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Narrative review – Theme Issue

Title: *Staphylococcus capitis* and NRCS-A clone: the story of an unrecognized pathogen in neonatal intensive care units

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Abstract

Background: In neonatal ICUs, nosocomial late-onset sepsis (LOS), mostly due to coagulase negative staphylococci, constitute a major cause of death or impairment. *Staphylococcus capitis*, usually considered as a poorly virulent species, has been reported as a cause of LOS.

Objectives: To review data regarding *S. capitis* neonatal LOS and the features of isolates involved.

Sources: PubMed was searched up to August 2018 to retrieve studies on the topic; the keywords used were “*S. capitis*”, “neonate”, “neonatal ICU”, “bloodstream infection”, “late onset sepsis”.

Content: Published data highlight the worldwide endemicity of a single *S. capitis* clone, named NRCS-A, specifically involved in LOS. NRCS-A harbours a multidrug resistance profile (including resistance to the usual first-line antibiotics used in NICUs). It is also able to adapt under vancomycin selective pressure that could confer an advantage for its implantation and dissemination in NICUs where this selective pressure is high. Moreover, a severe morbidity has been observed in NRCS-A-related LOS. The NICU environment, and especially incubators, constitute reservoirs of NRCS-A from which it could diffuse inside the setting. Finally, the virulome and resistome of *S. capitis* NRCS-A contain many genes potentially implicated in its specific epidemiology and pathophysiology, including the gene *nsr* that may be involved in its fitness and implantation in neonatal gut flora.

Implications: *S. capitis* must be considered as a true pathogen in neonates. The decreased susceptibility to vancomycin may be involved in failure of vancomycin therapy. Further studies are needed to better manage its diffusion inside each NICU but also worldwide.

Manuscript

Background

Each year approximately 15 million children world-wide are born prematurely (defined as all live births before 37 completed weeks) and these require intensive care and prolonged hospitalization [1]. In recent decades, technical and medical advances in neonatal intensive care units (NICUs) have improved the overall survival and prognosis of these preterm babies. Nevertheless, preterm birth-related complications still remain the major cause of neonatal death [2].

Among these serious complications, nosocomial late-onset sepsis (LOS; occurring after 3 days of life) is frequent in NICUs despite strict hygiene measures [3]. Between 20 to 30% of very low birth weight preterm babies develop LOS at least once during their stay in the NICU [4,5], and this is associated with a 5 to 10% mortality among those concerned [6] but may also result in respiratory or neurological impairments [7,8]. Nosocomial, especially catheter-related bloodstream infections, are the most frequent source of LOS because of the multiple indwelling devices used and invasive procedures performed in these vulnerable patients. Consequently, skin commensal coagulase-negative staphylococci (CoNS) are the most frequently involved pathogens [5].

Although *Staphylococcus epidermidis* has long been regarded as the main LOS-associated CoNS [9], the emergence of another CoNS species, *Staphylococcus capitis*, has been reported as a frequent cause of LOS in several studies [10–21]. This was unexpected because *S. capitis* is usually a non-pathogenic species and a member of the commensal flora [22]. Moreover, in adult patients, only a few sporadic cases of *S. capitis* infections have been reported (osteomyelitis, contamination of platelet concentrates, *etc.*) [23,24] and *S. capitis* is frequently considered as a contaminant of blood cultures or other human specimens [25].

The present narrative review gathers all available data regarding neonatal *S. capitis* LOS and the features of the strains involved.

Sources

An extensive search of PubMed (up to August 2018) was performed to identify relevant studies for the review. Search terms included “*Staphylococcus capitis*”, “neonate”, “neonatal ICU”, “bloodstream infection”, and “late onset sepsis”. The reference lists of all articles retrieved were

checked for additional relevant references. Studies published in English or French were considered in this review.

Results

Clinical features and prevalence data

Many studies concerning the epidemiology and clinical features of LOS do not distinguish the different CoNS species involved, and therefore little data is available about the prevalence and clinical characteristics of sepsis involving specifically *S. capitis* in neonates. The first study to have reported data on *S. capitis* LOS was published in 1999 and described 17 cases in a Taiwanese NICU [19]; among these patients there was one case of meningitis due to *S. capitis* LOS.

More recently, however, a single centre study that was conducted over a 4-year period in a French NICU and which included all preterm infants born at <34 weeks of gestation with LOS due to CoNS compared clinical severity of sepsis due to *S. capitis* to that due to other CoNS [10]. *S. capitis*-related LOS was associated with an increased rate of a composite index of death or serious morbidity during hospitalization (including chronic lung disease, grade ≥ 3 intraventricular haemorrhage, periventricular leukomalacia, grade ≥ 2 necrotizing enterocolitis). In this study, *S. capitis* was the most frequently involved species in LOS; the prevalence was 7% [10]. Another study conducted in the same French NICU during another period reported a prevalence of *S. capitis*-related LOS of 12%, indicating the persistence of *S. capitis* inside this NICU with fluctuation of prevalence over time [11].

