

Rapid publication

Evaluation of a novel endoluminal brush method for in situ diagnosis of catheter related sepsis

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Abstract

Aims—To determine the accuracy of a novel endoluminal brush method for the diagnosis of catheter related sepsis (CRS), which is performed in situ and hence does not require line sacrifice.

Methods—230 central venous catheters in 216 patients were examined prospectively for evidence of CRS or colonisation using an endoluminal brush method in conjunction with peripheral blood cultures. The results were compared with those obtained using methods that require line sacrifice: extraluminal sampling (Maki roll) or endoluminal sampling (modified Cleri flush) of microorganisms.

Results—Only 16% of 128 patients suspected clinically of having line associated infection were confirmed as having CRS. In addition, 2 of 102 patients not suspected of having line associated infection had CRS. Line colonisation was apparent in approximately twice as many catheters using the Maki roll criteria (92%) compared with either the endoluminal brush (43%) or Cleri flush (43%). Furthermore, colonised catheters sampled using the Maki roll technique yielded mixed growth twice as often as when examined by endoluminal methods (17 and 8 cases, respectively). It was rare to detect either only endoluminal (4 of 22 episodes) or extraluminal (1 of 22 episodes) microorganisms in cases of CRS. In contrast, catheters defined as being colonised most frequently (59% of episodes) yielded only significant extraluminal growth. Only one case of CRS (5%) would have been "missed" if lines yielding a negative result from endoluminal brush sampling had been left in situ. Conversely, four episodes of CRS (18%) would not have been diagnosed by relying on extraluminal sampling alone.

Conclusions—Diagnosis of CRS by the endoluminal brush method can be achieved without line sacrifice and is more sensitive (95%) and specific (84%) than extraluminal sampling of the catheter tip by the Maki roll technique (82% and 66%, respectively).

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The use of central venous catheters for nutrition, inotropic therapy, and monitoring is common in modern surgical and medical practice. Complications associated with central venous catheter use can be divided into those occurring at catheter insertion (pneumothorax, arterial cannulation and subsequent haemorrhage, catheter misplacement, and nerve injury), and those related to catheter use, including thrombosis and infection. The reported incidence of catheter related sepsis (CRS) ranges from 4-14%,¹⁻⁴ and it is estimated that approximately 0.5 million episodes occur annually in the United States.⁵ In one cohort of patients with CRS, major complications occurred in 32% of episodes.⁶ Despite many improvements, including aseptic protocols for catheter manipulation and dressing changes, dedicated catheter and nutrition teams, and variations in manufacture design, central venous catheters remain an important source of hospital acquired infection and cause a major proportion of the septicaemias due to coagulase-negative staphylococci, *Staphylococcus aureus*, and *Candida* spp.^{5,7}

The diagnosis of CRS can be difficult, particularly if the patient has many possible sources of infection. Removal of central venous catheters on clinical suspicion of infection alone results in subsequent line tip cultures being negative in 75-85% of cases.^{8,9} The decision to remove central venous catheters is further complicated in patients in whom access is difficult as a result of numerous previous line insertions. While alternatives such as quantitative blood cultures are occasionally used, confirmation of a CRS usually requires that an organism is isolated from both peripheral blood and catheter cultures; therefore, the diagnosis is retrospective.⁵ The majority of catheters are assessed semiquantitatively by rolling the tip across a culture plate (Maki roll),¹⁰ or quantitatively by immersing the end of the line in broth and then either sonicating or flushing (Cleri flush).¹¹ The in situ diagnosis of CRS, and consequent reduction of the needless removal of uninfected lines, would offer an obvious advantage over the former

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laboratory techniques. Endoluminal catheter sampling using a novel brush (FAS Medical, Sunbury) potentially allows for the diagnosis of suspected CRS without a reliance on line removal. The results of a pilot study evaluating the brush method have recently been published.¹² We present our experience to date of the brush method, in comparison with the Maki roll and modified Cleri techniques, in 230 central venous catheters used primarily for total parenteral nutrition (TPN) that were removed either routinely or on the grounds of suspected CRS.

