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Advancements in Topical and Systemic Antibiotic Management for Burn Wounds: A Comprehensive Literature Review

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ABSTRACT

Introduction: Antimicrobial treatment in burn patient include systemic and topical antibiotic care should be carefully deliberated to prevent the development of resistant organisms

Methods: This literature review was compiled using information from numerous open access web databases. Data were compiled and analyzed.

Results and Discussions: To prevent antibiotic resistance and prevent infection, the best prophylactic antibiotics for burn patients are topical antibiotics. However, for the treatment of patients with extensive burns or those with antibiotic resistance, especially antibiotics for gram-positive bacteria, systemic antibiotics can be used for treatment.

Conclusion: The use of antibiotics in patients with burns can be adjusted to the patient's needs. surgeons may consider its use to prevent antibiotic resistance in patients.

KEYWORDS: antibiotics, topical antibiotics, systemic antibiotics, burn wound

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INTRODUCTION

Burn injury occurs when the skin comes into contact with a heat source. Burn injuries differ in severity, and when a larger area of the body is affected, it can worsen wound complications and increase the likelihood of patient death. Additional crucial factors influencing the extent of injury include where the burn is located, the temperature, and how long the skin was exposed to the heat source, with these factors often interacting to exacerbate the injury.[1]

Burn injury according to the depth of the wound can be classified as superficial burns, partial-thickness, and full thickness. Superficial burns categorized as first degree, manifest as erythema, affecting only the epidermis and causing redness, slight swelling, and temporary pain that typically subsides within 48 to 72 hours.[1,2]

Partial thickness superficial burns, known as second degree burns, involve damage to both the epidermis and the dermis. It can be classified into two subtypes II A and II B. Type IIA burns affect the epidermis and superficial dermal layers, causing pain and blistering due to separation of the epidermis from the basement membrane. Healing occurs within 14 to 21 days. Type II B burns extend deeper into the dermis, resulting in red, moist, and painful skin. Epidermal necrosis may disrupt epithelialization, potentially leaving scars. Healing typically takes 21 to 35 days and often requires surgical intervention. Full-thickness deep burns, categorized as third-degree, penetrate through the entire thickness of the skin, resulting in dry, tough, and discolored skin without pain sensation. Surgical or reconstructive interventions are necessary for treatment. Full-thickness burns involving deeper tissues, classified as fourth-degree, combine characteristics of both second and third-degree burns. They can extend from the epidermis to the subcutaneous tissue layer, and in severe cases, may involve muscle or bone, leading to local necrosis. Treatment options may include conservative management or surgical intervention.[2]

The majority of burn survivors, even those who surpass the critical initial 24-hour period post-burn, often face mortality due to infection of the burned area and its ensuing complications. Several contributing factors include the breakdown of the skin barrier, high levels of bacterial presence on the skin surface, the potential transformation of normal skin flora into opportunistic pathogens, and significant suppression of the immune system. Sepsis remains the primary cause of death among burn patients, with approximately 73% of fatalities occurring within the initial 5 days post-burn, directly or indirectly attributed to septic processes. Common bacteria isolated from burn patients

include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella sp*., and various coliform bacilli. Pseudomonas has exhibited complete resistance to combinations of antibiotics such as ampicillin-sulbactam and ceftriaxone, while showing greater susceptibility to imipenem, amikacin, and vancomycin. *Methicillin-resistant Staphylococcus aureus* (MRSA) has also demonstrated resistance to commonly used antibiotics like ceftriaxone, ampicillin-sulbactam, and ceftazidime-clavulanic acid. Linezolid and vancomycin have shown effectiveness in 83.33% and 100% of cases, respectively. Moreover, a higher total body surface area (TBSA) affected by burns correlates with an increased risk of bacteremia and mortality.[3]

Antimicrobial treatment in burn patient care should be carefully deliberated to prevent the development of resistant organisms. A burn wound will invariably harbor organisms until closure occurs, and systemic antimicrobials will not eradicate colonization but may instead foster the emergence of resistant strains.[3]

METHODS

We compiled this literature review and analyzing information from numerous web databases. Our inclusion criteria included: (1) the journal was open accessible and (2) the articles which were matched and relevant to the subject matter covered in this literature review. We were using "Topical Antibiotic Management fo Burn Wounds" and "Systemic Antibiotic Management for Burn Wounds" keywords in the literature search on PubMed, Google Scholar, and Elsevier. Data were collected, organized, and summarized.

