European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:39–54
https://doi.org/10.1007/s10096-018-3393-5

REVIEW

The downside of antimicrobial agents for wound healing

Apirujee Punjataewakupt[1] · Supamas Napavichayanun[1] · Pornanong Aramwit[1]

Received: 12 June 2018 / Accepted: 26 September 2018 / Published online: 5 October 2018

Abstract

The use of topical antimicrobials is beneficial for infection control in wound care because wound infection is the major cause of delayed healing. The advantages of topical over systemic antimicrobials include a higher concentration at the target site, fewer systemic adverse effects, and a lower incidence of antimicrobial resistance. Nowadays, topical antimicrobials are divided into three groups: disinfectants, antiseptics, and antibiotics. Only antiseptics and antibiotics can be applied to living skin; therefore, this review will focus only on these groups. The advantages of each topical antimicrobial are well established; however, their disadvantages remain prominent. It is widely known that antiseptics show higher cytotoxicity and a broader spectrum of activity than antibiotics, whereas antibiotics show a higher probability of bacterial resistance development. However, there are still many adverse effects, resulting from each topical antimicrobial. This review aims to summarize the possible adverse effects of commonly used antiseptics (biguanide, silver, iodine, chlorine compounds, and other antiseptics), antibiotics (bacitracin, mafenide, mupirocin, neomycin, and silver sulfadiazine), and natural antimicrobials (curcumin and honey). Moreover, the antimicrobials that should be avoided in particular populations are also summarized in this review in order to increase awareness for antimicrobial selection in those populations.

Keywords Topical antimicrobials · Wounds · Adverse effect · Toxicity

Introduction

Wounds, especially chronic wounds, impose an important burden on the worldwide healthcare system, causing both economic costs to society [1, 2] and fatal harm to patients. Chronic wounds are non-healing wounds of multifactorial cause. Infection is one of the significant causes of delayed wound healing [3]; therefore, infection control should be a careful consideration in wound management. In order to control infection, wounds should be treated with aseptic technique, optimal debridement, and appropriate antimicrobial agents [4].

Due to the rise in antimicrobial resistance caused by antimicrobial abuse, especially from systemic antibiotic use, the roles of topical antimicrobials in wound therapy are increasing in importance [5–7]. Topical antimicrobials are directly applied to the wound, resulting in a high concentration at the wound site, low systemic side effects, and a low incidence of antimicrobial resistance. Topical antimicrobial agents, which consist of disinfectants, antiseptics, and antibiotics, are defined as agents that have the ability to kill, inhibit, or reduce the number of microorganisms [5, 8]. Disinfectants are agents that can eradicate all microorganisms, including spores; however, these agents cannot be applied on living tissue because of their toxicity. Antiseptics are chemical substances that can be used on intact skin, some open wounds, and mucous membranes in order to kill or inhibit the growth and development of microorganisms with non-specific activity or multiple microbial targets [3, 5]. However, they have some toxic effects on host tissues. Antibiotics, which are either naturally or synthetically produced, are chemical substances that have the ability to kill or inhibit microorganisms with specific cell targeting action, causing a narrower antimicrobial spectrum. Antibiotics are relatively non-cytotoxic; nonetheless, bacterial resistance to antibiotics is more common.

Although the antimicrobial efficacy of these substances has been determined in various studies, a summary of their adverse effects is lacking. Each antimicrobial has different adverse effects, which may limit their use in some populations. The adverse effects of antimicrobials can be separated into

✉ Pornanong Aramwit
aramwit@gmail.com

[1] Bioactive Resources for Innovative Clinical Applications Research Unit and Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

local and systemic effects. Local effects include pain, rash, and cytotoxic effects on the cells necessary for the wound healing process, such as epithelial cells, fibroblasts, endothelial and inflammatory cells, and others [9]. These effects occur only at the site of application. Systemic effects occur from the absorption of these substances into the systemic circulation, resulting in toxicity to the kidneys, liver, and other organs.

This paper aims to summarize the downside of topical antiseptics and antibiotics that are commonly used in wound care in order to indicate the possible adverse effects that can result from topical antimicrobial use and summarize the limitations of antimicrobial application in certain patients.

Adverse effects of antimicrobials

Antiseptics

Antiseptics exhibit a broad antimicrobial spectrum and residual anti-infective activity on wounds; however, they may be toxic to host cells or tissues (e.g., fibroblasts, keratinocytes, and possibly leukocytes) [9].

Biguanide compounds

Chlorhexidine Chlorhexidine (CHX) is a biguanide antibacterial agent that has been in wide use since the 1950s in several products. The recommend concentration of CHX for use in wounds is 0.05% [10, 11]. However, the toxicity of CHX was reported depending on both concentration and time [12, 13]. The possible mechanisms underlying its cytotoxicity were indicated that CHX was able to: (i) increase cell permeability, which contribute to leakage of cell components; (ii) cause mitochondrial injury leading to ATP depletion; (iii) suppress DNA synthesis, resulting in decrease of cell proliferation; (iv) alter cytoskeletal organization followed by change of cells configuration; (v) disturb protein synthesis and accumulation; (vi) induce endoplasmic reticulum stress owing to some proteins accumulation; and (vii) increase intracellular calcium ion, which conduce to reactive oxygen species (ROS) over generation [12–14]. The ROS generation also cause endogenous DNA damage leading to genotoxicity of CHX to several cells [15]. Different effects were observed on various cells involved in the wound-healing process, including fibroblasts, endothelial cells, macrophages, and lymphocytes [12–15]. Moreover, CHX showed toxicity to human osteoblasts [16] and human cartilage, especially osteoarthritic cartilage [17] so CHX should be used with caution to irrigate exposed cartilage. Allergic reactions, including anaphylaxis from products containing CHX, have been also presented especially mucous membrane treatment [10, 18]. For systemic effect, the toxicity was rarely reported because CHX is poorly absorbed through intact skin [19, 20]. Only small amounts of CHX (1 to 460 ng/mL) was detected in human blood [21].

Polyhexamethylene biguanide Polyhexamethylene biguanide (PHMB), also known as polyhexanide, is a biguanide substance. It is a strong base antimicrobial agent. At concentrations of > 20–50 μg/mL, PHMB binds to the plasma membrane, resulting in cell lysis, leakage of enzymes and cytokines, and eventually cell death by necrosis [22]. In addition, the cytotoxic effect of PHMB on chondrocytes may result from the inhibition of proteoglycan synthesis [23]. Several studies have indicated low antimicrobial cytotoxicity of PHMB [24, 25], whereas others have shown concentration- and time-dependent cytotoxic effects of PHMB on chondrocytes [26], endothelial cells [27], keratinocytes, fibroblasts, and osteoblasts [28]. Moreover, the concentrations at which PHMB negatively affect osteoblasts and endothelial cells are equal to or lower than the clinically recommended concentration [16, 27]. Besides the cytotoxicity of PHMB on cartilage [26, 29, 30], the efficacy of PHMB is suppressed in the presence of mucin and chondroitin sulfate, which can be found in nasal and joint fluid [29]. Accordingly, PHMB should be applied with caution on areas with exposed bone or cartilage [29]; however, this effect may be relieved by NaCl irrigation [30]. It should be noted that the combination of PHMB and additives with surface-tension-reducing properties can lead to higher cytotoxicity as well as antimicrobial efficacy of PHMB [29]. Furthermore, PHMB is incompatible with anionic detergents, soaps, alkyl sulfates, strong inorganic bases, and complex phosphates [29]. Lastly, severe anaphylaxis should be aware as it occurred after patients came into contact with PHMB used for cleaning surgical wounds [31] and PHMB-containing products [32].

Silver compounds

Silver has been used for infection control in wound care for centuries. The silver compounds that are well-known antiseptics in clinical practice are silver nitrate and silver nanoparticles.

Silver nitrate Silver nitrate ($AgNO_3$) is a traditional antimicrobial that has been used for burns for centuries [33]. It is a water-soluble salt in solution. This agent can stain the contacted area by turning black following exposure to light [34]. There are several mechanisms of silver nitrate leading to its toxicity or adverse effects. First, at concentrations lower than 0.5%, silver nitrate negatively affects mitochondrial function in a concentration- and time-dependent manner. Moreover, silver nitrate induces cell detachment, interacts with nuclear proteins, inhibits DNA synthesis, depletes intracellular ATP, and decreases cellular protein content [35]. Accordingly, silver nitrate showed cytotoxicity to fibroblasts [34–36], keratinocytes [36], and endothelial cells [35]; however, its cytotoxicity can be reduced by addition of fetal calf

serum and testing on a more complex arrangement of cells, which more closely mimics physiological conditions [36]. Secondly, nitrate is a pro-inflammatory and toxic substance to wounds, and it can be converted into nitrite, an oxidant substance that induces cell damage and retards wound healing, by gram-negative bacteria [34]. Thirdly, as a result of the deposition of inert precipitates of silver selenide and silver sulfide, argyria, which is blue, gray, or black discoloration of the skin commonly found in light-exposed areas, also occurs from the long-term use of silver nitrate [37]. The causative mechanism of argyria is still unclear, but it is suspected to relate to imbalances in soluble and insoluble silver in the middle or upper dermis and the reductive process involving lysosomal reductase and solar energy [38]. Lastly, nitrate anion can induce conversion of ferrous hemoglobin to the ferric state (methemoglobin), which is incapable of normal oxygenation. Methemoglobinemia in burn patients using 0.5% silver nitrate solution has been reported. This complication may be life threatening, which can be restored by intravenous methylene blue therapy. However, this complication is rare [38–40]. Apart from the abovementioned, due to its rapid inactivation, silver nitrate has no sustained effect; therefore, it should be reapplied frequently (up to 12 times per day), and this poses a problem for both practitioners and patients [34]. Patients not only suffer from the pain of dressing changes but also from the possible exposure to excess silver from frequent application. Silver can be absorbed into the systemic circulation, resulting in silver deposition in various organs such as the brain, liver, and kidneys. These depositions may produce toxicity to the involved organs [34].

