Diagnosis of intravascular catheter infection

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Purpose of review

To review the distinction between catheter-related and catheter-associated infections and to report the recent advances in the methods used for their diagnosis.

Recent findings

The distinction between device-associated and device-related infections affects the effective benchmarking of the rates of both types of infection. Numerous microbiological methods have been described to diagnose these infections. Studies comparing the performance of microbiological methods that avoid the removal of the intravascular device have recently suggested that they may be effective in daily life.

Summary

The present review summarizes recent advances in the methods currently available to diagnose intravascular catheter-related infections and their performance at the bedside.

Keywords

catheter, catheter-related infection, diagnosis, nosocomial infection

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Abbreviations

CVC central venous catheter
ICU intensive care unit

0951-7375

Introduction

Infections associated with the use of intravascular catheters or devices represent 10–20% of all nosocomial infections. They may complicate the stay of up to 10% of intensive care unit (ICU) patients. Almost all patients staying in an ICU require at least one intravascular device for fluid/drug administration, and approximately half are central venous catheters (CVCs) [1]. According to data from the National Nosocomial Infections Surveillance system, it is estimated that at least 48 600 ICU patients develop a CVC-related bloodstream infection every year in US ICUs (approximately five episodes per 1000 catheter-days). These infections, mostly caused by coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus* species, and *Candida* species, are associated with considerable morbidity (prolonged length of stay and increased costs) and mortality [2•]. Although debated by experts with regard to magnitude, the attributable mortality of these infections may correspond to 5000–15 000 deaths directly caused by catheter-related infections; the benchmarking of rates is currently included in the assessment of quality of care in many institutions [3•].

The diagnosis of infections attributable to the use of intravascular catheters or devices is the subject of intense clinical research. There is, however, no consensus on a true gold standard, and the accuracy of numerous microbiological methods has generated vigorous debate among experts [4]. In addition, the variability in the definitions used over the past decades has not simplified the understanding of the literature [5•].

In this context, the distinction between device-associated and device-related infections proposed in the 2002 guidelines for the prevention of intravascular catheter-related infections provided a useful tool [6]. Infection rates vary according to the type of surveillance. In studies designed to study complications associated with the use of intravascular devices, epidemiological definitions frequently result in higher infection rates. In studies dedicated to device surveillance, systematic microbiological investigation allows the determination of infection rates directly related to the colonization or infection of the device [7].

Diagnosis of infections associated with or related to vascular access

Before reviewing the methods available to diagnose intravascular catheter-related infections, it is important

to summarize the different definitions commonly used in the literature.

Definitions for vascular access-associated and related infections

Infections linked to the use of intravascular devices include exit-site infections, catheter colonization and both catheter-associated and catheter-related infections [6,8–15] (Table 1).

Catheter-associated infections include primary bloodstream infections and clinical sepsis, which are epidemiologically associated with the use of intravascular devices [6,7]. It should be emphasized that in the absence of device culture, defervescence after the removal of an implicated catheter from a patient with primary bloodstream infection is considered indirect evidence of catheter-associated bloodstream infection. Comparisons between infection rates in different types of ICUs are more accurate when infections are reported as incidence densities associated with the use of intravascular devices. According to this method, widely diffused by the National Nosocomial Infections Surveillance system and using epidemiological definitions, catheter-associated infections range between 2.3 and 16.8 episodes per 1000 CVC-days [1]. This may overestimate the rate of infections related to intravascular devices, but is probably more representative of daily life. This method allows the benchmarking of rates of infection after eventual adjustment for the case mix without the need for sophisticated laboratory work-up. Although included in some reports, secondary bacteraemia, which

Table 1 Definitions of infections potentially related to vascular access[a]

