Advances in Locking Solutions

The recent progress and current areas of study in catheter lock solutions.

BY STEPHEN R. ASH, MD, FACP

The practice of dialysis would not be possible today without tunneled central venous catheters for dialysis (CVCD). Through efforts such as Fistula First, the percentage of prevalent patients with fistulas has increased, and the percentage with grafts has decreased. However, the percentage of patients dialyzing with tunneled CVCD at 90 days after the start of dialysis has remained remarkably constant at about 50%.[1] Tunneled CVCD are often used to provide time to create a suitable fistula.

When we look at CVCD, we see an effective method for withdrawing and returning blood to perform dialysis. What bacteria "see" is a highway to the bloodstream with nice places to settle down and raise a biofilm colony. Luminal contamination causes approximately 80% of catheter-related blood stream infections (CRBSI) in tunneled CVCD, usually through the establishment of biofilm, in which bacteria have a quiescent metabolism and resistance to antibiotics. The dynamics of catheter colonization are dramatic. By culturing blood that has been removed from the catheter or by brush culture, 3% to 5% of catheters are contaminated with *Staphylococcus epidermidis* by 6 weeks of use (Figure 1).[2] By tip culture, it has been shown that a much greater number of catheters are contaminated, indicating that tip cultures probably include organisms collected directly from the skin during catheter removal.

The standard practice for locking a catheter after its use is to infuse a volume of anticoagulant equal to the volume of the catheter. Several studies have demonstrated that patients receiving a heparin catheter lock after dialysis become systemically anticoagulated, with partial thromboplastin time values > 200 seconds, even if the volume of the lock infused is exactly the same as the catheter volume.[3] When fluid flows through a catheter lumen at a reasonable flow rate, the flow is laminar, and the profile of flow is parabolic. The fluid at the edges of the catheter remains stationary, and most of the flow passes through the center of the lumen. Therefore, the volume at which most of the fluid flows is less than the catheter volume.

Even in catheters without sideholes, 15% to 20% of the fluid injected into a catheter exits the tip when the injected volume equals the catheter fill volume.[4] In catheters with sideholes, another 10% or so of the lock solution will quickly convect out of the catheter due to blood flowing through the sideholes and tip. Further catheter lock loss is due to gravitational effects if the density of the lock solution is considerably different from blood.[5] The only way to prevent systemic anticoagulation of the patient during catheter lock with heparin is to underfill each catheter by 15% to 20%. Of course, this means that there is a lower concentration of heparin at

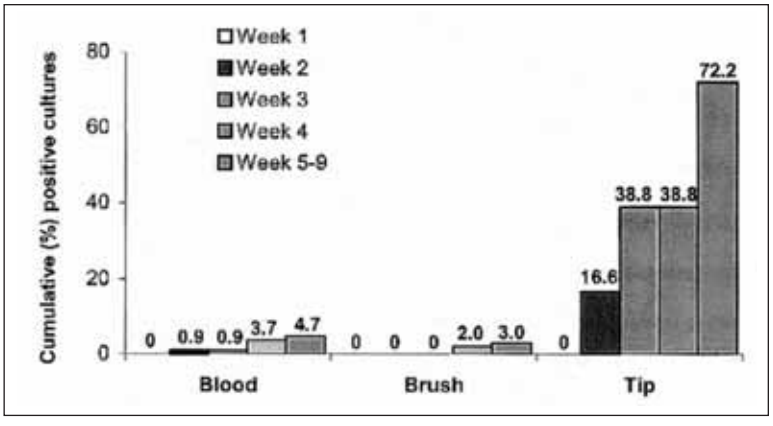

Figure 1. Dynamics of colonization with coagulase-negative staphylococci among 27 newly placed CVCD.

