



# Outcome of Late-onset Neonatal Sepsis at a Tertiary Hospital in Oman

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## ABSTRACT

**Objectives:** We sought to determine the prevalence, pattern of causative organisms, and mortality of newborns with culture-proven late-onset sepsis (LOS) and to determine and compare the risk factors linked to late-onset gram-positive and late-onset gram-negative sepsis in Sultan Qaboos University Hospital (SQUH). **Methods:** We conducted a cross-sectional retrospective study of data obtained between 1 January 2007 and 31 December 2014 (eight years) from infants in the neonatal intensive care unit (NICU) at SQUH. Infants born in SQUH (inborn) and other institutions (outborn) with positive blood cultures were included in the study. **Results:** The total number of live births and admissions during the study period were 26 289 and 3559, respectively. The total number of infants identified with LOS were 125 of whom 69 (55.2%) were gram-positive, 52 (41.6%) were gram-negative, and four (3.2%) were due to *Candida* species (spp.). The majority of infants (n = 113, 90.4%) were inborn; 69 (55.2%) were males and 56 (44.8%) were females. The prevalence of LOS among inborn admissions was 4.3 per 1000 live births. Most infections occurred in very low birth weight infants (n = 81, 64.8%). Eleven (8.8%) infants died due to gram-negative sepsis. *Klebsiella pneumoniae* followed by *Pseudomonas aeruginosa* were the leading cause of death. Maternal intrapartum antibiotics were the only independent risk factor correlating with gram-negative organisms in multivariate analysis ( $p = 0.003$ ). **Conclusions:** LOS poses a burden in the NICU, which could be due to the increasing survival of premature babies. The main contributing organisms to LOS are gram-positive bacteria. *Klebsiella* spp. is a major cause of mortality in LOS. The use of intrapartum antibiotic prophylaxis in mothers might explain the positive correlation of maternal antibiotics as a risk factor with gram-negative infections.

Neonatal sepsis, a clinical syndrome, emerges as a result of bacterial bloodstream infections in newborns. It is a serious global public health problem because it is a major cause of mortality and morbidity. It poses a challenge for neonatologists due to the unclear symptoms and absence of early diagnostic tests. More than one million of the estimated global newborn deaths per year occur due to severe infections. Neonatal sepsis is classified into early-onset sepsis (EOS) and late-onset sepsis (LOS). Late-onset infections are a major problem in neonatal intensive care units (NICUs) with 25% of very low birth weight (VLBW) infants affected. Late-onset gram-negative sepsis (LOGNS) and meningitis are considered a significant cause of morbidity and mortality in newborns.<sup>1</sup> VLBW infants are particularly at risk of late-onset infections since their undeveloped immune system is further

compromised by an immature skin barrier and the increased requirement for invasive equipment to withstand life-supporting care. Unlike EOS, where ascending transmission of microorganisms from mother to baby is accountable, LOS is believed to result from nosocomial sources resulting from a wide range of organisms. Most late-onset infections are due to coagulase-negative staphylococci (CoNS) followed by *Staphylococcus aureus* and gram-negative bacilli.<sup>2-6</sup> Potential risk factors related to both maternal and neonatal care as a cause for late-onset neonatal infections have been investigated in a variety of different studies.<sup>7-10</sup> However, it is difficult to determine the etiology as many of these risk factors are common among premature babies, making it difficult to draw conclusions regarding causality. The incidence of LOS varies across different countries. LOS has been reported to pose a major burden in the Arab states in the Gulf region due to

the increased survival of premature infants, which is related to improved care in recent decades. Lack of proper infection control measures and appropriate guidelines in some ICUs in the Gulf region might have a significant impact on the increasing incidence of neonatal infections and the outline of causative organisms.<sup>11</sup> In Oman, the incidence, risk factors, and causative organisms of LOS have not been studied comprehensively.

We sought to determine the prevalence, the pattern of causative organisms, and mortality of newborns with culture-proven LOS and the risk factors linked to late-onset gram-positive sepsis (LOGPS) and LOGNS in Sultan Qaboos University Hospital (SQUH).

