ANZPID Journal Club Submission

Title of the article:
Salvage strategy for long-term central venous catheter-associated Staphylococcus aureus infections in children: a multi-center retrospective study in France.

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Background:
Management of Staphylococcus aureus central-line–associated bloodstream infection (CLABSI) in children with long-term central venous catheters (LTCVCs) is challenging. While adult guidelines recommend prompt catheter removal, pediatric practice often favors catheter salvage strategies (CSS) due to limited vascular access and the need to avoid invasive procedures. Robust multicenter pediatric data to guide this decision are limited.

Main Findings:
This multicenter retrospective French study included 273 instances of *S. aureus* LTCVC-associated CLABSI in children across eight tertiary hospitals. CSS was attempted in 71% of cases and failed in 38%, most commonly due to persistent bacteremia or early relapse. Independent predictors of CSS failure were prior to catheter infection, use of an implantable venous access device, polymicrobial infection, and severe sepsis at presentation. Mortality was low (two deaths), and most isolates were methicillin-susceptible *S. aureus*.

Take home message:
Catheter salvage is frequently attempted and successful in approximately two-thirds of pediatric *S. aureus* LTCVC-associated CLABSI episodes. However, CSS should be avoided or reconsidered in children presenting with severe sepsis, polymicrobial infection, prior to catheter infection, or infections involving implantable ports. These findings support a selective, risk-stratified approach to catheter salvage rather than routine catheter removal in all pediatric cases.

Quiz Club Questions:

1) Which factor was independently associated with failure of the catheter salvage strategy in this study?

A) Meticillin-resistant S. aureus infection
B) Severe sepsis at presentation
C) Younger patient age
D) Use of antibiotic lock therapy
E) Tunnelled-cuffed catheter type

Correct answer: B

Explanation:
Severe sepsis at the initial stage of infection was independently associated with CSS failure (aOR 4.46). MRSA infection and age were not significant predictors, and tunneled-cuffed catheters were associated with lower failure risk compared with implantable ports.

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Salvage strategy for long-term central venous catheter-associated *Staphylococcus aureus* infections in children: a multi-centre retrospective study in France

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SUMMARY

Objectives: Catheter removal is recommended in adults with *Staphylococcus aureus* central-line-associated bloodstream infection (CLABSI) but is controversial in children with long-term central venous catheters (LTCVC). We evaluated the occurrence of catheter salvage strategy (CSS) in children with *S. aureus* LTCVC-associated CLABSI and assessed determinants of CSS failure.

Methods: We retrospectively included children (<18 years) with an LTCVC and hospitalized with *S. aureus* CLABSI in eight French tertiary-care hospitals (2010—2018). CSS was defined as an LTCVC left in place ≥72 h after initiating empiric antibiotic treatment for suspected bacteraemia. Characteristics of patients were reviewed, and multi-variable logistic regression was performed to identify factors associated with CSS failure (i.e., persistence, recurrence or complications of bacteraemia).

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Child

Results: We included 273 episodes of *S. aureus* LTCVC-associated CLABSI. CSS was chosen in 194 out of 273 (71%) cases and failed in 74 of them (38%). The main type of CSS failure was the persistence of bacteraemia (39 of 74 cases, 53%). Factors independently associated with CSS failure were: history of catheter infection (adjusted odds ratio (aOR) 3.18, 95% confidence interval (CI) 1.38—7.36), CLABSI occurring on an implantable venous access device (aOR 7.61, 95% CI 1.98—29.20) when compared with tunnelled-cuffed CVC, polymicrobial CLABSI (aOR 3.45, 95% CI 1.25—9.50), and severe sepsis at the initial stage of infection (aOR 4.46, 95% CI 1.18—16.82).

Conclusions: CSS was frequently chosen in children with *S. aureus* LTCVC-associated CLABSI, and failure occurred in one-third of cases. The identified risk factors may help clinicians identify children at risk for CSS failure.

Introduction

Many chronic paediatric diseases, such as cancer, chronic intestinal disease, and terminal renal failure, require prolonged vascular access. However, long-term central venous catheters (LTCVCs) increase the risk of infection [1], which is responsible for local and systemic complications, extension of hospital stay, and substantial additional costs [2]. Although the incidence of central line-associated/related bloodstream infection (CLABSI/CRBSI) in children varies depending on the device type and patients' medical background, the outcome of CLABSIs and their determinants in this specific population is less known [3—5]. Guidelines for adults from the Infectious Diseases Society of America (IDSA) and Centers for Disease Control and Prevention (CDC) recommend prompt removal of CVCs due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and fungi [6], as these infections are more frequently associated with treatment failure and complications such as endocarditis and suppurative thrombophlebitis [7]. Central venous catheter (CVC) removal seems even more critical for LTCVCs, as their main source of infection is intraluminal colonization of the catheter with subsequent biofilm formation [1,8].

