Review

Antibiotic Analgesic-Sedative and Antiseizure Medications Frequently Used in Critically Ill Neonates: A Narrative Review

Angeliki Kontou *, Eleni Agakidou, Ilias Chatziioannidis, William Chotas, Evanthia Thomaidou, Kosmas Sarafidis

Posted Date: 3 May 2024

doi: 10.20944/preprints202405.0151.v1

Keywords: neonatal infections; sepsis; antibiotics; antifungal; analgesics; sedatives; seizures; medications; pharmacokinetics; neonatal pain; preterm infants

Review

Antibiotic Analgesic-Sedative and Antiseizure Medications Frequently Used in Critically Ill Neonates: A Narrative Review

Angeliki Kontou [1,*,†], Eleni Agakidou [1,†], Ilias Chatziioannidis [1], William Chotas [2], Evanthia Thomaidou [3] and Kosmas Sarafidis [1]

[1] 1st Department of Neonatology and Neonatal Intensive Care, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Ippokrateion General Hospital, 54642 Thessaloniki, Greece; eagakidou@auth.gr (E.A.); ihatzi@auth.gr (I.C.),kosaraf@auth.gr (K.S.)
[2] Department of Neonatology, University of Vermont, Burlington VT 05405, Vermont, USA
[3] Department of Anesthesia and Intensive Care, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, AHEPA University General Hospital of Thessaloniki, 54621 Thessaloniki, Greece; evathom1975@yahoo.gr
* Correspondence: angiekon2001@yahoo.gr
† These authors contributed equally to this work.

Abstract: Several studies have shown that antibiotics, analgesic – sedative, and antiseizure medications are among the most commonly used medications in preterm and sick neonates. These infants are at high risk of developing nosocomial infections, central nervous system complications, and are exposed to numerous painful/stressful procedures. These severe, potentially life-threatening complications may have serious short- and long-term consequences and should be prevented and/or promptly treated. Previous studies and reviews have revealed significant variability in medications used in neonatal intensive care units (NICUs) worldwide, especially concerning the indications and dosages of first-line medications. This variability indicates the lack of adequate studies regarding the effectiveness and safety of these medications in neonates, especially the preterm ones. Important obstacles contributing to inadequate studies in preterm infants include difficulties in obtaining parental consent, physicians' unwillingness to recruit preterm infants, the lack of license for use in neonates, and other scientific and ethical concerns. This review is an update on the use of antimicrobials – antifungals, analgesics – sedatives, and antiseizure medications used in neonates, focusing on existing evidence or knowledge gaps regarding their pharmacokinetics, indications, safety, dosage regimen (dose, dosing interval, route of administration), and evidence-based guidelines for the optimal use in neonates.

Keywords: neonatal infections; sepsis; antibiotics; antifungal; analgesics; sedatives; seizures; medications; pharmacokinetics; neonatal pain; preterm infants

1. Introduction

Preterm and sick neonates admitted to neonatal intensive care units (NICUs) are at high risk of developing hospital-acquired infections which are associated with severe complications, extended need for intensive care, and increased mortality [1,2]. Factors contributing to the high incidence of infections in NICU neonates include their immature defense mechanisms, the multiple-resistant microorganisms colonizing neonates in NICUs, and the invasive procedures they are subjected to [1]. The latter problem exposes the NICU neonates to numerous painful and stressful procedures which may have serious short- and long-term consequences [3,4]. In addition, high risk neonates may suffer central nervous system (CNS) complications, such as peri-intraventricular hemorrhage and hypoxic-ischemic encephalopathy, which may present with seizures. All these severe and life-threatening

 doi:10.20944/preprints202405.0151.v1

complications should be prevented or promptly treated. To this aim, evidence-based management protocols should be applied by all neonatologists. However, previous studies and reviews revealed a wide variability in whether and which medications are used in NICUs worldwide [3,5,6]. A major factor contributing to this variability is the lack of adequate studies regarding the effectiveness and safety of medications administered to neonates, especially the preterm ones. Reported differences primarily concern the indications and dosage of the first-line medications [7].

Several studies have explored the pattern of medications used in NICUs in different countries. It was found that antimicrobials – antifungals and analgesics - sedatives are among the most commonly used medications in NICUs [8]. In this review, we address the antimicrobials – antifungals, analgesics – sedatives, and antiseizure medications used in neonatology, focusing on existing evidence or knowledge gaps regarding their indications, dosage, and potential side effects. We believe that this review could be useful in daily clinical practice to all of those involved in neonatal care. Future perspectives for the safe use and development of drugs, specifically for the neonatal population, are also discussed.

2. Method of Literature Review

Electronic databases (PubMed, Scopus, and the Cochrane Library) were searched up to March 2024 for articles on medications for the treatment of neonatal infections, pain/stress, and seizures. Additionally, a manual search of the reference lists of the included studies was conducted to find additional relevant articles. The MeSH terms used included “acetaminophen”, “alpha-2 agonists”, “analgesics”, “antibacterial”, “antibiotics”, “antifungal”, “antimicrobial”, “antiseizure”, “benzodiazepines”, “dexmedetomidine”, “drug therapy”, “fentanyl”, “ketamine”, “levetiracetam”, “midazolam”, “morphine”, “necrotizing enterocolitis”, “neonatal infections”, “neonatal pharmacotherapy”, “neonatal sepsis”, “neonate”, “pain”, “phenobarbital”, “phenytoin”, “phosphophenytoin”, “placebo”, “preterm infants”, “propofol”, “randomized controlled trials”, “remifentanil”, “review”, “sedatives”, “systematic review”, “topiramate”. Studies included full reports in the English language.

3. Antibiotics

3.1. Antimicrobial Agents

Neonatal sepsis, classified as either early- or late-onset, remains an undeniably significant cause of substantial morbidity and mortality in both high and low - middle income countries, although the precise estimates of its burden vary by setting [1,2,9]. Prompt empiric antimicrobial therapy is the “gold standard” regarding the management of neonates with suspected sepsis. Not surprisingly, in 305 NICUs (USA, 2005–2010), 26 of the 100 most commonly prescribed medicines were antibiotics with ampicillin, gentamicin, and vancomycin being at the top of the list; at the first, second, and fifth position, respectively [9]. Both ampicillin and gentamicin have retained their position in the list until recently [8,10]. From a global perspective, according to the NO-MAS-R (no-more-antibiotics and resistance) study, one out of five high-risk neonates receives at least one antimicrobial agent (92%, antibacterial; 19%, antifungal; 4%, antiviral). “Rule-out” sepsis (32%) and “culture-negative” sepsis (16%) were the most common indications for ampicillin (40%), gentamicin (35%), amikacin (19%), vancomycin (15%), and meropenem (9%) administration, while for definitive treatment of presumed/confirmed infection, vancomycin (26%), amikacin (20%), and meropenem (16%) were the most prescribed [11].

Wide inter-NICU variability and off-label use of antibiotic agents continue to characterize the treatment strategies in neonatal sepsis and antibiotic prescribing practices [12–17]. Management of neonatal sepsis varies among NICUs in Europe with less homogeneity in the combination of antibiotic regimens for late-onset sepsis (LOS) when compared to early-onset sepsis (EOS). For EOS, neonatologists prefer to prescribe ampicillin, penicillin, gentamicin, and amikacin with the most frequent combination being ampicillin plus gentamicin (54.6%). In cases of LOS, vancomycin (52.4%), gentamicin (33.9%), cefotaxime (28%) and meropenem (15.5%) are frequently chosen [6,18]. High

 doi:10.20944/preprints202405.0151.v1

variability in dosage is common in clinical practice, and this variability has been documented in European NICUs. For instance in one study, a total of 444 dosage regimens were used, yet only 41 different antibiotics were administered [19,20]. Limited knowledge exists for either pharmacokinetics (PKs), safety, dosage regimen (dose, dosing interval, route of administration, formulation), or evidence-based guidelines for the optimal antibiotic use in neonatal sepsis. The lack of robust evidence from high quality randomized controlled trials in neonates, especially in those born preterm, has led to the off-label/unlicensed use of anti-infective agents [10,17,21]. It is noteworthy, only 6 antibiotics have been approved by the Food and Drug Administration (FDA) since 1998, with the majority for term infants; ceftolozane/tazobactam, clindamycin, dalbavancin, ceftaroline-fosamil, ampicillin, meropenem, and linezolid [22].

The most recent Cochrane meta-analysis, aiming to assess the effect of different antibiotic regimens for EOS, failed to find superiority of any antibiotic combination due to the low quality of evidence in the included studies (5 trials with 865 participants) [23]. Similar conclusions were drawn regarding the effect of antibiotic regimens for LOS (5 trials) [24].

The general principle is that empirical therapy should be guided by the epidemiology of EOS and LOS, as well as local antimicrobial resistance patterns settings [1]. Thus, active infection surveillance programs should be implemented. EOS is most often caused by *group B streptococcus (GBS)* followed by *Escherichia coli (E. coli)*, with the latter pathogen predominating in very low birth weight infants (VLBWI). LOS is mainly caused by Gram-positive bacteria, most often *coagulase-negative Staphylococcus* (*CoNS*) [18,25]. However, in low-middle income countries *Klebsiella pneumonia* was found to be the leading cause of neonatal sepsis which stresses the importance of developing local infection surveillance programs [26]. Ampicillin and gentamicin are recommended by the American Academy of Pediatrics (AAP) as the first choice for empirical therapy of EOS. Another important issue neonatologists should be aware of is the increasing ampicillin resistance of *E. coli* and other Gram-negative pathogens, while the majority of them remains susceptible to gentamicin [27–29]. The National Institute for Health and Care Excellence (NICE) recommends the use of benzylpenicillin instead of ampicillin, while a combination of narrow-spectrum antibiotics (such as intravenous flucloxacillin plus gentamicin) is recommended for LOS, as well [30]. Third-generation cephalosporins, such as cefotaxime, or fourth-generation cephalosporins should be preserved for suspected Gram-negative meningitis. Nevertheless, their overuse should be avoided, as their administration has been associated with the emergence of multidrug resistant organisms and candidiasis.

Infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria require treatment with carbapenems, such as meropenem [31]. Treatment with piperacillin–tazobactam and ampicillin–sulbactam is being used increasingly in NICUs. However, penetration of tazobactam into the CNS is questionable and should not be used for treatment of meningitis. On the other hand, the β-lactamase inhibitor sulbactam, when combined with ampicillin, seems to achieve high concentrations in cerebrospinal fluid [1,32]. The use of vancomycin in the empiric therapy of LOS is based on the predominance of coagulase-negative Staphylococcus, and concerns for methicillin-resistant Staphylococcus aureus (MRSA) infection. Nevertheless, there are several arguments against its empiric use in empiric regimen, due to the risk of ototoxicity and nephrotoxicity. Active surveillance of local pathogen distribution, screening policies for methicillin-resistant Staphylococcus aureus colonization, and the use of oxacillin in empiric antibiotic therapy can reduce vancomycin overuse in VLBWI [25,33].

Written policies for antimicrobial use and auditing are essential for guiding clinical practice. Antibiotic stewardship programs in NICUs can help develop strategies to identify neonates at risk of EOS, optimize antibiotic choice - including dosage and route of administration both for empiric treatment and targeted therapy for definitive LOS, and standardize the decisions regarding the duration of therapy [33–35]. The value of such strategies has been recently highlighted in the NO-MAS-R study, since NICUs with specific Antimicrobial Stewardship Programs have lower antibiotic utilization rates regardless of the country's income level [11]. Such strategies should be implemented

 doi:10.20944/preprints202405.0151.v1

in every NICU to prevent the adverse associated with antibiotic overuse and misuse, including the emergence of multi-drug resistant organisms and increased health care costs.

In the era of antimicrobial resistance, neonatal LOS due to multidrug-resistant bacteria has become a significant issue in many NICUs worldwide [36]. In the Neonatal Antimicrobial Resistance Research Network, the resistance rates of Gram-negative isolates to cephalosporins ranged from 26% to 84% and to carbapenem from 0% to 81%, while glycopeptide resistance rates among Gram-positive isolates ranged from 0% to 45% [37]. Higher mortality and morbidity are attributed to multidrug-resistant organisms when compared to non-multidrug-resistant organisms causing neonatal sepsis, with case fatality rates for carbapenem resistant organisms reaching 36% [38–41]. The Infectious Diseases Society of America updates guidelines for the treatment of infections caused by extended-spectrum beta-lactamase and AmpC beta-lactamase producing Enterobacterales, carbapenem-resistant Enterobacterales and Acinetobacter baumannii, P. aeruginosa with difficult-to-treat resistance, and Stenotrophomonas maltophilia. These guidelines apply to both adult and pediatric patients, although data for the optimal treatment of such infections in children is limited [40,42]. Neonates are not included in these guidance reports. A recent systematic review aimed to identify and appraise the current antimicrobial options for multidrug-resistant bacteria and extensively drug-resistant Gram-negative bacterial infections in neonates. Colistin in combination with other antimicrobials such as meropenem, amikacin, ciprofloxacin, or tigecycline were used for carbapenem-resistant Enterobacterales infections, whereas colistin plus ciprofloxacin were prescribed for difficult-to-treat resistant and extensively drug-resistant P. aeruginosa. Authors concluded the following: (a) in the last two decades, colistin is the most frequently studied and used antimicrobial, especially in low - middle income countries, with variable evidence of efficacy; (b) carbapenems are still the leading antibiotics for extended-spectrum beta-lactamase Enterobacterales; and (c) newer antibiotics, such as beta-lactam agents / beta-lactamase inhibitor combination (e.g., ceftazidime–avibactam infrequently used as salvage therapy), are promising, but data are few and limited to high income countries [43,44]. Indications, dosing regimens, and side effects of antibacterial agents are summarized in Table 1, while more details are presented in the Supplementary Table S1 [25,31,36,44–50].

Table 1. Selective antimicrobial medications most commonly used in neonates.

