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BRIEF REPORT

Staphylococcus capitis isolated from bloodstream infections: a nationwide 3-month survey in 38 neonatal intensive care units

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Abstract

To increase the knowledge about *S. capitis* in the neonatal setting, we conducted a nationwide 3-month survey in 38 neonatal intensive care units (NICUs) covering 56.6% of French NICU beds. We demonstrated 14.2% of *S. capitis* BSI (*S.cap*BSI) among nosocomial BSIs. *S.cap*BSI incidence rate was 0.59 per 1000 patient-days. A total of 55.0% of the *S.cap*BSIs were late onset catheter-related BSIs. The *S. capitis* strains infected preterm babies (median gestational age 26 weeks, median birth weight 855 g). They were resistant to methicillin and aminoglycosides and belonged to the NRCS-A clone. Evolution was favorable in all but one case, following vancomycin treatment.

Keywords *Staphylococcus capitis* · NRCS-A clone · Bloodstream catheter-related infection · Neonatal Intensive Care Unit (NICU) · Preterm babies · Neonates · Nationwide active surveillance

Introduction

Catheter-related bloodstream infections (CRBSI) are associated with increased rates of morbidity in intensive care unit patients and in neonates [1]. The prevention of the avoidable

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part of CRBSIs is a public health priority [2, 3]. In this context, since 2019, all French hospitals and clinics are encouraged to participate in an annual 3-month survey of CRBSI coordinated by the national infection control SPIADI network. Over the last two decades, multidrug-resistant *Staphylococcus capitis* has been increasingly reported as a major agent responsible for CRBSI in preterm babies [4]. Therapeutic failures likely due to heteroresistance to vancomycin in this bacteria [5] and local epidemics have been identified and investigated in NICUs [5–7]. *S. capitis* seems to be particularly well-adapted to the NICU environment, possibly in connection with its ability to produce biofilm [8, 9]. However, the neonate contamination routes remain obscure. Recent studies performed in distinct parts of the world have demonstrated a single lineage within the *S. capitis* species, named NRCS-A, responsible for invasive neonatal infections worldwide [10, 11]. The mechanisms that have driven the global dissemination of this clone have not yet been elucidated. We report the results of the 3-month nationwide BSI survey conducted during the first quarter of 2019 in the largest series of NICUs located in 38 French hospitals. We present clinical data related to the neonates suffering from BSI, and the incidence rates and major characteristics of the neonatal BSIs. In addition, using molecular methods, we characterized the isolates responsible for *S. capitis* BSIs to establish whether or not they belong to the NRCS-A clone. We provide new data that increase the knowledge about *S. capitis* in the current neonatal setting.

Materials and methods

BSI epidemiological survey method

Study population Thirty-eight maternity hospitals comprising neonatal intensive beds participated in the study (Fig. 1). The 447 beds surveyed represented 56.6% of French neonatal intensive beds (https://www.data.gouv.fr/en/datasets/).

Study design The surveillance program involved a 3-month survey of all cases of nosocomial BSI between January 1 and April 30 2019. The survey covered 33,971 intensive care patient-days (PD). Nosocomial BSIs were defined according to international definitions (CDC). The variables studied included clinical data (i.e., sex, gestational age, birth weight, death within 7 days of BSI diagnosis), major characteristics of the BSI such as the portal of entry (skin [primitive cutaneous form or superinfection of a skin breach], lungs, urine, intravascular device, or digestive tract), and for catheter-related BSI, the time lag between the insertion of the catheter, and the appearance of the clinical signs of the BSI. The BSI incidence rates were calculated per 1000 PD. Ethical approval of the surveillance program was

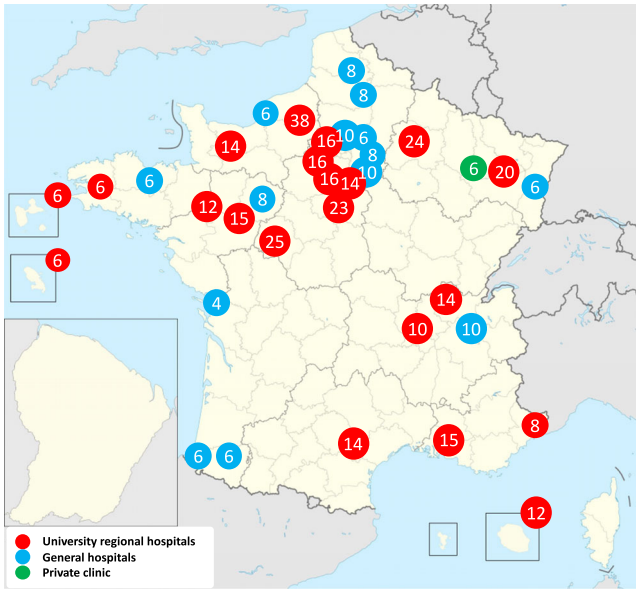

Fig. 1 Location of the 38 participating centers and number of neonatal intensive care beds

obtained at the national level from the Réseau de Prévention des Infections Associées aux Soins.

