CLINICAL REVIEW

Stability and compatibility of antimicrobial lock solutions

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Purpose. Published stability and compatibility data on a growing array of solutions used for antimicrobial lock therapy (ALT) are reviewed.

Summary. ALT involves the instillation of a highly concentrated antimicrobial, often in combination with an anticoagulant, into a central venous catheter (CVC) lumen; this technique is often used for prophylaxis after CVC insertion or as an adjunctive treatment in cases of central line–associated bloodstream infection (CLABSI) if catheter removal is not feasible. Optimal selection of stable and compatible antimicrobials and additives can maximize catheter dwell times, streamline pharmacy compounding practices, and help ensure patient safety. Of 98 articles on ALT solutions identified in a literature search, 17 met the prespecified criteria for the use of validated stability and compatibility methodology. Antimicrobials active against common CLABSI pathogens that may be appropriate for ALT include cefazolin, cefotaxime, ceftazidime, ciprofloxacin, daptomycin, gentamicin, linezolid, telavancin, ticarcillin–clavulanic acid, and vancomycin; validated data demonstrate the stability of these agents in solution with heparin or nonheparin anticoagulants over 72–96 hours or longer. Other antifungal agents and antiinfectives (e.g., ethyl alcohol) have been used in specific patients and ALT situations. The prolonged stability of several antimicrobial–additive combinations may allow for extended dwell times and less frequent lock solution exchanges.

Conclusion. Pharmacists' knowledge of diverse combinations of antimicrobial agents and additives in lock solutions, including several shown to be stable and compatible for extended periods, can help expand and optimize the use of ALT in both treatment and prophylactic modalities.

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Traditional preferred management of central line–associated bloodstream infections (CLABSIs) involves central venous catheter (CVC) removal and the administration of systemic antimicrobial therapy. Catheter removal, however, is not always feasible in patients with limited vascular access or those unable to tolerate an interventional procedure. The use of antimicrobial lock therapy (ALT) in combination with systemic antimicrobials is an option for treatment of CLABSIs when the CVC is retained or in a prophylactic modality after CVC insertion. ALT is a technique that involves the instillation of a highly concentrated antimicrobial solution, with or without additives such as anticoagulants, into the catheter lumen. Solutions are allowed to dwell (i.e., are "locked") in the catheter lumen for an extended period to overcome microbial biofilm, often the nidus of infection. ALT is commonly used for CVC management in a prophylactic modality in patients with protracted central venous access for hemodialysis (HD), chemotherapy, or total parenteral nutrition.[1-4]

The array of antiinfectives used in ALT has expanded beyond common antibacterials to include antifungals, such as fluconazole, echinocandins, and amphotericin B, and compounds with inherent antiseptic properties, such as taurolidine and ethyl alco-

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hol.[1] Heparin is the most commonly used anticoagulant additive in ALT, but other compounds, including trisodium citrate (TSC) and ethylenediaminetetraacetic acid (EDTA), which work synergistically with most antiinfectives, as well as thrombolytics, have been studied.[5-11]

Because of the increase in ALT utilization in both inpatient and outpatient settings and the continuing emergence of novel lock solutions, it is imperative that concise and validated stability and compatibility data are available to practitioners. This review details the available stability and compatibility data from evaluations of antimicrobial lock solutions used in combination with anticoagulants or other additives and provides recommendations for clinical application.

Literature review methodology

Given the expected number of studies, changes in terminology over time, and a lack of reliable relevant Medical Subject Headings terminology, three independent searches of MEDLINE and International Pharmaceutical Abstracts were performed using the search terms *antibiotic lock, antimicrobial lock,* and *antifungal lock.* The resulting lists of citations were screened against the inclusion criteria by each member of our investigative team. Reference lists of review articles were also screened for inclusion. An electronic compatibility database[12] was screened for potentially relevant publications.

All published, peer-reviewed, English-language articles that discuss ALT solutions containing at least one antiinfective in combination with at least one additive were included. Studies were screened for the use of appropriate methods to confirm stability and compatibility.[13,14] Studies meeting the minimum methodology requirements and reporting standards included those using validated stability-indicating assays.[13,14] All review articles were excluded. Case reports and case series, as well as clinical studies of ALT solutions commonly used in practice that did not meet the methodology criteria, were considered for discussion; if compatibility or stability was not discussed in these studies, we assumed that visual compatibility was assessed.

The initial searches yielded the following results (including duplications): *antibiotic lock,* 360 results; *antimicrobial lock,* 560 results; *antifungal lock,* 60 results. On screening, 17 articles met the prespecified inclusion criteria. Eighty-one articles did not meet the stability and compatibility testing standards but were included in the narrative portion of this review. Data are presented by antimicrobial class. Those without validated assessments are not discussed (e.g., carbapenems).

Antibacterials

Aminoglycosides. Aminoglycosides and anticoagulants in a lock solution have demonstrated potent in vitro antibacterial activity, including activity against gram-positive pathogens.[15] The clinical effectiveness of aminoglycoside-based solutions has been demonstrated in treatment and prophylactic modalities in several patient populations. Among the aminoglycosides, gentamicin is the agent for which the largest body of stability and compatibility data supporting use in ALT has been compiled. Stability data involving tobramycin- and amikacin-based lock solutions are limited to the assessment of physical compatibility with additives.[16,18] Clinicians should be aware that cloudiness may occur when combining an aminoglycoside with heparin in the setting of ALT; however, bioactivity and clinical success without adverse effects have been documented extensively.

Amikacin. Amikacin at concentrations of 2–50 mg/mL and heparin sodium at concentrations of 20–5,000 units/mL have been administered successfully, with no visual precipitation observed during dwell times ranging from 72 hours to 16 days.[16,18] Amikacin (5 mg/mL) has been combined with vancomycin (5 mg/mL) and heparin sodium (5,000 units/mL), with no visual precipitation noted for 72 hours.[19] Amikacin (0.02–4 mg/mL) in combination with teicoplanin (0.02–10 mg/mL) and heparin sodium (7–10,000 units/mL) visually precipitated at various concentrations.[20] Although stability data are limited, amikacin-based lock solutions, including those with vancomycin, may be useful in patients with polymicrobial infections and patients with multidrug-resistant organisms for whom there are few treatment options.

Gentamicin. Gentamicin and heparin have been studied in solution, but there are inconsistencies in the reported compatibility.[21-25] In one study, gentamicin at concentrations of ≥10 mg/mL precipitated immediately when mixed with heparin, but at lower concentrations (≤4 mg/mL) the solution remained clear for 72 hours at 37 °C.[21] Other studies have used higher concentrations of gentamicin (20–40 mg/mL) and heparin sodium (5000 units/mL), with no visual precipitation noted, though these studies did not employ validated stability-indicating assays.[22,23] Vercaigne et al.[24] confirmed the in vitro stability of gentamicin 5 mg/mL plus heparin sodium 5000 units/mL inside a CVC for 72 hours. Solutions of gentamicin 5 mg/mL and cefazolin 10 mg/mL plus heparin sodium 1000 units/mL were studied in a prospective study, with no reports of incompatibilities for up to 72 hours.[25] Lower concentrations of gentamicin and elevated temperatures, similar to that present in the intralumenal space, tend to promote compatibility. The conflicting reports regarding the stability and compatibility of gentamicin and heparin in solution warrant caution, especially if cloudiness or precipitation is encountered on preparation.

TSC has proven efficacy as an additive to gentamicin for ALT, and that combination has been found to be superior to heparin plus gentamicin.[26] Gentamicin 2.5 mg/mL with TSC 40 mg/mL remains stable, with no change in gentamicin concentration, for at least 112 days at room temperature.[5,7,8] Solutions of gentamicin 3 mg/mL and daptomycin 1 mg/mL with or without TSC 28 mg/mL maintained more than 90% of the original drug concentrations for 48 hours.[9]

Gentamicin 5 mg/mL has also been studied with EDTA 30 mg/mL, and visual compatibility for at least 72 hours at 25 or 37 °C was demonstrated. This combination provides an additional option when heparin or TSC is not desired.[15,27]

Data on gentamicin lock prophylaxis during HD are controversial regarding the emergence of gentamicin-resistant bacteremia.[28,29] Caution should be used with increasing prophylactic doses of gentamicin, as the potential for the emergence of resistance has not been clearly delineated.[28,29]

Tobramycin. Tobramycin has been studied in solution with several anticoagulants, including TSC, heparin, and tissue plasminogen activator (TPA). Tobramycin 2.4 mg/mL and TSC 40 mg/mL display visual compatibility at room temperature and at 37 °C for 48 hours.[7] Other studies have found tobramycin 5 mg/mL plus heparin sodium 5000 units/mL or TPA 1 mg/mL to be compatible for 12 hours at room temperature.[30-32] Although limited, compatibility data on tobramycin with TSC or TPA support the possibility of using those agents in combination for patients intolerant of other agents or patients requiring TPA for CVC patency.

