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Original article

A new approach to managing neonates born to mothers at risk for early-onset neonatal sepsis: is it cost-effective and can it reduce NICU admissions?

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Abstract

Introduction: In Minia University Hospital for Obstetrics and Gynecology and Pediatrics (Minia, Egypt), all neonates born to mothers with suspected or confirmed intrauterine inflammation or infection (triple I) or with group B *Streptococcus* (GBS) bacteriuria, were directly admitted to the neonatal intensive care unit (NICU) for clinical assessment and treatment of suspected sepsis for at least 48 hours, regardless of their clinical condition. Establishment of a risk-identification system for those high-risk neonates based on the EOS detection standard checklist may decrease NICU admissions and antibiotics exposure in asymptomatic neonates.

Methods: We marginally altered a standard checklist outlined by The American College of Obstetricians and Gynecologists for the early discovery of neonates at risk for EOS. Participants of the study were inborn neonates ≥ 34 weeks born to mothers with suspected or confirmed triple I or with GBS bacteriuria, who received intrapartum antibiotic prophylaxis (IAP) at least 4 hours before delivery. Neonates for mothers at risk for EOS who did not get IAP were excluded from the study. Numerous sessions were conducted to teach nursing and medical staff to apply the standard checklist for the identification of EOS within the nursery. Symptomatic neonates were admitted directly to NICU for laboratory evaluation and intravenous antibiotics. Asymptomatic neonates were closely observed within the nursery.

Results: From June 2017 to June 2019, there were 624 at-risk neonates recognized and assessed utilizing the standard checklist. Of these 624 neonates, 456 (73%) did not require admission to the NICU based on their risk assessment utilizing the standard checklist. Implementation of a

standard checklist for at-risk neonates decreased NICU rates of admission by 50%, decreased pediatrician practice variability, decreased the number of laboratory procedures, promoted family bonding, increased rates of breastfeeding at hospital discharge, diminished financial burden on the hospital and community, and promoted antibiotic stewardship.

Conclusion: This study concludes that utilization of the standard checklist for early identification of EOS can decrease the need for NICU admission of asymptomatic neonates at risk for EOS.

Keywords

Newborn, early-onset sepsis, management.

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Introduction

"Suspected sepsis" is one of the commonest causes for admission to Neonatal Intensive Care Units (NICUs), despite the uncommon occurrence of true culture-positive sepsis. Clinical diagnosis of neonatal sepsis is often vague and nonspecific. This includes symptoms and signs in the form of temperature variability, irritability, jaundice, hypoglycemia, feeding intolerance, heart rate variability (bradycardia or tachycardia), respiratory distress of varying grades, hypo-perfusion, lethargy, acidosis, and apnea with or without desaturation. However, infants who develop these symptoms and signs often do not have true neonatal sepsis [1]. Early-onset neonatal sepsis (EOS) occurs within the first 72 hours of a newborn's life.

Risk factors for EOS include maternal colonization with group B *Streptococcus* (GBS) (particularly in the presence of inadequate prophylactic treatment), premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), prolonged rupture of membranes, premature birth, maternal urinary tract infection, suspected or confirmed intrauterine inflammation or infection (triple I, the new title for chorioamnionitis), and maternal fever > 38ºC (**Tab. 1**) [2, 3]. Other factors that are associated with or predispose to EOS include low Apgar score (< 6 at 1 or 5 minutes), poor antenatal care, maternal malnutrition, poor socioeconomic status, black mother, history of recurrent abortion, maternal substance abuse, low birth weight, difficult delivery, birth asphyxia, meconium-stained liquor, and neonatal congenital anomalies [4].

Neonatal sepsis is currently the reason for about 1.6 million deaths per year in developing countries [5]. The incidence of neonatal sepsis varies from one place to another. Culture-proven EOS in the United States represents 0.3-2 per 1,000 live births. In developing countries, the incidence of neonatal sepsis is about 3.5-4.3 cases per 1,000 live births [6]. However, many large academic institutions report evaluation and treatment of up to 5-15% of all live births [7].

As the American Academy of Pediatrics (AAP), [8] the American College of Obstetricians and Gynecologists (ACOG) [9], and the Centers for Disease Control and Prevention (CDC) [10] all have recommended sepsis screening or treatment for various maternal risk factors for sepsis, many asymptomatic neonates now undergo an evaluation and are exposed to antibiotics. On the other hand, mortality from untreated sepsis can be as high as 50%, leading many clinicians to err on the side of treating asymptomatic neonates based on historical

Table 1. Triple I classification. Modified from: Higgins et al., 2016 [3].

Suspected triple I	Fever without a clear source plus any of the following: 1. Baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2. Maternal white blood cell count greater than 15,000 per mm^3 in the absence of corticosteroids 3. Definite purulent fluid from cervical os
Confirmed triple I	All the above plus: 1. Amniocentesis-proven infection through a positive Gram stain 2. Low glucose or positive amniotic fluid culture 3. Placental pathology revealing diagnostic features of infection

and maternal risk factors alone. This approach has been questioned in the past several years as more evidence emerges on the deleterious impact of unnecessary antibiotic exposure, including interference with the establishment of breastfeeding, alterations in the gut microbiome, increases in the incidence of childhood obesity, and development of antimicrobial resistance, amongst others [11]. The implementation of a prenatal screening and treatment protocol for GBS has resulted in a dramatic decrease in GBS sepsis incidence. This has changed the epidemiology of EOS [12].

