Uso de Antibióticos y Resistencia Antimicrobiana en la Unidad de Cuidado Intensivo Neonatal

Use of antibiotics and antimicrobial resistance in the Neonatal Intensive Care Unit

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Abstract

Neonatal sepsis constitutes one of the main causes of neonatal mortality in developing countries. Newborns, particularly premature newborns, have a higher risk of bacterial infections that result in frequent administration of antibiotics in the Neonatal Intensive Care Units (NICU), which is estimated to be as high as 70%. The clinical presentation of neonatal sepsis is non-specific, prompting the early use of empirical antibiotic prescription to avoid adverse consequences in the patients. Its non-specificity characterizes it as a challenging diagnostic, this aspect led several authors to design strategies to determine which newborns are true candidates for antimicrobial therapy.

Microbiology is closely linked to clinical practice. Thus, knowing the most frequent bacteria associated with neonatal sepsis will be closely related to the antibiotic spectrum that should be used to treat it. Furthermore, knowledge on basic pharmacology is key inasmuch as the antimicrobial treatment is not innocuous and can be related to an increase in mortality and morbidity. Clinical course and maternal risk factors are associated with the expected responsible germs that are already described in multiple descriptive studies worldwide.

Indiscriminate use of broad-spectrum antibiotics for the management of newborn infections is leading to antibiotic resistance increase. At the same

time, this is related to even higher rates of therapeutic failure with empiric antimicrobial treatment. Based on this, Antimicrobial Stewardship Programs play a determinant role to monitor the changes in local resistance to adjust and homogenize medical practice to regulate the use of antibiotics and mitigate the emergent and threatening antimicrobial bacterial resistance.

Key words: Drug resistance, microbial, neonatology, antimicrobial stewardship, intensive care, neonatal, antibacterial agents.

Introduction

Neonatal sepsis is one of the leading causes of neonatal mortality in developing countries (1) with data that estimates more than one million deaths worldwide each year (2). Approximately 7 cases are reported per 1,000 live births (LB), which increases to 162 cases per 1,000 LB in those newborns with very low birth weight (<1,500 gr) (3).

Newborns, particularly premature newborns, have a higher risk of bacterial infections, so antibiotic management is the most common therapy in NICUs, which is estimated to be as high as 70% (2,4). In addition, the clinical presentation of neonatal sepsis is nonspecific on many occasions, which means that empirical antibiotic therapy is started early to avoid harmful consequences for patients (2,4).

Among the events related to the use of antibiotics in newborns are the alteration of intestinal colonization, the increased risk of colonization by *Candida* and subsequent invasive candidiasis and increased risk of death (2). In addition, there is an increased risk of necrotizing enterocolitis, death, and late onset sepsis with prolonged duration of antibiotics, so antibiotic therapy is not exempt from serious adverse effects in negative culture scenarios. In fact, more than 95% of newborns in the NICU receive empirical antibiotics, but only 1-5% have initial positive blood cultures (4).

The indiscriminate use of broad-spectrum antibiotics for the management of infections in newborns over the years has generated an increase in antibiotic resistance, which in turn leads to higher rates of therapeutic failure with the use of empirical antibiotic therapies. Due to the above, the Antimicrobial Stewardship Programs play a decisive role in monitoring the change in resistance at the local level to adjust and standardize medical practice that can regulate the use of antibiotics and mitigate the emerging bacterial resistance.

Search strategy

The purpose of this document is to review the use of antibiotics in the Neonatal Intensive Care Unit, the role that the Antimicrobial Stewardship

Programs can have and the impact of antibiotic resistance due to their excessive and inappropriate use; additionally, this review will be used as an academic reference for consultation regarding the pharmacological basis of the most commonly used antibiotics in the NICU, with the addition of a proposal for an antibiogram interpretation algorithm that is useful in clinical practice. Therefore, a literature search was conducted between September 20 and September 26, 2020, in order to identify articles whose results were related to antimicrobial resistance in the NICU, surveillance programs for the use of antibiotics and pharmacological schemes frequently used in the NICU. This search was conducted in MEDLINE / PUBMED, SCIENCEDIRECT, Clinical and Laboratory Standards Institute (CLSI), Center for Disease Control (CDC), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the Infectious Diseases Society of America (IDSA) using the Medical Subject Headings (MeSH) "Intensive care, Neonatal", "Antibiotic use", "Drug Resistance" and "Antimicrobial Stewardship", in the different combinations allowed.

