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Antibacterial Effects of Laser in Treating Contaminated Wounds

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Abstract

Bacterial infections persist as a major worldwide health issue. Regarded as the most distressing factor affecting the wound healing process, resulting in prolonged healing time, increased patient trauma, elevated treatment expenses, and substantial mortality and morbidity. The prevalence of antibiotic resistance among bacteria has led to the emergence of bacterial wound infection as an alarming and complex health issue. The effectiveness of traditional antibiotic treatments is progressively limited, prompting the exploration of alternative therapeutic approaches. Antibacterial Photodynamic Therapy (aPDT) using laser technology has shown great potential in treating persistent bacterial infections. This review aims to provide an extensive overview of different wound treatment strategies and infection management modalities within and surrounding the wound bed as well as the use of aPDT against different bacterial pathogens, with a particular focus on its potential to tackle the worldwide problem of bacterial infections.

Keywords: Chronic Wounds; Femtosecond laser; Antibacterial; Photodynamic therapy; Bacterial infection

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1. Introduction

The skin is the largest sensory organ, with a surface area of about 2 square meters (Chang et al., 2020). It's a layered structure made up of cells, fibers, and other components. Skin integrity is difficult to maintain, but it is an essential protection measurement against potentially harmful toxic substances and invading pathogenic microorganisms. Any skin injury provides a warm, moist, and nutritious environment for pathogenic microorganisms to infiltrate and thrive in. Therefore, rapid repair of these injuries is critical to minimize the risk of infection. There are different types of injuries, ranging from minor wounds to wounds that may lead to major disability or even death (Chang et al., 2020).

Wound healing is a distinct biological process characterized by a well-organized sequence of events. The process of healing is crucial in order to reduce tissue damage and ensure sufficient tissue perfusion, oxygenation, proper nourishment, and a moist environment to restore both the anatomical continuity and functionality of the injured skin area (Pierce & Mustoe, 1995). Appropriate wound healing typically progresses through four phases: (i) Hemostasis, (ii) Inflammation, (iii) Proliferation, and (iv) Remodeling of the scar tissue (Schultz et al., 2003; Singer & Clark, 1999).

The process of homeostasis is initiated immediately following an injury by the constriction of blood vessels and the subsequent creation of a fibrin clot (Barchitta et al., 2019). This mechanism effectively stops excessive bleeding and promotes the entry of platelets and growth factors into the body. Inflammation follows, characterized by the invasion of neutrophils to cleanse the wound and the activation of macrophages to facilitate tissue regeneration. Proliferation includes the processes of cell proliferation and migration, which ultimately result in the creation of granulation tissue and the contraction of wounds (Xue & Jackson, 2015). Ultimately, the process of remodeling, which takes many months to years, involves collagen remodeling and the production of scars, augmenting the strength of wounds. Healing results are influenced by a range of factors, including the size of the wound, the quality of the tissue, and the presence of necrosis (Nourian Dehkordi et al., 2019). Inadequate healing or delayed healing might result in the formation of acute or chronic wounds (RASHIDI et al., 2015).

2. Types of wounds

2.1. Acute wounds

Acute wounds are temporary tissue injuries that fully heal within the anticipated timeframe, typically ranging from 8 to 12 weeks. These wounds undergo a systematic progression of wound healing, resulting in minimum scarring and infrequent consequences. There are many types of acute wounds including minor burns, traumatic and surgical wounds (Boateng et al., 2008).

2.2. Chronic wounds

Non-healing or chronic wounds refer to tissue injuries that do not undergo the typical healing process and are frequently trapped in one or more stages of wound healing for an extended duration (usually the inflammatory and/or the proliferative phases). These wounds usually have a prolonged healing time, beyond 12 weeks, and often reoccur. Chronic wounds have a huge socioeconomic burden as a public health concern with an estimated prevalence of 1-2% of the population in developed countries. Patients with chronic wounds suffer from severe emotional and physical trauma. Chronic wounds commonly include various forms, including pressure ulcers, leg ulcers, diabetic ulcers, and nonhealing surgical wounds. Usually, many complications can be associated with chronic wounds such as infection, sepsis, amputation, and death (Boateng et al., 2008).

