

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

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Neonatal sepsis is a serious medical condition characterized by systemic infection in infants younger than 28 days. Therapy for late neonatal sepsis is a 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 preferred therapeutic range. Due to the small sample size, the effect of gestational age, body weight, and serum creatinine concentration on serum vancomycin concentration weren't found to be statistically significant. However, descriptive statistics show that a significant difference can be found between these groups, suggesting a potential effect worth further investigation.

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Key words: neonatal sepsis, vancomycin, therapeutic drug monitoring

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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*, and *Streptococcus pneumoniae*, 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 begin 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 (e.g., 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.

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

Our research aims 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.

Materials 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 intravenously at a dose of 15 mg/kg every 8 hours. If patients were premature infants up to 29th weeks of gestation, they received vancomycin every 12 hours.

The study was conducted in premature infants up to the 32nd gestational week, premature infants between the 33rd and 36th gestational weeks, and term infants of both sexes with a diagnosis of neonatal sepsis. One blood sample was collected from each subject. 1 ml of

blood was taken from the subjects during the period when blood is sampled for routine biochemical analyses after reaching the equilibrium state of vancomycin in the body (30 to 60 minutes before the fourth dose of vancomycin), at the Clinic of Pediatrics of the University Clinical Center Niš. A portion of the sampled blood of 0.5 ml, used to determine the serum concentration of vancomycin, was centrifuged for 10 minutes at 3000 revolutions per minute, after which the separated serum was transferred to tubes for analysis. The remaining sampled blood of 0.5 ml was used to determine routine biochemical analyses.

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

The study was conducted in compliance with 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. To collect demographic data, medication data, and microbiological and biochemical analyses results, medical records were reviewed.

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 the first two groups of newborns ($p < 0.001$) (Table 1)

The majority of patients were admitted during the 1st day of age (40%) with a diagnosis of early neonatal sepsis, with initial antibiotic therapy of ampicillin and amikacin or ampicillin and gentamicin. If the initial therapy proved ineffective or after blood culture results arrived, the initial treatment would be replaced by a therapeutic combination of Vancomycin and meropenem. The majority of patients admitted during the first day of age were infants born before the 32nd week of gestation (50%). There was a moderate positive correlation between gestational age group and the age of admission ($p = 0.563$, $p < 0.01$).

Table 1. Average body weight of subjects (g)

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

Vancomycin therapy lasted for 7 days (52%) for the majority of subjects, while a smaller group (16%) was treated for just 5 days; 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. No statistically significant association was found between gestational age and the duration of vancomycin treatment.

Blood cultures were performed 29 times, 15 of which 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 have been 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 was insufficient to determine sensitivity. The highest number of blood cultures was *Staphylococcus epidermidis* (17%) and *E. coli* (10%). The presence of *Staphylococcus spp.*, *Staphylococcus haemolyticus*, *Enterococcus faecium*, and *Klebsiellae pneumoniae* was also recorded. (Table 2).

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

Table 2. Blood culture

<i>Staphylococcus epidermidis</i>	5
<i>Staphylococcus sp.</i>	1
<i>Sterilo</i>	15
<i>E. coli</i> ESBL+	3
<i>Staphylococcus haemolyticus</i>	1
<i>Enterococcus faecium</i>	1
<i>Klebsiellae pneumoniae</i>	2
Candida	1

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

Vancomycin serum concentration

The value of vancomycin serum concentration was expressed in $\mu\text{g/ml}$ (as the concentration was measured). Guidelines for vancomycin serum concentrations in adults recommend a reference range above 10 $\mu\text{g/ml}$, except for Methicillin-resistant *Staphylococcus Aureus* (MRSA) pneumonia, endocarditis, or bone infections in infants, while reference values between 15 and 20 $\mu\text{g/ml}$ are advised. It is necessary to note that the reference values were determined based on 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 $\mu\text{g/ml}$, while others suggest an even smaller range between 10 and 12 $\mu\text{g/ml}$ to avoid potential nephrotoxicity (8, 9).