RESULTS AND DISCUSSIONS

TOPICAL ANTIBIOTIC MANAGEMENT

Silver sulfadiazine (SSD)

The abundance of therapeutic choices for the topical treatment of burns poses challenges for healthcare professionals in determining the most appropriate procedures. For both second- and third-degree burns, *silver sulfadiazine* (SSD) remains the most commonly utilized medication due to its affordability and widespread availability.[4] Concerning burns, no beneficial effect of *silver sulfadiazine* (SSD) has been demonstrated in preventing wound infection in patients with partial-thickness burns.[5] The silver agents, known for their toxicity to bacterial cells, may also impact the cells of the skin itself, potentially leading to delayed healing. Specifically, *silver sulfadiazine* (SSD) is recognized for its ability to hinder the growth of keratinocytes and fibroblasts, further contributing to potential delays in the healing process.[6] Recent findings have suggested that compounds containing silver can impede the wound-healing process, with silver demonstrating significant cytotoxic activity in various host cells.[5] Silver, as a metal, is relatively inert. However, when it is ionized by fluids, it undergoes a transformation into a highly reactive state. In this state, it binds to the proteins present in cell membranes, resulting in cellular denaturation and mitochondrial dysfunction in a significant portion of cells. These cellular effects parallel the mechanisms observed in invading microorganisms.[6]

Antimicrobial nanoparticles

Antibiotic resistance-pathogens are a serious problem because they enhance mortality and morbidity rates, increase the risks of medical procedures and medical costs per procedure, prolong illness and convalescence periods, and attack preferentially immunocompromised and hospitalized patients, complicating their conditions. As a consequence, new antimicrobial agents and derivatives, anti-virulence drugs, ecologic and evolutionary management approaches, and even new therapeutic options like those derived from bacteriophages, enzyme-derived antibiotics (enzybiotics), and antimicrobial nanoparticles (ANPs) have been undertaken. Some of these strategies are, apparently, good candidates for the control of the whole phenomenon, but antimicrobial nanoparticles (ANPs) are of special interest as they have shown little potential for the development of bacterial resistance against them; despite this, they have not been shown to be entirely safe for their use as drugs.[7]

Nanomaterials are divided in mainly two groups, according to their chemistry, such being metallic and non-metallic. In general, several of the primary toxicological effects of nanoparticles occur through direct contact with the bacterial cell surface. Underscoring the importance of understanding their properties. Gram-positive bacteria possess a thick layer of peptidoglycan and negatively charged teichoic acids (phosphate groups), whereas Gram-negative bacteria feature a thinner layer of peptidoglycan associated with a phospholipid outer membrane containing lipopolysaccharides, also negatively charged. These structural characteristics are significant because the principal interaction of metal-based NPs with bacteria relies on electrostatic attraction between opposite charges, forming strong bonds that trigger biologically relevant mechanisms of action, which vary for each metal. Additionally, the structural attributes of NPs influence their antibacterial activity. For instance, their size (smaller size increases surface area, enhancing association with cell walls or membranes) morphology (shapes that increase surface area enhance functionality), and dose (higher concentrations yield greater results).[8]

Honey

Honey has been utilized for wound healing in numerous cultures worldwide for millennia. Honey is an acidic and hyperosmolar sugar solution derived from plant nectar by honey bees. Its composition includes enzymes, water, sucrose, glucose, fructose, amino acids, beeswax, pollen, pigments, minerals, and glucose oxidase. Glucose oxidase facilitates the conversion of sucrose into simple glucose and

fructose, while also producing gluconic acid. The effectiveness of honey in promoting burn healing can be attributed to its anti-inflammatory properties and its ability to stimulate cell proliferation. In the context of a review, three studies focusing on burn wounds were examined. Among these, two studies demonstrated the superiority of honey over other materials in promoting healing of burn wounds. In the honey-treated group, no scar tissue or depigmentation was observed following improvement, unlike the mafenide-treated group. Therefore, honey was shown to be superior and more cost-effective than mafenide for first-degree burns, accelerating wound healing and yielding more aesthetically pleasing results.[9]

