

REVIEW

Treatment of the afebrile patient after catheter withdrawal: drugs and duration

J. A. Paiva and J. M. Pereira

Serviço de Cuidados Intensivos, Hospital de S. Joao, Porto, Portugal

Catheter-related infections constitute 10–15% of all nosocomial infections, and constitute a relevant and growing problem, with an impact that is far from irrelevant, especially in the intensive care unit. The most frequent pathogens implicated come from the skin flora; Gram-positive cocci are responsible for about two-thirds of the infections, and *Candida* has emerged as another important cause. Questions about drug, route of administration, dosage and duration of antibiotherapy for patients who have become afebrile and with no signs of sepsis after catheter removal are still under debate, and far from being definitively answered. Decisions regarding these questions are based on three main factors: namely, which is the microorganism responsible for the infection, what was the time to response, and what kind of patient are we dealing with? However, the microorganism is clearly the main factor in making a decision. In summary, all catheter-related infections should be treated with appropriate antibiotics, regardless of the removal of the catheter, with parenteral drugs, using high doses and short courses, namely 1 week, and de-escalating to narrow-spectrum drugs on the basis of susceptibility tests as soon as possible. *Staphylococcus aureus* catheter-related infections constitute an exception, needing longer courses, as it is difficult to predict who will be high-risk patients.

Keywords Catheter-related infections, antibiotherapy, duration of antibiotherapy

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The epidemiology of catheter-related infection varies widely according to the population and type of unit, type of device and its site, and the therapy for which it is used. Catheter-related infections constitute 10–15% of all nosocomial infections. For example, they are responsible for 12% of the nosocomial infections in the EPIC study [1], as well as in our intensive care unit (ICU) during the year 1999 (Figure 1). The incidence of central venous catheter-associated infections also varies between 2.1 episodes per 1000 catheter days in respiratory ICUs and 30.2 episodes per 1000 catheter days in burn ICUs in the USA, and in the latest report it was 5.3 episodes per 1000 catheter days [2]. The ENVIN Study in Spain shows that this is not only a relevant problem, but also a growing one.

The impact of these infections is not as irrelevant as is sometimes thought. Crude mortality varied between 31.5% and 82.4%, and attributable mortality ranged from 4% to 47% [3–8]. Increases in both length of stay in hospital and costs are significant and undisputable [3,6,8].

The most frequent microorganisms implicated in catheter-related infections come from the skin flora, Gram-positive cocci being responsible for about two-thirds of the infections, and coagulase-negative *Staphylococcus* being the leading pathogen. *Staphylococcus aureus* and *Enterococcus* are also common pathogens; *Candida* spp. have emerged as an important cause, and Gram-negative bacilli, namely *Pseudomonas aeruginosa* and, less often, *Stenotrophomonas maltophilia* and *Acinetobacter* spp.; other Gram-positive bacteria, such as *Bacillus* and *Corynebacterium*, cannot be neglected as causative organisms [9].

Infection is usually a late event: more than 50% of the infections occur after the 14th day following admission, and, in our unit, *Staphylococcus* spp. comprised the cause of all catheter-related infections occurring in the first week after admission (Table 1).

Corresponding author and reprint requests: J. A. Paiva, Unidade de Cuidados Intensivos Polivalente da Urgência, Hospital S. Joao, Alameda Prof. Hernani Monteiro, Porto, Portugal
Fax: +35 1225496878
E-mail: ucipu@hsjoao.min-saude.pt

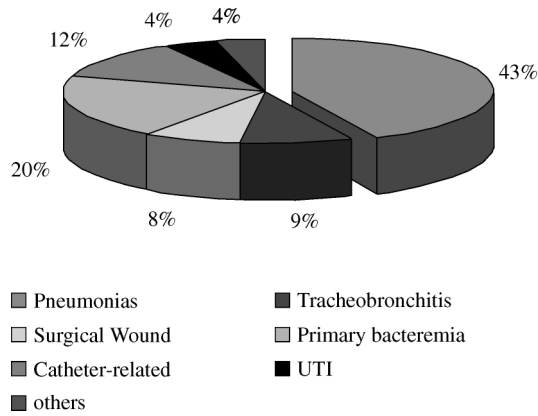


Figure 1 ICU-acquired infections in Unidade de Cuidados Intensivos Polivalente da Urgência-Hospital S. João-Porto, during 1999.

