

REVIEW ARTICLE

Microbial Robots to Treat the third Degree Burnt Patients: Review

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Abstract

Burn is responsible for an estimated 180,000 deaths annually. A burn is skin damage caused through either high temperature or because of radiation, radioactivity, electricity, or contact with chemicals. A burn is skin damage, which is resulted because of electricity, radiation, radioactivity, or exposure to chemicals. Skin is the primary barrier to infection and burns patients lose their skin the risk of infection persists as the barrier is absent. The leading cause of death after burn injury is sepsis. Sepsis is lethal organ dysfunction caused by a host's dysregulated response to infection. Multiple antibiotic-resistant bacteria are responsible for the majority of deaths due to sepsis. Third-degree burns go through the skin and deeper tissues are affected. Third-degree burns may need more thorough treatments. Treatment includes intravenous antibiotics to prevent infections, surgical excision, and skin grafting. Treatments given to third-degree burnt patients are not giving satisfactory results. As robotics is a suitable way to work in delicate environments it can be an effective way to deal with sensitive burnt areas. This review focuses on the cause of infection and treatment of burnt patients.

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1. Introduction:

In the globe, various health issues have been faced by mankind. Some of them are accidental and others are natural or artificial. Skin burns are one of the common problems found all over the world. Skin burns result in many deaths due to improper facilities in the medical field. The following infections after the burning of skin are responsible for serious health complications. The diabetic burn patient has a higher probability of

getting nosocomial infection [1]. After the biopsy, 105 organisms were detected in the patients suffering from nosocomial burn wounds [1]. Nowadays, interdisciplinary research is being promoted that has opened created opportunities for scientists across the globe.

Currently, robotics is a suitable way to work in delicate environments. The burns, especially, third-

degree burns keep the patient's life at greater risk and modern available medical facilities are not able to save the life of a person in such cases. In this review article, we discuss a microbial robot to work on burnt skin and repair it by killing infectious pathogens and then synthesizing normal skin. This will save thousands of lives across the globe per year since the microrobots can be used to control pathogenic infections in sufferers leading to saving their lives. This technology will open a new gateway to the medical microbiology branch with greater success. In this article, we analyzed the possibilities of making a bacterial robot that kills all types of pathogens in the burnt area and recovers skin damage, and reports the update on the screen board.

2. Need of study:

About 450,000 people are in search of treatment of injury by burn per year of which 40,000 were admitted to hospital and 3,000 died in the United States [3]. Inhalation injury increases the mortality and morbidity of the patients affected by burn injuries [4]. Burn injury mortalities have been increased in the past many decades because of increased knowledge, advanced resuscitation, earlier excision as well as grafting of the burn wounds, best methodologies of coverage of wounds, advanced anesthesia along with techniques of intensive care, diagnosis at an early stage, rapid treatment of infections, modified support methods in relation with nutrition [4].

Surgical treatment is required by burn-injured patients [4], which is not cost-effective and not always result in saving a life. Risk factors such as difficulty in airway anatomy, burn shock as well as resuscitation, and inhalation injury leads to an increased probability of both morbidity and mortality [4]. There is a need to investigate altered pharmacodynamics and pharmacokinetics in patients suffering from a burn injury [4]. Unfortunately, there is the probability of losses of the volume of blood along with body temperature in the intraoperative period [4]. More size of burning, injury of inhalation, and connected trauma is responsible for increasing deaths after-burn

incidences [6]. Social help may assist in the survival of patients [6].

3. Causes of deaths/infections after burn:

Streptococcus, Pseudomonas, Proteus, methicillin-resistant Staphylococcus aureus (MRSA), Enterobacter, Enterococcus causes diabetic wound burn wound cellulitis [1]. Piperacillin sodium, tazobactam sodium, sulbactam sodium, sulbactam sodium, ampicillin sodium is also used as antibiotics in this regard [1]. Moreover, nosocomial infections including sepsis, bacteremia, pneumonia, burn wound infections, urinary tract infections in both non-diabetic as well as diabetic patients were having infections by *S. aureus, Pseudomonas, Klebsiella, Enterococcus*, along with *Enterobacter*.

Shockingly, the patients suffering from diabetes are infected by *Proteus, Acinetobacter, MRSA* as well as *Candida* whereas *E. coli, Streptococcus, Hemophilus influenza, Candida* were considered as major culprits [1]. As well, the burnt diabetic patients may have cardiac as well as hypertensive comorbidities [1]. It was reported that 1 million patients with burn injury were found in the United States [8]. Shockingly, 60,000-80,000 people get admitted to hospitals and 5,000 patients die per year [8]. Advanced critical care and early excision, as well as grafting, increased survival rates of patients in the burn centers [7]. Additionally, rapid treatment related to pulmonary injury, proper early resuscitation can improve the health of burned patients [6].