Type of infection	Criteria
Exit-site infection	Clinically documented: a clinical infection (erythema, tenderness, induration or purulent discharge) at the skin insertion site Microbiologically documented: a positive (semi) quantitative catheter culture in the presence of clinical signs of infection at the insertion site
Catheter colonization	In the absence of clinical signs of infection at the insertion site, growth of microorganisms on the device according to microbiological criteria from quantitative (technique [8], sonication [9], vortexing technique [10]) or semi-quantitative (roll-plate technique [11]) cultures.
Positive blood culture	Microorganism potentially pathogen cultured from one or more blood cultures[b]
Bloodstream infection	Positive blood culture with at least one of the following clinical signs or symptoms: Fever ($>100.4^{\circ}F$; $>38^{\circ}C$) or hypothermia ($<98.6^{\circ}F$; $<37^{\circ}C$) Chills Low blood pressure (systolic blood pressure ≤ 90 mmHg or decrease >40 mmHg from baseline) In the absence of catheter culture, defervescence after removal of an implicated catheter from a patient with primary bloodstream infection is considered as indirect evidence of catheter-associated bloodstream infection
Primary bloodstream infection	Laboratory-confirmed bloodstream infection or clinical sepsis occurring without documented distal source of infection
Secondary bloodstream infection	Laboratory-confirmed bloodstream infection occurring in the presence of another documented infection
Clinical sepsis	Requires one of the following signs with no other recognized cause: Fever ($>100.4^{\circ}F$; $>38^{\circ}C$) or hypothermia ($<98.6^{\circ}F$; $<37^{\circ}C$) Low blood pressure (systolic blood pressure ≤ 90 mmHg or decrease >40 mmHg from baseline) Oliguria (<20 ml/h) and the presence of all of the following conditions: Blood cultures not performed or no organism detected in blood No apparent infection at another body site Physician institutes therapy for sepsis
Catheter-associated bloodstream infection	Primary bloodstream infection or clinical sepsis in the presence of an intravascular device
Catheter-related bloodstream infection	Laboratory-confirmed bloodstream infection in a patient with an intravascular access with at least one positive blood culture obtained from a peripheral vein, with clinical manifestations of infection (fever, chills or hypotension) and no apparent source of the bloodstream infection except the vascular access, and with one of the microbiological methods described in Table 2: A positive semi-quantitative culture (>15 cfu/catheter segment) with the same organism [11] A positive quantitative culture ($>10^3$ cfu/catheter segment) with the same organism [8–10] Paired quantitative blood cultures with a $\geq 5:1$ ratio device versus peripheral [12] Differential period of device culture versus peripheral blood culture positivity of >2 h [13]

cfu, Colony-forming units.

[a] Adapted from [6,12,14,15].

[b] One of the following:

Common skin contaminant (diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from two or more blood cultures drawn on separate sets.

Common skin contaminant (diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from one or more blood culture from a patient with a vascular access, and the physician institutes appropriate antimicrobial therapy.

Positive antigen test on blood and signs and symptoms with positive laboratory results are not related to an infection at another site.

is related to another documented focus of infection, should not be considered as being catheter related.

Catheter-related infections include colonization of the device by microorganisms, exit-site infection and microbiologically confirmed device-related bloodstream infection. In the absence of a gold standard reference technique, microbiological criteria are the subject of intense clinical research, and their clinical relevance is currently widely discussed among experts [4]. Maki *et al.* [16••] recently extracted the risk of bloodstream infections associated with different intravascular devices from a systematic review of 200 published prospective studies. Using microbiologically based criteria, they showed that all types of intravascular devices are at risk of device-related bloodstream infections. As rates of infections are likely to be used for benchmarking, they showed that expressing the risks of device-related bloodstream infections per 1000 device-days allows for more meaningful estimates of risk than measuring bloodstream infections per 100 devices. Peripheral and midline intravenous catheters are associated with the lowest rates of infection (0.1%, 0,4% and 0.5, 0.2 per 1000 device-days, respectively). The rates are slightly higher for arterial catheters used for haemodynamic monitoring (0.8%, 1.7 per 1000 device-days) and peripherally inserted CVCs in hospitalized patients (2.4%, 12.1 per 1000 device-days). According to these data, the rates are higher for non-impregnated CVCs inserted in critically ill patients (4.4%, 2.7 per 1000 device-days). The highest rates are reported for short-term non-cuffed and non-tunneled haemodialysis catheters (8.0%, 4.8 per 1000 device-days), for intra-aortic balloon pumps (3.0%, 7.3 per 1000 device-days), and for left ventricular assist devices (21.6%, 2.1 per 1000 device-days).

