Original article

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Effect of gestational age, body weight and serum creatinine concentration on serum vancomycin concentration in the treatment of neonatal sepsis: A Single-center Pilot Study

Hristina Trajković[1], Karin Vasić[2,3], Jelena Vučić[2,3], Dragana Stokanović[1], Gorana Nedin-Ranković[1], Dane Krtinić[1,4], Hristina Jovanović[1], Milica Ignjatović[3], Marija Andrejević[3], Radmila Veličković-Radovanović[1,5]

[1]University of Niš, Faculty of Medicine, Department of Pharmacology with Toxicology, Niš, Serbia

[2]University of Niš, Faculty of Medicine, Department of Pediatrics, Niš, Serbia

[3]University Clinical Center of Niš, Clinic of Pediatrics, Niš, Serbia

[4]University Clinical Center of Niš, Clinic of Oncology, Niš, Serbia

[5]University Clinical Center of Niš, Clinic of Nephrology, Niš, Serbia

Contact: Hristina Trajković

81 dr Zoran Đinđić Blvd., 18000 Niš, Serbia

E-mail: hristina93.ht@gmail.com

Neonatal sepsis is a serious medical condition characterized by systemic infection in infants younger than 28 days. Therapy for late neonatal sepsis is combination of vancomycin and meropenem. The aim of this single-center pilot study is to examine the influence of newborn body weight, gestational age and creatinine values on the serum concentration of vancomycin in the treatment of neonatal sepsis. The study included 13 patients admitted to the Pediatrics Clinic, University Clinical Center Niš with a diagnosis of neonatal sepsis in the period from June to October 2024. The value of serum vancomycin between 10 and 15 μg/ml was recorded in 38.5% of subjects, which is prefered therapeutic range. Due to small sample size, effect of gestational age, body weight and serum creatinine concentration on serum vancomycin concentration weren't found statistically significant.

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However, descriptive statistics show that significant difference can be found between these groups, suggesting a potential effect worth further investigation.

Keywords: neonatal sepsis, vancomycin, therapeutic drug monitoring

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Uticaj gestacijske starosti, telesne mase i koncentracije kreatinina u serumu na koncentraciju vankomicina u serumu u lečenju neonatalne sepse: Pilot studija jednog centra

Hristina Trajković[1], Karin Vasić[2,3], Jelena Vučić[2,3], Dragana Stokanović[1], Gorana Nedin Ranković[1], Dane Krtinić[1,4], Hristina Jovanović[1], Milica Ignjatović[3], Marija Andrejević[3], Radmila Veličković Radovanović[1,5]

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra Farmakologiju sa toksikologijom, Niš, Srbija

[2]Univerzitet u Nišu, Medicinski fakultet, Katedra Pedijatrija, Niš, Srbija

[3]Univerzitetski Klinički centar Niš, Klinika za pedijatriju, Niš, Srbija

[4]Univerzitetski Klinički centar Niš, Klinika za onkologiju, Niš, Srbija

[5]Univerzitetski Klinički centar Niš, Klinika za nefrologiju, Niš, Srbija

Kontakt: Hristina Trajković

Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija

E-mail: hristina93.ht@gmail.com

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Neonatalna sepsa je ozbiljno zdravstveno stanje koje karakteriše sistemska infekcija kod novorođenčadi mlađe od 28 dana. Terapija kasne neonatalne sepse je kombinacija vankomicina i meropenema. Cilj ove pilot studije je da se ispita uticaj telesne težine novorođenčeta, gestacijske starosti i vrednosti kreatinina na serumsku koncentraciju vankomicina u lečenju neonatalne sepse. Istraživanjem je obuhvaćeno 13 pacijenata primljenih na Kliniku za pedijatriju Univerzitetskog kliničkog centra Niš sa dijagnozom neonatalne sepse u periodu od juna do oktobra 2024. godine. Poželjna koncentracija vankomicina u serumu između 10 i 15 μg/ml zabeležena je kod 38,5% ispitanika. Zbog male veličine uzorka, uticaj gestacijske starosti, telesne težine i vrednosti kreatinemije na koncentraciju vankomicina u serumu nije statistički značajan. Međutim,

deskriptivna statistika pokazuje da se može naći značajna razlika između ovih grupa, što ukazuje na potencijalni efekat vredan daljeg istraživanja.

