

SUMMARY

[0012] ~~Embodiments of the present invention~~Examples described herein provide unique and effective microbial growth inhibiting solutions (e.g., locking solutions) that include effective amounts of a carboxylate antimicrobial agent, such as a C₄-C₉ carboxylate antimicrobial agent or antifungal agent, and a chelating agent. In a first aspect, the present invention refers to a microbial growth inhibiting solution comprising a C₄-C₉ carboxylate antimicrobial agent, a chelating agent and a buffer, wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL, and the buffer comprises citrate. ~~In one preferred embodiment~~example, the chelating agent is EDTA and the C₄-C₉ carboxylate antimicrobial agent is n-octanoic acid. In other embodiments, the microbial growth inhibiting solutions comprise a C₄-C₉ carboxylate antimicrobial agent and a chelating agent other than EDTA. A preferred combination includes a C₄-C₉ carboxylate antimicrobial agent and a calcium chelating agent, such as EGTA. Chelating agents that may be used in conjunction with the present invention include, but are not limited to, EDTA, EGTA, DTPA, dimercaptosuccinic acid ("DMSA"), deferoxamine, dimercaprol, triethylene tetramine dihydrochloride, zinc citrate, combination of bismuth and citrate, penicillamine, etidronate and pharmaceutically acceptable salts thereof. Preferred chelating agents include those that chelate divalent metal cations such as Ca, Mg, Mn, Fe and Zn.

[0013] It has been surprisingly found that a C₄-C₉ carboxylate antimicrobial agent in combination with a chelating agent present in an amount of about 2 mg/mL, 1 mg/mL or lower can effectively inhibit microbial or fungal growth in a catheter. In any of the ~~embodiments~~examples described herein, the microbial growth inhibiting solutions can include a combination of a chelating agent and a C₄-C₉ carboxylate antimicrobial agent, wherein the concentration of the chelating agent is present in an amount ranging from about 0.01 to about 2 mg/mL in the solution and the concentration of the antimicrobial agent is present in an amount ranging from about 0.05 mg/ml to about 5 mg/ml in the solution. In a preferred ~~embodiment~~example, the combination includes about 0.5 mg/ml of the chelating agent and about 1.15 mg/ml of the C₄-C₉ carboxylate antimicrobial agent.

[0014] Where n-octanoic acid is the antimicrobial agent of choice, it can be reconstituted to an appropriate concentration from a vial of n-octanoic acid and then

combined in the manner described herein to provide a solution with the concentration of n-octanoic acid desired according to methods well known to those of ordinary skill in the art of microbial growth inhibiting solutions. The carrier solution, by way of example, can comprise saline, phosphate buffered saline, dextrose in water, Ringer's solution or water pH adjusted to 5.2 or less.

[0015] In an ~~embodiment~~example, the microbial growth inhibiting solutions include a pharmacologically acceptable carrier solution, such as water, Ringer's solution or saline pH adjusted to 5.2 or less. The microbial growth inhibiting solutions can have an in-use pH of about 6.0, or below, generally in the range of about 3.5 to about 5.8, or most preferably in the pH range of about 3.5 to about 5.2. Within this acidic pH range, proper concentrations of the carboxylate compounds in the free acid form quickly and efficiently kill a wide variety of bacteria and fungi.

[0016] In an ~~embodiment~~example, the chelating agents provide potent glycocalyx inhibiting potential. In addition, C₄-C₉ carboxylate antimicrobial agents of the compositions, such as n-octanoic acid at high concentrations, preferably have a fungicidal effect and a unique ability to penetrate a polysaccharide-rich glycocalyx biofilm layer. The combination of the C₄-C₉ carboxylate antimicrobial agent and chelating agent can advantageously provide anticoagulant, glycocalyx inhibiting, antibacterial and antifungal agent for the prevention of thrombogenesis, microbial adherence and device-related infections. N-octanoic acid in combination with EDTA is one example of such a combination that may be preferred for use in a kit. Chelating agents other than EDTA that are desired include EGTA and DTPA.

[0017] In another ~~embodiment~~example, methods of using microbial growth inhibiting solutions including the chelating agent with the C₄-C₉ carboxylate antimicrobial agent in a variety of therapeutic applications are provided. One such therapeutic application is for preventing catheter infections. An example of a composition to be used in the practice of these methods comprises n-octanoic acid together with a chelating agent. EDTA is an example of a chelating agent contemplated for use in these methods; however, other chelating agents would also be expected to be useful.

[0017a)] In another aspect, the present invention refers to a method for coating a medical device, the method comprising:

exposing the medical device to a microbial growth inhibiting solution for a sufficient amount of time to provide a coating on the exposed surface of the device, wherein the microbial growth inhibiting solution comprises a C₄-C₉ carboxylate antimicrobial agent, a chelating agent and a buffer, wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate and is present in an amount ranging from about 0.05 mg/mL to about 5 mg/mL, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL, and the buffer comprises citrate.