Cephalosporins. Cefazolin, cefotaxime, and ceftazidime have been studied in combination with heparin in the setting of ALT using validated methodologies.[24,33-35] However, there are limited data on the use of cephalosporin-based lock solutions in clinical practice. Prophylactic use is not recommended due to the high rate of methicillin resistance among staphylococcal species, although targeted therapy for known pathogens may be appropriate.[1]

Cefazolin. Anthony and Rubin[33] performed an in vitro study with the combination of cefazolin (0.5 mg/mL) and heparin sodium 100 units/mL, which retained at least 90% of the cefazolin concentration at 25 and 37 °C for 10 days. Robinson et al.[37] used a higher concentration of cefazolin (10 mg/mL) with a range of heparin sodium concentrations (10–5000 units/mL), demonstrating physical compatibility for 14 days at 4 and 37 °C, but they noted a yellow color in many of the syringes. However, in another study of cefazolin 10 mg/mL and heparin sodium 5000 units/mL in CVCs maintained at 37 °C, cefazolin concentrations decreased by 27.4% at 72 hours.[24] While other pertinent research identified in our search did not involve validated stability-indicating assays, the reported data indicate that intermediate concentrations of cefazolin 5 mg/mL and heparin sodium 2500–5000 units/mL remain visually compatible for 72 hours.[15,31,38] Cefazolin 5 mg/mL with TPA 1 mg/mL was used in a clinical investigation.[28] It appears that cefazolin is a viable option for patients with susceptible isolates who may require extended dwell times.

Cefotaxime. Baker et al.[34] found that cefotaxime 10 mg/mL and heparin sodium 5000 units/mL were physically stable at 4, 27, and 40 °C for 72 hours, with more than 90% of the initial drug concentrations retained for 72 hours at 4 °C. However, at 27 and 40 °C, the cefotaxime concentration was degraded by 7% and the heparin concentration by 60% at 24 hours; the corresponding degradations at 72 hours were 18% and 95%. Saxena et al.[39-41] conducted several studies utilizing cefotaxime ALT. They found that solutions of cefotaxime 10 mg/mL and heparin sodium 5000 units/mL maintained visual compatibility for 72 hours. Based on the available data, there are concerns about increasing degradation of cefotaxime over extended time periods at higher temperatures, which are typically present in the catheter lumen. If cefotaxime is used for ALT, frequent exchanges may be required despite the prolonged stability documented under refrigerated conditions.

Ceftazidime. A range of ceftazidime concentrations have been studied.[33,35,36,42] Solutions of ceftazidime 0.5 mg/mL and heparin sodium 100 units/mL were found to be stable and compatible at 25 and 37 °C. At seven days, ceftazidime activity decreased by 28–36% at 37 °C.[34] Ceftazidime activity was retained (>90%) until day 10 at 25 °C.[34] Another study using a solution of ceftazidime 2 mg/mL with heparin sodium 100 units/mL found that intralumenal drug concentrations many times higher than the minimum inhibitory concentration for 90% of isolates of most susceptible organisms were maintained for 15 days.[35] The extended stability and compatibility appear limited to lower concentrations of ceftazidime and heparin. Ceftazidime 10 mg/mL plus heparin sodium 5000 units/mL in a CVC model resulted in a 40.2% decrease in ceftazidime concentrations at 72 hours.[24] Solutions of lower concentrations of ceftazidime (0.1–5 mg/mL) and heparin sodium 100 units/mL appear to be viable options for ALT in patients with susceptible infections, and the current data may support the use of such solutions over extended dwell times.

Cyclic lipopeptides. The calcium-dependent activity of daptomycin requires supplementation with a calcium-containing product such as lactated Ringer's (LR) solution.[9,15,43] Combinations of daptomycin 1–5 mg/mL in LR solution plus heparin sodium 100–5000 units/mL are stable and compatible for 72

hours.[9,15,44] Higher concentrations of daptomycin (5 and 25 mg/mL) plus heparin sodium 5–5000 units/mL are stable and compatible for at least 24 hours.[43] Daptomycin 5 mg/mL plus TSC 40 mg/mL has demonstrated physical compatibility for 48 hours.[7] Daptomycin 2.5 mg/mL has also been studied in vitro with 25% ethyl alcohol; the solution was used for simulated ALT entailing five days of 4-hour daily exposures at 37 °C, with no reported incompatibilities.[45]

The chemical stability of daptomycin with anticoagulants and antimicrobials was assessed by Bookstaver et al.[9] In solution with heparin sodium (100 or 1000 units/mL) or TSC 28 mg/mL, daptomycin (1 mg/mL) maintained greater than 98% of its original concentration for 72 hours. Daptomycin 1 mg/mL and azithromycin 5 mg/mL with heparin sodium (100 or 1000 units/mL) or TSC 28 mg/mL remained stable for 96 hours. Solutions of daptomycin 1 mg/mL and gentamicin 3 mg/mL, with or without TSC 28 mg/mL, remained stable for 48 hours. Despite compatibility data, lock solutions containing daptomycin with calcium chelators (e.g., TSC) should be avoided until bioactivity has been confirmed. In another study, there were no reports of incompatibilities with daptomycin 2 mg/mL and rifampin 2 mg/mL.[46]

The use of daptomycin ALT may be limited by cost considerations. However, the cost may be minimized when daptomycin is given concomitantly as a systemic therapy and lock solutions are prepared with reconstituted drug not used for the systemic dose.

Fluoroquinolones. The fluoroquinolone with the most available data regarding use in ALT is ciprofloxacin. Moxifloxacin has not been studied in combination with additives in the setting of ALT, and the data on levofloxacin in a lock solution are limited.

Ciprofloxacin. Ciprofloxacin and heparin have been studied in solution, with variable results. Anthony and Rubin[33] found that with a lower concentration of ciprofloxacin (0.125 mg/mL) plus heparin sodium 100 units/mL, more than 90% of the ciprofloxacin concentration was retained for 10 days at 25 and 37 °C. Macroscopic precipitation occurred at ciprofloxacin concentrations greater than 0.125 mg/mL. Vercaigne et al.[24] found that ciprofloxacin 10 mg/mL and heparin sodium 5000 units/mL immediately precipitated.

Droste et al.[20] found that solutions of ciprofloxacin 0.1–0.6 mg/mL plus heparin sodium (5,000–10,000 units/mL) did not precipitate; however, solutions of ciprofloxacin 0.8 mg/mL plus heparin sodium 10,000 units/mL and ciprofloxacin 1 mg/mL plus heparin sodium 10–10,000 units/mL resulted in precipitation after 72 hours and immediately, respectively. Contrary to these findings, Capdevilla et al.[47] found that ciprofloxacin 1 mg/mL plus heparin sodium 2,500 units/mL was physically stable through 72 hours. It is unknown whether the use of different ciprofloxacin formulations could have contributed to the discrepancies in compatibility data from these studies.

Caution should be employed when using ciprofloxacin with heparin-containing solutions, as precipitation has been reported with increasing concentrations of ciprofloxacin. The use of ciprofloxacin ALT should be reserved for a treatment modality targeted at gram-negative or multidrug-resistant organisms.

Levofloxacin. Levofloxacin 2–10 mg/mL has been studied in solution with heparin sodium 100 units/mL; this combination was found to result in macroscopic precipitation.[48] However, when levofloxacin (0.05 or 3.2 mg/mL) was combined with clarithromycin 200 mg/mL and heparin sodium 1000 units/mL, there were no incompatibilities.[49] Because of the additional reports of physical incompatibilities with the use of levofloxacin plus heparin in Trissel's text,[12] levofloxacin–heparin combinations should be avoided. Levofloxacin has also been used in combination with EDTA for ALT, but the agents' compatibility has not been confirmed.[50]

Glycopeptides. The most well-studied glycopeptide in the context of ALT is vancomycin, which has been used with heparin, TPA, and TSC-containing solutions. Additionally, the stability and compatibility of vancomycin in combination with other antibacterials have been documented. Teicoplanin and telavancin have also been studied, but there are limited published data using validated methodology.

Teicoplanin. In a study assessing visual compatibility, teicoplanin (0.02–10 mg/mL) did not precipitate over seven days at any concentration when mixed with heparin sodium (10–10,000 units/mL).[20] In another study, no incompatibilities were noted when teicoplanin 10 mg/mL was combined with heparin sodium 100 units/mL.[48] Teicoplanin at higher concentrations (20–33.3 mg/mL) has been combined with 1–3 mL of heparinized saline and administered once daily via CVC, with no reported incompatibilities.[51] However, teicoplanin in combination with amikacin, ciprofloxacin, or gentamicin precipitated when placed in solution with heparin sodium at various concentrations (7–10,000 units/mL) or citrate dextrose 4 mg/mL.[20] Although not available in the United States, teicoplanin may be best used for ALT at concentrations of 33 mg/mL or less combined with heparin sodium (10,000 units/mL or less). Due to the aforementioned report of precipitation,[20] ALT with teicoplanin and other antimicrobials should be used with caution.

Telavancin. Telavancin (2 or 5 mg/mL) has been studied as an ALT agent in combination with TSC (22 or 40 mg/mL) or heparin sodium (2500 units/mL); the stability and compatibility of all evaluated com-

binations were confirmed over 72 hours, with limited variability.[52] However, clinical effectiveness data on this lock solution are lacking, and supply issues have limited its use in the United States.