Silver nanoparticles Silver nanoparticles (SNP) range in size from 1 to 100 nm. Because of their small size and large surface area, SNP are expected to have high antimicrobial efficacy. At present, SNP are crucial substances for wound care, and SNP are impregnated in various advanced wound dressings. Despite having effective antimicrobial activity, SNP show cytotoxicity that result from cellular SNP uptake and subsequent oxidation of intracellular SNP by oxygen or other molecules, resulting in silver ion (Ag^+), which is toxic to cells. Ag^+ can cause oxidative stress via ROS production and damage to cellular components such as DNA, enzymes, antioxidant molecules, proteins, and cell membranes [41, 42]. In addition, the toxicity of SNP is dose and time dependent. Some studies have shown cytotoxic and genotoxic effects of SNP on several cell types [42], including fibroblasts [43] and keratinocytes [44]. Even Acticoat®, a novel dressing containing silver nanoparticles, showed a cytotoxic effect on keratinocytes [34] and fibroblasts [45]. It is noteworthy that a very low concentration of SNP can be absorbed through intact skin; however, absorption can increase in damaged skin [46]. Therefore, SNP application to wounds may lead to silver accumulation and toxicity to various cell lines, including lung, stomach, breast, and endothelial cells. Furthermore, in vivo studies found toxicity of SNP to the brain, lungs, liver, kidneys, and reproductive system [34, 42]. Although some studies showed that silver from SNP application was less absorbed than that from silver sulfadiazine (SSD) application [47, 48], abnormal liver function was documented in burn patients using dressing containing silver nanoparticles [49]. It is uncertain whether the increased liver enzyme levels were due to the silver nanoparticle dressing or to the burn itself [48]; therefore, the level of silver in plasma should be monitored in order to avoid the adverse systemic effects of silver nanoparticle application, especially in large wounds. Unlike other drugs, SNP have variation in physicochemical properties that can lead to variation in toxicity. The smaller size of SNP is suspected to result in higher toxicity. Regarding particle shape, spherical particles seem to induce less toxicity than wire-shaped and plate-shaped particles. Moreover, differently coated surfaces result in different toxicities of SNP due to differences in charge, aggregation, and surface functionalization. In addition, SNP can form complexes with protein in the circulation, resulting in changes in cellular uptake, stability, distribution, and toxicity. Biosynthesized SNP tends to exhibit less toxicity and higher specificity for normal cells than chemically synthesized SNP [42].

Iodine compounds

Povidone-iodine Povidone-iodine (PVP-I) is a complex between polyvinylpyrrolidone and iodine. The most commonly used formulation contains 10% PVP-I (1% available iodine). Its antimicrobial effects result from the free iodine, that is, released from the PVP-I molecule [50]. Released iodine can be toxic to microorganisms by irreversible binding with tyrosine residues of proteins, interfering the formation of hydrogen bonding by some amino acids and nucleic acids, oxidizing sulfhydryl groups, and reacting with sites of unsaturation in lipids. Povidone-iodine has been indicated as an agent that delays wound healing [51] which may attribute to the inhibition of fibroblast aggregation [52], induction of epithelial cell death [53], and inhibition of leukocyte migration [50]. Exposure to a high concentration of PVP-I seems to cause necrosis, while exposure to a low concentration of PVP-I causes apoptosis [53]. However, recent studies showed no advantage or disadvantage of iodine compared with other products [4]. Moreover, the effects of iodine can be diminished after exposure to exudate [50]; thus, its toxicity and efficacy can differ between in vitro testing and clinical practice. Furthermore, as PVP-I contains iodine in its chemical makeup, the absorption of released iodine through the large wound, burned areas, vaginal mucosa, oral mucosa, and in children even with normal skin into the systemic circulation resulting in iodine toxicity should be considered [54]. Excess iodine can influence thyroid function [55] and cause both

hypo- and hyperthyroidism (the latter is rarer) [56]. In most healthy patients, excess iodine can temporarily inhibit thyroid hormone secretion before spontaneously getting back to normal; however, remaining suppression of thyroid function in some patients because of unknown reasons can lead to hypothyroidism. Hyperthyroidism can be found in patients with goiters, after long-standing iodine deficiency, iodine-induced hyperthyroidism can occur because of sufficient iodine. Moreover, long standing of high iodine levels can result in classical thyroid autoimmunity (hypothyroidism and thyroiditis), so iodine-induced hyperthyroidism can also be an autoimmune pathogenesis [54, 56]. Iodine-induced nephrotoxicity is also reported in patients received topical povidone-iodine, which may lead to acute kidney injury (AKI), often in the form of tubular necrosis [57]. The pathogenesis has not been clearly understood; however, it may involve iodine-induced renal ischemia and tubular toxicity. As iodine is eliminated by the kidneys, problems of iodine excess may arise in patients with renal impairment, especially under conditions of metabolic acidosis. Moreover, thyroid functions should be carefully monitored in patients treated with PVP-I for a long time, especially in large wounds and children. In addition, iodides can cross placental barrier and also present in mother's milk so the risk of neonatal hypothyroidism should be taken into consideration when using iodine products in pregnant and lactating women [50]. Therefore, this antimicrobial agent should be used with cautions in patients with renal and/or thyroid impairment, children, and pregnant and lactating women. Allergic reactions were also found with PVP-I use, especially in leg ulcer patients [58].

Cadexomer iodine Cadexomer iodine is 0.9% *w*/w iodine [58] contained in hydrophilic-modified starch. This substance can absorb exudate from the wound, swell, and release iodine into the wound in order to control infection [59]. Because cadexomer iodine also contains iodine in its chemical structure, the released and absorbed iodine can produce toxicities that are similar to those found from PVP-I. The cytotoxicity of cadexomer iodine to cells is still controversial as some studies found cytotoxicity at concentrations higher than 0.45% *w*/*v* cadexomer iodine [60], while others found benefits to wound healing [61, 62]. Moreover, some studies revealed transient pain after cadexomer iodine application [63–65]. Although some studies showed no toxicity from iodine absorption after cadexomer iodine application [61], cadexomer iodine should still be used with caution in pregnant and lactating women, patients with large wounds, systemic complications such as renal failure or thyroid dysfunction, and severely immunocompromised patients [66]. Lastly, cadexomer iodine should be used with caution on low-exudate wounds as this substance can absorb fluid, resulting in insufficient moisture in the wound.

Chlorine compounds

Sodium hypochlorite Sodium hypochlorite (NaOCl) was introduced as a topical antiseptic for wounds in 1915 by Henry Dakin [67]. At concentrations between 0.5 and 5.25%, it is an alkaline solution with pH 11 to 13 that can eradicate microorganisms and also dissolve necrotic tissue. Hypochlorite solution contains two active compounds, hypochlorous acid (HOCl), an extremely active compound and hypochlorite ion (OCl^-), a less active compound [68]. Because NaOCl is a strong oxidizing agent, it can damage healthy tissue and its components, including human stratum corneum, collagen, fibroblasts, and immunological cells such as macrophages [69]. The cytotoxic mechanisms of NaOCl consist of cellular energy metabolism impairment, DNA synthesis reduction, progressive mitochondrial dehydrogenase dysfunction, and subsequent cell death [70]. Moreover, hemolysis can be induced by hypochlorous acid through membrane protein modification [71]. The toxic effect of NaOCl depends on its concentration and the duration of exposure. Although NaOCl showed toxic effects in an in vitro model [72], the dilute concentrations used in clinical practice seem to result in extremely low toxicity to tissue [71, 73]. NaOCl is unstable when exposed to light, heat, acids, and metallic substances. It is immediately degraded after exposure to blood or proteins in an open wound; therefore, systemic toxicity occurring from topical application is not suspected [71, 74]. Common adverse effect resulting from NaOCl application is pain at the wound site [75].

Other antiseptics

Hydrogen peroxide Hydrogen peroxide (H_2O_2) is an oxidizing agent used for wound irrigation and may be used to remove necrotic tissue from wounds. The concentration of hydrogen peroxide, that is, normally used for disinfection is 1–3% (324–972 mM) [76]. H_2O_2 is an important compound regularly found in the normal healing process. Moreover, its disinfectant effect is rapidly diminished because H_2O_2 is an unstable compound, that is, rapidly decomposed to water and oxygen. Hydrogen peroxide is a well-known oxidizing agent. It can generate hydroxyl radicals that induce lipid peroxidation leading to DNA damage and cell death. The toxicity effects of H_2O_2 can result from three mechanisms: corrosive damage, oxygen gas formation, and lipid peroxidation [77]. Some studies showed that applying a relatively low concentration of H_2O_2 can enhance healing (10–50 mM) [78, 79] and promote re-epithelialization (250–500 μM). However, these beneficial concentrations are much lower than those used in clinical practice [76]. The high concentrations of H_2O_2 do not only damage cells in the wound bed but also destroy the healthy cells in the surrounding wound [78, 79]. The cytotoxicity of H_2O_2 in fibroblasts [80] and keratinocytes [81] has been reported in several studies to result from oxidative stress.

Moreover, using H_2O_2 to irrigate wounds located in closed body cavities or under pressure should be avoided as it may lead to oxygen gas embolism or emphysema [77], especially when a high volume that exceeds the oxygen solubility in the blood is used. Data on the H_2O_2 dermal penetration rate are not yet available. Even though H_2O_2 is absorbed through the skin, it is metabolized rapidly by the enzymes catalase and glutathione peroxidase. Because H_2O_2 is an unstable compound, it rarely has systemic effects [82].

Antibiotics

Because the mechanisms of action of most antibiotics are specific to one or a few targets, the spectrum of activity of antibiotics is narrower than that of antiseptics. Moreover, resistance to antibiotics is more frequently found than resistance to antiseptics, which affect multiple targets with less specificity. However, the cytotoxicity of antibiotics seems to be less than that of antiseptics [9].

Bacitracin Bacitracin is a mixture of polypeptide antibiotics produced by *Bacillus subtilis*. Complexing with zinc results in a stable form of bacitracin. Bacitracin is commonly combined with other antibiotics, such as neomycin and/or polymyxin, in order to increase the spectrum of their activity [83]. The adverse effects of topical application can be burning, itching, increased irritation, or rash. Allergic contact reactions were reported [84], with some variations among studies depending on the form of bacitracin and geographic location [85]. Due to the increasing use of bacitracin, the number of allergic contact reactions from bacitracin is also increasing [86]. Moreover, allergic reactions to bacitracin seem to be delayed (96 h). The physician should therefore be aware of previous allergic contact reactions to bacitracin before prescribing it. Bacitracin can cause a hypersensitivity reaction from both systemic and, less commonly, topical application. In rare cases, anaphylactic reactions from bacitracin ointment application have been reported [87, 88]. Moreover, systematic administration of bacitracin can cause severe nephrotoxicity, especially in patients with renal impairment [83, 89]; however, topically applied bacitracin is not significantly absorbed [90], so this adverse effect is rarely found. It is necessary to state that some patients who were allergic to neomycin also showed allergic reactions to bacitracin, despite the differing structures of these compounds and the absence of a relationship between neomycin and bacitracin allergies [84]. Because bacitracin is commonly combined with neomycin, and they sometimes have coincidental sensitization, the healthcare provider should determine which antibiotic is the real cause of the allergic reaction.