Triple I occurs in about 4% of deliveries at term but occurs more frequently in preterm deliveries and premature rupture of membranes. In evaluating women with symptoms of triple I, studies showed a strong correlation between histologic and clinical types [13]. Histologic triple I with vasculitis is associated with a higher incidence of premature rupture of membranes and preterm delivery [14]. According to the presence or absence of clinical signs and laboratory evidence, triple I may be categorized as clinical and subclinical/histologic triple I [14-18]. Clinical triple I is characterized by the presence of maternal fever > 38°C, maternal tachycardia (> 100 beats/min), fetal tachycardia (> 160 beats/min), maternal leukocytosis (> 15,000 cells/mm^3), purulent or foul-smelling amniotic fluid, PPROM and/or uterine/fundal tenderness (**Tab. 1**) [19]. Subclinical/histologic triple I is asymptomatic and defined by inflammation of the chorion, amnion, and placenta, which is more common than clinical type [20].

Guidelines from the CDC and the Committee on Fetus and Newborn for the prevention of perinatal GBS disease recommend laboratory evaluation (complete blood count [CBC] and blood culture) and empiric antibiotic treatment for 48 hours duration for neonates born to mothers with triple I [21]. To limit the use of antibiotics in asymptomatic neonates in the immediate postnatal period, we marginally altered a standard checklist outlined by ACOG for early discovery of neonates at risk for EOS (**Tab. 2**), to estimate the risk of EOS in infants ≥ 34 weeks. This model utilizes maternal antepartum risk factors coupled with a neonate's clinical appearance at birth and over the first 24 hours of life to predict the risk for EOS.

Before the current study, the practice in NICU, Minia University Hospital, was to admit asymptomatic neonates ≥ 34 weeks born to mothers with suspected or confirmed triple I or GBS bacteriuria regardless of their clinical condition. All those neonates underwent partial sepsis workup, including CBC, C-reactive protein (CRP) and blood culture and were treated empirically with ampicillin and amikacin for a minimum of 48 hours. Also, if the result of CRP was > 10 and blood culture reported positive, lumbar puncture would be indicated for cerebrospinal fluid (CSF) analysis.

Table 2. Checklist for communication between the obstetric and neonatal teams to detect neonates at risk for early-onset neonatal sepsis (EOS). Modified from: Higgins et al., 2016 [3].

- Sex of the neonate
- Mode of delivery
- Gestational age
- Maternal tachycardia
- Fetal tachycardia
- Maternal white blood cell count greater than 15,000/mm^3
- Maternal GBS status
- Duration of rupture of membranes
- Duration of labor
- Purulent amniotic fluid
- Amniotic fluid evaluation (meconium stained or not and its odor)
- Highest intrapartum temperature
- Epidural anesthesia
- Prostaglandin use during delivery
- Antibiotics given prior to delivery
- Antipyretic used for maternal fever
- Spontaneous preterm birth
- Previous spontaneous preterm birth

GBS: group B *Streptococcus*.

This study aims to change our NICU practice, which mandates NICU admission for all asymptomatic neonates ≥ 34 weeks born to mothers with suspected or confirmed triple I or GBS bacteriuria who received intrapartum antibiotic prophylaxis (IAP) 4 hours before delivery. EOS standard checklist has been utilized to stratify newborns based on maternal antepartum risk factors and neonatal clinical evaluation.

Methodology

This study was approved by the research committee at the Faculty of Medicine, Minia University, Egypt. Written consent was taken from the parents of all neonates who participated in the study. The studied groups included neonates born at ≥ 34 weeks to mothers with suspected or confirmed triple I or GBS bacteriuria and received IAP 4 hours before delivery. Babies of mothers at risk for EOS who did not receive IAP were excluded from the study.

Risk factors of EOS used in the study are illustrated in **Tab. 3**.

This study implemented several stages for improvement of neonatal practice in taking care of neonates at risk for EOS (**Fig. 1**).

The first stage required proper communication between pediatric and obstetric teams regarding neonates born to mothers at risk for EOS. To facilitate the identification of this group of neonates, we utilized the "standard checklist", which outlined more detailed maternal antepartum risk factors for EOS (**Tab. 2**). This checklist was handled to the pediatric team immediately after delivery. The primary investigator manually tracked checklist utilization by frequent auditing of all studied cases in labor and delivery (L&D) rooms and the nursery.

The second stage was a proper examination of the neonate to determine the need for admission,

Table 3. Maternal factors associated with an increased risk for early-onset neonatal sepsis (EOS).

- Suspected or proved triple I
- Intrapartum maternal temperature ≥ 38ºC (100.4ºF)
- Delivery at < 37 weeks gestation
- Maternal GBS colonization and other findings that increase the risk of GBS infection in the neonate, including any of the following:
  i. Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
  ii. Previous infant with GBS disease
  iii. Documented GBS bacteriuria during the current pregnancy
  iv. Membrane rupture ≥ 18 hours – The risk of proven sepsis increases 10-fold when membranes are ruptured beyond 18 hours [22]

GBS: group B *Streptococcus*.