Paediatricians are usually reluctant to remove LTCVCs due to limited vascular access and in an attempt to minimize invasive procedures in young children [9,10]. North American and French guidelines leave the possibility to keep the LTCVC in paediatric cases of CRBSI, provided that a restrictive catheter salvage strategy (CSS) is used, combining prolonged systemic and lock antibiotic therapy [6,11]. In children, *S. aureus* is the second most common causal agent after coagulase-negative staphylococci in CLABSI [8,12,13] and might be the source of many complications such as secondary infection and death if the CVC is not removed [6]. Only a few studies evaluated CSS for *S. aureus* LTCVC-associated CLABSI in children [10,13—15]. In 2019, a French single-centre retrospective study assessed the practice of CSS in children with LTCVC-associated *S. aureus* CLABSI and found a much lower failure rate than in adults, with almost two thirds of CSS success [9]. However, this study was underpowered, and thus was unlikely to influence current recommendations.

The aim of this study was to evaluate the frequency of CSS in eight independent tertiary-care hospitals, and to identify risk factors for CSS failure in cases of paediatric *S. aureus* LTCVC-associated CLABSI.

Methods

General methodology

We conducted an observational multi-centre retrospective study in eight French tertiary-care teaching hospitals from six different cities. The study protocol was reviewed and approved by the Assistance Publique des Hôpitaux de Paris (APHP) institutional review board (Registration number No. 20200429162341). The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were used to report the study (Supplementary Table S1).

Inclusion criteria and data collection

We included all children, aged one month to 18 years who had an LTCVC (i.e., tunnelled-cuffed or non-cuffed CVC, which includes tunnelled dialysis catheter, and implantable venous access device) and a history of a probable or proven *S. aureus* CLABSI (see definitions for probable and proven CLABSI in Supplementary Table S2) [6]. Patients could be included twice if they had separate infectious episodes as defined by an interval of more than 30 days between the two episodes. Potential participants were identified by reviewing all blood cultures positive for *S. aureus* using the microbiological laboratory informatics systems and electronic medical records from each centre. Data on the type of catheter, and demographic, clinical, laboratory, and treatment characteristics were extracted from patient medical records. The study period was from 1st January 2010 to 31st December 2017. Although all centres are tertiary centres, clinical activity, and the number of patients under hospital care with LTCVCs vary from centre to centre. Due to changes in their microbiological database and electronic medical records, centres from Lyon and Armand-Trousseau (Paris) could provide data only for the periods 2017—2018 and 2014—2018, respectively (Table I).

Definitions

The 'initial stage of infection' was defined as the first three days (i.e., 72 h) following the first positive blood culture. Sepsis, organ dysfunction and severe sepsis were defined according to Goldstein *et al.* [16]. Local infectious signs included cutaneous rash or induration at the insertion point of the LTCVC. Local complications were defined as local abscess

Table I
Available data per hospital centre

Hospital centre (France)	Available data (years)	CLABSI episodes (% of total) $N = 273$	CSS attempt (% of CLABSI) $N = 194$	CSS failure (% of CSS attempts) $N = 74$
Necker–Enfants malades, Paris	2010–2017	76 (28)	54 (71)	19 (35)
Robert Debré, Paris	2010–2017	66 (24)	48 (73)	17 (35)
Lille	2010–2017	24 (9)	22 (92)	4 (18)
Armand–Trousseau, Paris	2014–2018	23 (8)	17 (74)	9 (53)
Nantes	2010–2017	38 (14)	17 (74)	10 (59)
Rennes	2010–2017	16 (6)	14 (88)	6 (43)
Lyon	2017–2018	21 (8)	14 (67)	5 (36)
Rouen	2010–2017	9 (3)	8 (89)	4 (50)

CLABSI, central line-associated bloodstream infection; CSS, catheter salvage strategy.

