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(57) Abstract: An antimicrobial composition comprising alexidine, a solvent, an optional carrier polymer and one or more excipient or additives is disclosed. The antimicrobial composition is used to provide antimicrobial properties to a surgical device during surgery and after surgery. The antimicrobial composition is also used to disinfect a surgical device or a surgical site.



DESCRIPTION

ANTIMICROBIAL COMPOSITIONS FOR SURGICAL APPLICATIONS

Technical Field

[0001] The present disclosure relates generally to antimicrobial compositions and methods of disinfecting, and more particularly to antimicrobial compositions containing alexidine to disinfect surgical devices, surgical sites of patients and a method to manufacture surgical devices with self-disinfecting properties.

Background

[0002] Pre-surgical preparation of the skin with a topical antimicrobial agent is necessary to reduce the likelihood that the patient will contract a hospital-acquired infection during a surgical procedure or post-surgical intervention and maintenance. Typically, the healthcare practitioners, for example, prep nurses, apply a topical antimicrobial agent to a surgical site before the surgical procedure. Similarly, it is essential that surgical instruments (i.e., retractors, forceps, surgical racks, scalpels, surgical knives, scissors, etc.) that breach the skin be disinfected prior to penetrating the skin at the surgical site or accessing an intravenous system. Healthcare practitioners typically sterilize these instruments using heat, gas or gamma radiation sterilization methods well known in the art. Alternatively, where such sterilizing techniques are not available, they may disinfect these instruments by applying or submerging the instruments in an antimicrobial solution, e.g., alcohol, prior to use. Such treatment reduces the infection rate at the site or within the blood stream by hindering the growth of microorganisms or disinfecting a wound, surgical incision, or needle puncture site.

[0003] Potential pathogens usually cannot enter the body if the skin and acid mantle remain intact. However, the integrity of the skin barrier is breached during surgical procedures, potentially exposing the surgical site or wound to microorganisms and increasing a patient's risk of infection. Thus, standard surgical procedures require that the skin at the surgical site be disinfected prior to surgery to reduce the patient's risk of infection. It is also required that post-surgery the wound site is kept infection free. Therefore, there is a need in the art for a topical agent that will both kill the transient and resident microorganisms quickly and provide sustained antimicrobial activity throughout the entire surgery or surgical procedure, and even post-surgery.

[0004] Furthermore, surgical devices are often implanted in a patient's body where they remain in place for hours and even several days post-surgery. The implantation of these surgical devices, however, poses an increased risk of infection to the patients. As a result, there is an overwhelming concern that these surgical devices are not only disinfected prior to surgery but are able to provide a sustained antimicrobial activity during surgery and after implantation. Therefore, surgical devices that have antimicrobial and self-disinfecting features are useful to prevent post-surgical infections, which can also aid in reducing inflammatory response and faster healing.

[0005] Many compositions have been developed for disinfecting surgical devices and surgical sites. For example, chlorhexidine is commonly used as an antimicrobial agent in many disinfecting solutions including topical skin disinfectants, wound closure systems and wound care products. Although chlorhexidine has been useful to some extent in disinfecting solutions for these applications, there are some serious drawbacks to chlorhexidine. For example, it is known that chlorhexidine has the ability to function as a sensitizing agent, and in rare cases it can trigger immediate hypersensitivity in the form of acute anaphylaxis. Another drawback is that chlorhexidine must be present in higher concentrations in order to function as a wide spectrum disinfectant. Higher concentrations of chlorhexidine may cause skin irritation or allergic reactions in some patients. Additionally, chlorhexidine may not be as effective against some microorganisms and/or may not kill microorganisms quickly. Therefore, there is an unmet need for an improved disinfecting solution having a higher level of antimicrobial activity and lower toxicity to the patient's tissue.

[0006] Alexidine is a disinfectant that is widely used as an antimicrobial in rinse solutions for oral and ophthalmic (for example, for contact lens cleaning and disinfecting) applications, and has been commercialized in various products, typically at levels of about 100 ppm or less for use with soft contact lenses. As an oral disinfectant, the typical concentration of alexidine is about 1%. Generally, it is desirable to provide the lowest possible level of antimicrobial that is consistent with reliable disinfection in order to provide a generous margin for safety and comfort. To date, alexidine, has not been used as an antimicrobial agent to disinfect surgical devices or surgical sites, or to reduce site infection post-surgery.

[0007] Both alexidine and chlorhexidine are antimicrobial agents known as bis-biguanides. Both antimicrobial agents possess the biguanide and the hexamethylene

structures. Alexidine however, differs from chlorhexidine by possessing ethyl-hexyl end groups instead of chlorophenyl end groups. Due to this structural difference, alexidine is shown to produce lipid phase separation and domains in the cytoplasmic membrane of microbes. The domain formation in the microbial membrane allows alexidine to cause significantly faster alteration in membrane permeability leading to more rapid bactericidal effect as compared to chlorhexidine. The rapid microbial action of alexidine makes it especially beneficial in a skin disinfectant composition which may be utilized in situations requiring quick disinfection (i.e., skin preparation prior to an emergency trauma surgery), as well as in providing long term antimicrobial protection post-surgery. Alexidine is also shown to promote apoptosis as an anti-cancer agent and possess anti-inflammatory and anti-diabetic properties which can aid in rapid wound healing. Furthermore, Alexidine is also shown to have significantly lower risk of causing IgE (Immunoglobulin E) mediated hypersensitivity as compared to chlorhexidine.

[0008] Accordingly, the antimicrobial compositions and methods disclosed herein are directed at overcoming one or more of the disadvantages in currently available antimicrobial compositions for surgical sites and surgical devices by using alexidine.

Summary

[0009] In accordance with one aspect of the disclosure, an antimicrobial composition used to disinfect a surgical device or a surgical site is disclosed. The antimicrobial composition includes alexidine, a solvent, an optional carrier polymer and one or more excipients or additives. The antimicrobial composition may be used as a surface application on a surgical instrument or a surgical device when applicable.

[0010] In accordance with another aspect of the disclosure, a method of disinfecting a surgical device is disclosed. The method includes applying an antimicrobial composition to at least a portion of the surgical device and drying the surgical device. The antimicrobial composition includes alexidine, a solvent, an optional carrier polymer, and one or more excipients or additives.

[0011] In accordance with another aspect of the disclosure, a method of coating a surgical device to provide it with antimicrobial properties is disclosed. The method includes applying an antimicrobial composition with alexidine to at least a portion of the surgical

device and drying the surgical device. The antimicrobial composition includes alexidine, a solvent, an optional carrier polymer, and one or more excipients or additives.

Brief Description of the Figures

[0012] FIG. 1 shows photographic images of the zone of inhibition results on day 1 obtained in the zone of inhibition assay using *Staphylococcus aureus* for the antimicrobial sutures in Example 4 according an aspect of the disclosure.

[0013] FIG. 2 shows photographic images of the zone of inhibition results on day 7 obtained in the zone of inhibition assay using *Staphylococcus aureus* for the antimicrobial sutures in Example 4 according an aspect of the disclosure.