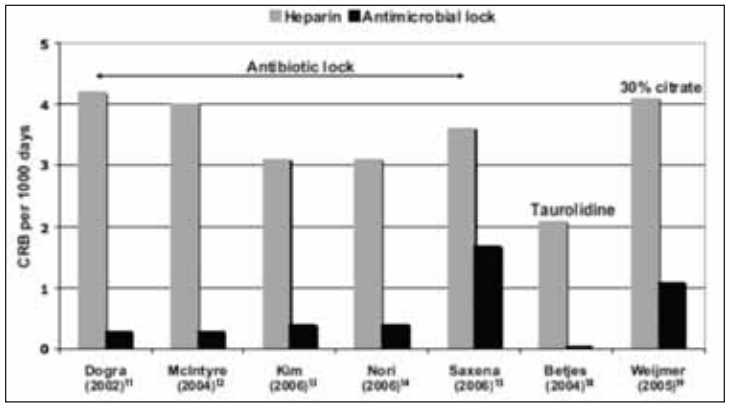

Figure 2. Summary of frequency of catheter-related bacteremia with antimicrobial locks versus heparin locks in published randomized clinical trials. Five trials used an antibiotic lock, one used taurolidine, and one used 30% citrate. In each study, the catheter-related bacteremia frequency was 50% to 100% lower in the group with antimicrobial lock as compared with the heparin controls.

the tip of the catheter than the concentration expected from the lock solution.

PREVIOUS STUDIES OF ANTIBACTERIAL CATHETER LOCK SOLUTIONS

A number of studies have shown that the longevity of tunneled CVCD is 40 weeks on average before serious complications prompt their removal.[6] Approximately three-quarters of the catheters are lost to infection at a rate of 10% per month. When there is clinical suspicion of bacteremia or proven positive blood cultures, it is likely that both the outside and the inside of the catheter is contaminated with bacteria. In order to salvage a catheter in the presence of bacteremia, it is necessary to expose all catheter surfaces to antibiotics or antiseptic solutions. If appropriate antibiotic locks are used, up to 70% of catheters may be salvaged, as shown in the study by Poole et al, which was also reviewed by Allon.[7,8]

Antibiotic or antiseptic catheter locks are also effective in preventing catheter infection. Recently, Snaterse and colleagues published a systemic review of randomized controlled trials of antibiotic-based catheter lock solutions.[9] Using a random effects model, they evaluated and compared the risk of CRBSI in 16 trials, nine of which were conducted in hemodialysis patients, six in oncology patients (mainly children), and one study on critically ill neonates. Antibiotic/citrate trials showed a statistically significant reduction in CRBSI as compared to heparin lock; however, results comparing antibiotic/ethylenediaminetetraacetic acid with heparin lock solution showed some advantage of the antibiotic/ethylenediaminetetraacetic acid lock solution but were statistically insignificant. The authors found that antibiotic-based lock solutions (compared to heparin) are effective in preventing CRBSI in hemodialysis patients but not in oncology patients. Three dialysis patients with tunneled CVCD needed prophylactic antibiotic/anticoagulant lock to prevent one infection per 5 months of catheter use, whereas nine cancer patients needed antibiotic/anticoagulant lock to prevent one infection for chronic infusion catheters per 7 months of catheter use. The authors did not recommend routine prophylactic use of antibiotic-based catheter lock solutions for either group due to the risks of antibiotic resistance and side effects of systemic antibiotic levels.

In a review of antibiotic and antiseptic catheter locks in tunneled CVCD, Jaffer et al demonstrated that in all studies, prophylactic use of antibacterial lock solution reduced the incidence of CRBSI by approximately 80% versus heparin.[10] There were varying definitions of CRBSI by the authors of these studies, but the conclusions were always consistent.

In an editorial accompanying these results, Dr. Allon reviewed Dr. Jaffer's article and presented these results graphically (Figure 2). The benefit of these locks in preventing CRBSI is even more apparent when presented graphically.[10]

BACTERIAL RESISTANCE WHEN USING ANTIBIOTIC CATHETER LOCK SOLUTIONS

Dr. Allon points out that of the antibacterial catheter locks that have been tested in randomized clinical trials,

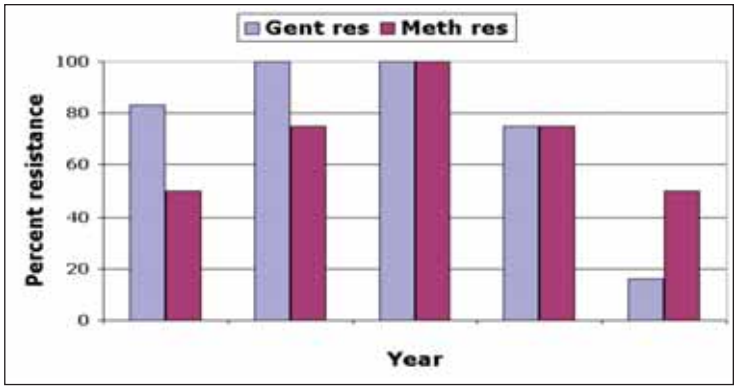

Figure 3. Percentage of isolates of *S. epidermidis* isolates resistant to gentamicin and methicillin after implementation of a gentamicin-containing catheter lock in a single dialysis unit (1-5 years).