Vancomycin. Consistent compatibility has been demonstrated with solutions of vancomycin, at concentrations ranging from 0.1 to 10 mg/mL, and heparin sodium 100–5000 units/mL for ALT.[33,35-37,47,52-55] There are anecdotal reports of visual haze with the use of higher concentrations of vancomycin (≥5 mg/mL) and heparin sodium (≥5000 units/mL) in solution, but agitation appears to alleviate this concern; the clinical significance of these findings is unknown, and the phenomenon may be manufacturer specific. Vancomycin and heparin sodium at lower concentrations (0.025–0.5 mg/mL and 10–100 units/mL, respectively) have been evaluated, with no reported incompatibilities, but this research entailed less well-validated methodologies.[2,3,16,38,42,56,57] A study of vancomycin 0.025 mg/mL and heparin sodium 9.75 units/mL demonstrated that the solution was chemically stable for 40 days and retained antibacterial and anticoagulant activity when stored at 4 and 23 °C.[58] However, a stability study by Baker et al.[34] found that low-dose vancomycin (0.025 mg/mL) in solution with low-dose heparin sodium (10 units/mL) demonstrated 19% degradation at 40 °C after 72 hours. A similar study noted 15–37% decreases in vancomycin concentrations after 24 hours when solutions of vancomycin 0.025 mg/mL plus heparin sodium 100 units/mL were stored at 37 °C.[59] Heparin concentrations decreased 20–27%. Yet, at 4 °C, stability was maintained for 14 days. Lower doses of vancomycin may not be sufficient to adequately penetrate biofilms and to eradicate biofilm-embedded organisms and thus cannot be recommended for routine use in ALT.[57]

Vancomycin has also been studied with TSC and TPA. The stability and physical compatibility of vancomycin at concentrations ranging from 1 to 10 mg/mL administered with TSC 40 mg/mL was demonstrated through 72 hours.[6,7] Incompatibilities with solutions of vancomycin 20 mg/mL plus TSC 40 mg/mL have been noted.[7] Vancomycin at concentrations of 2 and 5 mg/mL in combination with TSC at concentrations of 22 and 40 mg/mL is reported to be physically and chemically stable for 72 hours.[52] Solutions of vancomycin 5 mg/mL plus TSC 22 mg/mL initially precipitated, but after 10 minutes of incubation at 37 °C, no precipitation was noted. Vancomycin 5 mg/mL in combination with TPA 1 mg/mL and vancomycin 50 mg/mL with urokinase 1250 units/mL have been used, with no reports of incompatibilities, but further stability studies are needed.[31,60]

Vancomycin-containing lock solutions have been studied in combination with other antimicrobials. Solutions of vancomycin (2–25 mg/mL), gentamicin (2–40 mg/mL), and heparin sodium (100–5000 units/mL) were reported to remain visually compatible for 72 hours in several studies,[38,48,61,62] but those studies did not involve the use of stability-indicating assays. A solution of vancomycin 0.05 mg/mL, ciprofloxacin 0.002 mg/mL, and heparin sodium 9.75 units/mL retained more than 90% of its vancomycin concentration for 60 days at 4 °C and for 7 days at 23 °C; with a lower concentration of vancomycin (0.025 mg/mL) in the same solution, more than 90% of the vancomycin was retained for 36 days at 23 °C.[58] When vancomycin 0.1 mg/mL was combined with colistimethate sodium 0.1 mg/mL and heparin sodium 100 units/mL, the vancomycin concentration remained stable for 60 days at 4 °C and for 15 days at 25 °C.[63] Published reports on research into other combinations using vancomycin discuss solutions containing ceftazidime, amikacin, and rifampin, but these studies reported only on visual compatibility at varying concentrations.[19,46,64,65] These antibacterial lock solution combinations may be useful in patients with polymicrobial infections. When vancomycin is used in combination with heparin sodium 100–5000 units/mL or TSC 40 mg/mL for ALT, the optimal vancomycin concentration is in the range of 1–10 mg/mL.

Lincosamides. In a study of patients receiving home parenteral nutrition via CVC, clindamycin 60–100 mg/mL with 1–3 mL of heparinized saline was administered twice daily, with no reported incompatibilities.[51] Clindamycin in lock solutions may prove clinically useful against common gram-positive pathogens, but more data from studies using validated stability-indicating assays are needed.

Oxazolidinones. Linezolid has been evaluated as an ALT agent in combination with various concentrations of heparin and TSC 40 mg/mL, with only one stability study using validated methodology. Systemic linezolid use in the management of CLABSIs is discouraged; thus, opportunities for its concomitant use for ALT are limited.[66,67] Linezolid use in ALT should be reserved for rare cases of vancomycin nonsusceptible organisms with limited treatment options.

Solutions of linezolid 0.2–1.92 mg/mL and heparin sodium 10–10,000 units/mL displayed no visible precipitation when stored at 25 or 37 °C for seven days.[20] Chemical stability at these concentrations has not been established. Curtin et al.[68] found that linezolid 2 mg/mL and heparin sodium 10 units/mL are chemically stable at 37 °C for 72 hours. Linezolid 1 mg/mL plus TSC 40 mg/mL was physically compatible for 48 hours.[7]

Macrolides. Azithromycin and clarithromycin have been studied in ALT with anticoagulants and antimicrobi-

als, but there are minimal data obtained using validated methodology.

Azithromycin. Azithromycin 5 mg/mL has been studied with daptomycin 1 mg/mL plus heparin sodium 100 units/mL, heparin sodium 1000 units/mL, or TSC 28 mg/mL.[9] The combinations demonstrated chemical compatibility at room temperature for 96 hours.

Clarithromycin. In an in vitro study involving biofilm-embedded *Acinetobacter baumannii* strains, clarithromycin 200 mg/mL in combination with colistimethate sodium (0.8 mg/mL), levofloxacin (0.05 and 3.2 mg/mL), or tigecycline (0.024 and 0.2 mg/mL), with or without heparin sodium 1000 units/mL, was physically compatible for 96 hours.[49]

Penicillins. There is a dearth of data describing the use of penicillins in ALT. The relevant studies evaluating ampicillin, piperacillin, and piperacillin–tazobactam are limited to assessments of physical compatibility.[20,37,48,51,65,69-70] Ticarcillin–clavulanic acid is the only penicillin combination for which there are data obtained with validated stability-indicating assays.[33] Significantly less data supporting the use of other penicillins in ALT are available, and none of the data were obtained with validated assays.

Extended-spectrum penicillins in a lock solution are most appropriate when broad-spectrum coverage of potential pathogens is required or for targeted therapy against multidrug-resistant organisms. Penicillinase-labile penicillins are best used for ALT in situations where the causative pathogen and its susceptibilities are known.

Ampicillin. Solutions of ampicillin 10 mg/mL with heparin sodium 10–5000 units/mL have been shown to be physically compatible at 4 and 37 °C for 14 days.[37] Of note, a yellow color was reported after 3 days in many of the ampicillin solutions; the importance of this finding is unknown.

Piperacillin and piperacillin–tazobactam. Piperacillin at various concentrations (10, 40, 100, and 167 mg/mL) in combination with heparin sodium (10–5000 units/mL) has been studied, with no reports of incompatibilities.[37,48,51,69] There is a lack of confirmed stability data for the combination of piperacillin–tazobactam 10 mg/mL with heparin sodium 100 units/mL; however, in an observational study, lock solutions were changed daily and no precipitation was observed.[48] Piperacillin 40 mg/mL was found to be physically compatible with a variety of heparin sodium concentrations (10–5000 units/mL) for 14 days at 4 and 37 °C.[37] No precipitation was noted with piperacillin 100 mg/mL and heparin sodium 400 units/mL for 72 hours.[69] Piperacillin has been studied at higher concentrations (100–167 mg/mL) in combination with 1–3 mL of heparinized saline and administered twice daily in CVCs, with no reported incompatibilities.[51]

Ticarcillin–clavulanic acid. Solutions of ticarcillin–clavulanic acid (0.1–5 mg/mL) and heparin sodium 100 units/mL were found to retain more than 90% of antimicrobial concentrations when stored at 25 and 37 °C for 10 days.[33]

Other penicillins. Solutions of penicillin G 50,000 units/mL plus heparin sodium 2,500–5,000 units/mL and amoxicillin 5 mg/mL plus heparin sodium 2,500 units/mL were reported to be visually compatible for 72 hours.[69] Cloxacillin 100 mg/mL plus heparin sodium 1,000 units/mL was also visually compatible.[70] Flucloxacillin 0.02 mg/mL plus heparin sodium 4,000 units/mL was precipitate-free at 72 hours at 25 and 37 °C, with precipitation noted by day 7.[20] Oxacillin has been combined with other antimicrobials in ALT. Oxacillin 0.0005 mg/mL plus rifampicin 0.004 mg/mL, with and without ciprofloxacin 0.004 mg/mL or gentamicin 0.016 mg/mL, has been found visually compatible at 24 hours.[64]

Polymyxins. Colistimethate sodium (0.8 mg/mL) was shown to be physically compatible with clarithromycin 200 mg/mL or heparin sodium 1000 units/mL or both for 96 hours.[49] A solution of colistimethate sodium (0.1 mg/mL), vancomycin 0.1 mg/mL, and heparin sodium 100 units/mL was demonstrated to remain stable for 60 days at 4 °C. At room temperature (25 °C) through day 15, all components remained within 10% of the initial concentration or measured activity. At day 30, a 25% decrease in vancomycin concentrations was found; however, colistimethate and heparin activity remained within 10% of the initial activity.[63]