Methods

PATIENTS AND CATHETERS

A total of 230 central venous catheters in 216 patients (age range 15–93 years, median 66) in the surgical unit of Leeds General Infirmary were sampled using endoluminal and extraluminal methods during the period September 1994 to March 1996. Of the 230 catheters, 61% were non-cuffed, triple lumen catheters and the remainder were non-cuffed, single lumen catheters. The insertion site was either a subclavian vein (58%) or an internal jugular vein (42%), and the majority of catheters (90%) at some point were used for TPN. The 230 catheters remained in place for two to 150 days (median 9.5). CRS was suspected clinically (temperature > 37°C, exit site inflammation, or white blood cell count > $11 \times 10^9/l$) in 128 cases, and in the remainder sampling was performed immediately before line removal at the completion of intravenous therapy. The most common underlying conditions in the study patients were gastro-oesophageal disorders (40), colorectal disorders (40), inflammatory bowel disease (33), vascular diseases (24), neurological disorders (16), pancreatitis (15), miscellaneous gastrointestinal tract disorders (36), other (12).

BLOOD CULTURES

Peripheral blood cultures (two bottles per set; 10 ml per bottle) were taken immediately before endoluminal brush sampling and were processed by the automated VITEK system (Biomérieux, Marcy l'Étoile, France).

IN SITU CATHETER ENDOLUMINAL BRUSH SAMPLING

The sterile endoluminal brush (FAS Medical) was encapsulated in a polythene sleeve with a Luer lock, capped end piece, which attached to the hub of the catheter. The nylon bristled, discontinuously tapered brush (approximately 8 mm long) on the end of a stainless steel wire was introduced through the hub and passed down the catheter lumen in situ up to the distal end of the line, and then withdrawn into the polythene sheath. The brush was then cut off into a sterile universal container using the sterile wire cutting device supplied and sent to the laboratory for processing. In the case of triple lumen catheters the lumen used for TPN was brushed.

One millilitre of phosphate buffered saline (PBS), pH 7.4, was added to the brush universal container and the contents were sonicated

for one minute at 44 KHz (Sonomatic, Jencons Scientific, Luton) and then vortexed for 15 seconds at maximum oscillations (Maxmatic Vortexer, Jencons Scientific). Aliquots (10 µl and 100 µl) of the PBS were inoculated over the entire surfaces of two 5% blood agar plates using a sterile plastic spreader (Technical Service Consultants, Heywood). Following overnight aerobic incubation at 37°C, colonies were enumerated and the colony count per millilitre of PBS calculated. Significant counts were defined as more than 100 colony forming units (cfu)/ml.

POST-REMOVAL CATHETER EXTRALUMINAL OR ENDOLUMINAL SAMPLING

Following endoluminal brushing, catheters were removed within one hour in 96% of cases, and within 24 hours for the remainder, and the tips sent to the laboratory for processing. We used versions of previously described, widely accepted methods to recover either extraluminal or endoluminal microorganisms from catheter tips. The semiquantitative extraluminal sampling method of Maki *et al* (Maki roll)¹⁰ was used by rolling a 6 cm portion of the catheter tip across a 5% blood agar plate four times. Following overnight aerobic incubation at 37°C, significant counts were defined as more than 15 cfu.

The method of catheter tip sampling described by Cleri *et al*¹¹ recovers both extraluminal and endoluminal microorganisms by sonication and vortexing. We modified this method (henceforth referred to as Cleri flush) to recover only endoluminal bacteria by killing extraluminal organisms. This was achieved by rubbing a cotton wool swab impregnated with 2.5% chlorhexidine along the outer surface of a 6 cm portion of the catheter tip. After allowing the disinfectant to dry, the chlorhexidine swabbing process was repeated. Our modification of the Cleri method removes more than 95% of extraluminal bacteria as determined by the Maki roll technique (data not shown). The catheter lumen was then flushed with 1 ml PBS in a sterile container by introducing a plastic pipette into the proximal end of the catheter tip lumen; endoluminal flushing was repeated five times using 200 µl aliquots of the PBS. After vortexing the PBS for 15 seconds, 10 µl and 100 µl aliquots were inoculated over the entire surfaces of two 5% blood agar plates using a sterile plastic spreader. Following overnight aerobic incubation at 37°C, colonies were enumerated and the colony count per millilitre of PBS calculated. Significant counts were defined as more than 100 cfu/ml PBS.