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are multifunctional, immunomodulatory peptides with a broad spectrum of activity against various microbes. They are increasingly recognized as novel alternative therapeutic molecules. One of the key advantages of AMPs is their nonspecific mechanism of action, which reduces the likelihood of microbial resistance developing. Chronic infected burns and wounds can arise from conditions such as diabetic foot and venous leg ulcers, as well as infections at surgical sites. These wounds often experience persistent inflammation and are commonly infected with multiple microorganisms. Furthermore, these microorganisms can significantly contribute to the resistance and recurrence of infectious burns and wounds.[10]

Cationic antimicrobial peptides (AMPs) represent a distinct class of peptides that differ from traditional antibiotics. These AMPs interact with bacterial cell membranes by neutralizing their charge, allowing them to penetrate through the membranes and induce bacterial death. This mechanism reduces the likelihood of bacterial drug resistance. Additionally, AMPs exhibit several advantages over traditional antibiotics. They possess broad-spectrum antibacterial, antifungal, and antiviral activities, making them more efficient in combating various pathogens. AMPs demonstrate rapid germ-killing ability and require lower bactericidal concentrations compared to conventional antibiotics. They are effective against antibiotic-resistant strains and may even have synergistic effects with traditional antibiotics in neutralizing endotoxins. Furthermore, AMPs are generally safe with minimal or no toxic side effects and are less likely to induce bacterial drug resistance compared to conventional antibiotics. These membrane-permeabilizing AMPs offer a promising new approach for treating drug-resistant microbes, which contribute to increased morbidity and mortality. They hold potential for clinical application as a strategy to overcome the frequent resistance observed in many common microbes to conventional antibiotics.[11]

In the case of topical drugs, preparations that are generically equivalent may not necessarily be therapeutically equivalent. In addition to the components of the formulation, other factors can influence absorption. Furthermore, factors affecting efficacy include pH, ionic nature, viscosity, spreadability, and the proportions of oil/water/surfactants/preservatives/stabilizers. Exposure to heat or light and prolonged storage duration can also influence the relative stability of topical formulations due to oxidation or degradation.[12]

The skin functions as a heterogeneous multilayer tissue, serving as a robust barrier against the absorption of external compounds. The outermost layer, the stratum corneum, consists of densely arranged corneocytes interspersed with intercellular lipids. When hydrated, these corneocytes swell, increasing their thickness nearly threefold. This swelling reduces the diffusion path length and protein network density, thereby facilitating drug transport. Damage to the epidermis, such as wounds or burns, can further enhance permeation across the skin. Moreover, the dermis contains various drug-metabolizing enzymes, including cytochrome P450 enzymes (CYPs), transferases, hydrolases, and sulfatases, which can modify the structure and charge of drugs, influencing their permeability. Formulations with moderate pH values, typically higher than the isoelectric point of the skin are considered suitable for topical delivery.[13]

SYSTEMIC ANTIBIOTIC MANAGEMENT

Prophylaxis versus resistance

Patients with burn injuries often experience prolonged hospital stays and multiple episodes of infection, leading to the administration of multiple courses of antibiotics.[14] More than half of their hospital admission may be spent on antibiotic therapy. While prophylactic antibiotics upon admission for contaminated skin are sometimes utilized to reduce future infections, the efficacy data are inconclusive, and this practice is discouraged.[15] Patients who present late after the burn injury may seem to offer the best scenario for initiating antibiotics upon admission due to higher rates of wound infection, but careful assessment of the wounds may challenge the term "*prophylactic*".[16] As previously discussed, antimicrobial exposure can lead to resistance, necessitate the use of "last resort" or combination antimicrobials, or even result in death.[17] Additionally, efficacy is in question due to poor perfusion in deeper wounds with extensive vessel damage. It's important to note that antimicrobial use and the resulting changes in flora extend selection effects to the burn unit ecosystem and other patients. While prophylactic antimicrobials on admission may appear to be an attractive short-term option, they may ultimately lead to a challenging and ongoing battle against resistance and adverse effects.