Detailed Description

[0014] Before the present methods and devices are disclosed and described, it is to be understood that the methods and devices are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0015] As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

[0016] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0017] Throughout the description and claims of this specification, the word “comprise” and variations of the word, such as “comprising” and “comprises,” means “including but not limited to,” and is not intended to exclude, for example, other additives, components, integers or steps. “Exemplary” means “an example of” and is not intended to convey an indication of a preferred or ideal embodiment. “Such as” is not used in a restrictive sense, but for explanatory purposes.

[0018] As used herein, the term “alexidine” includes alexidine, alexidine base, alexidine hydrochloride, alexidine dihydrochloride, alexidine monoacetate, alexidine diacetate, alexidine gluconate, alexidine digluconate and mixtures thereof. In general, the alexidine used in the antimicrobial composition may be prepared by any of the processes known in the art for manufacturing alexidine.

[0019] As used herein, the term or phrase “disinfect” or “disinfecting” may, in one aspect, refer to, without limitation, the destruction and removal of viable microorganisms from a material including the spores of the microorganisms. The terms “disinfect” and “disinfecting” may, also without limitation, refer to a reduction of viable microorganisms and their spores and does not necessarily imply the complete removal of all viable microorganisms and their spores.

[0020] As used herein, the term or phrase “antimicrobial agent” may, in one aspect, refer to, without limitation, agent(s) that are responsible for, or cause the destruction and removal of viable microorganisms from a material including the spores of the microorganisms. The antimicrobial agent may, also without limitation, refer to agents that effect a reduction of viable microorganisms and their spores and does not necessarily imply the complete removal of all viable microorganisms and their spores.

[0021] As used herein, the term “surgical device” as used herein is intended to broadly mean any implement or instrument used during surgery either to shape, cut or form tissue or bone, or implanted or otherwise remain within tissue or bone. Examples of surgical instruments for use in the present disclosure include various forceps, occluders, dilators, trocars, retractors, hemostats, sutures, tissue clamps, and needle holders. Surgical instruments may also include a drill, reamer, implant, bone plate, scalpel, screws, etc.

[0022] As used herein, the term “excipient” refers to a non-therapeutic agent added to the antimicrobial composition for purposes of providing stability to the composition and/or achieving the desired rheological properties. Examples of excipients for use in the present

disclosure include binders such as various synthetic polymers, proteins, starches, cellulose, or preservatives.

[0023] As used herein, the term “additive” refers to a non-therapeutic agent added to the antimicrobial composition for purposes of providing modified coating properties and/or controlled and extended delivery of a therapeutic agent. Examples of additives for use in the present disclosure include a solvent such as ethyl acetate or an antioxidant such as Irganox[®] E 201 (Vitamin E).

[0024] As used herein, the term “hypoallergenic” refers to a reduced allergic reaction or a reduced tendency to trigger hypersensitivity responses to allergens and may be mediated by IgE (Immunoglobulin E) antibodies.

[0025] As used herein, the term “vitamin E” includes alpha, beta, gamma, and delta-tocopherols and their derivatives and conjugates. Vitamin E may include a combination of alpha, beta, gamma, and delta-tocopherols and their derivatives and conjugates.

[0026] As used herein, the term “implantable” refers to a surgical device to be positioned partially or wholly at a location within a body, such as within a body vessel. Additionally, the terms “implantation” and “implanted” refer to the positioning of a surgical device at a location, partially or wholly, within a body, such as within a body vessel or muscle.

[0027] As used herein, the term or phrase “surgical site” may, in one aspect, refer to, without limitation, the exact location where a surgical procedure is to be performed on a surgical patient. Alternatively, the term “surgical site” may, without limitation, refer to a predetermined location on a surgical patient that is sufficiently near or in close proximity to the exact location of a surgical procedure to be performed.

[0028] As used herein, the terms “minimum inhibitory concentration” and “MIC” are used interchangeably and refer to the minimum concentration of an antibacterial agent in a given culture medium below which bacterial growth is not inhibited.

[0029] As used herein, the terms “minimum bactericidal concentration” or “MBC” are used interchangeably and refer to the minimum concentration of an antibacterial agent in a given culture medium below which bacterial growth is not eliminated.

[0030] Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein,

for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

[0031] The present methods and devices may be understood more readily by reference to the following detailed description of preferred embodiments and the Examples included therein and to the Figures and their previous and following description.

[0032] Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[0033] The Antimicrobial Composition

[0034] The present disclosure makes use of alexidine in antimicrobial compositions for medical and non-medical applications. For example, the antimicrobial compositions disclosed herein may be used to disinfect surgical devices used in a surgical procedure. The antimicrobial compositions may also be used to provide surgical devices with self-disinfecting properties or to manufacture such devices with these properties. Additionally, the antimicrobial compositions may be used to disinfect a surgical site of a patient prior to surgery or to cleanse and disinfect skin generally.

[0035] In certain aspects of the disclosure, the antimicrobial composition may include alexidine, an excipient or an additive, a solvent and an optional carrier polymer. The antimicrobial composition may be in various forms depending on how the antimicrobial composition is used. In one aspect, these forms may include a solution, gel, suspension or solid dispersion.

[0036] The antimicrobial composition disclosed herein shows surprising and unexpected broad spectrum activity against various microorganisms. In particular, the antimicrobial effects obtained from antimicrobial compositions of the present disclosure, which include alexidine far exceed the results obtained from comparative antimicrobial compositions, which include chlorhexidine.

[0037] In one aspect, the antimicrobial composition has a broad spectrum antimicrobial effect against the gram positive bacteria, gram negative bacteria, and fungal pathogens responsible for infections. For example, the antimicrobial composition is effective against gram positive bacteria such as *Staphylococcus aureus*, gram negative bacteria such as

Pseudomonas aeruginosa or fungi such as *Candida albicans* to various extents. Therefore, methods of using the antimicrobial composition described herein may be provided for the prevention of infections caused by these microorganisms.

[0038] The antimicrobial composition may further include various therapeutic agents. In one aspect, the antimicrobial composition may promote wound healing. Wound healing may be achieved through alexidine alone or the incorporation of other suitable agents into the antimicrobial composition known in the art to promote wound healing. Additionally, the antimicrobial composition may also prevent the formation of a biofilm on the surface of the surgical device.

[0039] A surprising and unexpected finding of the antimicrobial composition disclosed herein is that it has been shown to be hypoallergenic, in particular as compared to antimicrobial compositions based on chlorhexidine. In another aspect, the antimicrobial composition may also be less likely to cause adverse reactions such as hypersensitivity and allergy. Methods and devices for the detection of allergic reactions and responses are described in U.S. Patent Application Publication No. 2014/0187892, the contents of which are incorporated herein by reference in their entirety. In certain aspects, the antimicrobial composition may also aid in reducing inflammatory responses such as erythema, phlebitis, and intimal hyperplasia.

[0040] Alexidine

[0041] The antimicrobial composition may include one or more of alexidine, alexidine base, alexidine hydrochloride, alexidine dihydrochloride, alexidine monoacetate, alexidine diacetate, alexidine gluconate, or alexidine digluconate. In general, the alexidine used in the antimicrobial composition may be prepared by any of the processes known in the art for manufacturing alexidine.