Injuries by burn are potential problems across the world even if there are advanced protocols for the prevention as well as safety of burn care [9]. Rapid as well as expert care is recommended for improving the health of burn injured patients [9]. Although modern therapies provide a warranty of burn injury treatments, the clinical practice may help the survival of patients [9]. Advanced measures in not only burn as well as critical care that include excision as well as grafting, fast resuscitation, as well as improvements in microbial therapy played a crucial role in reducing morbidity as well as mortality [10]. In contrast to this, death occurs

[10]. Patients may die due to sepsis, injuries, and failure of many organs [10].

When a person suffers a burn injury, sepsis occurs which is a major cause of death in which multiple drug-resistant bacteria are involved [10]. Modified strategies are recommended to increase the survival of patients. Burn injury leads to damage to protein and muscle catabolism, dysfunction of the heart, insulin resistance as well as considerable retardation in growth creating problems in proper development [11][12]. As well, patients suffer from supraphysiologic metabolic rates, accelerated levels of cytokines responsible for inflammation, failure of multi-organ system, and increased acute phase proteins [12]. Failure in attenuation of hypermetabolic response may lead to unrecoverable damage and even death [10].

The updated research in pharmacological, as well as non-pharmacological modulations of responses after burning, improved not only morbidity but also mortality [13]. Unluckily, the victim of severe burns may survive but death takes place still [10]. Trauma by burn leads to not only physical but also physiologic derangements [10]. Many deaths by burn may be prevented with better management of the airway along with appropriate resuscitative attempts [10]. The studies are required to know the proteomic as well as genomic changes that arise after burn in the affected individuals for identification of increased risk of having the probability of getting recalcitrant persons in relation with treatment modalities for multi-organ failure, sepsis along with constant respiratory failure [10]. There are various reasons for deaths of burn patients who are more than 65 years of age viz. related inhalation injury as well as earlier existing cardiopulmonary diseases [14].

Moreover, the deaths of burn patients who are aged can be occurred by earlier resuscitation of fluid, earlier excision of deep burn wounds as well as grafting, treatment or prevention of diverse complications which are life-threatening along with nutritional supplementation [14]. The syndrome in which many organs get failed after the burn incidence in the first 24

to 48 hours is responsible for major complications [15]. Unfortunately, the syndrome in which multiple organs get failed leads to incomplete fluid resuscitation [16]. The advanced studies in the resuscitation of burn shock have reduced deaths after injury within forty-eight hours [15].

Shockingly, infections are major causes of deaths in the patients after receiving enough control on the burn shock at the initial stage [15]. Infection of the bloodstream, pneumonia, and infection to the wound of burn are more common complications of patients [15] along with species of *Candida* as well as filamentous fungi, for instance, *Aspergillus* species that are responsible for the colonization of burn wound [18,19].

Acinetobacter calcoaceticus-baumannii (multiple drug resistant) is a regular reason for infections found in patients [15]. Bacteremia caused by *K. pneumoniae* can predict mortality [17]. The local microflora causes infection after burn with rapid colonization [18,20,21,22]. Afterburn injury, skin microbes such as *Staphylococcus aureus* as well as *Streptococcus pyogenes* that reside in skin appendages at deep, make the colonies in the wound within 24-48 hours [18,20]. Also, endogenous bacteria viz. *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* make their colonies in the wound within 48-72 hours [18,20].

Multidrug-resistant pathogens including *K. pneumoniae* (produces beta-lactamase which is extended-spectrum) and complex of *Acinetobacter calcoaceticus-baumannii* is the problem that is going on [15]. Filamentous fungi are the cause of invasive disease [23-26], for example, *Aspergillus sp.* and *Fusarium sp.* as well as individuals of Mucorales [28]. There are case reports of invasive wound infection due to a variety of dematiaceous fungi such as *Curvularia sp.* [22].

Unluckily, fungal infections prove laborious to precisely identify as distinguishing colonization from infection is challenging. A recent retrospective review found that a positive culture of mold, such as *Aspergillus*, increased the odds ratio of death nearly 12-fold. The most frequently isolated organism but had

the lowest associated mortality was *Candida* [4]. Viral infection of burn wounds is rarely reported but does occur. The most regular culprits are herpes simplex virus(HSV) and varicella-zoster virus (VZV) from the herpes virus family.

