Clinical Microbiology and Infection 26 (2020) 563–571

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

Validity of surrogate endpoints assessing central venous catheter-related infection: evidence from individual- and study-level analyses

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ARTICLE INFO

Article history:
Received 10 June 2019
Received in revised form
17 September 2019
Accepted 20 September 2019
Available online 3 October 2019

Editor: M Leeflang

Keywords:
Bacteraemia
Blood culture
Catheter-related infections
Surrogate endpoints
Vascular access devices

ABSTRACT

Objectives: The prevention of catheter-related bloodstream infection (CRBSI) has been an area of intense research, but the heterogeneity of endpoints used to define catheter infection makes the interpretation of randomized controlled trials (RCTs) problematic. The aim of this study was to determine the validity of different endpoints for central venous catheter infections.

Data sources: (a) Individual-catheter data were collected from 9428 catheters from four large RCTs; (b) study-level data from 70 RCTs were identified with a systematic search. Eligible studies were RCTs published between January 1987 and October 2018 investigating various interventions to reduce infections from short-term central venous catheters or short-term dialysis catheters. For each RCT the prevalence rates of CRBSI, quantitative catheter tip colonization, catheter-associated infection (CAI) and central line-associated bloodstream infection (CLABSI) were extracted for each randomized study arm.

Methods: CRBSI was used as the gold-standard endpoint, for which colonization, CAI and CLABSI were evaluated as surrogate endpoints. Surrogate validity was assessed as (1) the individual partial coefficient of determination (individual-pR^2) using individual catheter data; (2) the coefficient of determination (study-R^2) from mixed-effect models regressing the therapeutic effect size of the surrogates on the effect size of CRBSI, using study-level data.

Results: Colonization showed poor agreement with CRBSI at the individual-patient level (pR^2 = 0.33 95% CI 0.28–0.38) and poor capture at the study level (R^2 = 0.42, 95% CI 0.21–0.58). CAI showed good agreement with CRBSI at the individual-patient level (pR^2 = 0.80, 95% CI 0.76–0.83) and moderate capture at the study level (R^2 = 0.71, 95% CI 0.51–0.85). CLABSI showed poor agreement with CRBSI at the individual patient level (pR^2 = 0.34, 95% CI 0.23–0.46) and poor capture at the study level (R^2 = 0.28, 95% CI 0.07–0.76).

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https://doi.org/10.1016/j.cmi.2019.09.022
1198-743X/

Conclusions: CAI is a moderate to good surrogate endpoint for CRBSI. Colonization and CLABSI do not reliably reflect treatment effects on CRBSI and are consequently more suitable for surveillance than for clinical effectiveness research. **H.J. de Grooth, Clin Microbiol Infect 2020;26:563**

Introduction

The prevention of infectious complications associated with the use of intravascular devices has been a research priority for decades. However, several definitions are used to quantify infectious complications. Each measure has a specific purpose, but their interchangeable and simultaneous use hampers interpretation and comparison of study results.

The most frequently used infectious complication metrics are catheter tip colonization, catheter-related bloodstream infection (CRBSI), catheter-associated infection (CAI) and central line-associated bloodstream infection (CLABSI). Quantitative catheter tip colonization can be asymptomatic and denotes a substantial microbial load on the catheter [1,2], while CRBSI indicates that the same microorganism is present on the catheter and in peripheral blood culture [3–5]. CRBSI, therefore, establishes a high likelihood of a causal relation between the catheter and a bloodstream infection. CAI encompasses CRBSI or catheter colonization with clinical signs of systemic infection, increasing sensitivity to uncultured infection originating from the catheter. CLABSI establishes a temporal relation between bloodstream infection and a catheter *in situ*, and its ease of implementation makes it a popular measure for surveillance and quality monitoring [6].

To make appropriate guideline recommendations and treatment decisions, it is crucial to understand the relevance of surrogate outcomes such as catheter colonization, CAI and CLABSI for more patient-oriented outcomes [7,8]. Because CRBSI is a rare event, alternative primary endpoints have been considered in the design of clinical trials to increase the statistical power for a limited sample size.

The aim of the present study was to analyse the patient-oriented relevance and validity of different infectious definitions. From the perspective of patient-oriented benefit, we aimed to establish both the agreement between the CRBSI and its surrogates at the individual patient level, and the degree to which treatment effects on CRBSI are captured by the surrogates at the trial level.

