Antibiotic Stewardship in the NICU Reference List

Developed by the Optimizing Antibiotic Stewardship in California NICUs (OASCN) Collaborative (March 2021-February 2022). Annotations are bulletized.

NICU Stewardship Topic Areas

Antibiotic Stewardship in the NICU
Reference List

Antibiotic Resistance

Ramirez CB et al. Antibiotic resistance in the neonatal intensive care unit. NeoReviews 2019;20:e135.
- Good summary for NICU practitioners.

Munita JM et al. Mechanisms of antibiotic resistance. Microbiol Spectr 2016;4:10.1128/microbiolspec.VMBF-0016-2015.
- Very comprehensive and detailed summary on the general topic.

Antimicrobial Monitoring and Adverse Events

Donnelly PC et al. Ceftriaxone-associated biliary and cardiopulmonary adverse events in neonates: A systematic review of the literature. Pediatr Drugs 2017;19;21.
- This drug usually avoided, but no evidence supporting clinically significant hyperbilirubinemia.

Van Donge T et al. Key components for antibiotic dose optimization of sepsis in neonates and infants. Front Pediatr 2018;6:325.
- Great resource on the topic.

Murphy HJ et al. Nephrotoxic medications and acute kidney injury risk factors in the neonatal intensive care unit: clinical challenges for neonatologists and nephrologists. Pediatric Nephrol 2020 Nov;35(11):2077.
- Best paper on this topic.

Cotton CM et al. Adverse consequences of neonatal antibiotic exposure. Curr Opin Pediatr. 2016;28:141.

Umberto de Rose et al. Therapeutic drug monitoring is a feasible tool to personalize drug administration in neonates using new techniques: an overview on the pharmacokinetics and pharmacodynamics in neonatal age. Int J Mol Sci 2020;21:5898.
- Great up-to-date summary of the topic.

Bacterial Sepsis Diagnosis/Biomarkers

Cantey JB et al. Biomarkers for the diagnosis of neonatal sepsis. Clin Perinatol 2021;48:215-227.
- Summary by a real expert.

Rub DM et al. Role of microbiological tests and biomarkers in antibiotic stewardship. Semin Perinatol 2020 Oct 12:151328.
- Focuses mainly on blood cultures and PCR science, but also CRP and PCT in the NICU.

Weitkamp J-H. The role of biomarkers in suspected neonatal sepsis. 2020 Clin Infect Dis ep 3:ciaa869. doi: 10.1093/cid/ciaa869. Online ahead of print.
- Commentary on the best RCT study on use of CRP or PCT in EOS management. Says maybe doesn't add much to the sepsis calculator for <34 wkrs.

Perrone S et al. C-reactive protein in healthy term newborns during the first 48 hours of life. Arch Dis Child Fetal Neonatal Ed 2018;103;F163-6.
- CRP varies in healthy newborns in first 48 HOL.

Singh N et al. Antibiotic stewardship in NICU: De-implementing routine CRP to reduce antibiotic usage in neonates at risk for early-onset sepsis. J Perinatol 2021; 41:2488-2494.
- Stopping routine CRPs for EOS evaluation lowers number of R/O sepsis workup and antibiotic use.

Gyllensvärd et al. C-reactive protein- and clinical symptoms guided strategy in term neonates with early-onset sepsis reduced antibiotic use and hospital stay: a quality improvement initiative. BMC Pediatrics (2020) 20:531
- Only study in 2000s evaluating utility of CRP in neonates as a tool to stop antibiotic.

Greenberg RG et al. Traumatic lumbar punctures in neonates: test performance of the cerebrospinal fluid white blood cell count. PIDJ 2008;27:1047-51.
- Discusses how "correction" due to many RBCs is not especially helpful.

"Baseline" Antibiotic Use in NICUs

Cantey JB et al. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. Pediatr Infect Dis J 2015;34:267.
- Type and indication-specific duration for antibiotics in >1600 babies at Parkland Memorial.

Ho T et al. Adherence of newborn-specific antibiotic stewardship programs to CDC recommendations Pediatrics 2018;142:e20174322.
- 143 VON centers. Only 2 of 7 CDC core ASP elements were present in >50% of NICUs.

O'Leary EN et al. National Healthcare Safety Network 2018 baseline neonatal standardized antimicrobial administration ratios. Hosp Pediatr 2022 Feb 1;12(2):190-198.
- This is where CDC is regarding AUR "standard setting" in neonates.

Blood Culture Positivity, Timing and Contamination

Hamilton LF et al. A sterile collection bundle intervention reduces the recovery of bacteria from neonatal culture. Biomed Hub 2018;3:1-7.
- Pre v. post design and maximal sterile precautions lowered false (+) culture rates from 4.6% to 0.6%. Not blinded, but 4 yrs later false (+) rate still low (1.2%).