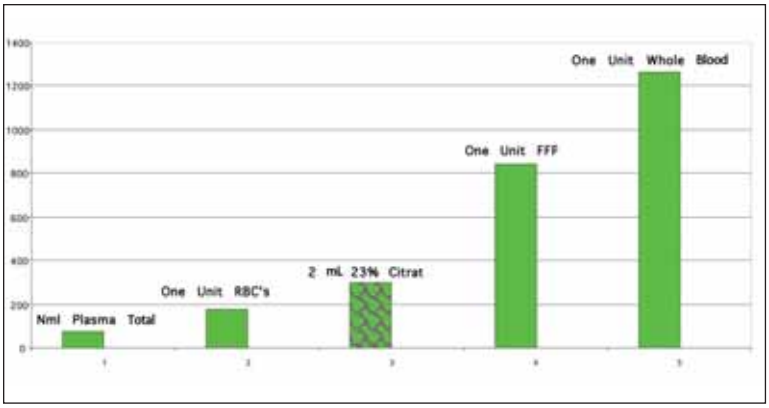

Figure 4. Comparative citrate content (in milligrams) in plasma, blood products, and 2 mL of 23% citrate as catheter lock. Abbreviations: RBCs, red blood cells; FFP, fresh frozen plasma.

all but two have included antibiotics.[11-15] Using antibiotics as prophylaxis for catheter infections is counter to the advice of most infectious disease experts. As Dr. Allon stated, "There is a very real concern that longer-term use of prophylactic antibiotics may result in selection for highly antibiotic-resistant micro-organisms and infections, since the development of resistant organisms is almost certain. A French dialysis unit routinely using prophylactic gentamicin locks in dialysis catheters obtained monthly cultures of the bacteria colonizing the catheter lumen.[16] After 2 years, 100% of the *S. epidermidis* isolates were resistant to gentamicin, methicillin, and quinolones. At that point, prophylactic antibiotic locks were discontinued. After an additional 2 years, only 50% of *S. epidermidis* isolates were resistant to methicillin, 16% were resistant to gentamicin, and 50% were resistant to quinolones." Figure 3 summarizes the results of the French study for one organism, *S. epidermidis*.

There are some studies that also show no development of resistance organisms in dialysis units using antibiotic prophylactic locks, as discussed by Dr. Jaffer. However, a recent report by Sweet et al described a 4-year period beginning in 2002 in which a gentamicin/heparin lock protocol was implemented in 1,488 chronic hemodialysis patients receiving dialysis through a tunneled CVCD.[17] Beginning 8 months after initiation of the gentamicin/heparin lock protocol, febrile incidents occurred in 17 patients with 26 episodes of coagulase-negative *S. aureus* that was resistant to gentamicin. During 4 years of gentamicin/heparin lock use, an additional eight patients developed 10 episodes of gentamicin-resistant CRBSI from which there was one death, two cases of septic shock requiring admission to the intensive care unit, and two cases of endocarditis. The use of antibiotic catheter lock was stopped after 4 years, in spite of the fact that it significantly reduced the incidence of CRBSI from 17 to 3.7 events per 1,000 patient days.

ANTISEPTIC CATHETER LOCK SOLUTIONS

Bacterial resistance is not a concern when using an antiseptic rather than antibiotic solution as a catheter lock, such as the taurolidine-citrate compound studied by Betjes[18] or the 30% citrate compound studied by Weijmer.[19] Antibiotics work at very low concentrations through specific biochemical mechanisms. Subtherapeutic antibiotic levels frequently induce resistant organism strains. Antiseptics work at higher concentrations through physical effects on the bacteria cell walls or cytoplasm. Subtherapeutic levels of antiseptics have no effect on microorganisms. However, antiseptic lock solutions are also relatively nonspecific and often have effects on bloodstream proteins and lipids, and they may have systemic effects. Studies of taurolidine have demonstrated an increased tendency toward the clotting of catheters in spite of the presence of 4% sodium citrate. This clotting is probably due to the protein denaturation that occurs with taurolidine.[24] Alcohol in high concentrations, such as 70%, also denatures proteins and may increase clotting tendency, but in lower concentrations of 30%, this is less of a problem because this concentration is compatible with 4% sodium citrate.[25,26] Currently, there is a randomized prospective trial in Australia comparing 70% alcohol with heparin as a catheter lock for tunneled CVCD but results are not yet available.[27]