[0042] One advantage of the antimicrobial composition of the present disclosure is that a greater antimicrobial effect is achieved using a lower concentration of alexidine than other antimicrobial agents, such as chlorhexidine. In one aspect, the antimicrobial composition may have a concentration ranging from 0.0001 wt % to 4.0 wt % of alexidine. In another aspect, the antimicrobial composition may have a concentration ranging from 0.01 wt % to 2.0 wt % of alexidine. In another aspect, the antimicrobial composition may have a concentration of at least about 0.05 wt % of alexidine. The concentration of alexidine in the antimicrobial composition, however, is not limited in the present disclosure.

[0043] In certain aspects of the present disclosure, the antimicrobial composition may not include chlorhexidine, triclosan, or silver. For example, in some aspects alexidine may be the only antimicrobial agent present in the antimicrobial composition.

[0044] Excipient, Additive, Solvent

[0045] In certain aspects of the disclosure, the excipient used in the disinfecting and antimicrobial composition may include a common excipient or an additive such as sodium citrate, sodium chloride, sodium saccharin, phenoxyethanol, hydroxybenzonates, sulfobetaine, ethylene glycol, etc. Other suitable excipients and additives are also contemplated for use in the present disclosure. For example, in one aspect, the antimicrobial composition may include an antioxidant such as Vitamin E. Irganox[®] E 201 is an example of an antioxidant manufactured by BASF that may be useful in the antimicrobial composition.

[0046] Solvent used in the antimicrobial composition may include water, an organic solvent, or any combination thereof. Suitable organic solvents, for example, may include without limitation, alcohol, dimethyl formamide, tetrahydrofuran (THF), ethyl acetate, butyl acetate, acetone, methyl ethyl ketone (MEK), citric acid, or mixtures thereof. Other suitable organic solvents may include, without limitation, methanol, butanol, t-butanol, ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol, glycerin, and propylene glycol, etc.

[0047] In one aspect according to the disclosure, the solvent used in the antimicrobial composition is an alcohol, such as isopropanol, methanol or ethanol or mixtures thereof. More than one solvent may be used in the disinfecting or antimicrobial composition. For example, in certain aspects, the solvent may comprise tetrahydrofuran (THF) and methanol, THF and ethanol, or THF and isopropyl alcohol, or THF and citric acid, or THF and isopropyl alcohol and citric acid.

[0048] The Carrier Polymer

[0049] In one aspect of the disclosure, the antimicrobial composition includes a carrier polymer. The carrier polymer, however, is used more specifically as a part of antimicrobial coating solutions for surgical devices such as sutures. The carrier polymer generally includes a polymer that is soluble in the solvent and also soluble in alexidine. The carrier polymer may also be a biocompatible polymer that does not have any detrimental effect on the disinfecting and antimicrobial properties of alexidine. Furthermore, the carrier polymer may be a polymer that does not adversely affect the integrity of the surgical device in any manner. Suitable carrier polymers include without limitation, polyurethane, polypropylene, polyester,

cellulose, poly(methyl methacrylate), acrylate, or combinations, thereof. In one aspect of the present disclosure, the carrier polymer is polyurethane.

[0050] Surgical Devices

[0051] The disinfecting and antimicrobial composition may be used to disinfect a variety of surgical devices known in the art. The surgical devices may be any implement or instrument used during surgery either to shape, cut or form tissue or bone, or implanted or otherwise remain within tissue or bone. Examples of surgical devices for use in the present disclosure include various retractors, hemostats, tissue clamps, and needle holders. Surgical devices may also include a drill, reamer, implant, bone plate, scalpel, screws, sutures, etc.

[0052] Surgical devices contemplated by the present disclosure may also include any endoscopic surgical instruments including, but not limited to, laparoscopic or arthroscopic instruments. The surgical device may be any tool routinely used in endoscopic surgery, including, for example, tissue forceps, hemostats, retractors, clamps, scissors, needle holders and drivers, and cautery tools.

[0053] In certain aspects of the disclosure, the surgical device may include without limitation a wound closure system, including sutures, staples, ligation systems and other similar devices; surgical instruments including sutures, hooks, grasper, retractor, positioner, clamp, holder, claspers and other similar instruments; catheters and tubes such as a peritoneal catheter, hydrocephalus shunt catheter, chest drainage tube, and similar devices. The surgical device may also in certain aspects be an instrument such as a surgical retractor, forceps, surgical racks, bone hooks, scalpels, surgical knives, scissors, tracheal dilator, tracheal tubes, surgical probes, speculums, surgical depressors and dilators, syringes, spatulas, endoscopes, gloves or arthroscopes. Other surgical devices, however, are contemplated and the present disclosure is not limited in this regard.

[0054] The surgical device of some aspects may be, without limitation, a surgical screw of any variety, a spinal or other orthopedic plate, a surgical rod, an interbody spinal device, a vertebral disc arthroplasty device, a nucleus replacement device, a corpectomy device, a vertebrectomy device, a mesh device, a facet fixation or arthroplasty device, a structural bone graft, a staple, a tether of synthetic material or wire, or other spinal fixation instrumentation, an intramedullary nail, an external fixation device, a hip prosthesis or therapeutic device, a knee prosthesis or therapeutic device, or an instrument useful with any of the previously recited devices.

[0055] The surgical devices may also include neuromodulators including deep brain stimulators (DBS), various pain control devices, and lead systems for stimulation of the spinal cord, muscles, and other nerves of the body; implantable diagnostic devices for monitoring cardiac function; cochlear implants; and drug pumps for administering periodic or demand based pharmacological therapy. Surgical devices may also include gastric band systems, vascular access ports, injection ports, implantable cardioverter defibrillators, heart pacemaker, intra-uterine device, coronary stent, and tympanostomy tubes.

[0056] In certain aspects, the antimicrobial compositions of the present disclosure may be used to form a surgical device or a component of a surgical device. In one aspect, the antimicrobial composition may include a layer or a coating on a surface of a surgical device that is intended for contact with the body. In another aspect, the antimicrobial composition provides an antimicrobial effect to the surgical device and to the patient during surgery and after surgery.

[0057] Methods of Disinfecting Surgical Devices

[0058] In certain aspects of the present disclosure, a method of disinfecting a surgical device is provided. The method of disinfecting may include applying the antimicrobial composition to at least a portion of the surgical device and then drying the surgical device. In one aspect, the surgical device may be soaked in the antimicrobial composition for a period of time of about 5 seconds to about 5 minutes. In another aspect, the surgical device may be soaked in the disinfecting composition for a period of time of about 2 seconds to about 2 minutes. In certain aspects, the surgical device is soaked in the antimicrobial composition for at least 4 seconds. However, the surgical device may be soaked in the disinfecting composition for longer periods of time without adversely affecting the integrity of the surgical device. One advantage of the present disclosure is that the antimicrobial composition is a rapid disinfectant and therefore, does not require long periods of time to effectively disinfect the surgical device. This advantage is particularly valuable during surgical procedures where it is necessary to immediately facilitate sterilization and/or disinfection of the surgical device.