and tunnel infection [6,17]. Systemic complications were defined as suppurative thrombophlebitis (i.e., the persistence of positive blood culture and signs of thrombophlebitis on ultrasound of the vascular system), endocarditis, and metastatic loci of infection [6,17]. A 'long time since catheterization' was defined as infection occurring more than 30 days after insertion of the LTCVC, as in previous studies [3,17]. A hospital-acquired infection was defined as infection occurring after 48 h of hospitalization, while other infections were considered healthcare-associated [18]. Empiric antibiotic treatment was deemed adequate if it comprised at least one intravenous antibiotic agent to which the isolate of *S. aureus*, as well as other infective agents in the case of polymicrobial infection, were susceptible according to EUCAST rules used at the time of the study [19], and with a dosage recommended by local guidelines of each centre. Target serum concentrations of vancomycin were considered adequate only if they were $\geq$15 mg/L before the end of the third day of treatment. Antibiotic lock therapy followed each centre procedure and was defined as adequate if the dwell time of lock therapy reached at least 8 h per day for at least three consecutive days. Catheter repair refers to the 'glued' procedure [20]. Immunocompromised patients were children with active malignant conditions, evolutive neutropenia, uncontrolled HIV infection, or under immunosuppressive therapy (e.g., prolonged high-dose corticosteroids, chemotherapy, immunomodulators).

CSS was defined as an LTCVC left in place at least 72 h after initiating empiric antibiotic therapy for suspected bacteraemia [9,17]. Failure of CSS was defined according to previously described criteria as either [6,9]: (i) persistence of positive blood culture(s) after 72 h of empiric adequate antibiotic treatment, (ii) persistence of clinical manifestations of infection without any other apparent source for infection than the catheter, (iii) occurrence or worsening of local or systemic infectious complication undetected at the time of the diagnosis, or (iv) early relapse, defined by a positive blood culture with an *S. aureus* strain harbouring the same antibiotic susceptibility pattern within the 30 days following end of adequate antibiotic treatment [21]. Successful CSS was defined as a treatment fully completed without occurrence of any of the CSS failure criteria described above.

Statistical analyses

Characteristics of *S. aureus* CLABSIs episodes treated with CSS were described and compared according to their success or failure. Univariable differences between groups were assessed using the Chi-squared method, Fisher's exact test, the Mann–Whitney *U* test, and Student's *t*-test when appropriate, with Bonferroni correction for multiple comparisons between groups. *P*-value less than 0.05 was considered to indicate a significant difference unless Bonferroni correction was applied. Then, a multi-variable logistic regression analysis was performed to identify factors independently associated with CSS failure. All baseline characteristics of patients and characteristics of CLABSI at the initial stage of infection with less than 10% of missing data were included in the multi-variable analysis, independent of the results of univariable analyses. Covariates considered included: age, sex, hospital centre, immune status, chronic digestive condition, type of LTCVC, history of CVC infection, long-time catheterization, hospital-acquired infection, local infectious signs, severe sepsis, C-reactive protein (CRP), meticillin-resistant *S. aureus* (MRSA), polymicrobial infection, CRBSI, and initial adequate antibiotic treatment, combined antibiotic therapy, and antibiotic lock. Variable selection involved a backward stepwise procedure with a *P*-value for removal of 0.157 [22]. Continuous variables were dichotomized using a median split. Associations were expressed as odds ratios (ORs) and adjusted ORs (aORs). In an additional analysis, we repeated the same modelling approach but used a different definition of CSS failure [17]. In this definition, we also included LTCVC removal after 72 h as a CSS failure, even if it was for reasons solely related to routine care (i.e., not because of the current infection). Statistical analyses were carried out using SPSS v25 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of patients and CLABSI episodes

During the study period, 273 *S. aureus* LTCVC-associated CLABSI episodes (Supplementary Table S3) occurred among 254 patients (19 patients had more than one episode over the study period, Figure 1). Most of the episodes were managed in gastroenterology ($N = 73$, 27%), haematology ($N = 72$, 26%) and intensive care departments ($N = 65$, 24%). The median age of patients was 2.4 years (interquartile range (IQR), 0.7–8.1), and 110 (40%) patients had a chronic digestive condition requiring parenteral nutrition.