Patton RG et al. Innovation for reducing blood culture contamination: initial specimen diversion technique. J Clin Microbiol 2010;48(12):4501-3.

Zimmerman FS et al. Modification of blood test draw order to reduce blood culture contamination: A randomized clinical trial. Clin Infect Dis 2020;71(5):1215-1220.
- Diversion lowered contamination from 5% to 2%.

Allen E et al. A quality improvement initiative to reduce blood culture contamination in the neonatal unit. Pediatric Qual Safety 2021;6(3), e413.
- Contamination rate lowered from 2% to 1%.

Bram S. Use of a sterile collection process to reduce contaminated peripheral blood cultures. Hosp Pediatrics 2021;11(11), 1205–1216.
- Intervention lowered contamination from 7% to 2%.

Kuzniewicz MW et al. Time to positivity of neonatal blood cultures for early-onset sepsis. PIDJ 2020;39:634-40.
- Blood cultures were positive by 24, 36, and 48 hours in 68%, 94%, and 97%, respectively.

Singh MP. The practice of blood volume submitted for culture in a neonatal intensive care unit. Arch Dis Child. Fetal and Neonatal Ed, 2020;105(6), 600–604.
- Pre-intervention blood culture volumes were 97%; post-intervention went down to 25%.

Early-Onset Sepsis (EOS) Management

Puopolo KM for COFN and COID. Management of infants at risk for group B streptococcal disease. Pediatrics. 2019;144(2):e20191881.

Puopolo KM for COFN and COID. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics 2018;142:e20182894.

Puopolo KM for COFN and COID. Management of neonates born at ≤34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics 2018;142:e20182896.

Benitz WE et al. Technical assessment of the neonatal early-onset sepsis risk calculator. Lancet Infect Dis. 2020 Oct 29:S1473-3099(20)30490-4.
- Very deep methodologic dive into the strengths/weaknesses of the Kaiser calculator.

Gong CL et al. Early onset sepsis calculator-based management of newborns exposed to maternal intrapartum fever: a cost benefit analysis. J Perinatology 2019;39:571
- Only cost effective eval of the Kaiser calculator – significantly lowers antibiotic use and societal costs.

Le J et al. Prolonged post-discontinuation antibiotic exposure in very low birth weight neonates at risk for early-onset sepsis. J Pediatric Infect Dis Soc 2021;10:615-621.
- Model that shows the prolonged utility of IV ampicillin after discontinuation, in VLBWs.

Berardi A et al. Are postnatal ampicillin levels actually related to the duration of intrapartum antibiotic prophylaxis prior to delivery? A pharmacokinetic study in 120 neonates. Arch Dis Child Fetal Neonatal Ed 2018;103(2).

ACOG's 2017 view on treatment of maternal intraamniotic infection

Early-Onset Sepsis (EOS) Impact of Prolonged Antibiotic Use

Ting JY et al. Duration of initial empirical antibiotic therapy and outcomes in very low birth weight infants. Pediatrics. 2019;143(3):e20182286. doi: 10.1542/peds.2018-2286.
- Large Canadian Network shows each day of antibiotic postnatally increases risk of bad outcomes later.

Underwood MW et al. Neonatal intestinal dysbiosis. J Perinatol 2020; 40, pages1597–1608(2020)
- Great summary of how antibiotic overuse may impact the microbiome and health.

Singer JR et al. Preventing dysbiosis of the neonatal mouse intestinal microbiome protects against late-onset sepsis. Nat Med 2019; 25: 1772.
- If you like mice and basic science, this is a must read!

Greenberg RC et al. Prolonged duration of early antibiotic therapy in extremely premature infants. Pediatr Res. 2019 Jun;85(7):994-1000.
- And this NIH NICU Network study does NOT show an impact of early antibiotics with later bad outcome.

Fungal Sepsis Prophylaxis, Diagnosis and Management

Ericson JE et al. Fluconazole prophylaxis for the prevention of candidiasis in premature infants: a meta-analysis using patient-level data. Clin Infect Dis 2016;63:604.
- Meta-analysis of all RCTs on the topic.

Leonart LP et al. Fluconazole doses used for prophylaxis of invasive fungal infection in neonatal intensive care units: a network meta-analysis. J Pediatr 2017;185:129.
- Meta-analysis to determine best dose: 3mg/kg/day.

Cohen JF et al. Diagnostic accuracy of serum (1,3)-beta-d-glucan for neonatal invasive candidiasis: systematic review and meta-analysis. Clin Microbiol Infect 2020;26:291.
- This is the Fungitell assay. Sensitivity (high) and specificity (not as high) vary with your lab's internal cutoff value.