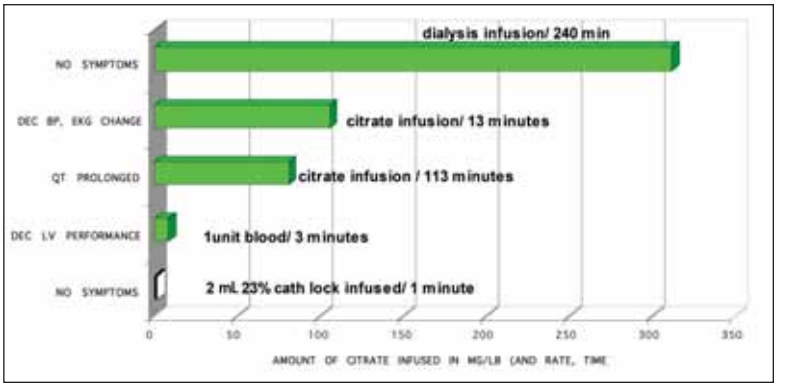

Figure 5. Human studies. Symptoms versus the amount and rate of citrate infusion without calcium reinfusion.[20-23]

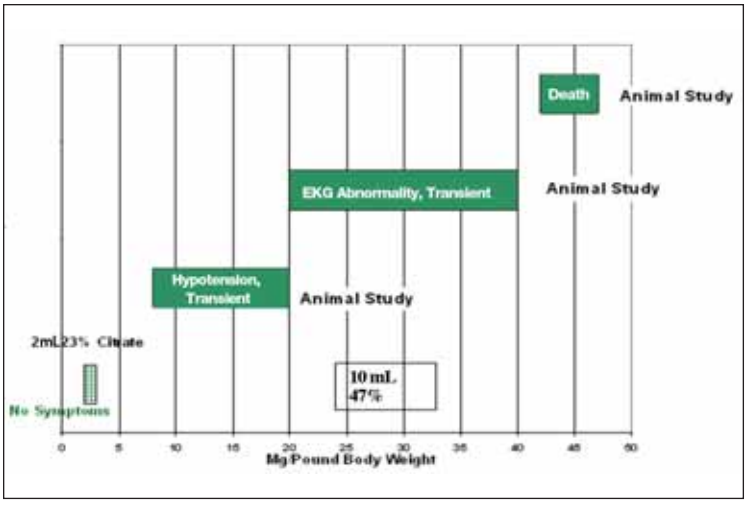

Figure 6. Animal study of safety of bolus intravenous citrate versus catheter lock amount.

SAFETY OF SODIUM CITRATE CATHETER LOCK SOLUTIONS

Because systemic hypocalcemia may occur with infusions of sodium citrate, what is the safety margin when using citrate as a catheter lock? How many times would the locking volume have to be injected to cause serious symptoms? Figure 4, from our article in 2000,[28] indicates the citrate content of normal plasma in the patient, of various solutions that are already frequently infused into our patients, and in 2 mL of 23% sodium citrate concentration.

The citrate content of the previously mentioned 23% solution would equal approximately that which is contained in 11 mL of 4% citrate. This is considerably less sodium citrate than in one unit of fresh frozen plasma. Fresh frozen plasma has been infused very rapidly into some patients, and studies have been done to indicate the limits for citrate infusion. Figure 5 shows the effects of very large amounts of citrate infusion during periods of 3 minutes to 6 hours. We include for comparison a slow infusion of 2 mL of 23% citrate, performed in volunteers and also by accidental infusion in some patients (which resulted in no cardiac abnormalities).

