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Review

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Review

Challenges and innovations in treating chronic and acute wound infections: from basic science to clinical practice

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Abstract

Acute and chronic wound infection has become a major worldwide healthcare burden leading to significantly high morbidity and mortality. The underlying mechanism of infections has been widely investigated by scientist, while standard wound management is routinely been used in general practice. However, strategies for the diagnosis and treatment of wound infections remain a great challenge due to the occurrence of biofilm colonization, delayed healing and drug resistance. In the present review, we summarize the common microorganisms found in acute and chronic wound infections and discuss the challenges from the aspects of clinical diagnosis, non-surgical methods and surgical methods. Moreover, we highlight emerging innovations in the development of antimicrobial peptides, phages, controlled drug delivery, wound dressing materials and herbal medicine, and find that sensitive diagnostics, combined treatment and skin microbiome regulation could be future directions in the treatment of wound infection.

Key words: Wound infections, Skin microbiome, Diagnosis, Antimicrobial wound dressings, Herbal medicine, Hydrogels, Antimicrobial peptides, Phages, Drug delivery

Highlights

- Both acute and chronic wound infection and associated microorganisms are reviewed.
- Current advances and challenges in treating wound infections, particularly diagnosis, non-surgical and surgical approaches are described.
- Innovations in wound infection control, including antimicrobial peptides, wound dressing materials and herbal medicine are discussed.

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Background

Acute and chronic wounds affect >6 million people every year in the USA States with a cost of $25 billion (USD) [1]. Uncomplicated, acute wounds can heal within a predictable period depending on the nature of the injury, with clinical signs of erythema, swelling, warmth and purulent discharges for infection. Chronic wounds, for instance diabetic ulcers, display delayed wound healing due to confounding factors such as aging, stage of diabetic disease, medication (or treatment) compliance, associated peripheral neuropathy, immunocompromised status and/or arterial and venous insufficiency. Despite significant advances in wound management over the last decades, scientists and clinicians continue to develop novel therapeutic approaches aimed at preventing and controlling infections for both acute and chronic wounds [2]. Intravenous injection or oral administration of antibiotics are widely used in general practice for acute wounds [3], while in treating chronic wound infections, antimicrobial creams, ointments or gels are accepted to eliminate the deep infections caused by the migration of bacteria or fungi to the subcutaneous tissues [4]. However, biofilm colonization, delayed healing and drug resistance remain as challenges in the management of wound infections. In this review, we outline acute and chronic wound infections with associated micro-organisms and discuss the challenges, innovations and future directions in treating wound infections, with focuses on diagnostics, therapeutic approaches and the regulation of the skin microbiome.

Review

Acute wound infection

Acute wounds normally heal within 14 days, depending on the type, severity and size of the injury as well as the patient's age, co-morbidities and post-injury care. Due to the damage of the skin barrier and local microbial colonization (moisture, temperature and nutrient conditions), infections occur in ~5.6–26% of wounds [5]. Burn, surgical site and traumatic wounds are the top three wounds that are prone to infection [6].

Burn injury caused by heat, flame, chemicals, electricity or radiation [7] is a major public health problem with high morbidity and mortality worldwide and ~180,000 deaths per year [8]. Moreover, burn wound infections are responsible for >75% of burn mortality worldwide [9,10]. Various pathogens have been identified in the acute phase post burn injury [11], including *Staphylococcus aureus (S. aureus), Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa)*, coagulase-negative *Staphylococci* [10] and many other aerobic and anaerobic microorganisms (Figure 1 and Table 1). Fetal methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci in burn injuries are found to be increasing every year, particularly in patients with full-thickness injury [11,12].

Acute surgical site wound infections (SSWIs) occur in many surgical wounds ranging from elective to traumatic non-elective procedures. During surgery, microorganisms on sutures or prostheses can induce both superficial and deep infection [13,14]. Studies have shown that acute SSWIs increase morbidity and mortality, while patients with acute SSWIs are 2–11 times more likely to succumb to complications than uninfected patients [14–16]. The most common pathogenic microorganisms for acute SSWIs are *Staphylococcus epidermidis* and *S. aureus*. As cutaneous commensal bacteria, *Staphylococcus* can form biofilms on the epidermis, which is the main virulence factor, and *S. aureus* is often found in medical device related infections [17]. Other microorganisms have also been isolated from acute SSWIs, including *E. coli*, *Clostridium difficile*, coagulase-negative *Staphylococci* [11], *Legionella pneumophila, Mycobacterium chelonae, Clostridium perfringens, Mycobacterium fortuitum, P. aeruginosa and Acinetobacter baumanii* [18].

Traumatic wounds include abrasions or laceration wounds with extensive tissue, bone and internal organ damage [19]. The common pathogens of traumatic wound infections are Gram-positive *S. aureus* and Gram-negative *P. aeruginosa* [20]. Infections in skin laceration wounds were noted mostly in elderly patients with chronic use of corticosteroids [20], while 2–10% of infections are reported to be of plantar puncture wounds, mainly caused by *Staphylococcus* or *Streptococcus* [21]. High mortality and septic complications, including abdominal infections, necrotizing fasciitis and diffuse septic peritonitis, can often be attributed to sepsis induced by wound infection [22]. Invasive fungal infection is also known as a serious complication for traumatic wounds, usually caused by agricultural accidents, war bombings and natural disasters, resulting in deep tissue wounds [23]. As fungi can survive in both acidic and iron-rich environments, they can stimulate severe pelvic injuries or limb amputations [24,25]. Although fungal infections are less reported compared to bacterial infections they lead to high amputation and mortality rates of 31 and 38%, respectively [25].

Chronic wound infection

In contrast to acute wounds, chronic wounds are complicated by having a delayed wound healing capacity. Chronic wounds occur more often in elderly people, patients with diabetes, vascular disease, obesity, malnutrition and chronic mechanical stress, or a combination of these factors [26]. Most chronic wounds are colonized by polymicrobial communities that can form biofilms, resulting in excessive inflammation and infection susceptibility which significantly delay wound repair [27] (Figure 1). Generally, Gram-negative bacteria are common colonizing organisms in chronic wounds, accounting for 61% of all microbial isolates. *S. aureus* is the most commonly found pathogen in chronic infections, followed by *P. aeruginosa*. Other pathogenic microorganisms are *Proteus mirabilis*,