Methods

Definitions and endpoint validity framework

The most commonly agreed-upon definitions of infectious catheter complications are summarized in Table 1 [9].

We considered CRBSI as the gold-standard patient-oriented endpoint to which the other measures were compared, as it has the best construct validity to establish causality between the catheter and a bloodstream infection and because it is significantly associated with increased mortality [4,10]. For this study, colonization, CAI and CLABSI were considered surrogate endpoints for CRBSI.

A surrogate can be considered valid when it is statistically associated to the patient-oriented endpoint, and when the effect of a treatment on the surrogate accurately reflects the effect of treatment on the patient-oriented endpoint [11]. The first criterion establishes individual-level surrogate validity: A surrogate can only be useful when it predicts the patient-oriented outcome for each patient [12]. The second criterion establishes trial-level surrogate validity: a surrogate endpoint must reliably capture the treatment effect on a patient-oriented endpoint to be useful as a research instrument [13]. A surrogate endpoint can only be considered valid and reliable when there is a strong association at the individual and at the study (intervention) level.

Following the surrogate validity framework operationalized by Buyse and Molenberghs [12,13], we evaluated both the individual-level surrogate validity and the trial-level surrogate validity.

Data

To analyse individual-level surrogate validity, we used individual catheter data from four randomized controlled trials: The 3SITES trial comparing insertion at the subclavian, jugular or femoral site [14]; the CLEAN trial comparing skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol [15]; the

Table 1
Definitions of infectious complications of central venous catheterization

Metric	Common definition(s)	Use or purpose
Catheter-related bloodstream infection (CRBSI)	1. Positive catheter tip colonization with the same organism cultured in peripheral blood (two positive peripheral blood cultures for suspected skin contaminants) [4,5]. 2. Differential time to positivity (of peripheral and central venous catheter drawn blood cultures) of 120 minutes or more [18].	Establishes a high likelihood that a bloodstream infection is caused or maintained by the catheter.
Catheter tip colonization	1. Semiquantitative method ('Maki roll'), cutoff ≥15 cfu/catheter [1]. 2. Quantitative (broth dilution) method, cutoff ≥1000 cfu/ml [2].	Identifies a significant degree of microbial catheter colonization [2].
Catheter-associated infection (CAI)[a]	CRBSI or catheter colonization with clinical signs of systemic infection not related to infection at another site.	CRBSI with broadened sensitivity to blood culture-negative infections.
Central line-associated bloodstream infection (CLABSI)	Positive peripheral blood culture in a patient with a central venous catheter or within 48 hours after removal of a central venous catheter, not related to infection at another site [6].	Establishes temporal association, used for surveillance and quality monitoring [6].

Adapted from [9].
[a] Alternative names for catheter-associated infection are, major catheter-related infections, or catheter-related clinical sepsis. cfu, colony forming units.

DRESSING-1 trial comparing chlorhexidine-impregnated sponges versus standard dressings [16], and; the DRESSING-2 trial comparing chlorhexidine dressings versus standard dressings [17]. Data from arterial catheters and dialysis catheters were excluded. These four trials were chosen arbitrarily based on data availability, methodological quality (multicentre, blinded adjudication of infectious complications) and sample size. Ethics committee approval and written informed were described in the original publications [14–17].

In all four trials, the diagnosis of CRBSI and CAI was adjudicated by blinded assessors. Individual catheter data on CLABSI was available only in the 3SITES and DRESSING-2 trials. We performed a sensitivity analysis for CLABSI to account for different peripheral blood culture protocols between the studies. We also performed a sensitivity analysis for CRBSI to the diagnosis by differential time to positivity (details and results in supplementary material) [18].

At the study level, to evaluate whether treatment effects on CRBSI are adequately captured by treatment effects on the surrogates, we performed a literature search to identify all randomized trials investigating an intervention related to infectious central venous catheter complications. The search query is described in the supplementary material and was last performed on 17 October 2018. Eligible studies were limited to randomized controlled trials published in English after 1987 (when the laboratory methods for catheter colonization were standardized [2]) and to trials investigating short-term central venous catheters or short-term dialysis catheters. Reasons to exclude trials were neonatal population, use of peripherally inserted central catheters, trials that did not report CRBSI or reported only one infectious complication metric (no comparison possible) or trials with a total sample size <50 to avoid publication bias from very small trials with high event rates.