Ključne reči: neonatalna sepsa, vankomicin, terapijsko praćenje lekova

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Introduction

Neonatal sepsis is a serious medical condition characterized by systemic infection in infants younger than 28 days. Various factors can influence the onset of neonatal sepsis, such as gestational age and birth weight. In relation to the time of appearance of the first symptoms, neonatal sepsis can be divided into early and late. Early neonatal sepsis occurs in the first 72 hours after birth and the most common causative agents are bacteria that colonize the birth canal. Late neonatal sepsis occurs after 72 hours of birth, and procedures performed in the intensive care unit, such as central venous and umbilical catheters, thoracic puncture and the use of parenteral therapy, are cited as a risk. The risk group includes infants with low birth weight, as well as infants who are on parenteral nutrition or mechanical ventilation. Due to long hospital stays and despite a number of preventive measures, late neonatal sepsis is a problem in intensive care units worldwide (1).

Infectious agents that lead to sepsis can be different. In neonatal sepsis, these are mainly bacteria, which can be divided into gram-positive and gram-negative. The most common gram-positive causative agents are *Staphylococcus aureus, Enterococcus, Streptococcus pneumonia*, while characteristic gram-negative causative agents are *Klebsiella pneumoniae, Enterobacter, Salmonella, E. coli*. *Staphylococcus aureus* is mostly sampled from purulent skin infections, while gram-negative bacilli such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Serratia* are mostly isolated from infants with tracheal intubation and mechanical ventilation (2, 3).

Treatment of neonatal sepsis must be started as early as possible. It is recommended to start empiric therapy before blood culture results. The choice of antibiotic depends on whether it is early or late neonatal sepsis.

The causative agents of early neonatal sepsis are mainly group B beta-hemolytic streptococci, as well as gram-negative bacteria, such as *E. coli*. Accordingly, antibiotic therapy is started with a combination of ampicillin and aminoglycosides (eg gentamicin, amikacin). A combination of aminoglycosides and third-generation cephalosporins can also be used in therapy. In case of suspicion of meningitis, it is necessary to double the doses of ampicillin or penicillin G and include a cephalosporin.

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Staphylococcus aureus is the main cause of late neonatal sepsis. In case of suspicion of a hospital strain of staphylococcus, vancomycin is included in the therapy as a backup antibiotic. In addition to staphylococci, the cause of neonatal sepsis can also be *Pseudomonas aeruginosa*, in which case the treatment involves a combination of an antipseudomonal cephalosporin with an aminoglycoside or carbapenems. In anaerobic infections, metronidazole or clindamycin is included in the therapy (4-6).

After obtaining the results of the antibiogram, it is necessary to correct the therapy depending on the causative agent. The length of therapy depends on the clinical picture and microbiological findings. In addition to causal treatment, treatment of neonatal sepsis requires symptomatic therapy.

The aim

The aim of our research is to examine the influence of newborn body weight, gestational age and creatinine values on the serum concentration of vancomycin in the treatment of neonatal sepsis. As well as whether the monitoring of these parameters is sufficient to determine the dose necessary for treatment.

Material and methods

The research included newborns admitted to the University Clinical Center Niš, at the Clinic of Pediatrics in the period from June to October 2024 with a diagnosis of neonatal sepsis, who received vancomycin as part of the therapy. Patients received vancomycin at a dose of 15 mg/kg intravenously every 8 hours. If patients were premature infants up to 29th gestational weeks, they received vancomycin every 12 hours.

