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PATTERN OF NEWBORN ANTIBIOTIC USE IN A TERTIARY LEVEL MATERNITY FOR FIVE YEARS

Florica Ramona Dorobanțu[1], Viviana Hodoșan[2], Alina Manuela Tîrb[1], Dana Carmen Zaha[1]*, Dorina Galușca[3], Nicolae Ovidiu Pop[4], Cătălin Dorin Dorobanțu[4]

1. ***Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania.***
2. ***Doctoral School of Biomedical Sciences, University of Oradea, 410087 Oradea, Romania.***
3. ***Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania.***
4. ***Department of Surgical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania.***

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ABSTRACT

Using antibiotics in hospitals is an important objective to prevent antimicrobial resistance. The classification of antibiotics based on WHO Essential Medicines categorize into Access, Watch, and Reserve (AWaRe) categories can enable interventions which are practical worldwide. Evaluating patterns of AWaRe antibiotic use in pediatrics was our intention this will allow its use in local and national stewardship interventions. Our retrospective observational study included all neonates from County Clinical Emergency Hospital of Oradea, Romania receiving antibiotherapy between 2017-2021. They patients demographics were analyzed which includes (gestational age, birth weight age, and gender), antimicrobial drugs, dose, method of administration, empirical and anticipated management and diagnosis. The WHO methodology and AWaRe classification have been employed in presenting the overall antibiotic prescriptions. The most common prescription of antibiotherapy was neonatal prophylaxis for risk factors of infants, then lower respiratory tract infection and neonatal sepsis. The pattern of antibiotic prescription displays an increasing trend despite the relatively constant number of patients. Gentamycin was the most prescribed antibiotic to hospitalized neonates being associated with ceftriaxone or ampicillin. During the first two years evaluated mainly antibiotics from group Watch were prescribed, while in 2019 and 2020 antibiotics from both categories Access and Watch were prescribed. To improve the control of antibiotic use as a key strategy to reduce antimicrobial resistance and the implementation and monitoring of antimicrobial stewardship actions, AWaRe classification could be used as a simple measure of appropriate antibiotic use. The efforts in the future should focus on developing and evaluating pediatric antibiotic stewardship programs.

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Introduction

Bacterial infections are a major causes of morbidity and death in newborns, especially in premature infants (that are born before 37 weeks of pregnancy) and newborns with low birth weight (under 1500 g). Infections are associated with complications, and increased length of hospital stay. In both newborns and premature infants, perinatal infections are crucial aspect in the initiation and growth of cerebral cortical lesions and deficient in neuromotor development. Early-onset bacterial neonatal infections (within 72 hours) have a higher incidence compared to late-onset infections and are often more severe [1, 2]. They appear in a percentage of 1.9% in newborns in this category [3]. These infections are usually caused by a microorganism in the mother's genital tract. Gram-positive bacteria, like group B *Streptococcus* (GBS), as well as gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella* spp are important for etiology of these infections [4]. Evolution is rapid, mortality is increased, particularly in premature infants weighing between 1500g and 2499g

Corresponding Author: Dana Carmen Zaha; Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania. E-mail: danaczaha@gmail.com.

[5, 6]. Even under antibiotic therapy, the incidence of mortality for early infections in low-birth-weight infants amounts 26% [7-9].

Exposure to GBS is common in newborns but the majority do not develop infections. The reported mortality is about 10% but is higher in premature infants. About 11% of newborns who survive a GBS infection develop neurological sequelae [10, 11]. Early neonatal infections with methicillin-resistant *Staphylococcus aureus* are less frequently [12]. The use of antibiotics in the neonatal period is important not only for therapeutic success but also for preventing the development of bacterial resistance. The resistance of antibiotics has become worldwide public health concern that is quickly spreading. The WHO has elaborated an action plan towards the resistance of antimicrobials globally, with one of the goals being to optimize antibiotic use [13]. In this context, a better control of antibiotic usage is among the vital strategies, but also inform the implementation and monitoring of antimicrobial stewardship actions, knowledge gaps about worldwide antibiotic use must be addressed [14, 15].

