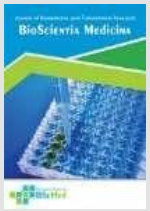
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Role of CysC Levels as Biomarkers for Renal Function in the Use of Gentamicin for Preterm Infants Aged 28-36 Weeks with Neonatal Sepsis: A Narrative Literature Review

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ARTICLE INFO

Keywords:
Cystatin C
Gentamicin
Neonatal sepsis
Preterm infants
Renal function

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i4.964

A B S T R A C T

Premature infants with neonatal sepsis often require antibiotics, such as Gentamicin, commonly used in the NICU to treat suspected Gram-negative infections associated with neonatal sepsis. However, to limit the risk of nephrotoxicity associated with minimum levels, the use of high-dose Gentamicin with extended dosing intervals has been widely adopted in NICU clinical practice. Gentamicin use can impact kidney function. The examination of Cystatin C (CysC) levels as a biomarker to assess kidney function and nephrotoxicity due to antibiotic use is highly recommended, especially in premature infants. Gentamicin use in preterm infants can influence CysC levels as a biomarker for kidney function. The correlation between Gentamicin use, changes in CysC levels, and the impact on kidney function highlights the need for strict monitoring of these parameters. This study concludes that CysC levels can be a crucial indicator in assessing the impact of Gentamicin use on kidney function in preterm infants with neonatal sepsis. Routine monitoring of CysC levels can aid in early identification of potential kidney issues and support appropriate clinical decision-making in the use of antibiotics for this vulnerable preterm infant population.

1. Introduction

Perinatal infections and hospital-acquired infections are severe issues in newborns, especially in neonates treated in the neonatal intensive care unit (NICU).[1] Premature infants are vulnerable to microbial infections as they often undergo invasive procedures, including central catheters for parenteral nutrition and ventilators for respiratory support.[2] The need for assistive devices can be a source of microbes, especially during prolonged hospital stays. Therefore, appropriate antibiotic therapy is often necessary to prevent systemic infections.[3] The most commonly used aminoglycoside antibiotics in premature infants are netilmicin, Gentamicin, and amikacin.[4]

The kidney is a major organ in the excretion of drugs and their metabolites, serving as a passive filter. The drug-handling mechanisms by the kidney involve glomerular filtration and, in some cases, include tubular secretion, tubular reabsorption, and intracellular enzymatic processes within the proximal tubular cells.[5] Physiological aspects of neonatal kidneys that can increase the likelihood of nephrotoxicity include that a significant portion of drugs is predominantly excreted through the kidneys, and there is a progressive concentration of compounds filtered and secreted in the renal tubule lumen.[6]

Exposure to aminoglycosides during the development of the kidneys can lead to a reduced

formation of nephrons, along with structural changes in the tubules and tubular damage.[5] Gentamicin is an aminoglycoside antibiotic with a narrow therapeutic index, posing risks of nephrotoxicity and ototoxicity. Like other antibiotics in this class, the pharmacokinetics of Gentamicin are highly influenced by the patient's age, body weight, and kidney function.[7] Gentamicin is often utilized in the Neonatal Intensive Care Unit (NICU) to treat suspected Gram-negative infections associated with neonatal sepsis. However, to mitigate the risk of nephrotoxicity linked to minimum levels, the practice of using high-dose Gentamicin with extended dosing intervals has been widely adopted in NICU clinical settings.[8]

Serum creatinine is a widely used endogenous marker for kidney function. There is a broad variation in sample collection methods and glomerular filtration rate (GFR) calculations, which can lead to overestimations of kidney function. These methods are impractical in neonates and small infants, necessitating an estimated glomerular filtration rate (eGFR) to assess kidney function. Due to significant developmental changes in neonatal kidneys, GFR assessments applicable to children over 18 months cannot be applied to neonates and infants.[9]

