Empiric Antibiotic Therapy for Sepsis in the Intensive Care Nursery
UCSF Benioff Children's Hospital San Francisco

This guideline applies to use of antibiotics in the Intensive Care Nursery for empiric treatment of presumed perinatal (early-onset, <=72 hours of age) or hospital-onset infections in infants at > 72 hours of age who have been hospitalized since birth (late-onset).

Recommendations:
Refer to the following algorithms for antibiotic selection guidance in infants presenting with clinical signs concerning for sepsis:

- *Empiric Antibiotic Therapy for Sepsis in the Intensive Care Nursery (ICN)*
- *Necrotizing Enterocolitis: Antibiotic Selection and Duration of Therapy*
- *Neonatal Dosing Guidelines* for all antibiotic dosing

For situations in which a neonatal clinician would previously have considered empiric use of vancomycin and gentamicin, we now recommend nafcillin and gentamicin except in those infants with history of prior MRSA colonization or infection, or for infants with sudden and inexplicable severe illness.

Prior history of MRSA can be identified as follows:

1. Review infant's Microbiology history for prior isolation of MRSA or detection of MRSA via nasal swab screening (performed if transferred from another hospital).
    a. This information can be located in APeX Microbiology Summary report
2. If an infant has any MRSA isolate or positive MRSA nasal swab, documentation of the result is recommended in team sign-out communication.
3. Decolonization may be considered and can temporarily eliminate MRSA colonization but recolonization is possible.

Rationale:
The goal of these guidelines is to reduce avoidable vancomycin exposure among hospitalized neonates. Previously, vancomycin has been included in empiric late onset sepsis (LOS) therapy to cover coagulase-negative staphylococci (CoNS), which are usually resistant to narrower spectrum antibiotics. Though CoNS is one of the most common causes of LOS, it is unlikely to lead to near term mortality compared to other LOS pathogens.[1,2] Empiric treatment vs. delayed treatment of CoNS (initiation of vancomycin when the blood culture is reported positive) has not been associated with a detectable mortality benefit in a large neonatal cohort study.[3]

Given the adverse effects of vancomycin exposure, including selection for antibiotic resistance, modification of the neonatal microbiome, nephrotoxicity, and ototoxicity, Choosing Wisely guidelines have recommended avoidance of routine empiric

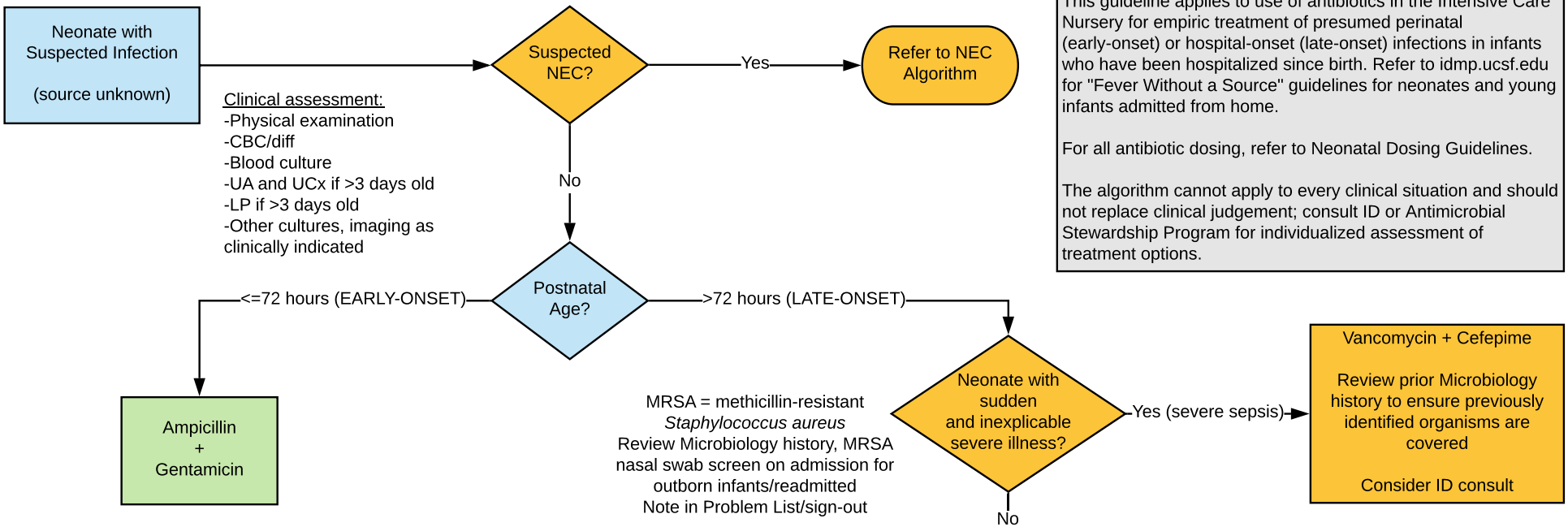
vancomycin use in neonatal intensive care patients.[4] Other institutions have implemented guidelines to reduce use of empiric vancomycin in LOS and reported reducing empiric vancomycin without identifiable detriment to LOS outcomes.[1,5–7]

Nafcillin is a narrow spectrum antibiotic with less impact on resistance and the neonatal microbiome, yet it covers major neonatal LOS pathogens including methicillin-susceptible *Staphylococcus aureus* (MSSA), group B streptococcus, and when combined with gentamicin has some activity against *Enterococcus faecalis*.[8,9] The combined regimen of nafcillin + gentamicin provides coverage against > 90% of sterile site microbiologic isolates in the UCSF Intensive Care Nursery (over Feb 2015-Aug 2018) and a majority of urine culture isolates. Nafcillin does not cover methicillin-resistant *Staphylococcus aureus* (MRSA); empiric vancomycin is indicated for infants who have a history of MRSA colonization or prior MRSA infection.