The implementation of systemic antimicrobial agents remains a subject of controversy due to concerns over their widespread use potentially exacerbating the burden of infections. However, there is recognition that employing targeted and specific antimicrobial therapy could offer advantages in certain circumstances. Current evidence suggests that routine prophylactic administration of systemic

antibiotics lacks efficacy in preventing infections and is unnecessary for managing non-invasive wound infections. Due to the escalating rates of drug resistance, systemic antimicrobial medications are usually preserved for patients with sepsis or those afflicted with invasive infections from burn wounds. Initially, burn wounds are colonized by gram-positive bacteria, succeeded by gram-negative microorganisms. Following these colonization patterns, septic patients in the initial phase of hospitalization are commonly treated with penicillins, aminopenicillins, or penicillinase-resistant antibiotics like methicillin, which exhibit efficacy against gram-positive *Staphylococci* and *Streptococci*. While early wound infections typically involve gram-positive bacteria, early occurrences of gram-negative infections can be addressed with third-generation cephalosporins.[18]

New antimicrobial agents

As previously emphasized, the rise in antibiotic resistance, coupled with a decline in the development of new antimicrobial agents, presents a significant challenge in managing critically ill burn patients. Consequently, there is a growing interest in the exploration and creation of novel antimicrobials. One such example is *firmocidin*, a newly discovered compound isolated from the culture supernatant of *Staphylococcus epidermidis*, a crucial component of the normal skin flora. *Firmocidin* is applied topically and demonstrates a broad spectrum of activity against both bacteria and fungi. Although there is currently no available patient data regarding the use of *firmocidin* in burn patients, in vitro bactericidal assays have shown its effectiveness against key pathogens commonly found in burn wounds, including MRSA, *Staphylococcus aureus*, and group A and B *Streptococci*.[18]

Linezolid is a synthetic antibiotic that works by impeding the synthesis of bacterial proteins. It achieves this by binding to ribosomal RNA (rRNA) on both the 30S and 50S ribosomal subunits. By interfering with the formation of the initiation complex, linezolid restricts the length of the resulting peptide chains and slows down the translation process. *Linezolid* has also been noted for its potential to hinder the expression of virulence factors, thereby reducing the production of toxins by Gram-positive pathogens. In the study, linezolid was employed alongside penicillin and clindamycin to suppress toxic shock syndrome (TSS). The patient under investigation had necrotizing fasciitis in the right upper extremity and TSS caused by group A *Streptococcus*. *Linezolid* was introduced into the treatment regimen due to the lack of improvement observed with penicillin and clindamycin alone. Moreover, research indicates that linezolid may offer efficacy in the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).[19]

Tigecycline, a glycylcycline antibiotic, has shown effectiveness against *Staphylococci*, notably MRSA, and their biofilms. Its optimal efficacy, however, has been observed when used in combination with other antibiotics. Notably, tigecycline has demonstrated a direct impact on wound healing in mice with S. aureus-infected wounds. This effect was achieved through the modulation of matrix metalloproteinase-9 expression, surpassing the efficacy of teicoplanin in comparative studies. Combining tigecycline with daptomycin or rifampicin has been found to result in better infection control, although in a mouse model infected with biofilm-producing *Staphylococcus aureus*, tigecycline exhibited superior wound healing compared to teicoplanin. This was attributed to its modulation of metalloproteinase-9 expression. These findings suggest that tigecycline may have a more pronounced effect on wound healing than teicoplanin, a prominent antibiotic for MRSA. Nonetheless, both antibiotics have demonstrated effectiveness in either controlling infection or promoting improved wound healing.[20]

Current guidelines and total body surface area (TBSA)

Current guidelines suggest using preoperative antibiotics for plastic surgery procedures in patients with risk factors, despite the lack of supporting evidence from randomized controlled trials. Given the existing evidence, it is challenging to recommend perioperative prophylaxis, particularly for early excision and patients with a total body surface area (TBSA) less than 40%. If systemic antimicrobials are utilized, caution should be exercised in selecting the appropriate agent, based on the local antibiogram, and dosing frequency. Improper selection of agents and prolonged exposure may result in the emergence of selected bacteria or resistance. Additionally, differences in pharmacokinetics and pharmacodynamics presented by patients with burn injuries should be considered, as certain agents may require redosing depending on the duration of the procedure and antibiotic half-life.[16]