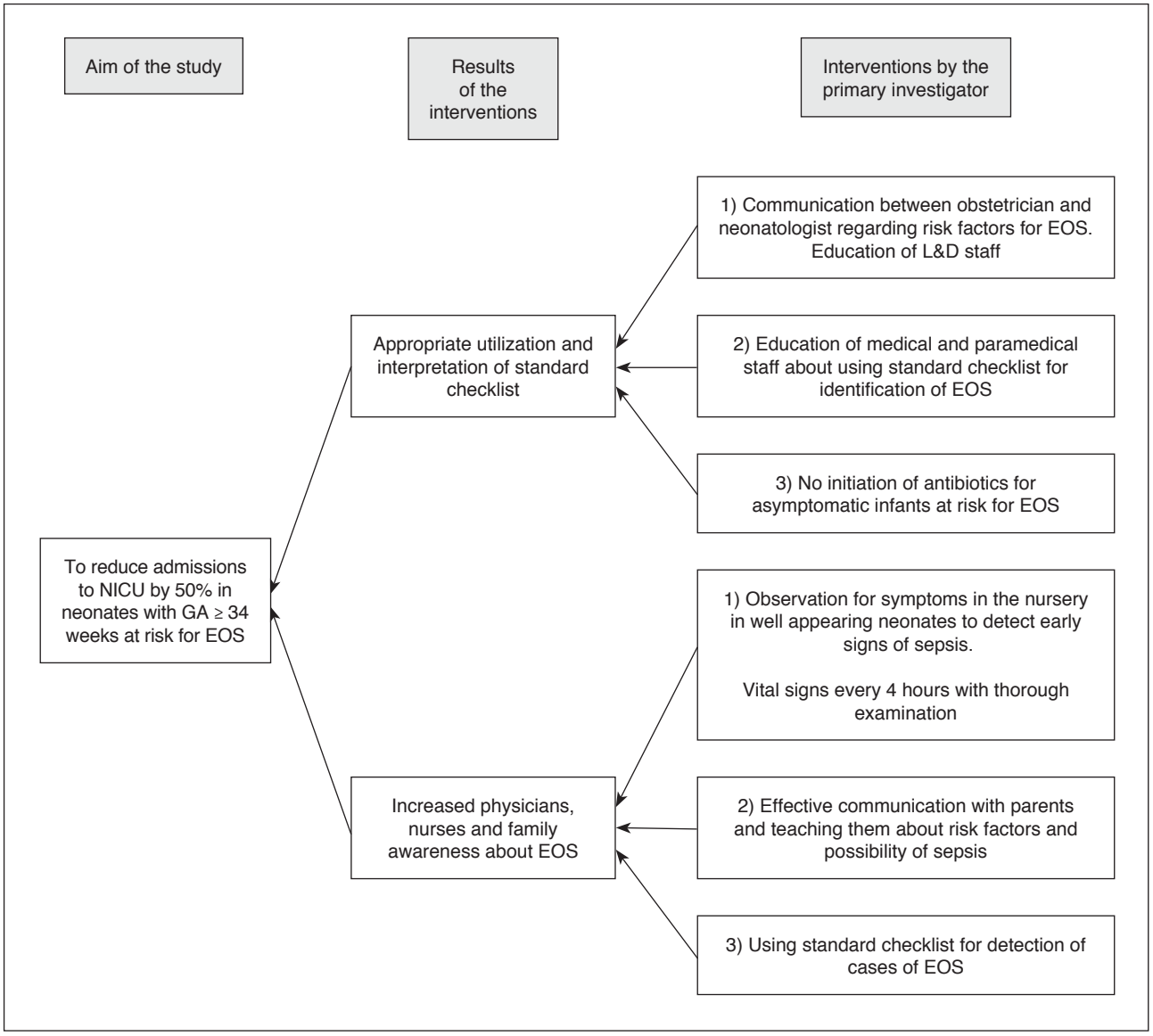

Figure 1. Service delivery diagram. Multi-disciplinary meetings and several stages for improvement were initiated to reach the aim.
GA: gestational age; EOS: early-onset neonatal sepsis; L&D: labor and delivery; NICU: Neonatal Intensive Care Unit.

laboratory workup and/or antibiotics. The local guidelines implemented in NICU were posted in the nursery and made into laminated cards for clinicians' badges (**Fig. 2**).

Symptomatic neonates were immediately transferred to the NICU for complete sepsis workup, including CBC, CRP, blood culture and lumbar puncture for CSF analysis and first-line antibiotic administration (ampicillin [50 mg/kg/dose every 12 hours] plus amikacin [15 mg/kg/dose every 24 hours]) based on local unit protocol.