Information on patterns of usage of antibiotic in children is insufficiently reported and variable by the level of development of the country and health system. Antibiotics are commonly prescribed in children, and there has been limited progress in building pediatric antibiotic stewardship programs. Among the biggest challenges in designing these programs are that the set daily dose technique employed in adult antibiotic control is ineffective in newborns and children, whose body weights vary greatly [16, 17]. Antibiotics for children were divided into three categories by the WHO Essential Medicines List (EML) Working Group in March 2017: Access, Watch, and Reserve [18]. Access groups include antibiotics, often narrow-spectrum antibiotics, indicated as first- and second-line treatment of most clinical infectious disease syndromes against a broad spectrum of common susceptible pathogens with low likelihood of resistance. The Watch group includes broad-spectrum antibiotics, which correspond to the agents with higher importance on the list of the crucial antimicrobial drugs for pathogens with higher resistance potential [19]. Antibiotics that are employed in multidrug-resistant illnesses are included in the Reserve category. The last group is that of unclassified antibiotics which includes every antibiotic that is not mentioned in the EML like as second-generation cephalosporins (ATC code: J01DC) and combinations of antimicrobials (ATC code: J01RA).

For a better understanding of the current antibiotic use among neonates and children around the world and to enable providing of simple, worldwide applicable pediatric antibiotic stewardship programs, is required the standardized information gathering. the current research aims at describing antibiotic usage in hospitalized neonates through applying the WHO methodology as well as AWaRe classification and clinical infectious syndrome in this population.

Materials and Methods

Information about antibiotic use in hospitalized neonates and their pathology between 2017 and 2021 was obtained from registry of County Clinical Emergency Hospital of Oradea, Romania, a teaching hospital with 500-1000 beds. Patient demographics (gestational age, birthweight age, gender), antimicrobial drugs, dose, method of administration, empirical and targeted treatment, and diagnosis were analyzed. Patients were newborn from our maternity and transferred from other hospitals with a smaller grade.

The Anatomical Therapeutic Chemical (ATC) classification method of WHO was used to code antibiotics [20]. Antibiotics that were categorized as antibacterial used for systemic were also included (ATC code: J01). Antifungal (ATC code J02), antiviral (ATC code J05), and TB (ATC code J04) prescriptions, as well as antibiotics for topical use, were excluded. Antibiotic use was expressed as DDD according to WHO methodology [20]. The Antibiotics were categorized as Access, Watch, and Reserve According to the EMLc [18]. Antibiotics that were absent in any of the Access, Watch, and Reserve groups were identified as uncategorized **(Table 1)**. We presented patterns of antibiotic use, the quantity of antibiotic used in every AWaRe group and clinical conditions. SPSS Statistics software version 26.0 was used for collected data and analysis. Ethical approval was obtained from Ethics Committee of Emergency Clinical County Hospital of Oradea.

Table 1. List of antibiotics, classified into Access, Watch, Reserve and Unclassified groups [18]

Access	Watch	Reserve	Unclassified
Amoxicillin	Anti-pseudomonal penicillin's		
Amoxicillin and clavulanic acid	with beta-lactamase inhibitor		
Ampicillin	(Piperacillin and tazobactam)		
Benzathine benzylpenicillin	Carbapenems or penems	Aztreonam	
Benzylpenicillin	(imipenem and cilastatin,	Cephalosporins, fourth	
Cefalexin or cefazolin	meropenem)	generation (cefepime)	
Chloramphenicol	Cephalosporins, third generation	Cephalosporins, fifth	Second-generation
Clindamycin	with or without beta-lactamase	generation (ceftaroline)	cephalosporins
Cloxacillin	inhibitor	Daptomycin	(ATC code: J01DC)
Doxycycline	(Cefixime, cefotaxime,	Fosfomycin (intravenous)	and combinations of
Gentamicin or amikacin	ceftazidime, ceftriaxone)	Oxazolidinones (linezolid)	antimicrobials
Metronidazole	Glycopeptides (teicoplanin,	Polymyxins (colistin,	(ATC code: J01RA)
Nitrofurantoin	vancomycin)	polymyxin B)	
Phenoxymethylpenicillin	Macrolides (azithromycin,	Tigecycline	
Procaine benzylpenicillin	clarithromycin, erythromycin)		
Spectinomycin	Quinolones and fluoroquinolones		
Sulfamethoxazole and trimethoprim	(ciprofloxacin, levofloxacin,		

Azithromycin	moxifloxacin, norfloxacin)
Cefixime	
Cefotaxime	
Ceftriaxone	
Ciprofloxacin	
Clarithromycin	
Piperacillin and tazobactam	
Meropenem	
Vancomycin	

Results and Discussion

Total number of 17434 individuals were part of the study, of these patients 1888 (10.82%) were preterm and 15 546 (89.17%) full-term babies. Preterm babies included low birth weight preterm babies 81.14%, very low birth weight preterm babies 12.02%, extremely low birth weight 6.83% babies. Most patients are born at term and weigh over 3000 g. The number of newborns is relatively the same in the five years studied. Male: female ratio is 1 **(Table 2)**.