The study was conducted in premature infants up to the 32nd gestational week, premature infants between the 33nd and 36th gestational weeks, and term infants of both sexes with a diagnosis of neonatal sepsis. One blood sample is collected from each subject. 1 ml of blood is taken from the subjects in the period when blood is sampled for routine biochemical analyzes after reaching the equilibrium state of vancomycin in the body (30 to 60 minutes before the fifth dose of vancomycin), at the Clinic of Pediatrics of the University Clinical Center Niš. A portion of the sampled blood of 0.5 ml, which is used to determine the serum concentration of vancomycin, is centrifuged for 10 minutes

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at 3000 revolutions per minute, after which the separated serum is transferred to tubes for analysis. The rest of the sampled blood of 0.5 ml is used to determine routine biochemical analyses.

Determining the serum concentration of vancomycin is a routine method for which the AU680 device, Beckman Coulter, is used in the Center for Medical and Clinical Biochemistry, UCC Niš.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University Clinical Center Niš, Serbia (EK 8604).

Results were statistically evaluated using Microsoft Excel.

Results

The study included 13 patients admitted to the Clinic of Pediatrics, University Clinical Center Niš with a diagnosis of neonatal sepsis. Medical records were reviewed to collect demographic data, medication data, and microbiological and biochemical analyses.

Of the 13 patients admitted to the Pediatrics Department, 6 patients were male (46%), while 7 patients were female (54%). In terms of gestational age, patients were divided into three groups: infants born before 32 weeks of gestation, infants born between 33 and 36 weeks of gestation, and infants born at term. Newborns born at term had significantly greater average body weight, compared to first two groups of newborns ($p<0.001$) (Table 1)

Table 1. Average body weight of subjects (g)

Newborns born before 32 weeks of gestation	1605±267	F=41.703
Newborns born between 32 and 36 weeks of gestation	2069±247	$p < 0.001$
Newborns born at term	3461±581	

The majority of patients were admitted during the 1st day of age (40%) with a diagnosis of early neonatal sepsis, with initial antibiotic therapy Ampicillin and Amikacin or Ampicillin and Gentamicin. If the initial therapy proved ineffective or after blood culture results arrive, the initial therapy would be replaced by a therapeutic combination of Vancomycin and Meropenem. The majority of patients

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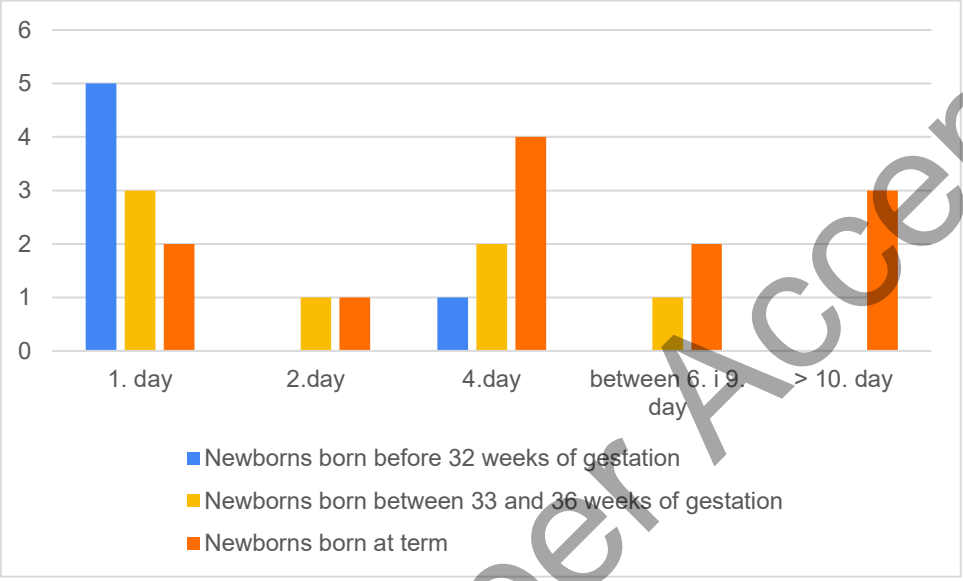
admitted during the first day of age are infants born before the 32nd week of gestation (50%) (Figure 1). There was a moderate positive correlation between gestational age group and the age of admission (ρ=0.563, p<0.01).