Microbiological study PFGE was used as a typing technique [12].

Statistical data The data were analyzed with R software. Chi-square tests and Fisher's exact test (two-tailed) were used to test associations, and a *P* value of 0.05 was considered significant.

Results

Epidemiology of neonatal BSI During the study period, 141 nosocomial BSIs were diagnosed in 81 male and 60 female neonates. The mean BSI incidence rate was 4.15 per 1000 PD (Table 1). The most frequently isolated micro-organisms were *S. epidermidis* (39.0%), *S. aureus* (17.0%), *S. haemolyticus* (15.6%), and *S. capitis* (14.2%). Twenty BSIs were polymicrobial (14.2%).

The portal of entry of the BSIs was suspected or proven in 83.7% of the cases. The digestive tract (12.1%), the skin (8.5%), and the pulmonary tract (6.4%) were minor portals of entry. Most of the BSIs were catheter-related (70 CRBSIs; 50.0 %) (Table 2). The CRBSI involved a central venous catheter (CVC) in 47 cases (67.1%), all but one associated with *staphylococci* (97.9%), and an umbilical venous catheter (UVC) in 23 cases (32.9%). The UVC-related BSIs were more diverse than those related to CVC: *enterococci*-, *Enterobacteriaceae*-, and *B. cereus*-BSIs

Table 1 BSI, B-cvc, and B-uvc incidence rates per 1000 PD according to the participating centers

enters			BSI incidence rates per 1000 PD								
	During the 3-month survey		BSI					B-cvc			B-uvc
	PD	Nosocomial BSI	All	*S. aureus*	*S. epidermidis*	*S. capitis*	*Enterobacteriaceae*	All	*S. aureus* B-cvc	*S. capitis* B-cvc	All
Participating centers with a neonatal intensive care unit											
University regional hospitals											
1	2,443	10	4.09	0.82	2.45	0.41	0.00	1.64	0.41	0.41	2.46
2	1,840	7	3.80	1.09	0.54	0.00	1.63	1.63	0.54	0.00	0.54
3	1,825	10	5.48	2.19	1.64	0.00	0.55	0.00	0.00	0.00	0.00
4	1,658	14	8.44	2.41	4.22	0.60	0.60	3.01	1.21	0.60	0.60
5	1,482	6	4.05	0.67	0.00	2.02	0.00	1.35	0.67	0.67	0.00
6	1,332	8	6.01	0.00	3.00	1.50	1.50	3.00	0.00	0.75	1.50
7	1,322	10	7.56	0.76	3.02	0.76	0.76	0.00	0.00	0.00	0.00
8	1,204	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
9	1,134	8	7.05	0.00	2.64	1.76	0.00	3.53	0.00	0.88	0.88
10	1,114	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
11	1,062	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
12	1,023	6	5.86	0.00	2.93	0.98	0.00	0.98	0.00	0.98	1.95
13	1,016	3	2.97	0.98	0.98	0.98	0.00	0.98	0.00	0.00	0.98
14	999	3	3.00	0.00	2.00	0.00	0.00	1.00	0.00	0.00	0.00
15	892	4	4.48	0.00	1.12	2.24	1.12	2.24	0.00	1.12	1.12
16	822	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
17	764	5	6.54	1.31	3.93	1.31	0.00	2.62	0.00	0.00	0.00
18	793	5	6.31	1.26	2.52	1.26	0.00	3.78	0.00	1.26	0.00
19	636	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
20	545	4	11.00	0.00	0.00	0.00	1.83	5.50	0.00	0.00	1.83
21	524	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
General hospitals											
22	972	3	3.09	1.03	1.03	1.03	0.00	2.06	1.03	1.03	1.03
23	893	1	1.12	0.00	0.00	1.12	0.00	1.12	0.00	1.12	0.00
24	890	5	5.62	2.25	2.25	1.12	1.12	1.12	1.12	0.00	1.12
25	769	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
26	753	6	7.97	3.98	0.00	1.33	2.66	1.33	1.33	0.00	0.00
27	595	2	3.36	0.00	1.68	0.00	0.00	1.68	0.00	0.00	0.00
28	570	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
29	493	6	12.20	0.00	6.08	0.00	0.00	2.03	0.00	0.00	10.14
30	401	0	0.00	0.00	0.00	0.00	0.00	0,00	0.00	0.00	0.00
31	396	1	2.52	0.00	2.52	0.00	0.00	2.52	0.00	0.00	0.00
32	369	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
33	353	2	2.68	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
34	320	3	9.38	0.00	6.25	0.00	3.12	0.00	0.00	0.00	0.00
35	308	7	22.72	0.00	9.74	0.00	6.49	9.74	0.00	0.00	0.00
36	275	2	7.27	3.64	0.00	0.00	3.64	3.64	3.64	0.00	0.00
Participating centers with intensive care beds in neonatal medical unit											
General hospital											
22	854	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Private clinic											