Medication [references]	Mechanism of action / bactericidal spectrum	Main neonatal indications	Neonatal dosing regimen	Side effects
AMPICILLIN (a beta-lactam antibiotic classified as aminopenicillins) [18,48]	Inhibition of bacterial cell wall synthesis. Bactericidal spectrum: susceptible Gram (+) (incl. Streptococcus spp, Enterococcus faecalis, Listeria monocytogenes) and Gram (-) bacteria (E. coli, Hemophilus influenzae, Neisseria meningitidis, Proteus mirabilis, Salmonellae).	Empiric and targeted treatment of suspected/proven LOS (incl. meningitis) combined with an aminoglycoside.	AAP recommendation: Septicemia: 50 - 75 mg/kg/dose, IV, q8 - q12 for 7 - 28 days, depending on GA & PNA. Meningitis: 75 - 100 mg/kg/dose, IV, q6 - q8 for ≤ 7 - 28 days depending on GA & PNA.	Allergic reactions, diarrhea, neurotoxicity including seizures, prolonged bleeding time with repeated doses.

 doi:10.20944/preprints202405.0151.v1

GENTAMICIN [28,45,50]	Inhibition of protein synthesis leading to cell death. Bactericidal spectrum: Enterobacteriaceae; Staph. aureus (MRSA and vancomycin–resistant isolates); P. aeruginosa. To a lesser extent Acinetobacter baumannii.	Empiric treatment of suspected EOS combined with ampicillin. Targeted treatment of infections caused by susceptible Gram (-) bacilli (e.g., Pseudomonas, Klebsiella, E. coli) combined with a β-lactam antibiotic.	Recommending dosages: 4–5 mg/kg/dose, dosing intervals 24–48 h depending on GA, PMA and PNA. TDM is strongly suggested in: therapy duration > 7 days, therapeutic hypothermia, renal impairment; target trough concentration: < 2 mg/L.	Nephrotoxicity, ototoxicity, hypersensitivity (very rare), neuromuscular blockade (reported only in adults).
AMIKACIN [36,44,45,47,49]	Inhibition of protein synthesis leading to cell death. Potent bactericidal activity against Enterobacteriaceae (E. coli, Klebsiella spp., Enterobacter cloacae, Providencia spp., Proteus spp., Serratia spp); good activity against Staph. aureus (MRSA and vancomycin- resistant isolates) P. aeruginosa; lower activity against acinetobacter baumannii.	Treatment of suspected or proven Gram-negative infection resistant to other aminoglycosides used in combination usually with a β-lactam antibiotics	12-14 mg/kg, IV, q24 – q48 depending on PMA & PNA. Increased dose intervals in perinatal asphyxia and therapeutic hypothermia, or in co-administration of indomethacin or ibuprofen. TDM: treatment duration ≥ 48 h, renal impairment. Target peak levels 24–35 mg/L and troughs <5 mg/L.	Nephrotoxicity, ototoxicity, neuro-muscular blockade
MEROPENEM [31,41,43,45,46]	Binds to membrane proteins disrupting bacterial cell wall synthesis. Bactericidal spectrum: i) Gram (-) pathogens: Enterobacteriaceae, ESBL- and AmpC-producing Enterobacteriaceae; ii) Gram (+) pathogens: Staph. aureus (methicillin/oxacillin-susceptible), Strept. pneumoniae (incl. penicillin resistant strains) and Strept. viridans; iii) anaerobes (Clostridium difficile).	Severe neonatal infections (e.g., septicemia, bacterial meningitis) due to multi drug resistant Gram (-) organisms.	Intra-abdominal and non-CNS infections (FDA label): 20 -30 mg/kg/dose, IV, q12 – q8 depending on GA & PNA. CNS infections (off-label): Recommended dose: 40 mg/kg/dose, IV, at q12 – q8, depending on GA & PNA.	Diarrhea, rash, vomiting, glossitis, neutropenia, leukopenia, elevated creatinine, direct bilirubin, live enzymes.

 doi:10.20944/preprints202405.0151.v1

VANCOMYCIN [25,29,45]	Interferes with cell wall synthesis, inhibits RNA synthesis and alters plasma membrane function.	Infections due to susceptible strains of Stap. (incl. MRSA), Streptococci, Enterococci, Diphtheroid, Listeria monocytogenes, Actinomyces, Bacillus spp.	Standard dose: 15 mg/kg/dose, IV, q18 – q8 depending on GA & PNA. Consider loading dose 20 mg/kg/dose in cases of severe sepsis, MRSA, bone infection, meningitis, endocarditis. TDM is strongly suggested; more frequently in renal impairment, use of nephrotoxic drugs or suspected severe sepsis.	Nephrotoxicity, ototoxicity, rash and hypotension (red man syndrome), neutropenia (reported in treatment duration >3 weeks).

3.2. *Antifungal Agents*

Although fungi are a less frequent cause of neonatal LOS, the EUROCANDY study revealed that neonates are the second most vulnerable age-specific group to invasive candidiasis among pediatric patients ≤18 years old [51,52]. The incidence of neonatal invasive candidiasis has been reduced in the last decade in high-income countries, but the burden of fungal disease is still significant in high-risk neonates, with severe neurodevelopmental sequelae and a high case-fatality rate of 20% up to 50% in extremely low birth weight infants [53]. Meanwhile, the majority of neonates with invasive candidiasis included in the NeoOBS invasive candidiasis sub-study (data from low-middle income countries) had gestational age > 28 weeks (81%) and birth weight > 1000 g (73%) [53–56]. Differences between NICU level of care, underlying comorbidities, feeding strategies, antifungal prophylaxis use, antibiotic stewardship, and infection prevention and control bundle measures may explain the great variance of the epidemiology of invasive candidiasis in different geographical regions [53,56–60]. While *Candida (C.) albicans* remains the leading cause, followed by *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*, whereas *C. auris* has emerged as the third most commonly encountered species causing neonatal invasive candidiasis in low - middle income countries [51,56,59,61]. In a recent European 12-week modified point prevalence study (mPPS) which included 26 NICUs, 17 hospitals, and eight countries, the median percentage of neonates receiving antifungal agents per mPPS week across all NICU Level III was 9.6% (range 7.5-11.4%). According to GARPEC-PPS study (Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children -PPS), 43.5% of all antifungal prescriptions were in the extreme preterm neonates (gestational age <28 weeks), whereas antifungals represented 17.3% and 13.4% of all antimicrobial drugs administered in this specific group in high and low - middle income countries, respectively (P=0.26) [62].

Antifungal drugs used against neonatal invasive fungal infections belong to the following 4 classes: **polyenes** (amphotericin B deoxycholate [AmB-D], liposomal AmB), **triazoles** (fluconazole, voriconazole, posaconazole), **echinocandins** (micafungin, caspofungin, anidoulafungin), and **nucleoside analogues** (flucytosine) [60]. Prophylaxis and empirical treatment are the main reasons for antifungal administration to neonates, with fluconazole being the most commonly prescribed drug followed by AmB-D. The most common reasons for prophylaxis are prematurity, birth weight <1000g, and central venous catheters. Variability in antifungal usage appears to be an important problem in neonates, with antifungal prophylaxis being frequently prescribed outside of common risk-factor based recommendations, in addition to reports of underdosing of fluconazole [62,63].

3.2.1. Polyenes and Triazoles

Existing guidelines for the treatment of neonatal invasive candidiasis are endorsed by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID, 2012) and more recently (last updated in 2016) by the Infectious Diseases Society of America [64,65]. AmB-D, the oldest of the polyenes, is strongly recommended at a dose of 1 mg/kg, IV, as a first-line therapy, including CNS infections [64]. Due to its effective penetration into the cerebrospinal fluid and urinary tract, fluconazole (12 mg/kg, q24h, IV or orally) is considered a reasonable alternative option, provided the neonate has not been on fluconazole prophylaxis. In cases of meningoencephalitis, it is

 doi:10.20944/preprints202405.0151.v1

suggested as a step-down therapy, after determination of in vitro susceptibility and proven clinical response to the initial therapy with AmB-D or liposomal AmB (5 mg/kg/day) [64,66]. It is active against most Candida spp. except for *C. krusei* and *C. glabrata*. Due to the reduced renal excretion of the lipid formulation of AmB B, the Infectious Diseases Society of America warns that it should be used with caution particularly in the presence of urinary tract infection and renal fungal balls [64,65]. Robust evidence for the preferred first-line empiric antifungal drug for neonatal invasive candidiasis is lacking, which underlies the existing variability in antifungal prescription practices among NICUs [61]. A higher mortality rate in infants treated with AmB lipid formulations compared to AmB-D or fluconazole was reported by Ascher et al. [67]. This could be attributed to inadequate penetration of the AmB lipid products into the kidneys, understudied dosage in preterm infants, or other unknown factors. In another study the case fatality rate was lower in the fluconazole treated infants (33%) compared to the AmB-D group (45%) and was found to have fewer side effects, despite the use of fluconazole at doses lower than current recommendations suggest for neonates [67,68]. Although nephrotoxicity is a common serious adverse effect of AmB-D therapy in adults, it seems that this is not the case in neonates. It is generally considered that its use in neonates is safer than in older children and adults, albeit clinicians should still monitor renal function [69,70]. An unfavorable impact of AMB-D use in pediatric patients from 13 months of age onwards suggests this age group, and not the neonatal period, as a turning point for increased adverse events [71]. Fluconazole seems to be safe in neonates with rare adverse effects, the most common of which comprises a mild elevation of liver enzymes that reverses after drug discontinuation.

Growing evidence from population PKs has shed more light on the optimal dosing of fluconazole in term and preterm neonates which has influenced expert opinion, and favors the use of higher doses than those labeled in term neonates, namely a loading dose of 25 mg/kg followed by 12 mg/kg/day [61,65,72–74]. A physiology-based PK model investigating fluconazole CNS exposure supported the above dosing regimen, as it resulted in a more rapid attainment of the target exposure in plasma and cerebrospinal fluid of preterm infants with CNS infection [75]. Furthermore, as part of the DINO (Drug dosage Improvement in Neonates, NCT02421068) study, a more recent PK study revealed that the actual body weight and serum creatinine are better predictors of fluconazole clearance, and an optimized dosing regimen has been proposed for VLBWI**.**

Based on a recent meta-analysis of nine randomized clinical trials on the prophylactic use of fluconazole in VLBWI, fluconazole is effective in reducing the Candida colonization rate, incidence of invasive candidiasis, and the in-hospital and infection-attributed mortality, which is similar to what was reported in previous systematic reviews and meta-analyses [66,76,77]. Several prophylactic dosage regimens have been studied, with different dose ranges (from 3 to 6 mg/kg), different dosing intervals (every 24 - 72 hours), and varying duration (4 to 6 weeks) [61]. Given that the higher dose (6 mg/kg) does not increase efficacy, while potentially increasing risk of toxicity and cost, the use of the lowest dose (3 mg/kg) seems to be preferred [78]. Both Infectious Diseases Society of America and European Society for Clinical Microbiology and Infectious Diseases recommend fluconazole prophylaxis in high-risk neonates in NICUs with a high frequency of invasive candidiasis (>10%). When prophylaxis is necessary, an interesting approach is that NICUs may choose to use either the 3 mg/kg or the 6 mg/kg dosing strategy based on local minimum inhibitory concentration (MIC) data, provided that surveillance and in vitro susceptibility testing are implemented (higher dose of 6 mg/kg for Candida spp. with MIC > 2-4 mg/L) (Table 2, Supplementary Table S2) [61].

3.2.2. Echinocandins

The role of echinocandins in neonatal invasive candidiasis is limited to salvage therapy or to situations in which resistance or toxicity preclude the use of AmB-D or fluconazole, and they are not recommended for the treatment of CNS infections in neonates [64]. Micafungin has been approved by the FDA (2019) and *European Medicines Agency* (EMA) (2016) for use in patients younger than 4 months without meningoencephalitis, with a dosing label of 4 mg/kg/day [79]. Target populations for this dose regimen include stable full-term infants younger than 4 months with line-related candidemia or those with significant toxicities of other antifungal drugs [79]. Micafungin at a dose of

 doi:10.20944/preprints202405.0151.v1

4 to 10 mg/kg/day is recommended for treatment of neonatal candidiasis by European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines. Given the difficulty of safely ruling out Candida meningoencephalitis in premature and critically-ill infants <4 months of age with candidemia and the risk of underdosing, experts appreciate that a substantially higher micafungin dose of at least 10 mg/kg once daily is likely needed for the treatment of candidemia with meningoencephalitis [79]. Micafungin seems to have a safe profile in term and preterm infants. Anidulafungin and caspofungin are not currently approved in neonates. Anidulafungin has approval for infants >1 month of age and caspofungin for infants >3 months of age, due to limited data in neonates (Table 2) [80].

The indications, dosing regimens and side effects of antifungal agents are summarized in Table 2, while more details are presented in the Supplementary Table S2.

Table 2. Selective antifungal medications most commonly used in neonates.

Medication [references]	Mechanisms of action / fungicide spectrum	Main neonatal indications	Neonatal dosing regimen	Side effects
Amphotericin B Deoxycholate (AmB-D) (Polyene) [60,64,67,69]	Loss of cell membrane integrity by binding to ergosterol. Potent and broad fungicidal activity.	Invasive fungal infections by susceptible Candida spp,, Aspergillus spp, and Cryptococcus spp. First-line therapy for neonatal IC including CNS infections.	First-line treatment: 1 mg/kg, IV, q24. Step-down treatment of CNS infections: 5 mg/kg, IV, q24	Nephrotoxicity (especially in co-adm. with other nephrotoxic drugs), electrolyte disturbances, anaemia, leukopenia, thrombocytopenia, elevated liver enzymes, diarrhoea, vomiting, thrombophlebitis at the injection site, infusion-related reactions (fever, hypotension, skin rashes). Monitoring: renal and liver function, electrolytes, and full blood count.
Liposomal Amphotericin B (AmB-D) (Polyene) [60]	Same as AmB-D	Same as AmB-D. Alternative therapy for neonatal IC (caution in renal infection or dysfunction). Drug of choice for invasive aspergillosis	3-5 mg/kg, IV, q24. Step-down treatment of CNS infections: 5 mg/kg, IV, q24.	Similar adverse events with AmB-D, but reduced incidence. Monitoring: renal and liver function, electrolytes, and full blood counts.
Fluconazole (Triazole) [60,61,65,72–74,78]	Inhibition of fungal cytochrome P450 activity and ergosterol synthesis, leading to cell membrane disruption.	Treatment of invasive infections by susceptible C. species. An alternative therapy of IC in neonates not been on fluconazole prophylaxis. A step-down treatment of C. meningitis. Prophylaxis of C. infections.	LD: 25 mg/kg, MD: 12 mg/kg/d once a day. Prophylaxis: 3-6 mg/kg every 72h for 4-6 weeks.	Most common adverse effects: Gastrointestinal irritation and elevation in liver tests. Rare: Rash, leukopenia, neutropenia, agranulocytosis, and thrombocytopenia. Weekly monitoring of SGOT, SGPT and ALP.

 doi:10.20944/preprints202405.0151.v1

Micafungin (Echinocandin) [60,64,78,79]	Inhibition of beta (1-3)-glucan synthase activity preventing synthesis of the fungal cell wall. Fungicidal spectrum: Candida spp. including resistant to fluconazole spp.)	Salvage therapy of invasive Candida infections or where resistance or toxicity preclude the use of AmB-D or fluconazole. There are concerns regarding the penetration of echinocandins into the CSF.	4 to 10 mg/kg/day, IV. Higher dose (≥ 10 mg/kg, q24) is likely needed for candidemia with meningoencephalitis.	Most common adverse events: infusion reactions and transient elevation of hepatic enzymes. Electrolyte disturbances, elevated creatinine, acute intravascular hemolysis, hemolytic anemia and hemoglobinuria, monocytosis, thrombocytopenia, fever, rash, diarrhoea, vomiting.

Adm, administration; AmB-D, amphotericin B deoxycholate; C, candida; CNS, central nervous system; CSF, cerebrospinal fluid; h, hours; IC, invasive candidiasis; IV, intravenously; LD, loading dose; MD, maintenance dose; spp, species.

4. Analgesics and Sedatives

During the last decades, it has become evident that fetuses and preterm infants, not only feel pain, but are more sensitive and show cardio-respiratory, hormonal, and metabolic stress responses similar to or even more intense than that seen in adults [81]. This is of great importance as neonates receiving intensive care are exposed to numerous painful and/or stressful procedures [82]. Moreover, cumulative evidence suggests that prolonged exposure to painful events in the neonatal period is associated with significant long-term consequences [83,84]. In this context, international scientific societies have provided guidelines for the prevention and management of pain and stress in neonates [85–87].

4.1. Analgesic Medications

4.1.1. Opioids

The opioids morphine, fentanyl, and remifentanil are the most frequently employed analgesic agents in neonates [4,8]. Typically, they are used for procedural or post-operative pain, either as monotherapy or in combination with other drugs [88,89]. Overall, the use of specific pain scales in neonates revealed that opioids reduce procedural pain. However, there is a considerable uncertainty regarding the relationship of opioids with episodes of bradycardia, hypotension, or severe apneas [90]. Therefore, the use of standardized protocols for pain management have been suggested to minimize the exposure to opioids [87,91].