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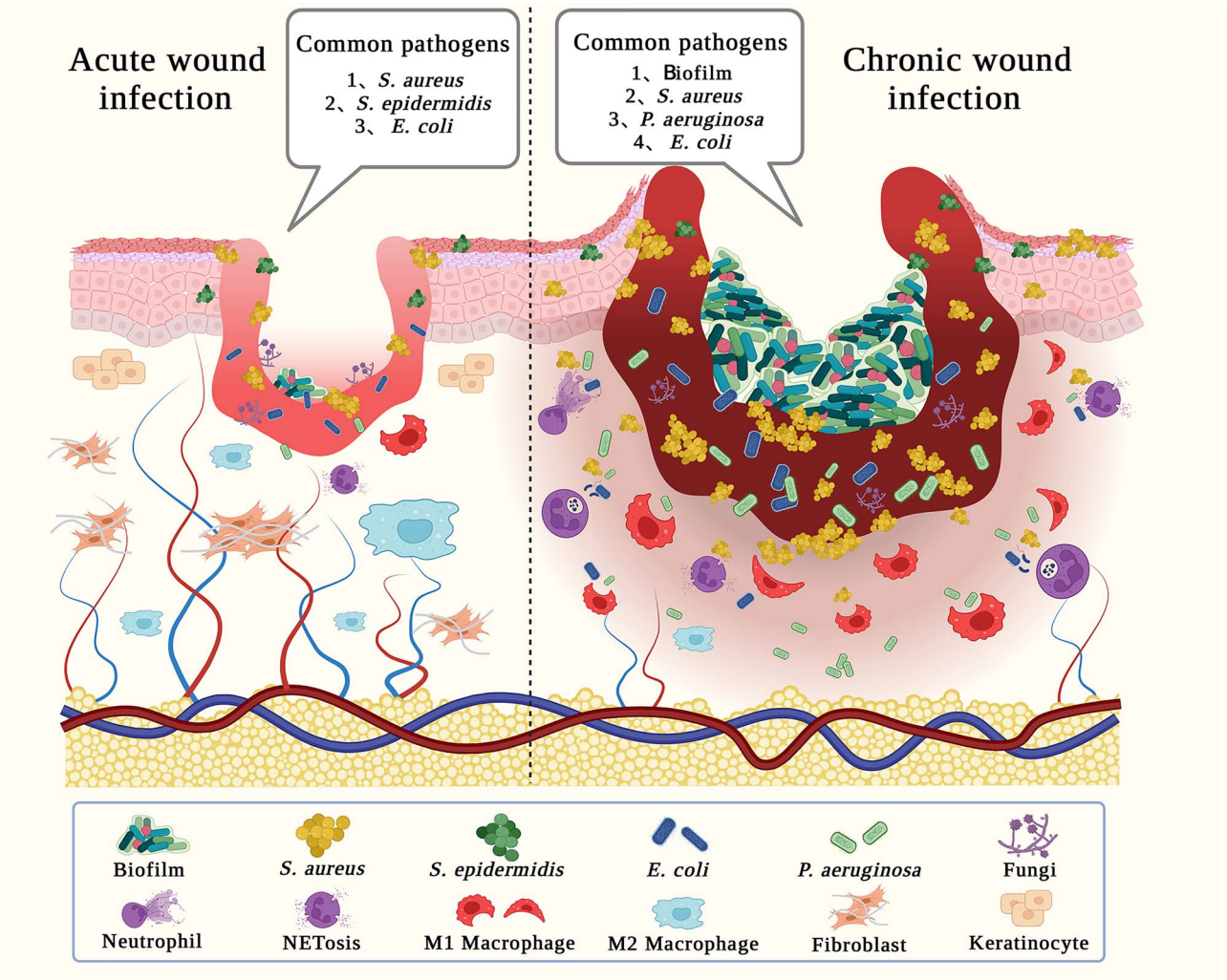

Figure 1. Differences between acute and chronic wound infection together with common pathogens. *S. aureus Staphylococcus aureus, S. epidermidis Staphylococcus epidermidis, E. coli Escherichia coli, P. aeruginosa Psuedomonas aeruginosa*

Table 1. Common pathogens causing acute wound infection

Group	Species
Gram negative	*Psuedomonas aeruginosa*, *Actinetobacter baumanni*, *Enterobacteriaceae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter spp.*, *Proteus spp.*, *Bacteroides spp.*
Gram positive	*Staphylococcus aureus*, *Streptococcus*, *Enterococcus*, *Micrococcus*, *Corynebacterium*, *Streptococcus pyogens*, *Corynebacterium diphtheria*, Coagulase-negative *staphylococci*
Fungi	*Candida spp.*, *Non-albicans Candida*, *Aspergillus*, *Blastomycosis*, *Mucor circinelloides*, *Candida spp.*, *Aspergillus spp.*, *Fusarium spp.*, *Alternaria spp.*, *Rhizopus spp. Mucor spp.*
Viruses	*Herpes simplex*, *Varicella-zoster*
Drug-resistant strains	Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococci*, extended-spectrum beta-lactamases, MDR *Psuedomonas aeruginosa*

E. coli, *A. baumanni* and *Klebsiella pneumoniae* [28]. Anaerobic bacteria in chronic wounds include *Prevotella, Peptoniphlus, Peptostreptococc, and Anaerococcus* [29].

Biofilm is one of the major challenges in the treatment of chronic wound infections. It occurs for >60% of chronic wound infections and only 6% of acute wound infections [30,31]. Biofilms are complex microbial communities of bacteria and fungi that exist as unicellular, planktonic or multicellular communities and aggregates, surrounded by a polymeric matrix of polysaccharides, lipids, proteins and nucleic acids. The matrix facilitates signaling among microorganisms by producing population-sensing molecules. This

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cross-communication can further aid microbial proliferation, optimize nutrient uptake and regulate virulence, leading to a persistent impairment of wound healing [29,30,32]. Bacterial endotoxin- and exotoxin-associated wound infections are found to induce non-specific and specific immune responses [33], while excessive inflammation can further trigger adverse outcomes, where inflammatory cells recruited at the wound site produce large amounts of proteases that degrade the extracellular matrix and delay wound healing [34].

Diabetic foot ulcer is a type of wound associated with chronic infection, and is a complication of diabetes mellitus, particularly in advanced disease including diabetic neuropathy [35]. *S. aureus* is known to be the most common infecting species (accounting for >50% of all wounds) [36,37], with other causative organisms including coagulase-negative *Staphylococcus*, *Streptococcus streptococci spp*., MRSA, *Enterococcus spp., Corynebacterium spp., Enterobacteriaceae* and *P. aeruginosa* [38]. Up to 90% of the bacteria found in diabetic ulcer wounds are pathogenic or exclusively anaerobic, including Gram-positive *cocci*, *Prevotella spp., Poryphyromonas spp*. and *Bacteroids fragilis* [38], whilst >75% of diabetic foot wounds are found to be colonized with fungi [39].