[0017b)] In a further aspect, the present invention refers to a medical device coated with a microbial growth inhibiting solution comprising a C₄-C₉ carboxylate antimicrobial agent, a chelating agent and a buffer, wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate and is present in an amount ranging from about 0.05 mg/mL to about 5 mg/mL, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL, and the buffer comprises citrate.

[0018] For use in maintaining catheter patency, the microbial growth inhibiting solutions may be efficaciously used with medical devices such as a central venous catheter, a peripheral intravenous catheter, an arterial catheter, a Swan-Ganz catheter, a hemodialysis catheter, an umbilical catheter, a percutaneous nontunneled silicone catheter, a cuffed tunneled central venous catheter, as well as with a subcutaneous central venous port.

[0019] ~~Embodiments of the invention~~Examples described herein also provide medical devices, such as catheters, that are coated with any of the foregoing microbial growth inhibiting solutions. In one ~~preferred embodiment~~example, the microbial growth inhibiting solution comprises EDTA and n-octanoic acid. Where the chelating agent is other than EDTA, the microbial growth inhibiting solution in one example includes EGTA together with an antimicrobial agent such

as n-octanoic acid. Particular exemplary medical devices that may be prepared and coated with the solutions of the present invention are provided in the above list.

[0019a)] In another aspect, the present invention refers to the use of a C₄-C₉ carboxylate antimicrobial agent, a chelating agent and a buffer for the preparation of a microbial growth inhibiting solution for the locking and/or flushing a lumen of an implanted catheter from bacteria and fungi, wherein the lumen of the implanted catheter open to a body lumen, and wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate and is present in an amount ranging from about 0.05 mg/mL to about 5 mg/mL, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL, and the buffer comprises citrate.

[0020] ~~Embodiments of the present invention~~Examples described herein also provide processes for preparing coated medical devices with the compositions described herein. In an ~~embodiment~~example, a process comprises exposing the medical device to a microbial growth inhibiting solution including a chelating agent combined with a C₄-C₉ carboxylate antimicrobial agent for a sufficient amount of time to provide a coating on the exposed surface of the device. Where the microbial growth inhibiting solution is in a liquid form, it can be allowed to dry on the device surface to form a film.

[0021] In a ~~preferred embodiment~~an example of the above described processes, the device is first treated with a surfactant before exposing the device to the microbial growth inhibiting solution. Such surfactants, by way of example, include tridodecylmethyl ammonium chloride and benzalkonium chloride.

[0022] In another ~~aspect~~example, a catheter flushing solution is provided. Most preferably, the catheter flushing solution comprises a glycocalyx inhibiting concentration of a chelating agent and an effective amount of a C₄-C₉ carboxylate antimicrobial agent in a pharmaceutically acceptable carrier solution (e.g., saline pH adjusted to 5.2 or less).

[0023] In one ~~preferred embodiment~~example of the solution, the chelating agent is EGTA and the C₄-C₉ carboxylate antimicrobial agent is n-octanoic acid. Another ~~embodiment~~example of the catheter flushing solution includes about 0.5 mg/mL EDTA and about 1.15 mg/ml n-octanoic acid. By way of example, one carrier solution is saline, water, or a Ringer's solution pH adjusted to 5.2 or less. The catheter flushing solution may advantageously be used to inhibit the formation of polysaccharide-rich glycocalyx. In this manner, infections characterized by such a formation may be effectively eliminated.

[0024] Another ~~aspect of the present invention~~example provides a method of preparing a biofilm-resistant medical device. In one ~~embodiment~~example, the method comprises exposing a device with the microbial growth inhibiting solutions described herein. Any of a variety of catheters may be treated or coated according to the described method employing coating techniques well known to those of ordinary skill in the art.

[0025] While the method may be used to coat virtually any surface where glycocalyx formation is to be desirably inhibited, use of the method in preparing a microbial biofilm-resistant catheter device is particularly envisioned. By way of example, catheters that may be prepared and treated according to ~~embodiments of the invention~~examples disclosed herein include a central venous

catheter and a triple lumen catheter. It is anticipated that the method will provide a device resistant to polysaccharide-rich glycocalyx formation, such as that typical of *Staphylococci*.

[0026] In a ~~preferred aspect~~ one example of the described method, a biofilm-resistant medical device is prepared using a microbial growth inhibiting solution of a chelating agent and a C₄-C₉ carboxylate antimicrobial agent. An example of such solution comprises a combination of n-octanoic acid and EDTA, or a combination of a chelating agent other than EDTA together with a C₄-C₉ carboxylate antimicrobial agent. The various concentration ranges of the C₄-C₉ carboxylate antimicrobial agents and chelating agents described above are also contemplated as useful in the compositions for coating a medical device.

