Treatment of long-term intravascular catheter-related bacteraemia with antibiotic-lock therapy

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Background: Bacteraemia is a major complication associated with the use of long-term intravascular catheters. Conservative treatment using antibiotic-lock therapy (ALT) has been shown to be useful in some studies, but the evidence supporting its impact in clinical care is still scarce.

Methods: We evaluated the outcome of the episodes of catheter-related bacteraemia (CRB) associated with long-term intravascular devices used for chemotherapy or parenteral nutrition and that were managed with ALT during a 44 month period in our hospital. Episodes of CRB associated with catheters implanted in the same department during the same period, and that were managed with only systemic antibiotics were used as a control group. Antibiotic-lock solution consisted of a heparin solution of 20 IU/mL including vancomycin (for Gram-positive microorganisms) or ciprofloxacin or gentamicin (for Gram-negative bacilli), all at a concentration of 2 mg/mL. ALT was used for a minimum of 8–12 h/day, during 5–14 days. Effectiveness was assessed by clinical and microbiological criteria.

Results: A total of 801 long-term intravascular devices were placed in 105 patients during this period. There were 127 episodes of bacteraemia documented in these patients, with 92 being CRB. Of these, 48 episodes fulfilled inclusion criteria for the analysis. Nineteen episodes were treated with ALT plus systemic antibiotics, and 29 episodes were treated only with systemic antibiotics. Isolated microorganisms were similar in the two groups. The catheter had to be removed during therapy in one episode in the antibiotic-lock group and in seven episodes in the control group. Relapse of the bacteraemia with the same microorganism after stopping therapy was observed in two and three patients in the study group and the control group, respectively. Overall, successful treatment was achieved in 84% and 65% of the episodes in the antibiotic-lock group and the control group, respectively (P = 0.27).

Conclusions: ALT appears as an effective conservative treatment in the management of CRB associated with long-term intravascular devices (84% in the present series), especially in infections caused by coagulase-negative staphylococci.

Keywords: catheter infection, conservative therapy, Hickman, totally implantable reservoirs

Introduction

Long-term intravascular devices are routinely used in the management of parenteral nutrition therapy, oncology, haematology, haemodialysis and other conditions. In particular, the use of tunneled Broviac–Hickman-type catheters and totally implantable venous access devices (ports), has increased notably over the past years.

As a result of the use of these devices, infection has become a significant clinical problem. Catheter-related bacteraemia (CRB) is the most frequent complication and catheters have to be removed even when an adequate parenteral antibiotic treatment is given. Currently, CRB is a major cause of patient morbidity, a reason for premature catheter removal and an explanation for the increase in cost and use of resources. The appropriate management of catheter-related infections has, therefore, become a major challenge for physicians.

Antibiotic-lock therapy (ALT) in addition to parenteral antibiotics has been suggested for the treatment of these infections. This mostly consists of a mixture of an antibiotic
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and heparin, with which the catheter is filled (‘locked’) when it is not in use. In this way, the concentration of the antibiotic inside the catheter can be orders of magnitude higher than the concentration reached during conventional treatment. Furthermore, these concentrations can remain in place for up to 24 h, when the catheter is not in use.

The majority of reported information related to ALT deals with patients receiving long-term parenteral nutrition. Nevertheless, some studies have also been performed in other settings such as patients requiring dialysis, oncological patients, as well as in AIDS patients. The results of open studies indicate that ALT may be considered as an alternative to the conservative treatment of ‘highly needed’ infected catheters.

Recently published guidelines on the management of catheter-related infections are in favour of the use of ALT for the treatment of bacteraemia-related infection in long-term intravascular devices. ALT is particularly appealing for treatment of non-complicated (absence of hypotension or organ hypoperfusion, septic thrombosis and septic emboli) central venous catheter-related infection of intraluminal origin, especially in patients with coagulase-negative staphylococci (CoNS) infections. However, the evidence supporting its use is still fragmentary.

Patients and methods

Long-term intravascular devices implanted in the Radiology department of our institution from January 2002 to April 2005 were revised. In this department, only Hickman catheters and totally implantable reservoirs used for chemotherapy or parenteral nutrition are implanted. No other catheters, including haemodialysis catheters, peripheral inserted central catheters and other long-term intravascular devices implanted in other departments of the hospital, were included in the analysis.