Table 1 (continued)

enters			BSI incidence rates per 1000 PD								
	During the 3-month survey		BSI					B-cvc			B-uvc
	PD	Nosocomial BSI	All	*S. aureus*	*S. epidermidis*	*S. capitis*	*Enterobacteriaceae*	All	*S. aureus* B-cvc	*S. capitis* B-cvc	All
40	330	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
All	33,971	141	4.15	0.71	1.62	0.59	0.50	1.38	0.26	0.29	0.68

Table 2 Major characteristics of the BSIs and infected neonates according to the micro-organism

	BSIs											Infected neonates				
	N	Portal of entry								Sex		Birth weight (g)		Gestational age (week)		Early death (%)
		CVC	UVC	Cutaneous	Pulmonary	Urinary	Digestive	Others	Not identified	Male	Female	< 1500 g	Median	< 33 weeks	Median	
Micro-organism																
All	141	47	23	12	9	1	17	9	23	81	60	112 (79.4)	980	113 (80.1)	28	22 (15.6)
S. aureus	24	9	4	4	4		1	1	1	12	12	16 (66.7)	1,100	16 (66.7)	30	7 (29.2)
S. epidermidis	55	20	11	6	1		4	1	12	35	20	43 (78.2)	910	43 (78.2)	27	5 (9.1)
S. haemolyticus	22	10	3		2		3	1	3	10	12	22 (100.0)	917	21 (95.4)	27	3 (13.6)
S. capitis	20	10	1	1	1		3		4	12	8	16 (80.0)	855	15 (75.0)	26	1 (5.0)
Enterococci	7	1	3				1	1	1	6	1	4 (57.1)	1,260	4 (57.1)	31	1 (14.3)
Enterobacteriaceae	17	1	2		2	1	4	5	2	9	8	9 (52.9)	1,480	11 (64.7)	29	5 (29.4)
Bacillus cereus	3		1	1					1	0	3	2 (66.7)	745	3 (100.0)	28	0

Table 3 Time lag between the insertion of the catheter and the appearance of the clinical signs of the CRBSI

	Number of CRBSIs	Time lag (days)			
		Mean	Median	< 10 days	≥ 10 days
Micro-organism					
S. aureus	13	7.2	6	11	3
S. epidermidis	31	8.0	6	26	5
S. haemolyticus	13	8.1	6	9	4
S. capitis	10	10.3	10	4	7
Enterococci	4	6.2	6	4	0
Enterobacteriaceae	3	4	4	3	0

were more frequent with UVC-BSIs (26.1%) rather than with CVC-BSIs (4.3%) (p = 0.022). The median time lag between the insertion of the catheter and the appearance of the clinical signs of the BSI was significantly longer for *S. capitis* (63.6%, ≥ 10 days) rather than for *S. aureus* (7.7%), *S. epidermidis* (16.1%), *S. haemolyticus* (30.8%), *enterococci*, and *Enterobacteriaceae* (no case) (p = 0.018; Table 3).

Characteristics of the infected neonates The gestational age of the infected neonates ranged between 24 and 41 weeks (median value 28), and their birth weight ranged between 455 and 4050 g (median value 1100); 15.6% of the neonates died during the 7-day period after the diagnosis of the BSI. BSIs involving *S. aureus*, *Enterobacteriaceae*, and *Enterococci* were associated with the highest prevalence of early death among infected neonates (29.4, 29.2, and 14.3% for *Enterobacteriaceae*-, *S. aureus*-, and *Enterococci*-associated BSIs, respectively). The prevalence of BSI in the neonates with the a gestational age ≥ 33 weeks and a birth weight > 1500 g differed according to the bacteria (Table 2): it was the highest for *Enterococci* (42.9%), *Enterobacteriaceae* (35.3%), and *S. aureus* (29.2%), lower for *S. capitis* (20.0%) and *E. epidemidis* (18.2%) and nil for *S. haemolyticus* and *B. cereus* (p = 0.056).

