AFCH and UPH-Meriter NICU NEC Guidelines

Stage*	Illness Severity	Systemic Signs	Intestinal Signs	Radiographic Signs**	X-Ray Frequency (minimum)	Antibiotics***	Antibiotic Course Length	Other
Ia. Suspected NEC	Suspicious, mildly ill	Temperature instability, apnea, bradycardia, feeding intolerance, lethargy	Residuals, mild distension, occult blood	Normal or mild ileus	Q12 hours x 24-48 hours	Ampicillin Gentamicin	48 hours	
Ib. Suspected NEC	Suspicious, mildly ill	Same as IA	Same as IA but gross blood	Same as IA	Same as IA	Ampicillin Gentamicin	48 hours	Consult Pediatric Surgery
IIa. Mild NEC	Mildly ill	Same as IA	Prominent abdominal distention & tenderness, absent bowel sounds, grossly bloody stools	Ileus, dilated bowel loops, focal pneumatosis intestinalis	Q 12 hrs x 48 hours	Ampicillin Gentamicin	7 days	Consult Pediatric Surgery
IIb. Moderate NEC	Moderately ill	Mild metabolic acidosis, thrombocytopenia	Abdominal wall edema & palpable mass	Extensive pneumatosis intestinalis, early ascites, portal venous gas	Q 8 hours x 48 hours	Ampicillin Gentamicin Metronidazole	7 days	Consult Pediatric Surgery. Discuss potential transfer to AFCH.
IIIA. Advanced NEC	Severely ill, bowel intact	Hypotension, respiratory & metabolic acidosis, oliguria, DIC, mechanical ventilation	Worsening wall edema & erythema with induration, peritonitis	Prominent ascites, fixed bowel loops, gasless abdomen	Q8 hours x 48 hours	Ampicillin Gentamicin Metronidazole	10 days	Consult Pediatric Surgery US Finding: Complex fluid, pneumatosis, portal venous gas
IIIB. Advanced NEC	Severely ill, perforated (not SIP)	Shock	Evidence of perforation (tense abdomen, bluish discoloration)	Pneumoperitoneum	X-rays prn	Ampicillin Gentamicin Metronidazole	10-14 days	Consult Pediatric Surgery US Finding: Free air

- *Stages (please document stage in medical chart)
    a. Suspected (I) – No radiographic evidence. Diferential includes ileus, other system infections and cow milk protein allergy
    b. Deinite (II) – Must have radiographic/ultrasound diagnosis

    c. Advanced (III)- Infants are severely ill with radiographic evidence (without or without evidence of perforation)
- **Radiographic Signs
    a. Radiographic imaging for a minimum of 48 hours for Bell's Staging IIa and above, but continue serial X-rays if ongoing concerns
    b. Consider the use of ultrasound for gasless abdomen and/or worsening clinical status without radiographic evidence of NEC
- ***Antibiotics
    a. Consider vancomycin instead of ampicillin if recent use of central line (UVC, UAC, PICC, CVL, etc)
    b. Use ceftazidime (or other available 3^{rd}-4^{th} generation cephalosporin (ie cefepime)) if clear systemic or laboratory indings consistent with acute kidney injury (AKI- see neonatal modiied KDIGO AKI Guidelines) or if already using vancomycin due to the history of a recent central line (don't automatically start cephalosporins instead of gentamicin unless clear AKI diagnosis or the use of vancomycin)
    c. Consider vancomycin and a 3^{rd}-4^{th} generation cephalosporin if there's a history of multi-drug resistant organism or clear neutropenia
    d. Consider monotherapy with Piperacillin-Tazobactam (Zosyn) instead of antibiotic trifecta (ampicillin/gentamicin/metronidazole) if worsening clinical status after 48h and/or issues with vascular access & line compatibility makes monotherapy essential to provide multiple medications and nutritional support (reminder that Zosyn may not cover MRSA/MRSE)
    e. Transition to targeted therapy as possible if positive blood culture with susceptibilities has returned
    f. Dosing- Use Pharmacy Dosing chart that bases recommendations of gestational age, weight, and day of life
- NPO Status
    a. Consider restart of feeds with return of bowel function (stooling, active bowel sounds, soft, non-tender abdomen, no evidence of ileus, stricture, etc). You do not have to wait until antibiotics are finished to start feeds.
    b. Ok to go slower than feeding guideline. Feeding volume advances should be made if clinical exam is reassuring and assurance of feeding tolerance at the previous volume.
    c. For Medical NEC- When restarting feeds, use weight-based algorithm (see both Meriter & AFCH Feeding Guidelines) for feeding advancement. Consider fortification at 100-120ml/kg/d.
    d. For Surgical NEC- When restarting feeds, use AFCH Enteral Nutrition Pathway for Surgical Neonates (From UW Health Enteral Nutrition- Neonatal – Inpatient Clinical Practice Guideline) and consider fortification at 100-120ml/kg/d.
- References