Rifamycins. Rifampin used synergistically with other antimicrobials for ALT displays potent elimination of biofilm and prevention of the occurrence of resistant organisms, but validated stability data are lacking.[46,71] Combinations of rifampin 2 mg/mL and daptomycin 2 mg/mL, minocycline 2 mg/mL, or tigecycline 2 mg/mL have been evaluated in vitro, with no reported incompatibilities.[46] Sherertz et al.[71] found that rifampin enhances the activity of ciprofloxacin but is possibly antagonistic with vancomycin in solution. Rifampin may be used as an adjunctive lock solution to enhance the efficacy of ALT solutions containing ciprofloxacin, daptomycin, linezolid, minocycline, or tigecycline, but it should be used cautiously in vancomycin-containing solutions.[46,71,72]

Sulfonamides. Trimethoprim 5 or 10 mg/mL in combination with EDTA 30 mg/mL and 25% ethyl alcohol has been studied as a lock solution in vitro, with no reported incompatibilities.[73,74] Two studies evaluated solutions of trimethoprim–sulfamethoxazole (10 or 16 mg/mL) and heparin sodium 100 units/mL, with no incompatibilities noted.[48,73] Trimethoprim–sulfamethoxazole 16 mg/mL combined with heparin remained visually compatible for

14 days. Activity against staphylococcal species makes trimethoprim–sulfamethoxazole a potential option for common CLABSI-causing organisms, but stability and compatibility data obtained via validated methodologies are lacking.

Tetracyclines and glycylcyclines. Studies evaluating tetracyclines and tigecycline as constituents of ALT solutions did not meet the specified minimum methodology requirements. Combinations of these antimicrobials have been evaluated in the setting of ALT, with either no reports of incompatibilities or confirmation of visual compatibility.[15,46,49,73,75-81] Tetracyclines and glycylcycline derivatives are not first-line treatments in bloodstream infections and are used primarily as preventive therapies in a lock solution.[82] These agents may be considered for the treatment of CLABSI secondary to infection with multidrug-resistant organisms with limited susceptibility to other antimicrobials.

Minocycline. Minocycline 2–3 mg/mL has been studied in combination with EDTA 30 mg/mL, with or without 25% ethyl alcohol, with no reports of incompatibilities.[73,75-77] Clinically, minocycline 3 mg/mL plus EDTA 30 mg/mL displayed effectiveness in the prevention of CLABSIs, with documented dwell times of up to seven days.[76] The use of minocycline-containing ALT may be particularly useful in the prevention of CLABSIs and for catheter salvage.

Doxycycline. Data suggest that doxycycline 3 mg/mL plus EDTA 30 mg/mL may be a viable alternative to minocycline-containing lock solutions, with visual compatibility confirmed for 72 hours.[78] Solutions of doxycycline (0.128–2.048 mg/mL) plus fluconazole (0.002–1.048 mg/mL) have been evaluated in vitro, but there is a lack of stability and compatibility data.[79]

Tetracycline. Tetracycline 1 mg/mL is visually compatible with EDTA 30 mg/mL, although tetracycline is not routinely recommended or regularly available on the U.S. market.[78]

Tigecycline. Bookstaver et al.[15] reported the visual compatibility of tigecycline 0.5 mg/mL and EDTA 30 mg/mL, with no occurrence of precipitation; a slight color change (to dark orange and brown) was observed in several syringes stored for more than 48 hours. No visual incompatibilities have been reported with the combination of tigecycline 1 mg/mL and acetylcysteine 80 mg/mL plus heparin sodium 2000 units/mL and solutions of tigecycline 2 mg/mL plus rifampin 2 mg/mL.[46,80,83] Solutions of tigecycline (0.024 and 0.2 mg/mL) plus clarithromycin 200 mg/mL or heparin sodium 1000 units/mL or both were physically compatible for 96 hours.[49] Tigecycline has also been evaluated with antifungal agents in the setting of ALT. Solutions of tigecycline 0.512 mg/mL and fluconazole 1.024 mg/mL, amphotericin B 0.0125–16 mg/mL, or caspofungin acetate 0.0025–0.064 mg/mL have been assessed in vitro, with no reports of incompatibilities over 24 hours with storage at 37 °C.[81]

Antifungals

Azoles. There is a lack of data from studies involving validated stability-indicating assays to evaluate the use of azoles in ALT. Fluconazole, the only azole antifungal that has been studied with other ALT additives, was demonstrated to have variable potency against *Candida* biofilms. Solutions of fluconazole 1.024 mg/mL plus tigecycline 0.512 mg/mL and fluconazole 0.002–1.048 mg/mL plus doxycycline 0.128–2.048 mg/mL have been evaluated in vitro, with no reports of incompatibilities over 24 hours.[79,81]

Echinocandins. Our literature search identified no studies evaluating echinocandins for ALT that used validated stability-indicating assays. Research on caspofungin and micafungin is limited to the assessment of physical compatibility, and anidulafungin has not been studied in solution with additives in the setting of ALT. In addition, with increasing concentrations of caspofungin, a paradoxical reduction of its activity against *Candida albicans* has been reported. This phenomenon seems to be specific to caspofungin (among the echinocandins) and observed less frequently in cases involving other *Candida* species.[84] Further study of echinocandins in combination with anticoagulants used in ALT is warranted.

Caspofungin. Caspofungin is physically incompatible with heparin, with a gross white precipitate reported to develop within 4 hours.[85] Additionally, caspofungin acetate at concentrations of 0.001–2 mg/mL in solution with heparin sodium 100 units/mL displayed instant cloudiness and precipitation after 1–2 hours (unpublished data from the authors). Caspofungin acetate in varying concentrations (0.001, 0.01, and 0.1 mg/mL) was found to be visually compatible with EDTA 30 mg/mL for 48 hours at 4 °C (unpublished data from the authors). At higher concentrations (1 and 2 mg/mL), caspofungin acetate was incompatible with EDTA. Caspofungin should not be coadministered in solution with heparin. Further study is required with caspofungin when combined in solution with EDTA.

Caspofungin has been combined with other antimicrobials; however, information on the durability of these solutions is lacking.[79,81] The addition of doxycycline 0.512 and 2.048 mg/mL to caspofungin acetate 0.016 mg/mL resulted in a reduction of the aforementioned paradoxical effect (i.e., decreased activity against *C. albicans* growth with increasing caspofungin concentrations), with no reports of incompatibilities.[79] Clinicians should be cognizant of this phenomenon when using increasing concentrations of caspofungin in ALT. The use of doxycycline to attenuate the paradoxical effect warrants further investigation.

The addition of tigecycline 0.512 mg/mL to caspofungin acetate 0.00025–0.008 mg/mL resulted in reduced caspofungin antifungal activity; therefore, caution should be employed when using these agents concomitantly in solution.[81]

Micafungin. The available published data suggest that a combination of micafungin sodium (at concentrations of 0.001, 0.01, 0.1, 1, and 2 mg/mL) and heparin sodium (100 units/mL) or EDTA (30 mg/mL) is physically stable for 24 hours with storage at 22 and 37 °C.[86]

Polyenes. There are limited data on the use of amphotericin with heparin or EDTA for ALT.[87,88] In a case series, amphotericin B at concentrations of 1–2.5 mg/mL displayed visual compatibility with heparin sodium 100–5000 units/mL for 72 hours.[87] The available data suggest that antimicrobial locks containing amphotericin and heparin may be feasible for up to 72 hours.[87] Amphotericin B 2 mg/mL in solution with EDTA 30 mg/mL was reported to display visual compatibility for 6- to 8-hour dwell times.[84]

Secondary prophylaxis. Antifungal lock solutions may be used for secondary prophylaxis if the CVC must be exchanged or for treatment aimed at CVC salvage. Echinocandins have demonstrated in vitro activity against biofilms, which may prove useful in a prevention or treatment modality targeted against biofilm-associated candidiasis.[89,90]

Miscellaneous antiinfectives

Ethyl alcohol. Ethyl alcohol-containing lock solutions have been studied in combination with several additives. A 30% ethyl alcohol/4% TSC solution and a solution of 70% ethyl alcohol and heparin sodium 10 units/mL have been evaluated over 24, 48, and 72 hours, with no reports of incompatibilities.[10,11,91] The stability and compatibility of ethyl alcohol with higher concentrations of heparin have not been investigated. A prefilled catheter lock syringe containing a solution of 30% ethyl alcohol and 4% sodium citrate is commercially available in Canada but is not approved in the United States.[92]

Rosenblatt et al.[93] studied ethyl alcohol in various combinations with TSC, glyceryl trinitrate (GTN), and propylene glycol (PG) kept at 37 °C for 2 hours, with no reported incompatibilities. A solution of 20% ethyl alcohol, TSC 70 mg/mL, GTN 0.0001 mg/mL, and 6% PG fully eradicated biofilms containing MRSA, methicillin-resistant *Staphylococcus epidermis*, *Pseudomonas aeruginosa*, and *C. albicans* at 2 hours. Combinations of 25% ethyl alcohol, minocycline 3 mg/mL, and EDTA 30 mg/mL have been used as lock solutions for 24–120 hours, with no reports of incompatibilities.[45,75,84]

An important consideration when selecting ethyl alcohol-containing solutions for ALT is that the characteristics of adherent pathogens and the antimicrobial activity of ethyl alcohol and water may be affected by the surface components of CVCs, including silicone, polyurethane, and polycarbonate.[94] It is also recommended that ethyl alcohol-containing lock solutions be aspirated from the catheter to minimize the risks associated with flushing, especially in vulnerable populations such as neonates.[91]

Ethyl alcohol-containing solutions are inexpensive and appear to be effective for use in prophylactic lock regimens.[10,11,91,95,96] Due to increases in bacterial resistance, novel options such as ethyl alcohol-based lock solutions may be a preferred option.