Mafenide acetate Mafenide is a synthetic antibiotic structurally closely related to sulfonamides. The difference between mafenide and sulfonamide structure is its methylene group between the benzene ring and the amino nitrogen, which differs from the basic sulfonamide structure [91]. Mafenide is not antagonized by p-aminobenzoic acid (PABA), serum, or pus, unlike other sulfonamides [92]. Moreover, it has excellent tissue penetration, including eschar. The cytotoxic mechanism of mafenide involves selectively inhibition of the de novo base synthesis pathway. Mafenide might inactivate the folic acid transport system via indirectly inhibition of folic acid transport by changing the concentrations of hormones, expression of folate receptors or carrier, or pH in the wound [93]. According to its cytotoxicity, mafenide acetate may delay wound healing and reduce the breaking strength of healed wounds [94]. For systemic effects, some of the mafenide from topical application can be absorbed through the skin and metabolized rapidly into the inactive metabolite p-carboxybenzene sulfonamide; however, it can result in blood dyscrasias, including hemolytic anemia, bone marrow suppression, and methemoglobinemia [92]. Moreover, mafenide should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency, as fatal hemolysis from topical mafenide application has been reported [95]. Hemolysis can be caused by oxidant drug such as sulfonamides as these drugs facilitate oxidation of hemoglobin, glutathione, and other compounds of the red cells [95]. Furthermore, mafenide and its acid metabolites can inhibit carbonic anhydrase in the renal tubules, resulting in metabolic acidosis, so it should be used with caution in patients with respiratory or renal dysfunction or large burns [96]. Pulmonary complications were also reported from mafenide cream application, but the mechanism is still unknown [97]. Furthermore, pain or burning resulting from topical mafenide application, which increased with increasing concentration, was the most frequent adverse effect [92, 96–98]. An allergic response to mafenide can result in rash, pruritus, facial edema, swelling, hives, blisters, erythema, and eosinophilia [92], as well as other skin reactions such as erythema multiforme and contact dermatitis [97]. There are some concerns to be noted before using mafenide. First of all, prolonged use of mafenide can lead to the growth of *Candida albicans* [94]. Secondly, mafenide should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency. Thirdly, mafenide should be used with caution in patients with respiratory or renal dysfunction or large burns, and acid-base balance should be monitored in these patients. Last but not least, although cross sensitivity to other sulfonamides has not yet been confirmed, patients with known allergies to sulfonamides should avoid mafenide [92].

Mupirocin Mupirocin is a short fatty acid side chain (9-hydroxynonanoic acid) linked to monic acid by an ester linkage produced by submerged fermentation of *Pseudomonas fluorescens*. It is a mixture of pseudomonic acids and is therefore classified as a pseudomonic acid. The major metabolite is pseudomonic acid A, which is responsible for most of the

activity, while three other minor metabolites (pseudomonic acids B, C, and D) have similar chemical structures and antimicrobial spectra [99, 100]. Its activity can be decreased if the pH increases above the normal skin pH of 5.5 [101]. The cytotoxic mechanism of mupirocin has not been indicated; however, a study by Balin et al. showed growth inhibition of fibroblasts after 4–6 days exposure to 700 μg/mL mupirocin. The clinical concentration of mupirocin is 2% or 20,000 μg/mL, which is much higher than that used in the study; however, the concentration of mupirocin in tissue from topical application is still unknown [102]. A delayed healing effect of mupirocin was also reported [94]. Although topical mupirocin application is considered as well tolerated [103], there have been reports of local side effects such as burning, itching, reddening [104], and allergic contact dermatitis [105]. Conjunctival application is contraindicated as it may cause irritation. Irritation and an unpleasant or abnormal taste, which are minor side effects, have also been recorded from nasal application [101]. Mupirocin can be absorbed through the skin, especially when skin lesions are present. Because mupirocin is rapidly metabolized in plasma [99], the percutaneous absorption of mupirocin can be measured from its metabolite monic acid. Urinary monic acid was evaluated after repeated applications of mupirocin, and the measured concentration of monic acid was higher in children than in adult patients. However, no systemic adverse effects resulting from mupirocin administration were observed. In order to avoid adverse effect to infant, pregnant and lactating women should use mupirocin with cautions. Because mupirocin can be absorbed, it may be able to pass into breast milk and may affect the infant. Moreover, the polyethylene glycol from the ointment base can be absorbed through open wounds or damaged skin, resulting in renal toxicity [106, 107]; therefore, mupirocin ointment application may not be suitable for patients with a very large open wound or those with renal impairment. It is worth noting that mupirocin should not be applied for longer than 10 days in order to avoid the development of bacterial resistance [94].

Neomycin Neomycin is one of aminoglycoside antibiotics. Neomycin fermented from *Streptomyces fradiae* consist of neomycin A, B, and C. The commercial product of neomycin is a mixture of neomycin B and neomycin C, supplied in sulfate form [108]. Contact allergy is the most common adverse effect of neomycin topical use. Rashes can be found in 6–8% of patients using topical neomycin [108]. Moreover, the risk factors for sensitization to neomycin include advanced age, leg dermatitis, and a high number of positive reactions to other allergens. In some countries where neomycin is an OTC drug, the frequency of exposure to neomycin is increased, resulting in an increased risk of sensitization to neomycin [109]. Neomycin can adversely affect the kidneys and auditory system. Topical application to wounds can result in hearing loss, especially in patients with renal impairment [108, 110] because neomycin, like other aminoglycosides, can cause apoptotic cell death of hair cells, mainly in the cochlea [111]. Therefore, neomycin should be avoided in patients with renal impairment. Systemic hypersensitivity reactions occurring from topical application were reported from both a neomycin-only formulation [112] and a combination neomycin–bacitracin formulation [113]. Because some patients who are allergic to neomycin are also allergic to bacitracin, hypersensitivity reactions should be carefully monitored, and the real cause of the adverse effect should be carefully determined, especially when using the combined formulation.

Silver sulfadiazine Silver sulfadiazine is produced by combination of silver nitrate and sulfadiazine; therefore, its antimicrobial effects are a combination of the effects of silver and sulfadiazine [34]. This antimicrobial has been used for topical treatment of wounds since the 1970s, and it is the main antiseptic used for burn wounds instead of silver nitrate. The cytotoxicity mechanisms of silver are mentioned in silver nitrate and SNP part. Moreover, the mechanisms leading to delay healing may also attribute to alteration of cytokine expression and disturbance of macrophage recruitment and activation [114]. In vitro and in vivo cytotoxicity of SSD on both keratinocyte growth [115] and fibroblast proliferation were shown [116]. Furthermore, impairment of re-epithelialization by SSD, resulting in a delay in the healing process, has been reported [117]. In addition, prolonged and/or extensive topical SSD application can also produce argyria in patients [34, 118], similar to that produced by silver nitrate. Moreover, pseudoeschar formation owing to the interaction of the drug with proteinaceous exudate in the wound after multiple applications of SSD can lead to difficulty estimating the depth of burn wounds [94, 119]. There is evidence of silver absorption and deposition after topical application of SSD [47, 120], resulting in toxicity to various organs such as the kidneys [121, 122], liver, and cornea [123]; therefore, the concentration of silver in the blood and/or urine should be monitored in patients using SSD, especially those with large burns, renal and hepatic impairment, and the prolonged and extensive use of SSD.

Due to SSD contains sulfadiazine, the adverse effects related to sulfonamide moiety should be aware. Firstly, it is important to note that dermatologic and allergic reactions, including anaphylaxis and life-threatening cutaneous reactions: Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and exfoliative dermatitis can occur in patients with sulfonamide allergies. Secondly, in patients with glucose-6-phosphate dehydrogenase deficiency, exposure to SSD which is oxidizing agent can cause hemolysis [37, 124]. Thirdly, as sulfadiazine is an oxidizing agent, it can convert the hemoglobin molecule from the ferrous reduced state to methemoglobin, the ferric oxidized state, resulting in methemoglobinemia

[37]. In addition, leukopenia occurring after prolonged application of SSD has been reported [34]; however, some studies revealed that SSD is not the cause of this adverse effect [37]. Moreover, the mechanism of leukopenia is not well understood. Lastly, sulfa drugs can compete with bilirubin-binding sites on albumin, leading to increased free bilirubin and jaundice in the newborn, so SSD should not be used on females who are pregnant or lactating [125]. As the abovementioned, SSD should be avoided in patients with known allergic to sulfonamides, patients with glucose-6-phosphate dehydrogenase deficiency, and pregnant or lactating women. Moreover, SSD should be used with cautions in patients with renal and hepatic impairment.

Natural antimicrobials

Curcumin Curcumin is a yellow-orange phenolic compound contained in the herb *Curcumin longa*, which has been used as a coloring agent, food additive, and traditional medicine since ancient times [126]. The efficacy of curcumin on wound healing has also been established [127, 128]. Although curcumin has been in use for a long time, its safety is not guaranteed. Due to its poor solubility in aqueous solution (it is a hydrophobic compound), low bioavailability, and rapid metabolism [129], the effects of curcumin are in doubt and seem to be local. The current development of formulations such as nanoscale formulations, complexation with a carrier [130], and encapsulation [127] may improve its properties, but it may also result in a higher possibility of adverse effects. The cytotoxicity of curcumin is still controversial. At low concentrations, curcumin acts like an antioxidant, whereas at high concentrations, curcumin can induce ROS production leading to damage to enzymes and DNA. Moreover, some studies showed that curcumin can decrease the cell viability of fibroblasts via several pathways [131, 132]; therefore, curcumin should be used with caution in wound care, especially at high concentrations. However, some studies showed the safety of curcumin on normal cells [133, 134]. Topically, applied curcumin is rarely absorbed into the systematic circulation because of the poor permeability of the skin to curcumin. The systemic adverse effects of topical use should be scarce; however, novel formulations and high concentrations of curcumin may lead to greater adverse effects. It is considerable to define that curcumin is a natural compound that may be contaminated with microorganisms; therefore, using raw curcumin as a traditional medicine without suitable sterilization may lead to wound infection.

Honey Honey is a viscous, hygroscopic fluid with a low pH, and high osmolarity, containing a high concentration of sugar and numerous natural substances produced by *Apis mellifera* (*A. mellifera*). It is one of the oldest traditional medicines in the world. Because honey is a natural product, its physicochemical properties, efficacy, and safety can differ depending on the type of plant, collecting season, age of the bees, storage condition, geographical location, and other factors [135, 136]. The antimicrobial activity of honey is derived from both peroxide and non-peroxide activities, which can also vary among products; therefore, quality control of its activity is important. Methylglyoxal (MGO) and defensing-1 are the active components of non-peroxide activity in honey. In spite of its antimicrobial properties, MGO is suspected to delay the healing effect by inducing rapid non-enzymatic modification of the free amino groups of lysine and arginine residues of proteins and peptides, leading to the generation of advanced glycation end products (AGEs), which are the cause of complications in diabetes [137]. Moreover, the time-dependent cytotoxicity of honey to human cell lines has also been reported [28]. Furthermore, stinging pain at the site of application is a common adverse effect of topically applied honey [138, 139], and atopic reactions are also found in some patients [139]. Allergies to honey may occur caused by pollens contained in honey; however, those pollens are removed from medical-grade honey, and there are still no reports of significant allergic reactions [140]. Contamination by microorganisms and their spores, such as *Clostridium botulinum* (*C. botulinum*), fungi, and yeast, in honey should be a concern, and there have been reports of contamination in several countries [141]. The proliferation of spores can produce botulinum toxin in the wound, which can result in systemic adverse effects of the toxin. Using medical-grade honey can diminish the risk of infection and adverse effects from toxin because contaminating spores in honey are inactivated by gamma irradiation in the final process [139]. Honey showed no systemic absorption from topical application, so it is not expected to affect blood glucose in diabetic patients [139]. Aside from abovementioned, honey should be avoided in immunocompromised patients and those with known allergies to bee venom.