The articles analyzed were chosen between 2010-2020, if an older article had content of great relevance to the subject review, an exception would be made. After reading the abstracts of the available articles, the full text of potentially eligible articles was obtained for a full reading. Of those relevant articles, a review of the references was carried out to identify more articles that were useful to us. The inclusion criteria were human-related articles, descriptive observational studies, topic reviews, and official society statements. Those articles that had duplicate information due to sharing results with other studies and those that by consensus did not contribute to the purpose of this topic review were excluded. A total of 89 articles were considered for reading, of which 62 were used for the development of this document.

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Results

1. Commonly used antibiotic regimens and reason for use in the Neonatal Care Unit NICU

According to the age of onset, neonatal sepsis can be divided into Early Onset Sepsis (EOS) that is characterized by the appearance of clinical manifestations in the first 72 hours of life (5); or Late Onset Sepsis (LOS) which occurs between 72 hours and 7 days of life in term newborns (6). This time of onset of symptoms, together with an adequate medical history and a complete physical examination play a fundamental role in the choice of the appropriate antibiotic (7).

Given the potential negative outcomes associated with neonatal sepsis (8), the antibiotics used to treat this entity usually include beta-lactams such as ampicillin, oxacillin, cefotaxime, piperacillin-tazobactam, and meropenem. Additionally, glycopeptides such as vancomycin and aminoglycosides are also included. Empirical antibiotic therapy should be guided by local resistance patterns, and the most common microorganisms present in each NICU (9).

Currently, the first-line antibiotic therapy recommended for the management of EOS is the use of ampicillin combined with an aminoglycoside, generally a gentamicin, since it covers the most common microorganisms such as *Escherichia coli* and Group B Beta-hemolytic *Streptococcus* (GBS), which are predominant in this age group (10). However, due to the increase of Gram-negative bacilli (GNB) producing extended-spectrum beta-lactamases (ESBL) in this population (11), close monitoring of local susceptibility patterns is required.

An additional advantage of the ampicillin plus gentamicin scheme is the synergistic effect observed in animal and laboratory models for coverage of *Listeria monocytogenes*, which is a pathogen that can cause pathology in this age group and in immunosuppressed patients (12). If meningitis is suspected, cefotaxime can be added as an empirical agent, since ceftriaxone, given the high protein binding in newborns, is not recommended due to the high risk of acute bilirubin encephalopathy and the risk of lactic acidosis (13). Another alternative for initial empirical management has been proposed that

«The use of cephalosporins in this type of patients does not provide any benefit in the antimicrobial spectrum over the combination of other beta-lactams and aminoglycosides.»

includes the combination of ampicillin and cefotaxime. However, there is evidence that in EOS this combination leads to greater resistance by Gram Negative bacteria in NICUs (14,15).

Regarding patients with LOS, different studies have shown that most isolated organisms in this population are susceptible to gentamicin plus flucloxacillin, and gentamicin plus amoxicillin (16). Coagulase Negative *Staphylococcus* (CNS) represents more than 50% of the isolates in this type of patients, but its true contribution to sepsis is not clearly defined since it is not easy to determine if it is a contaminating agent or a true pathogen. CNSs are low virulence organisms that typically cause silent disease, with fulminant sepsis in less than 1% of the cases (17). There is insufficient evidence of the benefit of administering empirical vancomycin for LOS, so its use as a second line or in those patients with a microorganism susceptible to this antibiotic (18) is recommended. The use of cephalosporins in this type of patients does not provide any benefit in the antimicrobial spectrum over the combination of other beta-lactams and aminoglycosides (19). In table 1. we summarize the clinical conditions, etiological agents, treatment of choice, and treatment lengths at which the clinician can be found in the NICU (20).

Tabl2 1. Use of Antibiotics and Antimicrobial Resistance in the Neonatal Intensive Care Unit