Statistical methods

The primary measure of individual-level surrogate validity was the partial coefficient of determination (pR^2) between CRBSI and the other measures. The individual-pR^2 (also known as the adjusted association in the surrogate endpoint literature) estimates the proportion of variance in CRBSI explained by the surrogate, while controlling for treatment [13]. We considered individual-pR^2 estimates of <0.50, 0.50–0.72, and >0.72 as poor, moderate and good agreement, respectively (corresponding to correlation coefficients of <0.70, 0.70–0.85 and >0.85) [19,20].

Using logistic regression, we defined the reduced models with CRBSI as dependent variable and treatment allocation as independent variable. The full models were defined with CRBSI as dependent variable and treatment allocation plus one of the surrogates as independent variables. The individual-pR^2 was calculated as the full model McFadden's pseudo-R^2 minus the reduced model McFadden's pseudo-R^2.

Individual-pR^2 estimates were calculated for each surrogate in each trial separately. The overall individual-pR^2 was calculated using all data in mixed-effect models with a random trial effect on intercept in the reduced models and a random trial effect on intercept and surrogate in the full models. Confidence intervals were bootstrapped with 1000 replications.

As adjuncts for the interpretation of individual-level surrogacy, we report Cohen's kappa coefficient of agreement, the positive predictive value and negative predictive value of colonization, CAI and CLABSI to detect CRBSI.

To test whether individual-patient characteristics influenced the association between CRBSI and the surrogate, we modelled CRBSI as a function of the surrogate outcomes with an interaction term between the surrogate outcomes and (a) randomization group, (b) the presence of immune deficiency and (c) the class of microorganism cultured from the catheter (*Staphylococcus* sp., versus other.)

The primary measure of trial-level surrogate validity was the study-level R^2 as a measure for the agreement between effect of the treatment on colonization, CAI or CLABSI compared with CRBSI [12,13]. The relative effect was estimated using a mixed-effects regression model with each trial's treatment effect on CRBSI as the dependent variable, the treatment effect on colonization, CAI or CLABSI as independent variable and a random intercept for each study. The regression slopes between treatment effects on CRBSI and (a) colonization, (b) CAI and (c) CLABSI reflected the average responsiveness of the surrogates to CRBSI. The study-R^2 represents the average proportion of treatment effects on CRBSI captured by the surrogate endpoint. Again, we considered R^2 estimates of <0.50, 0.50–0.72 and >0.72 as poor, moderate and good agreement, respectively [19,20].

All analyses were performed in the R language and environment for statistical computing, using the *epiR* and *boot* packages for individual catheter-level analyses and the *metafor* package for the study-level analyses [21–24]. The analysis code is available on request from the corresponding author.

Results

Individual catheter data

Individual catheter data were available for 9428 central venous catheters from 8908 patients (3471, 2155, 2051 and 1751 catheters from the 3SITES, CLEAN, DRESSING-1 and DRESSING-2 trials, respectively [14–17]). The incidences and crude associations between CRBSI and colonization, CAI and CLABSI are shown in Table 2. Colonization and CAI had high sensitivity to detect CRBSI while CAI had only moderate sensitivity. Aided by the low prevalence of CRBSI, all three surrogates had excellent negative predictive value to exclude CRBSI. CAI and CLABSI were most specific for the diagnosis of CRBSI. Overall, 10% of patients with positive colonization had CRBSI, 61% of patients with positive CAI had CRBSI and 36% of patients with positive CLABSI had CRBSI (the positive predictive value).

The individual catheter-level agreement between CRBSI and the surrogate endpoints is shown in Fig. 1. The overall individual-pR^2 estimates for agreement between colonization, CAI and CLABSI with CRBSI were 0.33 (95% CI 0.28–0.38), 0.80 (95% CI 0.76–0.83) and 0.34 (95% CI 0.23–0.46), indicating poor, good and poor agreement, respectively. Sensitivity analyses are reported in the supplementary material.

The associations between CRBSI and the surrogates were homogeneous in all pre-defined subgroup comparisons in all four trials and in the combined dataset (p for interaction all >0.1).

Meta-analysis of study-level data

Seventy eligible randomized controlled trials were identified for the study-level analysis (Fig. S1) [14–17,25–50,51–75,75–90]. The baseline characteristics of the included trials are shown in Table 3.