Figure 1. Age at admission (day)



Vancomycin therapy lasted for 7 days (52%) in the largest number of subjects, 5 days in the least number of subjects (16%) and all subjects were newborns born at term. In newborns born before the 32nd gestational week, as well as in newborns born between the 32nd and 36th gestational week, vancomycin therapy lasted for 7 days in the largest number of subjects. (Figure 2). No statistically significant association was found between gestational age and the duration of vancomycin treatment.,

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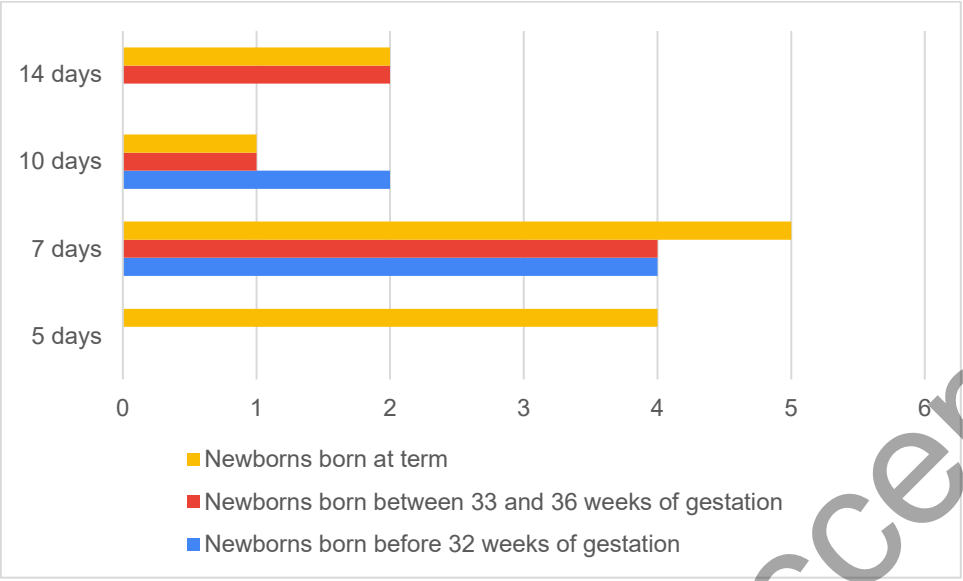
Figure 2. Duration of therapy



Blood cultures were performed 29 times, of which 15 were sterile (52%), which may be due to several different factors. One possible explanation is that in newborns, especially preterm infants, the number of bacteria present in the blood may be insufficient to be detected by standard techniques, while another possible explanation is that due to the need to minimize blood loss in newborns, the blood sample taken is insufficient to determine sensitivity. The highest number of blood cultures was *Staphylococcus epidermidis* (17%) and *E.coli* (10%). The presence of *Staphylococcus sp, Staphylococcus haemolyticus, Enterococcus faecium, Klebsiellae pneumoniae* was also recorded. (Table 2).

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Table 2. Blood culture

Staphylococcus epidermidis	5
Staphylococcus sp.	1
Sterilna	15
E. coli ESBL+	3
Staphylococcus haemolyticus	1
Enterococcus faecium	1
Klebsiellae pneumoniae	2
Candida	1

Vancomycin was used in combination with meropenem in the treatment of late neonatal sepsis (85%). The most common type of additional therapy was rehydration (36%), applied symptomatic therapy (28%), as well as systemic antimycotics (24%) and substitution with human albumins (20%). (Table 3.)