Repeated trauma, poor primary treatment, underlying physiological conditions, and many Additional factors contribute to the formation of chronic wounds. Therefore, identifying these factors is a primary clinical concern to provide appropriate treatment and prevention modalities (Boateng et al., 2008).

3. Factors affecting wound healing

Many factors may interrupt the healing process, causing prolonged trauma, higher treatment costs as well as significant mortality and morbidity. These factors are broadly classified into: Drugs: Some chemical agents have adverse effects on the healing process, such as Aspirin, Indomethacin, Tolmetin, Cytotoxic agents, radiation, immunosuppressants as well as chemotherapeutic drugs utilized in cancer treatment (Shpichka et al., 2019; Yildirimer et al., 2012).

Systemic factors: such as age (Enoch & Leaper, 2008), malnutrition (Demidova-Rice et al., 2012), as well as some underlying physiological conditions, for example, obesity, arterial disease, or diabetes (Boateng et al., 2008). Local factors: such as wound environment, moisture, local supply of blood and oxygen, as well as Infection; which is the single most crucial inevitable impairment to wound healing (Demidova-Rice et al., 2012; Shpichka et al., 2019).

Despite the presence of bacteria in the skin microbiome and wounds, a critical threshold of bacteria and the formation of clusters of these bacteria known as biofilms can potentially hinder the process of wound healing (Bowler et al., 2001). Infection can lead not only to chronic wounds but also to gangrene, amputation, and even death. The susceptibility to infection is present in both acute and chronic wounds (Gallo & Hooper, 2012). Chronic wounds are even more susceptible to bacterial infection and microbial colonization (Gallo & Hooper, 2012). In chronic wounds, the prolonged skin rupture and slower regenerative process (Nesi-Reis et al., 2018) increase the chances of microbial penetration and consequent proliferation (Lambrechts et al., 2005). Understanding these elements and their impact on wound healing is crucial in developing more effective therapeutic alternatives for chronic wounds infected by bacteria.

3.1. Bacterially infected wounds

Bacterial pathogens create a bioburden on the wound while competing for the limited oxygen and nutrient supply, resulting in weakened tissue that can easily be ruptured (Agren et al., 2000). The unlimited development of bacterial pathogens negatively impacts the progression of wound healing and causes local tissue damage (Frykberg & Banks, 2015; Schultz et al., 2003). This bacterial development starts as contamination with the presence and attachment of bacteria to the wound surface and progresses from acute to chronic colonization where the bacterial pathogen replicates till the wound reaches a critical colonization state and the healing has been impaired (Guo & Dipietro, 2010), to end as an infection with the bacterial pathogens invading the tissue and triggering a systematic response in a quick time course (hours to days) (Bowler et al., 2001; Coggan & Wolfgang, 2012).

A multitude of organisms can be identified within chronic wounds (Dowd et al., 2008; Sprockett et al., 2015). Despite the topical antibiotic treatment, many bacterial pathogens are difficult to manage, especially with the increase in antibiotic-resistant bacterial strains (Boucher et al., 2009; M. E. Jones et al., 2003; R. N. Jones, 2001; Livermore, 2007; Paterson, 2006; Rice, 2006; Spellberg et al., 2008). Staphylococcus aureus (S. aureus), and Pseudomonas aeruginosa (P. aeruginosa) are widely recognized as prominent resistant bacteria infecting chronic wounds. (Barsoumian et al., 2015). In the initial phases of the chronic wound, S. aureus remains within the superficial wound, while in advanced phases, P. aeruginosa is mostly present deeper in the wound (Cardona & Wilson, 2015). have acquired resistance to nearly all antibiotics and disinfectants licensed for clinical use. They are considered a real challenge because of their rapid colonization and survival ability (Barsoumian et al., 2015).