[0059] In certain aspects of the present disclosure, the surgical device may be dried at room temperature such that the solvent evaporates. In one aspect, the surgical device may be dried by removing the solvent from the antimicrobial composition. In another aspect, the solvent may be removed from the antimicrobial composition and an amount of alexidine may

remain on a surface of the surgical device. The remaining amount of alexidine on the surgical device may provide an antimicrobial effect to the surgical device, which will serve to further prevent infection during the surgical procedure and in some cases, after the surgical procedure.

[0060] The alexidine may remain on the surface of the surgical device in its free form. Alternatively, the alexidine may become embedded in the matrix of the carrier polymer, which may provide a longer term antimicrobial effect for the patient through the surgical device. In certain aspects of the disclosure, the antimicrobial composition may be infused, absorbed, penetrated, coated, adhered into or onto a surface of the surgical device.

[0061] The antimicrobial composition may be used to form an antimicrobial coating on the surgical device. The antimicrobial composition may be applied to the surgical device using any means known to those skilled in the art. For example, the surgical device may be soaked in the antimicrobial composition for a specified time period until a coating is formed. In one aspect of the present disclosure, the antimicrobial composition may be sprayed onto any of the surfaces of the surgical device. In other aspects, the surgical device may be dip coated in the antimicrobial composition. Alternatively, the antimicrobial composition may be brush coated, die coated, wiped, painted or rolled onto the surfaces of the surgical device. In yet other aspects, extrusion methods may be useful to form either an antimicrobial layer on the surgical device or for bulk distribution of alexidine in the device. Any of these techniques or methods of applying the antimicrobial composition may be used in combination and/or repeated multiple times to form the desired antimicrobial coating.

[0062] In one aspect, the antimicrobial composition may be a composition comprising an antimicrobial agent, an excipient or an additive, and a polymer, wherein the antimicrobial agent is alexidine and the antimicrobial composition is used to coat sutures including silk sutures, nylon sutures, polypropylene sutures, polyester sutures, polyglycolide or polyglycolic acid (PGA) sutures, poly(glycolide-co-(ε-caprolactone)) (PGCL) sutures, rapid polyglycolic acid (RPGA) sutures, and polydioxanone (PDA) sutures.

[0063] Surgical Sites

[0064] In certain aspects of the present disclosure, the antimicrobial composition disclosed herein may be used to disinfect the surgical site of a patient. The surgical site of the patient may include the outer skin surface, an open wound or a body cavity. The surgical

site may also include any internal tissue of the body. For example, muscle tissue, connective tissue, epithelial tissue and nervous tissue are all contemplated as being part of the surgical site. In some aspects, the antimicrobial composition may be used to disinfect a urinary bladder, genitourinary apparatus, intestine, peritoneal cavity, abdominal cavity, or similar space.

[0065] In one aspect, the antimicrobial composition may become infused, absorbed, penetrated, coated, and adhered into or onto the surgical site of the patient. In another aspect, the antimicrobial composition forms a film on the surface of the surgical site. For example, the antimicrobial composition may form an antimicrobial film on the surface of the patient's skin. This antimicrobial film may provide an additional safeguard against infection for the patient.

[0066] Methods of Disinfecting Surgical Sites

[0067] In certain aspects of the present disclosure, a method of disinfecting the surgical site of a patient is provided. The method of disinfecting the surgical site may include applying the antimicrobial composition to the surgical site and then drying the surgical site. In one aspect, the antimicrobial composition may be applied directly to the skin surface to disinfect the surgical site. Alternatively, an applicator may be used to topically apply the antimicrobial composition to the surgical site. Suitable applicators may include pre-soaked towels, sponges, swab sticks or cloths. These applicators may be composed of cotton, polytetrafluoroethylene (PTFE), cellulose, polyethelene, or polypropylene.

[0068] Application of the antimicrobial composition may occur either pre-operatively or post-operatively. After application, the surgical site may be air dried, evaporating the antimicrobial composition. In one aspect, an amount of alexidine remains on the surface of the surgical site and provides an antimicrobial effect to the surgical site.

[0069] In one aspect, a skin cleansing wipe moistened with an antimicrobial solution is disclosed. The antimicrobial solution comprises a solvent and an antimicrobial agent, wherein the antimicrobial agent is alexidine and the wipe is suitable to disinfect skin. The solvents disclosed herein may be used in the antimicrobial solution. In another aspect, the cleansing wipe is pre-moistened with the antimicrobial solution.

[0070] In one aspect, the antimicrobial composition may be an anesthetic gel composition comprising an antimicrobial agent and a gel-forming agent, wherein the antimicrobial agent is alexidine and the anaesthetic gel composition is used to introduce a catheter to a patient.

[0071] In certain aspects of the present disclosure, the antimicrobial composition may be used to prepare a patient for surgery by subjecting the patient to a bath of a solution of alexidine. The antimicrobial composition disclosed herein may also be a bath or shower additive, a liquid soap or a skin cleanser.

[0072] Surgical Scrub

[0073] In certain aspects of the present disclosure, the antimicrobial composition may be useful as a surgical scrub. The surgical scrub may be routinely used by surgeons, nurses and other hospital staff to scrub their hands and forearms prior to surgery. In one aspect, the surgical scrub may be used by a surgeon prior to gloving and gowning. The surgical scrub may be in form of a liquid or foam soap. For example, surgical scrubs that are liquid or foam soaps may be used in conjunction with water to cleanse and disinfect the skin.

[0074] Dry sponges and scrub brushes may be used as tools to apply the surgical scrub and mechanically scrub the skin. Alternatively, in certain aspects of the present disclosure, the surgical scrub may be incorporated in the scrub brushes and sponges for convenience. For example, a sponge may be pre-soaked with the surgical scrub and a brush may pre-loaded with the surgical scrub. These pre-soaked or pre-loaded sponges or brushes may be pre-packaged in a sterile wrapper and may be disposable after use. The user of the pre-soaked or pre-loaded sponge or brush may use the brush or sponge to apply the surgical scrub directly to the skin. In some aspects, water may necessary to use the impregnated or pre-loaded sponges and brushes.

[0075] Typically, the antimicrobial composition used in a surgical scrub includes alexidine, suitable surfactants and solvents. The surfactant may be any surfactant known to be used in surgical scrubs. In one aspect, the surgical scrub may include more than one surfactant. Suitable surfactants should be compatible with alexidine and may include without limitation, polyethyleneglycol (PEG) esters of fatty acids, PEG ethers of lanolin and fatty acid amides. In another aspect, polyoxyethylene/polyoxypropylene block copolymers may be useful as a surfactant in the surgical scrub. Any of the carrier polymers disclosed herein may also be suitable for use in the surgical scrub.

[0076] In certain aspects, the solvent in the surgical scrub may be an alcohol such as isopropanol, or ethanol. Other solvents such as water or dimethylsulfoxide may also be used. In one aspect, the surgical scrub may include more than one solvent. The solvents previously disclosed herein for use in the antimicrobial composition are also suitable for use in the surgical scrub. Any alcohol used in the surgical scrub is typically present in lower concentrations to avoid skin dehydration. In one aspect, the surgical scrub of the present disclosure may be an effective disinfectant yet mild enough on the skin so that it may be used in ample amounts and repeatedly.