Sixty-eight studies reported both treatment effects on catheter colonization and on CRBSI (Fig. 2a). In these studies, the median rate of catheter colonization was 6.7 times higher than for CRBSI (10.0% vs. 1.5%). Six studies compared more than two treatment arms, resulting in 80 treatment comparisons. Twenty studies (25%) showed opposite treatment effects on colonization and CRBSI (i.e. the treatment caused a decrease in colonization but an increase in CRBSI), but none of these opposite effects were statistically significant (all $p > 0.05$ on Fisher's exact test). There was an association between treatment effects on colonization and CRBSI ($p < 0.0001$),

Table 2
Individual catheter level associations between CRBSI and other infection measures

Trial endpoint	Study	Prevalence (%)	Incidence/1000 catheter-days	Kappa agreement with CRBSI	Sensitivity for CRBSI	Specificity for CRBSI	Positive predictive value for CRBSI	Negative predictive value for CRBSI
CRBSI	3SITES	1.27	1.97					
	CLEAN	0.70	0.85					
	DRESSING-1	0.73	0.98					
	DRESSING-2	1.1	1.34					
	Weighted mean (range)	0.98 (0.79–1.17)[a]	1.34 (1.08–1.63)					
Colonization	3SITES	9.4	14.65	0.22	1.00	0.92	0.13	1.00
	CLEAN	9.0	11.05	0.13	1.00	0.92	0.08	1.00
	DRESSING-1	8.9	11.99	0.11	0.80[b]	0.92	0.07	1.00
	DRESSING-2	7.8	9.70	0.15	0.68[b]	0.93	0.09	1.00
	Weighted mean (range)	8.9 (8.4–9.5)	12.14 (11.38–12.91)	0.16 (0.13–0.20)	0.90 (0.82–0.95)	0.92 (0.91–0.92)	0.10 (0.08–0.12)	1.00 (1.00–1.00)
CAI	3SITES	2.5	3.90	0.67	1.00	0.99	0.51	1.00
	CLEAN	0.88	1.07	0.88	1.00	0.99	0.79	1.00
	DRESSING-1	0.88	1.18	0.91	1.00	0.99	0.83	1.00
	DRESSING-2	1.6	2.05	0.79	1.00	0.99	0.66	1.00
	Weighted mean (range)	1.6 (1.4–1.9)	2.21 (1.85–2.54)	0.75 (0.69–0.81)	1.00 (0.96–1.00)	0.99 (0.99–1.00)	0.61 (0.53–0.69)	1.00 (1.00–1.00)
CLABSI	3SITES	1.93	3.08	0.31	0.46	0.99	0.24	0.99
	3SITES adjusted[c]	*9.56*	*15.20*	*0.25*	*1.00*	*0.92*	*0.15*	*1.00*
	DRESSING-2	1.65	2.05	0.66	0.84	0.99	0.55	1.00
	Weighted mean (range)	1.82 (1.39–2.21)	2.60 (2.03–3.16)	0.45 (0.34–0.56)	0.62 (0.47–0.76)	0.99 (0.98–0.99)	0.36 (0.25–0.48)	1.00 (0.99–1.00)

Overall mean incidences were weighted by each study's sample size. Colonization, quantitative catheter tip colonization; CAI, catheter-associated infection; CLABSI, central line-associated bloodstream infection.
[a] Numbers between brackets are 95% confidence intervals of the weighted mean.
[b] Sensitivity of colonization for CRBSI was <1 in the DRESSING-1 and DRESSING-2 trial because CRBSI could be diagnosed using differential time to positivity.
[c] Adjusted CLASBI for the 3SITES trial was a positive blood culture irrespective of clinical signs of infection (not included in weighted means).

with a study-level agreement (study-R^2) of 0.42 (95% CI 0.21–0.58). Including only studies with systematically cultured catheters (n = 73) did not improve the agreement (study-R^2 0.44, 95% CI 0.19–0.63).

Thirteen studies reported both treatment effects on CAI and on CRBSI (Fig. 2b). In these studies, the median rate of CAI was 1.4 times higher than for CRBSI (1.6% vs. 1.1%). Three studies compared more than two treatment arms, resulting in 18 treatment comparisons. Two studies (11%) showed contradictory treatment effects on CAI and CRBSI, but none of these contradictory effects were statistically significant. There was an association between treatment effects on CAI and CRBSI (p 0.022), with a study-level agreement (study-R^2) of 0.71 (95% CI 0.51–0.85).