Asymptomatic neonates transferred to the nursery were followed with vital signs every 4 hours by nursing staff to evaluate for physiologic abnormalities. The nursing staff was educated about early manifestations of EOS. The primary investigator taught the nursing staff to alert the attending physician about any concerns related to those neonates. The nursing staff was also instructed to notify the in-charge physician of any newborn with a vital sign abnormality or any other new concern. This notification alerted the in-charge physician to thoroughly evaluate the newborn at risk and decide the need for continuous observation, limited or complete laboratory evaluation, and/or NICU transfer for antibiotic therapy.

For all NICU admitted neonates, the investigator team tracked parameters related to the cause of transfer, time of initiation of first-line antibiotics, laboratory evaluation whether limited or complete and its results, length of hospital stay, and intended feeding method at birth and discharge.

The last stage of this new practice emphasized on additional steps to avoid missing any case presented with EOS. We kept all babies with suspected EOS for 48 hours in the nursery. During this period, a baby nurse monitored the newborn's vitals every 4 hours for the 48 hours of hospital stay. The parents of each baby with suspected EOS were required to have a scheduled follow-up appointment with a pediatrician within 24-48 hours after discharge.

Weekly audits for neonates with suspected EOS were conducted as an additional safety monitoring tool. Monthly reports were tracking

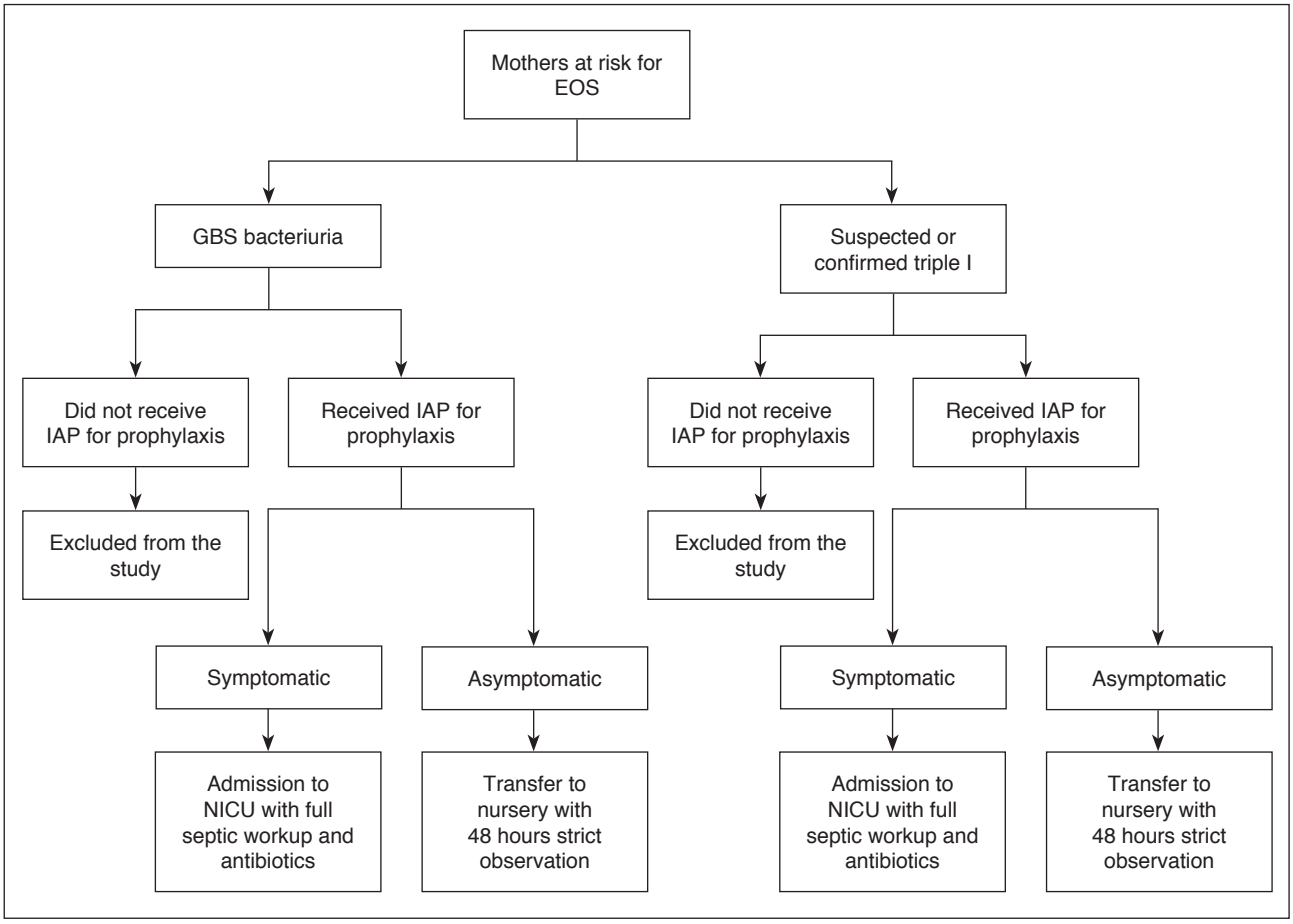

Figure 2. Algorithm for management of neonates at risk for early-onset neonatal sepsis (EOS).
EOS: early-onset neonatal sepsis; GBS: group B *Streptococcus*; IAP: intrapartum antibiotic prophylaxis; NICU: Neonatal Intensive Care Unit.

these neonates' nursery admissions, along with transfers, antibiotic utilization rates, and cases of culture-positive or clinical sepsis. Audits have been generated and reviewed by the investigator team.

