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Bacterial Pathogens in Wound and Burn Infections: A Comprehensive Review

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Abstract

Wound and burn injuries are a massive burden on healthcare in the world, and infection is the most common and severe complication that results in the delay of the healing process, sepsis, multi-organ failure, and death. The healing process is disturbed by the colonization and further infection of these injuries with bacterial pathogens and is a challenge to clinical management. This review includes a complete discussion of the bacterial ecology of wound and burn infections together with a focus on the most common pathogens, This includes the Gram positive (*Staphylococcus aureus* (especially MRSA) and Gram negative (*Pseudomonas aeruginosa, Acinetobacter baumannii* and multi drug resistant Enterobacteriaceae) the virulence factors as well as the development of antimicrobial resistance, and discuss existing methods of diagnosis, standard and emerging treatment approaches and point to the growing need of innovative anti-infective and biofilm disrupt This complicated landscape is important to understand in order to enhance patient outcomes during the era of increased antibiotic resistance.

Keywords: Wound Infection, Burn Infection, Bacterial Pathogens, Antimicrobial Resistance, Diagnosis, Novel Therapeutics.

Introduction

Wound and burn injuries are a deep-rooted and extensive problem for the global community's health systems, with huge mortality, chronic disability, and socioeconomic burden. The World Health Organization estimates that injuries collectively result in about 9% of mortality globally, with a significant percentage of them being made complex by infection. Homeostasis relies on the integrity of the skin, which is our major organ and the main defense line. Its weakness--mechanical trauma, surgery, ischemia, heat, etc.--forms a weak boundary between a sterile internal environment and a microbe-subject environment (1).

The pathway between a clean and healing wound and a chronically infected one is not a binary process but a dynamic and contentious process. First, any open wound is infested with microbes. This bioburden is, in most instances, handled by host mechanisms and adequate wound care, enabling hemostasis, inflammation, proliferation, and remodelling to proceed in a sequential manner. But as the growth of the microbes surpasses the control of the host, there will be critical colonization, which interrupts cellular functions and postpones repair without obvious clinical symptoms of infection. This may progress to local infection, which is typified by typical signs of rubor, color, dolor, and tumor. In extreme situations, especially in immunocompromised hosts or when there is a high virulence of the pathogen, invasive systemic infection develops, resulting in sepsis, multi-organ dysfunction, and mortality (2).

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The other end of the scale is burn wounds. Not only does the injury lead to immense cutaneous destruction, but it is also an extensive, systemic condition of burn-induced immunosuppression, with defects in neutrophil chemotaxis, T-cell crippling, and the loss of a pro-inflammatory to a hyper-catabolic, and anti-inflammatory state (3). This initiates an immunologically permissive surrounding that renders burn patients particularly vulnerable to invasive infection, which is the most common cause of death in patients who survive the initial resuscitation phase (4).

The microbial ecology of such infections has changed radically. Although *Staphylococcus aureus* and *Pseudomonas aeruginosa* have traditionally been considered the paradigms of enemies, the 21 st century was characterized by their growing and even pan-drug resistance. The unremitting emergence of Methicillin-Resistant *S. aureus* (MRSA), carbapenem-resistant *Pseudomonas* and *Acinetobacter baumannii,* and Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae have undermined the effectiveness of our antibiotic repertoire (5,6). What is making this crisis more complicated is the realization of the biofilm form of growth, in which microbial populations wrap themselves in a protective polymeric shell that makes them orders of magnitude more resistant to antimicrobials and host defense (7). It has been established that biofilms are the focal biological determinant of chronicity in non-healing wounds and, thus, the modern management of wound and burn infections requires a complex, multidimensional conceptualization combining traditional microbiology with immunology, molecular biology, and materials science (8).

Microbiology of Wound and Burn Infections

The pathway of microbial involvement of wounds and burns lies on a critical curve between superficial and systemic disease, with increasing bacterial load and host response. A contamination is the first step, the simple presence of non-replicating microorganisms on the wound surface, which is universal and harmless. This progresses to colonization, whereby the bacteria stick and reproduce without eliciting a local response or disrupting healing and reside in an equilibrium with the local defenses (9).

Once the balance is disrupted by the numbers and virulence factors of bacteria, local infection (or critical colonization) ensues, with localized delayed healing, exudate, and microcolonies and biofilms, without systemic manifestation. Uncontrolled infection extends beyond the margins of the wound into spreading infection, including cellulitis or fasciitis, of the deep tissues. The last and the gravest is systemic infection when the pathogens spread through the bloodstream, and Mathis develops bacteremia, sepsis, and multi-organ failure, the direct result of the loss of local containment and dysregulated host immune response (10).