Twelve studies reported both treatment effects on CLABSI and on CRBSI (Fig. 2c). In these studies, the median rate of CLABSI was 3.2 times higher than for CRBSI (8.4% vs. 2.2%). One study (8%) showed contradictory treatment effects on CLABSI and CRBSI, but this contradictory effect was not statistically significant. There was no significant association between treatment effects on CLABSI and CRBSI (p 0.143), with a study-level agreement (study-R^2) of 0.28 (95% CI 0.07–0.76).

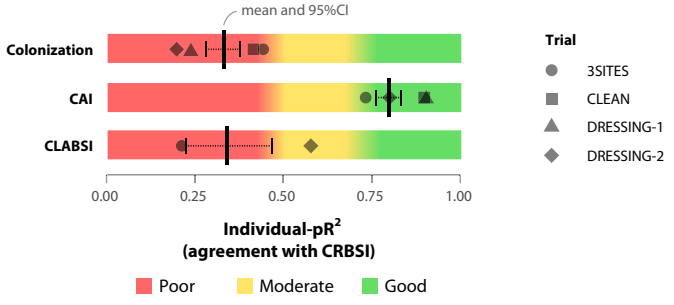

Fig. 1. Individual catheter-level agreement between catheter-related bloodstream infection (CRBSI) and surrogate endpoints among 9428 catheters from four randomized controlled trials. Differences in protocolized blood culture drawing may explain the inconsistent CLABSI results between 3SITES and DRESSING-II. A sensitivity analysis can be found in the supplementary material. Colonization, quantitative catheter tip colonization; CAI, catheter-associated infection; CI, confidence interval; CLABSI, central line-associated bloodstream infection.

Discussion

To be considered valid and reliable, a surrogate must be strongly associated with CRBSI both at the individual and at the study level. We found consistent results in the two types of analyses. Based on individual-level data on 9428 randomized catheters and study-level data from 70 randomized controlled trials, colonization offered substantial power advantages but was poorly consistent with treatment effects on CRBSI. CAI provided small power and operational advantages over CRBSI and was a moderate to good surrogate for treatment effects on CRBSI. Depending on the precise definition, CLABSI was a poor to moderate surrogate at the individual patient level and a poor surrogate at the trial level. Our results are consistent with the Centers for Disease Control Guidelines suggesting that CLABSI should be used in the routine setting for surveillance purposes while the CRBSI is preferred for clinical research [91].

Our findings regarding the poor performance of colonization contrast with a seminal 2002 meta-analysis, which showed that catheter colonization and CRBSI were correlated in different studies [92]. This analysis provided the basis for using colonization as a surrogate endpoint for CRBSI in many clinical studies. However, from the observation that colonization and CRBSI are correlated it does not necessarily follow that reducing the rate of colonization will also reduce CRBSI [93]. The present results indicate that treatment effects on CRBSI are not adequately captured by colonization.

Table 3
Characteristics of studies included in meta-analysis

	No. of trials (%) or median (IQR)
Included trials	70
Trial population	
Critically ill, adults	45 (64)
Haematology/oncology, adult	11 (16)
Mixed population, adult	9 (13)
Critically ill, paediatric	2 (3)
Haematology/oncology, paediatric	2 (3)
Acute renal replacement therapy, adult	1 (1)
Catheter type	
Central venous catheter, non-tunnelled	61 (87)
Central venous catheter, tunnelled	5 (7)
Acute haemodialysis catheter	3 (4)
Mixed catheter types	1 (1)
Randomized intervention	
Catheter coating/impregnation	29 (41)
Lock fluid	9 (13)
Skin cleaning/preparation	8 (11)
Catheter dressing	6 (9)
Connecting systems/hubs	4 (6)
Tunnelling	4 (6)
Insertion site	3 (4)
Other	7 (10)
Laboratory testing for catheter colonization	
Systematic (all catheters)	63 (90)
Non-systematic (only suspected infection)	2 (3)
Not described	5 (7)
Laboratory testing for bloodstream infection	
Systematic (all patients)	18 (26)
Non-systematic (only suspected infection)	30 (43)
Not described	22 (31)
CRBSI	
Reported in no. of studies	70 (100)
Median rate (IQR)	1.6% (0.7–3.4)
Catheter colonization	
Reported in no. of studies	68 (97)
Median rate (IQR)	10.0% (8.2–17.7)
CAI	
Reported in no. of studies	13 (19)
Median rate (IQR)	1.6% (0.9–4.2)
CLABSI	
Reported in no. of studies	12 (17)
Median rate (IQR)	8.4% (7.4–19.8)