Pressure ulcers are defined as 'a localized injury to the skin and underlying tissue usually over a bony prominence in combination with shear' [40], particularly when wounds are exposed to a fecal environment. A study by Norman *et al*., showed that among 145 patients with pressure ulcers, *S. aureus* and Gram-negative *bacilli* were detectable in 112 wounds [40]. Lower extremity venous ulcers are normally caused by venous hypertension [41] in aging and obese people with severe leg trauma or vascular surgery [42]. Wound sites having high moisture are ideal for microbial growth, therefore, all lower extremity venous ulcers are colonized by microorganisms, resulting in serious infections. The most common microorganisms at the ulcer site are *S. aureus* and *P. aeruginosa*, with *Streptococcus haemolyticus* and MRSA also being identified [42].

Current advances and challenges in treating wound infections

Clinical diagnosis Clinical diagnosis is the first step to prevent further complications (Figure 2). However, classification of wound infections remains a challenge in practice. In general, almost all wounds contain microorganisms, but not all wounds develop infections. A clinical report by Leaper *et al*. showed that ~50% of patients who have a local wound infection do not show any sign of systemic infection [43], making diagnosis difficult [44]. Currently, there is a lack of objective clinical diagnostic criteria for wound infection, and clinicians usually make subjective judgments based on experience. Diagnostic criteria (e.g. foul odor, friable or discolored granular tissue) are highly subjective [44,45], resulting in high rates of misdiagnosis or overtreatment with antibiotics. As a result, patients can be at risk of developing multi-resistance bacterial strains [46].

In vitro culture has been used as the golden standard for clinical identification of microorganisms since the 19th century [26]. However, it is only applicable for 1% of known microorganisms that can be cultured *in vitro* under laboratory conditions [47]. In contrast, most microorganisms, such as fungi and anaerobes, are yet to be identified using *in vitro* culture [26]. It takes ~24–48 h to obtain results by this method. Alternatively, 16S rRNA gene sequencing is a state-of-the art technology that is widely used in basic science for identifying bacteria in various types of wounds. The limitations of this technique are that it cannot distinguish alive or dead microorganism, it can only be used for the identification of bacteria but not fungi or viruses, while the cost is high and it is time-consuming [48,49].

Clinical wound dressing materials Wound dressings are used to temporarily cover wounds and to prevent or manage wound infections. However, wound dressing may become a favorable place for microorganisms and biofilm formation, resulting in increased microbial load and delayed wound healing [18]. The ideal wound dressing should be flexible and immune-compatible, forming a physical defensive barrier but allowing oxygen exchange [50]. Many novel clinical wound dressings have been developed and are utilized, including sponges, hydrofibers, hydrocolloids, fucoidan, collagen, hydrogels and films. Antimicrobial wound dressings can be categorized as antiseptic, ionic/nanocrystalline silver and antibiotic. An antiseptic wound dressing is a treatment that releases antiseptics to eliminate microorganisms within the tolerance limits of living tissue [51]. Products can contain either silver (e.g. Aquacel AG), nano-crystalline silver (e.g. ACTICOAT) or cadexomer iodine (e.g. Iodosorb™) as antimicrobials. Applications of silver compounds on acute wounds was a major milestone in topical therapy, which remarkably reduced the incidence of acute wound-induced sepsis and death. Bactigras™ are cotton roving fabrics containing 0.5% w/w chlorhexidine acetate for preventing wound infection by Gram-positive and Gram-negative bacteria, but not by spores, fungi and viruses [52]. Iandine is a low-adhesive knitted viscose fabric impregnated with a polyethylene glycol matrix containing 10% povidone iodine, which is the broadest spectrum antiseptic in human use, while Iodosorb™ is a unique antiseptic dressing composite of cadexomer microbeads with 0.9% elemental iodine. Iodosorb™ is effective against biofilm formation due to its high release rate of antimicrobials [53]. Ionic or nanocrystalline silver-containing dressings are also widely accepted in the control and treatment of wound infections because of their broad-spectrum antimicrobial activity [33].

Antibiotics The first antibiotics were discovered in the late 19th century, and over the past hundred years, various antibiotics such as sulfonamides, penicillin, streptomycin, tetracycline and vancomycin have been clinically used for infection

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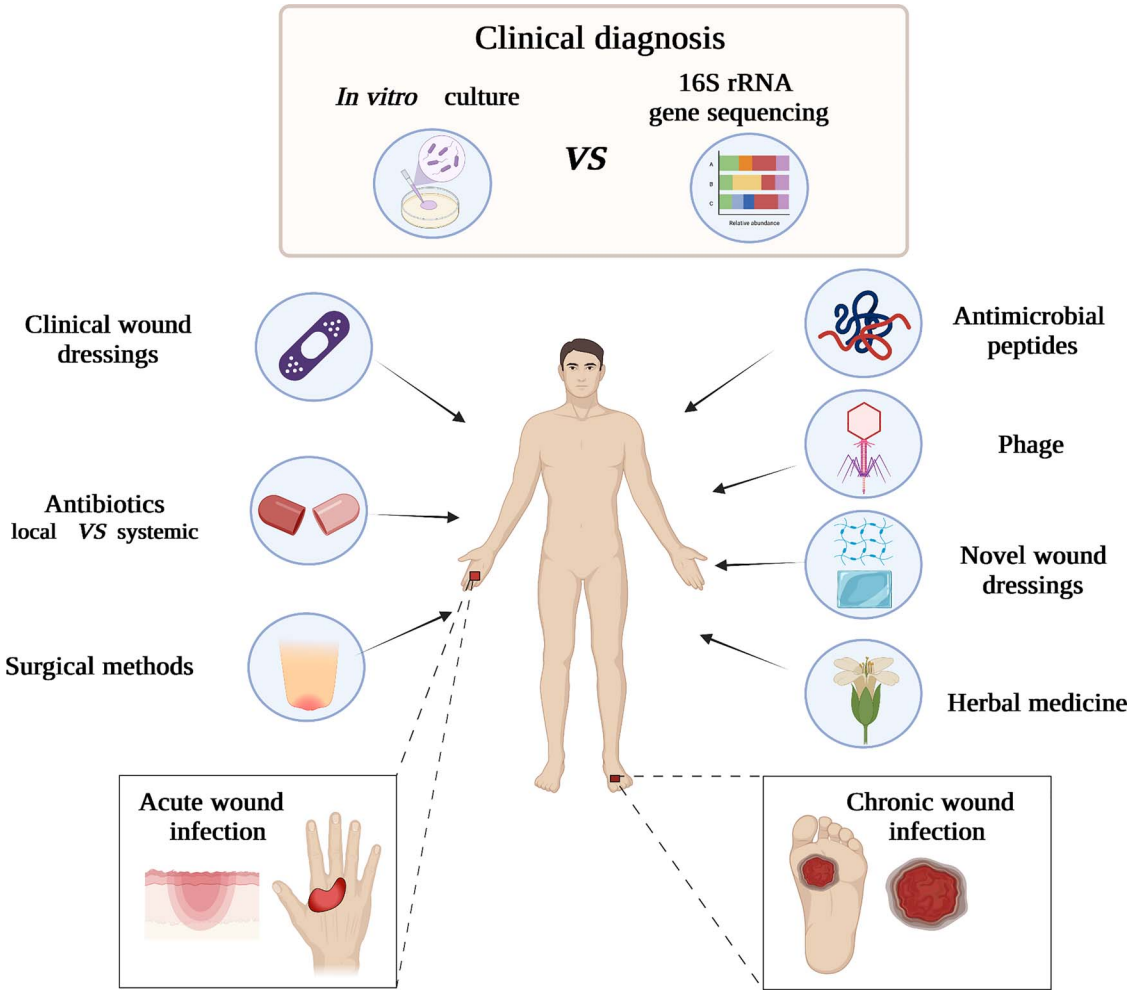