A retrospective, laboratory-based epidemiologic study conducted in all French NICUs reported that *S. capitis* accounted for up to 46% of all cases of positive blood cultures in neonates (median 13%, interquartile range [10%-20%]) and represented 19% of all CoNS strains isolated from the blood cultures of neonates [26]. In the Taiwanese study that considered the period between 1995 and 1997, *S. capitis* represented 18% of CoNS isolates [19], whereas during the period between 1998 and 2000 in a Dutch NICU Van der Zwet *et al.* reported that *S. capitis* was found in 30% of CoNS isolates [12].

Taken together, these findings highlight the substantial prevalence of *S. capitis* infections in the NICU population, and demonstrate that there are variations over time and/or between NICU settings, but also that *S. capitis* may lead to more severe LOS as compared to other CoNS.

Worldwide dissemination of a unique *S. capitis* clone in NICUs

In the study reported by Van der Zwet *et al.*, amplified fragment-length polymorphism (AFLP) analysis performed on the 48 *S. capitis* strains isolated during a 3-year period in a NICU found that a clonal spread of a single *S. capitis* strain had occurred over this period [12]. The clonality between *S. capitis* strains isolated from a single centre was also observed in subsequent studies; de Silva *et al.* reported that all 29 *S. capitis* strains collected during a 1-year period in a NICU in the United Kingdom, shared the same pulsed-field gel electrophoresis (PFGE) profile [20], and a similar finding was reported for a *S. capitis* outbreak in a French NICU [13].

These previous reports of cases or local epidemics of *S. capitis* neonatal LOS were initially not regarded as related epidemic bursts [12–16,19,20], however in 2012, Rasigade *et al.* reported that 40 *S. capitis* isolates from 7 distant NICUs spanning the French territory clustered into a same and unique clone, named NRCS-A, defined on the basis of the *SmaI* PFGE profile of the isolates [17]. To explore the possible unrecognized dissemination of the NRCS-A clone on a larger geographical scale a study including 100 methicillin-resistant *S. capitis* strains isolated from neonates (n=86) and adult patients (n=14), between 2000 and 2013 from 4 different countries (France, Belgium, the United Kingdom, and Australia) was conducted. It found that all *S. capitis* strains from remote NICUs shared the same *SmaI* PFGE profile and belonged to the NRCS-A clone [27]. Furthermore, a recent study demonstrated that *S. capitis* NRCS-A strains have spread across the globe (for instance, Europe, North and South America, Asia, and Oceania), while retaining their clonal population structure [26]. These results were obtained by analysing the PFGE profile of 154 *S. capitis* strains isolated between 1994 and 2015 in 34 NICUs from 17 countries. Of note, *S. capitis* isolates from non-neonatal patients harboured high genetic diversity and were all different to the specific PFGE NRCS-A profile [17,27]. This unexpected finding was confirmed using other molecular typing methods including PFGE performed with another

restriction enzyme (*SacII*), multilocus sequence typing (MLST) analysis, *dru*-typing, and *SCCmec* typing.

More recently, whole genome phylogenetic analysis based on single nucleotide polymorphisms (SNP) of 5 NICU isolates (from 4 different countries) confirmed the high genetic relatedness within the NRCS-A clone (at most 162 SNPs over more than 2 million bp between the 5 isolates). In 2018 in New Zealand, Carter *et al.* analysed the whole sequences of 122 *S. capitis* isolates (including 56 from neonates and 9 from a NICU environment) and compared it with the 13 publically available *S. capitis* genomes (including the 5 previously cited NRCS-A genomes) [18]. They highlighted a single *S. capitis* lineage associated with neonates and the NICU environment. They demonstrated a high genomic conservation inside this lineage but also between these isolates from New Zealand and the 5 NRCS-A isolates from France, Australia, United Kingdom and Belgium. These findings demonstrate at a core-genome level the unusual worldwide endemicity of the NRCS-A clone, specifically in NICUs, contrasting with an apparent genomic conservation.

Microbiological characteristics and antibiotic resistance pattern of *S. capitis* strains

When reported, all isolates involved in *S. capitis* LOS exhibited a multidrug resistant (MDR) pattern that included resistance to beta-lactams and aminoglycosides but frequent susceptibility to fluoroquinolones [13,17,19,27]. This atypical susceptibility profile is likely to reflect the specific antibiotic selective pressure that exists in the NICU settings, where beta-lactams and aminoglycosides are widely used but fluoroquinolones rarely [27].