Cystatin-C (CysC) is a small molecule of 13.3 kDa, a non-glycosylated cysteine protease inhibitor with 122 amino acids (lysosomal protease). It prevents the breakdown of specific intracellular and extracellular proteins in the body. This compound is constitutively expressed by all nucleated cells, and it is synthesized and released into the plasma at a stable rate.[10] Cystatin-C levels in the blood are not influenced by muscle mass, physical activity, gender, age, etc. Therefore, CysC is considered a more realistic marker for assessing glomerular function, even in conditions such as cachexia or acute kidney injury (AKI), where serum creatinine may underestimate actual kidney function. CysC is regarded as a specific marker for glomerular filtration rate (GFR) assessment rather than a primary marker for AKI, although it can be used to determine AKI. Numerous independent studies have shown the superiority of serum Cystatin-C compared to serum creatinine, especially in detecting minor changes in GFR decline. Researchers have recently begun using serum CysC as a GFR marker in some toxicology studies, although its clinical use has been widespread.[10,11]

Neonatal sepsis in preterm infants

Neonatal sepsis in preterm infants is a medical condition occurring in babies born before the pregnancy reaches 37 weeks. According to the World Health Organization (WHO), there are three categories of premature births based on gestational age: extremely preterm (<28 weeks), very preterm (≥28 weeks - <32 weeks), and moderate to late preterm (32-37 weeks).[12] Neonatal sepsis is a severe medical condition that occurs in infants aged < 28 days. Neonatal sepsis is associated with the body's vital response to bacterial, viral, or fungal infections. This infection triggers widespread inflammation in the newborn's body, disrupting normal blood flow to vital organs and body parts, leading to organ failure and even death. The definition of neonatal sepsis involves a systemic inflammatory response syndrome following suspected or existing infection, with or without the presence of bacteria in the blood, which can be confirmed through positive blood cultures during the first 28 days of the baby's life. This condition is a leading cause of morbidity and mortality in newborns, especially in middle and low-income countries. Therefore, for infants born before 37 weeks of pregnancy (preterm), it is essential to understand that preterm babies have an underdeveloped immune system, making them vulnerable to infections, including neonatal sepsis.[13–15]

Neonatal sepsis is divided into two categories based on the onset time after birth: early-onset sepsis (EOS) occurring within the first 72 hours of life and late-onset sepsis (LOS) occurring at ≥ 72 hours of life. These categories have different risk factors and causes.[15] Early-onset sepsis (EOS) occurs due to the vertical transmission of pathogens from the mother to the baby during childbirth as the baby passes through the vaginal canal. EOS is predominantly caused by

gram-positive pathogens such as Group B Streptococcus (GBS), coagulase-negative Staphylococcus, and gram-negative bacteria, including *Escherichia coli*, *Haemophilus influenzae*, and *Listeria monocytogenes*. Risk factors for EOS include conditions such as chorioamnionitis, GBS colonization, premature delivery, and prolonged rupture of membranes (>18 hours).[15,16]

In a study involving 4696 women, prenatal culture results indicated that 24.5% of them were colonized by Group B Streptococcus (GBS), and during delivery, the positive culture rate reached 18.8%. There were 10% of women who were initially culture-negative before delivery but tested positive during labour. In this study, 93.3% of cases involved the administration of intrapartum antibiotics as a preventive measure, and the incidence of early-onset GBS disease in infants was 0.36 per 1000 births.17 Conversely, late-onset sepsis (LOS) occurs through horizontal transmission of pathogens from the surrounding environment to the newborn, typically through contact with healthcare professionals or nurses or nosocomial infections due to prolonged hospitalization. The risk of LOS can also increase if the baby undergoes invasive procedures such as intravascular catheter placement, mechanical ventilation, challenges in early breastfeeding through breastfeeding, prolonged administration of nutrition through parenteral routes, surgical procedures, underlying respiratory and cardiovascular diseases, and length of hospital stay. Coagulase-negative *Staphylococci*, especially *Staphylococcus epidermidis*, are the primary cause of LOS in developed countries and account for more than 50% of LOS cases.[18,19]

Low birth weight (LBW) and prematurity are high-risk factors. Based on a multi-centre observational study, it is indicated that neonatal sepsis most commonly occurs in premature infants (82%) and LBW infants (81%).19 Premature infants have a higher risk of developing sepsis or infections compared to full-term infants, primarily due to several factors. These factors include an underdeveloped immune system, an immature innate immune system, and the frequent use of invasive devices often required in the care of vulnerable premature infants, making them susceptible to infections.[16,20]

