



RESISTANCE BACTERIA THAT COLONIZE CHRONIC SKIN WOUNDS: REVIEW

¹Salim S. Jaafar, ²Ehab Y. Jabber

¹Asst. Lecturer, ²Asst. Professor

^{1,2} University of Babylon, DNA research center, Babylon , Iraq

Abstract

Chronic wounds, represented by their three types: venous ulcers, diabetic foot ulcers, and pressure ulcers, are a source of concern for patients if they are resistant to antibiotics for a period exceeding the third week. Due to the continuous increase in the world's population, chronic wounds in the legs and feet represent an increasing burden on the health and economic system, as deep chronic wounds in the feet and legs contain tiny microscopic organisms that do not respond to treatment, and antibiotics have become of little benefit and weak in healing, and this weakness in healing unknown Antibiotics are commonly used to treat chronic wounds. These individuals receive prescriptions for antibiotics (both systemic and topical). A wound is a tissue injury resulting from a disruption of the skin membrane and typically occurs in three phases in healthy individuals: inflammation, proliferation, and to alter the structure of ,Wound healing typically begins with the inflammatory phase and progresses to the remodeling phase; however, chronic wounds continue in the inflammatory phase. This study aims to shed light on why chronic skin wounds do not respond to antibiotics

Keywords: Bacterial resistance, Infected wounds, Colonization

Introduction

There are four levels of the relationship between bacteria and skin ulcers, starting with contamination, then colonization, acute colonization, and the last level is infection [1] Chronic wounds are a polymicrobial environment where bacteria possess a biofilm and are able to modify their virulence mechanisms to escape host immune defenses, allowing pathogens to survive and persist in the wound and delay healing [2]

Wound resistance to treatment and care beyond the fourth week is a concern that affects a large segment of patients. There are three types of chronic wounds: diabetic foot ulcers(DFU) venous ulcers, and pressure ulcers(PU) Regular cleaning of the affected tissue is very important because it is the classic treatment to reduce the biofilm mass of organisms that colonize the wound. There is a synergistic interaction between the bacterial species colonizing the wound that facilitates the process of biofilm formation [3].

Most bacteria colonizing chronic wounds form biofilms[4] and biofilms are complex accumulations of microorganisms characterized by the secretion of an extracellular matrix that is incubated and adhesive and consists of polymeric materials that help in the complex cooperation between cells5 contribute to the disruption of healing and its persistence for long periods and thus increase the use of antibiotics and the result is increased bacterial resistance to antibiotics[6,7,8] where Abbas, M and Serena and their colleagues showed that the poor use of antibiotics increases bacterial resistance[9,10] and that bacteria acquired from hospitals have broad resistance to antibiotics[11] and biofilms contribute to antibiotic resistance[12].

Biofilm tolerance has risen [13], as bacteria chose resistance through pressure selection [14] and genetic transfer [15].

Signs of chronic wound infection

Researchers have classified the levels of interaction between ulcers and the causative bacteria into four levels: contamination, colonization, critical colonization, and infection. There is no evidence that contamination and colonization prevent wound healing, but the dividing line between colonization and

infection cannot be defined. "Critical colonization" is a term that describes a state of delayed healing due to a microbe [16], Purulent discharge and two or more of the following signs (heat, oedema, pain and redness) are considered signs of infection in a diabetic ulcer [17].

Venous leg ulcers should be considered infected if any of the following symptoms are present (redness, warmth, tenderness, heat, and induration). The British Dermatological Society has suggested other signs of infection such as serous discharge, prolonged healing time, and foul odor [18].

Microbes infecting chronic wounds

The researchers found that *Staphylococcus aureus* and coagulase(-ve) *Staph. aureus* were the most abundant organisms in samples isolated from foot and leg ulcers, with *Staphylococcus aureus* being found in more than 40% of infected leg ulcers and more than 85% of non-infected leg ulcers, while *Staphylococcus epidermidis* was found in 14% of venous ulcer samples [19], 20.6% of diabetic foot ulcers (DFUs), and approximately 33% of ulcers. [20] Other reported aerobic species include *Escherichia coli*, *Streptococcus* species [21], *Enterobacter* and *Klebsiella* species, *Enterobacter* species [22], and *Proteus* species. [18,20] This list is not exhaustive, but it illustrates the diversity of aerobic bacteria found in chronic wounds [24].

Antibiotics used in wound treatment

Howell-Jones et al. showed that the proportion of patients with chronic wounds who received antibiotic treatment for diabetes (68.3%) and (29.4%) of patients without chronic wounds of the same age and sex but who took other antibiotics such as flucloxacillin, trimethoprim, co-amoxiclav, metronidazole, cefaclor, erythromycin, ciprofloxacin and cephalexin [24].

