Use of antibiotic locks to treat colonized central venous catheters

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Infections that result from bacterial colonization of central venous catheters are a significant problem in modern healthcare. The most effective means of eradication of such infections is the removal of colonized lines, but line removal carries drawbacks of its own and in many cases the balance of risks favours treatment in situ. Systemic antibiotics are usually administered but these frequently fail to achieve sterilization, and accordingly attention has turned to intraluminal therapy using antibiotic locks, in which 1–2 mL of a concentrated antibiotic solution is instilled to fill the lumen, left for a predetermined period, and removed. The evidence in favour of this technique is anecdotal and should not be allowed to influence any decision about line removal, but is sufficiently encouraging to justify the use of locks when in situ treatment is deemed acceptable. Indications, agents and appropriate administration regimes are discussed.

Introduction

Accurate epidemiological data for infections associated with central venous catheters in the UK are difficult to find, but it has been estimated that 200 000 central lines are inserted each year, which, assuming a crude infection rate of 3–5%, would equate to over 10 000 episodes per annum. An alternative index is the time-adjusted infection rate, which has been reported as 3 per 1000 catheter days for cancer patients with Hickman lines, between 2.8 and 10 per 1000 catheter days for intensive care patients with non-tunnelled central lines and 14 per 1000 catheter days for permanent tunnelled renal dialysis catheters.

This represents a substantial burden of disease, and one with potentially grave consequences. For instance, despite daily follow up by a consultant microbiologist, six of 37 patients with catheter-associated bacteraemia died of related causes, and another developed a metastatic infection. Morbidity is greatest for infections caused by Staphylococcus aureus and yeasts. In a retrospective study of 50 episodes of S. aureus haemodialysis catheter-related bacteraemia, eight were complicated by metastatic seeding and a further 12 by persistent bacteraemia even after line removal. Similarly, in a large series focusing on infections associated with both central and peripheral venous catheters, seven of the 11 reported Candida infections were complicated by sustained fungaemia following line removal, a complication that is presumed to reflect infection of venous thrombus.

Current therapeutic options

Whilst it is hoped that infection rates will be reduced by technological advances such as new materials and antibacterial coatings, these have yet to find their place in routine practice. Current consensus is that the most important aspects of prevention are careful choice of line, site and insertion method, together with scrupulous asepsis during insertion and on-going care. The management of those lines that do become associated with infection, however, remains problematic. Non-tunnelled catheters, which by their nature are temporary, are usually removed and replaced, but this decision is much more difficult when the catheter is tunnelled and there are conflicting clinical imperatives. Dialysis catheters, together with cuffed lines such as Hickman and Broviac catheters, are designed to be left in place for months or even years, and their replacement may be difficult, uncomfortable or complicated by adverse events such as pneumothorax, nerve injury and haemorrhage. The cost of replacement is also a valid consideration when resources are finite.

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Systemic antibiotics are usually administered but, although generally effective in eliminating circulating bacteria, they frequently fail to sterilize the line, leaving the patient at continuing risk of complications or recurrence. For example, in one study only 12 of 38 infected dialysis lines initially treated in situ were successfully salvaged by systemic antimicrobials. The reported salvage rates are better among haematology and oncology patients with Hickman catheters, Broviac catheters and totally implantable devices, but in these patients it can be difficult to know whether apparent resolution represents line sterilization or marrow recovery and, in any case, around a quarter of lines still require removal.

In part, these failures reflect inadequate drug delivery to the site of infection. Although colonization may affect either or both of the internal and external surfaces of the catheter, selective sampling methods suggest that endoluminal colonization correlates best with clinical evidence of catheter-related infection. Studies in patients with haemodialysis lines have demonstrated that systemically administered agents do not diffuse back into the lumen in appreciable quantities, indicating that the luminal surface is exposed to antibiotics only for the duration of the injection or infusion. This may explain the inferior results observed with bolus teicoplanin compared with vancomycin given by infusion. In addition, colonizing organisms are usually enmeshed within a biofilm consisting of bacterial extracellular polysaccharides plus host factors, such as serum proteins and platelets, where they are protected from antibiotic killing by mechanisms the details of which remain to be clarified.

Nevertheless, it is clear from the literature that systemic antibiotics do permit catheter salvage in many cases. This suggests that the correct strategy is to balance the likelihood of success against the risks of failure, and to this end specific indications for catheter removal continue to be debated. For *S. aureus* infections there is good evidence that catheter removal is the safest option. In a series of 37 episodes of *S. aureus* bacteraemia in patients with Hickman lines, 15 were initially treated without catheter removal. During follow up there were three septic deaths and four relapses in this group, while in none of the eight who were successfully treated was the original bacteraemia unequivocally catheter related. Further, in a report of 50 patients with confirmed catheter-associated *S. aureus* bacteraemia, delayed catheter removal was associated with both persistent bacteraemia and greater mortality.