DEFINITIONS OF CATHETER COLONISATION AND CRS

Catheter colonisation was defined as the culture of significant numbers of microorganisms from either the endoluminal or extraluminal surface of a line, in the absence of a positive peripheral blood culture. CRS was defined as culture of the same microorganism from a peripheral blood sample and from either the endoluminal or extraluminal surface of a line (in significant numbers).

Table 1 Overall results of catheter cultures and blood cultures from patients with and without suspected catheter related sepsis (CRS)

Results of catheter culture*	Number (%) in each clinical category		
	Not suspected (n=102)	Suspected (n=128)	Overall (n=230)
CRS	2 (2)†	20 (16)†	22 (10)
Colonised	35 (34)	41 (32)	76 (33)
Not colonised	65 (64)	67 (52)	132 (57)

*Defined by any of the three methods for detecting CRS.
†p<0.001.

Table 2 Microorganisms causing catheter related sepsis (CRS) and catheter colonisation

Microorganism*	Number (%) of episodes	
	Colonisation (n=76)	CRS (n=22)
Coagulase-negative staphylococci	63 (83)†	9 (41)†
<i>Staphylococcus aureus</i>	5 (7)‡	4 (18)‡
Enterococci	5 (7)	3 (14)
Gram negative bacilli	1 (1)§	4 (18)§
<i>Candida</i> spp	1 (1)	2 (9)
Other	1 (1)	0

*Predominant microorganism in the case of mixed growth.
†p<0.001; ‡0.1>p>0.05; §p<0.01.

Results

Twenty two CRS episodes were identified of which 21, 18, and 15 were diagnosed using the brush, Maki roll, and Cleri flush methods, respectively (only 20 of 22 CRS cases were examined by the Cleri flush method). CRS was confirmed significantly more frequently for lines removed on clinical suspicion of infection compared with those removed routinely at the end of their use ($p < 0.001$). However, over half of the lines removed on suspicion of CRS yielded no significant growth and the majority of the remainder were defined as being colonised (table 1). In contrast, line colonisation was apparent in approximately twice as many catheters using the Maki roll criteria (92%) compared with either the brush (43%) or Cleri flush (43%). The microorganisms causing line colonisation and CRS are shown in table 2. Gram negative bacilli caused CRS significantly more frequently than line colonisation ($p < 0.01$). Conversely, coagulase-negative staphylococci were significantly more often implicated in line colonisation than in CRS ($p < 0.001$). We found that colonised catheters sampled using extraluminal and endoluminal methods yielded mixed growth in 17 and eight cases, respectively (in six cases mixed growth was obtained from both surfaces). The corresponding numbers of mixed growth episodes for catheters in cases of CRS were eight and six, respectively.

The brush method was found to be the most sensitive and specific of the three techniques used for the diagnosis of CRS, using composite definitions to define these values (table 3). Table 4 shows the relation between CRS or colonisation and the detection of significant numbers of extraluminal and endoluminal microorganisms, as detected by the Maki roll and Cleri flush or brush methods, respectively. Notably, it was rare to detect only endoluminal (4 of 22 episodes) or extraluminal (1 of 22 episodes) microorganisms in cases of CRS. In

Table 3 Sensitivities and specificities of three methods for the diagnosis of catheter related sepsis (CRS)

Technique	Sensitivity (%)	Specificity (%)
Brush	95	84
Maki roll	82	66
Cleri flush*	75	84

Sensitivity defined as (number of positive CRS results for a method divided by the total number of CRS positive results) $\times 100$.

Specificity defined as (number of negative CRS results for a method divided by the total number of CRS negative results) $\times 100$.

*Two patients with CRS did not have catheter tips examined by the Cleri flush method.