4. Wound Management

Many wound management modalities have been developed to optimize and accelerate the healing process of chronic wounds (Mustoe et al., 2006). These modalities consider general principles such as: 1) Wound cleaning and appropriate moisturization using non-irritating, nontoxic solutions to minimize any additional trauma or cytotoxicity, 2) Restoring the quality of the wound edge, 3) The elimination of any accumulated hindrances to wound healing such as necrotic tissue and excessive bacterial burden while preserving the vital surrounding tissue (AYELLO et al., 2004). Some of the most known wound healing therapeutic modalities are listed below in Table 1.

Table 1: Different wound healing therapeutic modalities:

Management modality	Based on	Reported for treating	Ref.
Systemic administration of drugs	This modality attempts to achieve local therapeutic effects and improve symptom management. Many drugs have been used, such as antibiotics, peptides (anti-tumor necrosis factor α (anti-TNF- α), or α-melanocyte-stimulating hormone), amino acids or their derivatives (proline or N-acetyl cysteine), corticosteroids, aspirin, warfarin, phenytoin, and many growth factors such as: epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), human granulocyte macrophage colony stimulating factor (GMCSF), platelet-derived growth factor (PDGF), or transforming growth factor beta (TGF-β). The systemic administration of these drugs has positively affected wound healing even better than their local administration. However, its effectiveness is constrained by the challenges associated with tissue targeting and the off-target adverse effects.	Wide variety of chronic wounds	(Las Heras et al., 2020; Otero-Viñas & Falanga, 2016)
Natural compounds	Several herbal extracts and natural substances, including rosemary oil, curcumin, berberine, Aloe Vera, thyme extract, and honey, have demonstrated antibacterial, angiogenic, and regenerative properties.	Wide variety of chronic wounds	(Hosseinkhani et al., 2017; Nagori & Solanki, 2011; Segev-Zarko et al., 2015; Shrestha et al., 2014)

Management modality	Based on	Reported for treating	Ref.
Debridement strategies	This modality represents a conventional approach to wound management, wherein the elimination of diseased tissue and foreign substances from the wound is achieved through various methods such as surgical, bio-surgical, mechanical, chemical, or enzymatic means. The technique of sharp debridement is widely recognized for its rapidity and efficacy.	Pressure, diabetes, and venous related ulceration (VLU)	(Steed, 2004)
Compression therapy	This modality helps to reduce ulceration by applying external and gradual pressure with special compression bandages systems. It is imperative to conduct a thorough clinical assessment prior to implementing any type of compression therapy, as it has the potential to result in severe consequences, such as limb gangrene.	Lower limb ulcers	(Cullum et al., 2001)
Skin grafting	This modality relies on using Composite tissue and artificial skin dressings to sustain wound closure. This procedure aims to reconstruct the skin tissue, especially in cases of thermal and burn injuries, providing sufficient wound covering and protection against bacteria.	Venous, neuropathic and pressure ulcers	(Las Heras et al., 2020)

Management modality	Based on	Reported for treating	Ref.
Dressing therapies	This approach employs biomaterial-based systems derived from biological sources, including fibrin, gelatin, collagen, chitosan, starch, and lactose, as well as synthetic chemicals like polyglycolic acid (PGA) and polylactic acid (PLA) as wound dressings. Dressing therapies serve to facilitate the regeneration of new tissue while simultaneously reducing pain, delivering moisturization, preventing friction or shear, and safeguarding both the peri-ulcer tissue and the skin. When selecting a suitable wound dressing, it is important to take into account the present stage of wound healing. Numerous contemporary dressings integrate various elements of wound bed preparation.	Wide variety of chronic and burn wounds	(Las Heras et al., 2020)
Negative pressure wound therapy	Another non-invasive traditional modality, that works by the removal of wound exudates with a vacuum device and generally is not used alone but applied after debridement. This modality is helpful in reducing edema, increasing local perfusion, promoting angiogenesis, decreasing overall wound size, and enhancing granulation tissue formation.	used to treat a wide range of chronic wounds	(Glass et al., 2014; Lalezari et al., 2017)
Electrical stimulation	Electromagnetic pulses are utilized as an adjuvant method to augment the treatment of chronic wounds. Research has demonstrated that it has the capacity to augment fibroblast activation and bolster collagen synthesis.	Various types of chronic wounds	(Khouri et al., 2017; Kloth, 2014)