Fusidic acid. Fusidic acid 4 mg/mL and heparin sodium 10 units/mL have been combined for use in ALT, with no incompatibilities noted.[97] More data are needed before the place of fusidic acid in CLABSI treatment can be clearly delineated.

Methylene blue. Methylene blue (0.05–0.15%) has been used for ALT in combination with 0.15% methyl paraben, 0.015% propyl paraben, and TSC 70 mg/mL or heparin sodium 10 units/mL, with no incompatibilities noted.[10,98-101] The use of methylene blue in ALT has not become widespread due to a relative lack of supportive data and logistical issues.

Taurolidine. Taurolidine 13.5 mg/mL with TSC (26.1 or 40 mg/mL) has been evaluated as an ALT solution, with no incompatibilities reported.[102-107] A lock solution containing taurolidine 13 mg/mL, TSC 40 mg/mL, and heparin sodium 500 units/mL was studied in patients on chronic HD for an average of 30.5 days, with no reported incompatibilities.[108] Taurolidine with TSC in solution is available with heparin (100 or 500 units/mL) or urokinase 25,000 units/mL as a prepacked product in Europe (TauroLock, Tauro-Implant GmbH, Winsen, Germany).[109]

Key considerations in ALT selection

Used in combination with concomitant systemic antimicrobials, ALT plays an integral role in the management of CLABSIs when the CVC is retained or for long-term prophylaxis after CVC insertion. Summary stability and compatibility data from evaluated studies using validated methodologies are available in Table 1. The practitioner's role in choosing ALT requires selecting antimicrobials targeted at the causative organisms, choosing compatible lock solutions, evaluating the duration of stability in light of the suggested administration schedule and dwell times, and selecting a cost-effective solution. The impact of storage environments (e.g., plastic versus glass, temperature) should be carefully assessed. The systemic therapy a patient is receiving may help guide agent selection and may itself be a logical selection for ALT if appropriate. Antimicrobial stability and compatibility data do not necessarily equate to effective-

ness against biofilm-producing organisms.

In addition, it is imperative that practitioners are cognizant of the cost of various agents used for ALT and the widespread drug shortages that may have a profound impact on ALT selection. Published data on many combination lock solutions are available; however, most data derive from clinical-use evaluations in which assessment of compatibil-

Table 1.
Summary Stability and Compatibility Data on Lock Solutions From Studies Using Validated Methodology[a]

Reference	Solution	Results
Aminoglycoside		
53	Gentamicin 0.1 mg/mL plus heparin 5000 units/mL	At 4 °C, compatible and stable for up to 4 wk; confirmed via particle-enhanced turbidimetric inhibition immunoassay
24	Gentamicin 5 mg/mL plus heparin 5000 units/mL	In CVCs, 92% of gentamicin concentration retained at 72 hr; confirmed via HPLC
5	Gentamicin 2.5 mg/mL plus TSC 40 mg/mL	At 37 °C, no decrease in gentamicin concentration for 96 hr; confirmed via HPLC
8	Gentamicin 2.5 mg/mL plus TSC 40 mg/mL	At room temperature, 100% of gentamicin concentration and 101.3% of TSC concentration retained for 112 days; confirmed via HPLC
Cephalosporins		
33	Cefazolin 0.5 mg/mL plus heparin 100 units/mL	At 25 and 37 °C, compatible and stable for up to 10 days; confirmed via bioassay
24	Cefazolin 10 mg/mL plus heparin 5000 units/mL	In glass test tubes stored at 37 °C, cefazolin concentration decreased by 9% at 72 hr; in CVCs, cefazolin concentration decreased by 27.4% at 72 hr; confirmed via HPLC
34	Cefotaxime 10 mg/mL plus heparin 5000 units/mL	Physically stable at 4, 27, and 40 °C for 72 hr; chemical stability decreased beyond 24 hr at 27 and 40 °C; confirmed via HPLC
33	Ceftazidime 0.5 mg/mL plus heparin 100 units/mL	Compatible and stable for up to 7 days at 25 and 37 °C; confirmed via bioassay
35	Ceftazidime 2 mg/mL plus heparin 100 units/mL	Compatible and stable for up to 15 days; confirmed via bioassay
24	Ceftazidime 10 mg/mL plus heparin 5000 units/mL	40.2% decrease in ceftazidime concentration at 72 hr; confirmed via HPLC
Cyclic Lipopeptide		
9	Daptomycin 1 mg/mL plus heparin 100 units/mL plus LR	At 25 °C, 99.4% and 82.1% of daptomycin concentration retained at 72 and 96 hr, respectively; confirmed via HPLC
9	Daptomycin 1 mg/mL plus heparin 1000 units/mL plus LR	At 25 °C, 98.3% and 84.0% of daptomycin concentration retained at 72 and 96 hr, respectively; confirmed via HPLC
43	Daptomycin 5 mg/mL reconstituted with LR plus heparin 5, 500, or 5000 units/mL	At 37 °C, daptomycin concentration decreased by ≤10% at 24 hr; confirmed via HPLC
9	Daptomycin 1 mg/mL plus TSC 28 mg/mL plus LR	At 25 °C, 93.3% of daptomycin concentration retained at 96 hr; confirmed via HPLC
Fluoroquinolone		
33	Ciprofloxacin 0.125 mg/mL plus heparin 100 units/mL	Compatible and stable for up to 10 days at 25 and 37 °C (confirmed via bioassay); macroscopic precipitation occurred at ciprofloxacin concentrations of >0.125 mg/mL
47	Ciprofloxacin 1 mg/mL plus heparin 2500 units/mL	Compatible and stable for up to 72 hr at 37 °C; confirmed via bioassay

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Table 1 (*continued*)

Reference	Solution	Results
Glycopeptides		
52	Telavancin 2 mg/mL plus heparin 2500 units/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Telavancin 5 mg/mL plus heparin 2500 units/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Telavancin 2 mg/mL plus TSC 22 mg/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Telavancin 2 mg/mL plus TSC 40 mg/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Telavancin 5 mg/mL plus TSC 22 mg/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Telavancin 5 mg/mL plus TSC 40 mg/mL	Physically compatible; >90% of telavancin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
58	Vancomycin 0.025 mg/mL plus heparin 9.75 units/mL	Stable at 4 °C for 40 days; confirmed via TDX
59	Vancomycin 0.025 mg/mL plus heparin 100 units/mL	At 4 °C, vancomycin concentration stable for 14 days; at 37 °C, concentration reduced by 15–37% at 24 hr; confirmed via TDX
34	Vancomycin 0.025 mg/mL plus heparin 5000 units/mL	Compatible and stable at 4 and 27 °C for 72 hr; at 40 °C, 81% of vancomycin concentration retained at 72 hr; confirmed via HPLC
53	Vancomycin 0.1 mg/mL plus heparin 5000 units/mL	Compatible and stable at 4 °C for up to 4 wk; confirmed via TDX
33	Vancomycin 0.5 mg/mL plus heparin 100 units/mL	≥90% of vancomycin concentration retained at 25 and 37 °C for up to 10 days; confirmed via bioassay
35	Vancomycin 2 mg/mL plus heparin 100 units/mL	When solution instilled in ports of patients and allowed to dwell for 2–34 days at room temperature, vancomycin concentration of ≥0.130 mg/mL retained for up to 28 days; confirmed via TDX
47	Vancomycin 2 mg/mL plus heparin 2500 units/mL	Compatible and stable at 37 °C for at least 72 hr; confirmed via TDX
52	Vancomycin 2 mg/mL plus heparin 2500 units/mL	Physically compatible; >90% of vancomycin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
54	Vancomycin 2.5 mg/mL plus heparin 2.5 units/mL	Decrease in vancomycin concentration gradient from proximal to distal segments of dialysis catheter at 48 hr; confirmed via particle-enhanced turbidimetric inhibition immunoassay
52	Vancomycin 5 mg/mL plus heparin 2500 units/mL	Physically compatible; >90% of vancomycin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
24	Vancomycin 10 mg/mL plus heparin 5000 units/mL	In glass test tubes stored at 37 °C, no change in vancomycin concentration at 72 hr; in CVCs, concentration decreased by 29.7% at 72 hr; confirmed via HPLC

Continued on next page

Table 1 (*continued*)