4. Treatment:

Palliative care service can provide an advantage to some patients suffering from burn injuries [2].

Table 1: Degrees of burn and their treatments [4]

| Degree of burn | Treatment |
|--|---|
| First-degree burn | It takes 3-6 days as healing time without scarring. |
| Second-degree burn (superficial) | A topical agent with cleaning and sterile dressing. Healing time is 7-21 days. |
| Deep-partial thickness(deep second degree) | Cleaning along with topical agent and a sterile dressing is preferred. There is a possibility of surgical excision as well as grafting. |
| Third-degree (full thickness) | Surgical excision as well as grafting. |
| Fourth degree | Surgical intervention is required for healing. Fluid resuscitation is another way of treatment. |

experienced in patients with critical burns. The earliest known report of skin grafting is in the Ebers Papyrus, an ancient Egyptian medical papyrus dating to 1500 BC. In India, skin grafting became very developed where reconstruction of noses and lips were done using pedicled flaps from the cheek or forehead and grafts containing skin and subcutaneous fat from the buttocks [35].

Sealing of wounds and conducting fast rehabilitation practices of the patient are the most constructive way to enhance the function of the wounded. One of the most widely used flaps is the superficial temporal fascia flap for the mending of burns and other wounds in the plastic surgery field. It is mainly used in maxillofacial surgery because of the acceptable features of this flap which include tenacity, elasticity, and extensibility. The fusing of the superficial temporal fascia free flap with thin split-skin grafting represents a satisfying strategy. It is very much suitable for the mending of deep injuries in the posterior talocrural area in critical burns patients [36].

The Nile tilapia is a fish from the species tilapia (*Oreochromis niloticus*). In Brazil the Nile tilapia skin is available and in previous studies, it is demonstrated that it gives satisfactory results when used as a xenograft in the treatment of experimental burns in an animal model. Noninfectious microflora and morphological structure having similarities with human skin are eye-catching features of tilapia skin. Bruno Almeida Costa et al. concluded that with the help of tilapia skin as xenograft 3- a year-old patient was operated on who was suffering from the superficial partial thickness burn. Tilapia skin represents good attachment to the burned area. It also showed a lack of toxicity and antigenicity. It promotes the formation of epithelium on the burn wound [34].

4.2. Phage therapy:

A crucial public health issue is antibiotic resistance and the antibiotics are running out of storage. Bacteriophages (phages) may provide an advanced means of infection treatment, which can be used with antibiotic treatment in combined or alternated ways

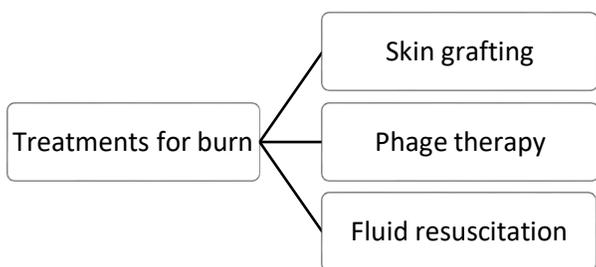


Figure 1: Treatments for burn patients

4.1 Skin grafting:

The utmost swift and productive procedure for closure of excised full-thickness burns is skin grafting [33]. Skin grafting is the type of graft surgery that involves skin transplantation. Skin grafting is the quality treatment for full-thickness skin loss, generally

and may amplify our abilities to successfully treat bacterial infections. Bacteriophages are the most copious and omnipresent organisms on Earth and are the natural predators of bacteria. Phages are the 'viruses' that infect and can lyse bacteria.



Figure 2: The Nile tilapia skin used as xenograft for skin grafting in burn patient.

Despite the antibiotic susceptibility of *S. aureus* or *P. aeruginosa*, these strains among others get infected by phages [29]. Phages are naturally safe in humans because they are appealingly specific in aiming and infecting bacterial cells. It infects bacteria to the species and frequently the strain level [31]. In early 1921 in Tbilisi, Georgia, and Poland phage therapy is also known as bacteriophage therapy has been utilized. In the 1930s and 1940s, it was extensively used around the world especially in Eastern European countries and in the former Soviet Union.