4.1.1.1. Morphine

Morphine is a commonly used medication for analgesia in neonates. It has a slow onset of action (mean onset in 5 min.), reaches peak effect in 15 minutes, and is metabolized in the liver via glucuronidation, oxidation, and sulfidation [89]. The glucuronide biproducts of morphine include morphine-3-glucuronide and morphine-6- glucuronide. The latter metabolite has strong affinity with the morphine receptor and thereby possesses analgesic properties and augments the analgesic effect of morphine [92,93]. The main indication for morphine analgesia is invasive mechanical ventilation in preterm neonates, while it is not recommended for procedural pain in non-ventilated neonates, such as examination for retinopathy of prematurity [94,95]. Variable dosing regimens have been recommended by various authors and scientific societies. Early studies by Quinn et al. and Chay et al., based on available PK studies, recommended morphine dosing regimens with of loading doses of 100 and 150 mcg/kg/h, respectively, for about 2 hours followed by a continuous IV infusion of 25 or 22.5 mcg/kg/h, respectively [96,97]. Based on these studies, Saarenmaa et al. administered morphine in ventilated neonates at a loading dose of 140 mcg/kg over one hour followed by a continuous IV infusion of 20 mcg/kg/h for at least 24 hours [93,97]. Five years later, Anand et al., in a study of 898 ventilated neonates from 16 centers, administered morphine at a dosing regimen based

 doi:10.20944/preprints202405.0151.v1

on PK studies available at the study-time [94]. The treatment protocol included a morphine loading dose of 100 mcg/kg in IV infusion over 1 hour, followed by continuous infusions ranging from 10 to 30 mcg/kg/h depending on GA. No increase in early neurological adverse effects was associated with morphine use, except for the hypotensive infants and the extremely low birth weight infants who received high doses (> 10 mcg/kg/h) [94]. Reported acute adverse effects include respiratory depression, miosis, hypotension, constipation, increased biliary pressure, urinary retention, tolerance and withdrawal [89,94]. Results of the NOPAIN pilot trial suggested that morphine administered prophylactically in ventilated preterm infants may improve neurologic outcomes [98]. However, as documented in a following randomized clinical trial (NEOPAIN), pre-emptive analgesia with morphine did not decrease the composite outcome of death, severe intraventricular hemorrhage (IVH), or periventricular leukomalacia in preterm neonates but intermittent boluses of morphine actually increased the incidence of the composite outcome [94]. Overall, the results of these studies in preterm infants warrant extreme caution with the use of this morphine during key stages of brain development, especially in extremely low birth weight infants. It should be noted, though, that it is difficult to solely attribute the adverse outcomes to morphine (and other opioids), as low GA, and pre-existing arterial hypotension are also associated with IVH [84,89,99–101]. Interestingly, the analgesic effectiveness of morphine in preterm neonates was questioned, as well. Results of the Procedural Pain in Premature Infants (POPPI) study showed no beneficial effect of morphine on procedural pain in preterm neonates, whereas a higher number of morphine treated neonates required non-invasive ventilation due to apneas compared to the placebo group [95].

4.1.1.2. Fentanyl

Fentanyl is a synthetic opioid characterized by a rapid onset of action, within 1-2 minutes when administered intravenously, and an intermediate duration of action (30 minutes) [102]. These properties have made this medication a suitable opioid for acute, short lasting procedural pain [89,93]. A randomized control trial comparing fentanyl to morphine as analgesia for ventilated neonates showed equal efficacy, with fentanyl having fewer side effects [93]. As a result, fentanyl has become the most commonly used analgesic-sedative medication in many NICUs [4,89,93]. PK studies for fentanyl use in neonates and children are scarce. A comprehensive review by Ziesenitz et al. showed significant age-related changes, and a great variability in fentanyl kinetics, in preterm infants following bolus or continuous intravenous infusion, with a clearance ranging widely between 3.4 to 58.7 mL/min/kg [103]. The dosing regimens used in studies in neonates included a loading dose ranging from 5 to 12.5 mcg/kg followed by a continuous infusion of 0.5 to 2.0 mcg/kg/h [104]. A recent PK study suggests a quickly increasing clearance threshold within the first three postnatal weeks in preterm infants allowing for a reduced infusion dose by 50% and 25% on postnatal days 0-4 and 5-9, respectively. These results support a decrease in fentanyl dose regimen potentially mitigating some of the adverse effect of fentanyl [105]. Schofer et al. suggested a dose of 3 mcg/kg of fentanyl IV three minutes prior to intubation. Doses greater than 5 mcg/kg have been associated with increased incidence of hypotension [106]. Serious adverse effects of fentanyl include dose-dependent respiratory depression, chest wall rigidity, and arterial hypotension [106]. Of note, in a retrospective study involving very low gestational age infants, fentanyl was independently associated with the need for inotropes [99]. Nevertheless, the effect of fentanyl on blood pressure in neonates is still unclear. A recent Cochrane review including 13 independent studies (enrolling 823 newborn infants) concluded that opioids probably are more effective in reducing pain scores than placebo. However, existing evidence cannot clarify the effect of opioids on episodes of bradycardia, hypotension, or apnea [90,103]. Thus no definite conclusion could be reached concerning the potential effect of opioids, in general, or fentanyl *per se*, on blood pressure in preterm and term infants [90,103]. A long-term study of infants treated with fentanyl early after birth did not find any significant correlation between cumulative fentanyl exposure and neurodevelopmental outcomes at five years of age [107]. These results were consisted with previous reports in VLBWI at the age of two years [108].

 doi:10.20944/preprints202405.0151.v1

4.1.1.3. Remifentanil

Remifentanil is another synthetic opioid and a selective morphine-receptor agonist, with rapid onset and ultra-short duration of action due to a quick degradation by nonspecific plasma and tissue esterases [109]. In neonatology, it has been used for brief procedural analgesia, i.e., prior to intubation, and prolonged sedation/analgesia with relative safety [89,110,111]. When using remifentanil (1 to 3 mcg/kg) as a single premedication for INSURE, a faster infusion over 30 seconds (compared to over 60 seconds) was associated with higher incidence of chest rigidity (43%) and shorter duration of sedation [112]. Due to the risk of chest wall rigidity, it should only be used in intensive care units with strict monitoring capabilities. Long-term consequences of remifentanil administration in neonates are unknown and, therefore, its optimal use in the neonatal population warrants further studies [89,109,111–114].

4.1.2. Non-Opioid Analgesics

In the context of the existing controversy on the effectiveness and safety of opioids, alternative analgesics, mainly paracetamol (acetaminophen), have been used for treatment of postoperative and procedural pain in neonates. It exerts its central analgesic effect via activation of descending serotonergic pathways, and inhibition of prostaglandin synthesis [115]. Pooled analyses of PK results suggest an oral dose of 25 mg/kg/day in preterm neonates at 30 weeks, 45 mg/kg/day at 34 weeks, 60 mg/kg/day in term neonates, and 90 mg/kg/day at 6 months of age [116,117]. Other authors recommend a loading dose of 20 mg/kg, followed by 10 mg/kg every 6 hours for 32-44 weeks' neonates. For neonates < 32 weeks, a loading dose of 12 mg/kg and a maintenance dose of 6 mg/kg every 6 hours is recommended [118]. The safety profile of paracetamol might have contributed to its increasing use in term and preterm neonates, despite the off-label use in this population [116,119]. A recent meta-analysis and a review showed that existing data are not sufficient to support a role for paracetamol in reducing procedural pain in neonates, but may reduce the need for morphine following major surgery [115,120].

4.2. Sedatives

4.2.1. Benzodiazepines

Benzodiazepines effectively relieve patients' stress, but they exert no analgesic action. Therefore, they are mainly used as an adjunct to analgesics and may rarely be used for in minor procedures [121]. Midazolam is the most common sedative utilized by the NICU physicians for sedation [4,8]. Due to its pharmacological advantages (lack of active metabolites), it has replaced diazepam [122]. Midazolam is a short-acting benzodiazepine that possesses sedative and anticonvulsant properties [121]. The advantages of midazolam over other sedatives are the rapid onset of action and fast termination of effects [123]. Various dosing regimens have been recommend, but one report suggested that when midazolam is used as the only sedative agent, the optimal dose was of 209 mcg/kg/hour (range: 100 to 500 mcg/kg/hour) [121]. However, the limited existing data raises significant concerns about its safety when given as continuous infusion for sedation in infants receiving intensive care [121].

Adverse effects reported in neonates include respiratory depression, hypotension, and a decrease in cerebral blood flow. Moreover, paradoxical agitation, such as hyperexcitability and myoclonus have been reported, which be attributed to the low number of GABA-A receptors in the neonate [124]. As documented in the most recent Cochrane review (2017) which included only three trials and 148 neonates, the duration of NICU stay was significantly longer in the midazolam group than in the placebo group. Moreover in one of the included studies, the incidence of a combined adverse outcome of death, grade 3 or 4 peri- intraventricular hemorrhage, or periventricular leukomalacia at 28 days' postnatal age was significantly higher in the midazolam group compared with the morphine group [98,125]. Consequently, the limited existing data raises significant concerns about its safety when given as continuous infusion for sedation in infants receiving intensive care.

 doi:10.20944/preprints202405.0151.v1

4.2.2. Ketamine

Ketamine is an analgesic and anesthetic (analgo-sedative) agent that has been used more in children than in neonates. It is an antagonist of n-methyl D-aspartate (NMDA) receptor, gamma-aminobutyric acid (GABA), and other brain receptors, and has a rapid action [126]. It is indicated as analgesia for minor procedures in neonates, such as cannulation for extracorporeal membrane oxygenation [127]. It has also been administered for endotracheal suctioning at a dose of 2 mg/kg [127]. Several administration routes have been used (intravenous, intramuscular, or intranasal). Recommended analgesic doses are 0.15–0.25 mg/kg, IV or 0.5–1 mg/kg intramuscularly [126]. Overall, it is believed to offer cardiorespiratory stability, as ketamine causes mild increases in BP and heart rate while having minimal effects on cerebral blood flow. Moreover, it decreases respiratory drive and induces bronchodilation [127]. Few perioperative complications and satisfactory operative conditions were reported with ketamine analgesia compared to general anesthesia during laser treatment for retinopathy of prematurity in a small group of infants [128]. In the larger "NOPAIN-ROP" randomized trial, IV fentanyl versus IV ketamine for pain relief during laser photocoagulation for retinopathy of prematurity in preterm infants was tested. With both drug regimens, adequate analgesia was provided only in a minority of infants [129]. Concerns regarding potential ketamine-mediated neurotoxicity in the immature brain give pause to the use of ketamine infusion as a therapeutic option for refractory neonatal seizures [130].

4.2.3. Propofol

Propofol is a highly lipophilic compound that is rapidly distributed from blood to subcutaneous fat and the CNS with subsequent redistribution and metabolic clearance. It positively modulates the inhibitory function of the neurotransmitter GABA through the ligand-gated GABAA receptors. It is a short acting sedative (without analgesic properties) that is rapid in its onset and short in duration. These properties make propofol attractive for short-duration interventions. On the other hand, due to the reduced clearance capacity, both preterm and term neonates in the first week of postnatal life are at risk for accumulation following propofol administration [131]. In a recent prospective trial investigating the optimal propofol dose in neonates requiring non-emergency endotracheal intubation, effective sedation without side effects was reported as "difficult to achieve"; optimal result was observed more often with the high starting dose of 2.0 mg/kg compared to the lower doses of 1.0 and 1.5 mg/kg. However, propofol-induced hypotension occurred in 59% of patients, and this risk was found even with low initial doses [132]. In a following study, the profound and prolonged decrease in blood pressure following propofol administration as premedication for intubation in neonates was mainly attributed to its starting dose rather than the cumulative dose [133]. There is only one Cochrane review on propofol for procedural sedation/anesthesia in neonates and it was published more than a decade ago. No practice recommendation could be made at that time [134]. As well, there has been no updated review which reflects the lack of available evidence regarding the use of propofol in neonates.

4.2.4. Alpha-2 Agonists

Centrally acting alpha-2 agonists, such as clonidine and dexmedetomidine, possess sedative, analgesic, and anxiolytic properties. The two main adverse effects of alpha-2 agonists are bradycardia and hypotension. However, contrary to opioids, they do not cause significant respiratory depression. Due to this advantage, alpha-2 agonists have been used in critically ill children as adjunctive sedative agents alongside opioids benzodiazepines and help to minimize the use of benzodiazepines and opioids in children and prevent withdrawal syndrome [135]. There are few data on the "off-label" use of clonidine and dexmedetomidine in neonates. The most recent (2017) relevant Cochrane review included only one small trial (112 neonates) comparing clonidine with placebo. Although sedation-pain scale values were lower among treated infants, clonidine was not associated with reduce death, duration of mechanical ventilation, or duration of stay in the NICU [136]. Interestingly, there are no studies regarding the use of clonidine for the prevention or treatment of procedural and

 doi:10.20944/preprints202405.0151.v1

postoperative pain, or pain associated with clinical conditions in non-ventilated neonates [137]. Clonidine has been used for neonatal abstinence syndrome, as well. In a systematic review of randomized clinical trials, clonidine was found to be more efficacious than morphine with respect to the duration of treatment, and better than phenobarbital in reducing morphine treatment days [138].

Like clonidine, dexmedetomidine was reported to be effective in achieving sedation/analgesia in neonates and reduce the need for adjunctive sedative or analgesic agents. Furthermore, it was found to decrease the time to extubation as well as the duration of mechanical ventilation [139]. It is worth noting that during the last several years, dexmedetomidine has attracted the interest of neonatologists as an analgesic/sedative agent in neonates undergoing therapeutic hypothermia due to its possible neuroprotective action [140,141] However, so far, there are insufficient data from randomized clinical trials evaluating the use of any analgesic-sedative agent during therapeutic hypothermia, including clonidine and dexmedetomidine [142]. Dexmedetomidine has been used in neonates at a starting dose of 0.2 to 0.3 mcg/kg/h, escalating in 0.1 mcg/kg/h increments depending on pain / sedation assessment scores, up to a median maximum dose of 0.5 mcg/kg/h (Table 3) [143].

The suggested dosing regimens of analgesics and sedatives which have been most frequently used in neonates are summarized in Table 3.

Table 3. Analgesics and sedatives most commonly used in neonates.