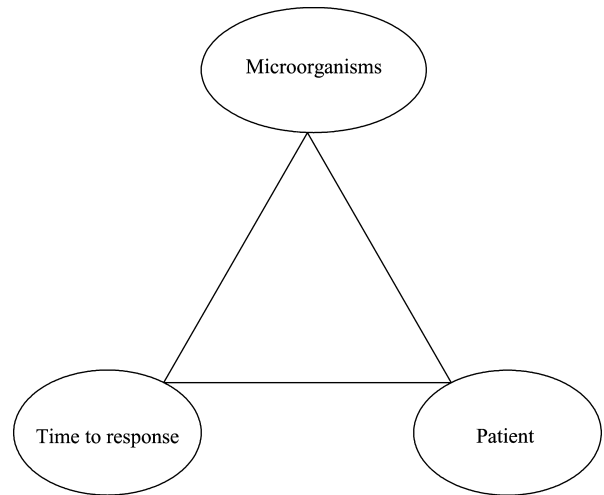


Figure 2 Decisions about antibiotherapy.

Table 1 Catheter-related infections: chronological pathogen distribution

| | 3 | 4 | 5 | 6 | 8 | 9 | 11 | 12 | 14 | 15 | >20 |
|--------------------------------|---|----|---|---|---|---|----|----|----|----|-----|
| MRSA | X | XX | | | | | X | X | | X | XXX |
| Acinetobacter spp. | | | | | | | | | | | XX |
| Coagulase-negative Staph | X | | X | | | | | | | | |
| Enterococci | | | X | | X | | | | XX | | XX |
| Enterobacteriaceae | | | | | | X | | | | | X |
| Pseudomonas + Stenotrophomonas | | | | | X | | | | | X | XX |

There are three main reasons for removing central venous lines in our daily ICU work (1): the central line becomes unnecessary (2); there is puncture site suppuration; or (3) there is suspicion of infection/sepsis without other detectable focus. For the first two scenarios, systemic antibiotherapy is not necessary, but for the third one, antibiotics are usually prescribed empirically. This review relates to the last situation: what to do with the patient who becomes afebrile without signs of sepsis after catheter removal?

There are, currently, two different scenarios, depending on the results of blood cultures. If the patient becomes afebrile without signs of sepsis, central line culture is positive, and blood cultures are negative, antibiotics should not be started or, if started, should be stopped. If, on the other hand, the patient becomes afebrile without signs of sepsis, central line culture is positive, and blood cultures are also positive with the same

agent, antibiotherapy is usually started or continued. Is this really the right thing to do?

Despite the large number of cases of central venous catheter-associated infections occurring throughout the world, the questions of drug, route of administration, dosage and duration of therapy do not appear to have been adequately addressed, either by randomized controlled trials or by any other appropriate methods. Consideration does not even appear to have been given to the possibility that antimicrobial therapy may not be required at all in some cases.

Decisions regarding these questions are based on the following factors: which is the microorganism responsible for the infection, what was the time to response, and what kind of patient are we dealing with (underlying diseases and complications) (Figure 2)? As the microorganism is clearly the main factor in making a therapeutic decision, we will now discuss the most frequent pathogens [10].

COAGULASE-NEGATIVE *STAPHYLOCOCCUS*

Most of the coagulase-negative *Staphylococcus* strains causing catheter-associated infections are methicillin resistant. Cure rates are not affected by catheter removal [11,12], but if the central venous catheter is not removed, there is a 20% chance that the bacteremia will recur, compared with only a 3% risk of recurrence if the catheter is removed [11], the risk being especially high if the catheter stays in place for more than 3 weeks after the bacteremic episode. Vancomycin and teicoplanin have been widely used, and the overall efficacies of both drugs are comparable, with high response rates [13–15]. Bolus doses of teicoplanin may be less effective because of limited exposure of the coagulase-negative staphylococci to the antibiotic [16]. If time to response is more than 72 h, a 14-day course of antibiotics should be used, but if time to response is less than 72 h, a 7-day course is quite enough [11].