[0027] In one ~~aspect~~ example, the method comprises preparing a microbial growth inhibiting solution of the desired combination in a biocompatible adherent coating carrier solution. The surface of the medical device of interest is then exposed to the microbial growth inhibiting solution for a period of time sufficient to allow the formation of a film or coating of the solution on the surface of the device. This may be accomplished, for example, by dipping the device in the solution. Most preferably, the device to be coated is a catheter. Such treatment provides a biofilm-resistant catheter.

[0028] ~~Embodiments of the present invention~~ Examples disclosed herein also provide methods for inhibiting glycoprotein-rich glycocalyx formation at a catheter port. The method in one ~~embodiment~~ example comprises flushing the catheter periodically with a microbial growth inhibiting solution comprising a glycocalyx-inhibiting concentration of a chelating agent and a C₄-C₉ carboxylate antimicrobial agent in a pharmacologically acceptable carrier solution.

[0029] The described methods can be used to inhibit infection at virtually any tunneled or untunneled catheter. As part of a catheter maintenance regimen, the catheter most preferably is to be flushed with a composition comprising a C₄-C₉ carboxylate antimicrobial agent and a chelating agent in a pharmaceutically acceptable carrier solution. The described regimen is repeated once a week, once every 4 days, once every 2 days, once a day (about every 24 hours), twice a day, every four hours or as needed according to patient needs.

[0030] In still another ~~aspect, embodiments of the invention provide~~ example methods are provided for eliminating microbial glycocalyx formation, particularly polysaccharide-rich (*Staphylococcal*) glycocalyx formation, at a catheter lumen. The method, in one

~~embodiment~~example, comprises preparing a microbial growth inhibiting solution comprising a chelating agent (e.g., EDTA, EGTA, or both) together with a C₄-C₉ carboxylate antimicrobial agent (e.g., n-butyric, n-pentanoic, n-hexanoic, n-heptanoic, n-octanoic or n-nonanoic acids

and/or pharmaceutically acceptable salts thereof) in a carrier solution to provide a flushing composition, and flushing the catheter with an amount effective to inhibit microbial growth of the flushing composition.

[0031] Most preferably, the catheter will be flushed with a volume of about 3 mL of the described n-octanoic acid and EDTA solution containing about 0.5 mg/mL EDTA and about 1.15 mg/ml n-octanoic acid. The catheter can be flushed periodically at intervals of once a week, once every 4 days, once every 2 days, once a day, twice a day, every four hours, or as needed according to patient needs with about 2-3 mL of the n-octanoic acid and EDTA solution. The catheter flushing regimen may simply constitute once every time that the catheter is used or changed. In ~~a preferred aspect~~ one example of the method, the catheter is to be flushed at 4 hour intervals with the herein described solutions.

[0032] The compositions describe herein preferably remain therapeutically effective for use as a catheter-flushing agent after storage at a refrigerated temperature. However, the n-octanoic acid and EDTA solution should be brought to room temperature before use on an animal or patient.

[0033] The present invention in still another aspect provides a kit. Thus, in one aspect, the present invention provides a kit for locking and/or flushing an implanted catheter, the kit comprising: a container holding a volume of a microbial growth inhibiting solution comprising a C₄-C₉ carboxylate antimicrobial agent, a chelating agent and a buffer, wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate and is present in an amount ranging from about 0.05 mg/mL to about 5 mg/mL, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL, and the buffer comprises citrate; and an implantable catheter lumen that receives the microbial growth inhibiting solution. In still another aspect, the present invention refers to a kit for locking and/or flushing an implanted catheter, the kit comprising: a container having a first compartment holding a C₄-C₉ carboxylate antimicrobial agent and a chelating agent in powder form and a second compartment holding a pharmacologically acceptable carrier solution, wherein the C₄-C₉ carboxylate antimicrobial agent comprises sodium caprylate and is present in an amount ranging from about 0.05 mg/mL to about 5 mg/mL, the chelating agent comprises disodium ethylenediaminetetraacetic acid and is present in an amount ranging from about 0.01 mg/mL to about 2 mg/mL when mixed with the pharmacologically acceptable carrier solution, and

wherein the first or second compartment further comprises a buffer comprising citrate. In one ~~embodiment~~example, the kit comprises a container, such as a syringe, holding a volume of one of the foregoing solutions containing a C₄-C₉ carboxylate antimicrobial agent and a chelating agent and an implantable catheter lumen to receive the solution. The kit may further comprise a package, such as a box, tray, tube, envelope, pouch, or the like, for holding the container. The volume of the solution in the container is typically in the range from 1 mL-20 mL, preferably from 2 mL-10 mL, usually being about 2 mL-4 mL. Optionally, the container will usually comprise a syringe, or device to permit direct introduction of the solution into the indwelling catheter.