After July 2004, ALT has been routinely used in our hospital to treat all catheter-related episodes of bacteraemia if catheter removal is not being considered. The study group (ALT group) included all patients with CRB associated with long-term intravascular devices and treated with ALT after July 2004. To evaluate the efficacy of ALT, the results were compared with the outcome of CRB episodes treated from January 2002 to July 2004 in patients with catheters implanted in the same Radiology Department and that were managed without removal and only with systemic antibiotics.

To be eligible for the study the following inclusion criteria had to be fulfilled in the two groups: to carry a long-term intravascular device, fever or signs of sepsis and no apparent clinical origin other than the catheter, and bacteraemia confirmed by differential time to positivity of ≥2 h of blood cultures taken through a peripheral vein puncture and through the catheter. For CoNS, the growth of at least three unrelated episodes of CRB. All these episodes were caused by CoNS occurring separately more than 3 months apart from each other. There were no significant differences between the control and the ALT groups with respect to age, gender, underlying diseases, type of catheter and causative agents. Catheters of the reservoir type were placed in 77% of the patients receiving ALT and in 48% of the control group. The median catheterization days until infection was 54 and 68 days in the study group and the control

The primary endpoint used in this study was failure to cure the episode of CRB. Treatment failure was defined as any of the following: (i) catheter removal during therapy or within the first month after the end of a full course of therapy and persistence of colonization on the catheter tip and (ii) relapse of bacteraemia with the same phenotypic strain (same species and antibiogram) when the catheter was maintained. Successful treatment was considered when signs of sepsis disappeared, blood cultures obtained 2–5 days after stopping therapy were negative, and there was no evidence of catheter tip colonization with the same agent in patients who had the catheter removed in the first month.

Results

During the study period, 801 long-term intravascular devices were placed (641 reservoir type and 160 Hickman type). In this period, 105 patients developed 127 episodes of bacteraemia. The median length of catheterization was around 300 days and the time-adjusted infection rate was close to 0.5 episodes per 1000 catheter-days.

Figure 1 shows the episodes of bacteraemia among patients carrying long-term intravascular devices and the selection criteria according to the source of bacteraemia and/or inclusion/exclusion criteria. Among the 127 episodes, 79 did not fulfill the criteria to be included in the study (a source other than the catheter was identified in 35 episodes, the catheter was removed in the initial management or had other exclusion criteria in 44 episodes). The remaining 48 episodes occurring in 39 patients were included in the study. Nineteen episodes were treated with antibiotic-lock plus systemic antibiotics (ALT group), and 29 episodes were treated only with systemic antibiotics (control group).

Table 1 presents the characteristics, aetiological agents and outcome of patients with CRB included in the study. There were eight patients with two unrelated episodes and one patient with three unrelated episodes of CRB. All these episodes were caused by CoNS occurring separately more than 3 months apart from each other. There were no significant differences between the control and the ALT groups with respect to age, gender, underlying diseases, type of catheter and causative agents. Catheters of the reservoir type were placed in 77% of the patients receiving ALT and in 48% of the control group. The median catheterization days until infection was 54 and 68 days in the study group and the control

| Patients with bacteraemia and LTID n = 127 | Other source of bacteraemia n = 35 |
| Proven or probable CRBSI n = 92 | Inclusion criteria not fulfilled n = 44 |
| Inclusion criteria n = 48 (in 39 patients) | Antibiotic-lock (study group) n = 19 |
| No antibiotic-lock (control group) n = 29 |

Figure 1. Selection and distribution of patients with bacteraemia and catheter-related bacteraemia systemic infection (CRBSI). LTID, long-term intravascular device.
Successful treatment was observed in 84% of episodes in the ALT group compared with 65% of episodes in the control group ($P = 0.27$). Specific analysis of CoNS episodes demonstrated that ALT cured 93% of them versus 79% in the control group ($P = 0.36$).

### Table 1. Characteristics of patients with long-term catheter-related bacteraemia (LT-CRB) according to the therapy administered