Among the 273 *S. aureus* LTCVC-associated CLABSI episodes, 130 (48%) were proven (and therefore identified as CRBSI), and

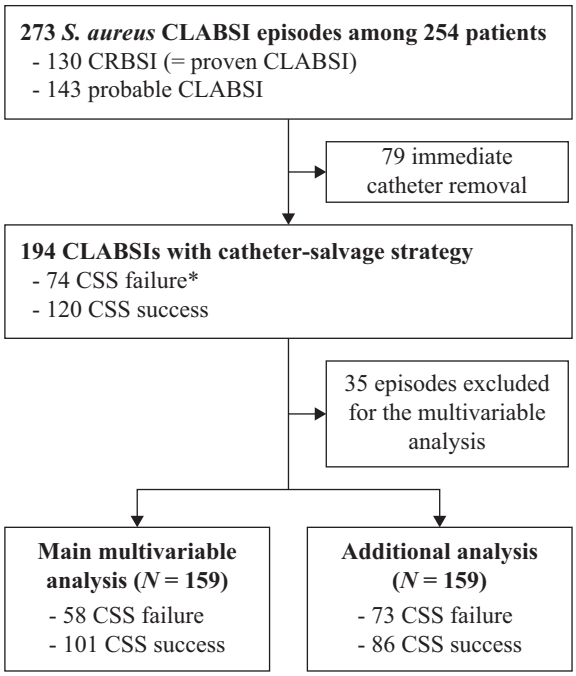

Figure 1. Flow chart. CLABSI, central-line-associated bloodstream infection; CSS, catheter salvage strategy; CRBSI, central-line-related bloodstream infection; *S. aureus, Staphylococcus aureus*.

143 (52%) were probable (Figure 1). MRSA was isolated in 22 (8%) cases. Most of *S. aureus* isolates were sensitive to rifampicin (100%), and gentamicin (97%) (Supplementary Table S4). Most CLABSIs occurred on tunnelled-cuffed CVC ($N = 200$, 73%), with a median delay from LTCVC placement to infection reaching 21 (IQR, 10—81) days.

Outcome of LTCVC-associated S. aureus *CLABSI with attempted CSS*

CSS was attempted in 194 cases (71%) of the 273 *S. aureus* LTCVC-associated CLABSI episodes (Figure 1) and failed in 74 cases (38%) (Figure 1). Characteristics of patients and infectious episodes treated with CSS are presented in Table II. Polymicrobial infections included coagulase-negative staphylococci ($N = 15$), other Gram-positive bacteria ($N = 9$), Enterobacterales ($N = 3$), and *P. aeruginosa* ($N = 2$). CSS failure was related to the persistence of a positive blood culture ($N = 39$), early relapse ($N = 26$), occurrence or worsening of local complication ($N = 12$), septic thrombophlebitis ($N = 8$) or secondary endocarditis ($N = 2$). Two patients died from refractory sepsis: one eight-month-old child with febrile neutropenia during chemotherapy for haematological malignancy had a CLABSI on an implantable venous access device caused by a meticillin-susceptible *S. aureus* (MSSA) and died on day 12 of infection. One two-year-old child with a history of chronic kidney failure had a CLABSI documented with MSSA on a tunnelled-cuffed catheter and died in the context of multi-organ failure despite adequate antibiotic treatment and LTCVC removal on day 5.

Among patients for whom CSS was attempted, LTCVC removal between day 4 and day 30 after the first positive blood sample culture occurred in 81 infectious episodes (42%, Supplementary Table S3). LTCVC removal was decided because of CSS failure in 47 (59%) patients, and for a reason exclusively related to routine care (i.e., not because of the current infection) in 34 (41%) episodes (Figure 1). For these 81 episodes, LTCVC removal occurred at a median of seven (range, 4—28) days, and 32 had initial non-complicated local signs of infection. Among patients with CSS failure, 26 did not have their LTCVC removed before day 30 of infection.

Predictors of CSS failure

In univariable analysis (Tables II and III), CSS failure was associated with implantable venous access device (OR 3.96, 95% CI 1.69—9.26) when compared with tunnelled-cuffed CVC, a delay since catheterization superior to 30 days (OR 1.89, 95% CI 1.05—3.43), and presence of severe sepsis at the initial stage of infection (OR 3.44, 95% CI 1.30—9.08).

For multi-variable analysis, 35 of the 194 patients were secondarily excluded because of missing data (Figure 1). In multi-variable analysis, failure of CSS was independently associated with an implantable venous access device (aOR 7.61, 95%CI 1.98—29.20) when compared with tunnelled-cuffed CVC, history of catheter infection (aOR 3.18, 95% CI 1.38—7.36), severe sepsis at the initial stage of infection (aOR 4.46, 95% CI 1.18—16.82), and polymicrobial infection (aOR 3.45, 95% CI 1.25—9.50) (Table III).