References:

1. Karlowicz M, Buescher E, Surka A. Fulminant late-onset sepsis in a neonatal intensive care unit, 1988 –1997, and the impact of avoiding empiric vancomycin therapy. *Pediatrics*. 2000;106:1387-1390.
2. Cantey JB, Anderson K, Kalagiri R, Mallett L. Morbidity and mortality of coagulase-negative staphylococcal sepsis in very-low-birth-weight infants. *World J Pediatr*. 2018;14(3):269-273.
3. Ericson JE, Thaden J, Cross HR, Reese H, Hornik CP, Smith PB. No survival benefit with empirical vancomycin therapy for coagulase-negative staphylococcal bloodstream infections in infants. *Pediatr Infect Dis J*. 2016;34(4):371-375.
4. American Academy of Pediatrics - Committee on Infectious Diseases, Pediatric Infectious Diseases Society. Choosing Wisely Recommendations. 2018.
5. Lawrence SL, Roth V, Slinger R, Toye B, Gaboury I, Lemyre B. Cloxacillin versus vancomycin for presumed late-onset sepsis in the neonatal intensive care unit and the impact upon outcome of coagulase negative staphylococcal bacteremia : a retrospective cohort study. *BMC Pediatr*. 2005;8:1-8.
6. Chiu C, Michelow IC, Ringer SA, Puopolo KM. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2011;30(4):273-278.
7. Holzmann-Pazgal G, Khan AM, Northrup TF, Domonoske C, Eichenwald EC. Decreasing vancomycin utilization in a neonatal intensive care unit. *Am J Infect Control*. 2015;43(11):1255-1257.
8. Glew RH, Moellering RC, Wennersten C. Comparative synergistic activity of nafcillin, oxacillin, and methicillin in combination with gentamicin against enterococci. *Antimicrob Agents Chemother*. 1975;7(6):828-832.
9. Watanakunakorn C, Glotzbecker C. Activity of nafcillin, oxacillin, and methicillin in combination with gentamicin and tobramycin against enterococci. *Antimicrob Agents Chemother*. 1977;11(1):88-91.

Empiric Antibiotic Therapy for Sepsis in the Intensive Care Nursery (ICN)
UCSF Benioff Children's Hospital San Francisco



This guideline applies to use of antibiotics in the Intensive Care Nursery for empiric treatment of presumed perinatal (early-onset) or hospital-onset (late-onset) infections in infants who have been hospitalized since birth. Refer to idmp.ucsf.edu for "Fever Without a Source" guidelines for neonates and young infants admitted from home.

For all antibiotic dosing, refer to Neonatal Dosing Guidelines.

The algorithm cannot apply to every clinical situation and should not replace clinical judgement; consult ID or Antimicrobial Stewardship Program for individualized assessment of treatment options.

Modification of Empiric Therapy:

Meningitis Suspected:
Consider ID consult
Replace Gentamicin with Ceftazidime at meningitic dosing (Cefotaxime is no longer available)

Neonates with Significantly Impaired Renal Function:
Ceftazidime may be used in place of Gentamicin for Early-Onset Sepsis
Cefepime may be used in place of both Nafcillin and Gentamicin for Late-Onset Sepsis (this regimen covers most important pathogens *except Enterococcus*).

Suspected HSV Infection:
For infants > 48 hours of age with ongoing unexplained sepsis and unexplained thrombocytopenia or hepatitis during the first week of life, or for older infants with seizure, cutaneous vesicles, CSF pleocytosis, thrombocytopenia and/or hepatitis, consider HSV evaluation and empiric Acyclovir for HSV

Follow-up Assessment:

If the patient is not responding to empiric therapy: ID consult recommended. Consider repeating cultures, broadening of therapy based on patient clinical presentation and risk factors.

If an infectious source is identified: Treatment should be modified to target the source of infection.

If no infectious etiology is identified after 36-48 hours: Antibiotics should be discontinued in most cases; if there is very high clinical suspicion for infection and the infant has responded to empiric therapy but with negative cultures, a defined course of therapy (5-7 days) should be set.

If initial blood culture grows Gram positive cocci:
Repeat blood cultures before changing antibiotics. Consider clinical suspicion for bacteremia, and patient's response to initial therapy.

If "probable *Staphylococcus*" and moderate-high suspicion for bacteremia, ADD Vancomycin, discontinue Gentamicin while awaiting organism identification and susceptibility.

If "probable *Streptococcus*" and moderate-high suspicion for bacteremia, change Nafcillin to Ampicillin.

ID consult recommended for patients with positive blood cultures.

Approved by UCSF Pharmacy and Therapeutics Committee 05/14/2019, Primary Content Owner: Rachel Wattier (Pediatric Antimicrobial Stewardship Program)