[0077] The surgical scrub may also include a foaming agent. Typical foaming agents may include amine foaming agents such as cetyldimethylamine oxide, lauryldimethylamine oxide, cetylmethylmyristylamine oxide and dimethylmyristylamine oxide. Other suitable foaming agents known in the art, however, may be used.

[0078] The surgical scrub may also include a moisturizer or an emollient to hydrate the skin. Suitable emollients may include without limitation, cetyl lactate, cyclomethicone, dimethicone, and oils. Additionally, the surgical scrub may include additives such as thickeners, emollients, fragrances, perfumes, coloring agents, and preservatives.

[0079] ABBREVIATIONS

[0080] The abbreviations used in the examples are as follows:

MBC	Minimum Bactericidal Concentration
MIC	Minimum Inhibitory Concentration
PGA	Polyglycolic acid
PGCL	Poly(glycolide-co-(εcaprolactone))
THF	Tetrahydrofuran
TNTC	Number of microbial colonies were Too Numerous To Count

[0081] EXAMPLES

[0082] Although the examples of the present invention will be set forth below, it will become apparent to anyone skilled in the art that the present invention is not limited by them

and that various alterations and modifications may be made within the scope of the appended claims.

[0083] EXAMPLE 1 - Composition of antimicrobial composition containing Chlorhexidine

[0084] An antimicrobial composition was prepared for application on a surgical device such as peritoneal catheter having the formulation shown in Table A.

TABLE A

Ingredients	Amount (%)
Chlorhexidine	2
Water	88
Ethylene glycol	10

[0085] EXAMPLE 2 - Composition of antimicrobial composition containing Alexidine

[0086] An antimicrobial composition was prepared for application on a surgical device such as a peritoneal catheter having the formulation shown in Table B.

TABLE B

Ingredients	Amount (%)
Alexidine	0.5
Water	89.5
Ethylene glycol	10

[0087] EXAMPLE 3 - Composition to make antimicrobial suture, dressing, drainage tube and similar devices

[0088] The representative antimicrobial sutures prepared with using three different types of base materials: PGA, polyester and PGCL. Each suture was then dip coated in a bath of the antimicrobial formulation shown in Table C for 30 seconds.

TABLE C

Ingredients	Amount (%)
Alexidine	2
Methanol	11.5

Ingredients	Amount (%)
THF	80
Polyether Urethane	5.5
Other (e.g. excipient and/or additive)	2

[0089] After the treatment with the above formulation, the sutures were dried and the alexidine content on the PGA, polyester and PGCL sutures was measured as 44.7 µg/cm, 51.8 µg/cm and 58.9 µg/cm respectively.

[0090] EXAMPLE 4 – Zone of inhibition testing of antimicrobial sutures

[0091] Half-centimeter segments from the antimicrobial PGA, polyester and PGCL sutures were applied on Müller-Hinton agar pre-swabbed with *Staphylococcus aureus*, and the agar plates were incubated at 37°C. Segments were transferred on fresh agar plates daily for 7 days.

[0092] The zones of inhibition on day 1 are shown in FIG. 1. The agar plates in the upper row in FIG. 1 show the zones of inhibition for the alexidine treated sutures. The first, second and third agar plates show the zones of inhibition for the alexidine treated polyester suture, the alexidine treated PGCL suture and the alexidine treated PGA suture. The agar plates in the lower row in FIG. 1 show the zones of inhibition for the untreated sutures. The first, second and third agar plates show the zones of inhibition for the untreated polyester suture, the untreated PGCL suture and the untreated PGA suture. As shown, all three of the alexidine treated sutures (polyester, PGCL, PGA) demonstrate excellent antimicrobial efficacy on day 1.

[0093] The zones of inhibition on day 7 are shown in FIG. 2. The agar plates in the upper row in FIG. 2 show the zones of inhibition for the alexidine treated sutures. The first, second and third agar plates in the upper row of FIG. 2 show the zones of inhibition for the alexidine treated polyester suture, the alexidine treated PGCL suture and the alexidine treated PGA suture. The agar plates in the lower row in FIG. 2 show the zones of inhibition for the untreated sutures. The first, second and third agar plates show the zones of inhibition for the untreated polyester suture, the untreated PGCL suture and the untreated PGA suture. As shown, all three of the alexidine treated sutures (polyester, PGCL, PGA) demonstrate excellent antimicrobial efficacy on day 7.

[0094] EXAMPLE 5 - Minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of Alexidine and Chlorhexidine.

[0095] Description of the Test Method Used:

[0096] From the stock solutions of the drugs Alexidine and Chlorhexidine, dilution series was prepared in the wells of a 96-well plate by performing 1:1 dilutions to cover a concentration range of 0 – 512ppm. Ten microliters from each of the drug concentration was mixed with 190μL of culture broth containing approximately 10^5 CFU/mL of bacteria or yeast species. The test plate was incubated for 18 -24 hours after which absorbance of each well was read at 670nm. The MIC value was the lowest concentration of the drug at which microbial growth was completely inhibited (with the absorbance reading at or below the reading of the drug control wells without any organisms). The wells containing growth should have had higher absorbance reading when compared to the drug control wells. After reading the absorbance for the MIC, 10μl of each test well was plated onto the surface of Dey Engley Neutralizing Agar (D/E agar) in 6 or 12 well microtiter plates to determine the MBC. The plates were incubated inverted at 37°C for 24-48 hours after which numbers of colonies were counted. The MBC value was the lowest concentration of the drug at which no growth was observed.

[0097] Test Results

The MIC and MBC results for Alexidine as compared to Chlorhexidine are shown in Tables D and E below. Both the MIC and MBC values for Alexidine were lower or similar to that of Chlorhexidine for most microorganisms tested indicating Alexidine as a much potent antimicrobial agent than Chlorhexidine.

TABLE D - MIC of Alexidine versus Chlorhexidine

Organism	MIC Alexidine ($\mu\text{g/mL}$)	MIC Chlorhexidine ($\mu\text{g/mL}$)
<i>Staphylococcus aureus</i>	0.5	0.5
<i>Candida albicans</i>	1	2
<i>Pseudomonas aeruginosa</i>	8	8
<i>Enterococcus faecalis</i>	0.5	2
<i>Acinetobacter baumannii</i>	0.5	16
<i>Enterobacter cloacae</i>	2	2
<i>Proteus mirabilis</i>	1	8

Table E - MBC of Alexidine versus Chlorhexidine

Organism	MBC Alexidine ($\mu\text{g/mL}$)	MBC Chlorhexidine ($\mu\text{g/mL}$)
<i>Staphylococcus aureus</i>	1	16
<i>Candida albicans</i>	1	4
<i>Pseudomonas aeruginosa</i>	128	64
<i>Enterococcus faecalis</i>	2	64
<i>Acinetobacter baumannii</i>	1	32
<i>Enterobacter cloacae</i>	2	32
<i>Proteus mirabilis</i>	2	8

[0098] **EXAMPLE 6** - Comparison of the Kill Time of Alexidine and Chlorhexidine

[0099] Description of the Test Method Used:

[00100] Alexidine and Chlorhexidine, both at a concentration of 128 ppm were exposed to a Gram positive bacteria (*Staphylococcus aureus*), a Gram negative bacteria (*Pseudomonas aeruginosa*), and a fungus (*Candida albicans*). The challenge concentration for each organism was $10^4 - 10^5$ CFU/mL, and the exposure time varied from 0.5 - 60 minutes. Table F below shows the Time to Kill results for both Alexidine and Chlorhexidine. Complete kill of all three organisms was observed within 0.5 -1 minute of Alexidine exposure. In contrast, with Chlorhexidine it took 60 minutes before complete kill was observed for *C. albicans* and *S. aureus*, and 5 minutes for *P. aeruginosa*.

