**Supplementary material**

SUPPLEMENTARY TABLE S1.Detailed presentation of selective antimicrobial medications commonly used in neonates.

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| **Medication [references]** | **Mechanism of action / bactericidal spectrum** | **Main neonatal indications** | **Neonatal dosing regimen** | **Side effects** |
| **AMPICILLIN** (beta-lactam antibiotic classified as aminopenicillins) [1,2] | - It inhibits bacterial cell wall synthesis by binding to the membrane-associated penicillin-binding proteins (PBPs), inhibiting the synthesis of peptidoglycan eventually leading to lysis and cell death. - Broad spectrum bactericidal activity against susceptible Gram-positive (including Strept. spp., Enterococcus faecalis, Listeria monocytogenes) and Gram-negative (E. coli, Hemophilus influenzae, Neisseria meningitidis, Proteus mirabilis and Salmonellae). | - Empiric treatment of suspected EOS (including meningitis) combined with an aminoglycoside - Targeted treatment of infections (bacteriemia, pneumonia, urinary tract infections, meningitis, endocarditis, gastrointestinal infections) caused by susceptible pathogens. | FDA label  - For meningitis and septicemia  GA ≤ 34 wks, PNA ≤ 7 days: 50 mg/kg/dose q12 GA ≤ 34 wks, PNA: 8-28 days: 75 mg/kg/dose q12 GA> 34 wks, PNA ≤ 28 days: 50 mg/kg/dose q8  AAP recommendation **-** For septicemia: as above - For meningitis GA ≤ 34 wks, PNA ≤ 7 days: 100 mg/kg q8 GA ≤ 34 wks, PNA: 8-28 days: 75 mg/kg q6 GA > 34 wks, PNA ≤ 28 days: 100 mg/kg q8 | - Allergic reactions: maculopapular or urticarial rash, fever (rare in neonates) - Diarrhea - Neurotoxicity including seizures (with high concentrations reported in adults) - Prolonged bleeding time with repeated doses. |
| **GENTAMICIN** [3–5] | - Bactericidal activity by binding irreversibly to 30S subunit of bacterial ribosomes, inhibiting protein synthesis and leading to cell death. - Potent bactericidal activity against Enterobacteriaceae (E. coli, Klebsiella spp., Enterobacter cloacae, E. aerogenes, Providencia spp., Proteus spp., Morganella spp., Serratia spp.), good activity against Staph. aureus (methicillin-resistant and vancomycin-intermediate and -resistant isolates), P. aeruginosa and to a lesser extent Acinetobacter baumannii. | - Empiric treatment of suspected EOS combined with ampicillin. - Treatment of infections caused by susceptible aerobic gram-negative bacilli (e.g. Pseudomonas, Klebsiella, E. coli) used in combination usually with a β-lactam antibiotic. | - Several dosing regimens have been proposed by most studies and neonatal drug formularies recommending dosages of 4–5 mg/kg/dose and prolonged dosing intervals (24–48 h) for term and preterm neonates with GA, PMA and PNA being the main determinant of the dosing interval.  - TDM is strongly suggested in: therapy duration > 7 days, therapeutic hypothermia and renal impairment.  (Measure trough concentrations before every dose.  Target trough concentration: < 2 mg/L).  Australasian Neonatal Medicines Formulary (2021) GA < 30 wks: 5 mg/kg q48 GA = 30 - 34+6 : 5 mg/kg q36 GA ≥ 35+0 : 5 mg/kg q24 - Treatment individualization can be achieved by measuring Gentamicin concentration at 22 h after the administration of the 2nd dose and subsequent dose interval is regulated according to drug levels as indicated:  ≤ 1.2 mg/L: every 24 h after previous dose  1.3-2.6 mg/L: every 36 h  2.7-3.5 mg/L: every 48 h   > 3.6 mg/L: hold dose, repeat drug level 24h later - Extension of dose interval by 12h in case of ibuprofen/indomethacin co-administration. | - Nephrotoxicity (renal tubular dysfunction with increased urinary losses of sodium, calcium, magnesium) - Ototoxicity - Hypersensitivity (very rare: rash, fever, eosinophilia, laryngeal oedema) - Neuromuscular blockade (rare, only reported in adults; increased risk when used with neuromuscular blocking agents, opioid analgesics and massive transfusions with citrate anticoagulated blood and in patients with hypermagnesemia). |
| **AMIKACIN** [5–9] | - Bactericidal activity by binding irreversibly to 30S subunit of bacterial ribosomes, inhibiting protein synthesis and leading to cell death. - Potent bactericidal activity against Enterobacteriaceae (E. coli, Klebsiella spp., Enterobacter cloacae, E. aerogenes, Providencia spp., Proteus spp., Morganella spp., Serratia spp), good activity against Staphylococcus aureus (methicillin-resistant and vancomycin-intermediate and -resistant isolates) Pseudomonas aeruginosa, and to a lesser extent Acinetobacter baumannii. | - Treatment of suspected or proven gram-negative infection resistant to other aminoglycosides used in combination usually with a β-lactam antibiotic. | Australasian Neonatal Medicines Formulary (2021) **PMA≤ 29 wks**  PNA 0-7 days: 14 mg/kg q48 (i.v)  