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

Out of the total number of subjects, only one had a concentration lower than 10 $\mu\text{g/ml}$,

which is also the lowest recorded dose. An equal number of respondents had values between 20 and 30 $\mu\text{g/ml}$ (23%), as well as over 30 $\mu\text{g/ml}$ (23%), while the largest number of respondents had values between 10 and 20 $\mu\text{g/ml}$ (46.2%). The value of serum vancomycin between 10 and 15 $\mu\text{g/ml}$ was recorded in 38.5% of subjects, while the values of vancomycin in serum between 15 and 20 $\mu\text{g/ml}$ were recorded in 7.7% of subjects (Figure 1).

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

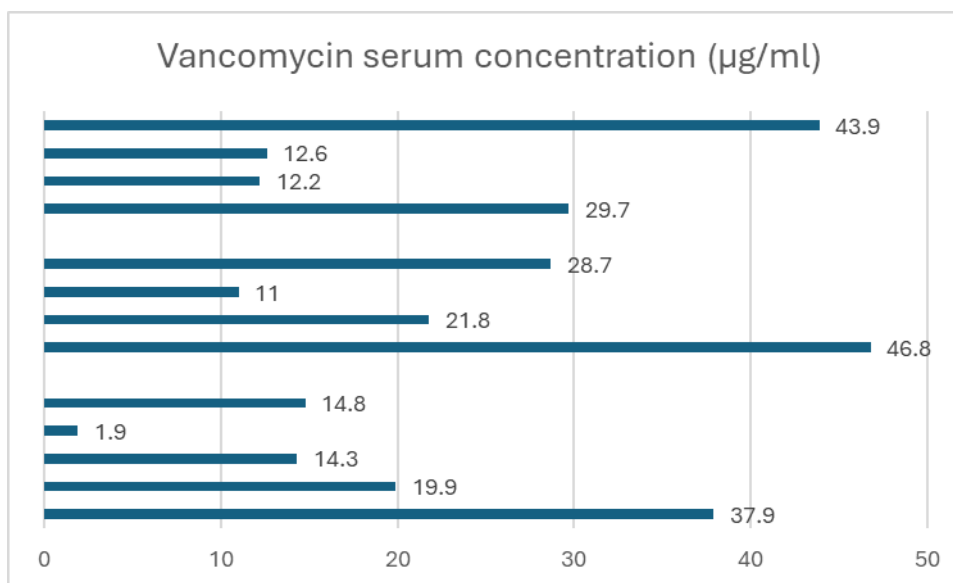


Figure 1. Vancomycin serum concentration ($\mu\text{g/ml}$)

Table 4. Effect of gestational week on serum vancomycin concentration

Weeks of gestation	average	min	max	F=0.518
Newborns born before 32 weeks of gestation	24.60 ± 15.23	12.2	43.9	p=0.611
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 $23.02 \pm 13.29 \mu\text{g/ml}$, while in newborns whose birth weight was between 2000 and 3000 it was $31.60 \pm 12.96 \mu\text{g/ml}$, and in newborns whose birth weight was over 3000g, the average concentration of vancomycin is $10.33 \pm 7.31 \mu\text{g/ml}$, 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, it was observed that 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.

In subjects whose measured values of serum creatinine were less than $60 \mu\text{mol/l}$, the

average value of vancomycin in serum was $17.24 \pm 13.26 \mu\text{g/ml}$, which is the smallest deviation from the reference values. With a serum creatinine concentration between 60 and $90 \mu\text{mol/l}$, there is also an increased level of vancomycin in the serum, namely the mean value is $22.62 \pm 13.56 \mu\text{g/ml}$, the lowest value is $11 \mu\text{g/ml}$, while the highest measured value is $46.8 \mu\text{g/ml}$. In the case when serum creatinine values exceed $90 \mu\text{mol/l}$, the value of vancomycin in serum also increases, with an average value of $36.80 \pm 10.04 \mu\text{g/ml}$, where the minimum value was $29.7 \mu\text{g/ml}$, and the maximum value was $43.9 \mu\text{g/ml}$ (Table 6). These differences were not found to be statistically significant. However, there are noticeable differences between different values of creatinine concentration, indicating that higher creatinine levels lead to increased vancomycin serum concentration.