## METHODS

We conducted a cross-sectional retrospective study over eight years (2007–2014). Data were collected retrospectively using a standardized data collection form. LOS was defined as the growth of a single potentially pathogenic organism from blood or cerebrospinal fluid (CSF) in infants 48 hours after birth with clinical and laboratory findings consistent with infection. Positive cultures were identified from the hospital microbiology database. One investigator collected data from the hospital information system. The required demographic, clinical and outcome details, and evidence on possible risk factors for infection were identified from previously published studies of LOS.<sup>11–14</sup> Neonatal risk factors data collected included the use of mechanical ventilation and duration, total parenteral nutrition (TPN) use and duration, central line use and duration, gestational age, and birth weight. Maternal risk factors included prolonged rupture of membranes (PROM), chorioamnionitis, intrapartum antibiotic prophylaxis (IAP) use, and use of antenatal steroids. For all patients, exposure to these risk factors was determined from their day of admission to the NICU until the day of their first positive culture with gram-positive or gram-negative organisms. We compared the risk factors between gram-positive and gram-negative patients using statistical analysis.

Data were analyzed using STATA 12 (StataCorp). Continuous variables were analyzed using *t*-test or Mann–Whitney U test. Categorical variables were analyzed using chi-squared test and non-parametric continuous variables using Mann–Whitney U

test. Multivariate logistic regression analysis was completed to detect the relationship between variables. For both univariate and multivariate analysis, statistical significance was defined as a *p*-value < 0.050.

## RESULTS

The total number of live births and admissions during the study period were 26 289 and 35 599, respectively. The total number of inborn infants (born at SQUH) was 113 (90.4%), and 12 (9.6%) were outborn (born outside SQUH and transferred after birth). Sixty-nine (55.2%) were male and 56 (44.8%) were female.

The total number of infants identified with LOS were 125; 69 (55.2%) were gram-positive, 52 (41.6%) were gram-negative, and four (3.2%) were due to *Candida* species (spp.). The overall prevalence among inborn admissions was 4.3 per 1000 live births. The prevalence among all NICU admissions was 3.5%. The mean gestational age and birth weight were 30.0±4.5 weeks and 1439.7±792.0 g, respectively. Most infections occurred in VLBW infants (*n* = 81, 64.8%; *p* = 0.020) and in those < 30 weeks gestation (*n* = 74, 59.2%; *p* = 0.020). Eleven (8.8%) infants died due to GNS (six males and five females). A wide variety of organisms were isolated [Table 1]. Of the total number of bacterial infections (*n* = 121), 69 (57.0%) were due to gram-positive organisms and 52 (43.0%) to gram-negative organisms. Two infants also had confirmed meningitis with positive bacterial

**Table 1:** Frequency of microbial causes.

Organisms	n	%
Coagulase-negative <i>S. aureus</i>	59	47.2
<i>Klebsiella pneumonia</i>	21	16.8
<i>Escherichia coli</i>	9	7.2
<i>Pseudomonas aeruginosa</i>	7	5.6
<i>Burkholderia cepacia</i>	7	5.6
Enterococcus	4	3.2
Methicillin-resistant <i>S. aureus</i>	3	2.4
<i>Serratia marcescens</i>	3	2.4
<i>S. aureus</i>	1	0.8
<i>Acinetobacter baumannii</i>	2	1.6
<i>Morganella morganii</i>	1	0.8
<i>Stenotrophomonas maltophilia</i>	2	1.6
Group B streptococcus	2	1.6
<i>Candida</i> species	4	3.2

*S. aureus*: *Staphylococcus aureus*.

**Table 2:** Potential risk factors for late-onset bacterial sepsis in univariate analysis.

Risk factors	Gram-positive, % (n = 69)	Gram-negative, % (n = 52)	p-value
TPN	68.1	78.8	0.220
MV	63.8	78.8	0.400
Central lines insertion	72.5	82.7	0.200
Chorioamnionitis	62.3	3.8	1.000
PROM	11.6	21.2	0.210
Maternal steroids	44.9	51.9	0.450
Intrapartum antibiotics	18.8	42.3	0.020
TPN duration	46.4	65.4	0.040
Inv proc duration	30.4	61.5	< 0.001
MV duration	27.5	50.0	0.010

TPN: total parenteral nutrition; MV: mechanical ventilation;  
PROM: prolonged rupture of membranes; Inv proc: invasive procedure.

growth in CSF. Another three infants whose blood cultures were positive with a gram-negative isolate, had evidence of meningitis with increased CSF cellularity. All infants with meningitis were treated empirically.