Management modality	Based on	Reported for treating	Ref.
Hyperbaric oxygen therapy	This modality involves the administration of medication by the elevation of atmospheric pressure within a chamber, while the patient is undergoing 100% oxygenation. This approach has the potential to enhance neovascularization, minimize proinflammatory enzymes, and stimulate the synthesis of collagen and growth factors. Hyperbaric oxygen has been associated with adverse outcomes such as seizures and pneumothorax.	Diabetic and vascular insufficiency ulcers	(Thom, 2009)
Shockwaves	Shockwaves modalities promote angiogenesis and reduce inflammation.	VLU	(Cooper & Bachoo, 2018; Qureshi et al., 2011)
Radiant heat dressing	This modality uses heat to improve oxygen flow, tissue oxygenation and increases subcutaneous oxygen tension.	Mainly postoperative wounds, diabetic, and pressure ulcers	(Price et al., 2000)

Management modality	Based on	Reported for treating	Ref.
Ultrasoundtherapy	This modality relies on the mechanical anti-inflammatory effect of both high-frequency and low-frequency ultrasounds, as they reduce macrophages.	Pressure ulcers, diabetic ulcers, and VLU	(Kavros & Coronado, 2018)
Hydrotherapy	Hydrotherapy is a unique wound treatment modality that provides an optimal healing environment. This modality is a form of mechanical debridement technique that aims to clear the wound from any cellular debris.	Pressure, VLC and other chronic wounds.	(Atkin & Ousey, 2016)
Electromagnetic therapy	This modality works by promoting cytokine synthesis.	Ischemic, pressure, and VLU	(Kwan et al., 2015)
Low Level Laser Therapy, photo-biostimulation, or Photo-biomodulation	Light emitted by light-emitting diodes (LEDs), lasers, and other light sources across the wavelength range spanning from vision to infrared has been used as a wound-healing modality. This modality can stimulate various biological processes with the least systemic side effects such as: 1) Increase blood perfusion, and vasodilation, 2) Reduce inflammation and neutrophil infiltration, 3) Enhance fibroblast proliferation, wound reepithelization, and closure, 4) Elevate ATP synthesis, oxygen generation, and protein synthesis, as well as 5) Induce mitotic cellular proliferation.	Wide variety of acute and chronic wounds	(Amini et al., 2021; Freidouni et al., 2015; Gao & Xing, 2009; Kuffler, 2016; Mizutani et al., 2004; RASHIDI et al., 2015; Sefati et al., 2018)

4.1. Infection management within and surrounding the wound bed

Any wound can develop into a chronic wound even in immune-competent individuals. Thus, appropriate wound treatment modalities aim to eliminate the causing factors of chronic wound development that hinder the healing process. These factors include ischemia and bacterial infection (AYELLO et al., 2004).

Despite being a part of the skin's microbiota, the continuous proliferation of bacterial pathogens leads to the accumulation of a bioburden on the wound (Bowler et al., 2001). Bacterial burden over 105-106 bacteria colony forming units per gram of tissue, or when any amount of β-hemolytic streptococci is present (Sibbald et al., 2000). Hence, it is imperative to decrease the amount of bacteria present in a wound in order to decrease the levels of local and systemic inflammatory substances, hence managing the extended inflammatory stage of chronic wounds (Sibbald et al., 2000). In chronic wounds, topical antibiotics and surgical debridement have been observed to reduce bacterial populations effectively (AYELLO et al., 2004).

4.1.1. Antibiotics

Antibiotics have saved countless lives since their discovery. Some antibiotics are synthetic, while others are formed naturally as some microbes produce substances that inhibit or kill other microbes competing for the same resources. These products, if successfully extracted and mass-produced, can be used as natural antibiotics drugs or modified as semi-synthetic antibiotics. They remain an essential tool for treating and controlling infectious diseases. Various bacteriostatic or bactericidal antibiotic classes such as quinolones, tetracyclines, aminoglycosides, and cephalosporins can assist wound healing (Kohanski et al., 2010).