Minia University Hospital for Obstetrics and Gynecology and Pediatrics has a 32-bed Level III academic NICU with an average of 11,000 deliveries per year and 1,250 annual admissions. Of these deliveries, 238 are diagnosed as triple I and 76 as GBS bacteriuria.

The primary outcome measure was the monthly rate of NICU admissions for sepsis evaluation/treatment in neonates ≥ 34 weeks born to mothers at risk for EOS. Secondary outcomes included monthly rates of sepsis amongst at-risk neonates and breastfeeding rates at discharge for neonates admitted to the NICU compared with those who remained in the nursery.

Process measures included the monthly rate of neonatal team notification of at-risk neonates by the L&D staff, the monthly rate of standard checklist utilization by the L&D staff, and the clinical indications for transfer at birth and subsequently to NICU of babies at risk for EOS.

Balancing measures included the number of neonates per month who were asymptomatic at birth and became clinically ill with suspected sepsis requiring admission to the NICU and the monthly rate of readmission for sepsis.

Results

From June 2017 to June 2019, 624 at-risk neonates were identified and evaluated by the standard checklist for EOS. Of these 624 neonates, 88 (14%) were symptomatic at birth and required immediate transfer from the delivery room to the NICU for full sepsis workup and antibiotics. Sixty neonates (68%) of transferred neonates were diagnosed as transient tachypnea of the newborn (TTN) or mild respiratory distress syndrome (RDS). An additional 80 neonates (13%) became symptomatic while they are in the nursery and required later transfer to the NICU. The remaining 456 (73%) neonates did not require admission to the NICU based on their risk assessment using the standard checklist.

Fig. 3 shows the number of symptomatic neonates admitted to NICU at birth with culture-positive sepsis. Most symptomatic neonates admitted for sepsis evaluation did not have culture-positive sepsis nor required prolonged antibiotics.

Over half of the initially asymptomatic neonates (54%) who subsequently required transfer to the NICU presented with temperature instability. This finding prompted the investigator team to evaluate immediate newborn care after epidural anesthesia is given to the mother. A high percentage of babies born to mothers who received epidural anesthesia were having low-grade fever after delivery and the

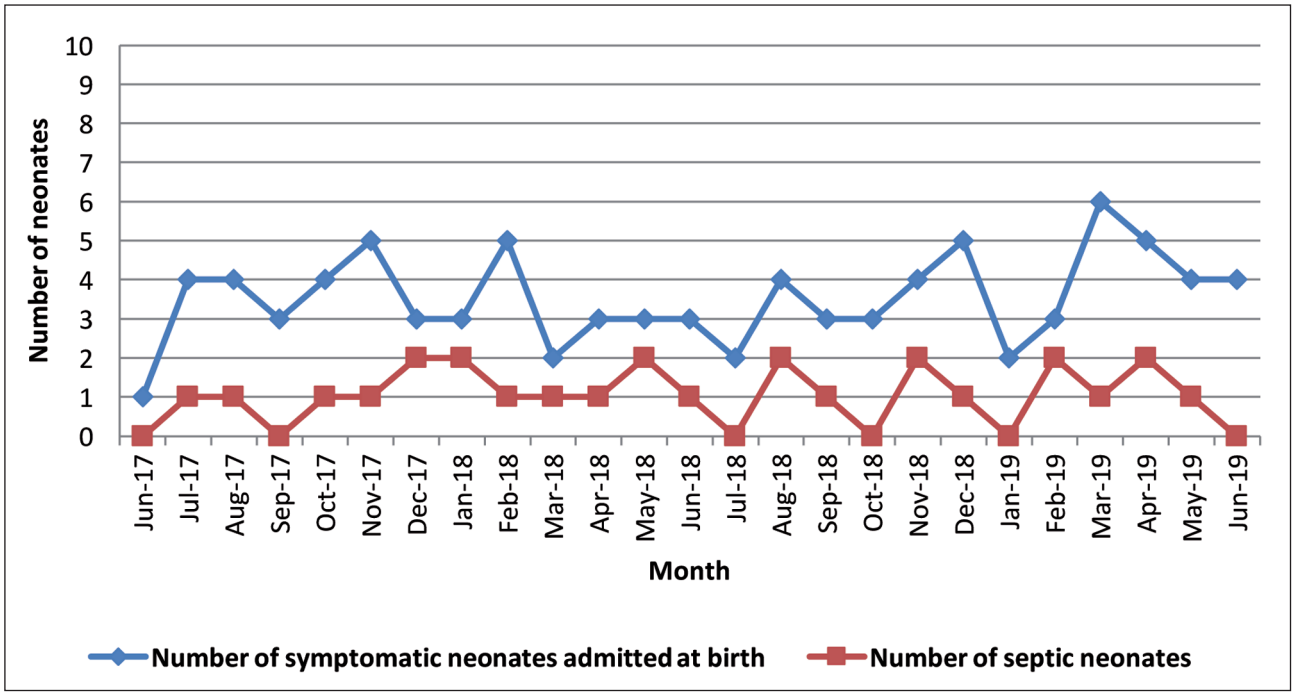

Figure 3. Number of septic neonates in relation to the total number of symptomatic neonates admitted to Neonatal Intensive Care Units (NICU) at birth.

investigator team decided not to admit them directly to NICU for sepsis workup and antibiotics. Those babies were observed in the nursery for 4 hours and if their temperature settled to normal the team decided not to admit them to NICU. This again reduced the number of total admissions to NICU.