The microbial ecology of a wound experiences a predictable chronology, which is due to the changing wound environment and the therapeutic interventions. During the acute phase (0-48 hours), the wounds and initially sterile burns are mostly colonized by the host skin flora, especially Gram-positive cocci, such as *staphylococcus aureus* and *streptococci*. This community transforms into the subacute to chronic period (≥1 week), with an ecology becoming more complex, typically polymicrobial (including Gram-negative bacilli, e.g., *Pseudomonas aeruginosa*) and anaerobic, especially in the necrotic or ischemic tissues (11).

An extended hospital stay leads to an additional shift to a nosocomial or hospital-acquired phase, often displacement or addition of multidrug-resistant (MDR) nosocomial pathogens such as MRSA, VRE, and carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae to construct the most difficult therapeutic problems. This evolution of a benevolent group of endogenous colonizers into an intricate, antibiotic-resistant community is a

reminder of the importance of the early detection and prevention of infection (12,13)

Major Bacterial Pathogens

Staphylococcus aureus

The most common pathogen in acute and chronic wounds is the *Staphylococcus aureus*. It has been successful because it has a broad range of virulence factors that help it colonize, destroy tissues, and evade immunity. Colonization is first carried out through adhesins (MSCRAMMs), which attach to the exposed host matrix proteins and are usually then covered by a strong biofilm that protects the bacterial community (14). It leads to serious tissue damage with strong toxins: alpha-toxin lyses the cells of the host and immobilizes immunity, and Panton-Valentine leukocidin (PVL) against neutrophils. At the same time, the pathogen uses advanced immune evasion mechanisms; The Protein A anti-antibody effect, and localized clotting by coagulase to form a safe niche. The severe therapeutic problem lies in the prevalence of methicillin-resistant *S. aureus* (MRSA) in the whole world and the shocking emergence of vancomycin-resistant strains (VRSA) that severely restrict treatment options and reveal the urgency to develop new antimicrobial measures and close up on infection control (15,16).

Enterococcus

Both *Enterococcus faecalis* and *Enterococcus faecium* are ideal examples of opportunistic pathogens whose clinical risk is not due to their efficiency and aggressiveness in virulence but rather due to their high degree of resilience and high antibiotic resistance ability (17). They often become synergistic partners in polymicrobial infections in wounds and burns, making them difficult to treat and causing chronicity. A combination of inherent resistance to disease, a powerful capacity of antibiotics, and ecological flexibility characterizes the clinical threat of *Enterococcus faecalis* and *E. faecium*. Their natural resistance makes them survive in extreme environments, and the core antibiotic resistance has an intrinsic tolerance to cephalosporins and high-level aminoglycoside resistance (HLAR), nullifying the synergies of therapy (18).

It leads to the crisis of vancomycin resistance (van genes) acquired, in which the treatment of infections has become incredibly challenging, and enterococci have become the reservoirs of resistance transfer to other pathogens. Besides, their expertise in biofilm development and polymicrobial synergy makes them the enduring, collaborative components of wound consortia, where they augment community stability and global antimicrobial forbearance, resulting in chronicity and treatment failure (19).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a model of opportunistic pathogenism in the impaired wound milieu. It flourishes in the damaged wound niche due to a combination of both intrinsic resistance, complex virulence factors, along with its highly adaptive lifestyle, robust biofilm lifestyle, and both intrinsic and acquired antibiotic resistance (20). It is particularly metabolically versatile and can therefore take advantage of the poor nutrient and often low oxygen levels found in chronic wounds by using a wide range of organic compounds and alternative electron acceptors. This viability is accompanied by an elaborate virulence toolkit, comprising demolishing exotoxins (Exotoxin A, elastase), redox-active phenazine pyocyanin, and the Type III Secretion System, which directly injects cytotoxic effectors into host cells, all controlled by quorum sensing at the population level (21).

At its persistence is the biofilm lifestyle, in which bacteria incorporate into a protective polysaccharide-based (e.g., alginate) matrix, a heterogeneous community into which bacteria are embedded, which has a lower metabolic activity and great resistance to antimicrobials and host defenses (22). This tolerance is enhanced by innate

mechanisms of antimicrobial resistance, including low-permeability outer membrane and active efflux pumps, which, together with acquired genetic mutations or transferred resistance genes, contribute to the development of multidrug-resistant (MDR) and extensively drug-resistant (XDR) clones, which are extremely difficult to eradicate and make *P. aeruginosa* a classic, recalcitrant opportunistic pathogen (23).