***S. capitis* BSI characteristics and antibiotic susceptibility of *S. capitis* strains** Twenty BSIs were associated with *S. capitis* (14.2%), resulting in a mean incidence of 0.59 per 1000 PD, ranging between 0 and 2.24 according to centers

Table 4 Antibiotic susceptibility of the *S. capitis* strains

Centers	Strain	Antibiotype*	MIC vancomycine (mg/L)	MIC teicoplanine (mg/L)
1	1	Oxa KTG Ri Fu	0.5	< 0.25
9	2	Oxa KTG Ri Fo	0.5	< 0.25
	3	Oxa KTG Ri Fo	0.5	< 0.25
4	4	Oxa KTG Ri Fo	–	–
7	5	Oxa AKTG Ri Fu Ery	–	–
13	6	Oxa TG Nor	1	2
6	7	Oxa G Cip Ery Ri	< 4	< 2
	8	Oxa G Cip Ery	< 4	< 2
5	9	Oxa ATG Ri Fo Te(I) Ery(I) Pr(I)	1	0.5
	10	Oxa ATG Ri Fo Te(I) Ery(I) Pr(I)	1	0.5
	11	Oxa ATG Ri Fo Te(I) Ery(I) Pr(I)	1	0.5
15	12	Oxa ATG Cip Fo	1	2
	13	Oxa ATG Cip Fo	1	1
17	14	Oxa AKTG Cip Fo	1	1
12	15	Oxa KTG Ery	2	4
22	16	Oxa AKTG	0.5	< 0.25
18	17	Oxa ATG Ri Fu	0.5	< 0.25
26	20	Oxa ATG Ri Fo Te(I) Ery(I) Pr(I)	1	2

Oxa oxacillin, *K* kanamycin, *T* tobramycin, *G* gentamicin, *A* amikacin, *Ri* Rifampicin, *Fu* fusidic acid, *Fo* fosfomycin, *Te* tetracyclin, *Ery* erythromycin, *Pr* pristinamycin, *Nor* norfloxacin, *Cip* ciprofloxacin

(Table 1); 39.5% of the NICUs reported at least one *S. capitis*-BSIs. The *S. capitis*-BSIs were significantly associated with the largest NICUs: at least one *S. capitis*-BSIs was reported in 15 of the 22 NICUs with ≥ 10 beds, whereas none was reported in the 14 NICUs with < 10 beds ($p < 0.001$). Four NICUs documented two ($n = 3$) or three ($n = 1$) *S. capitis*-BSIs during the survey period. The antibiotic susceptibility patterns of 18 strains were available (90.0%). Most of the strains were resistant to multiple antibiotics, i.e., methicillin (100%), gentamicin (100%), rifampicin (61.1%), fosfomycin (55.5%), erythromycin (44.4%), fluoroquinolones (33.3%), and fusidic acid (22.2%). Vancomycin and teicoplanin MIC values ranged between 0.25 and 4 mg/L (Table 4). Data regarding antibiotic treatment were available for 18 cases: 17 neonates received vancomycin over 2–24 days (median value: 8 days) and the remaining neonate received linezolid (11 days). A favorable outcome was observed in all but one case. An early death was observed for a preterm infected neonate (gestational age 25 weeks; birth weight 455 g), who received vancomycin over 3 days following the detection of a *S. capitis* and *S. haemolyticus*-associated CRBSI.

Twelve *S. capitis* BSI strains from 8 NICUs were available for molecular typing. A considerable homogeneity was demonstrated among the strains, and PFGE pattern analysis demonstrated that all strains belonged to the NRCS-A clone [10] (Fig. 2). Regarding the three NICUs that reported several *S. capitis*-BSI cases, the strains isolated in a same center shared the same pattern in two cases. In addition, the strains isolated from three distinct centers located in two distant French regions shared the same pattern.

Discussion

This nationwide study adds several elements to the available data on *S. capitis* responsible for neonatal BSI.

We provide a first mean incidence of *S. capitis* BSIs in French NICUs. *S. capitis* BSIs currently involve an average of one neonate per 1700 PD, which is lower than that observed for *S. aureus* and *S. epidermidis*, but higher than that of *Enterobacteriaceae* in the population of neonates surveyed. Our findings confirm *S. capitis* as a significant agent responsible for nosocomial BSI in the neonatal setting [10, 11, 13].