Figure 2. Therapeutical approaches and innovations in managing acute and chronic wound infection

control. At present, the extensive use and overuse (long-term or for uninfected wounds) of topical or systemic antibiotics has led to a global antibiotic resistance crisis [48]. It is estimated that ~70% of bacteria causing wound infections are now resistant to one antibiotic [33]. The spread of resistant strains has become a pandemic threat to human health with >700,000 deaths per year, and the number of deaths is expected to rise to 10 million annually by 2050 [54]. The International Committee of the Red Cross recommends that the best type of 'antibiotic' is the appropriate surgical treatment [55], and the Infectious Diseases Society of America recommends that antibiotics should be avoided for diabetic foot ulcers if there are no signs of infection [56]. Antiseptics with antimicrobial effects are being utilized more frequently to overcome drug resistance of antibiotics. Octenidine hydrochloride , polyhexamethylene biguanide, povidone-iodine and sodium hypochlorite are currently utilized in clinics as topical treatments for wound infections because of their high bactericidal and anti-biofilm forming activity [30].

Surgical methods The standard surgical approach to treating wound infection is debridement, and if the infection is deep into muscle or the adipose layer, amputation is required to prevent systemic infection or sepsis. Debridement is a common surgical approach for the treatment of acute wounds, such as burn injury. It can help to reduce bacterial diversity and promote wound epithelialization, while it can also reduce the blood load on the wound via removing necrotic infected tissue, apoptotic cells and biofilms from the wound [30,57,58]. High microbial loads can lead to wound deterioration, osteomyelitis and ultimately amputation [35]. Patients with severe limb ischemia usually require below-knee amputation, and postoperative wound closure is effective in reducing reinfection [59]. First pioneered in 1920, radiographic amputation was utilized in salvage surgery for proximal phalangeal dysfunction. It can also control wound infection, vascular insufficiency and congenital anomalies of the hand [60]. However, reinfection after amputation remains a risk as patients with diabetic foot ulcers have a fairly high risk (40%) of mortality after amputation [61].

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Table 2. Representative animal models of acute wound infection

Infection model	Animal species	Modeling methods	Microorganisms
Burn infections	Rodents and pig	Heat source used: boiling water, burning ethanol bath, gas flame, pre-heated double brass blocks, pre-heated single metal plate/bar, etc.	*Psuedomonas aeruginosa*, *Staphylococcus aureus, Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Candida albicans*.
Surgical site infections	Mouse, rat and pig	Incisional wounds with foreign bodies, subcutaneous injection of foreign bodies and microorganisms into pocket wounds with or without foreign bodies.	*Staphylococcus aureus*, *Psuedomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*.
Skin abrasion wound infections	Mouse, rat and rabbit	Needle scratch model, blade scrape model, tap striping model, sand paper model and dermatome model.	*Staphylococcus aureus*, *Psuedomonas aeruginosa* and *Candida albicans*.
Excisional wound infections	Mouse, rat, rabbit and pig	Removing the full-thickness skin.	*Staphylococcus aureus*, *Psuedomonas aeruginosa*, *Escherichia coli* and methicillin-resistant *Staphylococcus aureus*.
Lacerated wound infections	Guinea pig and rat	Non-crushed lacerated wounds and crushed lacerated wounds.	*Staphylococcus aureus*, *Streptococcus pyogenes*, *Psuedomonas aeruginosa, Klebsiella pneumoniae* and *Proteus mirabilis*.

Animal models Animal models aimed at studying the complex biochemical processes in the treatment of wound infections and evaluating the biosafety and efficacy of medical treatments have been well developed. Currently, animal models of wound infection vary between animal species, different modeling drugs and equipment, microbial species and inoculation amount, size and depth of the wound. For studying acute wound infection, large or small animals with burn infection, surgical site infection, skin abrasion infection or laceration wound infection are commonly utilized (Table 2) [20], while animal models of chronic wound infection are described for diabetic wound infection only (Table 3) [62,63]. Additionally, the model pathogenic microorganisms are *S. aureus* and *P. aeruginosa* [20]. Rodents such as mice have been found to be the most popular model due to the similarity of their immune systems to that of humans and the ability to create gene knockout varieties. However, FDA guidance recommends that all new drugs need to be assessed on two animal models involving a non-rodent large animal [62]. In such case, porcine models are commonly used to investigate new approaches for the treatment of wound infection. The skin structure of the pig is similar to human skin, and both pig and human wounds heal via re-epithelialization not by contractile healing [64]. However, limitations in using different animal models still exist as none of the models can completely mimic wound infection in humans [65]. Moreover, current animal studies mainly focus on local wounds, but the systemic conditions, including systemic inflammatory response and changes in metabolism, should also be considered [63].

Innovations in wound infection control

Antimicrobial peptides (AMPS) AMPs are an emerging class of drugs for the treatment of traumatic infections [57,66] and have tremendous research value in the treatment of severe chronic infections (Figure 2). To date, >2000 natural or synthetic AMPs have been developed with broad-spectrum antimicrobial properties that are less likely to develop drug resistance. AMPs that can be extracted from insects, animals or plants, including tylotoin, plant defensins and LL-37, have been investigated for their novel antimicrobial properties [67]. Peptides induce cell death by interacting electrostatically with microbial cell membranes, inducing porous membrane formation and inhibiting cell wall formation and protein synthesis, resulting in an inhibition of micro-organism proliferation [68]. Current investigations of AMPs are focussed on increasing their activity. Based on studying human thrombocidin-1-derived peptide L3 (a protein isolated from human blood platelets that has the ability to destroy microorganism) [69], a new AMPs named TC-19 was synthesized, with promising results against *S. aureus* and *A. baumannii*. Compared to rifampicin and ciprofloxacin, TC-19 exhibited minimal drug resistance [70]. In a full-thickness wound model, TC-19-containing hypromellose ointment was capable of suppressing *S. aureus* infection significantly [69]. In a study of a novel synthetic cationic peptide, AMC-19, effective antimicrobial results were reported in a MRSA-induced wound infection [71]. Results also showed high stability of AMC-19 with a 7-fold reduced bacterial load in 3 days, demonstrating its potential against MRSA via topical administration [72]. Because of their low activity, nonspecific cytotoxicity and susceptibility to proteolysis, ongoing studies aim to further develop a second generation of AMPs. In the second generation, a modified peptide, DGL13K, proved to have enhanced antimicrobial activity [73]. Topical administration of DGL13K ointment on a burn infection model showed a significantly decreased bacterial load post treatment [73]. Unfortunately, no topical AMP drugs are commercially available [57] and the clinical effects, long-term safety and side effects in patients are yet to be studied.