Additional analysis

When using an alternative definition of CSS failure that included all episodes where LTCVC was removed (Figure 1), multi-variable analysis confirmed severe sepsis as an independent factor associated with CSS failure (aOR 5.69, 95% CI 1.04—31.26) (Supplementary Table S5). The analysis also identified a significant centre effect and additional factors independently associated with CSS failure: presence of local infectious signs at initial presentation (aOR 6.94, 95% CI 2.53—19.07), CRBSI (aOR 3.22, 95% CI 1.26—8.18), hospital-acquired infection (aOR 4.00, 95% CI 1.36—11.82) and high CRP concentrations above the median value (aOR 2.74, 95% CI 1.11—6.78). Initial combined therapy appeared protective against CSS failure (aOR 0.31, 95% CI 0.11—0.86) (Supplementary Table S4).

Discussion

This retrospective study, the very first large-scale multicentre paediatric study about *S. aureus* LTCVC-associated CLABSI, demonstrated only one-third of CSS failure. We identified that a previous history of catheter infection, type of LTCVC, polymicrobial infection, and severe sepsis at the initial stage were independently associated with CSS failure.

Despite IDSA guideline recommendations of CVC removal [6], this multi-centre study found 71% of CSS attempts, indicating a high frequency of attempted CSS for *S. aureus* CLABSI in paediatric wards, in line with findings observed in our initial single-centre study [9]. The adoption of CSS exhibits variability across previous paediatric studies, with reported rates of CVC salvage attempts ranging from 28% to 80% in the case of *S. aureus* CLABSI [10,17,23—25]. None the less, the most recent literature emphasizes a growing inclination towards adopting CSS in paediatric settings for the management of *S. aureus*

Table II
Characteristics of catheter salvage strategy (CSS) episodes ($N = 194$)

Characteristics (%) [a]	N [b]	All N = 194	CSS failure N = 74	CSS success N = 120	P
Patient demographics					
Age, years; median [IQR]	194	2.5 [1.0—7.5]	2.2 [0.7—5.3]	2.7 [1.1—9.1]	0.12
Male	194	101 (52)	40 (54)	61 (51)	0.66
Hospital centre	194				0.23
Necker—Enfants malades, Paris		54 (28)	19 (26)	35 (29)	
Robert—Debré, Paris		48 (25)	17 (23)	31 (26)	
Lille		22 (11)	4 (5)	18 (15)	
Armand—Trousseau, Paris		17 (9)	9 (12)	8 (7)	
Nantes		17 (9)	10 (14)	7 (6)	
Rennes		14 (7)	6 (8)	8 (7)	
Lyon		14 (7)	5 (7)	9 (8)	
Rouen		8 (4)	4 (5)	4 (3)	
Underlying medical condition					
Immunodepression	194	69 (36)	24 (32)	45 (38)	0.47
Chronic digestive condition	194	82 (42)	27 (37)	55 (46)	0.20
Catheter characteristics					
Type of LTCVC	194				0.002
Tunnelled-cuffed (Broviac® type)		144 (74)	45 (61)	99 (83)	
Implantable venous access device		28 (14)	18 (24)	10 (8)	
Tunnelled		22 (11)	11 (15)	11 (9)	
Long time catheterization (>30 days)	187	87 (47)	41 (56)	46 (40)	0.03
History of past infection					
History of catheter infection	194	65 (34)	28 (38)	37 (31)	0.32
Vancomycin during the past 6 months	87	36 (41)	16 (49)	20 (37)	0.29
Characteristiscs of CLABSI at initial stage of infection					
Hospital-acquired infection	192	118 (62)	47 (64)	71 (60)	0.64
Local infectious sign [c]	182	56 (31)	25 (38)	31 (27)	0.12
Severe sepsis	194	20 (10)	13 (18)	7 (6)	0.009
Max CRP, mg/L; median [IQR]	186	62 [29—124]	75 [38—125]	53 [27—123]	0.43
MRSA infection	194	20 (10)	10 (14)	10 (8)	0.25
Polymicrobial infection [d]	194	29 (15)	15 (20)	14 (12)	0.10
CRBSI	194	75 (39)	33 (45)	42 (35)	0.18
Treatment at initial stage of infection					
Adequate empiric treatment	192	182 (95)	69 (95)	113 (95)	0.90
Glycopeptide	191	168 (88)	64 (88)	104 (88)	
Betalactam	186	91 (49)	33 (47)	58 (50)	
Combined therapy with aminoglycosides or rifampicin [e]	190	117 (62)	41 (57)	76 (64)	
Glycopeptide continuously infused on infected catheter	150	34 (23)	18 (31)	16 (18)	0.07
Measure of serum concentration of vancomycin	166	108 (65)	39 (63)	69 (66)	
Serum concentration, mg/L; median [IQR]	101	14 [8—22]	14 [8—24]	14 [8—20]	
Appropriate serum concentration (>15 mg/L)	107	49 (46)	18 (45)	31 (46)	0.90
Antibiotic lock therapy[f]	179	27 (15)	11 (16)	16 (14)	0.75
Modifications of treatment after initial stage of infection					
Antibiotic switch	148	90 (61)	36 (60)	54 (61)	
Duration of intravenous treatment, day; median [IQR]	173	14 [11—19]	15 [12—20]	14 [10—18]	
Oral therapy	184	20 (11)	6 (9)	14 (12)	
Total duration of treatment, day; median [IQR]	166	15 [12—20]	15 [12—21]	15 [13—20]	