Clinical condition	Etiological agents	*Treatment of choice	Treatment length
Early-onset sepsis	- *GBS* - *E. coli* - *Lysteria monocytogenes* - *Other Gram-negative bacteria: Klebsiella, Enterobacter, Citrobacter, Acinetobacter, and Pseudomonas*	Ampicillin + Aminoglycoside	10-14 days
Late-onset sepsis	- *Coagulase-negative Staphylococcus* - *E. Coli* - *S. aureus* - *GBS*	Ampicillin + Aminoglycoside or Cefotaxime	10-14 days
Meningitis	**Early start** - *GBS* - *E. Coli* **Late start** - *Coagulase-negative Staphylococcus* - *Gram-negative bacilli*	3rd generation cephalosporins: cefotaxime	14-21 days
Pneumonia	- *GBS* - *S. pneumoniae* - *Nontypeable H. influenzae* - *S. aureus* - *E. coli*, - *Klebsiella*	Empirical: Ampicillin + Aminoglycoside Consider additional Vancomycin to cover MRSA	7-10 days to uncomplicated Pneumonia
Urinary tract infection	- *E. Coli* - *Other Enterobacteria: Klebsiella,* - *Enterobacter, Proteus, Citrobacter, Salmonella and Serratia.*	Empirical: Ampicillin + Aminoglycoside Hospitalized patients with late-onset infections: Vancomycin + Aminoglycoside to cover CNS and MRSA	7-14 days
Osteomyelitis and septic arthritis	- *S. aureus* - *E. coli* - *GBS*	Vancomycin + Aminoglycoside or 3rd generation Cephalosporin.	4-6 weeks 8 weeks for MRSA osteomyelitis
Conjunctivitis of the newborn.	- *S. aureus* - *Nontypeable H. influenzae* - *S. pneumoniae* - *Enteric gram-negative bacilli* - *GBS* - *N. gonorrhoeae* - *Chlamydia trachomatis* - *Herpes simplex virus*	Ointment or solution topical antibiotic	7-10 days N. gonorrhoeae: Single dose of IM o IV Ceftriaxone. Chlamydia: Oral erythromycin for 14 days or azithromycin for 3 days.
Omphalitis	- *S. aureus* - *Group A Streptococcus* - *GBS* - *Gram-negative bacilli: including E. coli, Klebsiella and Pseudomonas*	Antistaphylococcal penicillin + Aminoglycoside. If high prevalence of MRSA: Vancomycin instead of antistaphylococcal penicillin.	10 days

*Antibiotic treatment schemes in neonatal infections (20). GBS: Group B Beta-hemolytic Streptococcus, MRSA: Methicillin-resistant Staphylococcus aureus, CNS: Coagulase Negative Staphylococcus..

2. Antibiotics pharmacology used in the NICU

The most commonly used antibiotics in the Neonatal Care Unit are grouped into three major groups: a) beta-lactams; b) aminoglycosides; c) glycopeptides. Each group is presented below, and the mechanism of action is described:

A. Beta-lactams:

a Penicillins:

- Aminopenicillins: ampicillin, amoxicillin
- Isoxazolylpenicillins: oxacillin
- Ureidopenicillins: piperacillin

b Cephalosporins:

- 1st generation: cephalexin, cefazolin, cephalothin
- 3rd generation: cefotaxime
- 4th generation: cefepime

c Carbapenems:

- Meropenem
- Imipenem

Action Mechanism: bactericidal agents that act by inhibiting the synthesis of the bacterial cell wall by inhibiting transpeptidation in the final stages of the synthesis of peptidoglycan, an essential polymer for the bacterial wall. This alteration produces the activation of autolytic enzymes that cause the destruction of the bacteria. Due to their mode of action, they always act in the cellular reproduction phase, so they are not effective against latent forms or against organisms that do not have a bacterial wall (21,22).

B. Aminoglycosides

- Gentamicin
- Amikacin

Action Mechanism: Once in the cytoplasm, they bind to the 16s RNA at the 30s ribosomal subunit, altering the translation of the mRNA and therefore leading to the formation of truncated or non-functional proteins (23).

The mechanism of the bactericidal activity of gentamicin has not yet been fully elucidated, but it is proposed that the truncated proteins are placed in the cell wall, compromising the permeability of the membrane. Others also suggest that the accumulation of reactive oxygen species can lead to bacterial death (23).

B. Glycopeptides

- Vancomycin

Action Mechanism: exerts its bactericidal effect by inhibiting the polymerization of peptidoglycans in the bacterial wall. This binds to D-alanyl D-alanine thus preventing the synthesis and polymerization of N-Acetylmuramic and N-Acetylglucosamine within the peptidoglycan layer. This inhibition weakens the bacterial cell walls and ultimately causes the leakage of intracellular components, resulting in the death of Gram-positive bacterial cells (24).

3. Most frequent germs in the UCIN

The most common pathogenic microorganisms in cases of neonatal sepsis in general are: *Klebsiella spp*, *methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Staphylococcus spp*, *Neisseria meningitidis*, *Streptococcus spp and E. coli* (1,3). GNB account for almost half of all blood cultures from newborns (1,3) .

EOS is caused in 43% by GBS, followed by E. coli in 29% (2). On the other hand, LOS is caused in 70% by Gram-positive microorganisms, mainly by CNS (48%) and S. aureus (8%). Although LOS due to GNB is less frequent (23%), it is associated with higher mortality (19-36%) (2,4).

