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EDITORIAL

Empiric therapy with vancomycin in the neonatal intensive care unit: let's ''get smart'' globally!☆,☆☆

Terapia empírica com vancomicina na unidade de terapia intensiva neonatal: vamos ''ficar espertos'' globalmente!

Pablo J. Sánchez[a,b,*], Mohannad Moallem[a,b], Joseph B. Cantey[c], Avante Milton[b], Ian C. Michelow[d,e]

[a] *Center for Perinatal Research, Division of Neonatology, Columbus, United States*
[b] *The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, United States*
[c] *Texas A&M Health Science Center College of Medicine, Baylor Scott & White, Temple, United States*
[d] *Rhode Island Hospital, Providence, United States*
[e] *Alpert Medical School of Brown University, Providence, United States*

Coagulase-negative staphylococci (CoNS) remain the most common organisms causing late-onset bloodstream infections (BSIs) among preterm infants in the neonatal intensive care unit (NICU).[1–4] Since the vast majority, if not all, of CoNS isolates are resistant to beta-lactam agents, including the penicillinase-resistant penicillins, vancomycin remains the drug of choice for proven infections. When CoNS emerged in the 1980s as the most frequently detected pathogen among preterm infants in the NICU,[5] many neonatologists and pediatric infectious disease specialists, including one of the authors (PJS), recommended the empiric use of vancomycin along with an aminoglycoside for suspected late-onset sepsis. The basis for this approach conformed to the traditional infectious diseases dogma that one should cover the most common organisms as part of empiric therapy.

With the emergence of vancomycin resistance among methicillin-resistant *Staphylococcus aureus* (MRSA)[6] and *Enterococcus faecium* isolates,[7] and its known association with previous vancomycin use,[8] it became imperative to consider the public health of our NICUs and decrease the usage of vancomycin. Outbreaks of vancomycin-resistant *Enterococci* along with reports of reduced vancomycin susceptibility among methicillin-resistant CoNS in the NICU added to the emergent situation.[9–12] Several studies in North America and Europe demonstrated that vancomycin reduction could be accomplished safely and without changes in mortality, duration of bacteremia, or complications attributable to late-onset sepsis.[13–18] Now, data are emerging from Latin America that such an approach works there as well![19,20] In Brazil, Bentlin et al.[20] surveyed the 16 centers of the Brazilian Neonatal Research Network on practices related to late-onset sepsis, and the center with the lowest incidence of late-onset sepsis used empiric therapy with oxacillin and an aminoglycoside.

Neonatologists are among the single largest users of vancomycin, and much of this use is inappropriate.[2,21–23] However, most antibiotic usage in the NICU is actually for empiric therapy.[24] Therefore, any strategy to reduce overall

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* Corresponding author.
E-mail: pablo.sanchez@nationwidechildrens.org (P.J. Sánchez).

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vancomycin usage must target initiation and not just discontinuation of therapy when cultures do not yield a pathogen susceptible only to vancomycin. Romanelli et al.[19] are to be commended for pursuing this much-needed investigation and worthy goal!

As others before them have shown, Romanelli et al.[19] have demonstrated that one can safely reduce the empiric use of vancomycin in very-low-birth-weight infants (VLBW; birth weight <1500 g). In an NICU with a high prevalence of CoNS and low rate of MRSA disease, the authors compared healthcare-associated infections (HAI) among high risk infants (VLBW, presence of a central venous catheter, use of mechanical ventilation, surgery, and treatment with an antimicrobial agent) during a period (January 2011–December 2012) when vancomycin was used for empiric therapy for possible late-onset sepsis (>48 hours of age) with a subsequent period (January 2013–December 2014), when oxacillin was the preferred agent. Their intent was to compare the bacteriology of HAIs that occurred during the two periods, and importantly, measure such safety outcomes as mortality. Among the 1229 infants enrolled during the study period, 367 (30%) had 538 HAI episodes, and the total number of HAIs was reduced significantly during the oxacillin treatment period. Also unexpectedly, and possibly due to a Hawthorne effect, there was a significant reduction in HAIs due to *S. aureus*, with all but one isolate susceptible to methicillin (during the empiric oxacillin treatment period). There was a concomitant increase in HAIs due to CoNS during the oxacillin period, so it is not unexpected that the duration of treatment with oxacillin decreased during the second period (median time, 11.5 to six days), while vancomycin use increased from a median of eight to nine days. Unfortunately, the authors did not provide the days of therapy per 1000 patient days for oxacillin and vancomycin in order to document their actual usage and the effect that the change in guideline had on overall use, nor did they provide information on the actual management of these infants – how many blood cultures were performed? The practice of obtaining two blood cultures from different sites helps to distinguish pathogens from contaminants, since the isolation of CoNS from just one of two blood cultures should be considered as contamination and not be treated with prolonged vancomycin therapy. Moreover, if a blood culture yielded CoNS, was a repeat culture performed before changing to vancomycin? Methicillin-resistant CoNS, isolated from a single blood culture in an infant who received empiric oxacillin therapy, should be considered a contaminant if a repeat blood culture before switching to vancomycin is sterile. Such practices can lead to a further decrease in vancomycin usage in NICUs. Finally, the authors did not provide information on what was used for empiric coverage of suspected Gram-negative infection. It is known that such coverage can significantly impact the types of microorganisms responsible for neonatal sepsis and their antibiotic resistance patterns.[16]