The prevalence of antibiotic resistance among bacteria has led to the emergence of bacterial wound infection as a significant and complex health issue (Rai et al., 2016). Although many bacteria are still susceptible to antibiotics (Rice, 2008), about 70% of wound-infecting bacteria are resistant to a minimum of one antibiotic (Friedman et al., 2016). S. aureus and P. aeruginosa are among these bacteria (Rice, 2008). Infections caused by antibiotic-resistant bacteria are exceptionally hard to treat. These infections are usually associated with a prolonged hospital stay and an approximately two-fold higher death rate (Fang

et al., 2016), with a predicted mortality of 10 million people per year by 2050 (Fang et al., 2016). Since the rate of acquisition of resistance is faster than the clinical introduction of new antibiotics, the development of alternative antimicrobial techniques to treat these infections is becoming necessary for public health throughout the world (Jackson et al., 2018; Kmietowicz, 2017; Kraus, 2008). Amidst the ongoing antibiotic crisis, several advancements in biotechnology, genetic engineering, and synthetic chemistry have introduced novel alternatives to traditional antibiotics for wound management, some are listed below in Table 2.

4.1.2. Alternative antibacterial therapeutic strategies

The following antibacterial therapeutic alternatives are arranged in three categories: (1) Naturally existing alternatives, (2) Synthetically generated strategies, and (3) Biotechnology-based strategies.

Table 2 *Different alternative antibacterial therapeutic strategies.*

<table>
<tr><th colspan="3">(1) Naturally Existing Alternatives strategies</th></tr>
<tr><td>Strategy</td><td colspan="2">Based on</td></tr>
<tr><td rowspan="3">Phage therapy</td><td colspan="2">Bacteriophages (phages) are viruses that propagate at the expense of bacteria. Their use as an antimicrobial agent is much older than the antibiotic (Gravitz, 2012).
Bacteriophages adhere to the bacterial cell wall and introduce their genetic material into the cytoplasm, thereby taking control of the bacterial cell machinery. This process facilitates the synthesis of phage components and the generation of novel phages within the bacterial infection. Over time, bacterial cells undergo dissolution, subsequently leading to the release of phage progeny, which can initiate a subsequent infection cycle (Abedon et al., 2011).</td></tr>
<tr><td>Advantages over antibiotics</td><td>Possible disadvantages</td></tr>
<tr><td>Self-replicating pharmaceuticals (Labrie et al., 2010).
Bacteriophages can distinguish between different bacterial populations, thus</td><td>High specificity.
Bacterial pathogens can develop resistance to phages (Abedon et al., 2011).</td></tr>
</table>

	provide an alternative yet selective antimicrobial strategy (Abedon, 2015; J. R. Clark & March, 2006). Responsive to genetic engineering, thus many of its limitations have been overcome with genetic engineering enabling their use in innovative ways (Braff et al., 2016).	High toxicity with the accumulation of endotoxins and pyrogenic substances after bacterial lysis. Their pharmacokinetics, challenges in phage preparation, its stability, and immunogenicity (Labrie et al., 2010).
Strategy	Based on	
Antimicrobial peptides (AMPs)	As the initial line of defense, host-defense peptides (HDPs) and antimicrobial peptides (AMPs) are released as soon as the pathogen invades the body (Brogden, 2005; Hancock & Sahl, 2006).	
	Advantages over antibiotics	Possible disadvantages
	Selective antibacterial, antifungal, antiviral, anticancer, antiplasmodial, antiprotozoal, insecticidal, and spermicidal agents with no activities against host cells (Zhang & Gallo, 2016). Not prone to resistance development	High toxicity (Zhang & Gallo, 2016). Difficult industrial scalability (Fosgerau & Hoffmann, 2015). Expensive large-scale production. Susceptible to proteolysis (Fosgerau & Hoffmann, 2015).
Strategy	Based on	
Bacteriocins	Bacteriocins are ribosomal synthesized small AMPs produced by many bacterial species as a self-defense mechanism against other bacteria within the population to increase their probability of survival (Rea et al., 2011). Different modes of action are exhibited by bacteriocins, including suppression of peptidoglycan production and forming pores in cell membranes (Cotter et al., 2013).	
	Advantages over antibiotics	Possible disadvantages
	Selective against some bacteria (Rea et al., 2011). Active against drug-resistant pathogens. Have high tolerance towards harsh conditions, such as heat and UV exposure. Thus, Bacteriocins have many applications in the food industry (Cotter et al., 2013).	Bacterial pathogens can develop resistance to bacteriocins (Ghosh et al., 2019). Expensive large-scale production (Ghosh et al., 2019). Susceptible to proteolysis (Ghosh et al., 2019).