The incidence of neonatal sepsis is estimated to range between 1 per 1000 and 12 per 1000 live births in high-income countries, while in low- and middle-income countries, the figures are estimated to be between 7.1 per 1000 and 38 per 1000 live births in Asia, 6.5 per 1000 and 23 per 1000 live births in Africa, and 3.5 per 1000 and 8.9 per 1000 live births in South America and the Caribbean. Early-onset sepsis occurs less frequently than late-onset sepsis, with research in the United States and Australia indicating an incidence of early-onset sepsis ranging from 1.5 per 1000 to 3.5 per 1000 live births, while late-onset sepsis reaches 6 per 1000 live births. The incidence of early-onset sepsis is higher in neonates with very low birth weight, reaching 4 per 1000 in low birth weight compared to 0.4 per 1000 in full-term neonates. The incidence of early-onset sepsis in high-income countries is around 1 per 1000 live births but increases with decreasing gestational age and birth weight, reaching around 11 per 1000 live births in neonates weighing 401 g to 1500 g.[13–15,19]

The use of gentamicin in neonatal sepsis

Neonatal sepsis presents with nonspecific and diverse clinical signs and symptoms, making it challenging to diagnose. Hence, adequate empirical antibiotic treatment is essential as neonatal sepsis can be effectively prevented in the early stages. The World Health Organization (WHO) recommends ampicillin combined with gentamicin as the first-line empirical treatment and third-generation cephalosporins as the second-line treatment. International guidelines vary in recommending gentamicin dosage regimens, with dose ranges between 4 - 5 mg/kg every 24-36 hours. The current WHO guidelines suggest a once-daily dose, ranging from 3 - 7.5 mg/kg/day, depending on the infant's age and weight.[22]

Gentamicin is a necessary aminoglycoside antibiotic to treat infections caused by gram-negative aerobic bacteria. Aminoglycosides, an antibiotic frequently employed in the neonatal intensive care unit (NICU), are often administered as initial therapy

to address potential infections in newborns. Aminoglycosides can accumulate in the kidneys, creating high concentrations in the renal cortex, which can eventually lead to injury in the kidney tubules.[22,23] Gentamicin has a narrow therapeutic range. The effectiveness of aminoglycosides is associated with a high peak concentration relative to the minimum inhibitory concentration (MIC) of the infectious microorganism, with a peak/MIC ratio >8–10. Conversely, low concentrations are linked to a lower risk of nephrotoxicity and ototoxicity (at least <2 mg/L, but <1 mg/L is often recommended). These antibiotics work by inhibiting protein synthesis and lysing the bacterial cell membrane. Gentamicin is a first-line choice for combating resistant gram-negative aerobic bacteria, especially with other antibiotics, such as β-lactams, to treat aerobic severe bacterial infections like pneumonia or sepsis. It is highly effective against *P. aeruginosa*, *Enterobacter*, *Klebsiella*, and *Serratia*. Adequate serum levels are required to maintain its effectiveness, which can potentially be toxic (<10 mg/L), but the trough concentration should be <2 mg/L to avoid toxicity. Gentamicin is both ototoxic and nephrotoxic. It stimulates the contraction and proliferation of mesangial cells, decreasing the surface area and filtration rate of the glomerulus. Additionally, with proximal tubule damage, there is an increased delivery of sodium to the distal nephron, activating the tubule-glomerular feedback mechanism, causing vasoconstriction of the afferent arteriole, subsequently reducing renal blood flow and glomerular filtration rate.[23]