These studies still do not answer the question of what happens with rapid bolus infusion of citrate, but Figure 6 provides a compilation of data from several animal studies with a comparison of the amounts of citrate contained in 2 mL of 23% citrate and 10 mL of 47% citrate. As you can see, the rapid infusion of 10 mL of 47% sodium citrate into a patient equals an approximate dose of 25 to 30 mg/pound body weight and should result in transient electrocardiogram abnormalities but not immediate death. However, one such accidental infusion of 47% sodium citrate did result in cardiac arrhythmias. The death of this patient occurred several days later, apparently from complications of arrhythmia, leading the US Food and Drug Administration to publish a warning and to preclude 47% citrate as a catheter lock.[29] From the previous analysis, infusion of 2 mL of 23% sodium citrate should result in no cardiac symptoms or adverse consequences. However, as noted in our study and the one by Dr. Weijmer, when catheters are locked with 23% or 30% sodium citrate, some patients do complain of a metallic taste and tingling of the fingers or lips. These side effects are due to the appearance of sodium citrate in the blood stream. Sodium citrate solutions of 23% or 30% are considerably more dense than blood, and this causes some of the sodium citrate to fall out of the catheter immediately after the lock procedure.[5] These mild side effects are bothersome to some patients and are worrisome to the staff.

With the use of 4% sodium citrate as a catheter lock, there is a 50- to 100-fold margin of safety, and there are virtually no symptoms when catheters are locked appropriately. Several studies have demonstrated that 4% sodium citrate as a catheter lock maintains catheter patency at least as well as heparin. A study by Lok et al demon-

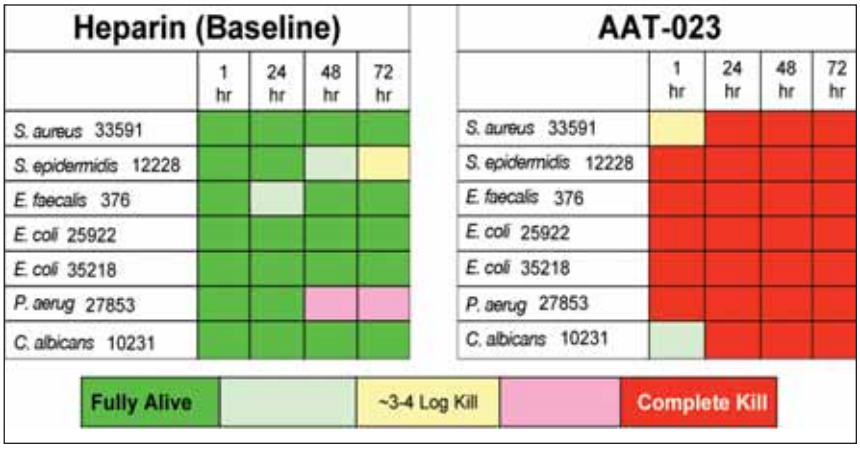

Figure 7. Comparison of antimicrobial effectiveness of heparin and Zuragen (Ash Access Technology, Inc., Lafayette, IN) for a variety of bacteria in medium-containing growth media and albumin. Exact strains of bacteria indicated by number.

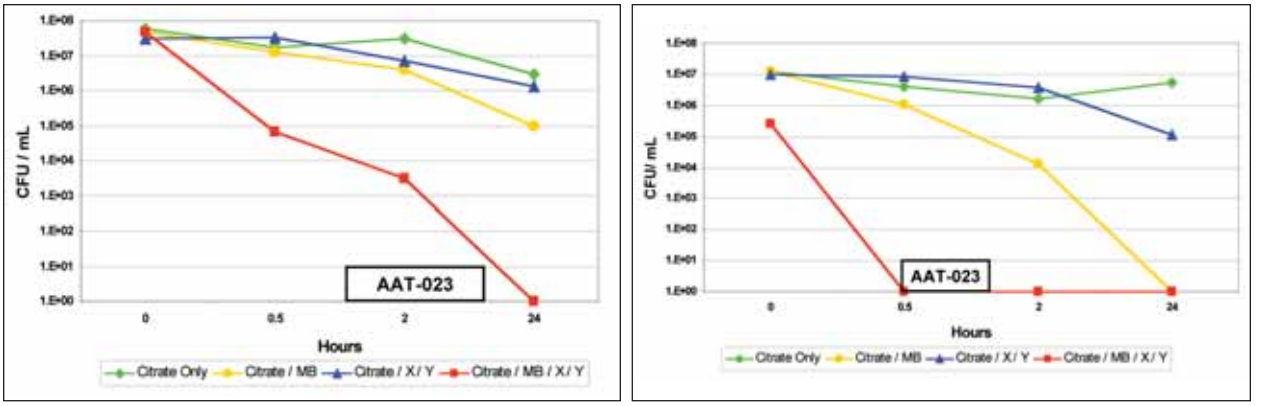

Figure 8. Antimicrobial effectiveness of Zuragen and its components versus *S. aureus* (left) and *E. coli* (right) in the presence of media and albumin.