In a particular Medline citation search from 1966-1996, for the treatment of a vast range of pathogens in adults as well as children, the Soviet and Polish people delivered a mixture of bacteriophages topically, systematically, and orally. *Proteus*, *Escherichia coli*, *Staphylococcus*, *Streptococcus*, *Klebsiella*, *Pseudomonas*, *Shigella*, and *Salmonella* spp were treated. 80-90% was success rate accompanied by occasional allergic and reversible gastrointestinal side effects [30]. Burned mice were saved from infection caused by *P.aeruginosa* and *Klebsiella pneumonia* with the help of phages. In 1990, 30 patients suffering from burn injuries were treated using dressings that are phage saturated in just 5-17 days [29].

Constant systematic and well-timed applications are required for antibiotic therapy and in comparison, to this, phages keep working so long on their prey, in this case, the population of bacteria sensitive to that phage has been abolished because phages capture their host, rise in number, breakdown the bacterial cell and come out, attack other cells and the cycle continues until its resistance has developed by the host [30].

A case report narrates the fruitful decolonization of *Pseudomonas aeruginosa* from the burn area using topical phage potentiating subsequent skin grafting 3-days later. The targeting topical phages were applied via impregnation of filter paper discs (103 pfu) once to the burned surface. The discs were observed and raised concentrations of phages were recorded by authors indicating effective killing of bacteria which involves phages. Subsequently, the application of phage to the total burn surface results in negative results for bacterial culture and enhanced successful skin transplantation [31].

4.3. Fluid resuscitation:

Fluid resuscitation is fluid replacement. It is used to replenish body fluids. Hypovolaemic, cardiogenic and distributive shock happens due to burning injuries. Elevated capillary permeability and fluid shifts are the reason for the primary depletion of the intravascular volume. The ground step of severe burns management is proper management of fluids. Burns involving greater than 15 to 20% total body surface area (TBSA) will result in hypovolaemic shock without preliminary and effective treatment [32]. Fast and effectual intravascular volume replenishment is crucial for the mitigation of burn shock.

Late or insufficient fluid replacement results in hypovolemia, tissue hypoperfusion, shock, and multiple organ failure [4]. Besides the local lesion, the burn encourages the discharge of inflammatory mediators that bring out an extreme systemic inflammatory response and results in the increase in vascular permeability in both the healthy and the affected tissue [37]. Resuscitation of severe major burns is a

demanding task to the burn care providers especially in the first 24 hours from the time of burns.

It is one of the important predictors of survival of burn patients. Various resuscitation formulae are accessible at the request of the burn care provider. Despite many important advances in the fluid management field, smooth resuscitation is not ensured by any method [38]. The Parkland formula is accepted worldwide and it is the consensus formula currently [32].

Baxter and Shires in 1968 gave the Parkland formula then the little progress has been made in the field of fluid therapy for burn resuscitation, despite advances in hemodynamic monitoring, the establishment of the 'goal-directed therapy' concept, and the development of new colloid and crystalloid solutions. Initial resuscitation is based on crystalloids. Colloids seem unsuitable during the first few hours colloids are not suitable because of the high capillary permeability of burn patient. The electrolytic balance in large replacement is protected by Ringer's acetate, and the crystalloids are the first choice for initial fluid replacement in patients suffering from burn injuries. Severe burn resuscitation should ideally be performed with thermodiution methods according to goal-directed therapy [37].

4.4. Microrobots:

Self-propelled micro-robots are developed by fusing motile bacteria with micro synthetic structures. The advancement of technology for the fabrication of these bacteria-based robots is a first stepping stone towards the understanding of functional minute and self-governing moving robots [41]. The most common type of tumor treatment is chemotherapy and it is an efficacious standard therapy against actively multiplying tumor cells. However, other types of rapidly growing, healthy normal cells, such as blood and hair cells get damaged by chemotherapy. Chemotherapy induces different adverse reactions and side effects. Chemotherapy can be the resistance to therapeutic response in the slowly cell proliferating hypoxic region by deficient angiogenesis.

The continuous, specified delivery of ideal quantities of drugs to target cells is one of the most important challenges in chemotherapy. Many research groups have examined the progression of a drug delivery system (DDS) by using biocompatible and biodegradable materials, which can administer the drug release from microstructures to reduce side effects which will help to overcome the challenge [40]. Lack of tumor selectivity, multidrug resistance, and non-specific toxicity are major drawbacks of conventional anti-cancer agents [39].

A new approach for the construction of a bacteria-based microrobot and check the tumor aiming feature of a bacteria-based microrobot was proposed by a group of scientists. They called this microbial robot "bacteriobot". A microbial robot was developed using high-motility attenuated bacteria and a microstructure. These bacteria help the microbial robot to head in direction of tumors and at the same, they play the role of microactuator, therapeutic agent, and microsensor.