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Table 3. Representative animal model of diabetic wound infection

Animal species	Induction of diabetes mellitus in animals	Induction of wound in diabetic animals	Microorganism
Mouse, rat, rabbit, dog, guinea pig, pig	1. Chemically-induced diabetes mellitus: streptozotocin, alloxan, dithizone, gold thioglucose, monosodium glutamate. 2. Genetic manipulation: db/db mouse, KK-Ay mouse, ob/ob mice, Goto–Kakizaki rat, Otsuka Long Evans Tokushima fatty rat, Spontaneous diabetic Torii rat, Zucker diabetic fatty rat, Watanabe heritable hyperlipidemic rabbit and Postprandial hyper- triglyceridemia rabbit. 3. Virus-induced diabetes mellitus: D-variant encephalomyocarditis, coxsackie B4 virus. 4. Hormone-induced diabetes mellitus: growth hormone, corticosteroid.	Excision wound model, incision wound model, burn wound model, ear wound model, dead space wound model, tape stripping wound model, pressure ulcer model, parabiosis wound model, denervated wound model, skinfold chamber model, xenograft wound model.	*Psuedomonas aeruginosa* and *Staphylococcus aureus*.

In order to avoid inactivation of AMPs caused by their degradation by various proteases secreted by human pathogens, such as *P. aeruginosa* elastase, *P. mirabilis* proteinase, *Enterococcus faecalis* gelatinase and *Streptococcus pyogenes* cysteine proteinase, researchers improved their antibacterial activity by enhancing their stability to proteases and their stability under high salt conditions. Methods include using terminal modifications such as N-terminal acetylation and/or C-terminal amidation, replacing amino acids in AMPs with non-encoded α-amino acid derivatives which can reduce the susceptibility of AMPs to microbial proteases, particularly the complete substitution of D-amino acids, and AMP multimerization. Moreover, the antibacterial ability can be improved by varying the hydrophobicity and amphiphilic affinity of AMPs or via stabilizing the structure through dimerization or cyclization of disulfide bonds. At present, novel therapeutics also include utilizing carriers and scaffolds such as liposomes and polymers to achieve controlled delivery of AMPS that can further increase the antimicrobial activity and stability and reduce toxicity and protease degradation [74–76].

Controlled drug delivery systems Drug delivery systems are widely used to deliver antibiotics, growth factors, genes and cells for preventing or curing wound infections. Microcarriers are designed and developed to incorporate unstable antibiotics for controlled drug release with significantly reduced risk of bacterial infection. However, due to the size of microcarriers, in the range of 10–50 μm, they are not suitable for intracellular delivery. Nanoparticles, such as polymer nanocarriers, lipid nanoparticles, and metal and metal oxide nanoparticles, can be precisely tailored to have specific drug properties or to target specific cell types. For instance, cationic polymers are reported as carriers for releasing anionic drugs [77]. Lipid-based nanoparticles normally exhibit sustained drug release based on smaller particle size and lipid composition, ensuring better interaction on the wound site with a prolonged release time [78]. Metal and metal oxide nanoparticles, such as silver, copper oxide, zinc oxide and titanium dioxide nanoparticles, have also been used as alternatives for the treatment of drug-resistant bacterial infections due to their high antibacterial activity. Because of the high surface area of metal nanoparticles, after binding with antibacterial agent, the area of the antimicrobial agent contact with bacteria is increased resulting in the destruction of bacterial membrane permeability and respiratory function [79]. The minimum inhibitory concentration value of gold nanoparticles immobilized with antimicrobial peptide surfactin is 80 times lower compared to that of free surfactin [80], and these nanoparticles were found to promote wound healing in a rat model of MRSA-infected wounds. Additionally, metal oxides (vanadium pentoxide, iron oxide and graphene) can be utilized as artificial enzyme catalysts to enhance the efficiency of H_2O_2 conversion to hydroxyl radicals (•OH), improving the antibacterial activity against *E. coli* and *Vitis vinifera* [81]. Innovative approaches such as *ex vivo* loading of neutrophils with antibacterial agents and use of cells as delivery vehicles have been reported previously [82].

Other advances and innovations in treating wound infection Phages are natural antibacterial agents that are highly abundant in the environment. Phages are capable of regulating bacterial populations via inducing bacterial lysis and disrupting bacterial metabolism, leading to self-destruction (Figure 2) [83]. Lytic tailed phages are increasingly subject to investigation for use in a clinical setting [84]. Lytic tailed phages consist of an icosahedral capsid head that contains double-stranded DNA (15–500 Kbp) and a tail covered by surface receptor proteins that interact with surface features of the host bacterium. Phages can adsorb to the host bacterium and inject phage DNA, delivering multiple phage virions which aim to kill the bacteria [85]. They are known to be highly specific to their bacterial host, targeting only one or a couple of different bacterial strains [86]. Cocktail therapy