Pharmacological principles

Understanding pharmacokinetic principles is crucial for optimizing systemic antibiotic management in burn patients. Absorption refers to the bioavailability, which is the percentage of drug that reaches systemic circulation. Intravenous administration is considered to achieve 100% bioavailability and serves as a control for comparisons with orally administered medications. However, certain antibiotics, such as β-lactams (e.g., penicillin, dicloxacillin, cefdinir), exhibit poor bioavailability (25%-60%) and may require chemical or dosage form modifications to enhance systemic absorption.[17] Some cephalosporins, like cephalexin and cefaclor, approach 90% bioavailability. Lipophilic drugs generally have higher absorption profiles due to improved passive diffusion across intestinal membranes, leading to the development of esterified formulations for certain β-lactam antibiotics.[21] It is also important to consider the impact of food or tube feeds on absorption; fatty foods can delay gastric emptying and may decrease peak concentrations of

antibiotics. In addition to bioavailability concerns, certain antibiotics are exclusively formulated for intravenous administration, primarily because they are typically prescribed for severe infections. Patients with severe infections may experience compromised absorption due to alterations in perfusion or gut flora, which can lead to decreased bioavailability when administered orally.[22]

Distribution refers to a movement of a drug substance from intravascular to extravascular compartments, and this process is best characterized by the volume of distribution. Distribution is critical for delivering antimicrobials to their target sites, as most sites of infection are located outside the bloodstream.[23] It is important to note that therapeutic drug monitoring of plasma concentrations may not always accurately reflect tissue concentrations. Lipophilic antimicrobials, such as triazole antifungals or fluoroquinolones, have the ability to penetrate various compartments and tissues, often achieving concentrations that exceed those in plasma.[24]

Metabolism involves the transformation of medications into biologically inactive components in preparation for elimination, such as the oxidation of linezolid. In rare cases, metabolic reactions can result in antimicrobial prodrugs being converted into their active moieties.[20] For example, colistimethate sodium requires activation via hydrolysis to yield the active antimicrobial colistin. Similar to metabolism, elimination of drugs is significantly altered in patients with burn injuries and is influenced by factors such as age, total body surface area (TBSA) affected by burns, comorbidities, time since injury, presence of organ dysfunction, and use of renal replacement therapies. For drugs that are primarily eliminated through the kidneys, most studies aim to correlate dosing regimens with creatinine clearance (CrCl). Creatinine clearance (CrCl) is traditionally calculated using the Cockcroft-Gault equation, which may not accurately reflect renal function in critically ill patients. This equation was developed in subjects with lower body weights and muscle mass, and the female correction factor was arbitrarily selected due to underrepresentation in the original study.[25]

Pharmacodynamics refers to the resultant biological effect stemming from the interactions between drugs and biological systems. This effect can arise from direct receptor binding or indirectly through inhibitory mechanisms. Certain antimicrobials can directly bind to cell membranes, leading to damage or inhibiting cross-linking (e.g., amphotericin B, β-lactams, colistin, and vancomycin). Others exert deleterious effects by inhibiting vital processes such as sterol or protein synthesis, necessary for membrane and DNA formation (e.g., macrolides, tetracyclines, and azoles). Antibacterials may exhibit bacteriostatic (relying on host immune function for efficacy) or bactericidal properties. For instance, linezolid, tigecycline, macrolides, and sulfonamides predominantly demonstrate bacteriostatic tendencies. Some antibacterials may exhibit both properties, depending on factors such as host immune response, drug concentrations, or the target pathogen. For example, while linezolid is bacteriostatic against *Staphylococcus sp.* and *Enterococcus sp.*, it displays bactericidal activity against *Streptococcus sp*.[20]