PNA 8-28 days: 12 mg/kg q36  PNA ≥ 29 days: 12 mg/kg q24  **PMA= 30-34 wks**  PNA 0-7 days: 12 mg/kg q36  PNA ≥ 8 days: 12 mg/kg q24  **PMA ≥ 35 wks** All: 12mg/kg q24  - Increase of the dose interval by 12 h in neonates with perinatal asphyxia and therapeutic hypothermia and by 10 h in co-administration of indomethacin or ibuprofen. - For treatment ≥ 48 h and for neonates with renal impairment perform early trough and peak levels (prior to and 1 hour after the second amikacin dose). Target peak levels 24–35 mg/L and troughs <5 mg/L. | - Nephrotoxicity  - Ototoxicity - Neuro-muscular blockade (rare, only reported in adults; increased risk when used with neuromuscular blocking agents, opioid analgesics and massive transfusions with citrate anticoagulated blood and in patients with hypermagnesemia). |
| **MEROPENEM** [5,10–12] | - It binds to PBPs, disrupting bacterial cell wall synthesis, leading to lysis and cell death. - Broad spectrum bactericidal activity against i) Gram-negative pathogens: Enterobacteriaceae, ESBL- and AmpC-producing Enterobacteriaceae, Haemophilus influenzae and Neisseria meningitidis, Pseudomonas aeruginosa, Acinetobacter baumannii, Burkholderia cepacian.  ii) Gram-positive pathogens:  Staph. aureus (methicillin/oxacillin-susceptible), Staph. epidermidis (oxacillin-susceptible), Strept. pneumoniae (including penicillin resistant strains) and viridans group strept. iii) anaerobes (Cl. difficile, Cl. perfringens). | - Severe neonatal infections (e.g. septicaemia, complicated intra-abdominal, urinary tract, skin and skin structure infections, pneumonia, bacterial meningitis) due to multi drug resistant Gram-negative organisms. | **FDA LABEL**  **Dosage regimen for:** A) intra-abdominal and non-CNS infectionsGA < 32 wks, PNA < 2 wks: 20 mg/kg/dose q12 GA < 32 wks, PNA ≥ 2 wks: 20 mg/kg/dose q8 GA ≥ 32 wks, PNA < 2 wks: 20 mg/kg/dose q8  GA ≥ 32 wks, PNA ≥ 2 wks: 30 mg/kg/dose q8  B) CNS infections (off-label) Data regarding appropriate dosing for neonatal CNS infections are lacking; suggested dose: 40 mg/kg/dose at the recommended age-specific dosing interval. | - Diarrhea, rash, vomiting, glossitis - Hematologic abnormalities: agranulocytosis, neutropenia, leukopenia - Elevated creatinine - Elevated direct bilirubin, aspartate transaminase (AST), alanine aminotransferase (ALT). |
| **VANCOMYCIN** [5,13,14] | - Bactericidal agent which interferes with cell wall synthesis, inhibits RNA synthesis and alters plasma membrane function leading to cell death.  - Bactericidal spectrum:Staphylococci (including MRSA), Streptococci, Enterococci, Diphtheroids, Listeria monocytogenes, Actinomyces Bacillus spp. | - Infections due to susceptible strains of gram-positive microbes; Staphylococci (including MRSA), Streptococci, Enterococci, Diphtheroids, Listeria monocytogenes, Actinomyces spp. | Νo consensus on optimal dosing and monitoring in neonates. Various dosing regimens have been recommended and/or used in relevant studies which are mainly based on neonatal age (GA, PMA, PNA), body weight and serum creatinine.  Most recently suggested dosing regimen by Australasian Neonatal Medicines Formulary (2021) Standard dose: 15 mg/kg/dose (IV) Consideration for giving a loading dose 20 mg/kg/dose in cases of severe sepsis, MRSA, bone infection, meningitis, endocarditis, although evidence is limited   |  |  |  | | --- | --- | --- | | **PMA** (wks) | **PNA** (days) | **INTERVAL** | | < 30 | 0-2 | q18 h | |  | 3+ | q12 h | | 30+0-36+6 | 0-14 | q12 h | |  | 15+ | q8 h | | 37+0 -44+6 | 0-7 | q12 h | |  | 8+ | q8 h | | ≥45+0 | 0+ | q6 h | | - Nephrotoxicity; ototoxicity;Rash and hypotension (red man syndrome): may appear rapidly and resolves within minutes to hours, by increasing the infusion time we eliminate the risk for subsequent doses; neutropenia (reported after administration for >3 wks).  **- TDM is strongly suggested:** Target Ctrough = 10-15 mg/kg. Measure Ctrough immediately prior to 3rd dose with the exception of:  1. <29+0 PMA wks – before 2nd dose,  2. therapeutic hypothermia – before 2nd dose  3. renal impairment – before 2nd dose  - Check concentration prior to the 4th dose after any change in dose or frequency. Once Ctrough target is reached, measure Ctrough every 3 days prior to consecutive doses.  - More frequent monitoring may be required in renal impairment, infants receiving other nephrotoxic drugs or suspected severe sepsis. |

Ctrough = Trough concentration; Cl, Clostridium; E. coli; ESBL, extensive-spectrum beta-lactamase; Escherichia coli; EOS, early-onset sepsis; GA, gestational age; h, hour(s); MRSA, Methicillin-resistant Staphylococcus aureus; PBPs, penicillin-binding proteins; PNA, postnatal age; PMA, postmenstrual age (PMA= GA+PNA); spp, species; TDM, therapeutic drug monitoring; wks, weeks.