Table 2. Patient demographics

		2017	2018	2019	2020	2021
Total newborns		3681	3616	3334	3301	3502
Gestational age	preterm	405	352	421	362	348
	full-term	3276	3264	2913	2939	3154
Birth weight	over 3000 g	2528	2529	2281	2295	2376
	2999-2500 g	748	735	632	644	778
	2499-2000 g	244	250	238	208	225
	1999-1500 g	77	51	92	80	67
	1499-1000 g	54	31	57	44	41
	under 999 g	30	20	34	30	15
Gender	Male	1794	1807	1704	1682	1759
	Female	1887	1809	1630	1619	1743

The most frequent diagnosis in children receiving antibiotics was neonatal prophylaxis for neonatal risk factors, followed by lower respiratory tract infection and neonatal sepsis **(Table 3)**.

Table 3. Reported clinical conditions for antibiotic prescriptions in neonates

Condition	2017	2018	2019	2020	2021
Neonatal sepsis	41	31	56	26	23
Conjunctivitis and dacriocystitis	7	10	9	3	10
Intraamniotic infection	33	24	10	17	42
Congenital pneumonia	81	56	31	31	81
Prophylaxis for new-born exposed to mothers with bacterial infection	65	42	91	81	45
Peritonitis	0	4	0	0	0
Total	227	167	197	158	201
Incidence	6.12%	4.6%	5.89%	4.78%	5.73%

Table 4 shows the antibiotic prescribing pattern displaying an ascending trend between 2017-2021 despite the relatively constant number of patients. Gentamycin was the most prescribed antibiotic to hospitalized neonates being associated with ceftriaxone or ampicillin. The same ascending trend presented the consumption of ciprofloxacin, amikacin, clindamycin and benzylpenicillin. In contrast, the prescription of meropenem, imipenem and cilastin, cefuroxime, vancomycin, amoxicillin and clavulanate showed a decreasing trend.

Table 4. Patterns of antibiotics prescription to neonates by drug expressed as DDD

	2017	2018	2019	2020	2021	Total
Gentamycin	1.64	1.10	2.05	2.10	91.43	98.31
Ceftriaxone	3.37	5.28	3.97	4.01	5.00	21.61

Ciprofloxacin	1.73	2.11	1.57	1.47	12.24	19.12
Ampicillin	1.19	0.82	3.12	1.08	8.05	14.26
Amikacin	0.00	0.00	0.00	0.00	14.03	14.03
Clindamycin	1.02	1.09	0.85	0.47	1.37	4.80
Benzylpenicillin	0.39	0.16	0.36	1.02	2.34	4.27
Meropenem	0.72	0.68	0.54	0.67	0.41	3.03
Imipenem and cilastin	0.57	0.50	0.56	0.27	0.39	2.30
Cefuroxime	0.06	0.20	0.38	0.44	0.09	1.17
Vancomycin	0.35	0.25	0.12	0.26	0.16	1.13
Amoxicillin and clavulanate	0.05	0.49	0.52	0.00	0.03	1.10
Teicoplanin	0.02	0.44	0.00	0.00	0.00	0.46
Ceftazidime	0.05	0.12	0.02	0.15	0.00	0.35
Metronidazole	0.00	0.00	0.05	0.20	0.08	0.33
Cefoperazone	0.07	0.00	0.00	0.00	0.00	0.07
Total	11.25	13.25	14.11	12.13	135.61	

The evolution of AWaRe antibiotics prescribed in neonates is shown in the **Figure 1**. If in 2017 and 2018 mainly antibiotics from group Watch were prescribed, in 2019 and 2020 antibiotics from both categories Access and Watch were prescribed. We reported low rates of unclassified antibiotic usage (cefuroxime)in yearly close proportions.