ANTIBIOTIC RESISTANCE AND FUTURE DIRECTIONS

Mortality rates from burn injuries have significantly decreased due to advancements in technology and medications, the evolution of surgical philosophies, and the continual expansion of burn-specific literature. However, alongside the increasing availability of antimicrobials, there is a concerning rise in multidrug-resistant strains. The escalating prevalence of multidrug-resistant (MDR) organisms is concerning, given their association with elevated rates of morbidity and mortality. Therefore, it's crucial to carefully select and utilize antimicrobials to minimize unnecessary exposure, costs, resistance, and mortality. Antimicrobials serve as a crucial tool in the armamentarium of burn clinicians, profoundly affecting infection-related mortality. While their usage is typically essential, irresponsible prescribing practices can lead to significant harm to patients. Optimal prescribing necessitates the integration of the unique pathophysiology, pharmacokinetics, and pharmacodynamics of patients with burn injuries. Clinical response on an individual basis should take precedence over predetermined discontinuation of therapy. Given the evident complexity involved, a proven multidisciplinary team-based approach is essential for ensuring the best possible outcomes for patients.[20]

There are some strategies to combat antibiotic resistance that involve antibiotic stewardship programs, development of novel agents, and alternative therapeutic approaches. Antibiotic stewardship programs (ASPs), aimed at encouraging appropriate antibiotic usage, constitute a pivotal aspect of the strategy to combat antibiotic resistance. Regulatory bodies such as the Joint Commission in the United States have established guidelines outlining the requisites for ASPs in acute care settings. These guidelines serve as crucial motivators for hospitals to adopt ASPs, which have demonstrated efficacy in reducing antibiotic resistance and enhancing the standard of care. The majority of ASPs indicated that they conduct prior authorization for specific antibiotics (81%) and antibiotic reviews with prospective audit and feedback (PAF) (84%). However, a smaller proportion of programs stated that they have computerized decision support systems in place at the time of antibiotic prescription (32%) or utilize antibiotic time-outs (33%).[26]

CONCLUSION

The use of antibiotics in patients with burns can be adjusted to the patient's needs. for prophylaxis, topical antibiotics are recommended. However, for the use of antibiotics in patients

with extensive burns or patients with a history of antibiotic resistance, the use of systemic antibiotics is recommended

REFERENCES

I. Żwierełło W, Piorun K, Skórka-Majewicz M, Maruszewska A, Antoniewski J, Gutowska I. Burns: Classification, Pathophysiology, and Treatment: A Review. Int J Mol Sci. 2023 Feb 13;24(4):3749.

II. Markiewicz-Gospodarek A, Kozioł M, Tobiasz M, Baj J, Radzikowska-Büchner E, Przekora A. Burn Wound Healing: Clinical Complications, Medical Care, Treatment, and Dressing Types: The Current State of Knowledge for Clinical Practice. Int J Environ Res Public Health. 2022 Jan 25;19(3):1338.

III. Mir MA, Khurram MF, Khan AH. What should be the antibiotic prescription protocol for burn patients admitted in the department of burns, plastic and reconstructive surgery. Int Wound J. 2017 Feb;14(1):194-7.

IV. Nímia HH, Carvalho VF, Isaac C, Souza FÁ, Gemperli R, Paggiaro AO. Comparative study of Silver Sulfadiazine with other materials for healing and infection prevention in burns: A systematic review and meta-analysis. Burns. 2019 Mar;45(2):282-92.

V. Hajská M, Slobodníková L, Hupková H, Koller J. In vitro efficacy of various topical antimicrobial agents in different time periods from contamination to application against 6 multidrug-resistant bacterial strains isolated from burn patients. Burns. 2014 Jun;40(4):713-8.

VI. Kempf M, Kimble RM, Cuttle L. Cytotoxicity testing of burn wound dressings, ointments and creams: a method using polycarbonate cell culture inserts on a cell culture system. Burns. 2011 Sep;37(6):994-1000.

VII. Yousefi M, Dadashpour M, Hejazi M, Hasanzadeh M, Behnam B, de la Guardia M, Shadjou N, Mokhtarzadeh A. Anti-bacterial activity of graphene oxide as a new weapon nanomaterial to combat multidrug-resistance bacteria. Mater Sci Eng C Mater Biol Appl. 2017 May 1;74:568-581.