Medication [references]	Mechanisms of action	Main indications	Dosing regimen	Side effects
Analgesic medications				
Morphine [84,93–97]	Opiate receptor agonist.	Pre-emptive-analgesia in intubated and-ventilated preterm neonates.	ID: 100-150 mcg/kg/h, IV; MD: 20-30 mcg/kg/h, IV, for =/> 24h. Lower doses may be needed in liver and renal dysfunction.	Respiratory depression, miosis, hypotension, constipation, increased biliary pressure, urinary retention; tolerance & withdrawal s.
Fentanyl [88,89,93,103,104,106]	Opiate receptor agonist.	Acute painful procedures, such as intubation.	LD: 5 to 12.5 mcg/kg, IV, followed by infusion of 0.5 to 2.0 mcg/kg/h, IV. Doses > 5 mcg/kg were associated with increased incidence of hypotension.	Respiratory depression, chest wall rigidity, and hypotension. No association with long-term neurodevelopment.
Remifentanyl [111–114]	Opiate receptor agonist.	Premedication prior to intubation. Procedures and surgeries of short duration.	Fast bolus of 1-3 mcg/kg IV within 60 sec.	Hypotension and chest wall rigidity. Insufficient sedation and severe side effects after fast adm.
Acetaminophen [89,116–120,144]	Activation of descending serotonergic inhibitory pathways.	Mild to moderate procedural or postoperative pain. Adjunctive therapy to opioids in moderate to severe pain; reduces the use of opioids. FDA approval for > 2 years.	Oral or rectal adm: 25-60 mg/kg/day, depending on GA. IV adm: 20-40 mg/kg/day depending on gestational age.	Hepatotoxicity, bradycardia, and hypotension.
Sedatives				

 doi:10.20944/preprints202405.0151.v1

Midazolam [98,121,124,125,127]	Induces the inhibitory function of GABA through $GABA_A$ receptors.	Adjunct to analgesics; rarely alone in minor procedures.	Dosing for sedation: 209 mcg/kg/h (range: 100 to 500 mcg/kg/hour) IV.	Respiratory depression with hypotension, decrease in CBF, agitation (hyperexcitability and myoclonus).
Ketamine [126,127,129,130]	NMDA receptor and other brain receptor antagonist.	Minor procedures (i.e., intubation, endotracheal suctioning, cannulation for ECMO).	Analgesic doses: 0.15–0.25 mg/kg, I.V. or 0.5–1 mg/kg intramuscularly. Endotracheal suctioning: 2 mg/kg, IV.	Mild increase in blood pressure and heart rate, minimal effects on CBF, suppresses respiratory drive, bronchodilation.
Propofol [131,133,134]	Induces the inhibitory function of GABA through $GABA_A$ receptors.	Short-duration interventions.	High ID (2.0 mg/kg) produces better results than lower doses (1.0 and 1.5 mg/kg).	Profound hypotension, especially with high dose. No practice recommendation.
α2-Agonists (clonidine; dexmedetomidine) [135,136,138–140,142,143]	Centrally acting alpha-2 agonists.	Adjunctive to opioids and benzodiazepines reducing their use. Therapeutic hypothermia Neonatal abstinence syndrome. Post-operatively after major surgeries.	Clonidine: 6 mcg/kg/d, titrated up to 9 mcg/kg/d. Dexmedetomidine: ID: 0.2 to 0.3 mcg/kg/h titrated up in 0.1 mcg/kg/h increments as required.	Clonidine: Hypotension, rebound hypertension, bradycardia, and syndrome of inappropriate antidiuretic hormone, postoperative apnea. At high anesthesia, probably respiratory depression. Dexmedetomidine: bradycardia and hypotension.

5. Antiseizure Medications

Antiseizure medications (ASMs) are used to treat seizures to which the neonatal brain is prone. In our era, hypoxic-ischemic encephalopathy, stroke, brain infections, intracranial hemorrhage, cerebral dysplasias, hypoglycemia, electrolyte disturbances, epileptic encephalopathies, inborn errors of metabolism, as well as benign familial neonatal epilepsy are the main causes of neonatal seizures [145,146]. Nevertheless, thus far, there is limited evidence regarding the best pharmacological treatment of neonatal seizures. This fact explains the existing variability among centers and neonatologists as to whether, when, and for how long ASMs should be used, as well as which medication should be chosen [147]. Additionally, there are concerns related to the side effects, drug interactions, monitoring of blood levels, and effects long-term neurodevelopment [147].

In general, the choice of the optimal ASM takes into consideration the etiology and severity of the seizures, but also the cardiac, renal, and liver function of the neonate. ASMs exert their actions via GABA receptors (i.e., phenobarbital), sodium channels (i.e., phenytoin, carbamazepine), by binding to synaptic vesicle protein SV2a (levetiracetam) or via the N-methyl-D-aspartate [NMDA] receptor as glutamate antagonists (ketamine) [146]. In contrast to adults and older children, only very few ASM have been licensed for use in infants and neonates [148].

Herein, we will briefly refer to phenobarbital, levetiracetam and phenytoin/fosphenytoin, which are the most commonly used ASMs for the treatment of clinically suspected and/or seizures confirmed *by electroencephalography* (EEG) in neonates (Table 4) [145].

 doi:10.20944/preprints202405.0151.v1

Table 4. Antiseizure medications most commonly used in neonates.

Medication [references]	Mechanisms of action	Main indications	Dosing regimen	Side effects
Phenobarbital [145,149–151]	Increases $GABA_A$ mediated inhibition of GABA.	1st line ASM regardless of seizures etiology.	LD: 20 mg/kg, IV, (up to a total dose of 40 mg/kg); MD: 5 mg/kg/day, IV or orally, in one dose.	Hypotension, poor feeding, sedation, respiratory depression, bradycardia, hepatotoxicity.
Phenytoin/ fosphenytoin [149,152]	Sodium channel blocker.	Second-line ASM	LD: 20 mg/kg, IV; MD: 5-7.5 mg/kg/day, IV or orally, in two doses.	Hypotension, cardiac arrhythmias, irritability/necrosis, hypotonia, and respiratory depression/arrest.
Levetiracetam [146,149,153]	Binds to synaptic vesicle protein SV2a	Second-line ASM; maybe first- line in some NICUs.	LD: 40 mg/kg/day, IV, up to a total dose of 60 mg/kg; MD: 40–60 mg/kg/day, IV or orally, in 3 doses.	Mild sedation, irritability, increased blood pressure.
Midazolam [121,123,125,149,154,155]	Binds to $GABA_A$ receptors.	Refractory neonatal seizures.	LD: 0.05–0.15 mg/kg IV, MD: 1-5 mcg/kg/min, continuous IV infusion, titrated up in steps of 1 mcg/kg/min to a *max*. of 5 mcg/kg/min.	Respiratory depression, hypotension, poor feeding, dyskinetic movements and myoclonus
Topiramate [156–159]	Inhibition of glutamate-receptors.,	Antiepileptic, potentially neuroprotective for HIE; Mainly therapeutic hypothermia.	Optimized dosing regimen: LD: dose of 15 mg/kg for cycle one; MD: 5 mg/kg for the following four cycles.	No adverse effects on respiratory and hemodynamic parameters, hematological and biochemical tests.

ASM, antiseizure medications; HIE, hypoxic – ischemic encephalopathy; IV, intravenously; LD, loading dose; MD, maintenance dose; NICU, neonatal intensive care unit.

5.1. Phenobarbital

Phenobarbital (or phenobarbitone) is a barbiturate with antiseizure and hypnotic/sedative properties. Phenobarbital sodium (powder for injection**)** is the first and only medication approved by the FDA for the treatment of neonatal seizures [150]. Phenobarbital acts by increasing GABAA mediated inhibition of GABA [150]. The drug is metabolized in the liver and excreted in urine. Regardless of the seizure etiology, phenobarbital is the most frequently used ASM in the NICU setting [145].

According to the recent recommendations by The Neonatal Task Force of the International League Against Epilepsy (ILAE), phenobarbital should be the first-line ASM (evidence-based recommendation) regardless of etiology (expert agreement), unless channelopathy is likely the cause for seizures (e.g, due to family history), in which case phenytoin or carbamazepine should be used. Phenobarbital should be given at a loading dose of 20 mg/kg IV, followed by a maintenance dose of 5 mg/kg/day IV or orally. A second loading dose at 10-20 mg/kg could be administered IV if required [149]. A 40% response was reported after the initial loading dose, but sequential administration of IV phenobarbital lead to improved control of seizures in term and preterm neonates [150]. Based on the results of a retrospective population PK study across a pediatric population including neonates, an initial phenobarbital dose of 30 mg/kg has the highest probability of attaining a therapeutic concentration at seven days. Moreover, postmenstrual age and drug-drug interactions should be incorporated into dosing regimen [160]. Monitoring of circulating levels (target concentration: 20-40 mcg/mL) should be considered if on maintenance therapy [149,160]. In asphyxiated neonates with seizures undergoing therapeutic hypothermia, a second loading dose of 20 mg/kg has been suggested

 doi:10.20944/preprints202405.0151.v1

for better seizure control. Nevertheless, prophylactic administration of phenobarbital before the onset of hypothermia is not recommended [151].

The most common adverse effects of phenobarbital include respiratory depression, hypotension, depressed consciousness, somnolence, and poor feeding [145,150]. Moreover, the fact that phenobarbital may cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans is alarming [161].

5.2. Phenytoin/Fosphenytoin

Phenytoin and fosphenytoin (the phosphorylated prodrug of phenytoin) [152] are still considered as second-line ASMs for most seizure etiologies in neonates not responding to phenobarbital [162]. However, its use declined during the last two decades and has been surpassed by levetiracetam as the second most widely used antiseizure medication in NICUs [163].

With respect to seizure control, two studies evaluating phenytoin and fosphenytoin in neonates, demonstrated similar efficacy to phenobarbital (45% and 56% became seizure free after initial treatment with phenytoin and fosphenytoin, respectively) [164,165]. In a recent meta-analysis, high uncertainty was expressed about the effect of phenobarbital compared to phenytoin on achieving seizure control after a maximal loading dose of the ASM [166].

A loading dose of phenytoin/fosphenytoin (20 mg/kg phenytoin equivalent IV over 30 min) is initially administered followed by maintenance (5 mg/kg/day IV or orally in two divided doses). Adjustments are made according to response (max. per dose 7.5 mg/kg) and plasma concentration (target level: 10–20 mcg/mL). Phenytoin has poor oral bioavailability and limited hepatic metabolism capacity. Low albumin levels and bilirubin displacement by phenytoin from its protein-binding sites may result in increased serum free levels of bilirubin. Levels may also increase in infants receiving therapeutic hypothermia [162].

Careful cardiac monitoring is needed during and after administering IV phenytoin/fosphenytoin because of the risk of severe hypotension and cardiac arrhythmias. Other common adverse reactions are infection, site irritability/necrosis, hypotonia, and respiratory depression/arrest [162]. Fosphenytoin is preferred over phenytoin due to lower risk of adverse effects [152]. Similar to phenobarbital, there are experimental data indicative of apoptotic neurodegeneration with phenytoin [161].

5.3. Levetiracetam

Levetiracetam is an FDA-approved ASM for adults and infants older than one month postnatal age since 2012, mainly used in combination with other anticonvulsive agents. According to a prospective cohort study, it is used off-label in neonates, being the next most commonly used ASM for neonatal seizures following phenobarbital [145]. A reduction by 50-88% in the frequency of seizures without serious side effects has been reported using levetiracetam [167,168]. Moreover, when used as a first-line antiepileptic drug for neonatal seizures, levetiracetam achieved better control than phenobarbital [153]. However, in another recent phase IIb study, phenobarbital was found to be more effective than levetiracetam for the treatment of neonatal seizures (80% versus 26%, respectively), although more adverse effects were seen in subjects assigned to phenobarbital [169]. This finding is also supported by a recent (2023) Cochrane meta-analysis; it was concluded that phenobarbital as a first-line ASM is probably more effective than levetiracetam in achieving seizure control after the first loading dose and after the maximal loading dose (moderate-certainty of evidence) [166]. It should be noted that levetiracetam might have a neuroprotective effect on the neonatal brain by reducing neuronal apoptosis, as shown in animal models [170].

The ILAE, suggested that levetiracetam should be administered as follows: a loading dose of 40 mg/kg IV, followed by a second loading dose of 20 mg/kg IV if required, and maintenance dose of 40–60 mg/kg/day IV or orally in three divided doses [162]. However, higher loading doses (60 mg/kg) may be more effective and substantially decreased the seizure burden [169]. Moreover, high doses seem to be well tolerated. Specifically, in a neonatal study, the initial cumulative dose of levetiracetam ranged from 50 to 100 mg/kg [171], while in another study involving infants suffering hypoxic-

 doi:10.20944/preprints202405.0151.v1

ischemic encephalopathy, the mean total and maintenance doses of levetiracetam were 63 and 65 mg/kg/day, respectively [172]. In clinical practice, transition from IV to oral administration should be done, when feasible, and at equivalent doses. Levetiracetam is mainly excreted from the kidneys and to a lesser degree from the liver resulting in fewer interactions with other drugs [146,169].

5.4. Midazolam

The use of midazolam as sedative in ventilated infants is discussed elsewhere in this article. Midazolam was approved in 2022 by the FDA for rescue treatment in adults with status epilepticus, but not in infants and neonates. However, this non-FDA approved benzodiazepine has been utilized for the management of refractory neonatal seizures as well [123,155]. Castro-Conde et al. reported that midazolam effectively controlled EEG-confirmed seizures in all non-responders (n=13) to phenobarbital/phenytoin, significantly improving their long-term neurodevelopment [155]. The authors proposed an antiseizure dosing regimen comprising 0.15 mcg/kg IV bolus, followed by a continuous infusion of 1 mcg/kg/min, increasing by 0.5 to 1 mcg/kg every 2 min, up to a maximum of 18 mcg/kg/min. In other studies, a lower efficacy was reported [173,174].

In the suggested by the ILAE treatments for the management of neonatal seizures, midazolam is included in the second-line ASM options. Its administration includes a loading dose of 0.05–0.15 mg/kg, followed by continuous infusion of a maintenance dose (1 mcg/kg), which may be titrated up in steps of 1 mcg/kg/min to a *max*. of 5 mcg/kg/min) [162]. Midazolam may cause respiratory depression, hypotension, poor feeding as well as dyskinetic movements and myoclonus [125,162]. Nevertheless, most worrisome is its potential effect on brain development and ultimately neurodevelopment. Animal data showed that benzodiazepines may induce apoptotic neurodegeneration of the developing brain [161], although these concerns have not been validated in human studies [175].

5.5. Topiramate

Topiramate, an anticonvulsant agent widely used in adults and children, is characterized by good absorption, high bioavailability, and good tolerability [176]. Due to the encouraging experimental evidence as neuroprotective agent (through several mechanisms including glutamate-receptor inhibition), topiramate has received additional interest as an adjunct treatment in neonates undergoing therapeutic hypothermia [156]. In the "NeoNATI" feasibility study, 21 neonates were allocated to hypothermia plus topiramate at a dose of 10mg/kg once daily for the first three days of life, and 23 to hypothermia alone. Co-administration of topiramate was safe and associated with a reduction in the prevalence of epilepsy while did not reduce the frequency of the combined outcome of mortality or severe neurological disability [177].

Investigators also evaluated the influence of hypothermia on topiramate PKs. In an early study by Filippi et al. (2009), 13 neonates undergoing whole body hypothermia were given oral topiramate (5 mg/kg once a day for the first three days of life) while seven had concomitant phenobarbital treatment. In most neonates (11/13), topiramate concentrations were within the reference range for the entire treatment duration [157]. A therapeutic range of 5-20 mg/L has been proposed for epilepsy therapy [158,159]. A more recent study evaluated topiramate PKs in hypothermic neonates. Aiming to decrease seizure events, topiramate was given at 5 mg/kg on day 1, and at 3 mg/kg on days 2-5. Based on PKs, the authors suggested an optimized alternative dosage regimen consisting of a loading dose of 15 mg/kg for cycle one and maintenance doses of 5 mg/kg for the following four cycles, to allow topiramate concentrations to be within the therapeutic range after the first dose in more than 90% of cooled neonates [159].

6. Future Perspective and Conclusions

In every-day clinical practice, neonatologists use several drug categories, often with very little proof of evidence as for their safety and efficacy. This fact is indicative of important gaps in knowledge in neonatal pharmacology and the need for new treatments. Therefore, there is an urgent

need for clinical trials, in which the diversity of neonates and their medical conditions will be taken into consideration. Only then, will we be able to identify the most effective (old or new) medication, and at the same time decrease the risk of adverse effects, primarily concerning the developing brain, thus improving neurodevelopmental outcomes. Additionally, scientific information derived from the application of new technologies (e.g., genetics, -omics) along with the analysis of pharmacometric parameters and clinical-imaging data, may allow for a more precise use of medications in the neonatal population. Although improvement have been made in legislation, infrastructure, and clinical trial methodology during the last decades ensuring a safer framework surrounding neonatal drug development, more work is still needed [178].