Table 4 Relation between significant extraluminal or endoluminal growth of microorganisms and the diagnosis of catheter related sepsis (CRS) and catheter colonisation

Site(s) of significant bacterial growth	% of catheters associated with	
	CRS	Colonisation
Extraluminal only	5	41
Extra- and endoluminal	77	53
Endoluminal only	18	7

contrast, catheters defined as being colonised most frequently (59% of episodes) yielded only significant extraluminal growth.

Discussion

Many methods have been described for the diagnosis of CRS. These can broadly be divided into those that do not require catheter sacrifice and those needing line removal. The former include quantitative and semiquantitative blood culture methods which are time consuming and expensive to process.¹³⁻¹⁷ Such methods are also dependent on the ability to withdraw blood back through the catheter and are influenced by the use of intravenous antimicrobial agents. Alternatively, CRS may be inferred if blood cultures taken through the line are positive but peripheral specimens remain negative. It is, however, not uncommon for both catheter and peripheral blood cultures to be positive in cases of CRS. Swab cultures of either catheter hubs or exit sites provide only supportive information and both approaches have generally been found to have poor positive predictive values for the diagnosis of CRS.¹⁸⁻²¹ The frequently favoured method of diagnosing CRS involves culture of the catheter tip by rolling, flushing, sonication, or a combination of these, in conjunction with the results of peripheral blood cultures. These techniques permit only retrospective diagnoses following line sacrifice.^{5 10 11} Furthermore, in order to prevent contamination, these methods rely for their accuracy on the careful removal and processing of catheters, which in practice are often less than ideal.

We found that the confirmed incidence of CRS was predictably higher in cases where there was clinical evidence of infection (16%) than in non-suspected patients (2%). However, our data confirm earlier findings^{9 9} that even when clinical parameters are used to select catheters considered to be infected, the majority (84%) of such lines are found to yield either no significant bacterial growth or to be colonised, when the results of the three study

methods are combined. Hence, the majority of catheters removed on suspicion of infection are needlessly sacrificed, increasing costs and risk to the patient if new catheter insertion is required. This approach also increases laboratory costs because of the investigation of many culture negative catheter tips. Widmer *et al*²² found that the results of Maki roll cultures of 157 central venous catheters from patients on a surgical intensive care unit had no clinical impact in 96% of episodes, and in most instances (86%) a new line was inserted.

The colonisation rates, combining the results of all three techniques studied, were very similar in patients suspected and not suspected of having CRS (32% and 34%, respectively). There are several possible explanations for this observation. Bacterial catheter colonisation may have no clinical significance, or it may be significant but not clinically detectable at the time of line sampling. Alternatively, our results support the theory that colonisation rates may be falsely elevated both in patients suspected and not suspected of having CRS. The colonisation rate as determined by extraluminal sampling (Maki roll) (92%) was approximately double that indicated by the two techniques measuring endoluminal bacteria (43% for both methods). The Maki roll technique is subject to contamination of the external surface of the catheter tip by exit site bacteria during line removal, particularly when localised skin infection is present. Such contamination during line removal may explain why the incidence of apparently colonised catheters yielding mixed growth with extraluminal sampling was more than double that obtained with endoluminal cultures (17 *v* 8 cases). With few exceptions, there was no attempt to disinfect the skin at the exit site before catheter removal, as such practice is difficult to achieve at the exact catheter entry point, may adversely affect the viability of (extraluminal) tip microorganisms, cannot be expected to influence bacteria or fungi in the subcutaneous tunnel, and is commonly not performed. Although the Maki roll method is highly sensitive for the detection of extraluminal catheter colonisation, it has relatively low specificity for the diagnosis of CRS. This is probably due to the use of too low a cut-off value (15 cfu) to define positive results, leading to a low power to differentiate between catheter contamination by skin bacteria and genuine CRS secondary to extraluminal microorganisms. The Maki roll technique was initially validated primarily on catheters inserted into peripheral veins, and only four cases of CRS were detected, each associated with at least 10³ cfu per rolled tip. Kristinsson *et al*²³ compared extraluminal and endoluminal sampling methods to culture quantitatively 236 line tips and found that counts of more than 100 cfu and growth from the inside of catheters were the best predictors of infection. Furthermore, central venous catheters associated with CRS were almost always colonised on both external and internal surfaces.²³