Asymptomatic neonates who developed symptoms suggestive of sepsis were transferred to NICU for sepsis workup and antibiotics, their laboratory markers for sepsis were unremarkable. Only 16 of them required prolonged (> 7 days) courses of antibiotics (**Fig. 4**).

Breastfeeding rates at discharge were 91% for neonates observed in the nursery. In contrast, only 56 % of neonates who required NICU admission for sepsis evaluation and treatment were breastfeeders at discharge. We followed the study population for readmission within our hospital system following discharge to ensure that there were no cases of "missed sepsis". Over the 24 months of the study period, 15 neonates were readmitted within 30 days of hospital discharge. None of them was diagnosed as bacterial sepsis. We looked at all hospital readmissions regardless of readmission diagnosis to exclude cases of missed sepsis.

Discussion

In this study, implementation of a standard checklist for diagnosis of EOS decreased NICU admissions to "rule out sepsis" in asymptomatic neonates born to mothers with suspected or confirmed triple I or GBS bacteriuria who received IAP at least 4 hours before delivery. It also reduced the need for antibiotics in this population, which before the implementation of the standard checklist was 100% for this group of neonates. Strict observation and close monitoring of newborn vital signs and thorough clinical examination enabled asymptomatic neonates to remain in the nursery. A post-discharge appointment with a pediatrician within 24-48 hours of hospital discharge was enforced to ensure adequate follow-up. In-charge nurses called families if they missed their appointments to ensure adequate follow-up. Implementation of the standard checklist for at-risk neonates also decreased pediatrician practice variability, decreased the number of unnecessary laboratory procedures, encouraged family bonding, diminished financial burden to the patient/hospital/community, and promoted antibiotic stewardship. Higher breastfeeding rates at newborn discharge were attributed to Kangaroo care for the duration of the newborn hospitalization. Therefore, we prevented the disruption of the mother-baby relationship by implementing the EOS standard checklist for the identification of neonates at risk for EOS. Before using the standard checklist for EOS, some pediatricians would treat based on screening laboratory results (such as CBC, CRP, and blood culture), whereas others would empirically treat all newborns of mothers with suspected or confirmed triple I or GBS bacteriuria.

As a result of this study, there was a change in the usual practice by observation of asymptomatic neonates who developed low-grade fever as a result of maternal epidural anesthesia: if fever subsided for 4 hours without any intervention, they continued in the nursery. Laboratory evaluation of asymptomatic neonates can result in nonspecific findings. These findings may lead a pediatrician to treat laboratory values empirically rather than to

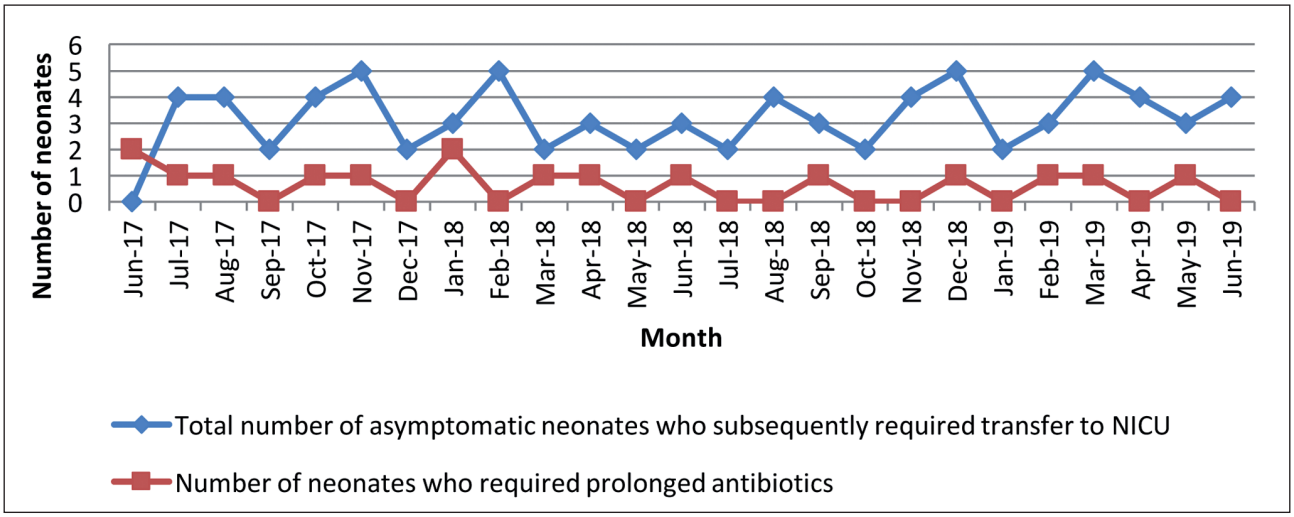

Figure 4. Asymptomatic neonates who subsequently required transfer to Neonatal Intensive Care Unit (NICU).