The authors also report no change in BSIs due to fungi or Gram-negative organisms.[19] The latter finding is of interest given the increase in Gram-negative BSIs in many NICUs in the United States – infections that tend to be of higher virulence[25] and more resistant to usual antimicrobial therapy. Of note, previous studies, one in children[26] and others in the NICU setting,[27–29] have associated prior vancomycin exposure with later development of Gram-negative BSIs. It may be that in the current report[19] the sample size was insufficient to find such an association.

Importantly, as seen in other studies,[15,17,30] the authors[19] found no change in either mortality or case-fatality rates between the two periods. In addition, there was no significant difference in the number of central-line-associated-BSIs, ventilator-associated pneumonia, or catheter-associated urinary tract infections between the two periods.

BSIs due to CoNS in preterm infants are associated with substantial short-term morbidity as well as long term neurodevelopmental impairment.[31] However, they are not associated with increased mortality, and in fact, CoNS BSIs have significantly less mortality than that due to other bacterial pathogens.[32] Moreover, preterm infants who have CoNS bacteremia have mortality rates similar to that observed among uninfected preterm infants.[2] With improvements in blood culture techniques that provide culture results approximately every 10 min, the neonatologist can treat neonates empirically with oxacillin/nafcillin safely until the infant's blood culture yields Gram-positive cocci suggestive of staphylococcal species, at which time a change to vancomycin therapy is prudent. Over 80% of blood cultures containing CoNS isolates are positive after 24 h of incubation and virtually all after 36–48 h. Moreover, since the majority of rule-out sepsis episodes are culture-negative and antibiotics are not continued beyond 48 h, the use of a non-vancomycin empiric regimen means that many infants are never exposed to this agent – an important goal in this era of widespread antimicrobial resistance! Increased routine use of technologies such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) and polymerase chain reaction (PCR) for determination of the mecA gene which confers methicillin resistance could assist in the early identification of these organisms and their resistance patterns, further obviating the need for empiric vancomycin therapy. However, a major caveat for a vancomycin reduction guideline must be knowledge of MRSA colonization of infants in the NICU in communities with a high prevalence of MRSA colonization/disease. MRSA-colonized infants should receive empiric vancomycin therapy, as the morbidity and mortality due to MRSA can be substantial.[33]

In conclusion, Romanelli et al.[19] should be applauded for their support of antimicrobial stewardship in their NICU. Their efforts, as well as those of others that support the recommendations of the Brazilian National Health Surveillance Agency,[34] should encourage other Latin American NICUs to change their prescribing habits, thus minimizing the emergence of antimicrobial resistance. Nonetheless, appropriate empiric antibiotic therapy is only the beginning – the next frontier must be duration of antimicrobial therapy, knowing that prolonged antibiotic therapy in high-risk preterm infants is associated with changes in the microbiome, resulting in necrotizing enterocolitis, late-onset sepsis, bronchopulmonary dysplasia, invasive candidiasis, and even death. With respect to CoNS, duration of therapy as short as three to five days may be sufficient.[35,36] In the meantime, prudent vancomycin use[1] must remain a global public health imperative in our NICUs!

Conflicts of interest

The authors declare no conflicts of interest.

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