Table 5. Effect of body weight on vancomycin concentration

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

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

serum creatinine concentration ($\mu\text{mol/L}$)	average	min	max	F = 1.587 P = 0.252
< 60	17.24 ± 13.26	1.9	37.9	
60–90	22.62 ± 13.56	11	46.8	
> 90	36.80 ± 10.04	29.7	43.9	

Discussion

Therapeutic drug monitoring entails adjusting medication dosage based on the serum concentration of the drug in blood in order to achieve the optimal 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. The determination of the lowest drug concentration is made immediately before administration of a new dose.

Determining the concentration allows for informed decisions to be made in order to maintain the drug concentration within therapeutic limits, which enables 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 research showed in subjects whose birth weight was over 3000 g, 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 3000 g is characteristic for full-term newborns. 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 other hand, 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).

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 serum creatinine levels. Vancomycin is also primarily eliminated by glomerular filtration. The reduced ability to excrete vancomycin can lead to an increase in vancomycin serum level. Concentration of serum creatinine can be a 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 increase 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 reduced vancomycin-associated AKI (19). Also, some drugs can affect the 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 should be between 10 and 15 µg/ml (22) to achieve its antibacterial effect in the treatment of gram-positive bacteria.

Research, such as a retrospective study conducted in Taiwan, shows that only half of the 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 the small sample size. However, to the best of our knowledge, this is the first time that this type of study is conducted in neonatal patients in Serbia. Another limitation of this study includes that the detailed Minimum inhibitory concentration 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 critically important, especially in newborns, due to the very pharmacokinetic specificity of this population.

Due to the small sample size, the effects 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. Additionally, only in the group of subjects whose body weight was over 3000 g was the serum concentration found to be within the reference values for newborns, suggesting a potential effect worthy of further investigation.

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UTICAJ GESTACIJSKE STAROSTI, TELESNE MASE I KONCENTRACIJE KREATININA U SERUMU NA KONCENTRACIJU VANKOMICINA U SERUMU PRILIKOM LEČENJA NEONATALNE SEPSE: PILOT STUDIJA JEDNOG CENTRA

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Neonatalna sepsa je ozbiljno zdravstveno stanje, koje karakteriše sistemska infekcija kod novorođenčadi mlađe od dvadeset osam dana. Terapija kasne neonatalne sepsa zasnovana je na kombinaciji vankomicina i meropenema. Cilj ove pilot studije bio je da se ispita uticaj telesne težine novorođenčeta, gestacijske starosti i vrednosti kreatinina na koncentraciju vankomicina u serumu prilikom lečenja neonatalne sepsa. Istraživanje je obuhvatilo trinaest pacijenata koji su od juna do oktobra 2024. godine primljeni na Kliniku za pedijatriju Univerzitetskog kliničkog centra Niš sa dijagnozom neonatalne sepsa. Poželjna koncentracija vankomicina u serumu, koja iznosi između 10 µg/ml i 15 µg/ml, zabeležena je kod 38,5% ispitanika. Budući da uzorak uzet u obzir nije velik, može se reći da uticaj gestacijske starosti, telesne težine i vrednosti kreatinina na koncentraciju vankomicina u serumu nije statistički značajan. Međutim, deskriptivna statistika pokazuje da se može uočiti značajna razlika između ovih grupa, tako da je poželjno obaviti dalja istraživanja.

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Ključne reči: neonatalna sepsa, vankomicin, terapijsko praćenje lekova

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