CLABSI, central-line-associated bloodstream infection; CRP, C-reactive protein; IQR, interquartile range; LTCVC, long-term central venous catheter; MRSA, meticillin-resistant *Staphylococcus aureus*.

[a] Values are numbers (percentages) unless stated otherwise.

[b] Number of available data.

[c] Extensive erythema or purulent swelling. *P*-value of the Chi-2, Fischer or Mann-Whitney tests between success and failure.

[d] Coagulase-negative Staphylococci ($N = 15$), other Gram-positive bacteria ($N = 9$), Enterobacterales ($N = 3$), *Pseudomonas aeruginosa* ($N = 2$).

[e] Aminoglycosides ($N = 103$), rifampicin ($N = 14$).

[f] A glycopeptide was used for all 27 locks. A Bonferroni correction of 20 was applied and $P<0.003$ was considered significant.

Table III
Factors associated with catheter salvage strategy (CSS) failure: univariable and multi-variable analyses

Characteristics	Crude OR [95% CI]	*P*	Adjusted OR [95% CI]	*P*
Hospital centre		0.23		0.21
Necker—Enfants malades, Paris	Ref [a]		Ref [a]	
Robert—Debré, Paris	1.01 [0.45—2.28]		2.21 [0.76—6.43]	
Lille	0.41 [0.12—1.39]		0.20 [0.01—2.44]	
Armand—Trousseau, Paris	2.07 [0.68—6.25]		1.73 [0.40—7.47]	
Nantes	2.6 [0.86—8.03]		5.60 [1.20—26.14]	
Rennes	1.38 [0.42—4.57]		1.72 [0.33—8.98]	
Lyon	1.02 [0.30—3.49]		0.50 [0.08—3.34]	
Rouen	1.84 [0.41—8.21]		0.65 [0.09—4.79]	
Type of catheter		0.002		0.01
Implantable venous access device	3.96 [1.69—9.26]		7.61 [1.98—29.20]	
Tunnelled	2.20 [0.89—5.45]		1.74 [0.51—5.96]	
Tunnelled-cuffed (Broviac® type)	Ref [a]		Ref [a]	
Long time catheterization (>30 days)	1.89 [1.05—3.43]	0.03	Not included in final model	
History of catheter infection	1.37 [0.74—2.51]	0.32	3.18 [1.38—7.36]	0.007
Severe sepsis at initial stage	3.44 [1.30—9.08]	0.009	4.46 [1.18—16.82]	0.03
Polymicrobial infection	1.93 [0.87—4.26]	0.10	3.45 [1.25—9.50]	0.02
CRBSI	1.50 [0.83—2.70]	0.18	2.21 [0.97—5.05]	0.06
MRSA infection	1.72 [0.68—4.35]	0.25	2.69 [0.80—9.11]	0.11
Combined therapy with aminoglycosides or rifampicin	0.73 [0.40—1.33]	0.31	0.54 [0.23—1.26]	0.15

Multi-variable logistic regression included all baseline features of patients and central-line-associated bloodstream infection (CLABSI) at initial stage of infection with less than 10% of missing data. 'Glycopeptide continuously infused on infected catheter', 'serum concentration of vancomycin', 'vancomycin during the past 6 months' were not included in the model as they had >10% missing data. Other variables (i.e., age, sex, immunodepression, chronic digestive condition, hospital-acquired infection, local infectious signs, C-reactive protein (CRP) levels, adequate empiric treatment, lock therapy) were not included in the final model following the stepwise selection procedure. Age and CRP were categorized based on their respective median. A total of 159 CLABSI episodes were included in the multi-variable analysis. CRBSI, central line-related bloodstream infection; LTCVC, long-term central venous catheter; MRSA, meticillin-resistant *Staphylococcus aureus*. *P*, *P*-value for univariable and multivariable logistic regression analyses.