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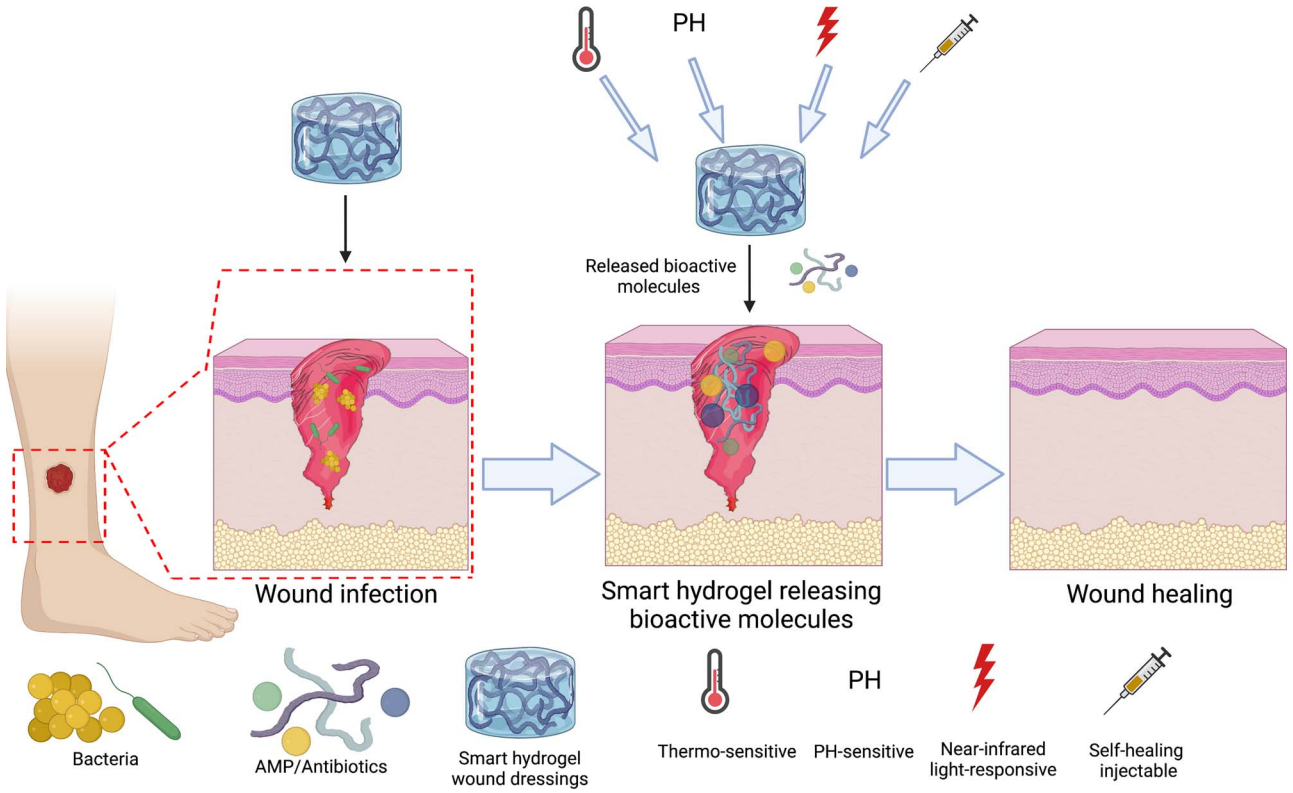

Figure 3. Smart hydrogel wound dressings in the treatment of wound infection. *AMP* antimicrobial peptide

using various phages in a single treatment has been studied in a clinical setting [87]. A phase I clinical trial using phage therapy showed that injection with *P. aeruginosa*, *S. aureus* and *E. coli* phages is safe and has high efficacy in treating chronic venous leg ulcers [88]. Topical administration of *Staphylococcal* phage S applied once a week was also found to heal small ulcers in 7 weeks and large ulcers in 18 weeks [89,90]. Despite advances in phage therapy research, there is no commercial phage product available yet [91].

Innovations in wound dressing materials

Advances have been made in the structure and properties of wound dressing materials, developing the ability for controlled release of antimicrobial drugs. Advanced wound dressings normally have the dual function of treating infections as well as promoting wound healing [68]. Recent advances in wound dressing materials can be sub-categorized into thermos-sensitive, pH-sensitive and light-responsive (Figure 3). These hydrogels have shifted the focus from traditional wound dressings to smart hydrogel wound dressings [92].

Thermo-sensitive hydrogels Thermo-sensitive hydrogels can change their characteristics in the context of temperature. With gelation time and temperature regulation being adjustable, thermo-responsive hydrogels can transform from the liquid state into a hydrogel, aiming for controlled delivery of active molecules or drugs [93,94]. Thermo-sensitive hydrogels have great clinical potential, particularly in the treatment of deep tissue damage or in the context of irregular wounds [95], allowing drugs to be precisely delivered to a target area. Natural and synthetic polysaccharides and proteins, such as chitosan and collagen [96], have been used in the production of thermos-sensitive hydrogels due to their biocompatibility with the wound environment. A thermo-sensitive hydrogel using chitosan cross-linked with β-glycerol phosphate was investigated in the treatment of a full-thickness surgical wound infected with *A. baumanni* and the results showed that the number of bacteria significantly decreased over 28 days [97].

pH-sensitive hydrogels The pH of wounds is different compared to healthy skin. Normally, the pH of healthy skin is 4.5–6.5, while the pH of a wound alkalizes to a value of 7.4. Due to alkaline byproducts of proliferating bacterial colonies, the pH of the wound can reach up to 9 [98–100]. Relying on pH variations between healthy and damaged tissue, a novel pH-sensitive hydrogel composed of red cabbage extract and methacrylate chitosan was successfully fabricated [101]. Results showed that red cabbage extract can be used to indicate the pH of the wound bed as well as accelerate wound healing [101]. This study indicates a new research avenue involving the synthesis of smart materials with 'diagnosis and curing' effects. pH-sensitive hydrogels can

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control the delivery of drugs in treating wound infections. A recent study showed that a nano-chitosan-enriched poly (ε-caprolactone) pH-sensitive nanofibrous membrane was used to release curcumin at a controlled rate according to changes in pH [102]. Under both acidic conditions of pH 1.2 and alkaline conditions of pH 7.4, ~48% of curcumin was released on day 15, but under neutral conditions, release of curcumin reached 71% on day 15 [102]. Similarly, a study by Ren *et al*. investigated a multi-functional hydrogel with a combination of tannic acid and keratin cross-linked with graphene oxide quantum dots. It could swell by >80% in alkaline conditions, which is better for wound healing. The high swelling rate, which allows the drug to be dispersed evenly, thus achieving a sustained-release, long term treatment of wound infection [103]. This multifunctional hydrogel promotes wound healing and is effective against *E. coli* and *S. aureus*. These findings suggest that pH-sensitive hydrogel should be further investigated as a new anti-infection wound dressing.

Near-infrared light-responsive hydrogels Light-responsive hydrogel is a smart hydrogel proportionally responsive to light wavelengths, allowing for controlled drug release. Among light-responsive hydrogels, near-infrared (NIR) light-responsive hydrogels have promising advantages in converting light into heat, utilized to destroy bacteria with no risk of drug resistance. Polydopamine nanoparticles (PDA-NPs) have also been used for their photothermal effects in biomedical applications due to their biocompatibility and biodegradability [68,104,105]. A study by Gao *et al*. investigated the photothermal effect of a PDA NIR-responsive hydrogel on wound infections in a *S. aureus* infected mouse wound model, showing encouraging anti-bacterial activity. An enhanced release of ciprofloxacin, a potent antibiotic that has the capability to destroy bacteria, was also instigated via local hyperthermia [106]. However, the uncertain biosafety of light-responsive hydrogel limits its translational research in clinical practice.