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antibiotic-lock group (n = 19)</th>
<th>Control group (n = 29)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, years)</td>
<td>52</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>13 (69%)</td>
<td>16 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haematological</td>
<td>9 (47%)</td>
<td>12 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>solid tumour</td>
<td>5 (26%)</td>
<td>9 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>parenteral nutrition</td>
<td>5 (26%)</td>
<td>8 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Type reservoir</td>
<td>14 (77%)</td>
<td>14 (48%)</td>
<td>NS</td>
</tr>
<tr>
<td>Type Hickman</td>
<td>5 (23%)</td>
<td>15 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>Microorganisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNS</td>
<td>14 (74%)</td>
<td>19 (65%)</td>
<td>NS</td>
</tr>
<tr>
<td>$S. aureus$</td>
<td>3 (16%)</td>
<td>4 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>GNB</td>
<td>2 (10%)</td>
<td>6 (21%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median days of LTID</td>
<td>54 days</td>
<td>68 days</td>
<td>NS</td>
</tr>
<tr>
<td>until infection episode</td>
<td>(range 2–304)</td>
<td>(range 4–276)</td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>3 (16%)</td>
<td>7 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>LT-CRB attributable mortality</td>
<td>1 (5%)</td>
<td>2 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>(CoNS)</td>
<td>(S. aureus &gt;2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CoNS, coagulase-negative staphylococci; GNB, Gram-negative bacilli; LTID, long-term intravascular device; NS, not significant.

The present study shows that in patients with a long-term-intravascular-device-related bloodstream infection the use of ALT, in addition to parenterally administered antibiotics, could increase the cure from 65% to 84%.

### Discussion

ALT consists of filling the catheter lumen with an antibiotic solution and allowing it to dwell for a period of time, in order to sterilize the device.\textsuperscript{1–3,24,25} With this method, a high local concentration of an appropriate antibiotic can be applied in the catheter lumen while avoiding systemic toxicity and the need to monitor serum drug levels. The technique was initially designed in the late 1980s by Messing \textit{et al.}\textsuperscript{5} Messing \textit{et al.} used a 2 mL saline antibiotic-lock with either 1–2 mg/mL of vancomycin or 1.5–3 mg/mL of amikacin. They calculated that vancomycin and amikacin levels \textit{in situ} would be 40- to 80-fold and 60- to 120-fold higher, respectively, with antibiotic-lock than the peak serum inhibitory concentrations achieved by conventional dosage of the corresponding systemic antibiotic.

Good evidence is available to support ALT in the prevention of CRB in neutropenic patients\textsuperscript{26–28} and patients on haemodialysis\textsuperscript{14,17} with several randomized, controlled trials proving its effectiveness. However, a generalized use of vancomycin associated with this approach could account for an increased epidemiological risk of glycopeptide resistance and it is no longer recommended.\textsuperscript{29} Successful results obtained in patients on dialysis with non-antibiotic substances such as tauridine citrate\textsuperscript{30} or EDTA alone\textsuperscript{31} or in combination with other antiseptics\textsuperscript{32} could resolve this problem.

The present study shows that in patients with a long-term-intravascular-device-related bloodstream infection the use of ALT, in addition to parenterally administered antibiotics, could increase the cure from 65% to 84%.

In spite of the limitations related to the study design, the results allow us to make some valid considerations. Patients included in the two groups belong to the same cohort and had similar baseline conditions, catheter indication, catheterization technique, length of catheterization and rate of infection.

A potential bias related to the selection of patients has been minimized by two facts. ALT has been routinely administered after July 2004 in all patients. Thus, ALT has not been conditioned by factors such as the severity of illness or the causative agent. The similarity of the characteristics of the two groups gives support to this consideration (Table 1). In addition, all patients in the ALT group were homogeneously managed during the period of study, with the same antibiotic concentration in the lock solution (2 mg/mL), and guaranteeing in all cases a minimal daily ALT duration of 12 h for more than 5 days. In episodes of CRB caused by CoNS, ALT was successful in 93% of them (13 of 14). On the other hand, ALT was only effective in one-third of $S. aureus$ CRB. These findings agree with other reports that have shown the poor outcome of $S. aureus$ CRB in patients without catheter removal.\textsuperscript{33–35}

Most reports analysing the efficacy of ALT are non-comparative series and include a low number of patients. Vancomycin is the most frequent antibiotic used, although there is a wide experience with the use of aminoglycosides or quinolones in the management of CRB caused by Gram-negative bacteria.
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Figure 2. Outcome of patients with long-term catheter-related bacteraemia treated with and without antibiotic-lock (AL) therapy.