The same is true of fungal infections. Catheter retention has been associated with an increased risk of morbidity and mortality in several retrospective series of line-related fungaemia, while in the largest prospective series yet reported, mortality among patients whose catheters had been retained (42/102; 41%) was twice that in those whose catheters had been removed (54/258; 21%). This point was given further emphasis by a series reporting the management and outcome of line-associated fungaemia in cancer patients, in which all of the nine episodes managed with antifungals but without early catheter removal ended with recurrence or death due to disseminated candidosis.

The benefits of catheter removal are more difficult to assess as far as Gram-negative infections are concerned, since clinical studies are sparse. However, in a 20 year retrospective study of 134 episodes of *Pseudomonas aeruginosa* bacteraemia, more frequent catheter removal was one of the factors associated with improved survival over the study period. Similarly, in a large series of bacteraemic episodes due to non-fermenting Gram-negative bacilli, catheter removal was the single most important prognostic factor, and led to complete cure regardless of the administration or otherwise of antibiotics.

Despite occasional reminders in the literature that serious complications such as endocarditis and other metastatic infections can occur, evidence supports the view that coagulase-negative staphylococci (CNS) can generally be regarded as benign by comparison. In a large prospective study among paediatric bone marrow transplant recipients, CNS accounted for 31% of catheter colonizations, 17% of catheter-related bloodstream infections, and none of the catheter-related deaths. Furthermore, in a retrospective study that focused directly on the outcome of CNS catheter-related infection, there was no difference in immediate mortality between patients whose catheters were left in place (four of 34) and those whose catheters were removed (four of 36). The risk of recurrence was significantly greater among the survivors in the former group (six of 30 versus one of 32), but all recurrences were successfully treated with catheter removal and antibiotics.

**Antibiotic lock technique**

Based on information such as this, current consensus is that infected catheters should be removed if they are associated with systemic sepsis, infective emboli or septic thrombophlebitis, or alternatively if they are colonized by organisms known to metastasize readily, such as *S. aureus* and yeasts. Conversely, it is generally accepted that lower risk infections (such as those caused by CNS) can initially be managed without removal of the catheter, but with this comes the caveat that removal will be necessary in the substantial minority for whom in situ treatment fails.

For these reasons, it is not surprising that attention has turned to the antibiotic lock technique, a therapeutic modality that permits the in situ treatment of colonized lines with the twin aims of improving the rates of catheter salvage and reducing the risks of antibiotic side effects. The technique, also known as intraluminal therapy, involves the instillation of a concentrated antibiotic solution into a colonized line, in a volume chosen to fill the lumen but not to spill out into the circulation. This ‘antibiotic lock’ is then left in place for a defined period of hours or days before being removed and, if appropriate, replaced.

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Much of the published experience with intraluminal therapy has been accumulated among adults receiving home total parenteral nutrition (TPN). In the first description, 22 catheter-related infections caused by a variety of Gram-positive and Gram-negative organisms were managed either with short-term systemic antibiotic therapy followed by antibiotic locks (vancomycin, amikacin or minocycline) or with locks alone. In this series the catheter was salvaged in 20 cases, but required removal in two because of secondary fungal infection. The authors claimed that no differences in course or outcome were observed between those treated with systemic antibiotics and those managed without, but the groups were small and had not been randomized. Nevertheless, the results were sufficiently promising to support further study, and the same cohort was followed prospectively for a further 2 years. During this period 27 catheter-related infections, similarly defined as fever and chills plus positive line cultures without evidence of an alternative source, were treated with locks alone. Catheter salvage was accomplished in 25 of these, although several episodes were recurrences and, in the absence of typing data to the contrary, might have represented relapses rather than re-infections. In another group of TPN patients, four episodes of bacterial sepsis related to colonized Hickman lines were treated with locks plus systemic antibiotics, and three with locks alone, with catheter salvage in all cases. A fourth series reported the use of locks alone for 22 episodes of catheter-related sepsis among six TPN patients; success and catheter salvage were claimed in 18 of these episodes although, again, a number might have been relapses.

With dialysis lines the results are similarly encouraging. In a Spanish study, 11 patients with catheter-related sepsis were treated with a combination of systemic antibiotics and locks, using vancomycin for Gram-positive infections and ciprofloxacin for Gram-negative infections. Nine cases (including two Staphylococcus aureus infections) were successfully treated with a single course, while the other two (both Pseudomonas) relapsed on cessation of treatment but were cured by a second course. Eight of these lines were sterile when removed later for unrelated reasons.