Clinical diagnosis of infections associated with vascular access

Except for some exit-site infections, the clinical diagnosis of infections related to vascular access is difficult. Most clinical signs are insensitive, non-specific or late, such as septic thrombophlebitis, endocarditis or septic emboli. Accordingly, they are clinically suspected when clinical sepsis develops without other obvious sources of infection.

The concept of 'clinical sepsis' is included in the surveillance definitions proposed by the Centers for Disease Control and Prevention for primary bloodstream infections to take into account sepsis episodes in which no pathogen has been cultured from blood [6]. This entity that is used for epidemiological purposes is relatively close to the definition of the syndromes of systematic inflammatory response, severe sepsis and septic shock in response to an inflammatory or infectious process [17,18].

The definition is sensitive but non-specific. The impact of clinical sepsis is very close to that of a microbiologically documented episode. In a prospective surveillance study of nosocomial infections in 1068 patients who stayed in a medical ICU for more than 48 h, Hugonnet *et al.* [7] analysed 109 episodes of bloodstream infections, including 32 episodes of microbiologically documented catheter-related infections and 77 of clinical sepsis. Exposure to central lines and arterial lines, censored at the time of the first episode of bloodstream infection, was similar in patients with a microbiologically documented episode and those with clinical sepsis, but was significantly lower in patients without bloodstream infection. The median ICU length of stay was longer in patients with microbiologically documented bloodstream infections (15.5 days; range 4–67) and clinical sepsis (14.0 days; range 3–48) than among patients without bloodstream infection (4 days; range 2–134; both $P < 0.001$). The hospital mortality rates in patients without a bloodstream infection, with a microbiologically confirmed bloodstream infection, and with clinical sepsis were 22.7, 32.1, and 39.7%, respectively ($P = 0.01$). These data strongly suggest that clinical sepsis and primary bloodstream infection microbiologically related to intravascular devices have the same impact.

If confirmed by large multicentre clinical trials, these data may justify the aggressive strategy currently applied at the bedside in many ICUs, where suspect intravascular devices are removed or exchanged over a guidewire in all cases of clinical sepsis associated with severe sepsis or septic shock developing without another obvious source of infection. This technique may increase the likelihood of infection of the new catheter, but reduces the rate of complications associated with CVC insertion in a new site [19]. Removal of the exchanged device with further insertion at a new site is then only required in the presence of a positive culture of the exchanged device [20].

Only approximately a quarter to one third of these episodes will be demonstrated to be caused by a microbiologically documented infection of the intravascular device, and experts suggested that '... nontunneled CVCs should not be routinely removed in patients with mild to moderate disease' [21,22].

Rijinders *et al.* [23] studied the impact of a clinical algorithm designed to avoid catheter removal in ICU patients developing clinical sepsis. Of 140 patients potentially eligible, 80 (55%) were excluded for haemodynamic instability, confirmed bacteraemia or local signs of infection at the insertion site. During the 10 days after inclusion, only 16 CVCs (38%) were removed in the 'watchful waiting' arm (32 patients) compared with 38 (100%) in the control group (32 patients), $P < 0.01$.

A catheter-related bloodstream infection developed in three (1%) compared with two (1%) patients, respectively, but in 47 (25%) of those excluded before randomization. This preliminary result confirms that some CVCs may be maintained, and further studies should now confirm the usefulness of this approach.

In this context, microbiological techniques likely to provide early laboratory confirmation of the clinical suspicion of device-related infection should be improved to avoid unnecessary intravascular device removal or exchange.

Microbiological diagnosis of infections related to vascular access

A large majority of primary bloodstream infections originates from infected vascular access, but a microbiological confirmation of an infection of the device is required to be scored as an intravascular access-related bloodstream infection.