    a. Pace E, Yanowitz TD, Waltz P, Morowitz MJ. Antibiotic therapy and necrotizing enterocolitis. Semin Pediatr Surg. 2023 Jun;32(3):151308. doi: 10.1016/j.sempedsurg.2023.151308. Epub 2023 Jun 1. PMID: 37295297.
    b. Cai X, Liebe HL, Golubkova A, Leiva T, Hunter CJ. A Review of the Diagnosis and Treatment of Necrotizing Enterocolitis. Curr Pediatr Rev. 2023;19(3):285-295. doi: 10.2174/1573396318666220805110947. PMID: 35929629.
    c. Roberts AG, Younge N, Greenberg RG. Neonatal Necrotizing Enterocolitis: An Update on Pathophysiology, Treatment, and Prevention. Paediatr Drugs. 2024 May;26(3):259-275. doi: 10.1007/s40272-024-00626-w. Epub 2024 Apr 2. PMID: 38564081.
    d. Pace E, Yanowitz TD, Waltz P, Morowitz MJ. Antibiotic therapy and necrotizing enterocolitis. Semin Pediatr Surg. 2023 Jun;32(3):151308. doi: 10.1016/j.sempedsurg.2023.151308. Epub 2023 Jun 1. PMID: 37295297.
    e. Tickell D, Duke T. Evidence behind the WHO guidelines: hospital care for children: for young infants with suspected necrotizing enterocolitis (NEC), what is the effectiveness of different parenteral antibiotic regimens in preventing progression and sequelae? J Trop Pediatr. 2010 Dec;56(6):373-8. doi: 10.1093/tropej/fmq110. PMID: 21109568.
    f. Gill EM, Jung K, Qvist N, Ellebæk MB. 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. PMID: 35086498; PMCID: PMC8793197.
    g. Goldfarb M, Gollin G. The Impact of Antibiotic Strategy on Outcomes in Surgically Managed Necrotizing Enterocolitis. J Pediatr Surg. 2024 Jul;59(7):1266-1270. doi: 10.1016/j.jpedsurg.2024.03.019. Epub 2024 Mar 14. PMID: 38561306.

Neonatal Antimicrobial Dosing

Recommended Dosing Tables

Ampicillin – Meningitis Dosing		
PNA	**Dose**	**Frequency**
≤ 7 days	100 mg/kg	Every 8 Hours
>7 days	75 mg/kg	Every 6 Hours

Ampicillin – Non-meningitis Dosing			
GA	**PNA**	**Dosing**	**Frequency**
≤ 34 weeks	0-7 days	50 mg/kg	Every 12 Hours
	>7-28 days	75 mg/kg	Every 12 Hours
>34 weeks	0-28 days	50 mg/kg	Every 8 Hours

Ampicillin – Non-meningitis Dosing		
PNA	**Dosing**	**Frequency**
> 28 days	50 mg/kg	Every 6 Hours

Gentamicin – Neonatal Dosing			
GA	**PNA**	**Dose**	**Frequency**
< 30 weeks	≤ 14 days	5 mg/kg	Every 48 Hours
	≥ 15 days	5 mg/kg	Every 36 Hours
30 – 34 weeks	≤ 10 days	5 mg/kg	Every 36 Hours
	11-60 days	5 mg/kg	Every 24 Hours
≥ 35 weeks	≤ 7 days	4 mg/kg	Every 24 Hours
	8-60 days	5 mg/kg	Every 24 Hours

Acyclovir – Neonatal Dosing		
PMA	**Dose**	**Frequency**
<30 weeks	20 mg/kg	Every 12 Hours
≥30 weeks	20 mg/kg	Every 8 Hours

Metronidazole – Neonatal Dosing		
Loading Dose: 15 mg/kg ONCE		
PMA	**Dose**	**Frequency**
<34 weeks	7.5 mg/kg	Every 12 Hours
34-40 weeks	7.5 mg/kg	Every 8 Hours
>40 weeks	10 mg/kg	Every 8 Hours

Ceftazidime – Neonatal Dosing		
PNA	**Dose**	**Frequency**
≤7 days	50 mg/kg	Every 12 Hours
8-28 days	50 mg/kg	Every 8 Hours

Vancomycin – Neonatal Dosing			
PMA	**PNA**	**Dose**	**Frequency**
≤29 weeks	0-14 days	15 mg/kg	Every 18 Hours
	>14 days	15 mg/kg	Every 12 Hours
30-36 weeks	0-14 days	15 mg/kg	Every 12 Hours
	>14 days	15 mg/kg	Every 8 Hours
37-44 weeks	<7 days	15 mg/kg	Every 12 Hours
	>7 days	15 mg/kg	Every 8 Hours

Cefepime – Neonatal Dosing		
Post NATAL Age (PNA)	**Dose**	**Frequency**
<30 Days	50 mg/kg	Every 12 Hours
≥ 30 Days	50 mg/kg	Every 8 Hours

Piperacillin/Tazobactam – Neonatal Dosing		
PMA	**Dose (Piperacillin component)**	**Frequency**
≤30 weeks	100 mg/kg	Every 8 Hours
>30 weeks	80 mg/kg	Every 6 Hours

Gestational Age (GA): Time elapsed between the first day of the last menstrual period and the day of delivery; reported in weeks
Postnatal Age (PNA): time elapsed after birth-often considered the chronological age; reported in days, weeks, months
Postmenstrual Age (PMA): gestational age plus postnatal age; reported in weeks

Antibiotic Selection Algorithm below.