We also observed that in the great majority of cases of CRS (77%) both extraluminal and

endoluminal microorganisms were present. Only one case of CRS (5%) would have been "missed" if lines yielding a negative result from endoluminal brush sampling had been left in situ. Conversely, four episodes of CRS (18%) would not have been diagnosed by relying on extraluminal sampling alone. The aetiology of CRS remains controversial, in particular the relative contributions of extraluminal and endoluminal microorganisms. As the duration of central venous catheter placement increases, so does the cumulative risk of contamination of the endolumen during repeated administration of fluids or drugs. Although we sampled predominantly catheters with a relatively short duration of placement (median 9.5 days), our findings support the hypothesis that endoluminal microorganisms are the major source of CRS. Raad *et al*²⁴ using quantitative culture and electron microscopy methods found that colonisation of long term central venous catheters (longer than 30 days) became predominantly endoluminal. They observed (by electron microscopy) that line colonisation was universal and frequently did not reflect culture results.²⁴ We have previously reported preliminary results of DNA fingerprinting of coagulase-negative staphylococci recovered from catheters in situ using the endoluminal brush method, compared with strains isolated from extraluminal surfaces of line tips after removal, and those obtained from swab cultures of hubs and skin exit sites. We found that in 29% of cases different strains were present on the endoluminal and extraluminal catheter surfaces.²⁵ Strains recovered from either catheter surface more commonly matched those found at the skin exit site (80–90%) than bacteria present on hubs (43–57%).²⁵

The sensitivity of the Cleri flush method may have been adversely affected by prior brushing of the catheter endolumen potentially dislodging adherent bacteria. We observed four episodes of CRS when the Cleri flush method was negative but the brush sample was positive. It is possible, however, that endoluminal colonisation may be present in the proximal but not distal parts of catheters—for example, following initial seeding of the lumen from the hub with subsequent growth towards the tip. The brush method has the advantage of sampling the entire catheter endolumen from hub to tip. The caveat to this situation is that if the brush is not progressed right up to the end of the catheter, or too narrow a brush is used (several different brush widths are available), then a false negative result may occur. Incomplete brush penetration may explain the 12 cases where we obtained a positive Cleri flush but negative brush results; however, in none of these cases was the result associated with an episode of CRS. A further possibility is that with a multilumen catheter, brush sampling of only one port may miss colonisation of other channels. In the present study we opted, in the case of multilumen catheters, to brush only the channel through which TPN was given, reasoning that this would be the most likely to be colonised by microorganisms.

We found that endoluminal brush sampling was easy to perform, and no patient experienced a clinical adverse event (for example, rigor, flushing) following brushing. It was not possible to examine accurately whether fever was induced by the technique as the majority of patients had a raised temperature before brushing. We are currently studying whether brushing results in bacteraemia, and if so to quantify the extent and duration of such episodes. However, it should be noted that potentially infected central venous catheters are often exchanged using the Seldinger technique, which involves passing a rigid guidewire through the old lumen, and so possibly resulting in the release of attached microorganisms. It is known that patients occasionally develop a fever when infected or colonised catheters are flushed or as they are removed, presumably due to transient bacteraemic episodes secondary to disruption of bacterial biofilm. Further studies are also currently in progress, using imaging techniques, to determine the extent to which bacteria are shed from central venous catheters during brushing compared with when lines are removed.

We believe that the endoluminal brush method is a cost effective approach to sampling lines suspected of causing CRS, which would otherwise normally be sacrificed, in order to determine whether they are indeed colonised. The current price of an endoluminal brush is approximately £17. Economic justification of such an approach is awaited, but given the costs of £9 and £20 for single and triple lumen catheters, respectively, the case is most obvious for the latter. Subsequent early removal of only those lines confirmed to be causing CRS would potentially have resulted in the saving of 84% of catheters (suspected of causing CRS) examined in the present study. Alternatively, a conservative protocol might retain only those catheters found not to be colonised following brushing, although the majority of lines yield relatively low pathogenicity microorganisms such as coagulase-negative staphylococci; this approach would still have saved 52% of catheters suspected of causing CRS.

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