Antibiotic resistance and chronic wounds

The relationship between chronic wounds and resistance to antibiotics has become an important issue of concern due to the increasing population at risk for delayed wound healing and the widespread prevalence of antibiotic-resistant microorganisms. Researchers believe that the polymicrobial nature of chronic wounds provides a favorable environment for genetic exchange. A study found that 40% of *Staphylococcus aureus* isolated from foot ulcers were methicillin-resistant (MRSA) [25], Olesky, A. S. and colleagues found that 50% of *Staphylococcus aureus* isolates isolated from leg ulcer patients were methicillin-resistant [26], while Davis, in his 2003 study, found that MRSA was 7.7% [27].

MacMahon found that macrolides and metronidazole are associated with clarithromycin and metronidazole resistance in *Helicobacter pylori* strains [28]. Biofilms formed by bacteria that cause high resistance to antibiotics pose a threat to human health in general and especially to patients with acute wounds. The use of antiseptic-containing disinfectants and proper wound management are beneficial for wound healing and infection control [29].

Despite the risk of excessive and early use of antibiotics, some experts have recommended early use if a diabetic foot ulcer is suspected [30].

Synergism between bacterial species

Aggregate-mediated quorum sensing-related auto-amplification plays an important role in chronic wounds in *S. aureus* and is an important virulence factor. Synergism between some bacterial species that colonize chronic wounds increases their virulence and is often found between Gram-positive bacteria such as *S. aureus* and *P. aeruginosa* by specific peptidoglycan fragments and acetylglucosamine [31].

Conclusion

It is clear from studies that antibiotics play a major role in treating chronic wounds and that the use of antibiotics is fraught with risks because the use of antibiotics at the individual level and for a long period is accompanied by difficulty in treating other accompanying diseases, Improving the care of chronic wounds is very important and studying and understanding the synergistic interactions between the colonizing microorganisms is one of the things that facilitates the process of improving wound management.

Reference

1- Chiller K, Selkin BA, Murakawa GJ. (2001).Skin microflora and bacterial infections of the skin. J. Investig. Dermatol. Symp. Proc. ;6:170–174.

2-Järbrink K., Ni G., Sönnergren H., Schmidtchen A., Pang C., Bajpai R., Car J.(2016).Prevalence and Incidence of Chronic Wounds and Related Complications: A Protocol for a Systematic Review. Syst. Rev. ;5:152. doi: 10.1186/s13643-016-0329-.

- 3-** Durand, B. A., Pouget, C., Magnan, C., Molle, V., Lavigne, J. P., & Dunyach-Remy, C. (2022). Bacterial interactions in the context of chronic wound biofilm: a review. *Microorganisms*, *10*(8), 1500.
- 4-** Pouget, C.; Dunyach-Remy, C.; Pantel, A.; Schuldiner, S.; Sotto, A.; Lavigne, J.-P. (2020). Biofilms in Diabetic Foot Ulcers: Significance and Clinical Relevance. *Microorganisms* *8*, 1580.
- 5-** Bjarnsholt, T.; Alhede, M.; Alhede, M.; Eickhardt-Sørensen, S.R.; Moser, C.; Kühl, M.; Jensen, P.Ø.; Høiby, N. (2013). The in Vivo Biofilm. *Trends Microbiol.* , *21*, 466–474.
- 6-** Bowler, P.G.; Welsby, S.; Towers, V.; Booth, R.; Hogarth, A.; Rowlands, V.; Joseph, A.; Jones, S.A. (2012). Multidrug-resistant Organisms, Wounds and Topical Antimicrobial Protection. *Int. Wound J*, *9*, 387–396.
- 7-** Lavery, L.A.; Fontaine, J.L.; Bhavan, K.; Kim, P.J.; Williams, J.R.; Hunt, N.A. (2014). Risk Factors for Methicillin-Resistant Staphylococcus Aureus in Diabetic Foot Infections. *Diabet. Foot Ankle* , *5*, 23575.
- 8-** Guan, H.; Dong, W.; Lu, Y.; Jiang, M.; Zhang, D.; Aobuliximu, Y.; Dong, J.; Niu, Y.; Liu, Y.; Guan, B.; *et al.* (2021). Distribution and Antibiotic Resistance Patterns of Pathogenic Bacteria in Patients with Chronic Cutaneous Wounds in China. *Front. Med.* , *8*, 609584.
- 9-** Abbas, M.; Uçkay, I.; Lipsky, B.A. (2015) In Diabetic Foot Infections Antibiotics Are to Treat Infection, Not to Heal Wounds. *Expert Opin. Pharmacother.* , *16*, 821–832.
- 10-** Serena, T.E.; Gould, L.; Ousey, K.; Kirsner, (2021). R.S. Reliance on Clinical Signs and Symptoms Assessment Leads to Misuse of Antimicrobials: Post Hoc Analysis of 350 Chronic Wounds. *Adv. Wound Care* .
- 11-** Demling, R.H and Waterhouse, B. (2007). The Increasing Problem of Wound Bacterial Burden and Infection in Acute and Chronic Soft-Tissue Wounds Caused by Methicillin-Resistant Staphylococcus Aureus. *J. Burns Wounds* , *7*, e8.
- 12-** Johani, K.; Malone, M.; Jensen, S.; Gosbell, I.; Dickson, H.; Hu, H.; Vickery, K. (2017). Microscopy Visualisation Confirms Multi-Species Biofilms Are Ubiquitous in Diabetic Foot Ulcers. *Int. Wound J.* , *14*, 1160–1169.
- 13-** Olsen, I. (2015). Biofilm-Specific Antibiotic Tolerance and Resistance. *Eur. J. Clin. Microbiol. Infect. Dis.* *34*, 877–886.
- 14-** Ahmed, M.N.; Porse, A.; Sommer, M.O.A.; Høiby, N.; Ciofu, O (2013). Evolution of Antibiotic Resistance in Biofilm and Planktonic Pseudomonas Aeruginosa Populations Exposed to Subinhibitory Levels of Ciprofloxacin. *Antimicrob. Agents Chemother*, *62*, e00320-18.
- 15-** Savage, V.J.; Chopra, I.; O'Neill, A.J.(1970). Staphylococcus Aureus Biofilms Promote Horizontal Transfer of Antibiotic Resistance. *Antimicrob. Agents Chemother.* *57*.
- 16-** Schultz, G. S., Sibbald, R. G., Falanga, V. *et al.* (2003). Wound bed preparation: a systematic approach to wound management. *Wound Repair and Regeneration* *11*, 1–28.
- 17-** American Diabetes Association (1999). Consensus development conference on diabetic foot wound care. *Diabetes Care* *22*, 1354–60.
- 18-** Douglas, W. S. & Simpson, N. B. (1995). Guidelines for the management of chronic venous leg ulceration. Report of a multidisciplinary workshop. *British Journal of Dermatology* *132*, 446–52.
- 19-** Urbančič-Rovan, V. & Gubina, M. (1997). Infection in superficial diabetic foot ulcers. *Clinical Infectious Diseases* *25*, S184–5.

