

Topic Expert Group: Medical care and clinical practice

Management of suspected early-onset neonatal sepsis (EONS)

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Target group

Term and late-preterm infants with suspected infection within the first 72 hours after birth and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Newborn infants with suspected early-onset infection receive prompt diagnosis and effective treatment of sepsis while avoiding overuse of antibiotics.

Rationale

The goal is to reduce morbidity and mortality from early-onset sepsis and adverse effects of overuse of antibiotics. Early diagnosis and treatment of early-onset neonatal sepsis (EONS) are critical in preventing severe and life-threatening complications and mortality. Diagnosis of EONS is difficult due to the often subtle, nonspecific clinical presentation and low predictive values of biomarkers. (1–4) Uncertainty about the presence of neonatal infection may result in unnecessary and prolonged antibiotic treatment. (5,6) Population-based studies in Norway and Switzerland reported a rate of around 2.5% of all term infants started on antibiotic therapy due to suspected EONS, whereas the incidence of culture-proven EONS was between 0.02 and 0.07% (7,8) In other European countries and the United States of America even higher proportions of all term infants are started on antibiotic therapy. (9) Physician's attitudes, such as complacency and fear, have been described as influential factors on antibiotic prescribing. (10)

Antibiotics may have several effects: life-saving for the individual with a severe infection; beneficial for the community hindering spreads of bacteria; problematic for the community regarding development of resistance and for the individual via collateral damage of the microbiome. In early life, antibiotic mediated alteration of the microbiome may have potential consequences for future health. (11–14) Therefore, reduction of unnecessary or prolonged antibiotic therapy is one of the key steps of antimicrobial stewardship to improve future health of the individual and to impede the emergence of multidrug resistant bacteria. (11–16)

Benefits

Short-term benefits

- Reduced mortality and morbidity (17–20)
- Reduced unnecessary and prolonged antibiotic therapy for suspected infection (7–9)
- Reduced separation of mother and infant with less interfering of breastfeeding (consensus)

Long-term benefits

- Reduced development of multidrug resistance (MDR) (12,15)



- Reduced alteration of the infant microbiome, with implication for later health (11–14)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents (at the hospital and at home) are informed by healthcare professionals about signs, treatment and consequences of early-onset neonatal infection (see Infant- & family-centred developmental care). (21–25)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on management for suspected early-onset neonatal sepsis (EONS) is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on management for suspected EONS is attended by all healthcare professionals.	B (High quality)	Training documentation
4. In healthy infants with risk factors for EONS, vital signs are observed and monitored for 24 hours, and infants do not receive antibiotics unless symptomatic. (8,21–26)	A (Moderate quality)	Guideline
5. Always consider to start parenteral antibiotic therapy if newborn infants have clinical signs possibly related to sepsis. (21–25)	A (Moderate quality)	Guideline
6. An aerobic blood culture (minimum 1ml) is drawn before start of antibiotic therapy. (21–25)	A (Moderate quality)	Guideline
7. The need for antibiotic therapy is re-evaluated after 24-36 hours. (21–25,27,28)	A (Moderate quality)	Guideline
8. Antibiotic therapy is streamlined as soon as blood culture results are available. (21–25)	A (Moderate quality)	Guideline
9. $\geq 3^{\text{rd}}$ generation cephalosporins or carbapenems are not routinely used for empiric therapy. (12,21–25)	A (Moderate quality)	Guideline

For neonatal unit		
10. A unit guideline for suspected EONS is available and regularly updated in conjunction with obstetric guidance on intrapartum prophylaxis. (21,29)	B (High quality)	Guideline
11. Depending on the current rate of neonates started on antibiotics, implementing the sepsis calculator to decrease exposure of antibiotics is considered. (21,30)	A (moderate quality)	Guideline
12. A unit-based antibiotic stewardship programme is established: minimum for use of $\geq 3^{\text{rd}}$ generation cephalosporins or carbapenems. (31–33)	A (Moderate quality)	Audit report
For hospital		
13. Training on management for suspected EONS is ensured.	B (High quality)	Training documentation
14. Analysis of blood cultures including determination of antibiotic resistance patterns with daily report of results is conducted. (15,16,34,35)	A (High quality)	Audit report
15. Hospital-based antibiotic stewardship programme is established: minimum recording of multidrug resistance (MDR). (31–33)	A (Moderate quality)	Audit report
For health service		
16. A national guideline on management for suspected EONS is available and regularly updated in conjunction with obstetric guidance on intrapartum prophylaxis. (29,34–36)	A (Moderate quality)	Guideline
17. Regional/national surveillance and reports of antibiotic resistance patterns of positive blood cultures are available. (15,16,34,35)	A (Moderate quality)	Audit report

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	

For neonatal unit	<ul style="list-style-type: none"> Develop an algorithm with biomarker guidance for duration of antibiotic therapy. (37–39) 	A (Moderate quality)
For hospital	<ul style="list-style-type: none"> Consolidate an antibiotic stewardship programme. (28–30) 	A (Moderate quality)
For health service		
N/A		

Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals about signs, treatment and consequences of early-onset neonatal infection.