Acinetobacter baumannii

Acinetobacter baumannii has become a truly pathogenic nosocomial pathogen, especially in intensive care units and burn units, where it results in devastating wound and bloodstream infections (24). This is due to its notorious environmental persistence and transmission, which is encouraged by an extraordinary capability to survive on dry surfaces and to create strong biofilms on medical equipment, promoting hard-to-control outbreaks (25). It is further aggravated by a severe multidrug resistance epidemic, because its highly flexible genome is easily infected with resistance genes, often making it carbapenem-resistant (CRAB) and leaving only second-line, often toxic, antibiotics such as colistin as treatment options. Although its pathogenicity in wounds is inherently moderate, several virulence factors, such as adherence mechanisms, strong biofilm formation on tissue, and efficient nutrient acquisition, enable it to take advantage of immunocompromised hosts, causing invasive, necrotizing infections that are unusually difficult to treat and control (26).

Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*)

The Enterobacteriaceae family, the major cause of wound infection, contains the most important pathogenic species, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which are common in two quite different, but occasionally overlapping clinical settings: fecal or environmental contamination of the wound, and nosocomial (hospital-acquired) infections in debilitated patients (27). The gut bacteria gain entry by contamination with fecal matter (e.g., traumatic injuries, diabetic foot ulcers) or through colonization of the debilitated in the hospital. This is because each species has certain virulence (28).

E. coli is able to enter into strong biofilms, *K. pneumoniae* has an anti-phagocytic capsule (hyper virulent forms cause severe infections), and *P. mirabilis* swarms across surfaces rapidly and generates problematic urease. They are most threatening; however, their greatest threat is multidrug resistance, predominantly by ESBLs (inactivation of penicillins and cephalosporins) and carbapenamases such as KPC and NDM (inactivation of last-line carbapenems to form CRE superbugs). This resistance pushes infections to be very hard to treat, resulting in delays in treatment, fewer therapeutic choices, high expenses, and death (29).

Biofilms in chronic wounds and burns

The biofilm paradigm is a radical change in the perception of chronic wound and burn infection by the realization that a majority of microbes are not present as solitary organisms but rather linked and embedded within an organized system of proliferating, surface-related, and matrix-enclosed communities (30,31). This mobile way of life, which is initiated by a reversible followed by irreversible adhesion of planktonic cells to a surface and ends in a mature and heterogeneous structure containing nutrient channels, involves extreme survival benefits in a highly organized, cooperative growth pattern as well as an active dispersal phase.

This community is characterized by the self-synthesized extracellular polymeric substance (EPS) matrix that is a hydrated gel-like complex of exopolysaccharide, extracellular DNA, proteins, and lipids that forms an imposing physicochemical barrier by hindering the diffusion of antimicrobial agents, as well as by entraping host defenses (32).

More importantly, biofilm-based tolerance, which differs with genetic resistance, is multifactorial, and

emerges not just through this barrier, but also through an altered microenvironment in the dense community comprised of gradients of oxygen and nutrients forming areas of slow- or non-growing cells that are inherently less vulnerable to antibiotics acting on active processes, as well as through the presence of a minor, metabolically dormant subpopulation of so-called persister cells with extreme phenotypic tolerance and capable of re-inoculating the biofilm following treatment, promoting the chronic (33).

Antimicrobial Resistance in Wound and Burn Pathogens.

The issue of antimicrobial resistance (AMR) is a significant challenge to treating wound and burn cases since such patients are also critically ill, immunocompromised, frequently exposed to broad-spectrum antibiotics, and undergo high-transmission hospital care (34). Burn units and surgical wards encourage the development and dissemination of multiple drug-resistant (MDR) and extensively drug-resistant (XDR) organisms because of recurrent empiric and protracted antibiotic therapy, recurrent infections, invasive apparatus (e.g., central lines, catheters, ventilation), and repeated procedures like debridement and grafting, which expose them to exposure of hospital flora and spread. The formation of biofilms also increases resistance by reducing antibiotic entry, safeguarding bacteria against host defense, stimulating the propagation of persister cells, and increasing horizontal gene transfer. There is also a factor of environmental persistence in that organisms such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* will survive on hospital surfaces, water systems, and equipment, resulting in outbreaks (35,36).