Other innovative hydrogels Self-healing injectable hydrogels are receiving more attention from researchers due to their multifunctionality. Self-healing injectable hydrogels can be prepared by two principles: dynamic covalent chemistry or weak interactions of supramolecular chemistry. Hydrogels prepared based on dynamic covalent chemistry are capable of achieving self-healing after the covalent bond is broken via introducing special covalent bonds, such as hydrazone bonds, imine bonds, disulfide bonds and Diels–Alder reversible covalent bonds. In contrast, hydrogels prepared based on supramolecular chemistry can fuse molecules or molecular chains through weak and reversible intermolecular forces to form cross-linked networks, such as hydrogen bond interactions, metal coordination bonds, ionic interactions and π–π interactions [107]. Self-healing injectable hydrogels with antibacterial activity, antioxidant, responsive, biocompatibility and electrical conductivity are all beneficial for the treatment of wound infection. A report showed that injectable self-healing carbon dot hydrogels with strong antibacterial activity using ε-poly(L-lysine) carbon dots and oxidized dextran can completely kill 10^7 CFU ml^{-1} *S. aureus* in 10 min [108].

Polypeptide hydrogels have optimized mechanical strength and can resist shear stress to the wound and selectively inhibit specific bacteria when incorporated with antibacterials to reduce drug resistance. In the past decade, peptide hydrogels with antibacterial effects have been effective in the treatment of all stages of infection, mainly for the treatment of *S. aureus*, *MRSA*, *S. epidermidis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae*, and future research will be focused on designing species-specific hydrogels [109]. Scientists found that when multi-domain peptide hydrogels have different charges, they can produce various regulatory effects on the host immune response. For instance, the multi-domain peptide hydrogels containing deprotonated carboxylic acids can trigger mild inflammation with minimal macrophage infiltration into the wound area and less secretion of inflammatory cytokines. However, multi-domain peptide hydrogels containing protonated amines normally induce severe inflammation, which diminishes over time, increase acute immune cells and promote host vascularization and tissue remodeling. Additionally, multi-domain peptide hydrogels containing guanidine ions trigger a long-term, highly pro-inflammatory response that is difficult to resolve [110]. These data showed that specific peptide hydrogels can be designed for different purposes in the treatment of wound infection [111].

Innovative herbal medicine

Herbal medicine has been used clinically since 5000 BC. Herbal medicine has minimal side effects and a low risk of drug resistance in treating wound infections (Figure 2). Natural products derived from insects such as *periplaneta Americana* extract [112], manuka honey [113] and the natural product chitin [114] have been clinically used in the treatment of various types of wound infection. A list of herbal medicines with antibacterial effects including herbal monomer and herbal compound is given in Table 4.

The therapeutic effect of herbal medicine is attributed to certain chemical components. Among them, natural tannins have shown remarkable antibacterial and antioxidant activities [115]. Tannins are polyphenolic compounds that are widely distributed in plants. A study showed that the total tannin content in *phaseoloides (L.) Merr* extract was found to be ~76.18% [116]. Transmission electron microscopy observations demonstrated that tannins could interfere with *S. aureus* and destroy the cell membranes, releasing their intracellular cytoplasm. This study showed that tannin promoted wound healing in rats infected with *S. aureus*. Subsequent to these investigations, tannic acid has been approved by the US FDA and clinically used for skin ulcers and burns due to its favorable antioxidant, hemostatic and antibacterial properties [117].

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Table 4. Some herbal medicines for infection wound healing

Herb	Sources of materials	Agent	Target microbes	Reference
Tannins	Extract of *Entada phaseoloides (L.) Merr*	Ointment	*Staphylococcus aureus (S. aureus)*	[116]
Tannic acid	Chemical reagent	Hydrogels	*Escherichia coli (E. coli), S. aureus*	[124]
Epigallocatechin gallate	Green tea	Cationic nanoliposomes	*E. coli*, methicillin-resistant *S. aureus*	[125]
Aloe vera	Extract of *Aloe vera* leaf	Nanofibers	*E. coli*	[126]
Aloe vera	Chemical reagent	Dressing	*E. coli, S. aureus*	[127]
Curcumin and *Aloe vera*	Chemical reagent	Dressing	*E. coli, S. aureus*	[128]
Trans-cinnamaldehyde and eugenol	Chemical reagent	Solution	*Acinetobacter baumannii*	[129]
Gentiana macrophylla	Extract of *Gentiana macrophylla* Roots	Solution	*E. coli, S. aureus*, *Staphylococcus epidermidis*, *Psuedomonas aeruginosa (P. aeruginosa)* , *Klebsiella pneumoniae*, *Micrococcus luteus*, *Enterococcus faecalis*, *Streptococcus uberis*	[130]
Allium sativum and *Cleome droserifolia*	Extracts of bulbs of fresh *A. sativum* and dried leaves of *Cleome droserifolia*	Nanofibers	*E. coli, S. aureus*, methicillin-resistant *S. aureus*	[131]
Rutin and quercetin	Chemical reagent	Nanofibers	*E. coli*, *S. aureus*	[132]
Extract of *Chamaecyparis obtusa* plant	*Chamaecyparis obtusa*	Solution	*S. aureus*, *Streptococcus pyogenes*	[133]
Salvia officinalis essential oil	The dried leaves of *Salvia officinalis*	Ointment	*S. aureus, P. aeruginosa*	[134]
Zataria multiflora essential oil	Chemical reagent	Ointment	*S. aureus, P. aeruginosa*	[135]
Rosemary essential oil	*Rosmarinus officinalis L*	Oil nanostructured lipid carriers (NLCs) in gel	*E. coli*, *S. aureus*, *S. epidermidis*, *Listeria monocytogenes*, *P. aeruginosa*	[136]
Olive oil and eucalyptus oil	Chemical reagent	NLCs	*S. aureus*, *Staphylococcus pyogenes*	[137]
Clove oil and sandalwood oil	Chemical reagent	Dressing	*E. coli*, *S. aureus*	[120]
Moringa oleifera seed polysaccharide	Extract of *Moringa oleifera* seed	Nanocomposite with silver	*E. coli*, *S. aureus, P. aeruginosa*	[122]

Essential oils extracted from herbals are also known to have antibacterial effects. Phenolic components are capable of fighting drug-resistant strains through their anti-biofilm activity [118,119]. The antibacterial clove oil contains eugenol, β-caryophyllene, oleic acid, lipids and small amounts of other ingredients [120]. According to Singh *et al*., eugenol, together with other phenolic compounds, denatures proteins and reacts with bacterial cell membrane phospholipids, affecting permeability, and subsequently causes cell lysis. The antibacterial activity of sandalwood oil is due to the destruction of cell wall and cell plasma membrane, leading to lysis and leakage of intracellular compounds. The combination of clove oil and sandalwood oil enhances antibacterial activity against *S. aureus* and *E. coli* by 98% [120]. In addition to its direct bactericidal effect, it can also mediate the secretion of antimicrobial peptides from HBD-3 and LL-37 through the olfactory receptor OR2AT4 to methicillin-sensitive *S. aureus*, MRSA and purulent [120]. In summary, it is expected that herbal derivatives are a group from which strong candidates for future treatment of chronic wound infections and biofilms will be selected.

