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► **To cite this version:**

M. Butin, O. Claris, F. Laurent. Clinical impact of vancomycin heteroresistance in staphylococcal strains involved in neonatal sepsis: Discussion of a case report. Archives de Pédiatrie, 2019, 26, pp.236 - 237. 10.1016/j.arcped.2019.03.002 . hal-03485087

**HAL Id: hal-03485087**

**<https://hal.science/hal-03485087>**

Submitted on 20 Dec 2021

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## **Clinical impact of vancomycin heteroresistance in staphylococcal strains involved in neonatal sepsis: discussion of a case report**

Short title: Clinical impact of vancomycin heteroresistance in staphylococcal strains involved in neonatal sepsis

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**Conflicts of interest:** none

***Abstract:***

Heteroresistance to vancomycin (HRV) represents a decreased susceptibility to vancomycin and is frequently observed in multidrug-resistant coagulase-negative staphylococci. The clinical significance of such heteroresistance is controversial, but several failures of vancomycin therapy have been related to HRV, especially in the neonatal population. Here we report the case of a preterm neonate, born at 26 weeks of gestation, who developed sepsis due to a multidrug-resistant HRV *Staphylococcus capitis* isolate. Bacteremia persisted despite adequate vancomycin serum concentration and catheter removal. The patient finally recovered after replacing vancomycin by linezolid. Through this case report, we would like to alert clinicians of the potential clinical impact of HRV and to discuss the lack of therapeutic alternatives in neonates.

***Keywords:***

Vancomycin, neonatal sepsis, *Staphylococcus capitis*, heteroresistance, linezolid, ceftaroline

## 1. Introduction

Heteroresistance to vancomycin (HRV) in staphylococcal strains is related to the presence of a minor proportion of resistant bacterial cells (at a frequency of  $10^{-5}$ – $10^{-6}$ ) among a majority of susceptible cells (defined by a vancomycin minimal inhibitory concentration [MIC]  $\leq$  2mg/L) [1]. HRV thus results in a decreased susceptibility to vancomycin but this phenotype is not routinely detected, and the strain is considered as fully susceptible by the usual methods of antibiotic susceptibility testing [1]. Several authors have previously reported HRV in clinical staphylococcal isolates, notably in the context of neonatal sepsis [2]. The coagulase-negative staphylococci are the most frequently affected species, especially the species *Staphylococcus capitis* [3,4]. The clinical significance of such heteroresistance is controversial; however, several cases of vancomycin therapy failures have been related to HRV in infected neonates [4]. Here, we report a case of persistent *S. capitis* bacteremia related to HRV in a preterm neonate.

## 2. Observation

A male preterm infant was born at 26 weeks' gestation by cesarean section because of severe growth restriction (birth weight 480 g, <3<sup>rd</sup> percentile) and fetal heart rate abnormalities. The infant had an Apgar score of 3-8-9-10 and developed a severe respiratory distress syndrome requiring early surfactant therapy and mechanical ventilation with high-frequency oscillation. Hemodynamic parameters were stable. No antibiotic course was initially prescribed because of the absence of risk factors for early-onset sepsis and blood culture sampled at day 0 was sterile. Early enteral feeding was administered but with poor tolerance and he received parenteral nutrition via an umbilical catheter for 3 days and then via an epicutaneous central catheter.

On day 7 his health status suddenly deteriorated with hypotension, tachycardia, gray color, anuria, abdominal distension, and increased respiratory support. Blood puncture was performed and he received antibiotics including vancomycin (continuous infusion of 25 mg/kg per day without loading dose), amikacin (one injection of 15 mg/kg) and cefotaxime (50 mg/kg every 12 h). Hemodynamic support was added (norepinephrine, vascular filling). The blood analyses revealed: C-reactive protein serum concentration of 17 mg/L, white blood cell counts of 4.7 G/L (neutrophils 1.1 G/L), and platelet counts of 53 G/L. The blood culture grew *S. capitis* and the antibiotic susceptibility test showed resistance to aminoglycosides and beta-lactams but susceptibility to vancomycin (MIC tested with E-test® 2 mg/L, resistance defined by EUCAST as MIC > 2 mg/L). After 48 h of therapy the patient was still unstable, the C-reactive dosage was 18 mg/L and the second blood culture grew with *S. capitis*, despite a vancomycin serum concentration of 19 mg/L (in-range). The central venous catheter was removed and a new catheter was immediately inserted to continue the required intravenous therapies. At 96 h of treatment, the patient improved with hemodynamic support withdrawal. However, the third blood culture grew *S. capitis*. The vancomycin serum concentration was 23 mg/L. No infected site was found during clinical and ultrasound examination of the heart, brain, and abdomen, suggesting the catheter was the single reservoir of bacteria. Lumbar puncture was not performed because of the absence of clinical or echographic signs of meningitis. The catheter was removed and replaced by a peripheral line for 48 h, but the fourth blood culture still grew *S. capitis*. Concomitantly the department of bacteriology reported that the isolate harbored an HRV phenotype (using macro E-test® analysis). Because the strain was susceptible to linezolid (MIC 2 mg/L, resistance defined by EUCAST as MIC > 4 mg/L), the therapeutic strategy was changed for intravenous linezolid at the dosage of 10 mg/kg every 12 h, leading to a sterile fifth blood culture after 48 h of therapy. The C-reactive protein serum concentration was <0.6 mg/L on day 10. Later, this infant developed severe