The study listed below is a pharmacokinetic study proposing new, de-escalated dosing strategies for ampicillin for the indication of non-meningitis neonatal sepsis to reduce the risk toxicity associated with high doses of ampicillin in neonates.

Study	Characterization of the Population Pharmacokinetics of Ampicillin in Neonates Using an Opportunistic Study Design
Citation	Tremoulet A, Le J, Poindexter B, et al. Characterization of the population pharmacokinetics of ampicillin in neonates using an opportunistic study design. Antimicrob Agents Chemother. 2014;58(6):3013-3020. doi:10.1128/AAC.02374-13
Objectives	- Characterize the developmental PK of ampicillin prescribed per standard of care to neonates across a wide age spectrum - Compare the pharmacodynamic target attainments of various dosing strategies
Study Design	- Open-label, multicenter, opportunistic, prospective PK study of ampicillin in neonates stratified by gestational age - 9 centers - N = 73 participants, 142 observed drug concentrations
Methods	- Drug concentrations measured by tandem mass spectrometry - OK Data analyzed using population nonlinear mixed-effects modeling - Monte Carlo simulations were conducted to determine the probability of target attainment for the time in which the total steady-state ampicillin concentrations remained above the MIC for 50%, 75%, and 100% of the dosing interval - N = 73 participants, 142 observed drug concentrations

Results	- Gestational Age ⍰ 34 weeks
	  o Postnatal Age 0-7 days - 50 mg/kg/dose, Intravenous, EVERY 12 HOURS
	  o Postnatal Age >7 days – 75 mg/kg/dose, Intravenous, EVERY 12 HOURS
	- Gestational Age >34 weeks – 50 mg/kg/dose, Intravenous, EVERY 8 HOURS

Use for new UW Health order panel	Will be used for de-escalation from meningitis dosing

The following organizations and studies were used in the NeoFax and Lexicomp recommendations and are considered high quality of evidence and strong recommendations per the GRADE criteria:

<table>
<tr><th>Organization</th><th>Citation</th><th>Recommendation</th><th>Notes</th></tr>
<tr><td>American Academy of Pediatrics</td><td>Puopolo KM, Lynfield R, Cummings JJ; American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Infectious Diseases. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics. 2019;144(2):e20191881</td><td>
<table>
<tr><th colspan="4">Ampicillin – Non-meningitis Dosing</th></tr>
<tr><th>GA</th><th>PNA</th><th>Dosing</th><th>Frequency</th></tr>
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<tr><td>>34 weeks</td><td>0-28 days</td><td>50 mg/kg</td><td>Every 8 Hours</td></tr>
</table>
</td><td>Used for NeoFax recommendation</td></tr>
<tr><td>Nelson's Pediatric Antimicrobial Therapy</td><td>Bradley JS, Nelson JD, Barnett ED, et al, eds. Nelson's Pediatric Antimicrobial Therapy. 28th ed. American Academy of Pediatrics; 2022:chap 2.</td><td rowspan="2">
<table>
<tr><th colspan="4">Gentamicin – Neonatal Dosing</th></tr>
<tr><th>GA</th><th>PNA</th><th>Dose</th><th>Frequency</th></tr>
<tr><td>< 30 weeks</td><td>≤ 14 days</td><td>5 mg/kg</td><td>Every 48 Hours</td></tr>
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</td><td>Used in Lexicomp and NeoFax recommendation</td></tr>
<tr><td>American Academy of Pediatrics (Red Book: 2021-2024 Report of the Committee on Infectious Diseases. 32nd ed. American Academy of Pediatrics; 2021)</td><td>Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021-2024 Report of the Committee on Infectious Diseases. 32nd ed. American Academy of Pediatrics; 2021.</td><td>Used in Lexicomp and NeoFax recommendation</td></tr>
<tr><td>Ampicillin Dose for Early and Late-Onset Group B Streptococcal Disease in Neonates</td><td>Lim SY, Miller JL. Ampicillin Dose for Early and Late-Onset Group B Streptococcal Disease in Neonates. Am J Perinatol. 2022;39(7):717-725. doi:10.1055/s-0040-1718880</td><td>Postnatal Age ≤ 7 days – 100 mg/kg/dose, Intravenous, EVERY 8 HOURS

Postnatal Age > 7 days – 75 mg/kg/dose, Intravenous, EVERY 6 HOURS</td><td>Ampicillin meningitis dosing as outlined up the new 2018 Red Book dosing</td></tr>
</table>