Serious toxicity becomes apparent after 7-10 days of treatment. To reduce toxicity, treatment is optimized to minimize side effects in infants with normal kidney function. The strategy of once-daily administration, with a high initial dose and low subsequent doses, is considered an effective approach. A loading dose is useful to increase peak concentration immediately after administration. The recommended dosage for preterm infants <35 weeks of gestation is 3 mg/kg as a single daily dose. For newborns >35 weeks of gestation, a single daily dose of 4 mg/kg is recommended, and for neonates with severe infections, 5 mg/kg daily in two divided doses is suggested. It is advised that infants with gestational age <32 weeks should receive 3 mg/kg gentamicin as a single dose every 36 hours during the first week. A single daily dose is recommended for all other infants, provided renal function is normal.[24] If given for more than 48 hours, serum gentamicin concentrations should be measured. Urinary alanine aminopeptidase, urinary β2-microglobulin, serum urea, and urinary β2-microglobulin have been measured in infants treated with gentamicin and ampicillin or cloxacillin for toxicity detection. Urinary aminopeptidase levels increased in almost all cases, indicating damage to the cells of the proximal tubules. Changes in urinary β2-microglobulin followed the normal physiological process in neonates after birth. Urea and β2-microglobulin levels in serum did not indicate any depression in glomerular filtration.[18,19,22–25]

Gentamicin is passively filtered unchanged by the glomerulus and concentrated in the urine. Healthy infants' half-life decreases by over 50% during the first 7-10 days after birth. The elimination phase of gentamicin is longer in newborns than in adults. The half-life ranges from 5.4-10 hours in premature neonates <1 week old but is 2-3 hours in adults. Postnatal age is a crucial factor influencing the half-life and clearance of gentamicin. At a postnatal age of 6 ± 2 days, the half-life and clearance are lower than in infants with a postnatal age of 15 ± 4 days. These differences reflect the maturation of kidney excretory function. Tubular damage to the kidneys is progressive over time and can even lead to a Bartter-like syndrome. Blood levels should constantly be monitored to minimize this risk. Gentamicin pharmacokinetics vary widely in infants. In premature infants, the half-life is longer, and clearance is more diminutive than full-term infants. Hypothermia, extracorporeal membrane oxygenation, and patent ductus arteriosus prolong the half-life of gentamicin. Patent ductus arteriosus is often found in premature neonates and has consequences for blood flow to the kidneys and liver and drug clearance through the

kidneys and liver. The volume of distribution tends to be larger, and elimination rates are lower in neonates with a patent ductus arteriosus. Postnatal age is a crucial determinant for the half-life of gentamicin; premature infants have a longer half-life than full-term infants. Concentrations should be kept below two mg/L to avoid toxicity.[24]

Physiology of the kidneys in preterm infants

The function of the kidneys undergoes continuous changes by adapting to the newborn and fetal stages. In the early developmental period, the placenta is primarily responsible for maintaining fetal fluid-electrolyte homeostasis, acid-base balance, and excretion needs. During this period, the fetal kidneys play a role in maintaining amniotic fluid levels and regulating fetal blood pressure. Urine production begins when the fetus reaches 16 weeks of gestation. Nephrogenesis in the fetus is completed around 34-36 weeks of gestation, with over 60% of nephrons formed in the last trimester of pregnancy. However, kidney maturation continues into the postnatal period.[26,27]

After birth, there is a rapid increase in glomerular filtration and a decrease in renal vascular resistance in response to the rise in mean arterial blood pressure. Nephrogenesis is considered complete in full-term infants. In full-term infants, there are typically 300 thousand to over 1 million nephrons, closely related to birth weight. Neonatal kidneys continue to mature during the first two years after birth as renal vascular resistance decreases, cardiac output to the kidneys increases, and the glomerular filtration rate (GFR) approaches adult levels.[26,27] The renal system in very low birth weight (VLBW) or premature infants is significantly different from that of full-term infants. There is a delay in renal function in VLBW infants due to immaturity, which may persist during the adaptation to extraterrestrial life.[27]

Premature infants born before 32 weeks were found to have a lower estimated glomerular filtration rate (eGFR), measured using cystatin C (CysC) at full-term gestational age. In contrast, the highly premature group born at <28 weeks of gestation was shown to have an eGFR comparable to full-term infants using urinary CysC despite having smaller kidneys. The authors concluded that this could be evidence of glomerular hyperfiltration and compensation for reduced nephron mass.[25]