<table>
<tr><th colspan="3">(2) Synthetically Generated Strategies</th></tr>
<tr><td>Strategy</td><td colspan="2">Based on</td></tr>
<tr><td rowspan="3">Synthetic mimics of antimicrobial peptides (SMAMPs)</td><td colspan="2">SMAMPs are simple, rapidly bactericidal molecules, that are synthesized to maintain the properties of antimicrobial peptides while overcoming their disadvantages (Ghosh et al., 2019).</td></tr>
<tr><td>Advantages over antibiotics</td><td>Possible disadvantages</td></tr>
<tr><td>Can turn back multi-drug resistant bacteria re-sensitive to antibiotics (Ghosh et al., 2019).
Ease of synthesis (Ghosh et al., 2019).
Broad-spectrum activity (Ghosh et al., 2019).</td><td>Toxicity (Konai et al., 2018).
Challenges in administration (Ghosh et al., 2019).
Bacterial pathogens can develop resistance to SMAMPs (Ghosh et al., 2019).</td></tr>
<tr><td>Strategy</td><td colspan="2">Based on</td></tr>
<tr><td>Antibacterial oligonucleotides</td><td colspan="2">Oligonucleotides have been used to treat many infectious diseases, where antisense oligonucleotides with sequences complementary to resistance-causing genes have been used to silence these genes, in what is known as gene silencing therapy. It is an alternative strategy against multidrug-resistant bacteria (Ayhan et al., 2016).</td></tr>
<tr><td>Strategy</td><td colspan="2">Based on</td></tr>
<tr><td rowspan="3">Innate defense regulatory peptides (IDRPs)</td><td colspan="2">IDRPs are antiendotoxin and immunomodulatory peptides with no direct antibacterial activity. A promising candidate to conventional antibiotics with proven activity against bacterial and malarial infections (Hilchie et al., 2013).</td></tr>
<tr><td>Advantages over antibiotics</td><td>Possible disadvantages</td></tr>
<tr><td>Modulate the immunesystem (Ghosh et al., 2019).
No resistance development (Ghosh et al., 2019).</td><td>Expensive production (Ghosh et al., 2019).
Susceptible to proteolysis (Ghosh et al., 2019).</td></tr>
<tr><td>Strategy</td><td colspan="2">Based on</td></tr>
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<table>
<tr><td>Inhibitors of Bacterial Virulence</td><td>The extracellular and cell-surface molecules that the bacterial pathogen produces to establish the infection are known as virulence factors. By targeting these virulence factors, the interaction between the bacterium and its host can be disrupted, thereby impeding the development of resistance in the bacterium. Consequently, this approach facilitates the elimination of the bacterium by the host immune system (Ghosh et al., 2019).</td></tr>
<tr><td colspan="2">(3) Biotechnology-Based Approaches</td></tr>
<tr><td>Strategy</td><td>Based on</td></tr>
<tr><td>Genetically Modified Bacteriophages</td><td>Genetically modified phages have been considered recently as an alternative strategy (Braff et al., 2016). With many modes of action, such as producing bacterial-biofilm-degrading enzymes (Lu & Collins, 2007). This particular approach has the potential to reverse the resistance of microorganisms, such as P. aeruginosa, rendering them susceptible to standard antibiotics (Libis et al., 2014; Lu & Collins, 2009).</td></tr>
<tr><td>Strategy</td><td>Based on</td></tr>
<tr><td>Lysins (Endolysins, Exolysins, and Autolysins)</td><td>One potential therapeutic approach that exhibits direct antibacterial activity is the utilization of either: 1) Endolysins generated by phages that facilitate the degradation of the bacterial cell wall (Nelson et al., 2012; Schmelcher et al., 2012), 2) Exolysins produced by bacteria to eliminate cells belonging to different strains or species or, 3) Autolysins which are synthesized during cellular growth and division (Basso et al., 2017).
<table>
<tr><td>Advantages over antibiotics</td><td>Possible disadvantages</td></tr>
<tr><td>Vulnerable to genetic manipulation.
Selective towards particular microorganisms (Ghosh et al., 2019).
Not prone to resistance development.</td><td>Production challenges (Ghosh et al., 2019).</td></tr>
</table></td></tr>
<tr><td>Strategy</td><td>Based on</td></tr>
<tr><td>CRISPR-Cas 9</td><td>The CRISPR (clustered, regularly interspaced, short palindromic repeats)-Cas9 systems comprise essential parts in the bacterial immune system, where 20 nt tiny RNA serves as a template for Cas9 to eliminate foreign genetic material at precise locations (Bikard & Barrangou, 2017). The CRISPR-Cas9 system was</td></tr>
</table>