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1. Detailed presentation of selective antimicrobial medications commonly used in neonates. Table S2. Detailed presentation of selective antifungal medications commonly used in neonates.

Author Contributions: KS: AK, EA, conceptualized the article; EA, KS, AK, IC, ET, writing - original draft; EA, KS, WC, ET writing - review & editing; KS, WC, supervised the writing and critically revised the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-forprofit sectors. The APC will be paid by the Research Committee (Eidikos Logariasmos Koldilion Erevnas, ELKE) of our Institution (Aristotle University of Thessaloniki).

Ethical issues: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest statement: All authors declare no competing interests.

References

1. Shane, A.L.; Sánchez, P.J.; Stoll, B.J. Neonatal Sepsis. *Lancet Lond. Engl.* **2017**, *390*, 1770–1780, doi:10.1016/S0140-6736(17)31002-4.
2. Bethou, A.; Bhat, B.V. Neonatal Sepsis-Newer Insights. *Indian J. Pediatr.* **2022**, *89*, 267–273, doi:10.1007/s12098-021-03852-z.
3. McPherson, C.; Grunau, R.E. Neonatal Pain Control and Neurologic Effects of Anesthetics and Sedatives in Preterm Infants. *Clin. Perinatol.* **2014**, *41*, 209–227, doi:10.1016/j.clp.2013.10.002.
4. Agakidou, E.; Tsoni, K.; Stathopoulou, T.; Thomaidou, A.; Farini, M.; Kontou, A.; Karagianni, P.; Sarafidis, K. Changes in Physicians' Perceptions and Practices on Neonatal Pain Management Over the Past 20 Years. A Survey Conducted at Two Time-Points. *Front. Pediatr.* **2021**, *9*, 667806, doi:10.3389/fped.2021.667806.
5. Borenstein-Levin, L.; Hochwald, O.; Ben-Ari, J.; Dinur, G.; Littner, Y.; Eytan, D.; Kugelman, A.; Halberthal, M. Same Baby, Different Care: Variations in Practice between Neonatologists and Pediatric Intensivists. *Eur. J. Pediatr.* **2022**, *181*, 1669–1677, doi:10.1007/s00431-022-04372-4.
6. Garrido, F.; Allegaert, K.; Arribas, C.; Villamor, E.; Raffaeli, G.; Paniagua, M.; Cavallaro, G. Variations in Antibiotic Use and Sepsis Management in Neonatal Intensive Care Units: A European Survey. *Antibiotics* **2021**, *10*, 1046, doi:10.3390/antibiotics10091046.
7. Al-Aweel, I.; Pursley, D.M.; Rubin, L.P.; Shah, B.; Weisberger, S.; Richardson, D.K. Variations in Prevalence of Hypotension, Hypertension, and Vasopressor Use in NICUs. *J. Perinatol. Off. J. Calif. Perinat. Assoc.* **2001**, *21*, 272–278, doi:10.1038/sj.jp.7210563.
8. Stark, A.; Smith, P.B.; Hornik, C.P.; Zimmerman, K.O.; Hornik, C.D.; Pradeep, S.; Clark, R.H.; Benjamin, D.K.; Laughon, M.; Greenberg, R.G. Medication Use in the Neonatal Intensive Care Unit and Changes from 2010 to 2018. *J. Pediatr.* **2022**, *240*, 66-71.e4, doi:10.1016/j.jpeds.2021.08.075.
9. Hsieh, E.M.; Hornik, C.P.; Clark, R.H.; Laughon, M.M.; Benjamin, D.K.; Smith, P.B. Medication Use in the Neonatal Intensive Care Unit. *Am. J. Perinatol.* **2014**, *31*, 811–822, doi:10.1055/s-0033-1361933.
10. Kontou, A.; Sarafidis, K.; Roilides, E. Antimicrobial Dosing in Neonates. *Expert Rev. Clin. Pharmacol.* **2017**, *10*, 239–242, doi:10.1080/17512433.2017.1279968.
11. Prusakov, P.; Goff, D.A.; Wozniak, P.S.; Cassim, A.; Scipion, C.E.A.; Urzúa, S.; Ronchi, A.; Zeng, L.; Ladipo-Ajayi, O.; Aviles-Otero, N.; et al. A Global Point Prevalence Survey of Antimicrobial Use in Neonatal Intensive Care Units: The No-More-Antibiotics and Resistance (NO-MAS-R) Study. *EClinicalMedicine* **2021**, *32*, 100727, doi:10.1016/j.eclinm.2021.100727.

12. Spyridis, N.; Syridou, G.; Goossens, H.; Versporten, A.; Kopsidas, J.; Kourlaba, G.; Bielicki, J.; Drapier, N.; Zaoutis, T.; Tsolia, M.; et al. Variation in Paediatric Hospital Antibiotic Guidelines in Europe. *Arch. Dis. Child.* **2016**, *101*, 72–76, doi:10.1136/archdischild-2015-308255.
13. Porta, A.; Esposito, S.; Menson, E.; Spyridis, N.; Tsolia, M.; Sharland, M.; Principi, N. Off-Label Antibiotic Use in Children in Three European Countries. *Eur. J. Clin. Pharmacol.* **2010**, *66*, 919–927, doi:10.1007/s00228-010-0842-1.
14. Schulman, J.; Dimand, R.J.; Lee, H.C.; Duenas, G.V.; Bennett, M.V.; Gould, J.B. Neonatal Intensive Care Unit Antibiotic Use. *Pediatrics* **2015**, *135*, 826–833, doi:10.1542/peds.2014-3409.
15. Cuzzolin, L.; Agostino, R. Off-Label and Unlicensed Drug Treatments in Neonatal Intensive Care Units: An Italian Multicentre Study. *Eur. J. Clin. Pharmacol.* **2016**, *72*, 117–123, doi:10.1007/s00228-015-1962-4.
16. Silva, J.; Flor-de-Lima, F.; Soares, H.; Guimarães, H. Off-Label and Unlicensed Drug Use in Neonatology: Reality in a Portuguese University Hospital. *Acta Med. Port.* **2015**, *28*, 297–306, doi:10.20344/amp.5271.
17. Gade, C.; Trolle, S.; Mørk, M.-L.; Lewis, A.; Andersen, P.F.; Jacobsen, T.; Andersen, J.; Lausten-Thomsen, U. Massive Presence of Off-Label Medicines in Danish Neonatal Departments: A Nationwide Survey Using National Hospital Purchase Data. *Pharmacol. Res. Perspect.* **2023**, *11*, e01037, doi:10.1002/prp2.1037.
18. Puopolo, K.M.; Lynfield, R.; Cummings, J.J.; COMMITTEE ON FETUS AND NEWBORN; COMMITTEE ON INFECTIOUS DISEASES Management of Infants at Risk for Group B Streptococcal Disease. *Pediatrics* **2019**, *144*, e20191881, doi:10.1542/peds.2019-1881.
19. Metsvaht, T.; Nellis, G.; Varendi, H.; Nunn, A.J.; Graham, S.; Rieutord, A.; Storme, T.; McElnay, J.; Mulla, H.; Turner, M.A.; et al. High Variability in the Dosing of Commonly Used Antibiotics Revealed by a Europe-Wide Point Prevalence Study: Implications for Research and Dissemination. *BMC Pediatr.* **2015**, *15*, 41, doi:10.1186/s12887-015-0359-y.
20. Leroux, S.; Zhao, W.; Bétrémieux, P.; Pladys, P.; Saliba, E.; Jacqz-Aigrain, E.; French Society of Neonatology Therapeutic Guidelines for Prescribing Antibiotics in Neonates Should Be Evidence-Based: A French National Survey. *Arch. Dis. Child.* **2015**, *100*, 394–398, doi:10.1136/archdischild-2014-306873.
21. Thompson, G.; Barker, C.I.; Folgori, L.; Bielicki, J.A.; Bradley, J.S.; Lutsar, I.; Sharland, M. Global Shortage of Neonatal and Paediatric Antibiotic Trials: Rapid Review. *BMJ Open* **2017**, *7*, e016293, doi:10.1136/bmjopen-2017-016293.
22. Commissioner, O. of the Pediatric Labeling Changes. *FDA* **2024**.
23. Korang, S.K.; Safi, S.; Nava, C.; Gordon, A.; Gupta, M.; Greisen, G.; Lausten-Thomsen, U.; Jakobsen, J.C. Antibiotic Regimens for Early-Onset Neonatal Sepsis. *Cochrane Database Syst. Rev.* **2021**, *5*, CD013837, doi:10.1002/14651858.CD013837.pub2.
24. Korang, S.K.; Safi, S.; Nava, C.; Greisen, G.; Gupta, M.; Lausten-Thomsen, U.; Jakobsen, J.C. Antibiotic Regimens for Late-Onset Neonatal Sepsis. *Cochrane Database Syst. Rev.* **2021**, *5*, CD013836, doi:10.1002/14651858.CD013836.pub2.
25. Jarugula, P.; Akcan-Arikan, A.; Munoz-Rivas, F.; Moffett, B.S.; Ivaturi, V.; Rios, D. Optimizing Vancomycin Dosing and Monitoring in Neonates and Infants Using Population Pharmacokinetic Modeling. *Antimicrob. Agents Chemother.* **2022**, *66*, e0189921, doi:10.1128/aac.01899-21.
26. Sands, K.; Carvalho, M.J.; Portal, E.; Thomson, K.; Dyer, C.; Akpulu, C.; Andrews, R.; Ferreira, A.; Gillespie, D.; Hender, T.; et al. Characterization of Antimicrobial-Resistant Gram-Negative Bacteria That Cause Neonatal Sepsis in Seven Low- and Middle-Income Countries. *Nat. Microbiol.* **2021**, *6*, 512–523, doi:10.1038/s41564-021-00870-7.
27. Puopolo, K.M.; Benitz, W.E.; Zaoutis, T.E.; COMMITTEE ON FETUS AND NEWBORN; COMMITTEE ON INFECTIOUS DISEASES Management of Neonates Born at ≤34 6/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. *Pediatrics* **2018**, *142*, e20182896, doi:10.1542/peds.2018-2896.
28. Hollander, E.M.; van Tuinen, E.L.; Schölvinck, E.H.; Bergman, K.A.; Bourgonje, A.R.; Gracchi, V.; Kneyber, M.C.J.; Touw, D.J.; Mian, P. Evaluation of Dosing Guidelines for Gentamicin in Neonates and Children. *Antibiot. Basel Switz.* **2023**, *12*, 810, doi:10.3390/antibiotics12050810.
29. Attia Hussein Mahmoud, H.; Parekh, R.; Dhandibhotla, S.; Sai, T.; Pradhan, A.; Alugula, S.; Cevallos-Cueva, M.; Hayes, B.K.; Athanti, S.; Abdin, Z.; et al. Insight Into Neonatal Sepsis: An Overview. *Cureus* **2023**, *15*, e45530, doi:10.7759/cureus.45530.
30. Overview | Neonatal Infection: Antibiotics for Prevention and Treatment | Guidance | NICE Available online: https://www.nice.org.uk/guidance/ng195 (accessed on 3 December 2023).
31. Baldwin, C.M.; Lyseng-Williamson, K.A.; Keam, S.J. Meropenem: A Review of Its Use in the Treatment of Serious Bacterial Infections. *Drugs* **2008**, *68*, 803–838, doi:10.2165/00003495-200868060-00006.
32. Sullins, A.K.; Abdel-Rahman, S.M. Pharmacokinetics of Antibacterial Agents in the CSF of Children and Adolescents. *Paediatr. Drugs* **2013**, *15*, 93–117, doi:10.1007/s40272-013-0017-5.
33. Mukhopadhyay, S.; Sengupta, S.; Puopolo, K.M. Challenges and Opportunities for Antibiotic Stewardship Among Preterm Infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **2019**, *104*, F327–F332, doi:10.1136/archdischild-2018-315412.

34. Gerber, J.S.; Jackson, M.A.; Tamma, P.D.; Zaoutis, T.E.; COMMITTEE ON INFECTIOUS DISEASES, PEDIATRIC INFECTIOUS DISEASES SOCIETY Antibiotic Stewardship in Pediatrics. *Pediatrics* **2021**, *147*, e2020040295, doi:10.1542/peds.2020-040295.
35. Katz, S.; Banerjee, R.; Schwenk, H. Antibiotic Stewardship for the Neonatologist and Perinatologist. *Clin. Perinatol.* **2021**, *48*, 379–391, doi:10.1016/j.clp.2021.03.009.
36. Darlow, C.A.; da Costa, R.M.A.; Ellis, S.; Franceschi, F.; Sharland, M.; Piddock, L.; Das, S.; Hope, W. Potential Antibiotics for the Treatment of Neonatal Sepsis Caused by Multidrug-Resistant Bacteria. *Paediatr. Drugs* **2021**, *23*, 465–484, doi:10.1007/s40272-021-00465-z.
37. Li, G.; Bielicki, J.A.; Ahmed, A.S.M.N.U.; Islam, M.S.; Berezin, E.N.; Gallacci, C.B.; Guinsburg, R.; da Silva Figueiredo, C.E.; Santarone Vieira, R.; Silva, A.R.; et al. Towards Understanding Global Patterns of Antimicrobial Use and Resistance in Neonatal Sepsis: Insights from the NeoAMR Network. *Arch. Dis. Child.* **2020**, *105*, 26–31, doi:10.1136/archdischild-2019-316816.
38. Donà, D.; Sharland, M.; Heath, P.T.; Folgori, L. Strategic Trials to Define the Best Available Treatment for Neonatal and Pediatric Sepsis Caused by Carbapenem-Resistant Organisms. *Pediatr. Infect. Dis. J.* **2019**, *38*, 825–827, doi:10.1097/INF.0000000000002381.
39. Wattal, C.; Kler, N.; Oberoi, J.K.; Fursule, A.; Kumar, A.; Thakur, A. Neonatal Sepsis: Mortality and Morbidity in Neonatal Sepsis Due to Multidrug-Resistant (MDR) Organisms: Part 1. *Indian J. Pediatr.* **2020**, *87*, 117–121, doi:10.1007/s12098-019-03106-z.
40. Chiotos, K.; Hayes, M.; Gerber, J.S.; Tamma, P.D. Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Children. *J. Pediatr. Infect. Dis. Soc.* **2019**, *9*, 56–66, doi:10.1093/jpids/piz085.
41. Lutsar, I.; Chazallon, C.; Trafojer, U.; de Cabre, V.M.; Auriti, C.; Bertaina, C.; Calo Carducci, F.I.; Canpolat, F.E.; Esposito, S.; Fournier, I.; et al. Meropenem vs Standard of Care for Treatment of Neonatal Late Onset Sepsis (NeoMero1): A Randomised Controlled Trial. *PloS One* **2020**, *15*, e0229380, doi:10.1371/journal.pone.0229380.
42. Tamma, P.D.; Aitken, S.L.; Bonomo, R.A.; Mathers, A.J.; van Duin, D.; Clancy, C.J. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-Lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas Aeruginosa with Difficult-to-Treat Resistance (DTR-P. Aeruginosa). *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2022**, *75*, 187–212, doi:10.1093/cid/ciac268.
43. Chiusaroli, L.; Liberati, C.; Caseti, M.; Rulli, L.; Barbieri, E.; Giaquinto, C.; Donà, D. Therapeutic Options and Outcomes for the Treatment of Neonates and Preterms with Gram-Negative Multidrug-Resistant Bacteria: A Systematic Review. *Antibiot. Basel Switz.* **2022**, *11*, 1088, doi:10.3390/antibiotics11081088.
44. Smits, A.; Kulo, A.; van den Anker, J.; Allegaert, K. The Amikacin Research Program: A Stepwise Approach to Validate Dosing Regimens in Neonates. *Expert Opin. Drug Metab. Toxicol.* **2017**, *13*, 157–166, doi:10.1080/17425255.2017.1234606.
45. ANMF - Australasian Neonatal Medicines Formulary Available online: https://www.anmfonline.org/ (accessed on 22 April 2024).
46. Germovsek, E.; Lutsar, I.; Kipper, K.; Karlsson, M.O.; Planche, T.; Chazallon, C.; Meyer, L.; Trafojer, U.M.T.; Metsvaht, T.; Fournier, I.; et al. Plasma and CSF Pharmacokinetics of Meropenem in Neonates and Young Infants: Results from the NeoMero Studies. *J. Antimicrob. Chemother.* **2018**, *73*, 1908–1916, doi:10.1093/jac/dky128.
47. Smits, A.; De Cock, R.F.W.; Allegaert, K.; Vanhaesebrouck, S.; Danhof, M.; Knibbe, C. a. J. Prospective Evaluation of a Model-Based Dosing Regimen for Amikacin in Preterm and Term Neonates in Clinical Practice. *Antimicrob. Agents Chemother.* **2015**, *59*, 6344–6351, doi:10.1128/AAC.01157-15.
48. Research, C. for D.E. and NIH Funded Pediatric Labeling Changes for Drugs Studied under the 409i Process. *FDA* **2024**.
49. Hughes, K.M.; Johnson, P.N.; Anderson, M.P.; Sekar, K.C.; Welliver, R.C.; Miller, J.L. Comparison of Amikacin Pharmacokinetics in Neonates Following Implementation of a New Dosage Protocol. *J. Pediatr. Pharmacol. Ther. JPPT Off. J. PPAG* **2017**, *22*, 33–40, doi:10.5863/1551-6776-22.1.33.
50. Neeli, H.; Hanna, N.; Abduljalil, K.; Cusumano, J.; Taft, D.R. Application of Physiologically Based Pharmacokinetic-Pharmacodynamic Modeling in Preterm Neonates to Guide Gentamicin Dosing Decisions and Predict Antibacterial Effect. *J. Clin. Pharmacol.* **2021**, *61*, 1356–1365, doi:10.1002/jcph.1890.
51. Warris, A.; Pana, Z.-D.; Oletto, A.; Lundin, R.; Castagnola, E.; Lehrnbecher, T.; Groll, A.H.; Roilides, E. Etiology and Outcome of Candidemia in Neonates and Children in Europe. *Pediatr. Infect. Dis. J.* **2020**, *39*, 114–120, doi:10.1097/INF.0000000000002530.
52. Shane, A.L.; Stoll, B.J. Recent Developments and Current Issues in the Epidemiology, Diagnosis, and Management of Bacterial and Fungal Neonatal Sepsis. *Am. J. Perinatol.* **2013**, *30*, 131–141, doi:10.1055/s-0032-1333413.
53. Pana, Z.D.; Roilides, E.; Warris, A.; Groll, A.H.; Zaoutis, T. Epidemiology of Invasive Fungal Disease in Children. *J. Pediatr. Infect. Dis. Soc.* **2017**, *6*, S3–S11, doi:10.1093/jpids/pix046.