Scott BL et al. Pharmacokinetic, efficacy, and safety considerations for the use of antifungal drugs in the neonatal population. Exp Opin Drug Metabol Tox 2020;7:605-616.

Infection Prevention and Stewardship

Akinboyo IC et al. SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to Staphylococcus aureus disease prevention. Infect Control Hosp Epidemiol 2020;41:1251-7.
- Discusses real-world decolonization strategies and notes data gap on systemic antibiotics for this purpose. Refers to the larger doc here.

Muller M et al. SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches for the prevention of central-line associated bloodstream infections. Infect Control Hosp Epidemiol 2022;Mar 4;1.
- Discusses real-world ways to minimize CLABSI including some on stewardship.

Mobley RE et al. Central line-associated bloodstream infections in the NICU: Successes and controversies in the quest for zero. Semin Perinatol 2017;41:166-174.
- Very nice summary of all the relevant topics. Also describes the successful 2006 CPQCC CLABSI collaborative.

Bratzler DW et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health-Syst Pharm 2013;70:195.
- Inter-society consensus guideline. No NICU-specific recommendations in print, but concepts the same.

Shalabi et al. Risk of infection using peripherally inserted central and umbilical catheters in preterm neonates. Pediatrics 2015;136:1073-9.
- Total N was 180/comparison group which is too small to detect a difference given known baseline incidence of CLABSI of 2-10/1000 pt-days.

Dubbink-Verheij GH et al. Bloodstream infection incidence of different central venous catheters in neonates: a descriptive cohort study. Front Pediatr 2017;5:142.
- 407 UVCs compared to 185 PICCs (NOT preterms and still too small sample size) = no difference.

Late-Onset & Culture-Negative Sepsis

Piantino JH et al. Culture-negative sepsis and systemic inflammatory response syndrome in neonates. NeoReviews 2013;14:c294.

Sanchez P et al. Empiric therapy with vancomycin in the neonatal intensive care unit: let's "get smart" globally! J Pediatr (Rio J) 2016;92:432.
- Comment on study that showed active restriction of vancomycin can be done safely in VLBWs.

Chu A et al. Antimicrobial therapy and late-onset sepsis. NeoReviews 2012;13:e94.
- A bit old, but still good.

Necrotizing Enterocolitis (NEC)

Cotten CM for NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009;123:58.
- >6500 babies, ~7% increase in aOR of later NEC for each day of initial empiric antibiotics (NNT 54). ~16% increase in aOR of death for each additional day (NNT 21).

Downard CD et al. Treatment of necrotizing enterocolitis: An American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatric Surgery 2012;47:2111.
- Good section on antibiotic use data.

Gill MA et al. Antibiotics in the medical and surgical treatment of necrotizing enterocolitis. A systematic review. BMC Pediatr 2022 Jan 27;22(1):66. doi: 10.1186/s12887-022-03120-9.

Smith MJ et al. Antibiotic safety and effectiveness in premature infants with complicated intraabdominal infection. PIDJ 2021;40:550-55.
- Compared 3 different regimens for <10d in <33wks GA babies.

Autmizquine J et al. Anaerobic antimicrobial therapy after necrotizing enterocolitis in VLBW infants. Pediatrics 2015;135:e117-25.

Quality Improvement in the NICU

Swanson JR et al. Roadmap to a successful quality improvement project. J Perinatol 2017;37:112.
- Focuses on the NICU.

Gupta M et al. The relationship between patient safety and quality improvement in neonatology. Sem Perinatol 2019 Dec;43(8):151173.
- Particularly good discussion of the relationship and the mechanics of QI and safety.

Stewardship in the NICU

Rajar P et al. Antibiotic stewardship in premature infants: A systematic review. Neonatology 2020;117(6):673-686.
- Good recent systematic review of the existing data.

Nash C et al. Antimicrobial stewardship in the NICU: Lessons we've learned. NeoReviews 2014;15:e116.

McPherson C et al. Antibiotic stewardship in neonates: challenges and opportunities. Neonatal Network 2018;37:1.
- Very good and data-driven summary of concepts from true experts.

Mukhopadhy S et al. Challenges and opportunities for antibiotic stewardship among preterm infants. Arch Dis Child Fetal Neonatal Ed. 2019;104(3):F327.
- Focus on preterms is very helpful.

Johnson SJ et al. Is double coverage of gram-negative organisms necessary? Am J Health Syst Pharmacy 2011;68:119-24.