Reference	Solution	Results
5	Vancomycin 1 and 3 mg/mL plus TSC 40 mg/mL	>92% of vancomycin concentration retained for 72 hr with storage at 4–23 °C in polyvinyl chloride syringes of HD catheters; confirmed via HPLC
52	Vancomycin 2 mg/mL plus TSC 22 mg/mL	Initial precipitation, but no precipitation noted after 10 min of incubation at 37 °C; >90% of vancomycin concentration retained at 72 hr; confirmed via HPLC
52	Vancomycin 2 mg/mL plus TSC 40 mg/mL	Physically compatible; >90% of vancomycin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
52	Vancomycin 5 mg/mL plus TSC 22 mg/mL	Initial precipitation, but no precipitation noted after 10 min of incubation at 37 °C; >90% of vancomycin concentration retained at 72 hr; confirmed via HPLC
52	Vancomycin 5 mg/mL plus TSC 40 mg/mL	Physically compatible; >90% of vancomycin concentration retained over 72 hr with incubation at 37 °C; confirmed via HPLC
Oxazolidinone		
68	Linezolid 2 mg/mL plus heparin 10 units/mL	Compatible and stable at 37 °C for up to 72 hr; confirmed via bioassay
Penicillin		
33	Ticarcillin–clavulanic acid 0.5 mg/mL plus heparin 100 units/mL	Compatible and stable for up to 10 days at 25 and 37 °C; confirmed via bioassay
Antibiotics in Combination		
9	Daptomycin 1 mg/mL plus azithromycin 5 mg/mL plus heparin 100 units/mL plus LR	At 25 °C, 101.4% of daptomycin concentration retained at 96 hr; confirmed via HPLC
9	Daptomycin 1 mg/mL plus azithromycin 5 mg/mL plus heparin 1000 units/mL plus LR	At 25 °C, 91.5% of daptomycin concentration retained at 96 hr; confirmed via HPLC
9	Daptomycin 1 mg/mL plus azithromycin 5 mg/mL plus TSC 28 mg/mL plus LR	At 25 °C, 103.3% of daptomycin concentration retained at 96 hr; confirmed via HPLC
9	Daptomycin 1 mg/mL plus gentamicin 3 mg/mL plus LR	At 25 °C, 91.6% and 79.0% of daptomycin concentration retained at 72 and 96 hr, respectively; 97.0% of gentamicin concentration retained at 96 hr; confirmed via HPLC
9	Daptomycin 1 mg/mL plus gentamicin 3 mg/mL plus TSC 28 mg/mL plus LR for total volume of 5 mL	At 25 °C, 90.7% and 86.7% of daptomycin concentration retained at 48 and 72 hr, respectively; 95.2% of gentamicin concentration retained at 96 hr; confirmed via HPLC
58	Vancomycin 0.025 mg/mL plus ciprofloxacin 0.002 mg/mL plus heparin 9.75 units/mL	At 23 °C, >90% of vancomycin concentration retained for 36 days; confirmed via TDX
58	Vancomycin 0.05 mg/mL plus ciprofloxacin 0.002 mg/mL plus heparin 9.75 units/mL	At 4 °C, >90% of vancomycin concentration retained for 60 days; at 23 °C, >90% of vancomycin concentration retained for 7 days; confirmed via TDX
63	Vancomycin 0.1 mg/mL plus colistin 0.1 mg/mL plus heparin 100 units/mL	At 4 °C, >90% of vancomycin concentration retained for 60 days; at 25 °C, >90% of vancomycin concentration retained for 15 days, with 25% decrease at day 30; confirmed via TDX

[a]CVC = central venous catheter, HPLC = high-performance liquid chromatography, TSC = trisodium citrate, LR = lactated Ringer's solution, TDX = fluorescent polarization immunoassay, HD = hemodialysis.

ity was limited to visual inspection. Further research on the stability and compatibility of various constituents of lock solutions must be conducted to advance the use of ALT in the prophylaxis and treatment of patients with CLABSIs.

Conclusion

Pharmacists' knowledge of diverse combinations of antimicrobial agents and additives in lock solutions, including several shown to be stable and compatible for extended periods, can help expand and optimize the use of ALT in both treatment and prophylactic modalities.

References

1. O'Grady NP, Alexander M, Burns LA et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; 52(9):e162-93.
2. Carratala J, Niubo J, Fernandez-Sevilla A et al. Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. *Antimicrob Agents Chemother*. 1999; 43:2200-4.
3. Garland JS, Alex CP, Henrickson KJ et al. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics.* 2005; 116:e198-205.
4. Kim SH, Song KI, Chang JW et al. Prevention of uncuffed hemodialysis catheter-related bacteremia using an antibiotic lock technique: a prospective, randomized clinical trial. *Kidney Int.* 2006; 69:161-4.
5. Battistella M, Vercaigne LM, Cote D, Lok CE. Antibiotic lock: in vitro stability of gentamicin and sodium citrate in dialysis catheters at 37 degrees C. *Hemodial Int*. 2010; 14: 322-6.
6. Battistella M, Walker S, Law S et al. Antibiotic lock: in vitro stability of vancomycin and four percent sodium citrate stored in dialysis catheters at 37 degrees C. *Hemodial Int*. 2009; 13:322-8.
7. Dotson B, Lynn S, Savakis K et al. Physical compatability of 4% sodium citrate with selected antimicrobial agents. *Am J Health-Syst Pharm.* 2010; 67:1195-8.
8. Cote D, Lok CE, Battistella M et al. Stability of Trisodium Citrate and Gentamicin Solution for Catheter Locks after Storage in Plastic Syringes at Room Temperature. *Can J Hosp Pharm*. 2010; 63:304-11.
9. Bookstaver PB, Premnath PN, Edwards JM. Evaluation of compatibility and stability of daptomycin in an antibiotic-anticoagulant lock solution. Presented at: American College of Clinical Pharmacy Annual Meeting, Hollywood, FL, October 21-24, 2012.
10. Shenep LE, Shenep M, Cheatham W et al. Efficacy of intravascular catheter lock solutions containing preservatives in the prevention of microbial colonization. *J Hosp Infect*. 2011; 79:317-22.
11. Takla TA, Zelenitsky SA, Vercaigne LM. Effectiveness of a 30% ethanol/4% trisodium citrate locking solution in preventing biofilm formation by organisms causing haemodialysis catheter-related infections. *J Antimicrob Chemother*. 2008; 62:1024-6
12. Trissel LA. Trissel's 2 clinical pharmaceutics database [electronic database]. Cashiers, NC: TriPharma Communications. Updated regularly.
13. Trissel LA, Flora KP. Stability studies: five years later. *Am J Hosp Pharm*. 1988; 45:1569-71.
14. Trissel LA. Avoiding common flaws in stability and compatibility studies of injectable drugs. *Am J Hosp Pharm.* 1983; 40:1159-60.
15. Bookstaver PB, Williamson JC, Tucker BK et al. Activity of novel antibiotic lock solutions in a model against isolates of catheter-related bloodstream infections. *Ann Pharmacother*. 2009; 43:210-9.
16. Fernandez-Hidalgo N, Almirante B, Calleja R et al. Antibiotic-lock therapy for long-term intravascular catheter-related bacteraemia: results of an open, non-comparative study. *J Antimicrob Chemother.* 2006; 57:1172-80.
17. Saxena AK, Panhotra BR, Naguib M. Sudden irreversible sensory-neural hearing loss in a patient with diabetes receiving amikacin as an antibiotic-heparin lock. *Pharmacotherapy*. 2002; 22:105-8.
18. Rao JS, O'Meara A, Harvey T et al. A new approach to the management of Broviac catheter infection. *J Hosp Infect*. 1992; 22(2):109-16.
19. Sánchez-Muñoz A, Aguado JM, López-Martin A et al. Usefulness of antibiotic-lock technique in management of oncology patients with uncomplicated bacteremia related to tunneled catheters. *Eur J Clin Microbiol Infect Dis.* 2005; 24(4):291-3.
20. Droste JC, Jeraj H, MacDonald A, Farrington K. Stability and in vitro efficacy of antibiotic-heparin lock solutions potentially useful for treatment of central venous catheter-related sepsis. *J Antimicrob Chemother*. 2003; 51:849-55.
21. Polgreen PM, Beekmann SE, Diekema DJ et al. Wide variability in the use of antimicrobial lock therapy and prophylaxis among infectious diseases consultants. *Infect Control Hosp Epidemiol.* 2010; 31(5):554-57.
22. Bailey E, Berry N, Cheesbrough JS. Antimicrobial lock therapy for catheter-related bacteraemia among patients on maintenance haemodialysis. *J Antimicrob Chemother.* 2002; 50:615-7.
23. Filiopoulos V, Hadjiyannakos D, Koutis I et al. Approaches to prolong the use of uncuffed hemodialysis catheters: results of a randomized trial. *Am J Nephrol*. 2011; 33(3):260-8.
24. Vercaigne LM, Siltar DS, Penner SB et al. Antibiotic-heparin lock: in vitro antibiotic stability combined with heparin in a central venous catheter. *Pharmacotherapy.* 2000; 20(4):394-9.
25. Silva TN, Mendes ML, Abrão JM et al. Successful prevention of tunneled central catheter infection by antibiotic lock therapy using cefazolin and gentamicin. *Int Urol Nephro*l. 2012 Dec 27. [Epub ahead of print]
26. Moran J, Sun S, Khababa I et al. A randomized trial comparing gentamicin/citrate and heparin locks for central venous catheters in maintenance hemodialysis patients. Am J Kidney Dis 2011; 59(1):102-107.
27. Chauhan A, Lebeaux D, Ghigo JM et al. Full and broad-spectrum in vivo eradication of catheter-associated biofilms using gentamicin-EDTA antibiotic lock therapy. *Antimicrob Agents Chemother*. 2012; 56 (12):6310-8.
28. Landry DL, Braden GL, Gobeille SL et al. Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol*. 2010; 5(10):1799-804.
29. Fernández-Gallego J, Martin M, Gutiérrez E et al. Prophylaxis with gentamicin locking of chronic tunnelled central venous catheters does not cause bacterial resistance. *Nefrologia*. 2011; 31:308-12.
30. Onder AM, Chandar J, Simon N et al. Comparison of tissue plasminogen activator-antibiotic locks with heparin-antibiotic locks in children with catheter-related bacteraemia. *Nephrol Dial Transplant*. 2008; 23:2604-10.
31. Onder AM, Chandar J, Billings AA et al. Comparison of early versus late use of antibiotic lock in the treatment of catheter-related bacteremia. *Clin J Am Soc Nephrol.* 2008; 3(4):1048-56.
32. Onder AM, Chardar J, Billings A et al. Prophylaxis of catheter related bacteremia using tissue plasminogen activator-tobramycin locks. *Pediatr Nephrol*. 2009; 24(11):2233-43.
33. Anthony TU, Rubin LG. Stability of antibiotics used for antibiotic-lock treatment of infections of implantable venous devices (ports). *Antimicrob Agents Chemother*. 1999; 43:2074-6.
34. Baker DS, Waldrop B, Arnold J. Compatibility and stability of cefotaxime, vancomycin, and ciprofloxacin in antibiotic lock solutions containing heparin. *Int J Pharmaceutical Compound.* 2010; 14(4):346-9.
35. Haimi-Cohen Y, Husain N, Meenan J et al. Vancomycin and ceftazidime bioactivities persist for at least 2 weeks in the lumen in ports: simplifying treatment of port-associated bloodstream infections by using the antibiotic lock techniques.