Microbiological methods

Many microbiological methods have been described to diagnose intravascular access-related infections, but in the absence of a true gold standard there is currently no consensus of opinion on which method to use. These methods may be divided schematically into those requiring study of the catheter itself and those that avoid removing the device. They are the subject of intense clinical research, and meta-analyses on the performance of some of these methods have recently appeared in the literature [8–13,15,21,24–35] (Table 2).

Of particular interest is the fact that paired qualitative blood cultures drawn from the device and venipunctures and cultures of swabs obtained from the skin insertion site or from the hub, which are less sophisticated from a microbiological point of view but are also cheaper, are characterized by a high specificity and have the highest negative predictive value. This may explain partly why more sophisticated microbiological methods with high sensitivity and the highest positive predictive value and accuracy are currently not widely used.

Comparison of methods

Some microbiological techniques have been carefully compared in a few prospective studies.

In a prospective cohort study on 128 CVCs suspected of causing catheter-related bloodstream infection, Kite *et al.* [30] compared the performance of four methods that allowed the device to remain *in situ*. The sensitivity of the Gram stain and acridine-orange leukocyte cytospin test was 96% and the specificity was 92%. By comparison, the tip-roll, tip-flush, and endoluminal-brush methods had sensitivities of 90, 95, and 92%, respectively, with specificities of 55, 76, and 98%, respectively. From these data, the authors concluded that the Gram stain and acridine-orange leukocyte cytospin test are simple and rapid methods for the diagnosis of catheter-related bloodstream infection, which compare favourably with other methods.

In a prospective cohort study of 125 CVCs suspected of causing catheter-related bloodstream infection, Catton *et al.* [36] compared the performance of three methods that allowed the device to remain *in situ*. The sensitivities of the endoluminal brush, of quantitative culture blood cultures, and of the differential time to positivity were 100, 89, and 72%, respectively, with corresponding specificities of 89, 97, and 95%, respectively. Blood could be directly aspirated from only 74% of all lumens; however, the authors concluded that the differential time to positivity was the most simple technique to perform. As a result of the high specificity of the method, they recommended its use as a first-line approach, with the endoluminal brush technique reserved for cases in which blood cannot be obtained from the device.

In a prospective cohort study of 204 CVCs suspected of causing catheter-related bloodstream infections in critically ill patients, Bouza *et al.* [37••] compared the performance of three methods that allowed the device to remain *in situ*. The sensitivity and specificity of cultures of swabs from the insertion site and from the hub were 78.6 and 92.0%, respectively; for differential quantitative blood cultures, 71.4 and 97.7%, respectively; and for the differential time to positivity, 96.4 and 90.3%, respectively. From these data, the authors argued that convenience in different medical contexts, the use of resources, and expertise should determine the choice of a technique. As a result of the ease of performance, low cost, and wide availability, they recommended combining semiquantitative superficial cultures and peripheral vein blood cultures for the screening of devices suspected of causing infection, and to use differential quantitative blood cultures as a confirmatory method.

Those studies suggested that the choice of a precise microbiological method, or of the eventual combinations of some of them, should be made according to technical availability and should be integrated in strategies discussed between clinicians and microbiologists in order to provide useful information at the bedside. In addition, economic considerations, such as cost-effectiveness, may also be taken into account.

Recommendations of experts

Experts have proposed algorithms taking into account most of these difficulties to help clinicians in the diagnosis of intravascular access-related infections. Worthington and Eliott [4] suggested obtaining for every patient two sets of paired blood cultures drawn through

Table 2 Summary of the most common microbiological techniques used for the diagnosis of catheter-related infections