Antimicrobial selection

There are several lines of evidence indicating toxic effects of antimicrobial application; therefore, the decision to select an antimicrobial should be performed by balancing its advantages and disadvantages. Moreover, the choice of an optimized concentration of each antimicrobial is also important in order to both suitably control infection and avoid toxicity from antimicrobial application. Due to the complexity of the wound-healing process, results from in vitro cytotoxicity tests may not represent the clinical situation. The cytotoxic effect of each antimicrobial can depend on the type of cell culture, number of cells, evaluation method, time of exposure, concentration of the antimicrobial, and other factors used in each experiment. However, in vitro assessment has been proven a useful method for characterizing cell toxicity mechanisms of topical antimicrobials [35], which may be difficult and complicated to

Table 1 Summary of commonly antimicrobials properties and products for wound care

Antimicrobials	Mechanism of action	Spectrum of activity	Disadvantages	Trade name (strength and dosage form)
Antiseptics				
Chlorhexidine (CHX)	Binds nonspecifically to negatively charged membrane and disrupts cytoplasmic membranes. [7, 11].	Gram (+), (−) bacteria (less against *Pseudomonas* species), yeasts, molds, and viruses [7, 11]	- Cytotoxicity [12–15, 17] - Contact dermatitis [10] - Anaphylaxis [18]	- Bactigras® (0.5% paraffin gauze) - Irrisept® (0.05% solution) - 0.5%, 0.75%, 2% solution
Polyhexamethylene biguanide (PHMB)	Interacts with acidic and (−) charged phospholipids in the bacterial membrane leading to increased permeability and loss of integrity, followed by the death of organism [29].	Gram (+), (−) bacteria, yeasts, molds, and viruses [29]	- Cytotoxicity [28] - Incompatibility with cartilage [29] - Anaphylaxis [31, 32]	- Prontosan® (0.1% solution and gel) - Lavasept® (20% solution) - Suprasorb® X + PHMB (0.3% dressing) - Kendall™ AMD (0.5% dressing)
Silver nitrate	Ag ion has strong affinity to thiol (–SH) groups on cell membranes leading to intracellular absorption, denaturation of membrane, key intracellular enzyme systems impairment resulting in defective respiratory pathways, and RNA and DNA replication [142].	Gram (+), (−) bacteria, yeasts, molds, and viruses [142]. Less affect bacterial spores, protozoal cysts, and mycobacteria	- Cytotoxicity [34–36] - Staining and argyria [37] - Short-actingleading to frequent re-application [34] - Silver deposition [34] - Methemoglobinemia [39, 40]	- Silver nitrate 0.5%, 10%, 25%, 50% topical solution - Grafco® 75% applicator sticks
Silver nanoparticles (SNPs)	SNP binds and penetrates cell wall leading to cell membrane damage. Penetrated SNPs release silver ion, produce free radical, and inactivate the enzymes by binding to thiol groups [143, 144].	Gram (+), (−) bacteria including MDR bacteria, yeasts, molds, and viruses [34, 143]	- Cytotoxicity [41, 43, 44] - Silver absorption and accumulation [34, 42] - Liver toxicity [49]	- Acticoat® (0.25 ± 0.4 mg silver per mg dressing) - BluRibbon®
Povidone-iodine (PVP-I)	PVP-I binds to cell membrane and releases iodine that can penetrate into microorganisms and bind with proteins, nucleotides, and fatty acids in the cytoplasm and cytoplasmic membrane [145].	Gram (+), (−) bacteria, some bacterial spores, yeasts, molds, and viruses [145]	- Cytotoxicity [50–53] - Allergic reactions [58] - Iodine toxicity [54] - Hyper/hypothyroidism [55, 56]	- Betadine® (10% solution, 10% ointment, 7.5% surgical scrub, 5% cream
Cadexomer iodine	Released iodine can penetrate into microorganisms and bind with proteins, nucleotides, and fatty acids in the cytoplasm and cytoplasmic membrane [145].	Gram (+), (−) bacteria, some bacterial spores, yeasts, molds, and viruses [145]	- Transient pain [63–65] - Cytotoxicity [60] - Hyper/hypothyroidism [55, 56]	- Iodosorb® (0.9% gel) - Iodoflex® (0.9% dressing)

Table 1 (continued)

Antimicrobials	Mechanism of action	Spectrum of activity	Disadvantages	Trade name (strength and dosage form)
Sodium hypochlorite (NaOCl)	Permeate into cell membrane and react with enzyme. Hypochlorous acid (HOCl) acts by several mechanisms: halogenation of the bacterial cell wall, decarboxylation of amino acids, and production of singlet oxygen [146].	Gram (+), (−) bacteria, fungi, and viruses	- Cytotoxicity [69, 72] - Pain [75] - Hemolysis [71] - Rapid degradation: short action [68]	- Dakin's solution (0.5%; full strength, 0.25%; half strength, 0.125%; quarter strength, and 0.0125%; 1/40 strength)
Hydrogen peroxide	Oxidation activity leading to disruptions in structure or function of molecules containing in microorganisms [147]	Gram (+), (−) bacteria, fungi, viruses, bacterial spores, and protozoal cysts [147]	- Cytotoxicity [77–81] - Oxygen gas embolism [77]	- 1%, 3%, and 6% solution - Crystacide® (1% cream)
Antibiotics				
Bacitracin	Prevent the formation of peptidoglycan chains needed for cell wall synthesis and alter membrane permeability [83].	Active against gram (+), less active in gram (−), while *Enterobacter* spp. and *Pseudomonas* spp. are resistant [148].	- Allergic contact reactions [84–86] - Hypersensitivity and anaphylactic reactions (rare) [87, 88]	- 500 units per gram ointment
Mafenide	Not known exact mechanism of action. May affect from inhibiting protein synthesis [91]	Some gram (+), many gram (−) including *Pseudomonas* spp.	- Pain [92, 96–98] - Allergic responses and skin reactions [92, 97] - Delay healing and reduce breaking strength [94] - Fungal growth from prolonged use [94] - Hypersensitivity [97] - Metabolic acidosis [96] - Pulmonary complication [97] - Blood dyscrasias (especially in G6PD def. patient) [92] - Not recommend for patient with sulfa allergy [92]	- Sulfamylon® (8.5% cream) - 5% aqueous solution
Mupirocin	Inhibits bacterial RNA and protein synthesis by binding to bacterial isoleucyl-tRNA synthetase [100]	Gram (+) including MRSA, beta-lactamase producing strains, and some *Streptococcus* species. Inactive against anaerobic streptococci, enterococci, gram (−), anaerobes, and fungi. [149]	- Cytotoxicity [94, 102] - Burning and itching [104] - Allergic contact dermatitis [105] - Renal toxicity from ointment base [106, 107] - Activity depending on pH of the skin [101] - Rapid development of resistant bacteria [94]	- Bactroban® (2% ointment, 2% cream)
Neomycin	Bind to bacterial 30 S ribosomal subunits		- Rash [108] - Contact allergy [109]	- 3.5 mg/g ointment or cream

Table 1 (continued)

Antimicrobials	Mechanism of action	Spectrum of activity	Disadvantages	Trade name (strength and dosage form)
	and interfere protein synthesis [150]	Gram (−) bacteria and less active against gram (+) bacteria	- Renal and auditory toxicity [108, 110] - Hypersensitivity [112]	
Silver sulfadiazine (SSD)	Ag ion denature membrane and impair intercellular enzyme. Sulfadiazine provides a specific synergetic effect in combination with Ag [151]. Moreover, SSD can inhibit transcription by binding to the base pairs in DNA helix [143].	Gram (+), (−) bacteria, yeasts, molds, and viruses [152]	- Cytotoxicity [115–117] - Argyria [34, 118] - Pseudo-eschar [94] - Hemolysis in G6PD def. patient [37] - Allergy reaction or anaphylaxis in sulfa allergy patient [37] - Renal toxicity [121, 122] or silver toxicity [47, 120, 123] - Leukopenia [34] - Avoid in pregnancy and lactation because of possibility of kernicterus [125]	- Silvadene®, Flamazine®, and Thermazene® (1% cream) - Allervyn® Ag - Urgotul SSD® (0.45 mg/cm^2 dressing)
Natural antimicrobials				
Curcumin	Inhibit cytokinesis and bacterial proliferation [153] and induce reactive oxygen species (ROS) production leading to apoptosis. At high concentration, induce membrane damage [154, 155].	Gram (+), (−) bacteria, viruses, fungi, and parasites [156]	- Poor permeability and rapid metabolism [129] - Cytotoxicity at high concentration [131, 132]	- Still during development
Honey	- From its properties: high osmolarity, acidity (low pH) - Containing hydrogen peroxide (H_2O_2) and non-peroxide components such as methylglyoxal (MGO) and defensin-1 [157]	Gram (+), (−) bacteria [157]	- Stinging pain [138, 139] - Variation of efficacy among products [135, 136] - Atopic reaction and allergic reaction [139] - May cause delay healing [137] - Risk of contamination [141]	- Medihoney® (100% honey, 80% gel, 95% dressings) - Elasto-Gel™ manuka wound dressing - Activon (100% manuka honey, 100% tulle dressing)

perform with in vivo and clinical studies. Furthermore, clinical studies seem to focus on the efficacy rather than the safety of antimicrobials. Accordingly, the safety of antimicrobials should be determined from the results of entire studies. In addition, the formulation of antimicrobials may influence their toxicity, as some formulations can enhance absorption and/or provide sustained release. Furthermore, as drug coated on medical devices can be released and present in systemic circulation, there is possibility for these drugs to cause adverse effects as same as the drug absorbed from topical application.

In order to select an antimicrobial for an individual patient, there are some points that should be considered aside from the size, location, causes of wound, and characteristics of wounds (color, odor, exudate, and pain) which are important factors in antimicrobial selection. Firstly, the spectrum of antimicrobial activity should be appropriate for the strain of microorganisms that are possibly found in a particular wound. The spectrum of activity of each antimicrobial is summarized in Table 1. Some antimicrobials may show cytotoxicity to cells; however, those antimicrobials may be necessary for wounds with a high risk of resistant bacterial contamination. The biocompatibility index (BI), which compares the antibacterial activity with the cytotoxicity of antimicrobials, may provide more information for antimicrobial selection. The rank order of the BI of antimicrobials was PHMB > CHX > PVP-I; however, BI was calculated from the IC_{50} of each antimicrobial, which are

considerably lower than the concentrations generally applied in clinical practice [24]. Therefore, the BI can be used as supplementary information. Other factors that may impact adverse effects of antimicrobials are discussed below.