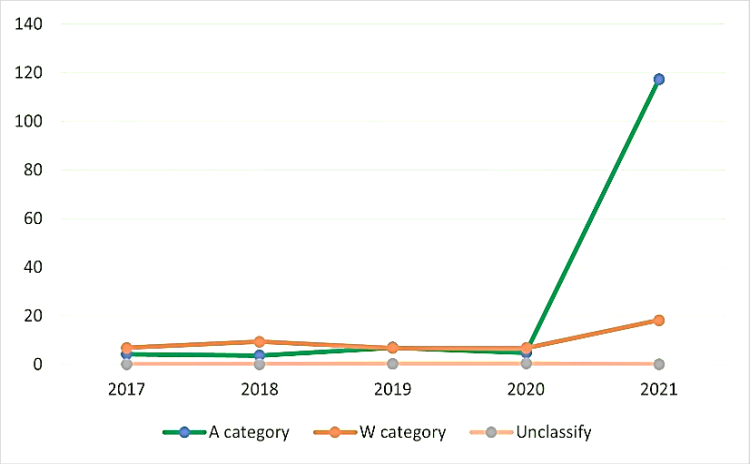

Figure 1. Patterns of AWaRe antibiotic prescription to neonates
(A category =Access, W category = Watch, and unclassified)

However, there is an upward trend in the use of antibiotics in Access category and no Reserve category antibiotics were prescribed during evaluated period. Access antibiotics most prescribed were gentamycin, amikacin, ampicillin **(Figure 2)**. We noticed a high consumption for aminoglycosides.

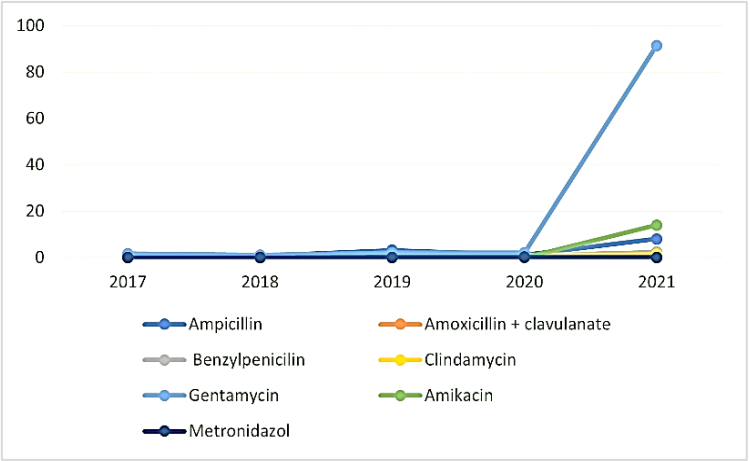

Figure 2. Access antibiotics prescribed to neonates

The Watch antibiotics prescribed were different in these years, the most prescribed were ceftriaxone and ciprofloxacin **(Figure 3)**. Ceftriaxone has been prescribed in high doses over the five years evaluated with constant trend. Ciprofloxacin was the second prescribed antibiotic between 2017-2020. In 2021, however, the amount of ciprofloxacin administered exceeded the amount of ceftriaxone. It is also worth noting the almost constant and low consumption of carbapenems (imipenem and cilastin, meropenem).

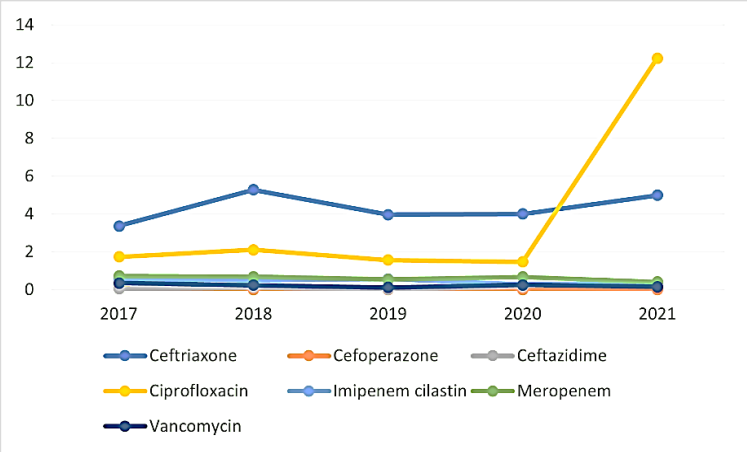

Figure 3. Watch antibiotics prescribed to neonates

There are data indicating that each and every day of therapy it further elevates the risk of adverse complications, such as acute kidney injury, *Clostridioides difficile* infection and evidences about drug-microbiota relationship [21]. The risk increases with every extra day of therapy together with for prophylaxis [22, 23]. The side effects of antibiotics given to the mother should also be considered [24].