Type of technique	Description of methods	Criteria for positivity	Sensitivity (%)	Specificity (%)	Comments
Methods requiring device removal					
Qualitative catheter segment culture	Incubation of a segment of the removed device in broth media [24]	Any growth	79–96	72–78	The least accurate method [12,15]
Semi-quantitative catheter segment culture	A 3–4 cm distal tip segment of the removed device is rolled across an agar plate and incubated overnight [11]	≥15 cfu	81–89	85–87	The 2nd most accurate method [12,15]
Quantitative catheter segment culture	A distal tip segment of the removed device is flushed with broth [8] or sonicated [9] or vortexed in broth [10] that is further incubated	≥1000 cfu	78–88	87–91	The most accurate method [12,15]
Methods not requiring device removal					
Culture of swabs of skin insertion site and of the hub	Semiquantitative cultures on agar plate [25–27]	Any growth	96–100	67–71	Good negative predictive value
Endoluminal brushing	Culture of sonicated and vortexed brush passed down the internal lumen to the device distal tip [28–30]	≥100 cfu	92–100	84–98	Arrhythmias, embolization
Acridine-orange leukocyte cytospin on blood drawn through the device	Staining with acridine orange of a slide from 50 μl blood and examined under ultraviolet light [12,15,30,31]	Any microorganism within the cellular monolayer in a minimum of 100 high-power field	80–96	89–97	Accuracy may be improved if performed on specimen obtained by endoluminal brushing; 4th most accurate test [15]
Unpaired qualitative blood culture	Blood cultures obtained through the device [12,15]	Any growth	84–98	83–89	5th most accurate test [15]
Unpaired quantitative blood culture	Blood cultures obtained through the device [12,15]	≥100 cfu	80–93	83–89	2nd most accurate test [15]
Paired qualitative blood cultures	Paired blood cultures obtained through the device and from a separate venipuncture [32–34]	Any growth	51–65	78–95	The lowest sensitivity and positive predictive value
Paired quantitative blood culture	Paired blood cultures obtained through the device and from a separate venipuncture [12,15,21]	Positive cultures from both sites and concentration of microorganisms from the device 5–10-fold higher than from the peripheral venipuncture	74–84	98–100	The most accurate test [15]
Differential time to positivity	Concomitant conventional qualitative blood cultures obtained from the device and from a separate venipuncture continuously monitored until growth of microorganisms [12,13,15]	Blood culture drawn through the device turns positive ≥120 min before those obtained from venipuncture	86–92	79–87	Currently available with most automated blood culture systems

cfu, Colony-forming units.

the device and peripherally from venipuncture. A sufficient volume of blood collected per set (20–30 ml) and inoculated into both aerobic and anaerobic media should allow the identification of 99% of detectable bacteraemias. In cases in which clinical judgement mandates the removal of the device, quantitative cultures should provide information likely to confirm the diagnosis. If the intravascular access is not removed, the differential time to positivity is then recommended as the first-line method, followed by quantitative blood cultures. Alternatively, if only qualitative blood cultures are available, the authors strongly recommend performing additional tests, such as culture of the device, to improve the sensitivity of the method. In any cases of positive microbiological cultures, the authors recommend applying more strict criteria in the presence of coagulase-negative staphylococci likely to reflect only contamination [4].

The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit suggested taking into account risk factors likely to increase the probability of an infection being related to an intravascular access in its management. Removal of the device is strongly recommended in the presence of severe sepsis or septic shock with episodes of hypotension when the catheter is flushed, with the catheter in place for more than 7 days or inserted in non-sterile conditions, or with evidence of exit-site infection. In the absence of bacteraemia but positive culture of the tip of the device, the hub or the exit-site, the infection is scored as a possible clinical catheter-related sepsis. It is scored as a catheter-related sepsis with bacteriological confirmation in the presence of bacteraemia with common skin commensals and positive culture of the tip or exit site with the same microorganism [18].

Conclusion

The distinction between device-associated and device-related infections has improved our ability to diagnose clinical infections at the bedside, and has clarified the situations in which further microbiological diagnostic methods should be performed. Despite the usefulness of the recently proposed algorithms, however, they all include some simplifications, and none has been validated in prospective clinical trials. In addition, the potential impact of concomitant systemic antibiotic treatment or the use of antiseptic/antimicrobial-coated devices on the accuracy of microbiological techniques remains to be determined.

Accordingly, precise diagnostic criteria should be clearly discussed and defined in each institution by a close collaboration between clinicians and microbiologists. They should then be used for eventual benchmarking and further integrated into global strategies targeted at the prevention of vascular access-related or associated infections.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 436).

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