For healthcare professionals

- Attend training on management for suspected early-onset neonatal sepsis (EONS).
- Reduce the use of unnecessary antibiotic therapy.

For neonatal unit

- Use published guidelines regarding management for suspected EONS.
- Develop and implement a unit guideline on management for suspected EONS in conjunction with obstetric guidance on intrapartum prophylaxis.
- Develop information material on signs, treatment and consequences of early-onset neonatal infection for parents.

For hospital

- Support healthcare professionals to participate in training on management for suspected EONS.
- Ensure facilities for rapid detection of bloodstream infection.
- Start or continue with an antibiotic stewardship programme.

For health service

- Use published guidelines regarding management for suspected EONS.
- Develop and implement a national guideline on management for suspected EONS in conjunction with obstetric guidance on intrapartum prophylaxis.

Description

Different national guidelines for the management of suspected EONS are published and may serve as examples. These guidelines are not uniform and differ in some points. (21,24,25,29,40,41) The diversity of the guidelines reflects the diversity of their national healthcare system. It is also a consequence of a different translation of available data to clinical practice such as the approach of maternal risk factors for EONS. Guidelines for the management of EONS have to be adapted to the specific healthcare practices such as screening for maternal colonisation with Group B streptococci, and possibilities for observation of newborn infants at increased risk for EONS. The introduction of the sepsis calculator as algorithm regarding start of antibiotics is mainly dependent on the current rate of newborn infants started on antibiotics. Whereas start of antibiotics due to risk factors alone is not reasonable (compare component 4), risk factors in combination with clinical signs are part of the algorithm of the sepsis calculator.

Source

1. Cantey JB, Lee JH. Biomarkers for the Diagnosis of Neonatal Sepsis. *Clin Perinatol*. 2021 Jun;48(2):215–27.
2. Escobar GJ, Li DK, Armstrong MA, Gardner MN, Folck BF, Verdi JE, et al. Neonatal sepsis workups in infants ≥ 2000 grams at birth: A population-based study. *Pediatrics*. 2000 Aug;106(2 Pt 1):256–63.
3. Stocker M, van Herk W, el Helou S, Dutta S, Schuerman FABA, van den Tooren-de Groot RK, et al. C-Reactive Protein, Procalcitonin, and White Blood Count to Rule Out Neonatal Early-onset Sepsis Within 36 Hours: A Secondary Analysis of the Neonatal Procalcitonin Intervention Study. *Clin Infect Dis*. 2021 Jul 15;73(2):e383–90.
4. Pak Cheung FN, Lam HS. Diagnostic markers for neonatal sepsis. *Curr Opin Pediatr*. 2006 Apr;18(2):125–31.
5. Berardi A, Fornaciari S, Rossi C, Patianna V, Bacchi Reggiani ML, Ferrari F, et al. Safety of physical examination alone for managing well-appearing neonates ≥ 35 weeks' gestation at risk for early-onset sepsis. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet*. 2015 Jul;28(10):1123–7.
6. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK, Smith PB, et al. Medication use in the neonatal intensive care unit. *Am J Perinatol*. 2014 Oct;31(9):811–21.
7. Mundal HS, Rønnestad A, Klingenberg C, Stensvold HJ, Størdal K. Antibiotic Use in Term and Near-Term Newborns. *Pediatrics*. 2021 Dec 1;148(6):e2021051339.
8. Zihlmann-Ji J, Braun C, Buettcher M, Hodel M, Lehnick D, Stocker M. Reduction of Duration of Antibiotic Therapy for Suspected Early-Onset Sepsis in Late-Preterm and Term Newborns After Implementation of a Procalcitonin-Guided Algorithm: A Population-Based Study in Central Switzerland. *Front Pediatr*. 2021;9:702133.
9. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. *JAMA Pediatr*. 2017 Apr 1;171(4):365–71.
10. Teixeira Rodrigues A, Roque F, Falcão A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents*. 2013 Mar;41(3):203–12.
11. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. *Science*. 2016 Apr 29;352(6285):539–44.
12. Fjalstad JW, Esaiassen E, Juvet L, Anker JN van den, Klingenberg C. Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. *J Antimicrob Chemother*. 2018;
13. Raymond SL, Rincon JC, Wynn JL, Moldawer LL, Larson SD. Impact of Early-Life Exposures to Infections, Antibiotics, and Vaccines on Perinatal and Long-term Health and Disease. *Front Immunol*. 2017;8:729.
14. Schulfer A, Blaser MJ. Risks of Antibiotic Exposures Early in Life on the Developing Microbiome. *PLoS Pathog*. 2015 Jul;11(7):e1004903.
15. Kollef MH, Bassetti M, Francois B, Burnham J, Dimopoulos G, Garnacho-Montero J, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. *Intensive Care Med*. 2017 Feb 4;
16. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet Lond Engl*. 2016 Jan 9;387(10014):176–87.



17. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. *Lancet Lond Engl*. 2004 Jan 24;363(9405):292–4.
18. Stoll B, Puopolo K, Hansen N, Sánchez P, Bell E, Carlo W, et al. Early-Onset Neonatal Sepsis 2015 to 2017, the Rise of *Escherichia coli*, and the Need for Novel Prevention Strategies. *JAMA Pediatr*. 2020;
19. Levent F, Baker CJ, Rench MA, Edwards MS. Early outcomes of group B streptococcal meningitis in the 21st century. *Pediatr Infect Dis J*. 2010 Nov;29(11):1009–12.
20. Mynarek M, Bjellmo S, Lydersen S, Afset JE, Andersen GL, Vik T. Incidence of invasive Group B Streptococcal infection and the risk of infant death and cerebral palsy: a Norwegian Cohort Study. *Pediatr Res*. 2021 May;89(6):1541–8.
21. National Institute for Health and Care Excellence (NICE). Neonatal infection: antibiotics for prevention and treatment. NICE guideline [NG195] [Internet]. NICE; 2021 [cited 2022 Jun 13]. Available from: <https://www.nice.org.uk/guidance/ng195>
22. Barrington K. Management of the infant at increased risk for sepsis. *Paediatr Child Health*. 2007 Dec;12(10):893–905.
23. Mahieu L, Langhendries JP, Cossey V, De Praeter C, Lepage P, Melin P. Management of the neonate at risk for early-onset Group B streptococcal disease (GBS EOD): new paediatric guidelines in Belgium. *Acta Clin Belg*. 2014 Oct;69(5):313–9.
24. 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 Dec;142(6):e20182894.
25. Stocker M, Berger C, McDougall J, Giannoni E, Taskforce for the Swiss Society of Neonatology and the Paediatric Infectious Disease Group of Switzerland. Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly*. 2013 Sep 19;143:w13873.
26. Vatne A, Klingenberg C, Øymar K, Rønnestad AE, Manzoni P, Rettedal S. Reduced Antibiotic Exposure by Serial Physical Examinations in Term Neonates at Risk of Early-onset Sepsis. *Pediatr Infect Dis J*. 2020 May;39(5):438–43.
27. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-Negative Early-Onset Neonatal Sepsis - At the Crossroad Between Efficient Sepsis Care and Antimicrobial Stewardship. *Front Pediatr*. 2018;6:285.
28. Cantey J, Prusakov P. A proposed framework for the clinical management of neonatal “culture-negative” sepsis. *J Pediatr*. 2022;
29. van Herk W, el Helou S, Janota J, Hagmann C, Klingenberg C, Staub E, et al. Variation in Current Management of Term and Late-preterm Neonates at Risk for Early-onset Sepsis: An International Survey and Review of Guidelines. *Pediatr Infect Dis J*. 2016 May;35(5):494–500.
30. Achten NB, Klingenberg C, Benitz WE, Stocker M, Schlapbach LJ, Giannoni E, et al. Association of Use of the Neonatal Early-Onset Sepsis Calculator with Reduction in Antibiotic Therapy and Safety: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2019;173(11):1032–40.
31. Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. *Infect Dis Clin North Am*. 2014 Jun;28(2):247–61.
32. Cantey JB, Wozniak PS, Pruszynski JE, Sánchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. *Lancet Infect Dis*. 2016 Oct;16(10):1178–84.
33. Patel SJ, Rosen E, Zaoutis T, Prasad P, Saiman L. Neonatologists' perceptions of antimicrobial resistance and stewardship in neonatal intensive care units. *Infect Control Hosp Epidemiol*. 2010 Dec;31(12):1298–300.



34. Centers for Disease Control and Prevention (CDC). CDC Campaign to Prevent Antimicrobial Resistance in Healthcare Settings 12 Steps to Prevent Antimicrobial Resistance Among Long-term Care Resident. 2004;
35. World Health Organization. Global action plan on antimicrobial resistance [Internet]. Geneva: World Health Organization; 2015 [cited 2022 Jun 13]. 28 p. Available from: <https://apps.who.int/iris/handle/10665/193736>
36. Håkansson S, Lilja M, Jacobsson B, Källén K. Reduced incidence of neonatal early-onset group B streptococcal infection after promulgation of guidelines for risk-based intrapartum antibiotic prophylaxis in Sweden: analysis of a national population-based cohort. *Acta Obstet Gynecol Scand*. 2017 Dec;96(12):1475–83.
37. Ehl S, Gering B, Bartmann P, Högel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. *Pediatrics*. 1997 Feb;99(2):216–21.
38. Philip AG, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. *Pediatrics*. 2000 Jul;106(1):E4.
39. Stocker M, Herk W van, Helou S el, Dutta S, Fontana MS, Schuerman FABA, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIs). *The Lancet*. 2017 Aug 26;390(10097):871–81.
40. Good PI, Hooven TA. Evaluating Newborns at Risk for Early-Onset Sepsis. *Pediatr Clin North Am*. 2019 Apr;66(2):321–31.
41. Zemlin M, Berger A, Franz A, Gille C, Härtel C, Küster H, et al. Bakterielle Infektionen bei Neugeborenen. Leitlinie der GNPI, DGPI, DGKJ und DGGG. (S2k-Level, AWMF-Leitlinien-Register-Nr. 024/008, April 2018). *Z Geburtshilfe Neonatol*. 2019 Jun;223(3):130–44.

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