Bacteria act as microsensor to sense the presence of tumor and microactuator responsible for movement and the microstructure acts as a therapeutic molecule. High amounts of drugs are carried in microstructure for treating the tumor. To treat incurable diseases like cancer, a brand-new drug delivery system with the different useful features of microorganisms which we called bacteribots can be used. A new anti-tumor therapy is represented by microbial robots which are created by the fusion of biotechnology and robot technology [40].

Sunghoon cho et al. proposed a method of using cross junction microfluidic channels for the production of biologically accepted polyethylene glycol microbeads. Hydrophilicity is not the reason behind the attachment between bacteria and the surface of polyethylene glycol microbeads. The Poly-L-lysine (PLL) was used to modify PEG microbeads selective surface which enhanced the attenuated *Salmonella typhimurium* adhesion using the submerging property of PEG microbeads on agarose gel: the bacteria could thus be attached to the PLL-coated surface region of the

PEG microbeads. In comparison with PEG microbeads not coated with the poly-L-lysine and microbeads completely coated with poly-L-lysine, PEG microbeads which are selectively coated with poly-L-lysine showed higher motility [39].

A well-built conjugation system that is based on streptavidin/biotin in between bacteria and microstructures was suggested and utilized for the assembly of the bacteria-based microrobot. Additionally, the motility and targeting properties of microrobot were assessed using new chemotactic microfluidic channels and syngeneic mouse tumor models, in vitro and in vivo respectively.

Attenuated *S. typhimurium* with high motility and with the faulty gene for the synthesis of guanosine 59-diphosphate39-diphosphate (DppGpp strain). Attenuated *S. typhimurium* expressing green fluorescent protein or bacterial luciferases. The bacteria were firmly attached to the microstructure by making use of the high-affinity interlinkage between biotin and streptavidin. In this case, bacteria were set up to display biotin in the outer membrane proteins (omps), which are thoroughly distributed on the surface of the bacterial cell.

Microstructures consisting of rhodamine-containing fluorescent PS carboxylated microbeads that were covalently fused to streptavidin-conjugated tandem fluorochrome composed of peridinin chlorophyll protein, which was further labeled by Cy5.5 (PerCP-Cy5.5) were linked with bacteria [40].

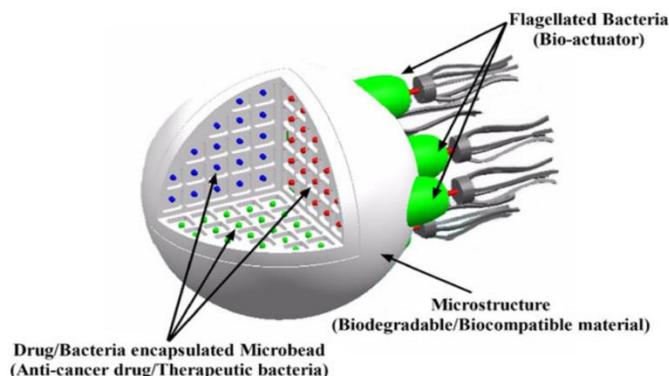


Figure 3: Conceptual design of bacteria based microrobot which consist of microstructure, anticancer drug and motile bacteria as microactuator [39].

5. Conclusion:

In this article, we have discussed causes of death or infections after burn, treatments for burn patients, and microbial robots. We have discussed treatments like phage therapy, fluid resuscitation, and skin transplantation. Treatments are given to first-degree and second-degree patients are giving satisfactory results but third-degree burn patients need intensive care and more critical treatment. To deal with sensitive burnt areas these treatments are not suitable. Here, we propose robotics as a suitable way of dealing with the delicate environment like third-degree burnt areas. Bacteria-based microrobots referred to as “bacteriobots” are used in cancer therapy as a drug delivery system. Bacteriobots act as microsensors, microactuators, and therapeutic agents in therapy. Chemotactic movement and tumor-specific targeting ability of bacteriobots were confirmed in experiments. These properties can be used to treat dainty burnt areas. The drug delivery system of bacteriobots can use to combat many bacterial infections in burn patients. The use of microrobots for the treatment of third-degree burn patients is a promising approach in the field of medical science.

Author contribution: RD: Developed an idea and wrote the manuscript, KB,LJ: verified the data.

Ethical Statement:

Since it is review article, no ethical permission required.

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