	delivered using bacteriophages to specifically target multidrug-resistant bacteria, rendering them susceptible (M. Goren et al., 2017).	
	Advantages over antibiotics	Possible disadvantages
	Specificity to certain strains (M. Goren et al., 2017; M. G. Goren et al., 2015).	Expensive production (Ghosh et al., 2019; Wang et al., 2016). Toxicity (Ghosh et al., 2019).

Some of these approaches show encouraging progress, yet many of them face many limitations usually related to; high production costs, toxicity, instability, and being strain- or species-specific rather than having the broad-spectrum effects of traditional antibiotics. For this reason, multiple therapeutics might be needed concurrently to treat wound infections.

5. Photodynamic therapy as a promising phototherapeutic approach for wound management

One interesting option is a simple, non-invasive, and inexpensive phototherapeutic method that causes no significant tissue damage known as laser-based antimicrobial photodynamic therapy (aPDT) (Dai et al., 2009; Ghorbani et al., 2018; Gois et al., 2010). Moreover, it is unlikely that bacteria will become resistant to aPDT (Gupta et al., 2018; Schastak et al., 2010). Phototherapy has many approaches based on the interaction between light photons and different tissues, one of which is laser-based aPDT, a type of photochemotherapy initially developed for cancer treatment (Mang, 2004; Mitton & Ackroyd, 2008).

Lasers use the physical phenomena of stimulated emission to generate a light beam that is monochromatic, coherent, and collimated, characterized by a small bandwidth and low divergence (MAIMAN, 1960). Lasers exhibit superior efficiency for aPDT in comparison to alternative light sources due to these three characteristics (Hode, 2005). The therapeutic effects of laser-based phototherapy depend on the irradiation parameters of the laser output including fluence, intensity, mode of action either continuous wave or pulsed, exposure duration, and most importantly, its wavelength. The selection of a laser type for a specific

application is determined by these criteria (Medrado et al., 2003; Samaneh et al., 2015).