54. Kelly, M.S.; Benjamin, D.K.; Smith, P.B. The Epidemiology and Diagnosis of Invasive Candidiasis Among Premature Infants. *Clin. Perinatol.* **2015**, *42*, 105–117, doi:10.1016/j.clp.2014.10.008.
55. Kilpatrick, R.; Scarrow, E.; Hornik, C.; Greenberg, R.G. Neonatal Invasive Candidiasis: Updates on Clinical Management and Prevention. *Lancet Child Adolesc. Health* **2022**, *6*, 60–70, doi:10.1016/S2352-4642(21)00272-8.
56. Cook, A.; Ferreras-Antolin, L.; Adhisivam, B.; Ballot, D.; Berkley, J.A.; Bernaschi, P.; Carvalheiro, C.G.; Chaikittisuk, N.; Chen, Y.; Chibabhai, V.; et al. Neonatal Invasive Candidiasis in Low- and Middle-Income Countries: Data from the NeoOBS Study. *Med. Mycol.* **2023**, *61*, myad010, doi:10.1093/mmy/myad010.
57. Ting, J.Y.; Roberts, A.; Synnes, A.; Canning, R.; Bodani, J.; Monterossa, L.; Shah, P.S.; Canadian Neonatal Network Investigators Invasive Fungal Infections in Neonates in Canada: Epidemiology and Outcomes. *Pediatr. Infect. Dis. J.* **2018**, *37*, 1154–1159, doi:10.1097/INF.0000000000001968.
58. Aliaga, S.; Clark, R.H.; Laughon, M.; Walsh, T.J.; Hope, W.W.; Benjamin, D.K.; Kaufman, D.; Arrieta, A.; Benjamin, D.K.; Smith, P.B. Changes in the Incidence of Candidiasis in Neonatal Intensive Care Units. *Pediatrics* **2014**, *133*, 236–242, doi:10.1542/peds.2013-0671.
59. Steinbach, W.J.; Roilides, E.; Berman, D.; Hoffman, J.A.; Groll, A.H.; Bin-Hussain, I.; Palazzi, D.L.; Castagnola, E.; Halasa, N.; Velegraki, A.; et al. Results from a Prospective, International, Epidemiologic Study of Invasive Candidiasis in Children and Neonates. *Pediatr. Infect. Dis. J.* **2012**, *31*, 1252–1257, doi:10.1097/INF.0b013e3182737427.
60. Downes, K.J.; Fisher, B.T.; Zane, N.R. Administration and Dosing of Systemic Antifungal Agents in Pediatric Patients. *Paediatr. Drugs* **2020**, *22*, 165–188, doi:10.1007/s40272-020-00379-2.
61. Hornik, C.D.; Bondi, D.S.; Greene, N.M.; Cober, M.P.; John, B. Review of Fluconazole Treatment and Prophylaxis for Invasive Candidiasis in Neonates. *J. Pediatr. Pharmacol. Ther. JPPT Off. J. PPAG* **2021**, *26*, 115–122, doi:10.5863/1551-6776-26.2.115.
62. Ferreras-Antolin, L.; Bielicki, J.; Warris, A.; Sharland, M.; Hsia, Y.; GARPEC Network Global Divergence of Antifungal Prescribing Patterns: Data From the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children Surveys. *Pediatr. Infect. Dis. J.* **2021**, *40*, 327–332, doi:10.1097/INF.0000000000002983.
63. Ferreras-Antolín, L.; Irwin, A.; Atra, A.; Dermirjian, A.; Drysdale, S.B.; Emonts, M.; McMaster, P.; Paulus, S.; Patel, S.; Kinsey, S.; et al. Neonatal Antifungal Consumption Is Dominated by Prophylactic Use; Outcomes From The Pediatric Antifungal Stewardship: Optimizing Antifungal Prescription Study. *Pediatr. Infect. Dis. J.* **2019**, *38*, 1219–1223, doi:10.1097/INF.0000000000002463.
64. Pappas, P.G.; Kauffman, C.A.; Andes, D.R.; Clancy, C.J.; Marr, K.A.; Ostrosky-Zeichner, L.; Reboli, A.C.; Schuster, M.G.; Vazquez, J.A.; Walsh, T.J.; et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2016**, *62*, e1–e50, doi:10.1093/cid/civ933.
65. Hope, W.W.; Castagnola, E.; Groll, A.H.; Roilides, E.; Akova, M.; Arendrup, M.C.; Arikan-Akdagli, S.; Bassetti, M.; Bille, J.; Cornely, O.A.; et al. ESCMID* Guideline for the Diagnosis and Management of Candida Diseases 2012: Prevention and Management of Invasive Infections in Neonates and Children Caused by Candida Spp. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* **2012**, *18 Suppl 7*, 38–52, doi:10.1111/1469-0691.12040.
66. Ericson, J.E.; Kaufman, D.A.; Kicklighter, S.D.; Bhatia, J.; Testoni, D.; Gao, J.; Smith, P.B.; Prather, K.O.; Benjamin, D.K.; Fluconazole Prophylaxis Study Team on behalf of the Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committeea; et al. Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-Analysis Using Patient-Level Data. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2016**, *63*, 604–610, doi:10.1093/cid/ciw363.
67. Ascher, S.B.; Smith, P.B.; Watt, K.; Benjamin, D.K.; Cohen-Wolkowiez, M.; Clark, R.H.; Benjamin, D.K.; Moran, C. Antifungal Therapy and Outcomes in Infants with Invasive Candida Infections. *Pediatr. Infect. Dis. J.* **2012**, *31*, 439–443, doi:10.1097/INF.0b013e3182467a72.
68. Driessen, M.; Ellis, J.B.; Cooper, P.A.; Wainer, S.; Muwazi, F.; Hahn, D.; Gous, H.; De Villiers, F.P. Fluconazole vs. Amphotericin B for the Treatment of Neonatal Fungal Septicemia: A Prospective Randomized Trial. *Pediatr. Infect. Dis. J.* **1996**, *15*, 1107–1112, doi:10.1097/00006454-199612000-00011.
69. Andrew, E.C.; Curtis, N.; Coghlan, B.; Cranswick, N.; Gwee, A. Adverse Effects of Amphotericin B in Children; a Retrospective Comparison of Conventional and Liposomal Formulations. *Br. J. Clin. Pharmacol.* **2018**, *84*, 1006–1012, doi:10.1111/bcp.13521.
70. Le, J.; Adler-Shohet, F.C.; Nguyen, C.; Lieberman, J.M. Nephrotoxicity Associated with Amphotericin B Deoxycholate in Neonates. *Pediatr. Infect. Dis. J.* **2009**, *28*, 1061–1063, doi:10.1097/INF.0b013e3181af6201.
71. Cavassin, F.B.; Baú-Carneiro, J.L.; de Araújo Motta, F.; Ville, A.P.M.; Staszczak, L.; de Queiroz-Telles, F. Amphotericin B in Pediatrics: Analysis by Age Stratification Suggests a Greater Chance of Adverse Events from 13 Months of Age Onwards. *Paediatr. Drugs* **2022**, *24*, 513–528, doi:10.1007/s40272-022-00523-0.

72. Wade, K.C.; Benjamin, D.K.; Kaufman, D.A.; Ward, R.M.; Smith, P.B.; Jayaraman, B.; Adamson, P.C.; Gastonguay, M.R.; Barrett, J.S. Fluconazole Dosing for the Prevention or Treatment of Invasive Candidiasis in Young Infants. *Pediatr. Infect. Dis. J.* **2009**, *28*, 717–723, doi:10.1097/INF.0b013e31819f1f50.
73. Leroux, S.; Jacqz-Aigrain, E.; Elie, V.; Legrand, F.; Barin-Le Guellec, C.; Aurich, B.; Biran, V.; Dusang, B.; Goudjil, S.; Coopman, S.; et al. Pharmacokinetics and Safety of Fluconazole and Micafungin in Neonates with Systemic Candidiasis: A Randomized, Open-Label Clinical Trial. *Br. J. Clin. Pharmacol.* **2018**, *84*, 1989–1999, doi:10.1111/bcp.13628.
74. Piper, L.; Smith, P.B.; Hornik, C.P.; Cheifetz, I.M.; Barrett, J.S.; Moorthy, G.; Hope, W.W.; Wade, K.C.; Cohen-Wolkowiez, M.; Benjamin, D.K. Fluconazole Loading Dose Pharmacokinetics and Safety in Infants. *Pediatr. Infect. Dis. J.* **2011**, *30*, 375–378, doi:10.1097/INF.0b013e318202cbb3.
75. Gerhart, J.G.; Watt, K.M.; Edginton, A.; Wade, K.C.; Salerno, S.N.; Benjamin, D.K.; Smith, P.B.; Hornik, C.P.; Cohen-Wolkowiez, M.; Duara, S.; et al. Physiologically-Based Pharmacokinetic Modeling of Fluconazole Using Plasma and Cerebrospinal Fluid Samples From Preterm and Term Infants. *CPT Pharmacomet. Syst. Pharmacol.* **2019**, *8*, 500–510, doi:10.1002/psp4.12414.
76. Xie, J.; Zeng, J.; Zheng, S. The Efficacy and Safety of Fluconazole in Preventing Invasive Fungal Infection in Very Low Birth Weight Infants: A Systematic Review and Meta-Analysis. *Ital. J. Pediatr.* **2023**, *49*, 51, doi:10.1186/s13052-023-01460-5.
77. Austin, N.; McGuire, W. Prophylactic Systemic Antifungal Agents to Prevent Mortality and Morbidity in Very Low Birth Weight Infants. *Cochrane Database Syst. Rev.* **2013**, CD003850, doi:10.1002/14651858.CD003850.pub4.
78. Leonart, L.P.; Tonin, F.S.; Ferreira, V.L.; Tavares da Silva Penteado, S.; de Araújo Motta, F.; Pontarolo, R. Fluconazole Doses Used for Prophylaxis of Invasive Fungal Infection in Neonatal Intensive Care Units: A Network Meta-Analysis. *J. Pediatr.* **2017**, *185*, 129-135.e6, doi:10.1016/j.jpeds.2017.02.039.
79. Taormina, G.; Gopinath, R.; Moore, J.; Yasinskaya, Y.; Colangelo, P.; Reynolds, K.; Nambiar, S. A Regulatory Review Approach for Evaluation of Micafungin for Treatment of Neonatal Candidiasis. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2021**, *73*, 2335–2340, doi:10.1093/cid/ciab025.
80. Scott, B.L.; Hornik, C.D.; Zimmerman, K. Pharmacokinetic, Efficacy, and Safety Considerations for the Use of Antifungal Drugs in the Neonatal Population. *Expert Opin. Drug Metab. Toxicol.* **2020**, *16*, 605–616, doi:10.1080/17425255.2020.1773793.
81. Anand, K.J.; Carr, D.B. The Neuroanatomy, Neurophysiology, and Neurochemistry of Pain, Stress, and Analgesia in Newborns and Children. *Pediatr. Clin. North Am.* **1989**, *36*, 795–822, doi:10.1016/s0031-3955(16)36722-0.
82. Cruz, M.D.; Fernandes, A.M.; Oliveira, C.R. Epidemiology of Painful Procedures Performed in Neonates: A Systematic Review of Observational Studies. *Eur. J. Pain Lond. Engl.* **2016**, *20*, 489–498, doi:10.1002/ejp.757.
83. Cong, X.; Wu, J.; Vittner, D.; Xu, W.; Hussain, N.; Galvin, S.; Fitzsimons, M.; McGrath, J.M.; Henderson, W.A. The Impact of Cumulative Pain/Stress on Neurobehavioral Development of Preterm Infants in the NICU. *Early Hum. Dev.* **2017**, *108*, 9–16, doi:10.1016/j.earlhumdev.2017.03.003.
84. McPherson, C.; Miller, S.P.; El-Dib, M.; Massaro, A.N.; Inder, T.E. The Influence of Pain, Agitation, and Their Management on the Immature Brain. *Pediatr. Res.* **2020**, *88*, 168–175, doi:10.1038/s41390-019-0744-6.
85. COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE Prevention and Management of Procedural Pain in the Neonate: An Update. *Pediatrics* **2016**, *137*, e20154271, doi:10.1542/peds.2015-4271.
86. Harris, J.; Ramelet, A.-S.; van Dijk, M.; Pokorna, P.; Wielenga, J.; Tume, L.; Tibboel, D.; Ista, E. Clinical Recommendations for Pain, Sedation, Withdrawal and Delirium Assessment in Critically Ill Infants and Children: An ESPNIC Position Statement for Healthcare Professionals. *Intensive Care Med.* **2016**, *42*, 972–986, doi:10.1007/s00134-016-4344-1.
87. McPherson, C.; Grunau, R.E. Pharmacologic Analgesia and Sedation in Neonates. *Clin. Perinatol.* **2022**, *49*, 243–265, doi:10.1016/j.clp.2021.11.014.
88. Kinoshita, M.; Stempel, K.S.; Nascimento, I.J.B. do; Bruschettini, M. Systemic Opioids versus Other Analgesics and Sedatives for Postoperative Pain in Neonates. *Cochrane Database Syst. Rev.* **2023**, doi:10.1002/14651858.CD014876.pub2.
89. Donato, J.; Rao, K.; Lewis, T. Pharmacology of Common Analgesic and Sedative Drugs Used in the Neonatal Intensive Care Unit. *Clin. Perinatol.* **2019**, *46*, 673–692, doi:10.1016/j.clp.2019.08.004.
90. Kinoshita, M.; Olsson, E.; Borys, F.; Bruschettini, M. Opioids for Procedural Pain in Neonates. *Cochrane Database Syst. Rev.* **2023**, *6*, CD015056, doi:10.1002/14651858.CD015056.pub3.
91. Tang, F.; Ng, C.M.; Bada, H.S.; Leggas, M. Clinical Pharmacology and Dosing Regimen Optimization of Neonatal Opioid Withdrawal Syndrome Treatments. *Clin. Transl. Sci.* **2021**, *14*, 1231–1249, doi:10.1111/cts.12994.
92. Choonara, I.A.; McKay, P.; Hain, R.; Rane, A. Morphine Metabolism in Children. *Br. J. Clin. Pharmacol.* **1989**, *28*, 599–604, doi:10.1111/j.1365-2125.1989.tb03548.x.