Antimicrob Agents Chemother. 2001; 45(5):1565-67.
36. Vercaigne LM, Zelenitsky S, Findlay I et al. An in vitro evaluation of the antibiotic/heparin lock to sterilize central venous haemodialysis catheters. *J Antimicrob Chemother*. 2002; 49:693-6.
37. Robinson JL, Tawfik G, Saxinger L et al. Stability of heparin and physical compatibility of heparin/antibiotic solutions in concentrations appropriate for antibiotic lock therapy. *J Antimicrob Chemother*. 2005; 56:951-3.
38. Krishnasami Z, Carlton D, Bimbo L et al. Management of hemodialysis catheter related bacteremia with an adjunctive antibiotic lock solution. *Kidney Int*. 2002; 61:1136-42.
39. Saxena AK, Panhotra B, Sundaram DS et al. Enhancing the survival of tunneled haemodialysis catheters using an antibiotic lock in the elderly: a randomised, double-blind clinical trial. *Nephrology*. 2006; 11:299-305.
40. Saxena AK, Panhotra B, Sundaram DS et al. Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement. *Kidney Int.* 2006; 70:1629-35.
41. Saxena AK, Panhotra BR. The impact of catheter-restricted filling with cefotaxime and heparin on the lifespan of temporary hemodialysis catheters: a case controlled study. *J Nephrol*. 2005; 18:755-63.
42. Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. *J Antimicrob Chemother*. 2005; 55(1):90-4.
43. Van Praagh AD, Li T, Zhang S et al. Daptomycin antibiotic lock therapy in a rat model of staphylococcal central venous catheter biofilm infections. *Antimicrob Agents Chemother.* 2011; 55:4081-9.
44. Del Pozo JL, Rodil R, Aguinaga A et al. Daptomycin lock therapy for grampositive long-term catheter-related bloodstream infections. *Int J Clin Pract*. 2012; 66(3):305-8.
45. Estes R, Theusch J, Beck A et al. Activity of daptomycin with or without 25 percent ethanol compared to combinations of minocycline, EDTA, and 25 percent ethanol against methicillin-resistant Staphylococcus aureus isolates embedded in biofilm. *Antimicrob Agents Chemother*. 2013; 57(4):1998-2000.
46. Raad I, Hanna H, Jiang Y et al. Comparative activity of daptomycin, linezolid and tigecycline against catheter-related methicillin-resistant Staphylococcus bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother*. 2007; 51:1656-60.
47. Capdevilla JA, Galvalda J, Fortea J et al. Lack of antimicrobial activity of sodium heparin for treating experimental catheter-related infection due to Staphylococcus aureus using the antibiotic-lock technique. *Clin Microbiol Infect*. 2001; 7:206-12.
48. Del Pozo JL, Alonso M, Serrera A, Hernaez S, Aguinaga A, Leiva J. Effectiveness of the antibiotic lock therapy for the treatment of port-related enterococci, Gram-negative, or Gram-positive bacilli bloodstream infections. *Diagn Microbiol Infect Dis*. 2009; 63:208-12.
49. Ozbek B, Mataraci E. In vitro effectiveness of colistin, tigecycline and levofloxacin alone and combined with clarithromycin and/or heparin as lock solutions against embedded Acinetobacter baumannii strains. *J Antimicrob Chemother.* 2013; 68:827-30.
50. Passerini de Rossi B, Feldman L, Pineda MS, Vav C, Franco M. Comparative *in vitro* efficacies of ethanol, EDTA and levofloxacin based catheter lock solutions on eradication of *Stenotrophomonas maltophilia* biofilms. *J Med Microbiol*. 2012 May 11. [Epub ahead of print].
51. Santarpia L, Pasanisi F, Alfonsi L et al. Prevention and treatment of implanted central venous catheter (CVC) - related sepsis: a report after six years of home parenteral nutrition. *Clin Nutr.* 2002; 21(3):207-11.
52. LaPlante KL, Woodmansee S, Mermel LA. Compatibility and stability of telavancin and vancomycin in heparin or sodium citrate lock solutions. *Am J Health-Syst Pharm.* 2012; 69:1405-9.
53. Bastani B, Amin K, Herr A. Prolonged stability of stored vancomycin, gentamicin, and heparin for use in the antibiotic-lock technique. *ASAIO J*. 2005; 51:761-3.
54. Soriano A, Bregada E, Marqués JM et al. Decreasing gradient of antibiotic concentration in the lumen of catheters locked with vancomycin. *Eur J Clin Microbiol Infect Dis.* 2007; 26:659-61.
55. Bastani B, Minton J, Islam S. Insufficient penetration of systemic vancomycin into the PermaCath lumen. *Nephrol Dial Transplant*. 2000; 15:1035-7.
56. Fortun J, Grill F, Martin-Davila P et al. Treatment of longterm intravascular catheter-related bacteraemia with antibiotic-lock therapy. *J Antimicrob Chemother.* 2006; 58:816-21.
57. Laplante KL, Mermel LA. In vitro activity of daptomycin and vancomycin lock solutions on staphylococcal biofilms in a central venous catheter model. *Nephrol Dial Transplant*. 2007; 22:2239-46.
58. Henrickson KJ, Powell KR, Schwart CL. A dilute solution of vancomycin and heparin retains antibacterial and anticoagulant activities. *J Infect Dis*. 1988; 157(3):600-1.
59. Yao JD, A.C., Karchmer AW. Vancomycin stability in heparin and total parenteral nutrition solutions: novel approach to therapy of central venous catheter-related infections. *JPEN J Parenter Enteral Nutr.* 1992; 16(3):268-74.
60. De Sio L, Jenkner A, Milano GM et al. Antibiotic lock with vancomycin and urokinase can successfully treat colonized central venous catheters in pediatric cancer patients. *Pediatr Infect Dis J* 1004; 23: 963-5.
61. Al-Hwiesh AK. Tunneled catheter-antibiotic lock therapy for prevention of dialysis catheter-related infections: a single center experience. *Saudi J Kidney Dis Transpl.* 2008; 19:593-602.
62. Dixon JJ, Steele M, Makanjuola AD. Anti-microbial locks increase the incidence of Staphylococcus aureus and antibiotic-resistant Enterobacter: observational retrospective cohort study. *Nephrol Dial Transplant.* 2012 May 2. [Epub ahead of print].
63. Vincentelli J. Formulation of a flush solution of heparin, vancomycin, and colistin for implantable access systems in oncology. *J Oncol Pharm Pract.* 1997; 3(1):18-23.
64. Poole CV, Carlton D, Bimbo L et al. Treatment of catheter-related bacteraemia with an antibiotic lock protocol: effect of bacterial pathogen. *Nephrol Dial Transplant*. 2004; 19(5):1237-44.
65. Qu Y, Istivan TS, Daley AJ et al. Comparison of various antimicrobial agents as catheter lock solutions: preference for ethanol in eradication of coagulase-negative staphylococcal biofilms. *J Med Microbiol.* 2009; 58(Pt 4):442-50.
66. *Information for Healthcare Professionals: Linezolid (marketed as Zyvox).* Food and Drug Administration Alert. [cited 2012 February 1]; Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm085249.htm.
67. Wilcox MH, Tack KJ, Bouza E et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. *Clin Infect Dis.* 2009; 48:203-12.
68. Curtin J, Cormican M, Fleming G et al. Linezolid compared with eperezolid, vancomycin, and gentamicin in an in vitro model of antimicrobial lock therapy for Staphylococcus epidermidis central venous catheter-related biofilm infections. *Antimicrob Agents Chemother*. 2003; 47:3145-8.
69. Boorgu R, Dubrow AJ, Levin NW et al. Adjunctive antibiotic/anticoagulant lock therapy in the treatment of bacteremia associated with the use of a subcutaneously implanted hemodialysis access device. *ASAIO J*. 2000; 46(6):767-70.
70. Davanipur M, Pakfetrat M, Roozbeh J. Cloxacillin as an antibiotic lock solution for prevention of catheter-associated infection. *Iran J Kidney Dis*. 2011; 5(5): 328-31.
71. Sherertz RJ, Boger M, Collins CA et al. Comparative in vitro efficacies of various catheter lock solutions. *Antimicrob Agents Chemother*. 2006; 50:1865-8.
72. Holmberg A, Morgelin M, Rasmussen M. Effectiveness of ciprofloxacin or linezolid in combination with rifampicin

