($n = 3$), wound ($n = 1$), and stool culture ($n = 1$). Thirteen neonates (81%) received prior courses of ampicillin and gentamicin as per the unit protocol for EOS. These were followed by several courses of broad-spectrum antibiotics for LOS that included cefotaxime in 14 cases (87%), vancomycin in eight cases (50%), and meropenem in seven cases (44%).

All 16 isolates were uniformly resistant to piperacillin-tazobactam (MIC >128 µg/mL), ceftazidime (MIC >32 µg/mL), cefepime (MIC >32 µg/mL), meropenem (MIC >16 µg/mL). Resistance to gentamicin (MIC >16 µg/mL) and amikacin (MIC >64 µg/mL) was shown by 15 of the 16 isolates, while 8 of the 16 isolates were resistant to ciprofloxacin (MIC >4 µg/mL). All isolates were susceptible to colistin as confirmed by the E-test (MIC 0.5 µg/mL).

Antimicrobial therapy was based on antibiotic susceptibilities. Colistin was used in 15 neonates with XDRAB infection/colonization. Three infected neonates received colistin as monotherapy. Three neonates were treated with the combination of colistin and ciprofloxacin and one neonate received dual therapy of colistin and amikacin (►**Table 2**). In

Table 1 Characteristics of neonates with XDRAB infection and colonization

Characteristics of patients	Infected infants ($n = 8$)	Colonized infants ($n = 8$)	*p*-Value
Sex: male	4 (50)	5 (62.5)	0.608[b]
Birth weight, g, median (IQR)	1630 (987.5)	1720 (761.2)	0.529[a]
C-section mode	3 (37.5)	5 (62.5)	0.619[b]
Gestation in weeks at admission, median (IQR)	31.5 (8.2)	33.5 (6.5)	0.460[a]
Duration of hospitalization in days, median (IQR)	25.5 (32.2)	42.5 (63.2)	0.093[a]
Time to XDRAB, median (IQR)	8.5 (25.5)	19 (27.2)	0.400[a]
Duration of ventilation (d, median [IQR])	10 (13.7)	27 (90.7)	0.370[a]
Surgery	4 (50)	4 (50)	1.0[b]
Outcome, death (%)	6 (75)	3 (37.5)	0.315[b]

Abbreviations: XDRAB, extensively drug-resistant *Acinetobacter baumannii*; IQR, interquartile range.
[a]By using Mann–Whitney *U* test.
[b]Fisher's exact test.
Note: Results are *n* (%) unless stated otherwise.

63% of the cases, colistin was started within 48 hours of the onset of symptoms, whereas the remaining neonates were started on colistin only after the culture result was available. One neonate had persistent positive blood culture in spite of being on colistin and amikacin. Another neonate developed recurrent bacteremia due to XDRAB with no obvious focus. The two infected neonates who survived were treated for 14 to 28 days after the first negative culture. All neonates with XDRAB colonization received a course of colistin monotherapy for 14 days.

Colistin was well tolerated in 15 neonates; there were no significant adverse effects noted, except for one case who developed high serum creatinine (90 mmol/L), which improved after colistin dose was adjusted.

Nine of the 16 infected/colonized neonates died. Of those, six neonates were among the infected group, five neonates were preterm, one had VATER association, and one had a tracheoesophageal fistula. XDRAB sepsis was the primary cause of death. The mean duration from XDRAB onset to death was 11 days. In the colonization group, the three neonates who died had comorbidities that were the primary cause of death, including hypoplastic left heart syndrome, Dandy–Walker syndrome, and congenital lung disease with ventilator dependence.

Discussion

Although XDR *A. baumannii* infection rates are rapidly rising worldwide, this is to our knowledge the first reported study of XDRAB infection in a pod-style NICU setting in Saudi Arabia. We have identified an alarming burden of XDRAB in our NICU with an alarming rate of high mortality. *Acinetobacter spp*. are typically considered environmental organisms, suggesting that the source of acquisition of these pathogens was more likely due to nosocomial spread of organisms through poor infection control measures, nonadherence with hand hygiene, and improper equipment disinfection, all work together to promote the transfer of these nosocomial pathogens.[11] Maternal transfer during delivery is less likely, though two of our neonates had XDRAB isolated on the 2nd and 3rd day of life without the identification of a maternal source.