bronchopulmonary dysplasia but sepsis did not recur during his hospitalization in the neonatal intensive care unit (NICU).

### **3. Discussion**

Nosocomial bacteremia is a major issue in daily practice in NICUs and vancomycin is usually prescribed as a first-line antimicrobial regimen because of the predominance of methicillin-resistant coagulase-negative staphylococci in this bacteremia [5]. Persistent bacteremia (defined as more than two blood cultures growing the same bacteria in more than 48 h) represents up to 40% of these cases of bacteremia [6,7].

The management of infants presenting with persistent bacteremia is not standardized. First, because central line catheters could be the reservoir of adhesive bacteria, some authors recommend removal of the central line [8]. However, this removal can expose the patient to other issues (necessary to insert a second central line, numerous venous punctures, etc.) and does not always allow for a resolution of the bacteremia, as observed in our case report. Furthermore, in the case of persistent bacteremia, secondary infectious sites (including osteo-articular, brain, endocarditis, intra-abdominal, etc.) have to be checked. In our patient, no secondary infectious sites were observed.

In the present case, the patient finally recovered after replacement of vancomycin by linezolid, which was decided by the medical staff because of the persistence of the bacteremia and because of the identification of HRV in the isolated strain. The screening of HRV is not performed routinely, both because of the delay of the results and because it includes expensive and time-consuming methods. In our case, this screening was performed because the clinician notified the laboratory about the persistence of the bacteremia.

However, HRV is becoming increasingly frequent in coagulase-negative staphylococci involved in neonatal sepsis. In particular, this phenotype is almost constantly found in multidrug-resistant *S. capitis* isolates involved in neonatal sepsis [3,4]. Some *S. epidermidis* isolates also harbor this specific profile [2]. All these HRV isolates belong to epidemic clones; it has been recently shown that all the *S. capitis* strains isolated from neonates belong to the worldwide-disseminated clone NRCS-A, which is intrinsically HRV or resistant to vancomycin [2,4]. This feature could explain the success of these staphylococci clones in NICU settings, where the selective pressure for vancomycin is very high. Hence, a previous study demonstrated that *S. capitis* NRCS-A was able to rapidly acquire vancomycin resistance under selective pressure and that this resistance remained stable without selective pressure [9].

HRV can lead to therapeutic failure and raises the issue of the lack of alternatives in the specific neonatal population. The usual alternatives proposed in cases of vancomycin resistance in adult patients are teicoplanin, daptomycin, linezolid, and ceftaroline. However, teicoplanin susceptibility is directly altered in the case of HRV [1]. Similarly, cross resistance with daptomycin has been reported [9]. Linezolid usually remains efficacious against multidrug-resistant staphylococci, which is why it was chosen in the case described here. However, even if this drug has already been widely used in neonates, its use has not been approved and it may expose patients to adverse effects [10]. Moreover, linezolid use should be limited to strict indications so as to avoid any emergence of resistance. Finally, the use of ceftaroline in neonates has not been reported and cannot be recommended hitherto before further studies are carried out.

#### **4. Conclusion**

In clinical practice, HRV may constitute a major issue but is poorly recognized by clinicians because of a lack of information and because of the limits of laboratory tests. Preventing the diffusion of HRV isolates is crucial and is based on a limited and rational use of vancomycin in NICUs. Clinicians should be aware of this microbial phenomenon, so as to rapidly adapt their therapeutic strategy in the case of persistent bacteremia that may be linked to HRV (especially in cases of *S. capitis* infection). Safe alternative antimicrobial stewardships are lacking and further studies focused on the neonatal population are urgently needed.

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