- 20-**Hansson, C., Hoborn, J., Möller, A. *et al.* (1995). The microbial flora in venous leg ulcers without clinical signs of infection. *Acta Dermato-Venereologica* 75, 24–30.
- 21-**Ge, Y., MacDonald, D., Hait, H. *et al.* (2002). Microbiological profile of infected diabetic foot ulcers. *Diabetic Medicine* 19, 1032–5.
- 22-**Schmidt, K., Debus, E. S., Jeßberger, S. *et al.* (2000). Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous, and the arterial ulcer? *Vasa* 29, 62–70.
- 23-**Bowler, P. G. & Davies, B. J. (1999). The microbiology of acute and chronic wounds. *Wounds* 11, 72–8
- 24-** Howell-Jones, R. S., Wilson, M. J., Hill, K. E., Howard, A. J., Price, P. E., & Thomas, D. W. (2005). A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. *Journal of antimicrobial chemotherapy*, 55(2), 143-149.
- 25-** Tentolouris, N., Jude, E. B., Smirnof, I. *et al.* (1999). Methicillinresistant *Staphylococcus aureus*: an increasing problem in a diabetic foot clinic. *Diabetic Medicine* 16, 767–71.
- 26-** Colsky, A. S., Kirsner, R. S. & Kerdel, F. A. (1998). Analysis of antibiotic susceptibilities of skin wound flora in hospitalized dermatology patients. The crisis of antibiotic resistance has come to the surface. *Archives of Dermatology* 134, 1006–9. 55. Dang, C. N., Prasad, Y. D. M., Boulton,
- 27-** Davies, C. E. (2003). The comprehensive analysis of the microbial community of clinically non-infected chronic venous leg ulcers. PhD thesis. Department of Oral Surgery, Medicine and Pathology, University of Wales College of Medicine, Cardiff, UK.
- 28-**McMahon, B. J., Hennessy, T. W., Bensler, J. M. *et al.* (2003). The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for *Helicobacter pylori* infections. *Annals of Internal Medicine* 139, 463–9.
- 29-** White, R. J., Cooper, R., & Kingsley, A. (2001). Wound colonization and infection: the role of topical antimicrobials. *British Journal of Nursing*, 10(9), 563-578.
- 30-** Jeffcoate, W. J. (1999). Use of antibiotics in uninfected ulcers may do more harm than good. *Diabetic Foot* 2, 132–5.
- 31-** Durand, B. A., Pouget, C., Magnan, C., Molle, V., Lavigne, J. P., & Dunyach-Remy, C. (2022). Bacterial interactions in the context of chronic wound biofilm: a review. *Microorganisms*, 10(8), 1500.