Several authors have also reported that *S. capitis* strains from neonates exhibited vancomycin resistance or heteroresistance [12,14,15,17,27], which is considered as an intrinsic characteristic of the NRCS-A clone by some authors [17,27], even if a recent analysis of a large collection of *S. capitis* isolates from a NICU in New Zealand did not identify such decreased susceptibility to vancomycin [18]. This may be responsible for potential therapeutic issues in infected neonates because vancomycin is classically used as the empirical first-line antimicrobial agents when a LOS is clinically suspected

[28]. For instance, in the first report of heteroresistance there was one fatal case despite vancomycin therapy [12].

This frequent decreased susceptibility to vancomycin could be the consequence of the adaptation of the NRCS-A clone to the vancomycin selective pressure existing in NICUs. Such adaptation has been demonstrated *in vitro* using a resistance selection model that mimics vancomycin selective pressure: in this model, *S. capitis* NRCS-A strains were shown to rapidly develop a stable resistance to vancomycin when subcultured with subinhibitory concentrations of vancomycin, without reversion when subcultured without vancomycin; of note this acquisition of vancomycin resistance was associated with an increase of cell wall thickness [29], as has been reported in *S. aureus* isolates [30]. However, the molecular determinants of vancomycin resistance/heteroresistance remain unknown. In addition, this acquisition of resistance occurred significantly faster in *S. capitis* NRCS-A than in *S. capitis* non-NRCS-A (from adult patients) and in other CoNS strains (from neonates). This might have contributed to the selection, then the establishment, and finally the success and diffusion of the *S. capitis* NRCS-A clone in NICUs, where vancomycin is widely prescribed.

Hence, alternatives to vancomycin have to be considered in case of *S. capitis* persistent bacteraemia. Interestingly, in the study of *in vitro* resistance selection described above, Butin *et al.* reported that vancomycin resistance in *S. capitis* NRCS-A was associated with an increase in daptomycin and teicoplanin minimal inhibitory concentrations (MICs), but not in linezolid MICs [29]. Linezolid thus appears as an interesting alternative. However it should be used cautiously because resistance to this drug has already been observed in *S. capitis* isolates from non-neonate patients [31] and because it exposes neonates to possible adverse effects [32]; in particular lactic acidosis during linezolid therapy has been reported as a frequent early side effect in children which should be carefully monitored [33].

Genomic and virulence features of *S. capitis* isolates involved in neonatal sepsis

S. capitis strains isolated from adult patients are classically poorly virulent. However, the high clinical severity of *S. capitis*-related LOS [10] suggests the presence of specific virulence factors in

NRCS-A isolates. Because biofilm formation is necessary for bacteria to colonise and invade the host using the catheter route, several authors have studied the ability of *S. capitis* isolates to produce this. It has been reported that a high proportion of *S. capitis* strains isolated from NICUs were able to form biofilm [16,18,34]. Nonetheless, the formation of biofilm may not be an indispensable feature for *S. capitis* infections as in a single NICU retrospective study of CoNS bloodstream infections, Hira *et al.* reported that most *S. capitis* isolates did not produce biofilm [21]. Differences in the conditions of biofilm measurement in these studies could explain these discrepancies because numerous environmental factors (i. e. medium supplementation with salt and/or glucose, material of the plate...) have an influence on biofilm production *in vitro*, and it is difficult to know which laboratory conditions are the closest to the physiological *in vivo* conditions.

Using a whole genome sequencing (WGS) approach, Simões *et al.* explored the virulence genes in NRCS-A clinical isolates and identified a large number of genes including the *icaABDCR* and *capABC* biofilm-related operons, Clp proteases, *embp* mediating adherence to fibronectin, and phenol soluble modulins (PSM) involved in pro-inflammatory activities [35]. Carter *et al.* recently confirmed these results on a large collection of NRCS-A isolates from New Zealand [18]. All these genes are not present exclusively in the NRCS-A clone, for instance this virulome is similar to that of *S. epidermidis* RP62A [36].

To identify genes that might be involved in the specific affinity of NRCS-A for neonates, Simões *et al.* compared 5 NRCS-A genomes with 7 publically available genomes of non-NRCS-A isolates [35]. Sixty-three genes were exclusively present in NRCS-A genomes. Among these 63 genes, 28 belong to a *SCCmec* cassette, whose the genetic structure and genomic environment are atypical and specific to the NRCS-A clone. Notably it is inserted next to another cassette harbouring genes of heavy metal detoxification, resulting in a composite cassette (*SCCmec-SCCcadlars/cop*) [37]. A remarkable feature of this cassette is the presence of a CRISPR element associated with *cas* genes, that is known to constitute a prokaryotic defense mechanism against foreign DNA, and that could confer an adaptive immune response in NRCS-A isolates [37].