Laser-based aPDT refers to the process of eradicating specific pathogens by the photochemical stimulation of naturally occurring Photosensitizers (PS) molecules. These molecules can become active after being exposed to a specific wavelength of light (Sternberg et al., 1998), which then triggers photochemical or photophysical processes within the microbial cell. The therapeutic efficacy of photodynamic therapy (PDT) relies on the in situ generation of cytotoxic reactive oxygen species (ROS), which cause oxidative damage to various cellular components, ultimately resulting in cell death (de Annunzio et al., 2018; Ravanat et al., 2000; Stark, 2005). ROS are generated via two photochemical processes that occur simultaneously (Hamblin & Hasan, 2004), The first process involves electron transfer (type I), resulting in the formation of oxygen, peroxide, or hydroxide radicals. The second process involves energy transfer reactions (type II), leading to the production of singlet oxygen (1O2) (Dolmans et al., 2003). These processes depend on the interaction between laser radiation and matter, which converts light energy into chemical energy (photochemical interaction) (Gois et al., 2010; Hanakova et al., 2014).

Femtosecond laser pulses have the unique ability to deposit energy into a microscopic volume on a very short time scale within a single laser pulse without affecting the surrounding surface of the tissue (El-Khordagui et al., 2017; RASHIDI et al., 2015). Both the pulse width and the repetition rate determine the heat accumulation in biological samples. If the heating duration is short, then the thermal energy can diffuse away more rapidly. And, if the duration between two pulses is long enough for the heat produced by the previous pulse to decay away, there will be no accumulation of heat (C. D. Clark et al., 2013). Femtosecond laser-based aPDT is one of the most promising emerging technologies for chronic wound management and infection as demonstrated in Table 3. Regrettably, an important challenge lies in determining the optimal wavelength, light dose, and fluence to effectively restrict bacterial growth while minimizing harm to the adjacent host tissue

Table 3: Investigating the bactericidal efficacy of femtosecond laser irradiation against different bacterial pathogens.

Light Source	Tested Organisms	External Photosen-sitizers	Irradiation Wavelength	Irradiation Parameters	Ref.
INSPIRE HF100 laser system (Spectra Physics) which was pumped by a mode-locked femtosecond Ti: sapphire laser MAI TAI HP (Spectra Physics)	- *Pseudomonas aeruginosa* - *Staphylococcus aureus*	-	370, 380, 390, 400, 410, 420,480, 495, 700, and 800 nm	Power density = 0.047, 0.0377, 0.0354, and 0.0348 W/cm^2 Irradiation time = 1, 3, 5, 5.5, 7, 9, 10, 10.5, 15, and 20 min	(Ahmed et al., 2020)
	- *Staphylococcus aureus*	-	380, 390, 400, 410, and 420 nm	Average Power = 75, 150, and 210 mW Irradiation time = 5, 10 and 15 min. Energy density = 79.6, 159, 223, 239, 318, 420, 477, and 630 J/cm^2.	(Ahmed et al., 2021)
	- *Pseudomonas aeruginosa* - *Listeria monocytogenes* - Methicillin-resistant *Staphylococcus aureus* (MRSA)	-	400 nm	Power = 50 mW Irradiation time = 15 min. Energy density = 160 J/cm^2	(El-Gendy et al., 2021)
	- *Pseudomonas aeruginosa* - Methicillin-resistant *Staphylococcus aureus* (MRSA)	-	400 nm	Power = 50 mW Irradiation time = 15 min. Energy density = 160 J/cm^2	(El-Gendy, Nawaf et al.

	- *Candida albicans* - *Escherichia coli* - *Enterococcus faecalis* - *Listeria monocytogenes* - Methicillin-resistant *Staphylococcus aureus* (MRSA)	-	400 nm	Power = 50 mW Irradiation time = 15 min. Energy density = 160 J/cm^2	(El-Gendy, Obaid, et al., 2022)

6. Conclusion and future perspectives

Bacterial infections pose a significant health burden globally and with the increasing ineffectiveness of conventional treatments alternative approaches are urgently needed. Laser-based aPDT has emerged as a promising alternative for infection management. Additional research is required to investigate the potential clinical uses of various laser systems against specific microbial populations in tissues, such as microbial biofilm and the microbial expression of distinct virulence factors.

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Data availability No datasets were generated or analysed during the current study.
Declarations

Conflict of interest The authors declare no conflict of interest.
Competing interests The authors declare no competing interests.

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