Numbers within parentheses are percentages. Colonization, quantitative catheter tip colonization; CAI, catheter-associated infection; CLABSI, central line-associated bloodstream infection; IQR, interquartile range.

Catheter-related bloodstream infection

For the purpose of this study, we defined CRBSI as the gold standard endpoint because it has the best face- and construct validity to establish a causal relation between a catheter and a bloodstream infection. It is the most patient-oriented endpoint with a well-established association with increased mortality and an estimated case-fatality rate of 11% [4,10].

Its drawbacks are the low incidence and a relatively complicated diagnostic process. At a median rate of 1.6%, any study aiming to detect an effect on CRBSI needs a substantially larger sample size than is needed for the other endpoints. A confirmatory diagnosis of CRBSI requires matching the catheter and blood culture results. Compared to the other endpoints, more prospective diagnostics and dedicated attention to the matching of the catheter tip and blood culture results are required. CRBSI establishes a causal relationship but secondary hematogenous seeding to the catheter cannot be excluded, although uncommon [94,95]. In addition, prompt empiric antibiotic therapy may increase the rate of false negative blood culture results.

Catheter colonization

With a median rate of 10%, a study powered to detect a decrease in colonization requires approximately seven times less patients than a study powered to detect a corresponding relative decrease in CRBSI. The downside is that the positive predictive value of colonization for CRBSI is very low at 0.10 (Table 2). Catheter colonization showed a statistically significant treatment effect more often than any of the other complication measures. This is in line with previous research in which trial endpoints more distal to patient-oriented benefit tended to show more significant results [7].

At the individual patient level, catheter colonization explained 44% (individual-pR^2) of the likelihood of CRBSI among 9428 catheters, indicating poor agreement with the reference standard endpoint.

At the study level, treatment effects on catheter colonization were associated with treatment effects on CRBSI. The regression slope of 0.93 means that, on average, treatment effects on catheter colonization overestimated the effect on CRBSI by 7%, which appears acceptable. However, 25% of studies showed contradictory treatment effects and only (study-R^2) 42% of the between-study variance in treatment effects on CRBSI was captured by catheter colonization (as shown by the wide dispersion around the regression curve in Fig. 2a). This can be due to between-study differences in patient characteristics, standards of care, systematic cultures, sampling or laboratory methods.

In summary, catheter colonization as an endpoint offers substantial power advantages over CRBSI. This could make catheter colonization suitable as an endpoint in small exploratory pilot studies. However, the poor individual patient-level and study-level agreement make catheter colonization unsuitable to establish definite patient-oriented benefit or harm.

Catheter-associated infection

With a median rate of 1.5%, a study powered to detect a decrease in CAI requires approximately 1.5 times less patients than a study powered to detect an equal (relative) decrease in CRBSI.

At the individual patient level, CAI explained 80% (individual-pR^2) of the likelihood of CRBSI among 9428 catheters, indicating good agreement. At the study level, we found that the confidence interval of the study-R^2 was consistent with moderate to good study-level agreement between CAI and CRBSI.

CAI includes all cases of CRBSI, with a wider sensitivity to blood culture-negative infections and therefore offers a moderate power advantage over CRBSI. The measurement and registration of CAI is easier to operationalize as the absence of a blood culture at the time of catheter removal still allows the diagnosis to be made.

As it appears to capture at least a moderate to good proportion of the treatment effects on CRBSI (both in the individual patient and on the study level), we think CAI could reasonably be used as an endpoint for clinical trials or quality improvement programs.

It should be noted that the performance of CAI will depend on local guidelines and customs with respect to the removal of catheters in patients with unexplained signs of low-grade infection. When catheters are removed early (rather than at the onset of signs of serious infection), the performance of CAI will be more similar to colonization. In the absence of a positive blood culture, blind adjudication of the diagnosis of CAI is important to prevent differential detection bias. Of note, only six of 35 RCTs comparing antimicrobial dressings had a blind outcome assessment [96].