Stewardship Intervention Data

Cantey JB et al. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis 2016 Oct;16:1178.
- Successful hard stop for rule out sepsis (2d), pneumonia (5d), and culture (-) sepsis (5d), >2500 babies at Parkland, antibiotic use 27% less.

Arora V et al. Optimizing antibiotic use for early onset sepsis: A tertiary NICU experience. J Neonatal Perinatal Med 2019;12(3):301.
- One recent experience with Kaiser calculator and 36 hr hard stop for ≤34 weeks GA babies. 29% less antibiotics, 24% less sepsis evaluations.

Dukhovny D, et al. A collaborative multicenter QI initiative to improve antibiotic stewardship in newborns. Pediatrics 2019;144:e20190589.
- QI initiative in 146 VON units led to 34% AUR reduction.

Meeker D et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices a randomized clinical trial. JAMA 2016;315(6):5.
- Requiring justification of antibiotic prescription and/or peer comparison lowers use for adult outpatients.

Hamdy R et al. Reducing vancomycin use in a level IV NICU. Pediatrics. 2020;146(2):e20192963
- Great paper on how ASP can reduce vancomycin use by 30-50%.

Chiu CH et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011;30(4):273-278.
- 35-62% reduction in vancomycin use in LOS.

Stewardship Data, CPQCC-Specific

Schulman J et al. Neonatal intensive care unit antibiotic use. Pediatrics 2015.135:826
- 40-fold variation in 127 NICUs in CPQCC. Much unjustified use.

Schulman J et al. Variation in neonatal antibiotic use. Pediatrics. 2018 Sep;142(3):e20180115. doi: 10.1542/peds.2018-0115.
- AUR declined 22% from 2013-2016, variation narrowed, but didn't vary with proven infection.

Flannery D et al. Neonatal antibiotic use: How much is too much? Pediatrics 2018;142:e20181942.
- Good context commentary on Schulman 2018 paper above.

Schulman J et al. Newborn antibiotic exposures and association with proven bloodstream infection. Pediatrics 2019;144:e20191105.
- Median 70 newborns got empiric antibiotics per confirmed EOS infection and 12 newborns/LOS infection. The current clinical reality.

Stewardship Principles, Team Building and Toolkits

Wiley KC et al. Antibiotic resistance policy and the stewardship role of the nurse. Policy Polit Nurs Pract 2019; 20:8.

Parente DM et al. Role of the pharmacist in antimicrobial stewardship. Med Clin North Am. 2018;102:929-936.

Barlam TF et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51.
CDC Core Elements of Antimicrobial Stewardship, 2019
- All age groups, not just NICU. Also discusses how to build a stewardship team.

Pediatric Infectious Diseases Society (PIDS) Pediatric ASP Toolkit
- Neonatal part of ASP toolkit developed by AAP Section on Infectious Disease and PIDS

Antimicrobial Stewardship Resources
- Has links to many institutional websites with ASP recs and references, some with NICU-specific utility.

Ha DR et al. A multidisciplinary approach to incorporate bedside nurses into antimicrobial stewardship and infection prevention. Jt Comm J Qual Patient Saf. 2019;45(9):600-605.

Schechner V et al. Epidemiologic interpretation of studies examining the effect of antibiotic usage on resistance. Clin Microbiol Rev 2013;26:289-307.
- If you really want to get into the concept, a very comprehensive and good review.

Pediatric Infectious Diseases Society (PIDS) Pediatric ASP Toolkit
- Neonatal part of ASP toolkit developed by AAP Section on Infectious Disease and Peds ID Society.

Using Vignette Methods to Describe Practice Variation, Practice Quality and Promote Change

Converse L, et al. Methods of Observing Variations in Physicians' Decisions: The Opportunities of Clinical Vignettes. J Gen Intern Med. 2015 Aug;
- Great review highlighting vignette methods as an ideal method of describing physician decisions relative to alternative options.

Patel S, et al. Clinical vignettes provide an understanding of antibiotic prescribing practices in neonatal intensive care units. ICHE 2011;32:597–602.
- 4 tertiary NICUs. Wide clinical practice variation. Identified specific "low hanging fruit" areas to target as priorities.

Payton K et al. Vignettes Identify Variation in Antibiotic Use for Suspected Early Onset Sepsis. Hosp Pediatrics 2021;11:770-4.
- Initial study using vignette methods within a CPQCC QI collaborative.

Payton K and Gould J. Vignette Research Methodology: An Essential Tool for Quality Improvement Collaboratives. Healthcare 2022 Dec 20;11(1):7.
- Review of CPQCC experience and lessons from implementing vignette research methods in quality improvement collaboratives. Describes theory supporting vignettes and practical applications in antibiotic stewardship.