strated that tunneled CVCD exchanges were 2.98 per 1,000 catheter days with heparin versus 1.65 per 1,000 patient days with citrate ($P = .01$).[30] The frequency of tissue plasminogen activator use was also higher in the heparin group versus the citrate group (5.49/1,000 patient days vs 3.3/1,000 patient days; $P = .002$). A study by Grudzinski et al compared dialysis patients in two periods of time and demonstrated that the rate of flow-related catheter exchange did not differ when using citrate versus heparin (1.81 vs 1.88 per 1,000 patient days; $P = .89$).[31] However, falsely elevated international normalized ratio values were eliminated with citrate. The frequency of use of tissue plasminogen activator was similar for groups using citrate versus heparin (4.1 vs 3.23 per 1,000 catheter days, respectively; $P = .07$).

In vitro studies in our laboratories and others have shown that 4% sodium citrate has almost no antibacterial effect. It is only when the concentration is higher, such as 10%, that the antiseptic effect is seen.[28] Not surprisingly, there are no data proving that 4% citrate is effective in preventing CRBSI when used as a catheter lock. In the Grudzinski study, the number of bacteremias was similar during the two periods (0.77 vs 0.94 per 1,000 catheter days, respectively; $P = .36$). A study by MacRae demonstrated 3.3 per 1,000 catheter days for heparin versus 2.2 per 1,000 catheter days for 4% citrate patients (not significant). As expected, there was a trend toward more systemic bleeds in the heparin patients as compared to the 4% citrate patients (11/29 [38%] vs 6/32 [19%]; $P = .09$).

The proper concentration of sodium citrate for locking catheters is actually 7%. This solution has a density of approximately 1.04, which is the same as blood density in a mildly anemic patient. Matching the density of the lock solution to blood will maintain the solution in the catheter considerably longer.[5] The higher citrate concentration should be somewhat more effective in preventing catheter clotting than 4% citrate and therefore be equal to or better than heparin. However, in order to obtain a catheter lock that is antibacterial, other components would be needed. In collaboration with other scientists and pharmacists, our company identified the following requirements for a desired antibacterial lock solution that could be used as a standard locking solution for central venous catheters:

- Anticoagulant properties comparable to heparin
- Components previously approved for intravenous administration and that are generally regarded as safe
- Lack of caustic effects and protein denaturation
- Safe for use prophylactically, with infusion of both lumen volumes
- Ability to physically remove biofilm, thus creating a cleaner catheter surface
- Ability to kill planktonic bacteria and fungal strains within 60 minutes
- Ability to kill sessile bacteria in biofilm
- No known bacterial resistance to components
- Not an antibiotic
- Relative density of 1.04
- Preferably has a color so that it is apparent when catheters are locked

CITRATE LOCK SOLUTION WITH SYNERGISTIC COMPONENTS

One catheter lock solution that fits these criteria is Zuragen, a combination of 7% sodium citrate (at neutral pH), 100 mg percent methylene blue, and 0.165% methyl- and propylparabens. Methylene blue is an antiseptic commonly included in suppressant medications for urinary infections. It is also used in topical antiviral therapy, especially when used in conjunction with light. As a "redox" compound, it removes and contributes electrons,

a function that partially accounts for its antibacterial effects (interfering with oxidative processes). Parabens are antiseptic compounds that affect permeability of the cell wall, changing the flux of potassium and water in the bacterium.

A number of in vitro studies have demonstrated that Zuragen (first called AAT-023) is rapidly bactericidal and fungicidal. In these studies, we exposed a wide variety of bacteria and fungus to Zuragen or heparin in the presence of small amounts of medium and albumin (to augment bacterial survival).[32] The results can be seen in Figure 7, where red indicates complete kill and green indicates growth of bacteria.

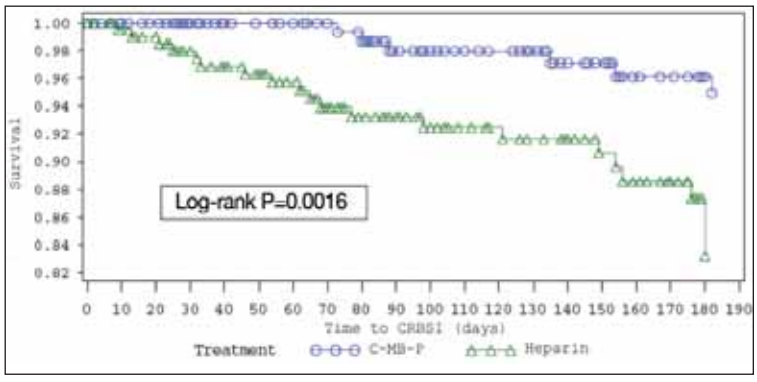

Figure 9. Kaplan-Meier graph comparing CRBSI-free survival of tunneled CVCD locked with Zuragen versus heparin.