VIII. Gómez-Núñez MF, Castillo-López M, Sevilla-Castillo F, Roque-Reyes OJ, Romero-Lechuga F, Medina-Santos DI, Martínez-Daniel R, Peón AN. Nanoparticle-Based Devices in the Control of Antibiotic Resistant Bacteria. Front Microbiol. 2020 Nov 25;11:563821.

IX. Yilmaz AC, Aygin D. Honey dressing in wound treatment: A systematic review. Complement Ther Med. 2020 Jun;51:102388.

X. Javia A, Amrutiya J, Lalani R, Patel V, Bhatt P, Misra A. Antimicrobial peptide delivery: an emerging therapeutic for the treatment of burn and wounds. Ther Deliv. 2018 May;9(5):375-86.

XI. Lei J, Sun L, Huang S, Zhu C, Li P, He J, Mackey V, Coy DH, He Q. The antimicrobial peptides and their potential clinical applications. Am J Transl Res. 2019 Jul 15;11(7):3919-31.

XII. Ray P, Singh S, Gupta S. Topical antimicrobial therapy: Current status and challenges. Indian J Med Microbiol. 2019 Jul-Sep;37(3):299-308.

XIII. Nair A, Jacob S, Al-Dhubiab B, Attimarad M, Harsha S. Basic considerations in the dermatokinetics of topical formulations. Brazilian J Pharm Sci 2013;49:423-34.

XIV. Lavrentieva A, Kontou P, Soulountsi V, Kioumis J, Chrysou O, Bitzani M. Implementation of a procalcitonin-guided algorithm for antibiotic therapy in the burn intensive care unit. Ann Burns Fire Disasters. 2015 Sep 30;28(3):163-70.

XV. Kirby JP, Mazuski JE. Prevention of surgical site infection. Surg Clin North Am. 2009 Apr;89(2):365-89, viii.

XVI. Ozbek S, Ozgenel Y, Etöz A, Akin S, Kahveci R, Heper Y, Ercan I, Ozcan M. The effect of delayed admission in burn centers on wound contamination and infection rates. Ulus Travma Acil Cerrahi Derg. 2005 Jul;11(3):230-7.

XVII. Wilkinson RE, Hill DM, Hickerson WL. Outcome analysis of colistin-treated burn center patients. Burns. 2017 Sep;43(6):1244-9.

XVIII. Vinaik R, Barayan D, Shahrokhi S, Jeschke MG. Management and prevention of drug resistant infections in burn patients. Expert Rev Anti Infect Ther. 2019 Aug;17(8):607-19.

XIX. Hashemian SMR, Farhadi T, Ganjparvar M. Linezolid: a review of its properties, function, and use in critical care. Drug Des Devel Ther. 2018 Jun 18;12:1759-67.

XX. Rizzetto G, Molinelli E, Radi G, Diotallevi F, Cirioni O, Brescini L, Giacometti A, Offidani A, Simonetti O. Role of Daptomycin in Cutaneous Wound Healing: A Narrative Review. Antibiotics (Basel). 2022 Jul 14;11(7):944.

XXI. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010 May;31(5): 431-55.

XXII. McKinnon PS, Davis SL. Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. Eur J Clin Microbiol Infect Dis. 2004 Apr;23(4):271-88.

XXIII. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. Clin Pharmacokinet. 2008;47(10):635-54.

XXIV. Wood GC, Chapman JL, Boucher BA, et al. Tobramycin bladder irrigation for treating a urinary tract infection in a critically ill patient. The Annals of Pharmacotherapy. 2004 Jul-Aug;38(7-8):1318-9.

XXV. Hill DM, Scott ES, William LH. Rational selection and use of antimicrobials in patients with burn injuries.Clin Plastic Surg. 2017;44(3): 521-4

XXVI. Doernberg SB, Abbo LM, Burdette SD, Fishman NO, Goodman EL, Kravitz GR, Leggett JE, Moehring RW, Newland JG, Robinson PA, Spivak ES, Tamma PD, Chambers HF. Essential Resources and Strategies for Antibiotic Stewardship Programs in the Acute Care Setting. Clin Infect Dis. 2018 Sep 28;67(8):1168-74.