Intraluminal therapy has also been used in the treatment of paediatric patients. In one study, locks alone were successful in treating seven colonized Hickman lines and one colonized dialysis line, although two subcutaneously implanted ports required removal, perhaps because of clots in the reservoirs. In another series, bacterial infections associated with Broviac lines among 11 children on an oncology unit were successfully treated with either locks alone or (in the presence of bacteraemia or neutropenia) locks plus systemic treatment. These authors used amikacin, which in the event of resistance was changed to another agent, and this strategy was refined in a follow-up study in which the amikacin was substituted for teicoplanin when Gram-positive bacteria were isolated. Using the same treatment criteria, 11 episodes were treated with locks alone and four with locks plus systemic antibiotics. Although the relative contributions of the amikacin and the teicoplanin are impossible to assess, treatment was successful in all cases. A later publication by the same authors appears to describe the same results.

Antifungal locks have also been occasionally reported. A line colonized with Malassezia furfur, and previously refractory to systemic antifungals, was sterilized by a 3 week course of amphotericin locks, while two Candida albicans infections were successfully treated using locks alone. However, failure of amphotericin locks has been reported for two Candida glabrata infections, and, at lower concentrations, for infections caused by Rhodotorula, Candida parapsilosis and Candida tropicalis.

This is the extent of the published clinical evidence concerning antimicrobial locks. Other descriptions in the literature report individual cases, or provide no information about the drug regimes used.

In vitro studies tend to support the clinical observations, but the evidence is similarly limited. In a model system consisting of PVC cannulae colonized with Staphylococcus epidermidis, different modes of antibiotic administration were compared over a 3 day period. When given by continuous infusion or intermittent dosing, vancomycin could be shown to reduce bacterial counts but line sterilization was not achieved. In contrast, consecutive 12 h vancomycin 5 mg/mL locks were successful in sterilizing all five lines tested. Similarly, in a silicone catheter model in which TPN infusions and antibiotic locks were alternated every 12 h for 7 days, a variety of antibiotics and antifungals were successful in eradicating staphylococci, Enterobacteriaceae and yeasts.

Discussion

A safe and effective in situ treatment for colonized central venous catheters would be an undoubted leap forward, but the evidence available does not permit the conclusion that antibiotic locks represent such an advance. The observations summarized here are certainly intriguing, but the data are limited, observational, uncontrolled and non-standardized. In particular there has been no systematic
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attempt to compare the three treatment strategies of antibiotic locks alone, antibiotic locks plus systemic antibiotics and systemic antibiotics alone, and clinicians should remain cautious unless and until such evidence becomes available. Nevertheless, current treatment modalities are imperfect, and in the opinion of these authors the preliminary reports are sufficiently impressive to justify the use of antibiotic locks in selected circumstances.

However, a number of important questions remain. First, when should locks be used, and perhaps more importantly, when should they not be used? Secondly, if locks are favoured, should they be used alone or in addition to systemic antibiotics? Thirdly, what are the best agents, concentrations and administration regimes to employ?

In addressing these questions it must be emphasized that current evidence demonstrates only that locks can successfully eradicate catheter-associated infection in some cases. In the absence of comparative data it is not known whether colonized lines containing antibiotic locks represent a lower continuing hazard than colonized lines treated systemically, and for this reason caution urges that the availability of locks should not be allowed to influence the initial decision between line removal and in situ treatment. It follows that until good evidence to the contrary exists, and unless the arguments for catheter retention are exceptional, conventional indications for line removal should continue to be observed. These indications include S. aureus, fungal and Gram-negative bacterial infections, systemic sepsis syndrome, severe local infection, septic emboli and metastatic infections. It also seems prudent to remove lines from infected patients if fever persists beyond 3 days of therapy, or in the event of relapse. Therefore, pending further evidence, locks should be seen as an additional therapeutic option for the in situ management of colonized lines when early line removal is not judged to be in the best interests of the patient. In most cases this will restrict their use to the attempted eradication of less virulent organisms such as CNS, corynebacteria, α-haemolytic streptococci and perhaps enterococci.

Most of the studies in which locks have been used alone refer to non-bacteraemic cases. Although line-related bacteraemia may resolve once the focus has been removed, common sense suggests that the role of locks is to sterilize the internal surfaces of infected lines, while any associated bacteraemia should continue to be treated systemically. For non-bacteraemic patients it might be argued that combined locks plus systemic treatment will always be more effective than locks alone, but the adverse consequences of systemic administration, although unquantifiable, should not be disregarded. In non-bacteraemic patients (and probably in those whose bacteraemia is a transient consequence of line flushing) the evidence supports the contention that locks can be used without systemic treatment.