base treatment on the neonate's clinical appearance. The evaluation of clinically asymptomatic neonates requires unnecessary laboratory procedures such as blood extractions, peripheral IV line insertion, lumbar punctures, and exposure to broad-spectrum antibiotics early in life [22, 23]. The evaluation and treatment of asymptomatic neonates born to mothers with suspected or confirmed triple I or GBS bacteriuria may lead to the unnecessary disruption of the parental-infant relationship, decrease early family bonding, and create difficulty in Kangaroo care and breastfeeding initiation. There is also a significant economic burden to the healthcare system of treating asymptomatic neonates with antibiotics in the NICU. The utilization of antibiotics in the early neonatal period is not without risk. There is a relationship between exposure to broad-spectrum antibiotics during the first 7 days of life and wheezing in infancy and early childhood [24, 25]. Antimicrobial resistance emerging from unnecessary antibiotic usage is of increasing concern [26]. Some studies link high body mass index and the occurrence of obesity in children to the early use of broad-spectrum antibiotics within the first 6 months after birth [27, 28]. Intestinal microbiome alterations can lead to the development of allergy and atopy [29].

There are other risks associated with empirical broad-spectrum antibiotic treatment, in addition to the potential of promoting bacterial antibiotic resistance [30]: broad-spectrum antibiotics have been associated with altered gut colonization [31], increased risk of *Candida spp.* colonization and subsequent invasive candidiasis [32] and increased risk of death. Prolonged antibiotic therapy has also been associated with late-onset sepsis (LOS). Antibiotic-resistant pathogenic microorganisms can cause serious infections, difficult to treat in neonates [33].

The concept of this study coincides with the results of Puopolo et al., who studied the management of neonates born at ≥ $35^{0/7}$ weeks' gestation with suspected or proven bacterial EOS and concluded that birth centers should consider the development of locally tailored, documented guidelines for EOS risk assessment and clinical management. Once guidelines are implemented, ongoing surveillance is recommended [34].

Limitations

This study was conducted at a single academic hospital with a high annual rate of deliveries and attached Level III NICU, which is the only referral center in Minia governorate, Egypt, which may restrain its broader application in Level I and II NICUs. This high level of patient observation may not be accessible in other non-academic hospitals. However, any hospital can apply the lessons learned and follow management protocols when taking care of newborns at risk for EOS. We only tracked newborn readmissions within our hospital system. Therefore, we do not have data related to other hospital readmissions. As another limitation, we did not compare the standard checklist for detection of EOS with EOS calculator, which is a clinical risk stratification tool increasingly used to guide empirical antibiotic use for newborns.

Conclusion

This study demonstrates that implementing the standard checklist at an academic medical center can diminish the number of asymptomatic neonates admitted to the NICU for empiric antibiotic treatment. A review of studied neonates identified by the standard checklist showed no missed cases of sepsis and no readmissions for EOS.

Declaration of interest

The Authors declare that there is no conflict of interest. There is no funding, no financial support, and no material support for this work.

References

1. Escobar GJ, Puopolo KM, Wi S, Turk BJ, Kuzniewicz MW, Walsh EM, Newman TB, Zupancic J, Lieberman E, Draper D. Stratification of risk of early-onset sepsis in newborns ≥ 34 weeks' gestation. Pediatrics. 2014;133:30-6.
2. Practice Bulletin No. 160: Premature Rupture of Membranes. Obstet Gynecol. 2016;127(1):e39-51.
3. Higgins RD, Saade G, Polin RA, Grobman WA, Buhimschi IA, Watterberg K, Silver RM, Raju TN; Chorioamnionitis Workshop Participants. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol. 2016;127:426-36.
4. Berardi A, Rossi C, Spada C, Vellani G, Guidotti I, Lanzoni A, Azzalli M, Papa I, Giugno C, Lucaccioni L; GBS Prevention Working Group of Emilia-Romagna. Strategies for preventing early-onset sepsis and for managing neonates at-risk: wide variability across six Western countries. J Maternal Fetal Neonatal Med. 2019;32(18):3102-8.
5. Medhat H, Khashana A, El kalioby M. Incidence of Neonatal Infection in South Sinai, Egypt. Int J Infect. 2017;4(1):e36615.
6. Yang YN, Tseng HI, Yang SN, Lu CC, Chen HL, Chen CJ. A strategy for reduction of antibiotic use in new patients admitted

to a neonatal intensive care unit. Pediatr Neonatol. 2012;53: 245-51.

7. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, Daily P, Apostol M, Petit S, Farley M, Lynfield R, Reingold A, Hansen NI, Stoll BJ, Shane AL, Zell E, Schrag SJ. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J. 2011;30:937-41.
8. Kimberlin DW, Brady MT, Jackson MA, Long SS; Committee on Infectious Diseases; American Academy of Pediatrics. Red Book 2018-2021. Report of the Committee on Infectious Diseases. 31st ed. Elk Grove Village, IL: American Academy of Pediatrics, 2018.
9. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee opinion no. 485: Prevention of early-onset group B streptococcal disease in newborns (reconfirmed in 2016). Obstet Gynecol. 2011;117(4):1019-27.
10. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep. 2002;51(RR-11):1-22.
11. Mukhopadhyay S, Lieberman ES, Puopolo KM, Riley LE, Johnson LC. Effect of early-onset sepsis evaluations on in-hospital breastfeeding practices among asymptomatic term neonates. Hosp Pediatr. 2015;5(4):203-10.
12. Garcia-Flores V, Romero R, Miller D, Xu Y, Done B, Veerapaneni C, Leng Y, Arenas-Hernandez M, Khan N, Panaitescu B, Hassan SS, Alvarez-Salas LM, Gomez-Lopez N. Inflammation-Induced Adverse Pregnancy and Neonatal Outcomes Can Be Improved by the Immunomodulatory Peptide Exendin-4. Front Immunol. 2018;9:1291.
13. Kim B, Oh SY, Kim JS. Placental Lesions in Meconium Aspiration Syndrome. J Pathol Transl Med. 2017;51(5):488-98.
14. Bastek JA, Weber AL, McShea MA, Ryan ME, Elovitz MA. Prenatal inflammation is associated with adverse neonatal outcomes. Am J Obstet Gynecol. 2014;210(5):450.e1-10.
15. Su BH. Histologic chorioamnionitis and neonatal outcome in preterm infants. Pediatr Neonatol. 2014;55:154-5.
16. Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: preterm birth and effects on development. J Pregnancy. 2013;2013:412831.
17. Smulian JC, Shen-Schwarz S, Vintzileos AM, Lake MF, Ananth CV. Clinical chorioamnionitis and histologic placental inflammation. Obstet Gynecol. 1999;94:1000-5.
18. Steel JH, O'Donoghue K, Kennea NL, Sullivan MHF, Edwards AD. Maternal origin of inflammatory leukocytes in preterm fetal membranes, shown by fluorescence in situ hybridization. Placenta. 2005;26:672-7.
19. Erdemir G, Kultursay N, Calkavur S, Zekioğlu O, Koroglu OA, Cakmak B, Yalaz M, Akisu M, Sagol S. Histological chorioamnionitis: effects on premature delivery and neonatal prognosis. Pediatr Neonatol. 2013;54:267-74.
20. Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: preterm birth and effects on development. J Pregnancy. 2013;2013:412831.
21. Mukhopadhyay S, Eichenwald EC, Puopolo KM. Neonatal early-onset sepsis evaluations among well-appearing infants: projected impact of changes in CDC GBS guidelines. J Perinatol. 2013;33:198-205.
22. Herbst A, Källén K. Time between membrane rupture and delivery and septicemia in term neonates. Obstet Gynecol. 2007;110(3):612.
23. Johnson CE, Whitwell JK, Pethe K, Saxena K, Super DM. Term newborns, who are at risk for sepsis: are lumbar punctures necessary? Pediatrics. 1997;99(4):E10.
24. Alm B, Erdes L, Möllborg P, Pettersson R, Norvenius SG, Aberg N, Wennergren G. Neonatal antibiotic treatment is a risk factor for early wheezing. Pediatrics. 2008;121:697-702.
25. Goksör E, Alm B, Thengilsdottir H, Pettersson R, Åberg N, Wennergren G. Preschool wheeze – impact of early fish introduction and neonatal antibiotics. Acta Paediatr. 2011;100(12):1561-6.
26. Cotten CM. Adverse consequences of neonatal antibiotic exposure. Curr Opin Pediatr. 2016;28:141-9.
27. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, De Russo PA. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr. 2014;168:1063-9.
28. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. Int J Obes (Lond). 2013;37:16-23.
29. Madan JC, Farzan SF, Hibberd PL, Karagas MR. Normal neonatal microbiome variation in relation to environmental factors, infection, and allergy. Curr Opin Pediatr. 2012;24:753-9.
30. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M; iCAP Group (Improving Antibiotic Prescribing in Primary Care). Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011;96(1):F4-8.
31. Gewolb I, Schwalbe R, Taciak V, Harrison T, Panigrahi P. Stool micro flora in extremely-low-birth weight infants. Arch Dis Child Fetal Neonatal Ed. 1999;80(3):F167.
32. Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT, Blumberg HM, Pfaller M, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. National Epidemiology of Mycoses Study Group. Risk factors for Candida species colonization of neonatal intensive care unit patients. Pediatr Infect Dis J. 2001;20(12):1119-24.
33. Cotton CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK; on behalf of the National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely-low-birth-weight infants. Pediatrics. 2006;118(2):717-22.
34. Puopolo KM, Benitz WE, Zaoutis TE. Committee on fetus and newborn; committee on infectious diseases. Management of Neonates Born at ≥ $35^{0/7}$ Weeks' Gestation with Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics. 2018;142(6): e20182894.