against Enterococcus faecalis in biofilms. *J Antimicrob Chemother.* 2012; 67:433-9.
73. Al Akhrass F, Hachem R, Mohamed JA et al. Central venous catheter-associated Nocardia bacteremia in cancer patients. *Emerg Infect Dis.* 2011; 17:1651-8.
74. Ghannoum MA, Isham N, Jacobs MR. Antimicrobial activity of B-Lock against bacterial and Candida spp. causing catheter-related bloodstream infections. *Antimicrob Agents Chemother.* 2011; 55(9):4430-1.
75. Raad I, Hanna H, Dvorak T et al. Optimal antimicrobial catheter lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol, rapidly eradicates organisms embedded in biofilm. *Antimicrob Agents Chemother.* 2007; 51:78-83.
76. Chatzinikolaou I, Zipf T, Hanna H et al. Minocycline-ethylenediaminetetraacetate lock solution for the prevention of implantable port infections in children with cancer. *Clin Infect Dis*. 2003; 36:116-9.
77. Raad I, Hachem R, Tcholakian RK et al. Efficacy of minocycline and EDTA lock solution in preventing catheter-related bacteremia, septic phlebitis, and endocarditis in rabbits. *Antimicrob Agents Chemother.* 2002; 46:327
78. Bookstaver PB, Sutton SS, Sherertz RJ. Bioactivity of tetracycline antibiotic lock therapy in a model of catheter infection (abstract 475). Presented at Fifth Decennial International Conference on Healthcare-Associated Infections. Atlanta, GA; 2010 March.
79. Miceli MH, Bernardo SM, Lee SA. In vitro analyses of the combination of high-dose doxycycline and antifungal agents against Candida albicans biofilms. *Int J Antimicrob Agents*. 2009; 34:326-32.
80. Olofsson, A, Hermansson M, Elwing H. N-acetyl-L-cysteine affects growth, extracellular polysaccharide production, and bacterial biofilm formation on solid surfaces. *Appl Environ. Microbiol.* 2003; 69:4814-22.
81. Ku TS, Palanisamy S, Lee SA. Susceptibility of Candida albicans biofilms to azithromycin, tigecycline and vancomycin and the interaction between tigecycline and antifungals. *Int J Antimicrob Agents*. 2010; 36:441-6.
82. Bleyer AJ, Mason L, Russell G, Raad II, Sherertz RJ. A randomized, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infect Control Hosp Epidemiol* 2005; 26: 520-4.
83. Aslam S, Trautner BW, Ramanathan V, Darauiche Ro. Pilot trial of N-acetylcysteine and tigecycline as a catheter lock solution for treatment of hemodialysis catheter-associated bacteremia. *Infect Control Hosp Epidemiol* 2008; 29: 894-7.
84. Stevens DA, Espiritu M, Parmar R. Paradoxical effect of caspofungin: reduced activity against Candida albicans at high drug concentrations. *Antimicrob Agents Chemother*. 2004; 48:3407-11.
85. Condie CK, Tyler LS, Barker B, Canann DM. Visual compatibility of caspofungin acetate with commonly used drugs during stimulated Y-site delivery. *Am J Health-Syst Pharm.* 2008; 65,5:454-57.
86. Bookstaver PB, Harris J, Sides MB, Rudisill CN. Stability and compatibility of candidate antifungal lock solutions of micafungin (abstract 134). Presented at American College of Clinical Pharmacy 2010 Annual Meeting. Austin, Texas; 2010 Oct.
87. Bailey E, Berry N, Cheesbrough JS. Antimicrobial lock therapy for catheter-related bacteraemia among patients on maintenance haemodialysis. *J Antimicrob Chemother.* 2002; 50:615-7.
88. Raad I, Hachem R, Hanna HA et al. Role of ethylene diamine tetra-acetic acid (EDTA) in catheter lock solutions: EDTA enhances the antifungal activity of amphotericin B lipid complex against Candida embedded in biofilm. *Int J Antimicrob Agents*. 2008; 32:515-8.
89. Nweze EI, Ghannoum A, Chandra J et al. Development of a 96-well catheter-based microdilution method to test antifungal susceptibility of Candida biofilms. *J Antimicrob Chemother.* 2012; 67(1):149-53.
90. Uppuluri P, Srinivasan A, Ramasubramanian A et al. Effects of fluconazole, amphotericin B, and caspofungin on Candida albican biofilms under conditions of flow and on biofilm dispersion. *Antimicrob Agents Chemother.* 2011; 55(7):3591-3.
91. Takla TA, Zelenitsky SA, Vercaigne LM. Effect of ethanol/trisodium citrate lock on microorganisms causing hemodialysis catheter-related infections. *J Vasc Access.* 2007; 8:262-7.
92. Excelsior Medical. Excelsior Medical's New Catheter Lock Solution. Approved by Health Canada. www.excelsiormedical.com/pdfs/Health-Canada-2010.pdf (accessed 2012 July 7).
93. Rosenblatt J, Reitzel R, Dvorak T et al. Glyceryl Trinitrate Complements Citrate and Ethanol in Eradicating Biofilm Organisms: A Novel Antimicrobial Catheter Lock Solution. *Antimicrob Agents Chemother*. 2013 May 13. [Epub ahead of print]
94. Chambers ST, Peddle B, Pithie A. Ethanol disinfection of plasticadherent micro-organisms. *J Hosp Infect*. 2006; 63:193-6.
95. Mouw E, Chessman K, Lesher A et al. Use of an ethanol lock to prevent catheter-related infections in children with short bowel syndrome. *J Pediatr Surg*. 2008; 43(6):1025-9.
96. Slobbe L, Doorduijn JK, Lugtenburg PJ et al. Prevention of catheter-related bacteremia with a daily ethanol lock in patients with tunnelled catheters: a randomized, placebo-controlled trial. *PLoS One*. 2010; 5(5):e10840.
97. Filippi L, Pezzati M, Di Amario S et al. Fusidic acid and heparin lock solution for the prevention of catheter-related bloodstream infections in critically ill neonates: a retrospective study and a prospective, randomized trial. *Pediatr Crit Care Med*. 2007; 8(6):556-62.
98. Al Akhrass F, Al Wohoush I, Chaftari AM et al. *Rhodococcus* bacteremia in cancer patients is mostly catheter related and associated with biofilm formation. *PLoS One.* 2012; 7(3):e32945.
99. Sauer K, Steczko J, Ash SR. Effect of a solution containing citrate/Methylene Blue/parabens on Staphylococcus aureus bacteria and biofilm, and comparison with various heparin solutions. *J Antimicrob Chemother.* 2009; 63(5):937-45.
100. Steczko J, Ash SR, Nivens DE et al. Microbial inactivation properties of a new antimicrobial/antithrombotic catheter lock solution (citrate/methylene blue/parabens). *Nephrol Dial Transplant.* 2009; 24(6):1937-45.
101. Maki DG, Ash SR, Winger RK et al. A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: a multi-center, controlled, randomized trial. *Crit Care Med.* 2011; 39(4):613-20.
102. Filiopoulos V, Hadjiyannakos D, Koutis I et al. Approaches to prolong the use of uncuffed hemodialysis catheters: results of a randomized trial. *Am J Nephrol*. 2011; 33(3):260-8.
103. Allon M. Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. *Clin Infect Dis*. 2003; 36(12):1539-44.
104. Betjes MG, Van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. *Nephrol Dial Transplant.* 2004; 19(6):1546-51.
105. Simon A, Ammann R, Wiszniewsky G et al. Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. *BMC Infect Dis.* 2008; 8:102.
106. Solomon LR, Cheesbrough J, Ebah L et al. A randomized double-blid controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. *Am J Kidney Dis.* 2010; 55(6):1060-8.
107. Shah CB, Mittelman MW, Costerton JW et al. Antimicrobial activity of a novel catheter lock solution. *Antimicrob Agents Chemother.* 2002; 46(6):1674-9.
108. Zwiech R, Adelt M, Chrul S. A Taurolidine-Citrate-Heparin Lock Solution Effectively Eradicates Pathogens From the Catheter Biofilm in Hemodialysis Patients. *Am J Ther.* 2013 May 9. [Epub ahead of print]
109. TauroLock™. Available at: http://www.taurolock.com (accessed 2013 Apr 1).