[0034] In another ~~embodiment~~example, the kit comprises a container, such as a compartmentalized syringe, that comprises a plurality of compartments. For example, the container can have three compartments, where one compartment comprises a C₄-C₉ carboxylate antimicrobial agent, such as n-octanoic acid; the second compartment comprises a chelating agent, such as EDTA; and the third compartment comprises a diluent, such as saline, Ringer's solution, or water pH adjusted to 5.2 or less. Kits that include a carrier adapted to receive at least two compartments constitute still another embodiment of the kit. In these embodiments, the chelating agent would be included together with the C₄-C₉ carboxylate antimicrobial agent within a compartment of the container. The second compartment would comprise a diluent, such as the ones described above. In an

~~embodiment~~example, the chelating agent and antimicrobial agent are included together in a first compartment of the device in dry powder form. The dry components would preferably be combined with the diluent of a second compartment to provide a solution suitable for use.

[0035] In these various ~~embodiments~~examples, the kit preferably includes a chelating agent. In ~~particular embodiment~~some example, the chelating agent is EDTA, and the C₄-C₉ carboxylate antimicrobial agent is, by way of example, n-octanoic acid.

[0036] In yet another ~~aspect of the present invention~~example, a method for disinfecting an implanted catheter is provided that includes introducing a solution comprising a C₄-C₉ carboxylate antimicrobial agent and a chelating agent in a pharmaceutically acceptable carrier solution into a lumen of a catheter where at least a portion of the catheter is sufficiently porous to permit diffusion of the solution outwardly from the lumen to the outer surface of the catheter and into the tissues or the bloodstream surrounding the catheter to inhibit infection. The implanted catheter may be a subcutaneous or transcutaneous indwelling catheter.

[0037] The ability to inhibit or prevent infection of the implanted catheter can be improved by utilizing catheters where at least a portion of the catheter body is sufficiently porous to allow the antimicrobial locking solution to permeate the catheter body and, preferably, pass outwardly (i.e., seep, ooze, leak, diffuse) into the tissue region surrounding the catheter. While the use of such porous or partially porous catheter bodies can be beneficial with many antimicrobial locking solutions, such as those taught in U.S. Patent Nos. 4,186,745; 4,767,400; 4,968,306; 5,077,281; 5,913,856; 6,949,087; 7,004,923; and U.S. Patent Publication Nos. 2006/0074388 and 2006/0253101, it is particularly useful with the ~~acids of the present invention~~disclosed herein. It will be appreciated that C₄-C₉ carboxylate antimicrobial agents have molecular weights and other qualities that enable them to readily penetrate into and through many porous materials. Exemplary porous materials for construction of the catheter body include silicone rubber, expanded PTFE (e.g., GORE-TEX[®], medical membranes), TEFLON[®] films, natural, regenerated or semi-synthetic cellulosic materials such as cellulose acetate, cellulose diacetate, cuprophane, and the like. Such materials may be formed into the tubular catheter bodies or may be incorporated as separate component(s) into the catheter bodies.

[0038] The described microbial growth inhibiting solutions are expected to be effective in preventing the adherence and colonization of catheter surfaces by *S. aureus*, *S.*

epidermidis, and fungi, as well as effective in both treating and eliminating already formed glycocalyx formations of these infectious organisms.

[0039] It is contemplated that whenever appropriate, any embodiment ~~of the present invention~~example can be combined with one or more other embodiments ~~of the present invention~~example, even though the embodiments examples are described under different aspects or embodiments ~~of the present invention~~examples. Additional features and advantages are described herein, and will be apparent from, the following Detailed Description and the figures.

BRIEF DESCRIPTION OF THE FIGURES

[0040] Figs. 1 A and 1B illustrate methods according to the present invention for locking and disinfecting a transcutaneous catheter.

[0041] Figs. 2A-2C illustrate methods according to the present invention for flushing, locking and disinfecting a subcutaneously implanted catheter.

[0042] Figs. 3A-3C illustrate methods according to the present invention for flushing, locking and disinfecting a peritoneal dialysis catheter.

[0043] Fig. 4 illustrates an embodiment of the present invention where an antimicrobial locking solution permeates into an implanted catheter body and preferably into the tissue surrounding the catheter body.

[0044] Fig. 5 illustrates a kit constructed in accordance with the principles of the present invention.

[0045] Fig. 6 shows a comparison of Na Octanoate/EDTA and Heparin by aPTT.

DETAILED DESCRIPTION

[0046] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present Specification will control.

[0047] Definitions

[0048] The terms below have the following meanings unless indicated otherwise.

[0049] The term “biofilm” as used herein refers to a polysaccharide-rich glycocalyx that typically accompanies microbial surface colonization.