One limitation of herbal medicine is its low activity compared to metals or synthetic drugs. At present, research has shifted to combining biomaterials or natural products, including silver (Ag^+), gold (Au) and other known antibacterial agents. A study has shown that 87.1% of δ-trienol and 12.9% of γ-trienol extracts obtained from *Bixa Orellana* L. (Bixaceae) seeds are isomers of vitamin E, which can be used as an immune adjuvant to increase the effectiveness of the antibiotic daptomycin in treating MRSA-infected wounds. This study suggests that the activity of antibiotics can be increased by boosting systemic immune responses against drug-resistant pathogens [121]. Another study demonstrated that polysaccharides isolated from *Moringa oleifera* seeds can be used to stabilize silver nanoparticles (AgNPs) [122]. *Moringa oleifera* seed polysaccharides have strong antimicrobial activity against pathogens collected from wounds, with minimal cytotoxicity toward mouse fibroblasts cells, and promote the migration of cells. In recent years, the multi-functionality and plasticity of herbal medicine and their derivatives are being investigated for their use as novel antimicrobial biomaterials. Cellulose microfibers (CM) extracted from Gleditsia triacanthos have been developed into a wound dressing via freeze-drying CM [123]. Controlled release of phenolic compounds from CM was found to be effective against Gram-negative and Gram-

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positive bacteria. A study showed pro-anthocyanidins and carrageenan conducting chemical reactions under various pH conditions and can be used as a visual system to monitor skin wound infections [100]. This finding also suggests that herbal medicines and their derivatives can serve not only in the treatment of infected wounds but can also have a role in the design of methods of detection and diagnosis.

Future directions

Early diagnosis An accurate diagnosis of wound infections is crucial to prescribe appropriate wound treatment. However, current approaches are speculative and time-consuming, with varying specificity and sensitivity. Novel diagnostic methods have been developed using the methods of PCR and auto-fluorescent imaging. A PCR kit, DxWound, has been developed to detect anaerobic bacteria, aerobic bacteria and fungi, allowing on-time monitoring for wound infections [138], while a portable autofluorescence imaging devices (e.g. MolecuLight™) has been utilized clinically for diagnosing wound infections [139]. Future directions may involve denaturing gradient-gel electrophoresis, fluorescence *in situ* hybridization, metabolomics and genomics, techniques currently demonstrating great potential for the development of accurate, rapid, simple, noninvasive, inexpensive and specific diagnosis in wound infections [140,141].

Combined therapies for wound infection For the treatment of acute or chronic wound infection, monotherapies, such as using antimicrobials, still have a high risk of antimicrobial resistance. Moreover, the spatial distributions of the microorganisms in the wound are complicated, the community behaviours of the bacteria are dynamic and the interactions between the polymicrobial and human immunity are undefined [142]. In response to these, dual therapies are expected to potentiate development of effective therapies for wound infections. For instance, silver-impregnated foam and topical negative pressure have been shown to have a synergistic effect in destroying bacterial biofilms in the wound [143]. Moreover, silver nanoparticles and neomycin have shown strong synergistic efficacy against MDR *P. aeruginosa* with faster wound contraction in a mouse model [144]. Some combination therapies like ultrasound-assisted debridement and vacuum pump therapy have also been studied to treat deep sternal wound infections in clinical trials [145]. All these pioneering studies demonstrated significant potential in wound treatment and prevention of infections. Other combinations include antimicrobial agents (antibiotics, herbal medicines and synthetics), immune-based antimicrobial molecules (antimicrobial peptides), therapeutic microorganisms (probiotics and bacteriophages) and cell therapy. These combinations are expected to lead to future developments in the treatment of wound infection, while external stimuli such as antimicrobial phototherapy (NIR based therapies), laser therapy, light-emitting diode, high-frequency ultrasound and microcurrent electrical stimulation may also be utilized in wound infection therapy.

Targeting skin microbiome as a new direction Skin microbiome is vital in maintaining the epithelial barrier function of skin and preventing the invasion of pathogenic microorganisms. Loss of microbial diversity in wound sites is known to stimulate prolonged inflammation. Clinical applications have demonstrated the efficacy of targeting the skin microbiome in the healing of atopic dermatitis by reintroduction of antimicrobial *Lactobacillus johnsonii* or *Vitreoscilla filiformis* [29]. Interestingly, *Lactobacillus plantarum* can inhibit *Pseudomonas* colonization, reduce collagen accumulation and accelerate wound repair with minimal scarring post burn injury [146,147]. Probiotics have also been observed to significantly reduce the length and depth of chronic wounds, suggesting their great potential in conjugating with antibiotics to treat wound infections. Ongoing studies of the skin microbiome are focusing on isolation and engineering of functional probiotics or microbiota, and studying the interactions between wound microbiome and regulation of host skin microbiome [148]. However, pioneering research findings suggest that pathogenic bacteria could play a beneficial role in wound healing by mediating the inflammatory response and tissue regeneration [149,150]. Therefore, future research may shift from killing or preventing the wound microbiome to controlling skin microbiome-mediated inflammatory responses.

Conclusions

Infection remains a challenge in both acute and chronic wounds, leading to increased morbidity, mortality and healthcare-associated costs. Gram-positive bacteria, such as *E. coli* and *P. aeruginosa*, and Gram-negative bacteria, like *S, aureus*, are found to be the most predominant pathogens, with multi-resistant strains continuing to increase in incidence. Promising findings in novel antimicrobial peptides, phages, cell therapy, development of pH- or NIR-responsive hydrogels together with herbal medicine will address current issues in wound infection and translate to general practice eventually. Early detection of wound infections, combination therapies and understanding the skin microbiome can also aid in the treatment and prevention of wound infections.

Abbreviations

AMP: Antimicrobial peptide; CM: Cellulose microfibers; CFU: Colony forming unit; FDA: Food and drug administration; MDR: Multiple drug resistence; NETosis: NETosis is a programme for formation of neutrophil extracellular traps; NIR: Near-infrared; PCR: Polymerase chain reaction; PDA-NP: Polydopamine nanoparticles; SSWIs: Surgical site wound infections.

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Conflicts of interest

None declared.

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