In a study carried out in Mexico with patients who had EOS and LOS, it was found that the most frequent bacteria in EOS are Enterobacteria (67.6%) and Streptococcus spp. (17.6%) (25). In the case of LOS, Enterobacteria also occupied the first place (44.9%), with Klebsiella pneumoniae by being the most common microorganism, followed by Staphylococcus spp. (34.7%). Of the isolated nosocomial enterobacteria, 40% were found to be ESBL producers (25). Similar findings have been found in other studies (26).

Dharmapalan et al. reported in their work that approximately half of the isolates of *S. aureus* were *methicillin-resistant*, and in the case of Gram-negative germs, high rates of resistance were reported for ampicillin, gentamicin, and cefotaxime in *K. pneumoniae* and *E. coli* (27).

4. Most frequent NICU germs resistance can develop to the most frequently used antibiotics

Antibiotic resistance can be generated by inappropriate treatment durations, an insufficient antibiotic concentration at the site of infection, the use of poor-quality antibiotics, or misuse / overuse (28). The increase in antibiotic resistance in both Gram-negative and Gram-positive pathogens involved in infections of newborns hospitalized in the NICU, generates limitations and difficulties in the proper management of these patients, which leads to an increase in the neonatal morbidity and mortality (1,28).

a. Gram-Negative Bacilli

Among the most common cultivated species of GNB *are Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*.

In Latin America, Klebsiella spp., *Escherichia coli*, and *P. aeruginosa* are the most frequently isolated germs in the neonatal population. General infection rates in NICU and pediatric ICU are of concern, which are higher in Latin America compared to developed countries (5-36% vs 6-15%). In addition, one third of NICU patients die, with a higher incidence in low birth weight newborns and those with GNB infections (29).

These pathogens are often resistant to at least one class of antibiotics used as standard in the treatment of newborns, including beta-lactams and aminoglycosides. Among the mechanisms of resistance expressed are the production of enzymes that inactivate or alter the target site of the antibiotic (e.g., beta-lactamases, carbapenems, aminoglycoside-modifying enzymes), decreased antibiotic permeability (porin closure) and removal of the antibiotic within the bacterium (expulsion pumps) (28,30).

The resistance expressed by *E. coli* is multifactorial and is mainly due to the production of beta-lactamases, which are enzymes that mediate the destruction of beta-lactams by hydrolysis. An increase in the prevalence of *E. coli* strains with ESBL has been observed which give them resistance against penicillins, cephalosporins (first to fourth generation, except for cefamicins), and aztreonam, making them a challenge for treatment. Resistance through AmpC-type beta-lactamases also occurs in strains of *E. coli* but is less common than ESBL production. AmpC-type beta-lactamases inactivate cephalosporins, beta-lactam/beta-lactamase inhibitor, cephamycins (e.g., cefoxitin) and aztreonam. *E. coli* can also acquire carbapenems, which gives it resistance against all beta-lactams. In the case of Klebsiella and *Enterobacter spp*. resistance also occurs through ESBL and AmpC, although it is worth remembering the emerging presence of carbapenem-resistant *Klebsiella* and *Enterobacter spp* (30).

On the other hand, Pseudomonas aeruginosa has resistance by multiple mechanisms including the production of beta-lactamases, expulsion pumps

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and porin closure, which makes antibiotics such as broad-spectrum penicillins, cephalosporins and carbapenems may be ineffective in treatment. In addition, they may develop resistance to fluoroquinolones by making mutational changes in DNA gyrase and/or topoisomerase. Resistance to aminoglycosides occurs due to the presence of aminoglycoside inactivating enzymes or methylase coding genes. The selection of appropriate antibiotic therapy is complex in infections caused by P. aeruginosa (30).

b. Methicillin-resistant *Staphylococcus aureus* (MRSA)

Newborns are likely to acquire the S. aureus through the birth canal, breastfeeding, contact with people, and the surrounding environment. The increase in MRSA colonization rates in hospitalized newborns compared to non-hospitalized newborns (31) is alarming.

After the development of beta-lactamase-resistant semi-synthetic penicillins in the 50s, different outbreaks of methicillin-resistant S. aureus were reported (3,32). Today, there has been a steady increase in blood cultures with MRSA, from 0.9% in 1990 to 13% in 2000 (33). MRSA colonization rates in newborns range from 5 to 50%, compared to MSSA which are between 18 and 81% (3).

Resistance occurs through the acquisition and expression of the mecA gene, which encodes the penicillin-binding protein 2a (PBP-2a), leading to a very low affinity for most beta-lactam antibiotics. It is also common for MRSA, especially strains associated with health care, to have increased resistance to macrolides and clindamycin through ribosomal modifications and ejection pumps. In the case of quinolones, resistance occurs due to overexpression of ejection pumps and mutations of topoisomerase IV and gyrase(32).