AMR has clinical manifestations of MDR (resistant to ≥1 agent in ≥3 classes), XDR (resistant to only 1-2 classes), and PDR (resistant to all classes), common in burn care. The resistance is evaded by β-lactamases (ESBLs, carbapenemases including KPC, NDM, and OXA enzymes), target modification (MRSA via mecA / mecC), loss of porin, efflux pumps, and biofilm tolerance (37). Therefore, wound and burn infections are progressively becoming MRSA, VRE (E. faecium), MDR/XDR *P.aeruginosa,* carbapenem-resistant *A.baumannii* (CRAB), and ESBL/CRE Enterobacterales, with limited treatment options, including vancomycin/linezolid/daptomycin, newer antipseudomonal β-lactam combinations, and CRAB with colistin or sulbactam-based combinations. AMR causes treatment failure, retarded healing, loss of grafts, sepsis, and increased healthcare burden. Such drivers as improper use of antibiotics, insufficient infection control, and the necessity of stewardship, rapid diagnostics, stringent preventive measures, and culture-oriented therapy are revealed (38,39).

Diagnostic Approaches

The most significant step in the process of managing wound and burn infection is accurate and timely diagnosis, which should not rely on a subjective clinical picture anymore but on objective and pathogen-specific data. It is a transition of slow, culture-dependent diagnostic strategies to fast, comprehensive, and point-of-care diagnostic technologies that is more of the complexity of these infections (40). Microbiological culture of deep tissue biopsy or wound fluid is still the gold standard in the identification of pathogens and in informing antimicrobial therapy, and deep biopsy is preferable to superficial swabs since the latter tends to pick up the colonizing flora and may be negative on anaerobes and organisms with biofilms (41)

Culture, however, has drawbacks of delays (usually 24-72 hours, even longer to achieve full susceptibility testing), diminished sensitivity in biofilm-associated and VBNC infections, and an incomplete view of polymicrobial diversity or pathogen behaviour (42). To close these gaps, more powerful molecular and proteomic diagnostics, such as PCR/multiplex panels, can quickly identify

typical wound pathogens and major resistance genes directly on samples in 2-5 hrs so that they can be treated earlier (43).

In the case of culture-negative/complex wounds, 16S rRNA sequencing and shotgun metagenomics are able to give a wider profile of the polymicrobial community, uncover uncultivable organisms, and potentially identify resistance and virulence genes, whereas MALDI-TOF MS can identify organisms within minutes after isolating colonies. Meanwhile, technologies at point of care are becoming more and more able to assess the presence of an infection at the bedside, such as fluorescence imaging (e.g., MolecuLight(r) maps showing the location of the bacteria burden in real time to inform debridement and sampling, biomarker tests (e.g. MMPs, elastase) can distinguish between colonization and an infection of clinical relevance, and newer lateral flow assays or compact molecular devices can detect pathogens such as MRSA or *P. aeruginosa* (44). Additional imaging and histopathological methods, such as OCT and high-frequency ultrasound, can be used to visualize the biofilms and the deep wound, whereas biopsy-based histology can identify the presence of invasive infection, identify the existence of biofilm clusters (e.g., PNA-FISH), and characterize the host inflammatory response (45).

Therapeutic Strategies and Challenges

Infected wound treatment methods are based on a synergistic approach of systemic antimicrobials, along with optimized wound care, along with increasing trends posed by multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms (46). Empirical broad-spectrum coverage (targeting local epidemiology and wound severity) may be used as an initial approach to antimicrobial therapy, then de-escalated when culture and susceptibility data are available, although resistance patterns are raising the cost of the more needed last-resort agents, including colistin, tigecycline, or more recent combinations (ceftazidime-avibactam) (47). The adjunctive and topical therapies are needed as well as systemic treatment, and local wound care is the foundation of management, especially effective debridement (surgical, enzymatic, or autolytic) to eliminate the necrotic tissue and disorganize biofilms (48).

Other interventions are topical antimicrobials (e.g., silver sulfadiazine, mupirocin, metronidazole gel, polyhexamethylene biguanide [PHMB], and iodine-based dressings or skin substitutes that cover the wound and aid in the regulation of the wound microenvironment. In the future, future treatments are multiplying choices to challenging infections, such as anti-biofilm agents (such as dispersin B, lactoferrin, and quorum-sensing inhibitors), anti-microbial peptides (AMP) with membrane-perturbing ability and possibly reduced resistance pressure, immunomodulatory strategies to correct defective host immunity, and nanotechnology-based therapies to increase targeted delivery or endow intrinsic antimicrobial action (e.g., silver or chitosan nanoparticles) (49).