Types of wounds

Different types of wounds might not directly impact adverse effects; however, the factors that influence adverse events are more likely to be size, depth, and location of wounds. Due to burns are commonly extensive wounds, and an increased surface area leads to increased absorption of drugs, adverse events are frequently reported in burns. Moreover, patients with chronic ulcer such as venous leg ulcers have a higher chance of sensitization to topical medications than patients with acute wounds [158].

Age of patients

In addition, the structure of skin varies with age. Infant skin can easily absorb substance because of the high proportion of water and the thin epidermis layer. Moreover, the ratios of surface area to weight in children are higher than those in adults, resulting in higher absorption. Children may require more attention to safety monitoring than adults, and antimicrobials with low absorption into the systemic circulation should be considered for children, especially for infants. According to their low systemic absorption, antimicrobials such as CHX [159, 160], Dakin's solution [71, 74] and bacitracin [90] seem to be suitable for pediatric patients. However, further investigations into their safety in pediatric patients are still needed. Moreover, the ease and frequency of application should be taken into account for pediatric patients, so advanced dressings with controlled release of antimicrobials, such as the SNP dressing, may also be a suitable choice [161]. In elderly, the differences in absorption of drugs between adult and elderly may not play an important role; however, other pharmacokinetics including drug metabolism and excretion may be altered due to reduction in the function of some organs. Therefore, antimicrobial selection should be considered from the capability of each function or patients' condition.

Patients' condition

Patient comorbidities and/or conditions should be considered because certain adverse effects can occur in particular patients. Impairment of renal and hepatic function could lead to decrease of drug elimination and increase of drug accumulation, so the risk of drug toxicity is enhanced. Moreover, as iodine is an element that influences production of thyroid hormone, patients with thyroid impairment should be aware for possible adverse effects from iodine containing products. As mafenide and its acid metabolites can inhibit carbonic anhydrase resulting in metabolic acidosis, it should be used with caution in patients with respiratory dysfunction. Furthermore, glucose-6-phosphate dehydrogenase (G6PD) is the enzyme responsible for generation of nicotinamide–adenine dinucleotide phosphate (NADPH) needed for glutathione reduction in order to act as a scavenger for oxidative substances. G6PD deficiency is a genetic disorder caused by a lack of the G6PD enzyme so the adverse effects from some oxidant drugs can be induced in G6PD deficiency patients. Therefore, drugs with oxidizing properties may be not suitable for G6PD deficiency patients. Antimicrobials that can be absorbed into systemic circulation should be avoided in pregnancy and lactation as drugs may negatively affect fetus or infants. Antimicrobials that should be avoided in particular patients are summarized in Table 2.

Conclusion

Each antimicrobial shows different adverse effects, both local and systemic. For local effects, most antiseptics show cytotoxic effects on the key cellular participants in the

Table 2 Patient comorbidities/condition and inadvisable topical antimicrobials

Patient comorbidities/ condition	Inadvisable topical antimicrobials
Renal impairment	- Iodine compounds including PVP-I and cadexomer iodine - Mafenide - Mupirocin ointment base - Neomycin - Silver sulfadiazine
Hepatic impairment	- Silver compounds including silver nitrate, silver nanoparticles, and silver sulfadiazine
Thyroid impairment	- Iodine compounds including PVP-I and cadexomer iodine
Respiratory impairment	- Mafenide
Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)	- Mafenide - Silver sulfadiazine
Known allergy to sulfonamides	- Mafenide - Silver sulfadiazine
Pregnancy and lactation	- Iodine compounds including PVP-I and cadexomer iodine - Mafenide - Mupirocin - Silver sulfadiazine
Exposed bone or cartilage area	- Chlorhexidine - PHMB

wound-healing process, such as keratinocytes, epithelial cells, fibroblasts, and endothelial cells, which can lead to a delay in wound healing. The cytotoxic effects on various cells mostly depend on concentration and time of exposure.

Systemic adverse effects also differ between antimicrobials. Besides concentration and exposure time, systemic effects also depend on the physicochemical properties of each substance, which influence absorption, distribution, elimination, and accumulation in the body. Moreover, the size and condition of applied area also affects the toxicity of each antimicrobial. From this review, some antimicrobials showed various levels of systemic toxicity, while others showed rare toxicity. However, toxicity to the liver, kidneys, and other organ functions should be monitored after any antimicrobial application, especially for large wounds and long durations of use. Patients' characteristics may impact the adverse effects of antimicrobials which may attribute to elimination of drug or specific mechanisms to some organs.

Funding This work was supported by the Thailand Research Fund through the Research and Researcher for Industry Programme (RRi) (Grant No. PHD58I0006) to Apirujee Punjataewakupt and Pornanong Aramwit, Thailand.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Guest JF, Ayoub N, McIlwraith T, Uchegbu I, Gerrish A, Weidlich D, Vowden K, Vowden P (2015) Health economic burden that wounds impose on the National Health Service in the UK. BMJ Open 5(12):e009283. https://doi.org/10.1136/bmjopen-2015-009283
2. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT (2009) Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 17(6):763–771. https://doi.org/10.1111/j.1524-475X.2009.00547.x
3. Gottrup F, Apelqvist J, Bjarnsholt T, Cooper R, Moore Z, Peters EJ, Probst S (2013) EWMA document: antimicrobials and non-healing wounds. Evidence, controversies and suggestions. J Wound Care 22(5 Suppl):S1–S89. https://doi.org/10.12968/jowc.2013.22.Sup5.S1
4. Vermeulen H, Westerbos SJ, Ubbink DT (2010) Benefit and harm of iodine in wound care: a systematic review. J Hosp Infect 76(3):191–199. https://doi.org/10.1016/j.jhin.2010.04.026
5. Lipsky BA, Hoey C (2009) Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis 49(10):1541–1549. https://doi.org/10.1086/644732
6. Thomas GW, Rael LT, Bar-Or R, Shimonkevitz R, Mains CW, Slone DS, Craun ML, Bar-Or D (2009) Mechanisms of delayed wound healing by commonly used antiseptics. J Trauma 66(1):82–90; discussion 90-81. https://doi.org/10.1097/TA.0b013e31818b146d
7. Lio PA, Kaye ET (2009) Topical antibacterial agents. Infect Dis Clin N Am 23(4):945–963. https://doi.org/10.1016/j.idc.2009.06.006
8. Atiyeh BS, Dibo SA, Hayek SN (2009) Wound cleansing, topical antiseptics and wound healing. Int Wound J 6(6):420–430. https://doi.org/10.1111/j.1742-481X.2009.00639.x
9. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J (2017) Topical antimicrobial agents for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev 6:Cd011038. https://doi.org/10.1002/14651858.CD011038.pub2
10. Chlorhexidine (2016) In: Aronson JK (ed) Meyler's side effects of drugs, Sixteenth edn. Elsevier, Oxford, pp 239–248. https://doi.org/10.1016/B978-0-444-53717-1.00474-1
11. Karpinski TM, Szkaradkiewicz AK (2015) Chlorhexidine–pharmaco-biological activity and application. Eur Rev Med Pharmacol Sci 19(7):1321–1326
12. Giannelli M, Chellini F, Margheri M, Tonelli P, Tani A (2008) Effect of chlorhexidine digluconate on different cell types: a molecular and ultrastructural investigation. Toxicol in Vitro 22(2):308–317. https://doi.org/10.1016/j.tiv.2007.09.012
13. Hidalgo E, Dominguez C (2001) Mechanisms underlying chlorhexidine-induced cytotoxicity. Toxicol in Vitro 15(4–5):271–276
14. Faria G, Cardoso CR, Larson RE, Silva JS, Rossi MA (2009) Chlorhexidine-induced apoptosis or necrosis in L929 fibroblasts: a role for endoplasmic reticulum stress. Toxicol Appl Pharmacol 234(2):256–265. https://doi.org/10.1016/j.taap.2008.10.012
15. Li YC, Kuan YH, Lee SS, Huang FM, Chang YC (2014) Cytotoxicity and genotoxicity of chlorhexidine on macrophages in vitro. Environ Toxicol 29(4):452–458. https://doi.org/10.1002/tox.21771
16. Voros P, Dobrindt O, Perka C, Windisch C, Matziolis G, Rohner E (2014) Human osteoblast damage after antiseptic treatment. Int Orthop 38(1):177–182. https://doi.org/10.1007/s00264-013-2107-y
17. Best AJ, Nixon MF, Taylor GJS (2007) Brief exposure of 0.05% chlorhexidine does not impair non-osteoarthritic human cartilage metabolism. J Hosp Infect 67(1):67–71. https://doi.org/10.1016/j.jhin.2007.05.014
18. Krautheim AB, Jermann TH, Bircher AJ (2004) Chlorhexidine anaphylaxis: case report and review of the literature. Contact Dermat 50(3):113–116. https://doi.org/10.1111/j.0105-1873.2004.00308.x
19. Karpanen TJ, Worthington T, Conway BR, Hilton AC, Elliott TSJ, Lambert PA (2008) Penetration of chlorhexidine into human skin. Antimicrob Agents Chemother 52(10):3633–3636. https://doi.org/10.1128/AAC.00637-08
20. Case DE, McAinsh J, Rushton A, Winrow MJ (1976) Chlorhexidine: attempts to detect percutaneous absorption in man. In: Williams JD, Geddes AM (eds) Special problems in chemotherapy. Springer US, Boston, pp 367–374. https://doi.org/10.1007/978-1-4684-3120-9_57
21. Nonami K, Saitoh S, Nishimura-Danjobara Y, Ishida S, Oyama Y (2016) Chlorhexidine possesses unique cytotoxic actions in rat thymic lymphocytes: its relation with electrochemical property of membranes. Environ Toxicol Pharmacol 48:17–21. https://doi.org/10.1016/j.etap.2016.09.024
22. Creppy EE, Diallo A, Moukha S, Eklu-Gadegbeku C, Cros D (2014) Study of epigenetic properties of Poly(HexaMethylene Biguanide) hydrochloride (PHMB). Int J Environ Res Public Health 11(8):8069–8092. https://doi.org/10.3390/ijerph110808069