5. Inappropriate use impact of antibiotics in the NICU

The inappropriate use of antibiotics has health and economic consequences. Schulman et al. conducted a retrospective cohort study of 127 Neonatal Intensive Care Units (NICU) in California that included 52,061 patients (34). It showed that the Antibiotic Use Rate (AUR) varied 40-fold among NICUs (from 2.5% patient-days to 97.1% patient-days) (34). Additionally, there was no relationship between AUR and proven infection, Necrotizing Enterocolitis (NEC), volume of surgical cases, or mortality in NICU (34). From this type of studies, it can be inferred that there is a high prescription of antibiotics that lacks justification and adherence to local epidemiological information for rational use of antibiotics. Consequently, the

indiscriminate and prolonged use of antibiotics leads to undesirable effects such as alterations in the intestinal microbiota of newborns (NB), NEC, ototoxicity, hepatotoxicity, hematological anomalies, nephrotoxicity, and the need to obtain blood samples repeatedly (35,36). The manifestations of early neonatal infection are subtle, promoting empirical and early use of antibiotics to avoid delaying treatment of a true infection, exposing about 100% of the extreme preterm population to ampicillin and an aminoglycoside (37–40).

Antibiotic resistance (AR) has become a problem because the speed at which new antibiotics are developed is outpaced by the speed at which resistance emerges as it is conditioned by the appearance of enzymatic mechanisms easily shared through plasmids between bacteria. The resistance mechanisms are the result of the selective pressure exerted by antibiotics; therefore, the greater the exposure, the greater the appearance of resistance (41). The steady growth of AR will lead to 10 million people dying a year by 2050, at a global cost of $100 trillion dollars (42). Latin America is estimated to contribute 392,000 deaths a year by 2050 due to AR (42). Sepsis is a condition of increasing concern to the World Health Organization (WHO), as it is a health care priority due to its contribution to global mortality and morbidity (43,44). It is estimated that there will be an incidence of 3 million annual cases of Neonatal Sepsis (NS) and 1.2 million annual cases of Pediatric Sepsis (PS) (45). Despite the above, there is insufficient information from low- and middle-income countries to calculate the overall burden for NS and PS, therefore further research is required in this field (45). The relationship between cases of sepsis, mortality, and morbidity may be even more bleak in the context of AR, as the range of antibiotics to be used becomes increasingly narrow, leading clinical practice to a post-antibiotic era.

Countries in poverty, with poor infrastructure, and inequitable health care provision are factors that contribute to the high incidence of NS (46). In South Asia, the incidence of NS can be up to four times higher than that reported in England and the United States (47). The etiology is characteristically different in developing countries, with GNB being responsible for more than 60% of infections, with the three main agents *Klebsiella spp*, *Escherichia coli*, and *Acinetobacter spp* (47). In Brazil, a prospective 10-year surveillance study of nosocomial infections in the NICU was conducted by Couto et al., who described that 64.1% of 290 isolates of *Klebsiella pneumonia* and 19.2% of 104 isolates of *Escherichia coli* were resistant to third

generation cephalosporins (48). Staphylococcus aureus also occupies an important place in the rate of hospital-acquired neonatal infections in Africa and South Asia, while coagulase-negative *Staphylococcus* are more frequent in Latin America and the Middle East (49). Something in common among the *Staphylococcus* is the possibility of developing resistance to oxacillin and cefazolin, which would cause the germ to be denoted as methicillin resistant. The remaining strategy to treat these germs, and even more so in bacteremia, is vancomycin a glycopeptide that requires monitoring of plasma levels, dose adjustment in the presence of renal failure, and that results in nephrotoxicity with its prolonged use (21).

The overtreatment of sepsis with negative cultures, the scarcity of resistance surveillance studies in the community and in the hospital, and the difficulty of access to microbiological methods of rapid diagnosis are factors that have conditioned the high degree of resistance to first-line antibiotics (ampicillin, gentamicin, and third generation cephalosporins) (47,50,51). Other behaviors that contribute to increased resistance have been described, such as treatments that were not pathogen-oriented, failure to practice antimicrobial control, failure to treat infection and treat colonization or contaminant, and failure to stop treatment when there is evidence of cure or when infection is unlikely (52). Colombia is currently facing a challenge with Gram-negative bacteria resistant to carbapenems, as bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter spp* express enzymes capable of hydrolyzing carbapenems, last-line antibiotics against bacteria resistant to other beta-lactams such as cephalosporins (53). In the face of this adversity, health care costs, hospital stay, and mortality will increase.