STAPHYLOCOCCUS AUREUS

The catheter must definitely be removed; otherwise serious infectious complications may arise: septic thrombosis, severe sepsis and/or deep-seated infections [17]. Also, retention of the catheter can lead to persistence of *Staphylococcus aureus* bacteremia, to relapse, and to increased mortality; only 18% of all infected patients and only 10% of those with exit-site infection were cured without catheter removal [18].

Conventional treatment for any *Staphylococcus aureus* bacteremia has been a 4–6-week course of antibiotics, on the basis that: (1) classical physical findings of endocarditis are not usually present, making it difficult to exclude this diagnosis; (2) the sensitivity of two-dimensional echocardiography for detecting vegetation in *S. aureus* endocarditis seems to be as low as 59%; and (3) there is a high prevalence of endocarditis among cases of *S. aureus* bacteremia [19]. There is a tendency, however, to reduce the duration of antibiotherapy to a 2- or 4-week course. Two large retrospective trials showed that there was no recurrence after catheter removal followed by at least 10 days of antibiotics [17,20], and that treatment of uncomplicated *S. aureus* bacteremia for less than 10 days was associated with a significantly higher rate of relapse. Rahal et al. [21] performed the only

randomized trial that addressed the question of late complication rate, but it was small, and the results showed no significant difference between those given short-course therapy and those treated for 4 weeks. A meta-analysis [22] including 11 studies and 132 patients, from 1976 to 1992, using antibiotherapy for not more than 2 weeks, showed a percentage of late complications varying between 0% and 29%, with a pooled estimate of 6.1% (2.0–10.2%). From this meta-analysis, we may conclude that certain late complications occur following the short-course regimen, but the large majority of patients on the short-course regimen did respond and did not develop complications.

Therefore, our clinical practice consists of using a 2-week course of antibiotics for uncomplicated *S. aureus* infection, occurring in patients with no underlying valvular disease who respond within 3 days, and a 4-week course for patients with complications such as endocarditis or septic thrombosis.

CANDIDA SPP.

Removal of the central venous catheter is clearly necessary in certain cases [23–26]. In a group of patients judged suitable for management by catheter removal alone, disseminated fungal infections were found in 35% of those who eventually came to autopsy [27]. In another study [28] with 26 patients treated by central venous catheter removal alone, four developed endophthalmitis and three lost their vision. In the case of candida infection, usually by the time culture results are available all signs of infection have disappeared; however our policy consists of treatment for 14 days after the last positive blood culture. Amphotericin B is used for *Candida krusei* and *Torulopsis glabrata* infections, and fluconazole is used for all other candida infections [23,24,29].

GRAM-NEGATIVE BACILLI

Pseudomonas aeruginosa, *Stenotrophomonas maltophilia* and *Acinetobacter* spp. are also relatively common causes of catheter-associated infections. Removal of the catheter is important, as failure to remove it results in significantly higher rates of treatment failure and recurrence of bacteremia, while the rate of cure is 100%, irrespective of the appropriateness of antibiotic therapy, if the

catheter is removed [30]. Some authors accept that infections caused by *Enterobacteriaceae* may be managed by central venous catheter removal alone (without antibiotics). Nevertheless, a 1-week course of antibacterial antibiotics is usually given [31].

GRAM-POSITIVE BACILLI

To treat infection caused by *Corynebacterium* or *Bacillus*, vancomycin is usually prescribed, although treatment should be de-escalated on the basis of susceptibility tests.

CONCLUSIONS

In conclusion, all catheter-related infections should be treated with appropriate antibiotics, regardless of the removal of the catheter, with parenteral drugs, using high doses and short courses, namely 1 week, followed by de-escalation to narrow-spectrum drugs on the basis of susceptibility tests as soon as possible. Catheter-related infections caused by *S. aureus* are an exception, and require longer courses, as it is difficult to predict which patients are at high risk.

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