23. Röhner E, Hoff P, Winkler T, von Roth P, Seeger JB, Perka C, Matziolis G (2011) Polyhexanide and hydrogen peroxide inhibit proteoglycan synthesis of human chondrocytes. J Histotechnol 34(1):35–39. https://doi.org/10.1179/014788811X12949268296121
24. Muller G, Kramer A (2008) Biocompatibility index of antiseptic agents by parallel assessment of antimicrobial activity and cellular cytotoxicity. J Antimicrob Chemother 61(6):1281–1287. https://doi.org/10.1093/jac/dkn125
25. Kramer A, Roth B, Muller G, Rudolph P, Klocker N (2004) Influence of the antiseptic agents polyhexanide and octenidine on FL cells and on healing of experimental superficial aseptic wounds in piglets. A double-blind, randomised, stratified, controlled, parallel-group study. Skin Pharmacol Physiol 17(3):141–146. https://doi.org/10.1159/000077241
26. Röhner E, Seeger JB, Hoff P, Dahn-Wollenberg S, Perka C, Matziolis G (2011) Toxicity of polyhexanide and hydrogen peroxide on human chondrocytes in vitro. Orthopedics 34(7):e290–e294. https://doi.org/10.3928/01477447-20110526-02
27. Ince A, Schutze N, Hendrich C, Jakob F, Eulert J, Lohr JF (2007) Effect of polyhexanide and gentamycin on human osteoblasts and endothelial cells. Swiss Med Wkly 137(9–10):139–145 https://doi.org/2007/09/smw-11434
28. Yabes JM, White BK, Murray CK, Sanchez CJ, Mende K, Beckius ML, Zera WC, Wenke JC, Akers KS (2016) In vitro activity of manuka honey and polyhexamethylene biguanide on filamentous fungi and toxicity to human cell lines. Med Mycol. https://doi.org/10.1093/mmy/myw070
29. Hubner NO, Kramer A (2010) Review on the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic. Skin Pharmacol Physiol 23(Suppl):17–27. https://doi.org/10.1159/000318264
30. Röhner E, Kolar P, Seeger JB, Arnholdt J, Thiele K, Perka C, Matziolis G (2011) Toxicity of antiseptics against chondrocytes: what is best for the cartilage in septic joint surgery? Int Orthop 35(11):1719–1723. https://doi.org/10.1007/s00264-010-1178-2
31. Polyhexanide (2016) In: Aronson JK (ed) Meyler's side effects of drugs, Sixteenth edn. Elsevier, Oxford, p 859. https://doi.org/10.1016/B978-0-444-53717-1.01315-9
32. Kautz O, Schumann H, Degerbeck F, Venemalm L, Jakob T (2010) Severe anaphylaxis to the antiseptic polyhexanide. Allergy 65(8):1068–1070. https://doi.org/10.1111/j.1398-9995.2009.02299.x
33. Klasen HJ (2000) Historical review of the use of silver in the treatment of burns. I. Early uses. Burns 26(2):117–130
34. Atiyeh BS, Costagliola M, Hayek SN, Dibo SA (2007) Effect of silver on burn wound infection control and healing: review of the literature. Burns 33(2):139–148. https://doi.org/10.1016/j.burns.2006.06.010
35. Hidalgo E, Dominguez C (1998) Study of cytotoxicity mechanisms of silver nitrate in human dermal fibroblasts. Toxicol Lett 98(3):169–179
36. Poon VK, Burd A (2004) In vitro cytotoxity of silver: implication for clinical wound care. Burns 30(2):140–147. https://doi.org/10.1016/j.burns.2003.09.030
37. Fuller FW (2009) The side effects of silver sulfadiazine. J Burn Care Res 30(3):464–470. https://doi.org/10.1097/BCR.0b013e3181a28c9b
38. Lansdown AB (2010) A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharmacol Sci 2010:910686. https://doi.org/10.1155/2010/910686
39. Sterling JP (2014) Silver-resistance, allergy, and blue skin: truth or urban legend? Burns 40. Supplement 1:S19–S23. https://doi.org/10.1016/j.burns.2014.10.007
40. Chou T-D, Gibran NS, Urdahl K, Lin EY, Heimbach DM, Engrav LH (1999) Methemoglobinemia secondary to topical silver nitrate therapy-a case report. Burns 25(6):549–552. https://doi.org/10.1016/S0305-4179(99)00031-5
41. McShan D, Ray PC, Yu H (2014) Molecular toxicity mechanism of nanosilver. J Food Drug Anal 22(1):116–127. https://doi.org/10.1016/j.jfda.2014.01.010
42. Riaz Ahmed KB, Nagy AM, Brown RP, Zhang Q, Malghan SG, Goering PL (2017) Silver nanoparticles: significance of physicochemical properties and assay interference on the interpretation of in vitro cytotoxicity studies. Toxicol in Vitro 38:179–192. https://doi.org/10.1016/j.tiv.2016.10.012
43. AshaRani PV, Low Kah Mun G, Hande MP, Valiyaveettil S (2009) Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano 3(2):279–290. https://doi.org/10.1021/nn800596w
44. Szmyd R, Goralczyk AG, Skalniak L, Cierniak A, Lipert B, Filon FL, Crosera M, Borowczyk J, Laczna E, Drukala J, Klein A, Jura J (2013) Effect of silver nanoparticles on human primary keratinocytes. Biol Chem 394(1):113–123. https://doi.org/10.1515/hsz-2012-0202
45. Burd A, Kwok CH, Hung SC, Chan HS, Gu H, Lam WK, Huang L (2007) A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant, and animal models. Wound Repair Regen 15(1):94–104. https://doi.org/10.1111/j.1524-475X.2006.00190.x
46. Larese FF, D'Agostin F, Crosera M, Adami G, Renzi N, Bovenzi M, Maina G (2009) Human skin penetration of silver nanoparticles through intact and damaged skin. Toxicology 255(1):33–37. https://doi.org/10.1016/j.tox.2008.09.025
47. Brandt O, Mildner M, Egger AE, Groessl M, Rix U, Posch M, Keppler BK, Strupp C, Mueller B, Stingl G (2012) Nanoscalic silver possesses broad-spectrum antimicrobial activities and exhibits fewer toxicological side effects than silver sulfadiazine. Nanomedicine 8(4):478–488. https://doi.org/10.1016/j.nano.2011.07.005
48. Vlachou E, Chipp E, Shale E, Wilson YT, Papini R, Moiemen NS (2007) The safety of nanocrystalline silver dressings on burns: a study of systemic silver absorption. Burns 33(8):979–985. https://doi.org/10.1016/j.burns.2007.07.014
49. Trop M, Novak M, Rodl S, Hellbom B, Kroell W, Goessler W (2006) Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma 60(3):648–652. https://doi.org/10.1097/01.ta.0000208126.22089.b6
50. Zamora JL (1986) Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. Am J Surg 151(3):400–406. https://doi.org/10.1016/0002-9610(86)90477-0
51. Kramer SA (1999) Effect of povidone-iodine on wound healing: a review. J Vasc Nurs 17(1):17–23
52. Balin AK, Pratt L (2002) Dilute povidone-iodine solutions inhibit human skin fibroblast growth. Dermatol Surg 28(3):210–214
53. Sato S, Miyake M, Hazama A, Omori K (2014) Povidone-iodine-induced cell death in cultured human epithelial HeLa cells and rat oral mucosal tissue. Drug Chem Toxicol 37(3):268–275. https://doi.org/10.3109/01480545.2013.846364
54. Polyvidone (povidone) iodine (2016) In: Aronson JK (ed) Meyler's side effects of drugs (Sixteenth Edition). Elsevier, Oxford, pp 875–882. https://doi.org/10.1016/B978-0-444-53717-1.01320-2
55. Leung AM, Braverman LE (2014) Consequences of excess iodine. Nat Rev Endocrinol 10(3):136–142. https://doi.org/10.1038/nrendo.2013.251
56. Burgi H (2010) Iodine excess. Best Pract Res Clin Endocrinol Metab 24(1):107–115. https://doi.org/10.1016/j.beem.2009.08.010
57. Perrin T, Hemett OM, Menth M, Descombes E (2012) Contrast-induced acute kidney injury following iodine opacification other