6. Role of the Antibiogram and Antimicrobial Stewardship Programs in the NICU

It is up to the treating clinician to decide which infants to treat, what to treat with, and how long to treat (54). The intention of the Antimicrobial Stewardship Programs (ASP) is to reduce the inappropriate use of antibiotics based on 5 fundamental pillars called the “Five-Ds” (41). These include

«The overtreatment of sepsis with negative cultures, the scarcity of resistance surveillance studies in the community and in the hospital, and the difficulty of access ... »

Diagnosis, Drug (Drug), Dosage, Duration, and De-escalation. The low specificity of clinical signs, the presence of a normal physical examination in the presence of true infection, the presence of suggestive infection symptoms caused by another type of pathology, and the absence of paraclinical tests with sufficient sensitivity to exclude neonatal infection, are factors that make diagnosis difficult (55). Sometimes the microbiological growth in the cultures is not evident but the newborn persists with clinical manifestations compatible with sepsis, which is why the antibiotic treatment continues (55). It is important to consider the clinical manifestations of prematurity and the prescription of Intrapartum Prophylaxis as two conditions that the cultures are negative, and the manifestations do not correspond to a neonatal infection (55). These are the scenarios that justify the development of strategies that facilitate the clinician to make decisions regarding whether or not to start antibiotics.

Due to a low proportion of newborns receiving antibiotics have a true bacterial infection, Yang et al. in 2012 developed a tool to reduce the rate of antibiotic use in the NICU (56). Neonatal Bacterial Infections Screening Score (NBISS) is a tool that integrates maternal risk factors, clinical presentation, and laboratory parameters of patients newly admitted to the NICU (56). In total there are 25 criteria in the NBISS, distributed as follows: 5 maternal risk factors, 15 clinical criteria, and 5 laboratory parameters (Table 2).

«Sometimes the microbiological growth in the cultures is not evident but the newborn persists with clinical manifestations compatible with sepsis, which is why the antibiotic treatment continues.»

Table 2. Criteria of the Neonatal Bacterial Infections Screening Score-NBISS

Maternal risk factors	*Score
☐ Premature or prolonged rupture of membranes (>18 hours)	☐ 1
☐ Peripartum maternal fever	☐ 1
☐ Positive maternal screening for SGB	☐ 1
☐ Maternal pyuria	☐ 1
☐ Amniotic fluid with meconium or chorioamnionitis	☐ 1
Newborn clinical presentation	**Score**
☐ Respiratory rate >60 breaths per minute	☐ 1
☐ Severe chest retraction	☐ 1
☐ Nasal flaring	☐ 1
☐ Groaning/Growling	☐ 1
☐ Seizures	☐ 1
☐ Bulging fontanelle	☐ 5
☐ Ear fluid	☐ 5
☐ Erythema around umbilical cord or belly button	☐ 5
☐ Temperature >37.7 °C or <35.5 °C	☐ 1
☐ Lethargy or unconsciousness or decreased movements	☐ 5
☐ Inability to feed	☐ 5
☐ Complete inability to suck	☐ 1
☐ Cyanosis	☐ 1
☐ Reduced capillary filling	☐ 1
☐ Shock	☐ 1
Laboratory parameters	**Score**
☐ Leukocytosis or Leukopenia	☐ 1
☐ Immature/Total Neutrophils Ratio (I/T Ratio) >0.2	☐ 1
☐ C-Reactive Protein >6 mg/L	☐ 8
☐ IgM >20 mg/dl	☐ 1
☐ Need to carry out a cerebrospinal fluid study	☐ 1

*Neonatal Bacterial Infection Screening Score. A score >8, with weighted variables, can make a diagnosis of bacterial infection, helping in the decision to administer antibiotics to newborns admitted to the NICU. Adapted from: Yang, TN et al (56)..