Previous studies have shown that premature babies are at higher risk of bacteremia due to their immature innate immunity. In addition, a prolonged length of NICU stay increases the risk of acquiring nosocomial infections. However, it is debatable whether a prolonged unit stay increases the risk of acquiring antibiotic resistant bacteria (e.g., XDRAB).[12] A case series of an outbreak of carbapenem-resistant *A. baumannii* infection among neonates revealed that all were extremely low birth weight, had central venous catheters, and were treated with broad-spectrum antibiotics before their culture-positive status.[13] In addition, a younger age at admission (age <7 days) was reported as a risk factor for multidrug-resistant *A. baumannii* infection.[14,15]

The neonates in our study had several of the risk factors for colonization and infection with XDRAB that were previously identified in pediatric and neonatal studies. These risks included prolonged length of stays in the NICU, having undergone invasive procedures including central venous catheter insertion, mechanical ventilation or surgery, prior exposure to the broad-spectrum antibiotics, and/or underlying severe illness.[15–17] Our results showed that infants infected or colonized with XDRAB had prior antibiotic exposure (with antibiotics that had minimal to no activity against *Acinetobacter*), in accordance with a majority of the previously published studies in adults and children.[18,19] The presence of XDRAB in health care environments is likely maintained by several concurrent factors, including the presence of other individuals infected or colonized with the XDR strain, presence of susceptible hosts, selective pressure from antimicrobial use, and nonadherence with infection control standards, a common occurrence in many NICUs.

XDRAB infections caused a variety of clinical diagnoses in our NICU, including pneumonia, with respiratory distress, VAP, bacteremia, meningitis, and urinary tract infections. Other reported XDRAB-associated infections in neonates included endocarditis, wound- and soft-tissue infections.[15,17]

Table 2 Clinical characteristics of the neonates with extensively-resistant *Acinetobacter baumannii* infection

Case no.	Gestational age (wk)	Weight at birth (g)	Duration of ventilatory support (d)	Antibiotic therapy before XDRAB infection	Time to XDRAB infection (d)	Source	Antibiotic type and duration	Comorbid medical conditions	Outcome
1	30	1,600	7	Ampicillin, Gentamicin, Cefotaxime, Teicoplanin, Meropenem	5	Blood	Colistin, Amikacin, 2 d	Prematurity	Died
2	26	850	109	Ampicillin, Gentamicin, Cefotaxime Meropenem, vancomycin	93	Blood ETT Urine	Colistin Ciprofloxacin, 17 d	Prematurity	Died
3	32	1,660	3	Ampicillin, Gentamicin Cefotaxime	3	Blood ETT	Non	Prematurity	Died
4	31	1,400	31	Ampicillin, Cefotaxime Vancomycin, Fluconazole	11	Blood CSF ETT	Colistin, Ciprofloxacin, 28 d	Prematurity, intraventricular hemorrhage	Recovered
5	28	725	15	Ampicillin, Gentamicin Cefotaxime, Vancomycin, Meropenem	2	Blood ETT	Colistin Ciprofloxacin, 11 d	Prematurity	Died
6	36	2,895	22	Ampicillin, Cefotaxime, Meropenem	34	Blood ETT	Colistin, 3 d	Tracheo Esophageal fistula	Died
7	37	2,000	3	Ampicillin, Cefotaxime	14	Blood ETT	Colistin, 21 d	Tracheo Esophageal fistula, Solitary Kidney	Recovered
8	37	2,590	26	Ampicillin, Gentamicin, Cefotaxime, Meropenem, Vancomycin	6	Blood ETT	Colistin, 2 d	Imperforated anus, Multiple congenital anomalies	Died

Abbreviations: CSF, cerebrospinal fluid; XDRAB, extensively drug-resistant *Acinetobacter baumannii*; ETT, endotracheal tube.