The care of newborns at risk of developing early infections varies from unit to unit. Sometimes antibiotics are not needed such as bacterial colonization. The incidence of neonatal infections in our unit is higher to that reported in the Europe and systemic and lung damage rank first in neonatal infections [25]. Due to their increased risk to infections, antibiotics are highly used in the newborns. The effects of antibiotic therapy are increasingly affected through the physiological immaturity of the newborn, characterized by an immature process adaptive from intrauterine to extrauterine life. Other factors that influence antibiotic therapy: gestational age, birth weight, intrauterine growth restriction, chronological age and especially immaturity of renal and hepatic function. Dosage and rate of administration should be considered in terms of distribution, metabolism, biotransformation, and excretion and type of infection according to protocols [26]. Dose adjustment and duration of therapy are based on pharmacokinetics and pharmacodynamics [27, 28].

Considering the type of the pathogen the time for the antibiotic therapy was adjusted, therapy response, and also the likelihood of the antibiotic to penetrate to the infection site. The baby's clinical status, laboratory tests, and response to treatment were monitored. The improvement of clinical findings in the first 24-48 hours from the beginning of treatment, the normalization of CRP level, I/T ratio and white blood cell count in 48-72 hours was indicated an appropriate response is received [29, 30].

According to guidelines, the treatment of any infection was giving on time and all the time within one hour before decision to start treatment. The antibiotic management is first empirical and according to many factors like as the beginning of age, probable pathogens, and the patterns of antibiotic susceptibility, However appropriate samples are collected before the culture sample and commencing antibiotic therapy. Beta-lactams (ampicillin, cephalosporins, monobactams and carbapenems), aminoglycosides (gentamycin) and glycopeptides (vancomycin) are amongst the initial antibiotics used in treating neonatal infections.

In our hospital children with acute bacterial infection were managed empirically with third generation cephalosporins (Ceftriaxone). A neonate at risk of infection (i.e., membranes ruptured > eighteen hours prior to delivery, mother with fever > 38 °C prior to delivery or at labor, or amniotic fluid was foul smelling or purulent) received prophylactic ampicillin and gentamicin for minimum of two days. After that, the neonate was reassessed, and treatment continued only if there are signs of sepsis (or a positive blood culture). Due to the etiological variation of sepsis, the best empirical therapy has been the association of ampicillin with gentamicin for many years. Fourth and fifth generation cephalosporins have a broader spectrum of, and higher, activity and are more resistant to extended -spectrum beta-lactamases. In contrast monobactams are almost exclusively active against Gram-negative bacteria aerobic respiration, including *P. aeruginosa*.

Quinolones added to beta-lactam antibiotics are currently recommended as a second-line empiric regimen in sepsis. There has been an increased use cephalosporin (most commonly ceftriaxone) or a quinolone (most commonly ciprofloxacin) as a first line option to treat especially early and late onset sepsis. Cephalosporins (ceftriaxone) combined with aminoglycosides (gentamycin) is also used as an alternative for early onset sepsis. Despite efforts with promising results [31], vancomycin was often considered if staphylococcal infection is suspected.

For the treatment of lower respiratory tract infection, febrile neutropenia, fever, or sepsis, the Reserve antibiotics mostly consisted of the fourth and fifth generation, cephalosporins and monobactams and they should only be used as a last resort; that is, in the case of a serious or life-threatening multi-drug resistant infection that is not responding to first- or second-line treatments [32, 33].

Narrow-spectrum antibiotics such as benzylpenicillin and gentamicin are prescribed also in our patients. These antibiotics are specific for SBG and *Escherichia coli* most identified organisms. Most gram-negative organisms are sensitive to gentamicin, but the disadvantage of using aminoglycosides is the need to monitor their blood levels. At high doses there is a possibility that gentamicin may cause hearing impairment.

Other therapeutic options are cephalosporins, amoxicillin, co-amoxiclav. They are active on many microorganisms but increase the risk of antibiotic resistance, progression to necrotic ulcerative enterocolitis and the treatment could be more expensive. Ampicillin and cephalosporins are used as antibacterial prophylaxis in women giving birth by cesarean section to reduce the risk of maternal-fetal infection. The widespread use of broad-spectrum antibiotics in maternity wards favors the development of antibiotic-resistant organisms [34].

Conclusion

Despite the development of bacterial resistance and possible immune disorders in late childhood prompt administration of antibiotics for neonatal infections can save lives. Beta-lactam antibiotics feature in all three categories of antibiotics, encompass many drugs, are still the most prescribed drugs. Blood culture is the gold standard in diagnosis and treatment of neonatal septicemia. Multiple antibiotic resistances among neonatal sepsis are currently one of the greatest challenges to the effective management of infections. Antenatal and intrapartum administration of antibiotics may be considered in the prevention and treatment of early-onset neonatal infections. But administration of antibiotics during pregnancy can have significant consequences for the newborn.

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