In the investigation by Yang et al., cases defined as Bacterial Infection (BI) in newborns were established through positive blood cultures, positive urine culture, positive CSF culture, or pneumonia (56). After exclusion, 250 patients were examined (250/254), of whom 29 were diagnosed with BI. Weighting the C-Reactive Protein (CRP) with 8 points if elevated, and with 5 points to the following clinical criteria: bulging fontanel, ear canal fluid, erythema around the belly button, reduction of spontaneous movements, and inability to feed, generated a value of 0.60 for the Receptor Operating Characteristic (ROC) curve. The diagnosis of BI could be made with a weighted

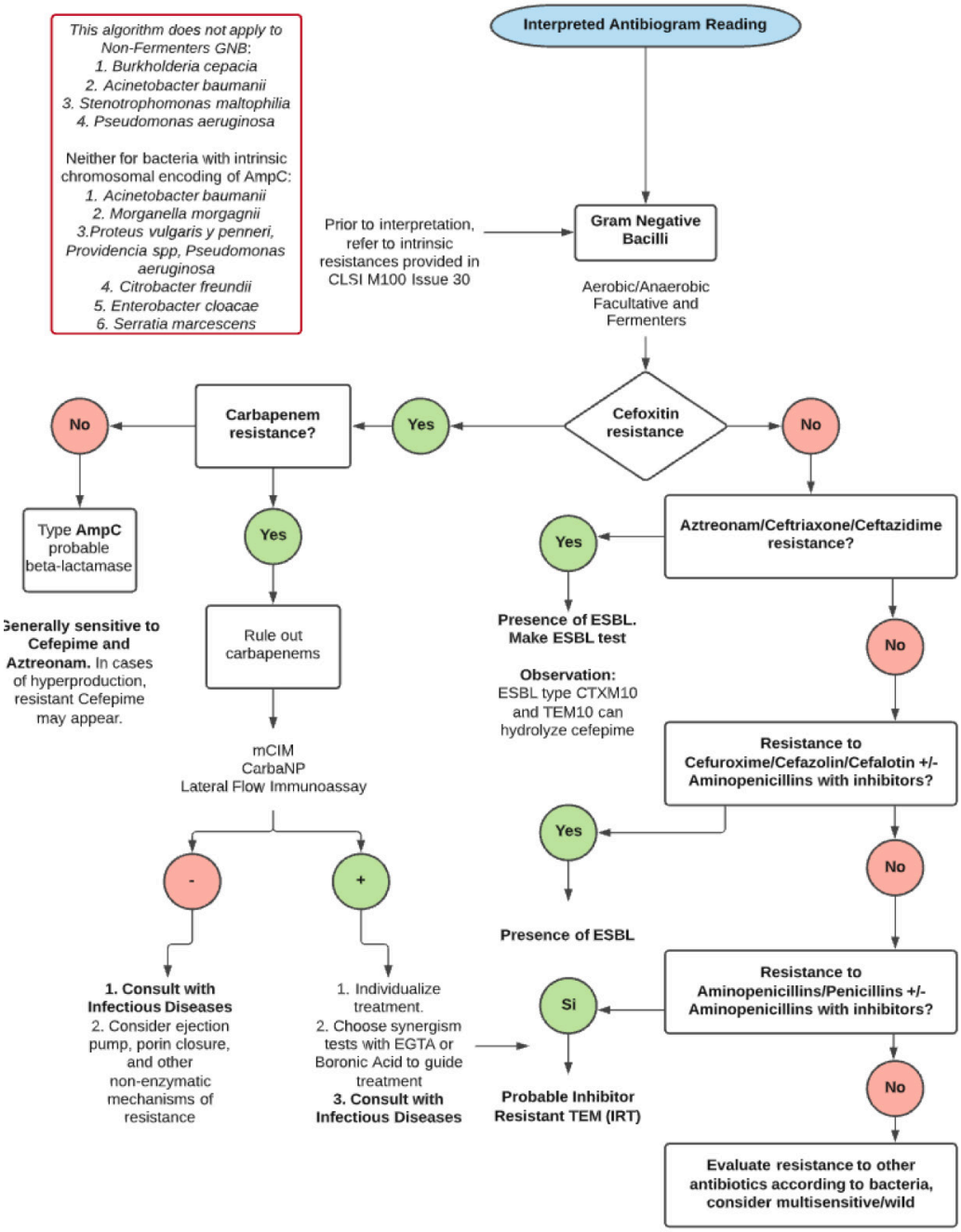
score > 8 points (56). Similarly, other strategies to detect NBs at risk of early neonatal sepsis have been developed with the aim of guiding the decision of timely initiation of antibiotic (39,57,58).

The Center for Disease Control (CDC) has been at the forefront of fighting the inappropriate use of antibiotics and preventing AR. One of the most recognized campaigns was implemented in 2002 through 12 steps to prevent AR in hospitalized patients (59). The first study evaluating adherence to the CDC's 12 steps found that the main step to which there was no adherence was "Pathogen-oriented treatment" (39% of all inappropriate therapies) (52).