In this test with augmentation of bacterial growth, heparin kills almost no planktonic organisms, while Zuragen kills all organisms, most within 1 hour of exposure. The various components of Zuragen are synergistic, as seen in the study of effects of various components on *S. aureus* and *E. coli* (Figure 8). In this study, bacterial growth is augmented both with albumin and with small amounts of medium. Within Zuragen, there is synergy between citrate, methylene blue, and parabens to rapidly kill bacteria.

In 7% sodium citrate only, there is a very slow killing rate for *S. aureus*. The addition of methylene blue augments the killing of citrate to some degree, as does the addition of components X and Y. However, when the same concentrations of methylene blue and X and Y are added together with citrate, the resulting Zuragen compound has a much greater bactericidal action. The reasons for this synergy are not entirely clear, but each component has a separate mechanism of action.

For an antibacterial catheter solution to prevent CRBSI, it is important to kill not only planktonic bacteria but also bacteria within the biofilm. Biofilm is a glycoprotein matrix that is partially deposited by plasma proteins and partially secreted by bacteria. Within biofilm, the metabolism of bacteria changes completely, and they become largely resistant to antibiotics.[33] Numerous tests have demonstrated that Zuragen not only kills all bacteria within growing and mature biofilms within 1 hour but also physically eliminates biofilm from polymer surfaces within 10 minutes.[34]

Ash Access Technology has completed a large, randomized, prospectively controlled trial to determine whether Zuragen will decrease the incidence of CRBSI in end-stage renal disease patients with tunneled CVCD for access. As reported at the American Society of Nephrology scientific sessions in 2009, the trial had the following features:[35]

- Prospectively randomized study in 26 centers for end-stage renal disease patients with tunneled CVCD
- 6 months of follow-up (mean, 3.7 months)
- Internal jugular tunneled CVCD of all types and ages, incident and prevalent
- Endpoints:
  - Incidence of CRBSI (defined as concordant bacterial culture from catheter and peripheral blood)
  - Incidence of catheter patency failure (defined as removal of the catheter for flow failure after demonstration of at least 20% decrease in blood flow measured at -200 mm Hg arterial pressure)

Final data collection in this trial was completed in June 2008. The trial had 407 participants (total, 49,565 catheter days), 206 in the heparin group and 201 in Zuragen group. Patients in the two groups were comparable for risk factors predisposing to CRBSI. Catheters locked with the Zuragen solution were significantly less likely to have CRBSI (0.24 vs 0.82 per 1,000 catheter days; risk ratio, 0.29; 95% confidence interval, 0.12–0.7; $P = .005$), and the time to CRBSI was significantly reduced (log-rank $P = .0016$). Also, catheters locked with the Zuragen solution were less likely to be lost due to patency failure (log-rank $P = .04$). Adverse events were few and transient with Zuragen. Figure 9 is a Kaplan-Meier graph comparing CRBSI-free survival of tunneled CVCD locked with Zuragen versus heparin. Due to careful adherence to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines for catheter access procedures, there was a low incidence of CRBSI in both the Zuragen and heparin arms. Zuragen is now under US Food and Drug Administration review for approval to market it as a catheter lock in tunneled CVCD.

CONCLUSION

The practice of dialysis will be greatly aided by an antibacterial catheter lock that can be used routinely in all

patients with tunneled CVCD. Although catheter access will still be less preferable than use of a fistula, at least the catheter will not create significant dangers of systemic infections if there is a catheter lock that maintains catheter patency while diminishing CRBSI, making it a safe access for use until the arteriovenous fistula has matured and allows suitable and safe dialysis access. ■

Stephen R. Ash, MD, FACP, is Chairman of the Board of Directors, Director of Research and Development at Ash Access Technology, Inc. in Lafayette, Indiana. He has disclosed that he has a patent or part ownership in and is an owner or shareholder of Ash Access Technology, Inc. Dr. Ash may be reached at sash@ashaccess.com.

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