93. Saarenmaa, E.; Huttunen, P.; Leppäluoto, J.; Meretoja, O.; Fellman, V. Advantages of Fentanyl over Morphine in Analgesia for Ventilated Newborn Infants after Birth: A Randomized Trial. *J. Pediatr.* **1999**, *134*, 144–150, doi:10.1016/s0022-3476(99)70407-5.
94. Anand, K.J.S.; Hall, R.W.; Desai, N.; Shephard, B.; Bergqvist, L.L.; Young, T.E.; Boyle, E.M.; Carbajal, R.; Bhutani, V.K.; Moore, M.B.; et al. Effects of Morphine Analgesia in Ventilated Preterm Neonates: Primary Outcomes from the NEOPAIN Randomised Trial. *Lancet Lond. Engl.* **2004**, *363*, 1673–1682, doi:10.1016/S0140-6736(04)16251-X.
95. Hartley, C.; Moultrie, F.; Hoskin, A.; Green, G.; Monk, V.; Bell, J.L.; King, A.R.; Buckle, M.; van der Vaart, M.; Gursul, D.; et al. Analgesic Efficacy and Safety of Morphine in the Procedural Pain in Premature Infants (Poppi) Study: Randomised Placebo-Controlled Trial. *Lancet Lond. Engl.* **2018**, *392*, 2595–2605, doi:10.1016/S0140-6736(18)31813-0.
96. Quinn, M.W.; Wild, J.; Dean, H.G.; Hartley, R.; Rushforth, J.A.; Puntis, J.W.; Levene, M.I. Randomised Double-Blind Controlled Trial of Effect of Morphine on Catecholamine Concentrations in Ventilated Pre-Term Babies. *Lancet Lond. Engl.* **1993**, *342*, 324–327, doi:10.1016/0140-6736(93)91472-x.
97. Chay, P.C.; Duffy, B.J.; Walker, J.S. Pharmacokinetic-Pharmacodynamic Relationships of Morphine in Neonates. *Clin. Pharmacol. Ther.* **1992**, *51*, 334–342, doi:10.1038/clpt.1992.30.
98. Anand, K.J.; Barton, B.A.; McIntosh, N.; Lagercrantz, H.; Pelausa, E.; Young, T.E.; Vasa, R. Analgesia and Sedation in Preterm Neonates Who Require Ventilatory Support: Results from the NOPAIN Trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch. Pediatr. Adolesc. Med.* **1999**, *153*, 331–338, doi:10.1001/archpedi.153.4.331.
99. Stathopoulou, T.; Agakidou, E.; Paschaloudis, C.; Kontou, A.; Chatzioannidis, I.; Sarafidis, K. Strong Association between Inotrope Administration and Intraventricular Hemorrhage, Gestational Age, and the Use of Fentanyl in Very Low Gestational Age Infants: A Retrospective Study. *Child. Basel Switz.* **2023**, *10*, 1667, doi:10.3390/children10101667.
100. Hall, R.W.; Kronsberg, S.S.; Barton, B.A.; Kaiser, J.R.; Anand, K.J.S.; NEOPAIN Trial Investigators Group Morphine, Hypotension, and Adverse Outcomes among Preterm Neonates: Who's to Blame? Secondary Results from the NEOPAIN Trial. *Pediatrics* **2005**, *115*, 1351–1359, doi:10.1542/peds.2004-1398.
101. Steinhorn, R.; McPherson, C.; Anderson, P.J.; Neil, J.; Doyle, L.W.; Inder, T. Neonatal Morphine Exposure in Very Preterm Infants-Cerebral Development and Outcomes. *J. Pediatr.* **2015**, *166*, 1200-1207.e4, doi:10.1016/j.jpeds.2015.02.012.
102. Robinson, S.; Gregory, G.A. Fentanyl-Air-Oxygen Anesthesia for Ligation of Patent Ductus Arteriosus in Preterm Infants. *Anesth. Analg.* **1981**, *60*, 331–334.
103. Ziesenitz, V.C.; Vaughns, J.D.; Koch, G.; Mikus, G.; van den Anker, J.N. Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review. *Clin. Pharmacokinet.* **2018**, *57*, 125–149, doi:10.1007/s40262-017-0569-6.
104. Roth, B.; Schlünder, C.; Houben, F.; Günther, M.; Theisohn, M. Analgesia and Sedation in Neonatal Intensive Care Using Fentanyl by Continuous Infusion. *Dev. Pharmacol. Ther.* **1991**, *17*, 121–127, doi:10.1159/000457510.
105. Völler, S.; Flint, R.B.; Andriessen, P.; Allegaert, K.; Zimmermann, L.J.I.; Liem, K.D.; Koch, B.C.P.; Simons, S.H.P.; Knibbe, C.A.J.; DINO study group Rapidly Maturing Fentanyl Clearance in Preterm Neonates. *Arch. Dis. Child. Fetal Neonatal Ed.* **2019**, *104*, F598–F603, doi:10.1136/archdischild-2018-315920.
106. Schofer, J.M. Premedication during Rapid Sequence Intubation: A Necessity or Waste of Valuable Time? *Calif. J. Emerg. Med.* **2006**, *7*, 75–79.
107. Mills, K.P.; Lean, R.E.; Smyser, C.D.; Inder, T.; Rogers, C.; McPherson, C.C. Fentanyl Exposure in Preterm Infants: Five-Year Neurodevelopmental and Socioemotional Assessment. *Front. Pain Res. Lausanne Switz.* **2022**, *3*, 836705, doi:10.3389/fpain.2022.836705.
108. Lammers, E.M.; Johnson, P.N.; Ernst, K.D.; Hagemann, T.M.; Lawrence, S.M.; Williams, P.K.; Anderson, M.P.; Miller, J.L. Association of Fentanyl with Neurodevelopmental Outcomes in Very-Low-Birth-Weight Infants. *Ann. Pharmacother.* **2014**, *48*, 335–342, doi:10.1177/1060028013514026.
109. Penido, M.G.; Garra, R.; Sammartino, M.; Silva, Y.P.E. Remifentanil in Neonatal Intensive Care and Anaesthesia Practice. *Acta Paediatr.* **2010**, *99*, 1454–1463, doi:10.1111/j.1651-2227.2010.01868.x.
110. Galinkin, J.L.; Davis, P.J.; McGowan, F.X.; Lynn, A.M.; Rabb, M.F.; Yaster, M.; Henson, L.G.; Blum, R.; Hechtman, D.; Maxwell, L.; et al. A Randomized Multicenter Study of Remifentanil Compared with Halothane in Neonates and Infants Undergoing Pyloromyotomy. II. Perioperative Breathing Patterns in Neonates and Infants with Pyloric Stenosis. *Anesth. Analg.* **2001**, *93*, 1387–1392, table of contents, doi:10.1097/00000539-200112000-00007.
111. Pereira e Silva, Y.; Gomez, R.S.; Marcatto, J. de O.; Maximo, T.A.; Barbosa, R.F.; Simões e Silva, A.C. Morphine versus Remifentanil for Intubating Preterm Neonates. *Arch. Dis. Child. Fetal Neonatal Ed.* **2007**, *92*, F293-294, doi:10.1136/adc.2006.105262.

112. de Kort, E.H.M.; Hanff, L.M.; Roofthooft, D.; Reiss, I.K.M.; Simons, S.H.P. Insufficient Sedation and Severe Side Effects after Fast Administration of Remifentanil during INSURE in Preterm Newborns. *Neonatology* **2017**, *111*, 172–176, doi:10.1159/000450536.
113. Giannantonio, C.; Sammartino, M.; Valente, E.; Cota, F.; Fioretti, M.; Papacci, P. Remifentanil Analgosedation in Preterm Newborns during Mechanical Ventilation. *Acta Paediatr. Oslo Nor. 1992* **2009**, *98*, 1111–1115, doi:10.1111/j.1651-2227.2009.01318.x.
114. Maroni, A.; Aubelle, M.-S.; Chollat, C. Fetal, Preterm, and Term Neonate Exposure to Remifentanil: A Systematic Review of Efficacy and Safety. *Paediatr. Drugs* **2023**, *25*, 537–555, doi:10.1007/s40272-023-00583-w.
115. Allegaert, K.; van den Anker, J.N. Perinatal and Neonatal Use of Paracetamol for Pain Relief. *Semin. Fetal. Neonatal Med.* **2017**, *22*, 308–313, doi:10.1016/j.siny.2017.07.006.
116. Cuzzolin, L.; Antonucci, R.; Fanos, V. Paracetamol (Acetaminophen) Efficacy and Safety in the Newborn. *Curr. Drug Metab.* **2013**, *14*, 178–185.
117. Anderson, B.J.; van Lingen, R.A.; Hansen, T.G.; Lin, Y.-C.; Holford, N.H.G. Acetaminophen Developmental Pharmacokinetics in Premature Neonates and Infants: A Pooled Population Analysis. *Anesthesiology* **2002**, *96*, 1336–1345, doi:10.1097/00000542-200206000-00012.
118. Mian, P.; Knibbe, C. a. J.; Calvier, E. a. M.; Tibboel, D.; Allegaert, K. Intravenous Paracetamol Dosing Guidelines for Pain Management in (Pre)Term Neonates Using the Paediatric Study Decision Tree. *Curr. Pharm. Des.* **2017**, *23*, 5839–5849, doi:10.2174/1381612823666170921143104.
119. Ceelie, I.; de Wildt, S.N.; van Dijk, M.; van den Berg, M.M.J.; van den Bosch, G.E.; Duivenvoorden, H.J.; de Leeuw, T.G.; Mathôt, R.; Knibbe, C.A.J.; Tibboel, D. Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery: A Randomized Controlled Trial. *JAMA* **2013**, *309*, 149–154, doi:10.1001/jama.2012.148050.
120. Ohlsson, A.; Shah, P.S. Paracetamol (Acetaminophen) for Prevention or Treatment of Pain in Newborns. *Cochrane Database Syst. Rev.* **2020**, *1*, CD011219, doi:10.1002/14651858.CD011219.pub4.
121. Pacifici, G.M. Clinical Pharmacology of Midazolam in Neonates and Children: Effect of Disease—A Review. *Int. J. Pediatr.* **2014**, *2014*, e309342, doi:10.1155/2014/309342.
122. Anand, K.J.S.; Eriksson, M.; Boyle, E.M.; Avila-Alvarez, A.; Andersen, R.D.; Sarafidis, K.; Polkki, T.; Matos, C.; Lago, P.; Papadouri, T.; et al. Assessment of Continuous Pain in Newborns Admitted to NICUs in 18 European Countries. *Acta Paediatr. Oslo Nor. 1992* **2017**, *106*, 1248–1259, doi:10.1111/apa.13810.
123. Hu, K.-C.; Chiu, N.-C.; Ho, C.-S.; Lee, S.-T.; Shen, E.-Y. Continuous Midazolam Infusion in the Treatment of Uncontrollable Neonatal Seizures. *Acta Paediatr. Taiwanica Taiwan Er Ke Yi Xue Hui Za Zhi* **2003**, *44*, 279–281.
124. Ancora, G.; Garetti, E.; Pirelli, A.; Merazzi, D.; Mastrocola, M.; Pierantoni, L.; Faldella, G.; Lago, P. Analgesic and Sedative Drugs in Newborns Requiring Respiratory Support. *J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet.* **2012**, *25 Suppl 4*, 88–90, doi:10.3109/14767058.2012.715036.
125. Ng, E.; Taddio, A.; Ohlsson, A. Intravenous Midazolam Infusion for Sedation of Infants in the Neonatal Intensive Care Unit. *Cochrane Database Syst. Rev.* **2017**, *2017*, CD002052, doi:10.1002/14651858.CD002052.pub3.
126. Zanos, P.; Moaddel, R.; Morris, P.J.; Riggs, L.M.; Highland, J.N.; Georgiou, P.; Pereira, E.F.R.; Albuquerque, E.X.; Thomas, C.J.; Zarate, C.A.; et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol. Rev.* **2018**, *70*, 621–660, doi:10.1124/pr.117.015198.
127. Hall, R.W. Anesthesia and Analgesia in the NICU. *Clin. Perinatol.* **2012**, *39*, 239–254, doi:10.1016/j.clp.2011.12.013.
128. Sanatkar, M.; Dastjani Farahani, A.; Bazvand, F. Ketamine Analgesia as an Alternative to General Anesthesia During Laser Treatment for Retinopathy of Prematurity. *J. Pediatr. Ophthalmol. Strabismus* **2022**, *59*, 416–421, doi:10.3928/01913913-20220225-01.
129. Madathil, S.; Thomas, D.; Chandra, P.; Agarwal, R.; Sankar, M.J.; Thukral, A.; Deorari, A. "NOPAIN-ROP" Trial: Intravenous Fentanyl and Intravenous Ketamine for Pain Relief during Laser Photocoagulation for Retinopathy of Prematurity (ROP) in Preterm Infants: A Randomised Trial. *BMJ Open* **2021**, *11*, e046235, doi:10.1136/bmjopen-2020-046235.
130. Huntsman, R.J.; Strueby, L.; Bingham, W. Are Ketamine Infusions a Viable Therapeutic Option for Refractory Neonatal Seizures? *Pediatr. Neurol.* **2020**, *103*, 8–11, doi:10.1016/j.pediatrneurol.2019.09.003.
131. Allegaert, K. The Clinical Pharmacology of Short Acting Analgo-Sedatives in Neonates. *Curr. Clin. Pharmacol.* **2011**, *6*, 222–226, doi:10.2174/157488411798375912.
132. de Kort, E.H.M.; Prins, S.A.; Reiss, I.K.M.; Willemsen, S.P.; Andriessen, P.; van Weissenbruch, M.M.; Simons, S.H.P. Propofol for Endotracheal Intubation in Neonates: A Dose-Finding Trial. *Arch. Dis. Child. Fetal Neonatal Ed.* **2020**, *105*, 489–495, doi:10.1136/archdischild-2019-318474.