Central line-associated bloodstream infection

With a median rate of 8.4%, a study powered to detect a decrease in CLABSI requires approximately four times less patients than a

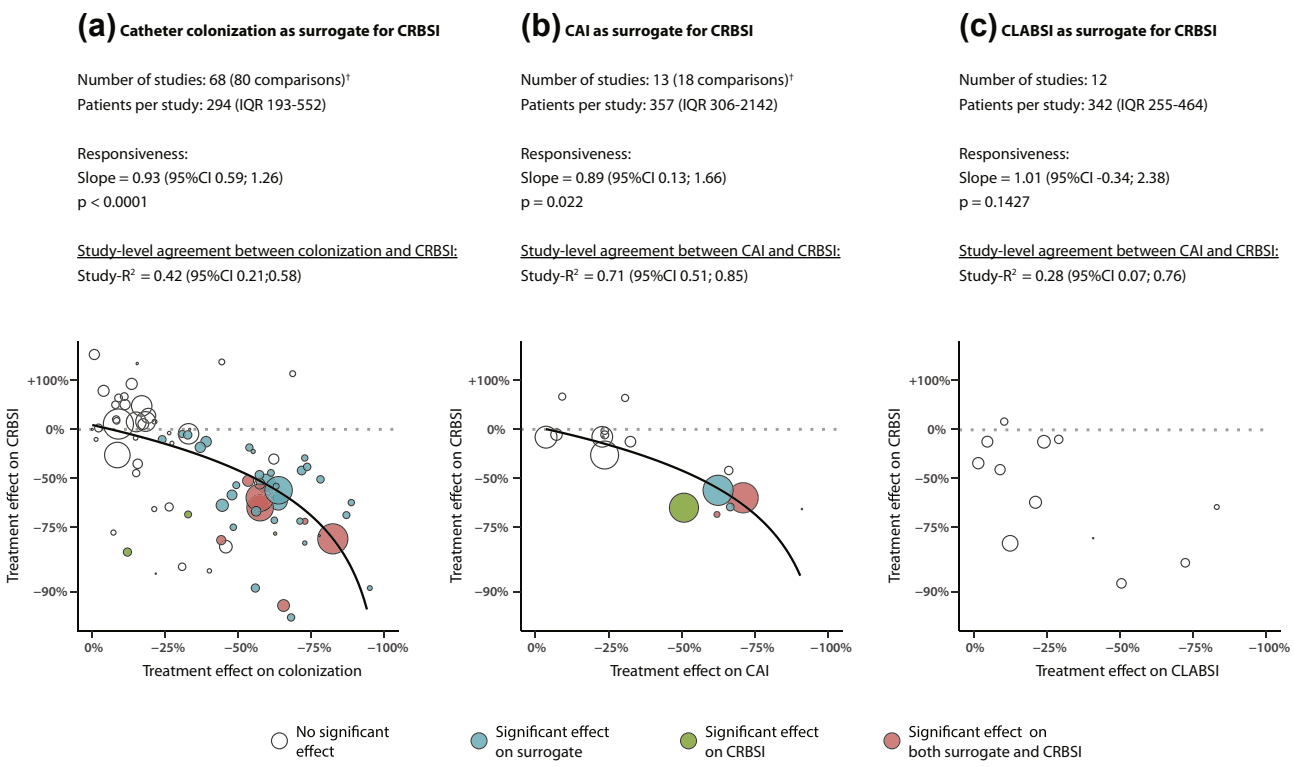

Fig. 2. Study-level agreement between CRBSI and catheter colonization, CAI and central-line-associated bloodstream infection (CLABSI). Circle sizes are proportional to study sample sizes. The regression curves represent a significant study-level association between treatment effects on colonization and CRBSI and between treatment effects on CAI and CRBSI. The estimated regression function is $log(RR_{crbsi}) = intercept + slope \cdot log(RR_{surrogate})$. CAI, catheter-associated infection; CI, confidence interval; CLABSI, central-line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; IQR, interquartile range. †Studies with more than two treatment groups (more than one treatment comparison) are shown as separate comparisons (plot points).

study powered to detect an equal (relative) decrease in CRBSI. The main limitation of this definition is the absence of catheter tip culture, reducing the likelihood of causality between the catheter and a bloodstream infection.