than by intravascular injection. Clin Kidney J 5(5):456–458. https://doi.org/10.1093/ckj/sfs102
58. Cooper RA (2007) Iodine revisited. Int Wound J 4(2):124–137. https://doi.org/10.1111/j.1742-481X.2007.00314.x
59. Noda Y, Fujii K, Fujii S (2009) Critical evaluation of cadexomer-iodine ointment and povidone-iodine sugar ointment. Int J Pharm 372(1–2):85–90. https://doi.org/10.1016/j.ijpharm.2009.01.007
60. Zhou LH, Nahm WK, Badiavas E, Yufit T, Falanga V (2002) Slow release iodine preparation and wound healing: in vitro effects consistent with lack of in vivo toxicity in human chronic wounds. Br J Dermatol 146(3):365–374
61. Laudanska H, Gustavson B (1988) In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. J Int Med Res 16(6):428–435
62. Ohtani T, Mizuashi M, Ito Y, Aiba S (2007) Cadexomer as well as cadexomer iodine induces the production of proinflammatory cytokines and vascular endothelial growth factor by human macrophages. Exp Dermatol 16(4):318–323. https://doi.org/10.1111/j.1600-0625.2006.00532.x
63. Skog E, Arnesjo B, Troeng T, Gjores JE, Bergljung L, Gundersen J, Hallbook T, Hessman Y, Hillstrom L, Mansson T, Eilard U, Ekloff B, Plate G, Norgren L (1983) A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. Br J Dermatol 109(1):77–83
64. Bianchi J (2001) Cadexomer-iodine in the treatment of venous leg ulcers: what is the evidence? J Wound Care 10(6):225–229. https://doi.org/10.12968/jowc.2001.10.6.26085
65. Holloway GA Jr, Johansen KH, Barnes RW, Pierce GE (1989) Multicenter trial of cadexomer iodine to treat venous stasis ulcer. West J Med 151(1):35–38
66. Murdoch R, Lagan KM (2013) The role of povidone and cadexomer iodine in the management of acute and chronic wounds. Phys Ther Rev 18(3):207–216. https://doi.org/10.1179/1743288X13Y.0000000082
67. Dakin HD (1915) On the use of certain antiseptic substances in the treatment of infected wounds. Br Med J 2(2852):318–320
68. Ponzano GP (2007) Sodium hypochlorite: history, properties, electrochemical production. Contrib Nephrol 154:7–23. https://doi.org/10.1159/000096810
69. Cardile AP, Sanchez CJ Jr, Hardy SK, Romano DR, Hurtgen BJ, Wenke JC, Murray CK, Akers KS (2014) Dakin solution alters macrophage viability and function. J Surg Res 192(2):692–699. https://doi.org/10.1016/j.jss.2014.07.019
70. Hidalgo E, Bartolome R, Dominguez C (2002) Cytotoxicity mechanisms of sodium hypochlorite in cultured human dermal fibroblasts and its bactericidal effectiveness. Chem Biol Interact 139(3):265–282. https://doi.org/10.1016/S0009-2797(02)00003-0
71. Peck B, Workeneh B, Kadikoy H, Patel SJ, Abdellatif A (2011) Spectrum of sodium hypochlorite toxicity in man—also a concern for nephrologists. NDT Plus 4(4):231–235. https://doi.org/10.1093/ndtplus/sfr053
72. Kozol RA, Gillies C, Elgebaly SA (1988) Effects of sodium hypochlorite (Dakin's solution) on cells of the wound module. Arch Surg 123(4):420–423
73. Heggers JP, Sazy JA, Stenberg BD, Strock LL, McCauley RL, Herndon DN, Robson MC (1991) Bactericidal and wound-healing properties of sodium hypochlorite solutions: the 1991 Lindberg Award. J Burn Care Rehabil 12(5):420–424
74. Bruch MK (2007) Toxicity and safety of topical sodium hypochlorite. Contrib Nephrol 154:24–38. https://doi.org/10.1159/000096812
75. Sood A, Granick MS, Tomaselli NL (2014) Wound dressings and comparative effectiveness data. Adv Wound Care 3(8):511–529. https://doi.org/10.1089/wound.2012.0401
76. Loo AEK, Halliwell B (2012) Effects of hydrogen peroxide in a keratinocyte-fibroblast co-culture model of wound healing. Biochem Biophys Res Commun 423(2):253–258. https://doi.org/10.1016/j.bbrc.2012.05.100
77. Watt BE, Proudfoot AT, Vale JA (2004) Hydrogen peroxide poisoning. Toxicol Rev 23(1):51–57
78. Bryan N, Ahswin H, Smart N, Bayon Y, Wohlert S, Hunt JA (2012) Reactive oxygen species (ROS)–a family of fate deciding molecules pivotal in constructive inflammation and wound healing. Eur Cell Mater 24:249–265
79. Loo AEK, Wong YT, Ho R, Wasser M, Du T, Ng WT, Halliwell B (2012) Effects of hydrogen peroxide on wound healing in mice in relation to oxidative damage. PLoS One 7(11):e49215. https://doi.org/10.1371/journal.pone.0049215
80. Hoffmann ME, Meneghini R (1979) Action of hydrogen peroxide on human fibroblast in culture. Photochem Photobiol 30(1):151–155. https://doi.org/10.1111/j.1751-1097.1979.tb07128.x
81. Vessey DA, Lee K-H, Blacker KL (1992) Characterization of the oxidative stress initiated in cultured human keratinocytes by treatment with peroxides. J Invest Dermatol 99(6):859–863. https://doi.org/10.1111/1523-1747.ep12614831
82. Hydrogen peroxide (2010) In: Greim H (ed) The MAK-collection for occupational health and safety: MAK Value Documentations, vol 26. Wiley, Weinheim, pp 192–214. https://doi.org/10.1002/3527600418.mb772284e0026
83. Howard B (2007) Bacitracin. In: Enna SJ, Bylund DB (eds) xPharm: the comprehensive pharmacology reference. Elsevier, New York, pp 1–4. https://doi.org/10.1016/B978-008055232-3.61280-2
84. Held JL, Kalb RE, Ruszkowski AM, DeLeo V (1987) Allergic contact dermatitis from bacitracin. J Am Acad Dermatol 17(4):592–594. https://doi.org/10.1016/S0190-9622(87)70241-2
85. Katz BE, Fisher AA (1987) Bacitracin: a unique topical antibiotic sensitizer. J Am Acad Dermatol 17(6):1016–1024. https://doi.org/10.1016/S0190-9622(87)70292-8
86. Jacob SE, James WD (2004) From road rash to top allergen in a flash: bacitracin. Dermatol Surg 30(4 Pt 1):521–524. https://doi.org/10.1111/j.1524-4725.2004.30168.x
87. Schechter JF, Wilkinson RD, Carpio J (1984) Anaphylaxis following the use of bacitracin ointment: report of a case and review of the literature. Arch Dermatol 120(7):909–911. https://doi.org/10.1001/archderm.1984.01650430095017
88. Cronin H, Mowad C (2009) Anaphylactic reaction to bacitracin ointment. Cutis 83(3):127–129
89. Bacitracin (2016) In: Aronson JK (ed) Meyler's side effects of drugs (Sixteenth Edition). Elsevier, Oxford, pp 807–808. https://doi.org/10.1016/B978-0-444-53717-1.00347-4
90. Shorr RI (2007) In: Hoth AB, Rawls N (eds) Drugs for the geriatric patient. W.B. Saunders, Philadelphia, pp 115–172. https://doi.org/10.1016/B978-141600208-6.50006-1
91. Dash AK, Saha S (1996) Mafenide Acetate. In: Brittain HG (ed) Analytical Profiles of Drug Substances and Excipients, vol 24. Academic Press, San Diego, pp 277–305. https://doi.org/10.1016/S0099-5428(08)60696-6
92. Scholar E (2007) Mafenide. In: Enna SJ, Bylund DB (eds) xPharm: the comprehensive pharmacology reference. Elsevier, New York, pp 1–4. https://doi.org/10.1016/B978-008055232-3.62088-4
93. Zhang X-J, Heggers JP, Chinkes DL, Wolf SE, Hawkins HK, Wolfe RR (2006) Topical sulfamylon cream inhibits DNA and protein synthesis in the skin donor site wound. Surgery 139(5):633–639. https://doi.org/10.1016/j.surg.2005.10.013
94. Cambiaso-Daniel J, Gallagher JJ, Norbury WB, Finnerty CC, Herndon DN, Culnan DM (2018) 11 - Treatment of Infection in Burn Patients. In: Herndon DN (ed) Total burn care (fifth edition). Elsevier, Edinburgh, pp 93–113.e114. https://doi.org/10.1016/B978-0-323-47661-4.00011-3

95. Marsicano AR Jr, Hutton JJ, Bryant WM (1973) Fatal hemolysis from mafenide treatment of burns in a patient with glucose-6-phosphate dehydrogenase deficiency. Case report. Plast Reconstr Surg 52(2):197–199
96. Mafenide acetate cream: a review (1971) Drugs 1(6):434–460. https://doi.org/10.2165/00003495-197101060-00002
97. Mafenide (2016) In: Aronson JK (ed) Meyler's side effects of drugs (Sixteenth Edition). Elsevier, Oxford, p 728. https://doi.org/10.1016/B978-0-444-53717-1.01011-8
98. Harrison HN, Shuck JM, Caldwell E (1975) Studies of the pain produced by mafenide acetate preparations in burns. Arch Surg 110(12):1446–1449. https://doi.org/10.1001/archsurg.1975.01360180016003
99. Lamb YJ (1991) Overview of the role of mupirocin. J Hosp Infect 19:27–30. https://doi.org/10.1016/0195-6701(91)90199-I
100. van Bambeke F, Mingeot-Leclercq M-P, Glupczynski Y, Tulkens PM (2017) 137 - mechanisms of action. In: Cohen J, Powderly WG, Opal SM (eds) Infectious diseases (fourth edition). Elsevier, pp 1162-1180.e1161. https://doi.org/10.1016/B978-0-7020-6285-8.00137-4
101. Fraise AP (2010) CHAPTER 23 - mupirocin. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ (eds) Antibiotic and chemotherapy, Ninth edn. Saunders, London, pp 290–291. https://doi.org/10.1016/B978-0-7020-4064-1.00023-3
102. Balin AK, Leong I, Carter DM (1987) Effect of mupirocin on the growth and lifespan of human fibroblasts. J Invest Dermatol 88(6):736–740. https://doi.org/10.1111/1523-1747.ep12470407
103. Gisby J, Bryant J (2000) Efficacy of a new cream formulation of mupirocin: comparison with oral and topical agents in experimental skin infections. Antimicrob Agents Chemother 44(2):255–260
104. Bork K, Brauers J, Kresken M (1989) Efficacy and safety of 2% mupirocin ointment in the treatment of primary and secondary skin infections–an open multicentre trial. Br J Clin Pract 43(8):284–288
105. Mupirocin (2016) In: Aronson JK (ed) Meyler's side effects of drugs (Sixteenth Edition). Elsevier, Oxford, p 1138. https://doi.org/10.1016/B978-0-444-53717-1.01113-6
106. Herold DA, Rodeheaver GT, Bellamy WT, Fitton LA, Bruns DE, Edlich RF (1982) Toxicity of topical polyethylene glycol. Toxicol Appl Pharmacol 65(2):329–335. https://doi.org/10.1016/0041-008X(82)90016-3
107. Mueller RS (2008) Chapter 24 - topical dermatological therapy. In: Maddison JE, Page SW, Church DB (eds) Small animal clinical pharmacology (second edn). Saunders, Edinburgh, pp 546–556. https://doi.org/10.1016/B978-070202858-8.50026-9
108. Lovering AM, Reeves DS (2011) CHAPTER 12 - Aminoglycosides and aminocyclitols. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ (eds) Antibiotic and chemotherapy (ninth edition). Saunders, London, pp 145–169. https://doi.org/10.1016/B978-0-7020-4064-1.00012-9
109. Pádua CAMD, Schnuch A, Lessmann H, Geier J, Pfahlberg A, Uter W (2005) Contact allergy to neomycin sulfate: results of a multifactorial analysis. Pharmacoepidemiol Drug Saf 14(10):725–733. https://doi.org/10.1002/pds.1117
110. Masur H, Whelton PK, Whelton A (1976) Neomycin toxicity revisited. Arch Surg 111(7):822–825
111. Huth ME, Ricci AJ, Cheng AG (2011) Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol 2011:937861. https://doi.org/10.1155/2011/937861
112. Ansari IA, Onyema E (2008) Severe generalised hypersensitivity reaction to topical neomycin after cataract surgery: a case report. J Med Case Rep 2:57–57. https://doi.org/10.1186/1752-1947-2-57
113. Goh CL (1986) Anaphylaxis from topical neomycin and bacitracin. Australas J Dermatol 27(3):125–126
114. Rosen J, Landriscina A, Kutner A, Adler BL, Krausz AE, Nosanchuk JD, Friedman AJ (2015) Silver sulfadiazine retards wound healing in mice via alterations in cytokine expression. J Invest Dermatol 135(5):1459–1462. https://doi.org/10.1038/jid.2015.21
115. McCauley RL, Li Y-Y, Poole B, Evans MJ, Robson MC, Heggers JP, Herndon DN (1992) Differential inhibition of human basal keratinocyte growth to silver sulfadiazine and mafenide acetate. J Surg Res 52(3):276–285. https://doi.org/10.1016/0022-4804(92)90086-F
116. Lee A-RC, Moon HK (2003) Effect of topically applied silver sulfadiazine on fibroblast cell proliferation and biomechanical properties of the wound. Arch Pharm Res 26(10):855–860. https://doi.org/10.1007/bf02980032
117. Chung DH, Colon NC, Herndon DN (2012) Chapter 26 - Burns. In: Coran AG (ed) Pediatric surgery (Seventh edn). Mosby, Philadelphia, pp 369–384. https://doi.org/10.1016/B978-0-323-07255-7.00026-X
118. Rowland Payne CE, Bladin C, Colchester AF, Bland J, Lapworth R, Lane D (1992) Argyria from excessive use of topical silver sulphadiazine. Lancet 340(8811):126. https://doi.org/10.1016/0140-6736(92)90458-F
119. Ungureanu M (2014) Concepts in local treatment of extensive paediatric burns. J Med Life 7(2):183–191
120. Wang X-W, Wang NZ, Zhang OZ, Zapata-Sirvent RL, Davies JWL (1985) Tissue deposition of silver following topical use of silver sulphadiazine in extensive burns. Burns 11(3):197–201. https://doi.org/10.1016/0305-4179(85)90070-1
121. Chaby G, Viseux V, Poulain JF, De Cagny B, Denoeux JP, Lok C (2005) Topical silver sulfadiazine-induced acute renal failure. Ann Dermatol Venereol 132(11 Pt 1):891–893
122. Maitre S, Jaber K, Perrot JL, Guy C, Cambazard F (2002) Increased serum and urinary levels of silver during treatment with topical silver sulfadiazine. Ann Dermatol Venereol 129(2):217–219
123. Wan AT, Conyers RA, Coombs CJ, Masterton JP (1991) Determination of silver in blood, urine, and tissues of volunteers and burn patients. Clin Chem 37(10 Pt 1):1683–1687
124. Eldad A, Neuman A, Weinberg A, Benmeir P, Rotem M, Wexler MR (1991) Silver sulphadiazine-induced haemolytic anaemia in a glucose-6-phosphate dehydrogenase-deficient burn patient. Burns 17(5):430–432
125. Bardal SK, Waechter JE, Martin DS (2011) Chapter 18 - Infectious diseases. In: Dimock K, Hyde M, Cicalese B (eds) Applied pharmacology. Saunders, Philadelphia, pp 233–291. https://doi.org/10.1016/B978-1-4377-0310-8.00018-X
126. Gupta SC, Kunnumakkara AB, Aggarwal BB (2017) Chapter 12 - Curcumin, the holistic Avant-Garde. In: Patwardhan B, Chaguturu R (eds) Innovative approaches in drug discovery. Academic Press, Boston, pp 343–349. https://doi.org/10.1016/B978-0-12-801814-9.00012-X
127. Krausz AE, Adler BL, Cabral V, Navati M, Doerner J, Charafeddine RA, Chandra D, Liang H, Gunther L, Clendaniel A, Harper S, Friedman JM, Nosanchuk JD, Friedman AJ (2015) Curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent. Nanomedicine 11(1):195–206. https://doi.org/10.1016/j.nano.2014.09.004
128. Mohanty C, Sahoo SK (2017) Curcumin and its topical formulations for wound healing applications. Drug Discov Today 22(10):1582–1592.https://doi.org/10.1016/j.drudis.2017.07.001
129. Siviero A, Gallo E, Maggini V, Gori L, Mugelli A, Firenzuoli F, Vannacci A (2015) Curcumin, a golden spice with a low bioavailability. J Herb Med 5(2):57–70. https://doi.org/10.1016/j.hermed.2015.03.001
130. Rachmawati H, Edityaningrum CA, Mauludin R (2013) Molecular inclusion complex of curcumin–β-cyclodextrin nanoparticle to enhance curcumin skin permeability from hydrophilic matrix gel. AAPS PharmSciTech 14(4):1303–1312. https://doi.org/10.1208/s12249-013-0023-5