Table 2. Antibiotics used in patients with long-term catheter-related bacteraemia

<table>
<thead>
<tr>
<th>Agents (no. of patients)</th>
<th>Lock (antibiotic/median duration in days/interval)</th>
<th>Systemic (antibiotic/median duration in days/interval)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT group (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNS (14)</td>
<td>vancomycin/12 days/5–14 days</td>
<td>vancomycin/5 days/3–10 days</td>
<td>catheter removal during therapy was performed in one patient with an episode of CoNS bacteraemia due to persistent fever for 5 days after stopping therapy, two patients (treated for 5 and 10 days with ALT and 10 and 14 days with systemic antibiotics) presented a relapse</td>
</tr>
<tr>
<td>MSSA (3)</td>
<td>vancomycin/10 days/5–14 days</td>
<td>cloxacillin/10 days/7–14 days</td>
<td></td>
</tr>
<tr>
<td>GNB (2)</td>
<td>gentamicin 14 days, ciprofloxacin 14 days, respectively</td>
<td>ceftazidime 10 days, ceftazidime 11 days</td>
<td></td>
</tr>
<tr>
<td>(P. aeruginosa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNS (19)</td>
<td>vancomycin/12 days/11–15 days</td>
<td></td>
<td>after stopping therapy a patient presented a bacteraemic relapse and in two more patients the catheter had to be removed due to persistent fever and the catheter tip analysis confirmed colonization</td>
</tr>
<tr>
<td>MSSA (4)</td>
<td>cloxacillin/3 days/3–14 days</td>
<td></td>
<td>catheter removal during therapy had to be applied in three episodes (at the third, third and fifth day, respectively). The other patient received 14 days of intravenous cloxacillin</td>
</tr>
<tr>
<td>GNB (6)</td>
<td>cefazidime/7 days/5–15 days</td>
<td></td>
<td>catheter removal in two episodes (at fifth and seventh day, respectively)</td>
</tr>
<tr>
<td>P. aeruginosa (3)</td>
<td>cefotaxime, 14 days</td>
<td></td>
<td>catheter removal at 12th day</td>
</tr>
<tr>
<td>E. coli (1)</td>
<td>cefotaxime, 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella sp. (1)</td>
<td>co-trimoxazole, 12 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. maltophilia (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT, antibiotic-lock therapy; CoNS, coagulase-negative staphylococci; MSSA, methicillin-susceptible S. aureus; GNB, Gram-negative bacilli.
bacilli. In these series, catheters are usually locked for more than 8–12 h per day and for a period of 14 days, although success has been reported after only 5 days of ALT. Most authors include heparin in the ALT solution, at a concentration of 20–100 U/mL with a demonstrated compatibility, but some have communicated favourable results with ALT not including heparin. In general, the cure rate with ALT in these series is above 80%, significantly higher than the cure rate with conservative techniques not including ALT.

The first comparative, randomized, double-blind clinical trial analysing the role of ALT in the management of CRB has been recently published. Rijnders et al. compared the efficacy of an ALT administered in a solution combining heparin (100 U/mL) and vancomycin (0.5 mg/mL) in Gram-positive CRB, or cefazidime (0.5 mg/mL) in Gram-negative bacilli CRB, versus heparin alone. ALT was administered for 14 days and all patients (cases and controls) received systemic antibiotics for 14 days. In 44 patients included in the study the rate of relapse with the same strain (same species and antibiogram) was 14% versus 43% (P = 0.06). The use of antibiotics other than vancomycin has been analysed. The experience with teicoplanin in ALT is unequal. Studies including patients receiving parenteral nutrition present successful rates ranging from 42%, with a low concentration in lock solution (2.5 mg/mL), to 85%, with higher concentrations (13 mg/mL). A high cure rate using taurodilute citrate in ALT after failure of other therapies has been reported. The experience with linezolid and eperezolid in ALT is very promising. An in vitro model on biofilms confirmed that linezolid (at a concentration of 2 mg/mL) and eperezolid (at a concentration of 4 mg/mL) eradicate CoNS after 24 h of ALT, in comparison with vancomycin (10 mg/mL) or gentamicin (10 mg/mL) that require >10 days to get the same results. Finally, a comparative study of quinupristin/dalfopristin, linezolid, vancomycin and ciprofloxacin in experimental catheter-related infection due to S. aureus demonstrated that quinupristin/dalfopristin at 1024 μg/mL produced the greatest reduction in the number of microorganisms recovered from the catheters.

To date, on the basis of the available evidence, there are several questions that remain unresolved about the use of ALT. In particular, the usefulness of different types of antibiotics, their optimum concentration, as well as the duration of treatment and the necessity of concurrent systemic treatment should be defined.

In conclusion, ALT was successful in 84% of all episodes and in 93% of episodes caused by CoNS in the present series. Failure was observed in two-thirds of S. aureus CRB. ALT appears as an effective conservative treatment in the management of CRB in long-term intravascular devices, especially in patients with CoNS infections.

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Transparency declarations
None to declare.

References
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