Second, such as *S. epidermidis* and *S. haemolyticus*, we showed that *S. capitis* preferentially infects the more fragile neonates and thus confirmed that *S. capitis* is an opportunistic pathogen, devoid of great virulence potential. Concordant with previous studies [13], all the *S. capitis* strains responsible for BSIs displayed resistance to methicillin and gentamicin, but remained susceptible to vancomycin. *S. capitis*-BSIs have been taken into account by the clinicians, and vancomycin probably played a crucial role in the recovery of neonates.

Third, we identified one particularity distinguishing *S. capitis* among the bacteria associated with CRBSI cases. Our study reveals a doubled lag time between insertion of the catheter and the first signs of the BSI involving *S. capitis* when compared with other bacteria. The absence of early infection likely excludes

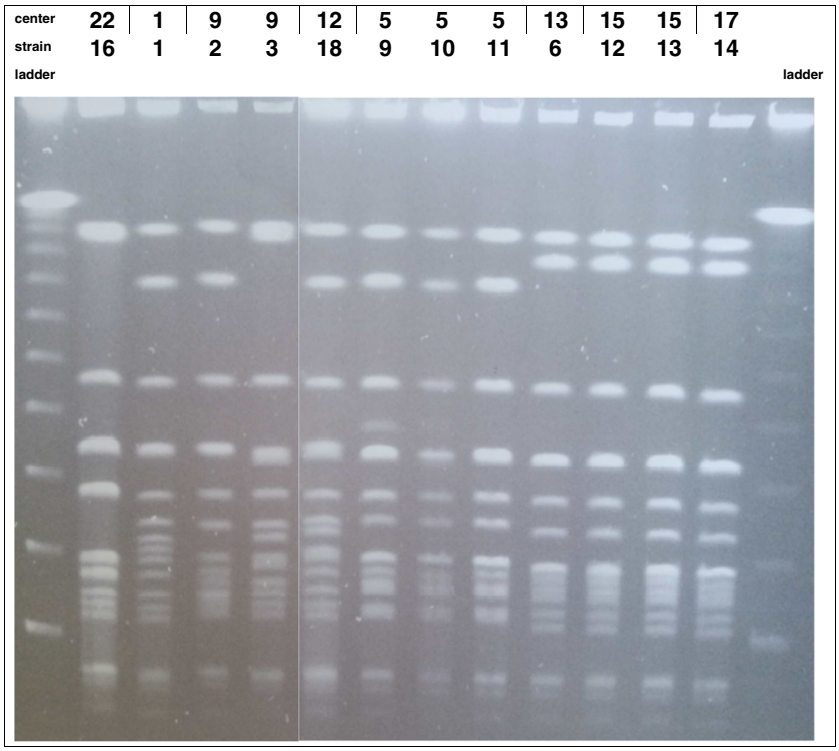

Fig. 2 *Sma*I PFGE patterns of the *S. capitis* strains responsible for neonatal BSI

a contamination of the catheter at the time of its insertion, but rather indicates that the contamination of the catheter may have occurred following catheter manipulations among neonates presenting the longest periods of catheterization.

Finally, the molecular analysis of a large part of the *S. capitis* strains indicates that they belong to the multidrug-resistant NRCS-A clone and highly suggests likely epidemic phenomena among the NICUs presenting the highest incidence rates of *S. capitis* BSIs.

Conclusion

Our data confirm the clone NRCS-A particularly well-suited to the neonatal setting and its cumbersome epidemiology [10, 11, 13]. In most NICUs, *S. capitis* BSIs remain relatively infrequent among neonates, but concern primarily the most fragile ones. In order to better determine the factors involved in the occurrence of these infections, monitoring of BSIs should be continued and complemented by a systematic investigation when several cases are identified over a 3-month period in the same NICU.

Authors' contribution MD conducted the study, SDS performed the molecular typing, RM conducted the statistical analysis, FG designed and developed the website for data collection and analysis, SLV participated with the data analysis, NVDM designed and conducted the study and wrote the manuscript.

All the others are participating members from each of the 41 NICUs (the infection control practitioner, the microbiologist, and the clinician responsible for the NICU). They collected the data and strains.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The nationwide survey was conducted under the control of the national agency Santé Public France and with the authorization by the CNIL (a national committee for data protection). Ethical review and approval was not required for the study on human participants in accordance with the French national legislation and institutional requirements.

Informed consent In each participating hospital, a quality commitment charter was signed by the general director and the infection control physician. Patients were informed and ask for consent about the 3-month national survey.

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