Furthermore, among the 63 genes specifically present in NRCS-A isolates reported by Simões *et al.*, authors identified the *nsr* gene, coding for resistance to nisin, a bacteriocin usually produced by some bacteria of the gut microflora, especially those that efficiently colonized the gut during the first weeks of life [38]. The authors demonstrated the functional expression of the nisin resistance gene using a disk diffusion test. Nisin resistance might provide a fitness advantage to NRCS-A isolates. Further analysis is required to validate the hypothesis of the authors that resistance to nisin might be responsible for an increase in the ability of the NRCS-A clone to implant and maintain itself in the gut microflora of neonates.

Pathophysiology of *S. capitis* colonization and infection in neonates

The speculative role of nisin resistance in the ability of NRCS-A to colonize the gut reinforces the suggestion of several authors that the source of *S. capitis* NRCS-A might be the gut rather than the skin. This hypothesis is supported by several observations previously reported; in the study of Wang *et al.*, no catheter-related infection due to *S. capitis* was identified [19]. In addition, in the study reported by Hira *et al.*, the absence of production of biofilm in most *S. capitis* isolates suggested that bloodstream infection do not necessarily originate from the catheter [21]. Furthermore, in a case report of persistent LOS due to *S. capitis*, authors noted that the neonate did not have any central catheter at the time of the sepsis, and that he presented with gut disorders, indicating that the origin of the bacteria may be the gastro-intestinal tract [14]. To further explore this hypothesis, a prospective cohort study was conducted, including 229 neonates of a single NICU centre. The prevalence of *S. capitis* gut colonization was high since 36% of neonates had at least one *S. capitis*-positive stool culture during hospitalization [11]. Surprisingly, the presence of *S. capitis* in the gut microbiota was not a risk factor for *S. capitis* LOS.

This means that the gut may be the reservoir of *S. capitis* but that the presence of *S. capitis* in the gut is not sufficient to induce LOS, suggesting that another factor is implicated in its pathogenesis. One such factor could be vancomycin administration as this has been reported to enhance the risk of

colonization and infection by *S. capitis* in neonates [11]. Similarly, Wang *et al.* previously found that patients infected with *S. capitis* had frequently received antibiotics in pre-2-weeks period [19].

Spread and reservoirs of *S. capitis* inside NICU settings

Epidemiological data revealed that when introduced into a NICU, *S. capitis* NRCS-A is able to settle and to diffuse within it, suggesting the presence of reservoirs inside the NICU [26]. In 2002, Gras-Le Guen *et al.* reported an outbreak of *S. capitis* inside a NICU and identified bottles of almond oil used for routine skin care as a possible vehicle for propagating the outbreak [13]. In the study reported by Carter *et al.*, *S. capitis* has been isolated in the NICU environment, notably on fomites such as stethoscopes and neonatal incubators [18]. If the healthcare workers are usually incriminated as reservoir and vectors of bacteria in nosocomial infections, Carter *et al.* has shown that among 41 samples from NICU staff members, none but one has grown with *S. capitis* NRCS-A. This suggests that in NICUs the reservoir of NRCS-A is rather the environment than the staff. It is hypothesized that the persistence of *S. capitis* in the environment could be related to a resistance to disinfection procedures, because data demonstrated a decreased susceptibility to antiseptics in *S. capitis* strains [18,39].

It is of note that a new method of screening that enables the identification of MDR *S. capitis* isolates in plurimicrobial environmental or clinical samples has been recently described; it is based on the use of a chromogenic agar that has been adapted from its primary use (screening of methicillin resistant *S. aureus*) to detect the NRCS-A clone with a high specificity and sensitivity [40]. This new method will facilitate further studies exploring the environmental niches of NRCS-A inside a NICU setting.

Discussion

S. capitis is unquestionably a significant pathogen in the NICU setting. The emergence of the NRCS-A clone in NICUs worldwide is worrisome because it harbours a MDR profile to both antibiotics and antiseptics and because it may be responsible for serious infections in neonates. An almost constant feature of the NRCS-A clone is its resistance or heteroresistance to vancomycin that

could confer it an affinity for the NICU setting where vancomycin selective pressure is high. This phenomenon raises important questions regarding the potential environmental reservoirs of poorly-virulent bacteria that may be selected by wide-spectrum antibiotics and that may express opportunistic pathogenicity in specific vulnerable populations. Hence studies are urgently required to identify and evaluate alternatives to vancomycin and to optimize its use in NICU patients, both to prevent the emergence and diffusion of MDR strains such as the NRCS-A clone and to better manage neonates infected with MDR staphylococci,. More generally, the global spread of NRCS-A requires further investigation; it is crucial to better understand the routes of its worldwide dissemination between distant NICUs, but also to identify its environmental niches and vectors of transmission within NICUs.

Conflicts of Interest: none.

Contributions: Acquisition of the data (MB), draft of the article (MB), final approval of the manuscript (FL).

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