133. de Kort, E.H.M.; Twisk, J.W.R.; van t Verlaat, E.P.G.; Reiss, I.K.M.; Simons, S.H.P.; van Weissenbruch, M.M. Propofol in Neonates Causes a Dose-dependent Profound and Protracted Decrease in Blood Pressure. *Acta Paediatr. Oslo Nor. 1992* **2020**, *109*, 2539–2546, doi:10.1111/apa.15282.
134. Shah, P.S.; Shah, V.S. Propofol for Procedural Sedation/Anaesthesia in Neonates. *Cochrane Database Syst. Rev.* **2011**, CD007248, doi:10.1002/14651858.CD007248.pub2.
135. Hayden, J.C.; Breatnach, C.; Doherty, D.R.; Healy, M.; Howlett, M.M.; Gallagher, P.J.; Cousins, G. Efficacy of A2-Agonists for Sedation in Pediatric Critical Care: A Systematic Review. *Pediatr. Crit. Care Med. J. Soc. Crit. Care Med. World Fed. Pediatr. Intensive Crit. Care Soc.* **2016**, *17*, e66-75, doi:10.1097/PCC.0000000000000599.
136. Romantsik, O.; Calevo, M.G.; Norman, E.; Bruschettini, M. Clonidine for Sedation and Analgesia for Neonates Receiving Mechanical Ventilation. *Cochrane Database Syst. Rev.* **2017**, *2017*, CD012468, doi:10.1002/14651858.CD012468.pub2.
137. Romantsik, O.; Calevo, M.G.; Norman, E.; Bruschettini, M. Clonidine for Pain in Non-Ventilated Infants. *Cochrane Database Syst. Rev.* **2020**, *4*, CD013104, doi:10.1002/14651858.CD013104.pub2.
138. Ghazanfarpour, M.; Najafi, M.N.; Roozbeh, N.; Mashhadi, M.E.; Keramat-roudi, A.; Mégarbane, B.; Tsatsakis, A.; Moghaddam, M.M.M.; Rezaee, R. Therapeutic Approaches for Neonatal Abstinence Syndrome: A Systematic Review of Randomized Clinical Trials. *DARU J. Pharm. Sci.* **2019**, *27*, 423–431, doi:10.1007/s40199-019-00266-3.
139. Portelli, K.; Kandraju, H.; Ryu, M.; Shah, P.S. Efficacy and Safety of Dexmedetomidine for Analgesia and Sedation in Neonates: A Systematic Review. *J. Perinatol. Off. J. Calif. Perinat. Assoc.* **2023**, doi:10.1038/s41372-023-01802-5.
140. O'Mara, K.; Weiss, M.D. Dexmedetomidine for Sedation of Neonates with HIE Undergoing Therapeutic Hypothermia: A Single-Center Experience. *AJP Rep.* **2018**, *8*, e168–e173, doi:10.1055/s-0038-1669938.
141. Paris, A.; Mantz, J.; Tonner, P.H.; Hein, L.; Brede, M.; Gressens, P. The Effects of Dexmedetomidine on Perinatal Excitotoxic Brain Injury Are Mediated by the alpha2A-Adrenoceptor Subtype. *Anesth. Analg.* **2006**, *102*, 456–461, doi:10.1213/01.ane.0000194301.79118.e9.
142. Bäcke, P.; Bruschettini, M.; Sibrecht, G.; Thernström Blomqvist, Y.; Olsson, E. Pharmacological Interventions for Pain and Sedation Management in Newborn Infants Undergoing Therapeutic Hypothermia. *Cochrane Database Syst. Rev.* **2022**, *11*, CD015023, doi:10.1002/14651858.CD015023.pub2.
143. Dersch-Mills, D.A.; Banasch, H.L.; Yusuf, K.; Howlett, A. Dexmedetomidine Use in a Tertiary Care NICU: A Descriptive Study. *Ann. Pharmacother.* **2019**, *53*, 464–470, doi:10.1177/1060028018812089.
144. Allegaert, K. A Critical Review on the Relevance of Paracetamol for Procedural Pain Management in Neonates. *Front. Pediatr.* **2020**, *8*, 89, doi:10.3389/fped.2020.00089.
145. Glass, H.C.; Shellhaas, R.A.; Wusthoff, C.J.; Chang, T.; Abend, N.S.; Chu, C.J.; Cilio, M.R.; Glidden, D.V.; Bonifacio, S.L.; Massey, S.; et al. Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study. *J. Pediatr.* **2016**, *174*, 98-103.e1, doi:10.1016/j.jpeds.2016.03.035.
146. Mruk, A.L.; Garlitz, K.L.; Leung, N.R. Levetiracetam in Neonatal Seizures: A Review. *J. Pediatr. Pharmacol. Ther. JPPT* **2015**, *20*, 76–89, doi:10.5863/1551-6776-20.2.76.
147. Slaughter, L.A.; Patel, A.D.; Slaughter, J.L. Pharmacological Treatment of Neonatal Seizures: A Systematic Review. *J. Child Neurol.* **2013**, *28*, 351–364, doi:10.1177/0883073812470734.
148. Pressler, R.M.; Lagae, L. Why We Urgently Need Improved Seizure and Epilepsy Therapies for Children and Neonates. *Neuropharmacology* **2020**, *170*, 107854, doi:10.1016/j.neuropharm.2019.107854.
149. Pressler, R.M.; Abend, N.S.; Auvin, S.; Boylan, G.; Brigo, F.; Cilio, M.R.; De Vries, L.S.; Elia, M.; Espeche, A.; Hahn, C.D.; et al. Treatment of Seizures in the Neonate: Guidelines and Consensus-Based Recommendations-Special Report from the ILAE Task Force on Neonatal Seizures. *Epilepsia* **2023**, *64*, 2550–2570, doi:10.1111/epi.17745.
150. Acar, D.B.; Bulbul, A.; Uslu, S. Current Overview of Neonatal Convulsions. *Sisli Etfal Hastan. Tip Bul.* **2019**, *53*, 1–6, doi:10.14744/SEMB.2018.22844.
151. Donovan, M.D.; Griffin, B.T.; Kharoshankaya, L.; Cryan, J.F.; Boylan, G.B. Pharmacotherapy for Neonatal Seizures: Current Knowledge and Future Perspectives. *Drugs* **2016**, *76*, 647–661, doi:10.1007/s40265-016-0554-7.
152. Ziobro, J.M.; Eschbach, K.; Shellhaas, R.A. Novel Therapeutics for Neonatal Seizures. *Neurother. J. Am. Soc. Exp. Neurother.* **2021**, *18*, 1564–1581, doi:10.1007/s13311-021-01085-8.
153. Gowda, V.K.; Romana, A.; Shivanna, N.H.; Benakappa, N.; Benakappa, A. Levetiracetam versus Phenobarbitone in Neonatal Seizures - A Randomized Controlled Trial. *Indian Pediatr.* **2019**, *56*, 643–646.
154. Rosen, D.A.; Rosen, K.R. Intravenous Conscious Sedation with Midazolam in Paediatric Patients. *Int. J. Clin. Pract.* **1998**, *52*, 46–50.
155. Castro Conde, J.R.; Hernández Borges, A.A.; Doménech Martínez, E.; González Campo, C.; Perera Soler, R. Midazolam in Neonatal Seizures with No Response to Phenobarbital. *Neurology* **2005**, *64*, 876–879, doi:10.1212/01.WNL.0000152891.58694.71.

156. Filippi, L.; Fiorini, P.; Daniotti, M.; Catarzi, S.; Savelli, S.; Fonda, C.; Bartalena, L.; Boldrini, A.; Giampietri, M.; Scaramuzzo, R.; et al. Safety and Efficacy of Topiramate in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia (NeoNATI). *BMC Pediatr.* **2012**, *12*, 144, doi:10.1186/1471-2431-12-144.
157. Filippi, L.; la Marca, G.; Fiorini, P.; Poggi, C.; Cavallaro, G.; Malvagia, S.; Pellegrini-Giampietro, D.E.; Guerrini, R. Topiramate Concentrations in Neonates Treated with Prolonged Whole Body Hypothermia for Hypoxic Ischemic Encephalopathy. *Epilepsia* **2009**, *50*, 2355–2361, doi:10.1111/j.1528-1167.2009.02302.x.
158. Patsalos, P.N.; Berry, D.J.; Bourgeois, B.F.D.; Cloyd, J.C.; Glauser, T.A.; Johannessen, S.I.; Leppik, I.E.; Tomson, T.; Perucca, E. Antiepileptic Drugs--Best Practice Guidelines for Therapeutic Drug Monitoring: A Position Paper by the Subcommission on Therapeutic Drug Monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* **2008**, *49*, 1239–1276, doi:10.1111/j.1528-1167.2008.01561.x.
159. Marques, M.R.; Garcia-Robles, A.; Usach, I.; Vento, M.; Poveda, J.L.; Peris, J.E.; Mangas-Sanjuan, V. Topiramate Pharmacokinetics in Neonates Undergoing Therapeutic Hypothermia and Proposal of an Optimised Dosing Schedule. *Acta Paediatr. Oslo Nor. 1992* **2020**, *109*, 300–308, doi:10.1111/apa.14944.
160. Moffett, B.S.; Weingarten, M.M.; Galati, M.; Placencia, J.L.; Rodman, E.A.; Riviello, J.J.; Kayyal, S.Y. Phenobarbital Population Pharmacokinetics across the Pediatric Age Spectrum. *Epilepsia* **2018**, *59*, 1327–1333, doi:10.1111/epi.14447.
161. Bittigau, P.; Sifringer, M.; Genz, K.; Reith, E.; Pospischil, D.; Govindarajalu, S.; Dzietko, M.; Pesditschek, S.; Mai, I.; Dikranian, K.; et al. Antiepileptic Drugs and Apoptotic Neurodegeneration in the Developing Brain. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 15089–15094, doi:10.1073/pnas.222550499.
162. Pressler, R.M.; Abend, N.S.; Auvin, S.; Boylan, G.; Brigo, F.; Cilio, M.R.; De Vries, L.S.; Elia, M.; Espeche, A.; Hahn, C.D.; et al. Treatment of Seizures in the Neonate: Guidelines and Consensus-Based Recommendations-Special Report from the ILAE Task Force on Neonatal Seizures. *Epilepsia* **2023**, *64*, 2550–2570, doi:10.1111/epi.17745.
163. Ahmad, K.A.; Desai, S.J.; Bennett, M.M.; Ahmad, S.F.; Ng, Y.-T.; Clark, R.H.; Tolia, V.N. Changing Antiepileptic Drug Use for Seizures in US Neonatal Intensive Care Units from 2005 to 2014. *J. Perinatol. Off. J. Calif. Perinat. Assoc.* **2017**, *37*, 296–300, doi:10.1038/jp.2016.206.
164. Painter, M.J.; Scher, M.S.; Stein, A.D.; Armatti, S.; Wang, Z.; Gardiner, J.C.; Paneth, N.; Minnigh, B.; Alvin, J. Phenobarbital Compared with Phenytoin for the Treatment of Neonatal Seizures. *N. Engl. J. Med.* **1999**, *341*, 485–489, doi:10.1056/NEJM199908123410704.
165. Alix, V.; James, M.; Jackson, A.H.; Visintainer, P.F.; Singh, R. Efficacy of Fosphenytoin as First-Line Antiseizure Medication for Neonatal Seizures Compared to Phenobarbital. *J. Child Neurol.* **2021**, *36*, 30–37, doi:10.1177/0883073820947514.
166. Abiramalatha, T.; Thanigainathan, S.; Ramaswamy, V.V.; Pressler, R.; Brigo, F.; Hartmann, H. Anti-Seizure Medications for Neonates with Seizures. *Cochrane Database Syst. Rev.* **2023**, *10*, CD014967, doi:10.1002/14651858.CD014967.pub2.
167. Abend, N.S.; Gutierrez-Colina, A.M.; Monk, H.M.; Dlugos, D.J.; Clancy, R.R. Levetiracetam for Treatment of Neonatal Seizures. *J. Child Neurol.* **2011**, *26*, 465–470, doi:10.1177/0883073810384263.
168. Khan, O.; Chang, E.; Cipriani, C.; Wright, C.; Crisp, E.; Kirmani, B. Use of Intravenous Levetiracetam for Management of Acute Seizures in Neonates. *Pediatr. Neurol.* **2011**, *44*, 265–269, doi:10.1016/j.pediatrneurol.2010.11.005.
169. Sharpe, C.; Reiner, G.E.; Davis, S.L.; Nespeca, M.; Gold, J.J.; Rasmussen, M.; Kuperman, R.; Harbert, M.J.; Michelson, D.; Joe, P.; et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. *Pediatrics* **2020**, *145*, e20193182, doi:10.1542/peds.2019-3182.
170. Kilicdag, H.; Daglıoglu, K.; Erdogan, S.; Guzel, A.; Sencar, L.; Polat, S.; Zorludemir, S. The Effect of Levetiracetam on Neuronal Apoptosis in Neonatal Rat Model of Hypoxic Ischemic Brain Injury. *Early Hum. Dev.* **2013**, *89*, 355–360, doi:10.1016/j.earlhumdev.2012.12.002.
171. Verwoerd, C.; Limjoco, J.; Rajamanickam, V.; Knox, A. Efficacy of Levetiracetam and Phenobarbital as First-Line Treatment for Neonatal Seizures. *J. Child Neurol.* **2022**, *37*, 401–409, doi:10.1177/08830738221086107.
172. Venkatesan, C.; Young, S.; Schapiro, M.; Thomas, C. Levetiracetam for the Treatment of Seizures in Neonatal Hypoxic Ischemic Encephalopathy. *J. Child Neurol.* **2017**, *32*, 210–214, doi:10.1177/0883073816678102.
173. Yamamoto, H.; Aihara, M.; Niijima, S.; Yamanouchi, H. Treatments with Midazolam and Lidocaine for Status Epilepticus in Neonates. *Brain Dev.* **2007**, *29*, 559–564, doi:10.1016/j.braindev.2007.02.003.
174. Shany, E.; Benzaqen, O.; Watemberg, N. Comparison of Continuous Drip of Midazolam or Lidocaine in the Treatment of Intractable Neonatal Seizures. *J. Child Neurol.* **2007**, *22*, 255–259, doi:10.1177/0883073807299858.
175. Ji, D.; Karlik, J. Neurotoxic Impact of Individual Anesthetic Agents on the Developing Brain. *Children* **2022**, *9*, 1779, doi:10.3390/children9111779.
176. Guerrini, R.; Parmeggiani, L. Topiramate and Its Clinical Applications in Epilepsy. *Expert Opin. Pharmacother.* **2006**, *7*, 811–823, doi:10.1517/14656566.7.6.811.

 doi:10.20944/preprints202405.0151.v1

177. Filippi, L.; Fiorini, P.; Catarzi, S.; Berti, E.; Padrini, L.; Landucci, E.; Donzelli, G.; Bartalena, L.; Fiorentini, E.; Boldrini, A.; et al. Safety and Efficacy of Topiramate in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia (NeoNATI): A Feasibility Study. *J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet.* **2018**, *31*, 973–980, doi:10.1080/14767058.2017.1304536.
178. Lewis, T.; Wade, K.C.; Davis, J.M. Challenges and Opportunities for Improving Access to Approved Neonatal Drugs and Devices. *J. Perinatol. Off. J. Calif. Perinat. Assoc.* **2022**, *42*, 825–828, doi:10.1038/s41372-021-01304-2.