131. Thayyullathil F, Chathoth S, Hago A, Patel M, Galadari S (2008) Rapid reactive oxygen species (ROS) generation induced by curcumin leads to caspase-dependent and -independent apoptosis in L929 cells. Free Radic Biol Med 45(10):1403–1412. https://doi.org/10.1016/j.freeradbiomed.2008.08.014
132. Kloesch B, Becker T, Dietersdorfer E, Kiener H, Steiner G (2013) Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. Int Immunopharmacol 15(2):400–405. https://doi.org/10.1016/j.intimp.2013.01.003
133. Chakravarti N, Kadara H, Yoon DJ, Shay JW, Myers JN, Lotan D, Sonenberg N, Lotan R (2010) Differential inhibition of protein translation machinery by curcumin in normal, immortalized, and malignant oral epithelial cells. Cancer Prev Res (Phila) 3(3):331–338. https://doi.org/10.1158/1940-6207.capr-09-0076
134. Choudhuri T, Pal S, Das T, Sa G (2005) Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 phase of cell cycle in a p53-dependent manner. J Biol Chem 280(20):20059–20068. https://doi.org/10.1074/jbc.M410670200
135. Irish J, Blair S, Carter DA (2011) The antibacterial activity of honey derived from Australian flora. PLoS One 6(3):e18229. https://doi.org/10.1371/journal.pone.0018229
136. El Sohaimy SA, Masry SHD, Shehata MG (2015) Physicochemical characteristics of honey from different origins. Ann Agric Sci 60(2):279–287. https://doi.org/10.1016/j.aoas.2015.10.015
137. Majtan J, Klaudiny J, Bohova J, Kohutova L, Dzurova M, Sediva M, Bartosova M, Majtan V (2012) Methylglyoxal-induced modifications of significant honeybee proteinous components in manuka honey: possible therapeutic implications. Fitoterapia 83(4):671–677. https://doi.org/10.1016/j.fitote.2012.02.002
138. Jull A, Walker N, Parag V, Molan P, Rodgers A (2008) Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. Br J Surg 95(2):175–182. https://doi.org/10.1002/bjs.6059
139. Simon A, Traynor K, Santos K, Blaser G, Bode U, Molan P (2009) Medical honey for wound care—still the 'latest resort?'. Evid Based Complement Alternat Med 6(2):165–173. https://doi.org/10.1093/ecam/nem175
140. Oryan A, Alemzadeh E, Moshiri A (2016) Biological properties and therapeutic activities of honey in wound healing: a narrative review and meta-analysis. J Tissue Viability 25(2):98–118. https://doi.org/10.1016/j.jtv.2015.12.002
141. Grigoryan K (2016) Chapter 12 - Safety of honey. In: Prakash V, Martín-Belloso O, Keener L et al. (eds) Regulating safety of traditional and ethnic foods. Academic Press, San Diego, pp 217–246. https://doi.org/10.1016/B978-0-12-800605-4.00012-8
142. Lansdown AB (2006) Silver in health care: antimicrobial effects and safety in use. Curr Probl Dermatol 33:17–34. https://doi.org/10.1159/000093928
143. Rai MK, Deshmukh SD, Ingle AP, Gade AK (2012) Silver nanoparticles: the powerful nanoweapon against multidrug-resistant bacteria. J Appl Microbiol 112(5):841–852. https://doi.org/10.1111/j.1365-2672.2012.05253.x
144. Rai M, Yadav A, Gade A (2009) Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv 27(1):76–83. https://doi.org/10.1016/j.biotechadv.2008.09.002
145. Durani P, Leaper D (2008) Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. Int Wound J 5(3):376–387. https://doi.org/10.1111/j.1742-481X.2007.00405.x
146. Djordjević VB (2004) Free radicals in cell biology. In: Jeon KW (ed) Int Rev Cytol, vol 237. Academic Press, Amsterdam, pp 57–89. https://doi.org/10.1016/S0074-7696(04)37002-6
147. McDonnell G (2009) The use of hydrogen peroxide for disinfection and sterilization applications. In: Marek I (ed) PATAI'S chemistry of functional groups. Wiley, New York. https://doi.org/10.1002/9780470682531.pat0885
148. Greenwood D (2010) CHAPTER 31 - Miscellaneous antibacterial agents. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ (eds) Antibiotic and chemotherapy (Ninth edn). Saunders, London, pp 356–365. https://doi.org/10.1016/B978-0-7020-4064-1.00031-2
149. Lee VJ (2007) 7.22 - Anti-gram positive agents of natural product origins. In: Taylor JB, Triggle DJ (eds) Comprehensive medicinal chemistry II. Elsevier, Oxford, pp 653–671. https://doi.org/10.1016/B0-08-045044-X/00222-4
150. Kester M, Karpa KD, Vrana KE (2012) 4 - Treatment of infectious diseases. In: Hyde M, Hall A (eds) Elsevier's integrated review pharmacology (second edn). W.B. Saunders, Philadelphia, pp 41–78. https://doi.org/10.1016/B978-0-323-07445-2.00004-5
151. Heyneman A, Hoeksema H, Vandekerckhove D, Pirayesh A, Monstrey S (2016) The role of silver sulphadiazine in the conservative treatment of partial thickness burn wounds: a systematic review. Burns 42(7):1377–1386. https://doi.org/10.1016/j.burns.2016.03.029
152. Carr HS, Wlodkowski TJ, Rosenkranz HS (1973) Silver sulfadiazine: in vitro antibacterial activity. Antimicrob Agents Chemother 4(5):585–587
153. Rai D, Singh JK, Roy N, Panda D (2008) Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. Biochem J 410(1):147–155. https://doi.org/10.1042/bj20070891
154. Yun DG, Lee DG (2016) Antibacterial activity of curcumin via apoptosis-like response in Escherichia coli. Appl Microbiol Biotechnol 100(12):5505–5514. https://doi.org/10.1007/s00253-016-7415-x
155. Tyagi P, Singh M, Kumari H, Kumari A, Mukhopadhyay K (2015) Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. PLoS One 10(3):e0121313. https://doi.org/10.1371/journal.pone.0121313
156. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K (2014) A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int 2014:186864. https://doi.org/10.1155/2014/186864
157. Mandal MD, Mandal S (2011) Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed 1(2):154–160. https://doi.org/10.1016/S2221-1691(11)60016-6
158. Wound dressings (2016) In: Aronson JK (ed) Meyler's side effects of drugs (Sixteenth edn). Elsevier, Oxford, pp 525–526. https://doi.org/10.1016/B978-0-444-53717-1.01644-9
159. Tamma PD, Aucott SW, Milstone AM (2010) Chlorhexidine use in the neonatal intensive care unit: results from a national survey. Infect Control Hosp Epidemiol 31(8):846–849. https://doi.org/10.1086/655017
160. Chapman AK, Aucott SW, Gilmore MM, Advani S, Clarke W, Milstone AM (2013) Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates. J Perinatol 33(10):768–771. https://doi.org/10.1038/jp.2013.61
161. Shah AR, Liao LF (2017) Pediatric burn care: Unique Considerations in Management. Clin Plast Surg 44(3):603–610. https://doi.org/10.1016/j.cps.2017.02.017