[00101] Test Results:

TABLE F - Time to Kill Comparison for Alexidine versus Chlorhexidine

	Exposure Time (Minutes)							
	0.5	1	5	60	0.5	1	5	60
	Alexidine (128ppm)				Chlorhexidine (128 ppm)			
<i>Candida albicans</i>	Number of Microbial Colonies							
Replicate 1	3	0	0	0	TNTC	TNTC	30	0
Replicate 2	0	1	0	0	TNTC	TNTC	20	0
Replicate 3	0	0	0	0	TNTC	TNTC	32	0
Replicate 4	0	0	0	0	TNTC	TNTC	24	0
Replicate 5	0	0	0	0	TNTC	TNTC	TNTC	0
<i>Staphylococcus aureus</i>								
Replicate 1	0	0	0	0	TNTC	TNTC	TNTC	1
Replicate 2	0	0	0	0	TNTC	TNTC	TNTC	1
Replicate 3	0	0	0	0	TNTC	TNTC	TNTC	0
Replicate 4	0	0	0	0	TNTC	TNTC	TNTC	0
Replicate 5	0	0	0	0	TNTC	TNTC	TNTC	0
<i>Pseudomonas aeruginosa</i>								
Replicate 1	0	0	0	0	7	1	0	0
Replicate 2	0	0	0	0	4	1	0	0
Replicate 3	0	0	0	0	5	1	0	0
Replicate 4	0	0	0	0	2	1	0	0
Replicate 5	0	0	0	0	1	1	0	0

[00102] Safety Assessment:

[00103] The biocompatibility and toxicity of the antimicrobial compositions of Example 3 were assessed using the six tests described below. The test results show no adverse effects and demonstrate the safety and biocompatibility of surgical devices treated with alexidine. These results surprisingly further show that the antimicrobial composition is hypoallergenic.

[00104] EXAMPLE 7 - The Intracutaneous Injection Test (ISO) was performed. Test rabbits received an intracutaneous injection of the antimicrobial composition of Example 3. All test rabbits increased in body weight and showed no signs of toxicity at the 24 hour, 48 hour and 72 hour observation points.

[00105] EXAMPLE 8 - The Kligman Maximization Test (ISO) was performed. The skin of guinea pigs was treated with the test article extract and exhibited no reaction to the challenge (0% sensitization).

[00106] EXAMPLE 9 - A 28 day Systemic Toxicity via Intramuscular Implantation was performed. The test articles did not demonstrated any local or systemic signs of toxicity when test articles composed of the antimicrobial composition of Example 3 was implanted into the muscle tissue of five rats for 28 days.

[00107] EXAMPLE 10 - The Intramuscular Implantation Test (ISO) was performed. Macroscopic evaluation of the test article implantation site indicated no significant signs of

inflammation, encapsulation, hemorrhage, or necrosis. However, microscopic evaluation (histology) of these sites indicated moderate reactivity when compared to the control sites having no implantation.

[00108] EXAMPLE 11 - Intravascular implantation in a Sheep Model to determine safety and efficacy was performed. The test device composed of the antimicrobial composition disclosed in Example 3 was well tolerated. All test animals remained healthy for the entire 7 and 30 day study duration and no signs of organ toxicity were observed. Alexidine-treated device was highly effective in reducing colonization by *Staphylococcus aureus* (the challenge organism used to infect the implantation site) on the device and the vein tissue surrounding the device. As compared to the un-treated control device, Alexidine-treated device led to 7 to 8 Log₁₀ reduction in bacterial colonization on the device and the surrounding tissue. Alexidine-treated device also led to 99% reduction in weight and 92% reduction in length of the device-associated thrombus when compared to the un-treated control device. There was also significant reduction in inflammatory response from the alexidine treated device compared to the untreated device.

[00109] EXAMPLE 12 - The hemolytic index (HI) of the antimicrobial composition of Example 3 was also tested. The HI of the antimicrobial composition of Example 3 was shown to be comparable to chlorhexidine.

CLAIMS

We claim:

1. An antimicrobial composition comprising alexidine, a solvent, an optional carrier polymer, and one or more excipients or additives, wherein the antimicrobial composition is used to disinfect a surgical device or a surgical site.
2. An antimicrobial composition comprising alexidine, a solvent, an optional carrier polymer, and one or more excipients or additives, wherein the antimicrobial composition is used to provide antimicrobial properties to a surgical device during surgery and after surgery.
3. The antimicrobial composition of claims 1 or 2, wherein the solvent is selected from the group consisting of: water, an alcohol, dimethyl formamide, tetrahydrofuran, ethyl acetate, butyl acetate, acetone, methyl ethyl ketone (MEK) or mixtures thereof.
4. The antimicrobial composition of claim 3, wherein the alcohol is isopropanol, ethanol, or methanol.
5. The antimicrobial composition of any one of the preceding claims, wherein the excipient or the additive is selected from the groups consisting of: sodium citrate, sodium chloride, sodium saccharin, phenoxyethanol, hydroxybenzonates, sulfobetaine, and ethylene glycol.
6. The antimicrobial composition of any one of the preceding claims, wherein the excipient or the additive comprises an antioxidant.
7. The antimicrobial composition of claim 6, wherein the antioxidant comprises vitamin E.
8. The antimicrobial composition of any one of the preceding claims, wherein the composition has a concentration ranging from 0.0001 wt % to 4.0 wt% of alexidine.
9. The antimicrobial composition of any one of the preceding claims, wherein the carrier polymer comprises at least one of polyurethane, polypropylene, polyester, cellulose, poly(methyl methacrylate), acrylate, or mixtures thereof.