[a] Reference categories for univariable and multi-variable logistic regression analyses.

CLABSI. In contrast, adult studies tend to show stricter adherence to international guidelines recommending the withdrawal of CVC in case of *S. aureus* CLABSI [26—31]. This discrepancy may, in part, be attributed to the young age of patients in the present study (median age 2.5 (1.0—7.5) years), who typically exhibit more restricted vascular access and often require long-term vascular access due to chronic illness. Additionally, for these patients, catheter replacement often necessitates general anaesthesia.

Furthermore, the attempt to salvage in adult studies is typically associated with high failure rates and serious complications in *S. aureus* CLABSI, reaching 60% [26,27,31—33]. Our study found lower failure rates (38%) of CSS compared with studies involving adults. Similar results have already been observed in previous studies with smaller sample sizes, showing a 16—33% rate of CSS failure [10,13,17,24,34]. A recent meta-analysis comprising 19 publications demonstrated that CSS is achievable in children with *S. aureus* CLABSI, with success rates of 68% (95% CI: 59—77) and 77% (95% CI: 69—85) when treated with antibiotics alone or in conjunction with antibiotic locks, respectively [35].

Regarding the study population and the CLABSI episodes' characteristics, our patients were comparable with other paediatric studies, with 10% of MRSA [8,17,20]. Many paediatric patients in our population had an LTCVC to ensure parenteral nutrition, with a lower proportion of onco-hematology patients than in previous studies [17,20]. The low failure rate of CSS in our study may also be explained by these characteristics, as previous reports have indicated that patients receiving total parenteral nutrition tend to experience a milder course of *S. aureus* bacteraemia and are therefore less susceptible to failure, complications and mortality [29]. Additionally, the low number of immunocompromised patients, who are more often affected by *S. aureus* CLABSIs with poor outcomes [3,24,36,37], could contribute to this finding.

The main reason for CSS failure was the persistence of positive blood cultures after 72 h and early relapse with 40 and 25 patients, respectively, which is consistent with previous evidence. Park *et al.*, showed 60% of CSS failure [26], which was defined as LTCVC removal, bacteraemia relapse, or severe complication. Apart from LTCVC removal, relapse was the main type of CSS failure. In another study involving 304 *S. aureus* CLABSI episodes, persistent bacteraemia (25%) and relapse (9%) were identified as the main complications of CSS [38]. Finally, fatal outcomes were scarce in our series, as only two patients died from *S. aureus* CLABSI, which is far less than the results of previous adult studies [23,38]. This might be explained by a lower rate of underlying diseases in children.

We identified several factors strongly associated with CSS failure. Some of them had already been identified previously, such as polymicrobial infection [21] and sepsis [38,39]. Our study confirms that CSS is not a reasonable strategy for patients with *S. aureus* CLABSI who present with severe sepsis, as evidenced by an aOR for failure of 4.4. In our previous single-

centre study [9], we also observed that polymicrobial bloodstream infection was strongly associated with CSS failure in *S. aureus* LTCVC-associated CLABSI. This previous study also found that non-adequate empiric treatment or insufficient serum vancomycin concentration was associated with CSS failure, confirmed by a recent adult study [40]. The present study did not confirm these results, as most of the empiric antibiotic therapies were adapted to *S. aureus* susceptibility (>90% of cases), with frequent use of glycopeptides, as also observed in adult studies [41]. The type of LTCVC was associated with CSS failure. Despite a reduction in the risk of infection due to total implantation under the skin, a related infection on an implantable venous access device (port) can occur in 3–10% [42], with a risk of a port-pocket abscess considered more difficult to treat. The increased risk of CSS failure with a port, when compared with a tunnelled catheter, has been observed in several studies on CLABSIs involving *S. aureus*, as well as infections involving other various pathogens [17,34,43,44].