In 2011, the CDC launched the Get Smart campaign (60). The objective of this was based on the five components of ASP, emphasizing that the Drug (Drug), used as empirical therapy, must be guided by local epidemiology and accumulated antibiograms. The interpreted reading of the antibiogram to make an appropriate choice of antibiotic is of great value, since identifying the pattern of resistance may avoid increasing mortality by helping to De-escalate, discontinue, or continue empirical antibiotic therapy (60). (Figure 1).

« The interpreted reading of the antibiogram to make an appropriate choice of antibiotic is of great value, since identifying the pattern...»

Figure 1. Interpretation of Antibiogram in Gram Negative Aerobic/Anaerobic Facultative Fermenters Bacilli. (E.g., Escherichia coli, Klebsiella pneumoniae)



*ESBL= Extended Spectrum Beta-lactamase, IRT= Inhibitor Resistant TEM, CLSI= Clinical and Laboratory Standards Institute. This algorithm does not apply to Non-Fermenters GNB such as Pseudomonas aeruginosa. It is important to keep in mind that there are bacteria that produce chromosomal AmpC beta-lactamases such as Acinetobacter baumannii, Morganella morgagnii, Proteus vulgaris, Enterobacter cloacae, among others. You can consult the phenotypic tests for the detection and differentiation of carbapenems in the article made by Villegas et al. (64).

** Own elaboration figure.

Culture reports are also useful to distinguish between a germ that generates a true infection (coagulase-positive Staphylococcus) and a colonizing or contaminating germ (coagulase-negative Staphylococcus). Similarly, it is essential to know the intrinsic susceptibility of the most frequently isolated germs, widely reported by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee for the Evaluation of Antimicrobial Susceptibility Testing (EUCAST) (61–63), where Klebsiella pneumoniae is described as intrinsically resistant to ampicillin, as well as Enterococcus faecium, and Enterobacter spp.

An ASP should have a team composed, ideally, of a neonatologist, an infectious disease physician, an infection prevention specialist, a bio-informatics expert, and a neonatal care nurse (55). The participation of all these professionals will depend on the availability of resources of the health center. The team has the responsibility to quantify and report metrics that they consider important to implement changes and make the ASP sustainable (Table 3.). The team should rely on institutional microbiological data to establish their empirical therapy for germs with the highest isolation frequency. It is important to consider the homogenization of practice against Neonatal Infection among clinicians in charge of decision making (55).

Table 3. Useful antimicrobial stewardship metrics for the NICU

Primary commands	Secondary Mandates	Metrics
Avoid redundant use of antibiotics	Reduce concomitant use of antibiotics with an anaerobic spectrum.	DOT with concomitant use of piperacillin/tazobactam, meropenem, or imipenem with metronidazole >1 day
Reduce broad-spectrum antibiotic use	Reduce the use of antibiotic prophylaxis for clean surgical procedures Reduce vancomycin use Reduce the use of third generation cephalosporins.	DOT with non-cephazolin-based perioperative prophylaxis for cardiac surgery
Reduce duration of antibiotic use	Avoid prolonged use of post-surgical prophylaxis. Avoid prolonged use in culture-negative sepsis	DOT with perioperative prophylaxis >48 hours Inter-quantile range of DOT duration of treatment in culture-negative sepsis.
Avoid inadequate therapy	Reduce episodes of drug-germ mismatch for LOS treatment.	Inadequate therapy DOTs per 100 LOS assessed.

*DOT (Days of Treatment); LOS (Late Onset Sepsis). Taken from: Cantey & Patel (55).

Conclusions

The existence of antibiotics has dramatically reduced mortality from bacterial infections, although their efficacy may decrease with prolonged, inappropriate use and in non-indicated scenarios due to the great threat of antibiotic resistance that bacteria can develop. The efficiency of resistance transmission by conjugation mechanisms makes even more worrisome the speed at which resistance can appear, overcoming the rate at which new antibiotics are produced.

It can be concluded that the scenario of EOS and LOS is a therapeutic challenge. This is reflected in the need to develop studies that allow the design of strategies to help clinicians in the decision-making process regarding when to initiate antimicrobial therapy in a newborn. The impact of antibiotic use, whether indicated or not, on the newborn is not negligible since it is related to fatal conditions such as NEC or renal injury.

Strict surveillance of the germs responsible for neonatal infections and resistance patterns is needed. The rational use of antibiotics based on local epidemiology should be the premise that prevails in medical practice. The training of treating physicians on microbiology and treatment-oriented should be part of continuing education. Studies are required to determine the burden of neonatal infection from antibiotic-resistant germs and to design and validate strategies that seek to promote the rational use of antibiotics such as NBISS. The implementation of an ASP should be done outside and inside the NICU, with the aim of homogenizing the medical practice of antibiotic use.

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