Table 2 shows the maternal and neonatal risk factors for sepsis in univariate analysis. Table 3 shows the maternal and neonatal risk factors for sepsis in multivariate analysis with intrapartum administration of antibiotics being the only significant risk factor in favor of gram-negative infections.

**Table 3:** Potential risk factors for late-onset bacterial infections in logistic regression analysis.

Risk factors	Gram-positive, % (n = 69)	Gram-negative, % (n = 52)	p-value
TPN	68.1	78.8	0.350
MV	63.8	78.8	0.970
Central lines insertion	73.5	82.7	0.320
Chorioamnionitis	62.3	3.8	0.210
PROM	11.6	21.2	0.210
Maternal steroids	44.9	51.9	0.610
Intrapartum antibiotics	18.8	42.3	0.020
TPN duration	46.4	65.4	0.420
Inv proc duration	30.4	61.5	0.450
MV duration	27.5	50.0	0.140

TPN: total parenteral nutrition; ; MV: mechanical ventilation;  
PROM: prolonged rupture of membranes; Inv proc: invasive procedure.

## DISCUSSION

We described the incidence and burden of LOS in a tertiary NICU over eight years with an emphasis on the causative organisms and potential risk factors. Comparing patients infected with gram-positive and gram-negative organisms, we identified that intrapartum antibiotic administration was the only independent risk factor for LOGNS. The importance of this approach is evident from the high number of patients with LOGPS with risk factors relevant to susceptibility to patients with gram-negative infections. Several studies have examined the incidence, causative organisms, and risk factors in Western countries, but only a few studies have looked at the incidence and causative organisms in the Arab states from the Gulf region. Probable risk factors for infection have been considered in other studies from Western countries, but have mostly focused on specific gram-negative bacteria in the setting of epidemics or as section of another study.<sup>15-17</sup>

Survival of extreme preterm newborns has considerably improved over the last two decades in the Gulf leading to increased survival of preterm babies who are more vulnerable to infections.<sup>11</sup> The incidence of LOS in our unit was 4.3 per 1000 live births, which is higher than developed countries (3-3.7 per 1000), but much lower compared to other Gulf countries where the reported incidence of LOS was 11.6 per 1000 live births<sup>11</sup> in Saudi Arabia, the UAE, and Kuwait. The incidence in other developing countries has been reported as 11 per 1000 live births.<sup>18</sup>

Although CoNS is a normal contaminant and forms part of the skin flora, it has been described as the most common cause of LOS. The commonest organisms isolated in this study were gram-positive organisms with CoNS being the commonest [Table 2], which was also seen in other developed countries.<sup>19-21</sup> Likewise other Gulf countries including Kuwait,<sup>22</sup> the UAE, and Saudi Arabia have reported a higher incidence of CoNS.<sup>23</sup> All patients with CoNS in this study had positive blood cultures and were clinically symptomatic for sepsis and this confirms that it was a true infection and not a contaminant. CoNS developed in the last few years in an increasing number as a major cause of nosocomial infections in NICUs, mainly as a bloodstream infection. Our results were different from other countries, where *S. aureus* has been described as a major cause of LOS following

CoNS.<sup>24-27</sup> Our incidence of neonatal meningitis was 0.08 per 1000 live births, which is lower than that reported from neighboring countries<sup>11</sup> and developed countries.<sup>28</sup> The use of lumbar puncture plays a major role in determining the incidence of meningitis; 10% of newborns with positive blood cultures have meningitis. However, not all patients in NICU with positive blood culture receive lumbar puncture, and some patients with meningitis can still have normal CSF parameters.<sup>29</sup>