Table 3. Additional drugs used in therapy

Rehydration	9
Symptomatic therapy	7
Systematic antimycotic	6
Phototherapy	6
Substitution with human albumins	5
Vitamin K	4
Caffeine Citrate	4
Surfactant	3
Fresh frozen plasma	2
Phenobarbitone	2
Substitution of filtered erythrocytes	2

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Vancomycin serum concentration

The value of vancomycin serum concentration was expressed in μg/ml (as the concentration was measured). Guidelines for vancomycin serum concentrations in adults recommend a reference range above 10 μg/ml, except for MRSA pneumonia, endocarditis, or bone infections in infants, when reference values between 15 and 20 μg/ml are advised. It is necessary to note that the reference values were determined on the basis of research carried out on adults, without a study that would determine the corresponding reference values in the neonatal population (7). Some studies suggest that in newborns the reference values should be between 10 and 15 μg/ml, while some suggest even smaller range between 10 and 12 μg/ml to avoid potential nephrotoxicity (8, 9).

The highest value of serum vancomycin determined in our research is 46.8 μg/ml, and was recorded in a newborn born at 36 gestational weeks, with a body weight of 2090g, while the lowest value is 1.9 μg/ml and was measured in newborns born at term, with a body weight of with a mass of 3600g.

Out of the total number of subjects, only one had a concentration lower than 10 μg/ml, which is also the lowest recorded dose. An equal number of respondents had values between 20 and 30 μg/ml (23%), as well as over 30 μg/ml (23%). While the largest number of respondents had values between 10 and 20 μg/ml (46.2%). The value of serum vancomycin between 10 and 15 μg/ml was recorded in 38.5% of subjects, while the values of vancomycin in serum between 15 and 20 μg/ml were recorded in 7.7% of subjects (Figure 3).

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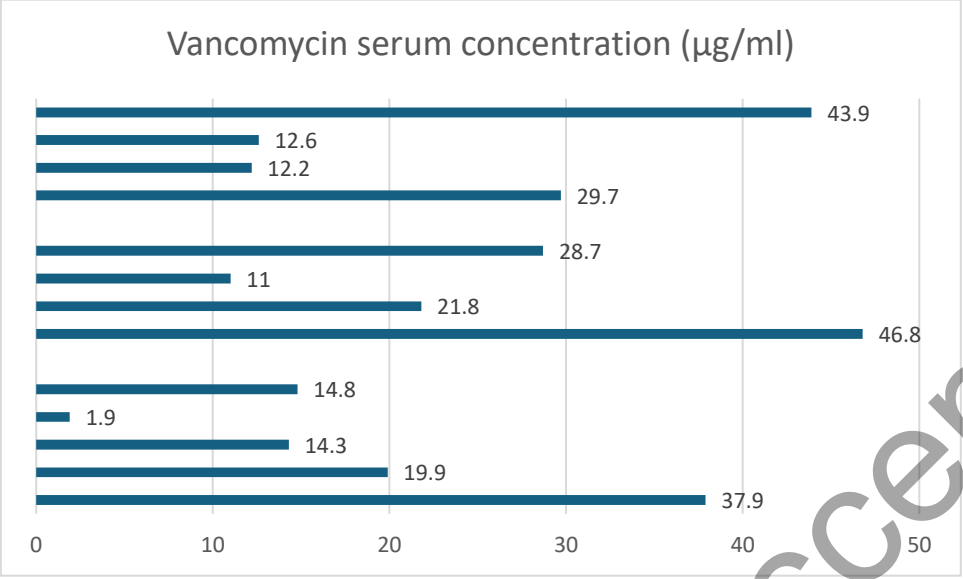
Figure 3. Vancomycin serum concentration (µg/ml)



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In infants born before 32 weeks of gestation, the mean value of vancomycin concentration in the blood was 24.6 ± 15.23 µg/ml, the minimum value was 12.2 µg/ml, while the highest was 43.9 µg/ml. In infants born between 32 and 36 weeks of gestation, the mean value was similar and was 27.08 ± 15.03 µg/ml, the lowest measured value in this group was 11 µg/ml, while the highest was 46.8 µg/ml. In the group of newborns born at term, the average value of serum vancomycin concentration was 17.76±13.06 µg/ml, the lowest value was 1.9 µg/ml, while the highest was 37.9 µg/ml (Table 4.). The differences in vancomycin concentration between three gestational age groups, were not statistically significant.