Without comparative efficacy data, the choice of agent and administration regime must rest upon clinical experience and practicality. Vancomycin, teicoplanin, gentamicin

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<th>Dose regime</th>
<th>Duration (days)</th>
<th>Heparin</th>
<th>Systemic treatment</th>
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Table. Glycopeptide and aminoglycoside lock regimes used successfully in clinical reports
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and amikacin have been the most widely reported, and the regimes that have been used successfully are listed in the Table. Between them, these agents are likely to be active against most of the organisms responsible for catheter-related infections. Other drugs for which success has been reported include minocycline, ampicillin, ampicillin and gentamicin, mezlocillin, nafcillin, ceftazidime, ceftriaxone, ciprofloxacin, erythromycin and clindamycin, but experience with these is more limited. It might be surmised that disinfectants (e.g. ethanol) would make effective locks, but to our knowledge they have not been used therapeutically in this way.

In comparing agents it is tempting to make use of pharmacodynamic data, but observations derived from the in vitro study of organisms in optimal growth conditions should be applied with great care. For example, the concentration of an antibiotic within a lock may exceed its MIC for the colonizing organism by 1000-fold or more, yet it is clear that organisms within biofilms can survive much higher concentrations than can the same organisms in dispersed suspension. It should also be remembered that the concepts of ‘susceptible’ and ‘resistant’ as defined by published breakpoints are not directly applicable to antibiotic locks. However, it seems sensible to prefer bactericidal over bacteriostatic agents, and at least to be guided by the results of conventional susceptibility testing.

Regardless of the agent chosen, first principles would suggest that the higher the concentration used, the greater the chance of eradication. The highest practicable concentrations of the agents recommended would be gentamicin 40 mg/mL (as supplied), amikacin 250 mg/mL (as supplied), vancomycin 50 mg/mL (500 mg diluted in 10 mL) and teicoplanin 133 mg/mL (400 mg diluted in 3 mL). However, only vancomycin and teicoplanin have been used at such high concentrations, and the potential for adverse consequences was not addressed in these studies. Toxicity might arise by diffusion of highly concentrated agents into the systemic circulation, or alternatively by sudden flushing of the lock into the patient, an event that might occur inadvertently or of necessity if withdrawal was impossible. These concerns are speculative, and the dose received would be small, but is clear that optimal concentrations remain to be defined.

It is also necessary to consider the role of heparin. In appropriate concentrations, vancomycin, cefazolin, ceftazidime and gentamicin have been shown to be compatible with heparin and to retain their activity over at least 72 h, but ciprofloxacin precipitates in its presence, and there are no data for amphotericin. Nor has it been demonstrated that heparin retains its activity in the presence of antibiotics. Furthermore, heparin does not seem to contribute to the therapeutic activity of antibiotic locks, and the evidence that it reduces the risk of central venous catheter thrombosis is poor. Thrombolytic agents such as urokinase or streptokinase are sometimes used, particularly to maintain the patency of dialysis lines, but currently there are no data concerning their compatibility with antibiotics.

Conclusions and recommendations

The most effective way to eliminate a catheter-related infection is removal of the catheter. However, when this conflicts with other clinical imperatives, in situ treatment is acceptable provided that the balance of risks is carefully and individually weighed with particular emphasis on the infecting organism. Usually this decision is translated into the administration of systemic antibiotics, but we believe that the theoretical and clinical evidence is sufficient to justify the use of antibiotic locks, either as an adjunct to systemic therapy in bacteraemic patients, or in place of systemic therapy in non-bacteraemic patients. We do not believe, however, that locks should be regarded as a routine treatment modality until their use has been validated in properly controlled studies. In this we are at variance with the authors of guidelines for the management of intravascular catheter-related infections that were published during the preparation of this manuscript, who recommend the use of antibiotic locks for tunnelled lines in patients with uncomplicated infections caused by S. aureus, CNS and Gram-negative bacilli.

Concerning administration schedules, the evidence available does not permit us to offer authoritative guidance, but the regimes that we favour are vancomycin 10 mg/mL, teicoplanin 10 mg/mL, gentamicin 10 mg/mL and amikacin 10 mg/mL, administered for a total of 10 days in each case. The addition, or otherwise, of heparin is left to individual preference. These regimes are convenient, practicable, easily remembered and will provide a basis for comparison; in some circumstances higher concentrations might be justified but there is little precedent for this and the risks of toxicity would be increased. The antibiotic solution is instilled into each lumen of the line in a volume chosen to fill the lumen but not spill into the systemic circulation, usually 1–2 mL; if the luminal volume is not printed on the outside of the line it may be necessary to contact the manufacturer for this information, since calculated volumes are likely to be imprecise. We suggest that for in-patients locks are removed and replaced daily, but for patients on thrice-weekly dialysis it is probably sufficient to lock once between each visit. Ideally locks should be left in for 24 h a day, but if necessary the line may be used between locks unless this gives rise to rigors or fever.

It is to be hoped that antibiotic locks will be subject to randomized controlled trials of sufficient power to confirm or refute their use. Meanwhile, clinicians faced with the problem of catheter-related bloodstream infection should consider for themselves the available data concerning antibiotic locks. Doctors who choose this approach are encouraged to audit their results and report their outcomes.
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References


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