10. The antimicrobial composition of any one of the preceding claims, wherein the surgical device is selected from the group consisting of: wound closure system including sutures, staples, ligation systems and other similar devices; surgical instruments including hooks, grasper, retractor, positioner, clamp, holder, claspers and other similar instruments; catheters and tubes such as a peritoneal catheter, hydrocephalus shunt catheter, chest drainage tube, and similar devices.
11. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition has a broad spectrum antimicrobial effect against the gram positive bacteria, gram negative bacteria, and fungal pathogens responsible for surgical site infections.
12. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition has an antimicrobial effect on *Staphylococcus* species such *Staphylococcus aureus* and *Staphylococcus epidermidis*, *Candida* species, *Pseudomonas aeruginosa*, *Enterococcus* species, *Klebsiella* species such as *Klebsiella pneumoniae*, *Providencia stuartii*, *Proteus mirabilis*, *Enterobacter* species, *Acinetobacter* species, and *Escherichia coli*.
13. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition contains alexidine at a concentration above the minimum inhibitory concentration for *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Candida* species, *Pseudomonas aeruginosa*, *Enterococcus* species, *Klebsiella pneumoniae*, *Providencia stuartii*, *Proteus mirabilis*, *Enterobacter* species, *Acinetobacter* species, and *Escherichia coli*.
14. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition has a greater antimicrobial effect than a comparative antimicrobial composition comprising chlorhexidine as the antimicrobial agent.
15. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition has a much less potential to cause microbial resistance than a comparative antimicrobial composition comprising chlorhexidine as the antimicrobial agent.

16. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition is infused, absorbed, penetrated, coated, adhered into or onto a surface of the surgical device.
17. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition promotes wound healing.
18. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition aids in reducing inflammatory responses such as erythema, phlebitis, and intimal hyperplasia.
19. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition aids in reducing inflammatory responses such as erythema, phlebitis, and intimal hyperplasia.
20. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition has a much less potential to cause adverse reactions such as hypersensitivity and allergy than a comparative antimicrobial composition comprising chlorhexidine as the antimicrobial agent.
21. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition is hypoallergenic.
22. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition prevents the formation of a biofilm on the surface of the surgical device.
23. The antimicrobial composition of any of the preceding claims, wherein the surgical device is an instrument selected from one of: a surgical retractor, forceps, surgical racks, bone hooks, scalpels, surgical knives, scissors, tracheal dilator, tracheal tubes, surgical probes, speculums, surgical depressors and dilators, syringes, spatulas, endoscopes, gloves and arthroscopes.
24. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition is infused, absorbed, penetrated, coated, adhered into or onto the surgical site of the patient.

25. The antimicrobial composition of any one of the preceding claims, wherein the surgical site of the patient includes a skin surface, an open wound or body cavity.
26. The antimicrobial composition of any one of the preceding claims, wherein the surgical site of the patient includes internal tissue.
27. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition forms a film on the surface of the skin.
28. The antimicrobial composition of any one of the preceding claims, wherein the antimicrobial composition is used to prepare a bath for a patient in preparation for surgery.
29. A method of preparing a patient for surgery comprising subjecting the patient to a bath of a solution of alexidine.
30. The antimicrobial composition of claim 1, wherein the antimicrobial composition is a bath or shower additive, a liquid soap, a surgical scrub, or a skin cleanser.
31. A method of preparing an antimicrobial composition comprising: combining an antimicrobial agent with a solvent, wherein the antimicrobial agent is alexidine and the antimicrobial composition is used to disinfect a surgical site of a patient or a surgical device.
32. A method of disinfecting a surgical device comprising:

applying an antimicrobial composition to at least a portion of the surgical device; and

drying the surgical device, wherein the antimicrobial composition comprises alexidine, a solvent, an optional carrier polymer and one or more excipients or additives.
33. The method of claim 28, wherein the applying the antimicrobial composition to a surgical device includes soaking the surgical device in the antimicrobial composition for a period of time of about 5 seconds to about 5 minutes.

34. The method of claim 28, wherein the applying the antimicrobial composition to a surgical device includes soaking the surgical device in the antimicrobial composition for a period of time of about 2 seconds to about 2 minutes.
35. The method of claim 28, wherein the drying the surgical device includes evaporating the antimicrobial composition on the surgical device or removing the solvent in the antimicrobial composition, wherein an amount of alexidine remains on the surface of the surgical device and provides an antimicrobial effect to the surgical device.
36. The method of claim 28, wherein the drying the surgical device includes evaporating the antimicrobial composition on the surgical device or removing the solvent in the antimicrobial composition, wherein an amount of alexidine remains on the surface of the surgical device either in the free form or embedded in the matrix of the carrier polymer to provide long term antimicrobial effect from the surgical device.
37. A method of disinfecting a surgical site of a patient, the method comprising:
- applying an antimicrobial composition to the surgical site of the patient; and
- drying the surgical site of the patient, wherein the antimicrobial composition comprises alexidine and a solvent.
38. The method of claim 33, wherein the applying the disinfecting composition to the surgical site of the patient includes applying the disinfecting composition directly to the skin surface of the patient to disinfect the surgical site.
39. The method of claim 33, wherein the drying the surgical site includes evaporating the disinfecting composition on the surgical site or removing the solvent, wherein an amount of alexidine remains on the surface of the surgical site and provides an antimicrobial effect to the surgical site.
40. A skin cleansing wipe moistened with a disinfecting solution comprising a solvent and an antimicrobial agent, wherein the antimicrobial agent is alexidine and the wipe is suitable to disinfect skin.
41. A disinfecting composition comprising an antimicrobial agent and a solvent, wherein the antimicrobial agent includes alexidine and the disinfecting composition is used to

- disinfect a urinary bladder, genitourinary apparatus, intestine, peritoneal cavity, abdominal cavity, or similar space.
42. An anesthetic gel composition comprising an antimicrobial agent and a gel-forming agent, wherein the antimicrobial agent is alexidine and the anesthetic gel composition is used to introduce a catheter to a patient.
43. A kit for preparing a patient's skin for surgery, the kit comprising: a disinfecting solution and means for delivering the disinfecting solution to the patient's skin, wherein the disinfecting solution includes alexidine.
44. The kit of claim 39, wherein the means of delivering the solution to the patient's skin includes at least one of a pre-soaked towel, sponge, scrub, cloth or swab stick comprising: cotton, polytetrafluoroethylene (PTFE), cellulose, polyethelene, or polypropylene.
45. A surgical scrub comprising the antimicrobial composition of any of the preceding claims.
46. The surgical scrub of claim 41 further comprising a surfactant.
47. A sponge comprising the surgical scrub of claim 41, wherein the sponge is pre-soaked with the surgical scrub.
48. A scrub brush comprising the surgical scrub of claim 41, wherein the scrub brush is pre-loaded with the surgical scrub.
49. A method of forming an antimicrobial coating on a surgical device comprising: applying an antimicrobial composition to a surface of the surgical device, wherein the antimicrobial composition comprises alexidine, a solvent, an optional carrier polymer, and one or more excipients or additives.
50. The method of claim 44 wherein the applying comprises at least one of dip coating, soaking, rolling, brush coating, wiping, spraying, painting, die coating and extruding.