Table 4. Effect of gestational week on serum vancomycin concentration

Weeks of gestation	average	min	max	F=0.518 p=0.611
Newborns born before 32 weeks of gestation	24.60±15.23	12.2	43.9	
Newborns born between 33 and 36 weeks of gestation	27.08±15.03	11	46.8	
Newborns born at term	17.76±13.06	1.9	37.9	

In newborns whose birth weight was less than 2000 g, the average value of vancomycin concentration was 23.02±13.29 μg/ml, while in newborns whose birth weight was between 2000 and 3000 it was 31.60±12.96 μg/ml, and in newborns whose birth weight was over 3000g, the average concentration of vancomycin is 10.33±7.31 μg/ml, which is the closest to the reference values of vancomycin in serum (Table 5.). These differences were not found to be significant. Although there are no statistically significant differences, as the body weight increases over 3000g, the concentrations of vancomycin in the serum decrease, while in the other groups of subjects (birth weight less than 2000g and birth weight between 2000g and 3000g) the results were well above the reference values.

Table 5. Effect of body weight on vancomycin concentration

Body weight	average	min	max	F=2.599
< 2000	23.02±13.29	11	43.9	p=0.123
2000 - 3000	31.60±12.96	19.9	46.8	
> 3000	10.33±7.31	1.9	14.8	

In subjects whose measured values of serum creatine were less than 60 μmol/l, the average value of vancomycin in serum was 17.24±13.26 μg/ml, which is the smallest deviation from the reference values. With a serum creatinine concentration between 60 and 90 μmol/l, there is also an increased level of vancomycin in the serum, namely the mean value is 22.62±13.56 μg/ml, the lowest value is 11 μg/ml, while the highest measured value is 46.8 μg/ml. In the case when serum creatinine values exceed 90 μmol/l, the value of vancomycin in serum also increases, with an average value of 36.80±10.04 μg/ml, where the minimum value was 29.7 μg/ml, and the maximum value was 43.9 μg/ml (Table 6.). These differences were not found to be statistically significant. But there are noticeable differences between different values of creatinine concentration, showing that higher creatinine levels lead to increased vancomycin serum concentration.

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Table 6. Effect of serum creatinine concentration on serum vancomycin concentration

serum creatinine concentration (μmol/L)	average	min	max	F=1.587
< 60	17.24±13.26	1.9	37.9	p=0.252
60 - 90	22.62±13.56	11	46.8	
> 90	36.80±10.04	29.7	43.9	

Discussion

Therapeutic monitoring involves adjusting the dose based on the serum concentration of the drug in the blood, in order to achieve the appropriate effect with minimal toxicity. The most accurate method for monitoring the efficacy and safety of vancomycin is the determination of the trough concentration of the drug in the serum. Determination of the lowest drug concentration is determined immediately before administration of a new dose.

Determining the concentration allows informed decisions to be made in order to maintain the drug concentration within therapeutic limits, which allows us to optimize therapy while minimizing toxic effects. Therapeutic monitoring is extremely important especially in newborns due to the very pharmacokinetic specificity of this population, which leaves little room for error (10, 11).

Our reserch showed in subjects whose birth weight was over 3000g, the smallest deviations from the reference values were recorded, which may be the result of several factors. The first is the development of the kidneys, because a birth weight of over 3000g is characteristic for full-term newborns. While as another factor we have to take into account that in newborns with a lower birth weight, there is a higher proportion of body fluid (80-85%) and a lower proportion of fat compared to newborns with a higher birth weight. In low-weight infants, the combination of a high proportion of body fluid and a much smaller proportion of body fat leads to an uneven distribution of vancomycin, i.e. higher concentrations in the blood. On the contrary, as newborns with a higher birth weight have a higher percentage of fat in relation to body fluid, the distribution of the drug will be more even, thus a lower concentration of vancomycin in the serum is recorded (12, 13).