Prevention and Control

Prevention is not merely supportive in wound and burn care, particularly in the high-risk environment of healthcare facilities; due to the serious implications of infection and the escalating crisis of antimicrobial resistance, proactive and multi-layered infection prevention and control (IPC) measures are necessary to assure patient safety, better outcomes, and preserve treatment options by preventing the chain of infection through meticulous hand hygiene (alcohol-based rub or soap and water) before and after every patient contact, immediate contact precautions and patient isolation or co-housing of patients colonized or infected with multid (50).

such measures are to be strengthened by the following: environmental decontamination and source control, e.g. frequent disinfection of patient rooms and high-contact surfaces with hospital-grade agents with spore-killing and MDRO-killing effects (with particular focus on the desiccation-resistant

pathogen such as *Acinetobacter baumannii*), hospital water safety programs to prevent Legionella colonization and biofilm-forming pathogens such as *Pseudomonas aeruginosa* (e.g. with flushing, point-of-use filters, monitoring, etc.), and lastly, wound-specific and patient-centered approaches including standardized evidence-based wound care bundles, judicious use of topical antimicrobial prophylaxis (e.g., silver sulfadiazine, mupirocin to decolonize MRSA) when necessary and advanced barrier dressing materials that ensure optimal moisture balance prove essential, and in burns, timely wound closure using autografts or skin substitutes is the most conclusive preventive measure due to the removal of the necrotic nidus to infection (51,52).

Conclusion

Bacterial wound and burn infections constitute one of the most urgent areas of contemporary medicine that is characterized by the intricate interaction of highly adaptive pathogenic organisms, impaired host defenses, and a protective barrier biofilm (53). These infections are not mere contaminations but are dynamic ecological phenomena where organisms like *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* endure owing to their potent virulence determinants, rapid adaptability as well as the capability to adopt biofilm lifestyle which provides them with remarkable antimicrobial and immune evasion; it is concomitant with burn patients frequently developing severe immune dysregulation, in which initial hyperinflammation is succeeded by sustained immunosuppression (54). Despite the advanced nature of the present management techniques, they are still more reactive than traditional diagnostics, which are too slow to be able to capture the reality of polymicrobial and biofilm-based processes. The systemic use of antibiotics is starting to lose its sense due to the multidrug resistance, and the old paradigm of aggressive debridement and the empiric therapy with a wide range of antibiotics becomes too slow to be able to adapt to the emerging truth of the biofilm and polymicrobial reality (55).

The future thus requires a transition to precision medicine and ecological wound care due to convergent innovations, such as real-time, bedside diagnostics (including point-of-care molecular platforms, fluorescence imaging of bacterial burden, and biomarker panels to assess host response and proteolytic activity) that can enable the delivery of targeted first-time-right therapy, and novel anti-biofilm and anti-virulence interventions that arm pathogens instead of necessarily killing them (56).

Some of these approaches involve biofilm matrix disruptors (e.g., dispersin B, DNase, and chelating agents that disrupt the EPS scaffold), quorum-sensing inhibitors that disrupt bacterial communication and virulence without high selective pressure to resist, and bacteriophage-based approaches or engineered lysins that can penetrate biofilms and selectively lyse pathogens (57). Immunomodulatory treatments to correct dysfunctional host immunity, neutrophil-restoring macrophage polarization balance-neutralizing bacterial proteases, such as using topical MMP inhibitors, responsive, smart wound technologies (e.g., active dressings, nanofibers based on chitosan), and real-time biosensors to continuously monitor infection and healing biomarkers are equally important (58).

Finally, it will be necessary to utilize systems-based prevention, which will include environmental genomics to track outbreaks, AI-driven risk prediction to identify vulnerable patients, and a strong antimicrobial stewardship deep-rooted across wound care to maintain the quality of current and emerging treatments (59). Eventually, the resolution of the crisis of wound and burn infections necessitates the abandonment of reductionist models of the past and instead treating the wound as a complex pathologic ecosystem with success being

achieved through the interdisciplinary combination of microbiology, immunology, materials science, and data analytics to break the communities of pathogens, balance host responses, and promote regeneration, thereby transforming the clinical objective of preventing infection to actively reestablishing the physiological healing cascade (60,61).

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