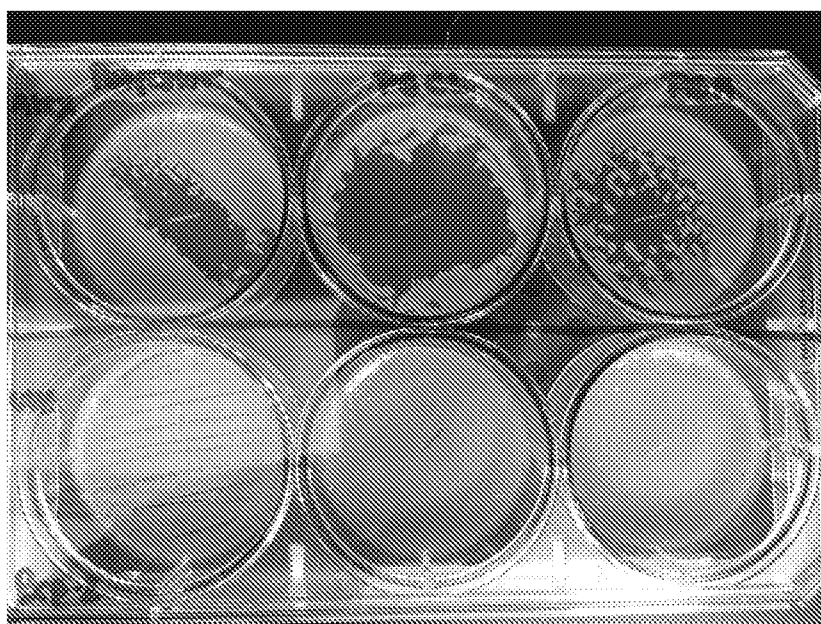


FIG. 1

2/2

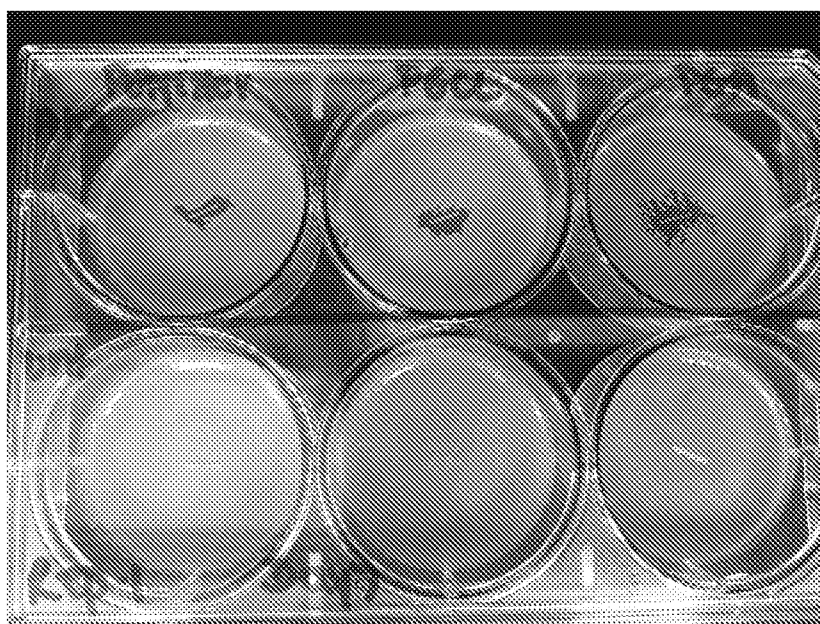


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/43543

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A01N 25/30, A01N 25/10, A61L 2/18 (2016.01)
 CPC - A61L 12/141, A61L 12/142

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC(8) - A01N 25/30, A01N 25/10, A61L 2/18 (2016.01)
 CPC - A61L 12/141, A61L 12/142

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC - 514/839, 514/840; Patents and non-patent literature (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PatBase, Google Scholar (non-patent literature), Google Patents; search terms: antimicrobial, alexidine, solvent, polymer, excipients, additives, surgical device, site

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 8,877,882 B1 (Salamone et al.) 04 November 2014 (04.11.2014), entire document, especially abstract, col 3 ln 47, col 4 ln 19-21, col 4 ln 33, col 6 ln 37, col 5 ln 33-35, col 7 ln 43-44	1-4, 32, 41, 43-44, 49-50 ----- 30, 42
Y	US 2002/0122831 A1 (Mowrey-McKee et al.) 5 September 2002 (05.09.2002), entire document, especially abstract, para [0030]	30
Y	US 2013/0150451 A1 (Salamone et al.) 13 June 2013 (13.06.2013), entire document, especially abstract, para [0026], [0106], [0107]	42
A	US 2010/0137472 A1 (Ou-Yang) 03 June 2010 (03.06.2010), entire document	1-4, 30, 32, 41-44, 49-50

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 November 2016

Date of mailing of the international search report

15 DEC 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/43543

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-28, 33-36, 38-39, 45-48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
---See Supplemental Box---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-4, 30, 32, 41-44 and 49-50
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/43543

Continuation of Box III: Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-4, 30, 41-44 directed an antimicrobial composition and kit comprising alexidine

Group II: Claim 29 and 37, directed to a method of preparing a patient for surgery comprising subjecting the patient to a bath of a solution of alexidine.

Group III: Claim 31, directed to a method of preparing an antimicrobial composition comprising alexidine

Group IV: Claims 32 and 49-50, directed to a method of disinfecting a surgical device comprising alexidine

Group V: Claim 40, directed to a skin cleansing wipe moistened with a disinfecting solution comprising alexidine.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group II requires method of preparing a patient for surgery comprising subjecting the patient to a bath of a solution of alexidine, not required by group I and III-V.

Group III requires a method of preparing an antimicrobial composition comprising alexidine, not required by group I-II and IV-V

Group IV requires A method of disinfecting a surgical device comprising alexidine, not required by group I-III and V

Group V requires a skin cleansing wipe moistened with a disinfecting solution comprising alexidine, not required by group I-IV

Common Technical Features

Groups I-V share the technical feature of A comprising an antimicrobial agent alexidine.

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 8,877,882 B1 to Salamone et al. (hereinafter 'Salamone'). Salamone teaches an antimicrobial composition (col 6 in 42-43, antimicrobial polymer coating compositions) comprising alexidine (col 6 in 37), a solvent (abstract; col 4 in 33), an optional carrier polymer (abstract; col 3 in 47, polymer-containing coating material), and one or more excipients or additives (col 5 in 33-35, polymer film can have various antimicrobial agents, anti-infective agents, medicants or other biologically-active agents incorporated therein; col 27 in 8-11, biologically-active agents include various antimicrobial agents, essential oils, skin care additives, emollients, humectants, a local anesthetic and a vitamin/antioxidant), wherein the antimicrobial composition is used to disinfect a surgical device (col 4 in 19-21, coating on a device or dressing additionally provides biocidal activity against microbial contamination and/or growth) or a surgical site (col 7 in 43-44, antimicrobial coating for pre- and post-surgical sites).

Therefore, Groups I-V lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note:

Claims 5-28; 33-36, 38-39, 45-48 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

claim 44 is improperly depending from claim 39. For the purpose of completing this ISR, claim 44 is interpreted as it is depending from claim 43.

claim 46-48 are improperly depending from claim 41. For the purpose of completing this ISR, claims 46-48 are interpreted as they are depending from claim 45.

claim 50 is improperly depending from claim 44. For the purpose of completing this ISR, claim 50 is interpreted as it is depending from claim 49