Gram-negative organisms have been reported as a major cause of infection and mortality in some developing countries.<sup>24,25</sup> *Klebsiella* spp. were the predominant cause of gram-negative LOS in our study and were responsible for more than half of deaths. A study from Iran reported that CoNS and *Klebsiella pneumoniae* were the commonest causes of neonatal sepsis in hospitalized neonates. Moreover, the hands of mothers and staff, baby bottles, and the breast milk contained inside were the commonest sources of bacteria in the unit.<sup>30</sup>

In our unit, the incidence of candidiasis was only 3.2% in contrast to other neighboring countries where the incidence was reported at 11.8%. The rate of *Candida* infections varies significantly between centers. Cefotaxime use as an initial sepsis treatment has been associated with an increased incidence of *Candida* infections.<sup>11</sup> Third generation cephalosporins are used as a third-line antimicrobial for sepsis treatment in our unit or in cases of suspected meningitis, which might have resulted in a lower incidence of fungal sepsis compared to other Gulf countries.

Mortality occurred in 11 (8.8%) patients where gram-negative infections were the primary cause of death in all patients. *Klebsiella* spp. resulted in more than 50% of neonatal deaths (seven out of 11) followed by *Pseudomonas aeruginosa*. *P. aeruginosa* and *K. pneumoniae* have been reported to be the highest cause of mortality in other Gulf countries<sup>11</sup> and settings.<sup>31</sup>

In our NICU, overcrowding, disparity between the number of nurses and the number of admitted sick infants, and lack of compliance with hand hygiene, seems to be major risk factors for hospital-acquired infections.

Many reports have proposed that while the use of IAP for group B streptococcal infection has considerably decreased the prevalence of early-onset group B streptococcal sepsis in newborns, it may have increased the incidence of early-onset gram-negative

infections, predominantly in VLBW and preterm infants.<sup>32-34</sup> Similarly, the association between IAP and late-onset bacterial infections in term infants has been reported.<sup>35</sup> The use of IAP was high among mothers with gram-negative infections and remained the only independent risk factor with a significant difference noted in multivariate analysis. The use of antenatal steroids in pregnant mothers has also been linked to neonatal sepsis.<sup>36</sup> Likewise, PROM and chorioamnionitis have been linked to EOS. The frequency of using antenatal steroids, PROM, and chorioamnionitis was similar in both groups. These results are comparable to findings from the National Institute of Child Health and Human Development Neonatal Research Network.<sup>1</sup>

The relation between LOGNS with mechanical ventilation,<sup>37</sup> duration of noninvasive ventilation,<sup>17</sup> TPN,<sup>38</sup> and duration and use of central lines<sup>39</sup> as independent risk factors have been reported in previous studies.

Though considerable numbers of infants with both gram-positive and gram-negative infections have required mechanical ventilation, TPN, and central lines, there was no significant difference between the two groups in univariate and multivariate analysis. On the other hand, the duration of mechanical ventilation, TPN duration, and umbilical venous catheter use for more than one week were all associated significantly in univariate analysis with gram-negative infections. However, none were found to be independent risk factors in multivariate analysis. The relation between TPN and sepsis has been reported, but the mechanism is not clear. It has been hypothesized that the gut is an important source of bacteria that may result in sepsis in newborn babies, which may be the case in those receiving TPN.<sup>40</sup>

The retrospective nature of this study made it difficult to precisely find out the amount and types of enteral feeds used and so we could not draw a conclusion to other influential factors related to artificial formula, breast milk, or mixed feeding. It is possible that we missed other risk factors, which therefore makes it possible that any difference found between the patients with gram-positive and gram-negative infections might reflect other unmeasured factors. It is possible that the real burden of LOS in non-hospitalized patients in the community might be underestimated in this study since we only included newborns with LOS in the NICU.

## CONCLUSION

LOS is a major burden in our institute, which is most likely related to the rising number of preterm babies. Gram-negative organisms, especially *Klebsiella* spp., seem to have a growing role in LOS and is a major cause of death. The use of intrapartum antibiotics is an important independent risk factor for LOGNS and although it has been recognized earlier, we have further elucidated its independent role. It is suggested that medical staff working in NICU should be trained and compliance with hand hygiene should be firmly monitored. We strongly recommend proper disinfection during venipuncture, catheterization, and endotracheal intubation.

### Disclosure

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