It is of particular concern that all affected infants in this study received empiric antibiotic therapy (ampicillin and cefotaxime) due to clinical manifestations suggestive of sepsis prior to blood culture resulting in XDRAB, as increasing use of third generation cephalosporins has been coupled with progressive decrease in their effectiveness against *Acinetobacter*.[20,21] The multidrug-resistant pattern observed in our isolates may be associated with the high frequency at which these antibiotics were used for both prophylaxis and therapy for hospitalized newborns. This practice may have exerted selective pressures leading to the emergence of XDRAB and multiresistant strains, which in turn may have stimulated the acquisition of genes encoding resistance mechanisms via horizontal transfer mechanisms between environments.[22]

After the diagnosis of the second case, the pediatric infectious diseases service was consulted, and antibiotic regimen for the cases was directed by isolated antimicrobial susceptibilities. Colistin combined with ciprofloxacin was effective in treating XDRAB bacteremia and meningitis in one neonate in our series. Synergy between colistin and other antibiotics like rifampin was reported in colistin-susceptible strains of *A. baumannii*. Among severely ill adult patients with multidrug-resistant *Acinetobacter* infections treated with colistin, a cure or improvement rate of 57 to 77% was reported.[16] However, data on the use of colistin in pediatric patients are very limited.[23]

Mortality of the neonates with XDRAB infection in our study was 75%, which is higher than previously reported percentages. The infected neonates in our cohort succumbed within an average of 11 days. In contrast, neonates who were colonized stayed alive from 4 to 105 days. Reported mortality of XDRAB bacteremia among neonates is around 47 to 49.2%.[4,19] An earlier study that included 13 neonates found a mortality rate of 54% in XDRAB infection, compared with 11% in those with sensitive *A. baumannii* bacteremia.[13] Previous studies in NICU population that looked into predictors of mortality among bacteremic neonates found that inappropriate antibiotic therapy is an important factor.[24] Moreover, failure to cover predominant multidrug resistant organisms was associated with inappropriate antibiotic regimens with a median (range) duration of 2 (2–3) days.[24]

We observed the median duration of inappropriate antibiotic therapy for XDRAB to be 4 days. Collectively, these data suggest the need to institute antibiotic guideline for neonates with sepsis based on risk stratification to cover predominant multidrug resistant bacteria among high-risk neonates. We hypothesized that the delayed administration of appropriate antibiotic in our cases could relate to several factors. First, there was a prolonged turnaround time for identification and susceptibility tests for *A. baumannii*, where the microbiology laboratory usually takes 5 days till the final report of the isolate. Second, given that the majority of our XDRAB is also resistant to all other antibiotics, there was no other available antibiotic choice to administer to the neonates, except for colistin and amikacin. In addition, in view of the limited information on the dose and adverse effect of colistin in premature babies, the consultant neonatologists did not feel comfortable using colistin. The degree of antibiotic resistance observed in our study population may signify an emerging trend among sepsis isolates recovered from neonates in NICUs in developing countries.

Study Strengths and Limitations

There are few limitations of this study. This study was conducted at a single center and may not represent other center findings in Saudi Arabia. Since this was a retrospective review, we were not able to assess all the variables and were limited by the completeness of the chart documentation by the treating physicians. The cases emerged over a 2-year period; outcomes might have been influenced by different interventions and therapeutic decision-making. Also, due to the retrospective nature of the study, we were unable to assess infection control practices for central venous catheters insertion and maintenance. Lastly, study of factors such as colonization pressure, NICU style characteristics, nurse-to-patient ratio were not within the scope of this study.

However, this study has a few strengths. Our study demonstrates the occurrence of XDRAB infection/colonization among the NICU population in Saudi and association with high mortality. Moreover, our findings highlight the importance to reduce antibiotic selective pressure in NICU through establishment of antimicrobial stewardship program. Finally, our study enforces the need to develop guidelines for antibiotics management of XDRAB infection, along with the efforts to minimize inappropriate antibiotic therapy in a subset of high-risk neonates.

Conclusion

Though the sample size is small, our study indicates the emergence of XDRAB in neonatal populations. Prematurity, low birth weight, the use of vascular devices, prior use of cefotaxime played major roles in XDRAB infection and colonization in our unit. It is crucial to consider early start of effective agents like colistin for neonate at risk and those with certain underlying chronic conditions, either alone or in combination therapy, especially who manifest with sepsis and VAP. Colistin was well tolerated in our neonates. Further prospective and randomized control trials are needed to confirm its efficacy and safety and to validate other therapeutic options in premature neonates.

Author contributions

S.A., Z.A., and M.A. designed the study. S.A. and Z.A. contributed to the clinical diagnosis and management of the patients. S.A. revised the data, wrote the first draft, and prepared ►**Table 1**. Z.A. collected the data and prepared ►**Table 2**, and revised the manuscript. M.N.A. collected the data. B.A. and M.A. revised and edited the final version.

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Conflict of Interest
None declared.

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