Many premature infants are born during their nephrogenesis, with some born before reaching the peak period of nephron development. Nephron development continues after very premature birth with active glomerulogenesis, characterized by basophilic S-shaped bodies, extending up to 40 days postnatal. Very premature infants aged over 40 days who experience acute kidney injury (defined as an increase in creatinine >2.0 mg/dL) have fewer nephrons than premature infants without a history of kidney failure. During normal kidney development, nephrons grow from the corticomedullary junction towards the nephrogenic zone beneath the kidney capsule, forming "generations" of nephrons. Therefore, the newest nephrons are in the outer part of the kidney cortex. A recent autopsy study revealed that many premature infants have abnormal glomeruli in their outer kidney cortex, implying that nephrons developing in utero cannot mature normally. Autopsy studies also showed that preterm birth is associated with accelerated kidney maturation and a more significant proportion of morphologically abnormal glomeruli compared to age-matched stillborn controls. Thus, the number of nephrons formed in the first 4-6 weeks after birth is crucial in shaping the lifetime nephron mass in premature infants and should be supported as much as possible to avoid postnatal kidney injury.[25,26]

In premature infants, kidney function dynamically changes in the first weeks of life: The kidneys initially receive 2.5-4% of cardiac output at birth, which increases to 15-18% at six weeks of life, approaching adult values of 20-25%. Subsequently, GFR increases from 10-20 to 30-40 ml/minute/1.73 m^2 within a few days, reaching adult values >75 ml/minute/1.73 m^2 around two years of age. Glomerular and tubular function maturation in premature neonates depends on gestational age and postnatal age. Glomerular function is influenced by the initially low GFR, which

increases over time. On day 28, creatinine clearance is much lower than in full-term infants. There is a high incidence of pathological proteinuria, which may be caused by immaturity or acute kidney injury (AKI). However, there is significant variability in urinary albumin and β-2-microglobulin (β2-M), which do not correlate with renal injury markers.[26]

Renal examination

Assessment of kidney function in premature infants and its disorders is challenging and limited. Clinical signs may be delayed or nonspecific, such as oliguria or anuria, oedema, and electrolyte imbalance with the accumulation of nitrogen waste products. Newborns with pre-renal or hypoxic-ischemic renal failure are more likely to respond with oliguria/anuria due to cortical necrosis, while infants with nephrotoxic kidney disorders due to medications are more likely to maintain expected urine output, thus leaving limited clinical symptoms. Serum creatinine is the most commonly used marker for kidney function and is considered the gold standard for diagnosing acute kidney injury (AKI). Creatinine is influenced by age, muscle mass, maturity, and maternal creatinine in the first 72 hours of life, after which it gradually increases. Cystatin C is a new marker that is independent of body composition and size and is believed not to be influenced by maternal kidney function. Increased compensatory surface and reduced glomerular hyperfiltration can affect serum creatinine and cystatin C levels. However, assessing GFR using cystatin C as a marker is considered superior. More accessible in the NICU, it may facilitate the clearance of typical neonatal drug pharmacokinetics such as aminoglycosides, which also estimate adequate kidney plasma flow.[26]

Cystatin C is produced by all nucleated cells, freely filtered by the glomerulus, and entirely reabsorbed by the proximal tubules. Serum cystatin C, in some situations, may be more accurate than creatinine because muscle mass, dietary patterns, gender, or tubular secretion do not influence it. Serum cystatin C-based formulas perform well in estimating glomerular filtration rate. However, thyroid dysfunction, high-dose glucocorticoid therapy, and systemic inflammation can elevate cystatin C independent of kidney function. Based on numerous published studies, serum cystatin C stands out as the most promising biomarker for antibiotic-induced nephrotoxicity. Serum cystatin C increases before serum creatinine and can predict worsening stages of acute kidney injury (AKI) in premature infants receiving amikacin and in non-critically ill children receiving aminoglycosides.23 Serum cystatin C has a higher sensitivity (93.4%) compared to serum creatinine levels (86.8%) in determining glomerular filtration rate in normal kidney function. Cystatin C increases when the GFR reaches 88 mL/min/1.73m², while serum creatinine levels only rise after the GFR reaches 75 mL/min/1.73m².[28]