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Elevated concentrations of serum creatinine are commonly indicative of reduced renal function. When renal function is reduced, the efficiency of glomerular filtration is also reduced causing an increase of creatinine serum levels. Vancomycin is also primarily eliminated by glomerular filtration. The reduced ability to excrete vancomycin can lead to increase of vancomycin serum level. Concentration of serum creatinine can be valuable marker for determining appropriate dosing of vancomycin to avoid potential toxicity (14-16).

Research has shown that when the value of the lowest concentration of vancomycin is greater than 15 μg/ml, there is an increase in the incidence of nephrotoxicity by 2.67 times. The increased incidence of vancomycin-induced nephrotoxicity also leads to prolonged duration of therapy. A retrospective observational study conducted in 10 US medical centers showed that in patients treated with vancomycin for 7 days, approximately 20% of subjects developed vancomycin-induced nephrotoxicity (17).

Meta-analysis done by Tsutsuura et al. showed that acute kidney injury (AKI) incidence rates reportedly increase with trough concentrations ≥15 μg/mL and further increased for trough concentrations ≥20 μg/mL. They believe that vancomycin trough concentrations should be kept below 20 μg/mL at all times and minimized wherever possible (18).

Longer duration of vancomycin can also lead to reduce vancomycin-associated AKI (19), also some drugs can affect serum concentration of vancomycin, for example ibuprofen treatment may increase the risk of overly high trough levels (20).

Research conducted in Europe showed that in intensive care units, the combination of ampicillin and gentamicin is most often prescribed as therapy for early neonatal sepsis, while vancomycin, gentamicin, cefotaxime and meropenem are most often prescribed for late neonatal sepsis (21).

Certain studies recommend that the dosing of vancomycin in newborns should be guided by body weight, gestational age and serum creatinine concentration. Due to the high degree of variability of pharmacokinetics in infants, it is considered that the concentration of serum vancomycin in order to achieve its antibacterial effect in the treatment of gram-positive bacteria should be between 10 and 15 μg/ml (22).

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Research, such as a retrospective study conducted in Taiwan, shows that only half of examined infants receiving vancomycin as part of empiric therapy for late neonatal sepsis achieved the target serum concentration of 10 to 20 μg/ml. Risk factors for elevated serum levels of vancomycin include elevated serum creatinine levels, as well as therapeutic use of ibuprofen (23).

These results are confirmed by a retrospective study conducted in China, which shows that the percentage of subjects who achieved the target serum concentration was 45% with the empirical initial regimen, while in the case of dose adjustment, that percentage was 55.2%. These results indicate that the optimal serum concentration of vancomycin cannot be achieved based on empirical dose adjustment alone (24).

Limitations

The main limitation of this study is small sample size. However, to the best of our knowledge, this is the first time that this type of study is being conducted in the neonates patients in Serbia. Other limitation of this study includes the detailed MICs of vancomycin were not available in the analysis of the effectiveness of vancomycin target trough concentrations.

Conclusion

Sepsis represents a complex clinical syndrome, with potential life-threatening organ dysfunction. A big challenge in therapy is the use of antibiotics in neonates with sepsis. Especially the use of antibiotics such as vancomycin, in which, due to physiologically reduced function of organs in newborns and pathophysiological changes caused by sepsis, potentiation of nephro- and ototoxicity can occur. Therapeutic monitoring of vancomycin is extremely important especially in newborns due to the very pharmacokinetic specificity of this population.

Due to small sample size, effect of gestational age, body weight and serum creatinine concentration on serum vancomycin concentration in newborns were not found to be statistically significant. However, descriptive statistics show that significant differences can be found in these groups, especially in the group examining effects of serum creatinine on serum vancomycin concentration, which shows that higher creatinine levels lead to increased serum vancomycin concentrations, also only in the group of subjects whose body weight was over 3000g was the value of the serum

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concentration obtained as part of the reference values for newborns, suggesting a potential effect worth further investigation.

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