At the individual patient level, CLABSI explained 34% (individual-pR^2) of the likelihood of CRBSI among 5222 catheters, indicating poor agreement. However, with an adjustment in the definition of CLABSI in the 3SITES trial (so that any positive blood culture irrespective of clinical infection counted as CLABSI), the overall agreement with CRBSI improved to a 95% CI consistent with poor to moderate agreement (43–59%).

At the study level, we found that treatment effects on CLABSI poorly captured treatment effects on CRBSI. This can be partly attributed to a lack of power, but CLABSI also had very poor study level agreement (study-R^2 21%).

Therefore, CLABSI appears to be an unsuitable surrogate endpoint to detect patient-oriented effects of interventions aimed at reducing infectious complications related to the catheter.

Limitations

For the purpose of this study, we considered CRBSI the reference standard endpoint, but its attributable mortality [4,10] in the context of critically ill patients has been controversial [97,98]. Further work is needed to establish whether the prevention of CRBSI does indeed translate to a reduction in mortality. Nevertheless, the association between catheter colonization, CAI and CLABSI with mortality have been less well established, and these endpoints were therefore considered surrogates in this study.

The four trials using in the individual-catheter analysis were selected based on availability and were conducted in France. However, these trials were multicentre and the individual catheter-level results were consistent with the study-level results, indicating good generalizability.

Our sample of studies for the meta-analysis was limited by five foreign language reports, the unavailability of 24 full reports (all older studies) and the exclusion of studies with sample sizes smaller than 50 patients or catheters. These excluded studies may have influenced the results. The sample of included studies was inherently heterogeneous, with different populations, interventions and a publication span of 30 years. However, the broad range of included studies strengthens the generalizability of the results and we do not expect that the study heterogeneity materially affects the differential treatment effects on the surrogate endpoints *vs.* CRBSI.

Conclusions

Understanding the relevance of surrogate endpoints for more patient-oriented outcomes (such as CRBSI or mortality) is crucial to make correct guideline recommendations for treatment decisions and for governmental agencies to assess new devices or new technologies designed to prevent CRBSI [7,8].

In the present study we have not taken correlation between endpoints as satisfactory evidence that these endpoints can be used interchangeably [92,93], but rather analysed the candidate endpoints using a thorough surrogate validity framework by combining high-quality and blindly adjudicated individual catheter data with systematically searched study-level data.

We have found that CAI offers a small power advantage over CRBSI and is the best alternative to CRBSI when the logistics needed for the diagnosis of CRBSI cannot be assured. Catheter colonization

is appropriate for small exploratory studies but cannot be used to establish definite harm or benefit of an intervention. We recommend against the use of CLABSI outside of surveillance purposes, as it does not appear to capture the effects of interventions on CRBSI.

Access to data

The individual-catheter data from the four randomized controlled trials are guaranteed by J.J.P. (for 3SITES), OM (for CLEAN), JFT (for DRESSING-1 and DRESSING-2). H.J.d.G. has full access to the aggregated data. R codes are available from the corresponding author on request.

Transparency declaration

Conflicts of interest: H.J.d.G. no conflict; J.F.T. has no conflict directly related to the article but serves on the advisory boards of MSD, Pfizer, Bayer pharma and Nabriva, has given lectures at MSD, Pfizer, Biomerieux, and his university or research team had received research grants from Pfizer and MSD; L.M. no conflict; O.M. received research grants, lecture and consultancy fees from CareFusion; N.B. no conflict; D.d.C. no conflict; H.M.O. no conflict; J.J.P. no conflict. Funding: 3SITES and DRESSING-1 were supported by grants from the Hospital Program for Clinical Research, French Ministry of Health (PHRC-N 2010, 06-03 and PHRC-N 2005-PHN01, respectively). CLEAN was supported by the University Hospital of Poitiers and CareFusion. DRESSING-2 was supported by University of Grenoble and 3M Company. N.B. was supported by a Postdoc. Mobility grant from the Swiss National Science Foundation (grant number P400PM_183865) and the Bangerter-Rhyner Foundation. Clinical Trials Registration: NCT01479153, NCT00417235, NCT01189682, NCT01629550.

Acknowledgments

We thank all contributing investigators of the 3SITES, CLEAN, DRESSING-1 and DRESSING-2 trials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.09.022.

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