SUPPLEMENTARY TABLE S2. Detailed presentation of selective antifungal medications commonly used in neonates.

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| **Medication [references]** | **Mechanisms of action / fungicide spectrum** | **Main neonatal indications** | **Neonatal dosing regimen** | **Side effects** |
| **Amphotericin B Deoxycholate** (AmB-D) (Polyene)  [15–18] | - Loss of cell membrane integrity by binding to ergosterol. The polyene-ergosterol complex creates pores in the fungal cell membrane, leading to electrolyte leakage, cell lysis and cell death. Potent and broad fungicidal activity. | - Treatment of invasive fungal infections by susceptible fungi including Candida spp., Aspergillus spp. and Cryptococcus spp. - First-line therapy for neonatal IC including CNS infections.  - An alternative therapy of invasive aspergillosis in neonates. | 1 mg/kg, IV, daily. | Nephrotoxicity (acute kidney injury and electrolyte-wasting tubular acidosis); Increased risk of nephrotoxicity in co- administration with other nephrotoxic drugs (vancomycin, aminoglycocides). Electrolyte disturbances: hypokalemia, hypomagnesaemia, hypocalcaemia. Hematological: anaemia, leukopenia, thrombocytopenia. Gastrointestinal: elevated liver enzymes, diarrhoea, vomiting. Thrombophlebitis at the injection site. Infusion-related reactions: fever, hypotension (rare in neonates). Skin rashes. Monitoring of renal function, liver function, electrolytes and full blood count. |
| **Liposomal Amphotericin B**  (Polyene) [15] | Same as AmB-D | - Same as AmB-D.  - An alternative therapy for neonatal IC with caution in the presence of urinary tract infections because of reduced renal excretion.  - Drug of choice for neonatal invasive aspergillosis. | 3-5 mg/kg, IV, daily. | - Similar adverse events with AmB-D.  - Reduced toxicity as compared with AmB-D.  - Monitoring of renal function, liver function, electrolytes and full blood count. |
| **Fluconazole** (Triazole)[15,19–25] | - Inhibition of fungal cytochrome P450 activity and ergosterol synthesis, with accumulation of toxic sterols in the cell membrane leading to fungal cell membrane disruption, cell content leakage, lysis and cell death. | - Treatment of invasive infections by susceptible Candida species (minimal activity against *C. glabrata,* no activity against *C. kruseii),* mucosal candidiasis (oropharyngeal, oesophageal), cryptococcal meningitis. - An alternative therapy of IC in neonates not been on fluconazole prophylaxis.  - A step-down treatment of Candida meningitis after response to initial therapy.  - Prophylaxis of Candida infections, in nurseries with high rates (>10%) of IC. | - Treatment: Loading dose: 25 mg/kg, IV; maintenance dose: 12 mg/kg/d once a day, starting 24 hours after loading dose. - Prophylaxis: 3-6 mg/kg every 72h for 4-6 weeks. | - Most common adverse effects: gastrointestinal irritation and elevation in liver function tests.  - Rare: Rash, leukopenia, neutropenia, agranulocytosis and thrombocytopenia. Weekly monitoring of liver enzymes. |
| **Micafungin**  (Echinocandin)  [15,16,26] | - Inhibition of β(1-3)-glucan synthase activity preventing synthesis of the fungal cell wall. It exerts fungicidal activity against Candida spp. (even against C. glabrata and C. kruseii resistant to fluconazole). | - As salvage therapy of invasive Candida infections or in situations where resistance or toxicity preclude the use of AmB-D or fluconazole.  - There are concerns regarding the penetration of echinocandins into the CSF. Insufficient data in neonates do not yet allow the recommendation of their use in CNS infections. | - 4 to 10 mg/kg/day - Clinical and non-clinical studies indicate that higher dose of at least 10 mg/kg daily is likely needed for candidemia with meningoencephalitis. | - Most common adverse events: infusion reactions and transient elevation of hepatic enzymes.  - Hyponatremia, hypochloremia, hypokalemia, elevated creatinine, acute intravascular hemolysis, hemolytic anemia and hemoglobinuria, monocytosis, thrombocytopenia, fever, rash, diarrhoea, vomiting have been reported. |

AmB, Amphotericin B; AmB-Deoxycholate, AmB-D; C, Candida; h, hour(s); CNS, central nervous system; IC, invasive candidiasis; IV, intravenously; spp, species

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