Our study did not find any association between CSS failure and several risk factors already described in the literature, such as MRSA infections [26]. A recent meta-analysis found MRSA to be a risk factor for mortality in *S. aureus* bacteraemia [45]. One hypothesis could be the low prevalence of MRSA strains in our series compared with other studies [26,38]. Another explanation could be the frequent empiric use of glycopeptides. Many studies have demonstrated the superiority of combining antibiotic lock therapy with systemic antibiotics over systemic antibiotics alone when attempting CSS [35,44,46]. Although IDSA guidelines recommend antibiotic lock therapy in the case of CSS [6], we observed a scarce use of this strategy in our study, with more common use of continuous infusion of vancomycin on the infected LTCVC. Consequently, our study revealed another paediatric-specific challenge: the difficulty in implementing an antibiotic lock for catheter salvage, given that most LTCVCs used in children are single-lumen devices primarily utilized for parenteral nutrition. Continuous infusion of vancomycin provides a constant adequate antibiotic level on the catheter and might be considered an alternative to locks [47,48]; this deserves further research.

Finally, the additional analysis, which used an alternative definition of CSS failure that included all episodes with a LTCVC removal after 72h, yielded similar results regarding the main predictor of CSS failure: severe sepsis at the initial stage of infection. Other factors also identified in baseline analyses, however, did not reach significance, such as polymicrobial infection and the type of LTCVC. Another risk factor for CSS failure, which had already been suggested but never clinically demonstrated, is the delay from LTCVC insertion to infection [1,3]; this might be explained by biofilm production and subsequent lower efficacy of the antibiotic therapy and higher risk of infection relapse [49]. In our study, although univariable analysis and additional multi-variable analysis found an association between a long time since LTCVC insertion (>30 days) and CSS failure, this was not confirmed by our principal multivariable analysis. Another identified predictor found in the additional analysis is the local infectious signs at initial presentation. Previous findings have shown that signs of tunnel infections are associated with CSS failure [24]. Current guidelines recommend CVC removal in such cases [6]. The link between initial local signs and CSS failure might have been underestimated in the primary analysis; one possible explanation is that catheter removal after an initial CSS in some cases with initial local infectious signs (57%) may have prevented the development of complications, such as tunnel infection or abscess. The other predictors of CSS failure only identified by this additional analysis might be explained by the possible heterogeneity of indications for catheter withdrawal during the weeks following infection and competitive risks.

This study has several limitations. Firstly, this is a retrospective study, with potential measurement bias and missing data. Secondly, all CLABSI were included in the analysis, and not only CRBSI, but some of the bacteraemia episodes that we included might not have been related to the LTCVC. However, this situation is frequent in clinical wards, and therefore improves the applicability of our results. Thirdly, this study cannot be generalized to other causes of CLABSIs, as only *S. aureus* CLABSI has been analysed. Nevertheless, focusing on *S. aureus*, a highly pathogenic bacterium with frequent involvement in CLABSI, provides results applicable to a specific clinical situation. Furthermore, *S. aureus* is one of the most challenging infectious agents in LTCVC salvage strategy, given the high risk of failure and complications associated with this pathogen. Additionally, the design of this multi-centre study did not allow for the estimation of the proportion of CLABIs due to *S. aureus* among all CLABIs that occurred over the study period. Finally, this was a multi-centre study, enhancing statistical power and applicability of the results, but the data may lack homogeneity, and there might be a centre effect that was not fully captured; multi-level models might be more appropriate for future studies.

In conclusion, this multi-centre series of paediatric *S. aureus* LTCVC-associated CLABSI, CSS was frequently attempted and succeeded in two-thirds of cases. CSS failure was strongly associated with several factors that could help clinicians identify patients at high risk for CSS failure. These findings may deserve confirmation in large-scale prospective series.

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Author contributions

J.T. conceived the study, and J.T., J.F.C. and M.C. designed the study. C.D. collected the data, and J.T. and C.D. were responsible for data management and analysis. J.T. and J.F.C. supervised the statistical analyses. A.F. was involved in isolate collection and microbiological analyses. N.P., J.L., E.L., A.C., N.V., P.B., P.P., L.T., Y.P., D.P., M.L., F.D., M.C. and A.O. were involved in patients' care, and clinical data collection. C.D. wrote the first draft of the manuscript, J.T. and J.F.C. had access to and verified the source data, and J.T. was responsible for the decision to submit the manuscript. All authors drafted the manuscript for important intellectual content, contributed to the revision of the final version of the manuscript, and approved the final version submitted. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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