Recently, a neonatal definition for AKI has been proposed by kidney disease: Improving Global Outcomes (KDIGO), relying on an acute increase in serum creatinine above the baseline by 150-200% (stage 1), 200-300% (stage 2), or >300% (stage 3). This definition modifies the adult AKI definition and can be applied to neonates within the first 120 days of life. Utilizing this definition, 18% of low-birth-weight infants experience AKI during their hospital stay, which is independently associated with a 42% increase in mortality.[26,28]

Impact of gentamicin usage on alterations in cystatin C levels

Globally, 15% of all neonatal deaths are attributed to neonatal sepsis. Premature infants face a higher risk of infection or sepsis compared to term-born infants due to several factors, including an underdeveloped immune system, immature innate immunity, and the frequent use of invasive devices in the care of premature infants, rendering them susceptible to infections.[15,16,29]

Table 1. Adapted from KDIGO neonatal AKI definition 2013.[26]

Stage	Serum creatinine (µmol/l) rise by	Serum creatinine rise × reference value*	Urinary output (ml/kg/h)
0	< 26.5	< 1.5	≥0.5
1	≥26.5 (48 h)	≥1.5–1.9 (7 days)	<0.5x 6-12 h
2		≥2–2.9	<0.5x >12 h
3	≥221 or dialysis	≥3	<0.3x ≥ 24 h or anuria x ≥12h

*Reference creatinine is defined as the lowest previous serum creatinine value.

One of the antibiotics frequently administered in the neonatal intensive care unit (NICU) for initial therapy to address infections in newborns is Aminoglycoside. This antibiotic can accumulate in the kidneys, creating high concentrations in the renal cortex and ultimately injuring the renal tubules. A commonly used drug in treating neonatal sepsis is gentamicin, which disrupts bacterial protein synthesis and cell membrane integrity by binding to the 30S ribosomal subunit. Gentamicin is the first choice in addressing resistant aerobic gram-negative bacteria, especially in combination with other antibiotics like β-lactams, to treat serious aerobic bacterial infections such as pneumonia or sepsis. It is highly effective against *P. aeruginosa*, *Enterobacter*, *Klebsiella*, and Serratia. Maintaining sufficiently high serum levels is crucial for its effectiveness, as it can potentially be toxic (<10 mg/L). However, the lowest concentration should be <2 mg/L to avoid toxicity.[23,25,28] Gentamicin can cause damage to the proximal tubules in the S1 and S2 segments, with ultimate changes in the S3 segment. Additionally, with proximal tubule damage, there is an increase in sodium delivery to the distal nephron. This activates the tubule-glomerular feedback mechanism, causing vasoconstriction of the afferent arteriole and reducing renal blood flow and glomerular filtration rate. This increases the risk of acute kidney injury (AKI) in premature infants. The consequences of premature birth and low birth weight (LBW) result in alterations in the final number and development of nephrons, thereby increasing the risk of AKI and chronic kidney disease.[23,25,28]

Based on numerous published studies, serum cystatin C is the most promising biomarker for antibiotic-induced nephrotoxicity. This is because serum cystatin C, in certain situations, is more accurate than serum creatinine, as it is not influenced by muscle mass, diet, gender, or tubular secretion. Therefore, serum cystatin C increases before serum creatinine and can predict the worsening stages of acute kidney injury (AKI) in premature infants and non-critically ill children receiving aminoglycosides.[23]

2. Conclusion

Based on the results of various previously published studies, serum cystatin C emerges as the most promising biomarker for nephrotoxicity due to antibiotic use, particularly in premature infants. The superiority of serum cystatin C lies in its higher accuracy than creatinine, mainly because it is not influenced by factors such as muscle mass, diet, gender, or tubular secretion. Therefore, the increase in serum cystatin C levels can be detected earlier than serum creatinine, which can predict the progression of more severe stages of acute kidney injury (AKI). These findings apply to both premature infants and non-

critically ill children receiving aminoglycosides. Controlled randomized trials are needed to determine the appropriate cystatin C levels associated with gentamicin use in the perinatal period.

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