Burn injury: Challenges and advances in burn wound healing, infection, pain and scarring

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Abstract

- Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn injured patients by reducing mortality rate and days of hospital stay. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain a major challenge in burn research and management. In the present article, we review and discuss issues in the current treatment of burn injuries; the advances and novel strategies developed in the past decade that have improved burn management; and also, pioneer ideas and studies in burn research which aims to enhance burn wound care with a focus on burn wound infection, pain management, treatments for scarring and skin tissue engineering.

1. Introduction

- In Australia, over 10,000 people are hospitalized each year because of severe burn or scald injuries. According to the World Health Organization (WHO), 180,000 deaths annually are related to burn injury and in 2004, nearly 11 million people worldwide were severely burned and required medical treatment.
- Both small burn and large severe burn injuries initiate the wound healing process which consists of several highly integrated and overlapping phases: inflammation, cell recruitment, matrix deposition, epithelialization and tissue remodeling.
- Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn patients by reducing mortality rate and days of hospital stay.

2. Clinical practice in the treatment of burn injury

Skin grafting

The gold-standard treatment for partial- and full-thickness burn injuries is early excision of necrotic tissue followed by autologous skin grafting.

Autologous skin grafts can be full thickness, consisting of epidermis and dermis, or split-thickness, consisting of the epidermis and upper part of the dermis. Unfortunately, in practice, donor skin is extremely limited for patients with severe burn injury >50% TBSA. This problem can be overcome by repeated harvesting of the donor sites over a period of time. However, healing of donor sites can be slow with additional scarring and possible pigmentation disorder.

Skin substitutes

- Since 2000, over 30 new skin substitutes have been tested or used in the treatment of burn injuries. Skin substitutes can be categorized into biological substitutes, synthetic substitutes or a combination of both.
- Biological skin substitutes have components that resemble natural skin, yet these skin substitutes are relatively simple compared to the complexities of human skin.
- The majority of skin substitutes available for clinical practice contain allogenic biological products, and the risk of disease transmission poses as a limitation particularly for natural biological skin substitutes. Despite extensive and strict sterilization procedures, current methods are insufficient to certify biological skin substitutes to be free of any unknown diseases or prion diseases from animal material, such as Creutzefled-Jakob disease.

- In contrast to biological substitutes, synthetic substitutes are free from any risk of disease transmission. However, only a few synthetic skin substitutes are on the market today. Although synthetic materials have greater structural integrity compared to natural products, its poor bioactivity remains a major concern.
- The development of bio-engineered skin is increasing due to innovative possibilities with new techniques and biomaterials, providing a glimpse into a promising future.
- These steps have promoted a shift in focus from traditional surgical interventions to skin tissue-engineered regeneration.

Wound dressings

- Wound dressings can be categorized into four groups: biological dressings; conventional dressings; biosynthetic dressings and antimicrobial dressings.
- Although biological dressings are effective in terms of improving the quality of wounds for further skin grafting, they cannot be used as a permanent skin replacement due to immunological disparities. many issues are associated with biological dressings, such as inconsistent quality, limited supply, and the risk of pathogen transfer.
- Conventional dressings which do not contain antibiotics or medications are also widely used to temporarily cover wounds during re-epithelialization. However, these dressing tend to adhere to the wound surface and their need for frequent changes traumatizes the newly epithelialized surface and delays healing.
- Biosynthetic dressings are designed to use materials that mimic the function of skin by replacing the epidermis or dermis, or both.
- Antimicrobial dressings are widely used in burn management to prevent wound infection, by minimizing bacterial colonization. These products can contain either silver, nano-crystalline silver, cadexomer iodine or honey as antimicrobials.
- Application of silver compounds on burn wounds was a major milestone in topical burn therapy, which remarkably reduced the incidence of burn wound induced sepsis and death.

Negative pressure wound therapy (NPWT)

- It was first demonstrated to be effective at halting partial thickness wound progression compared to most other pharmacological means available. NPWT was further utilized as part of temporary abdominal closure in acute burn patients or in a high risk burns patient who underwent pre-operative optimization prior to skin grafting.
- the use of NPWT has been acknowledged to be helpful by allowing surgical teams to effectively manage acute burns, as well as their chronic sequelae.
- The use of NPWT with skin substitutes or templates has been utilized in clinical practice to improve poor skin graft take and infection as NPWT has been hypothesized to prevent shear.
- A case control study demonstrated a significantly reduced number of infections in the NPWT treatment compared to normal therapy.
- a study using a porcine burn model with locally applied Pseudomonas aeruginosa infection found that NPWT effectively reduced bacterial proliferation and alleviated sepsis progression compared to usual wound treatment.

NPWT instillation (NPWTi):

NPWT instillation (NPWTi) is a cyclical process whereby a solution of choice is instilled into a wound covered by NPWT dressings.

NPWT continuous irrigation (NPWTci):

- NPWT continuous irrigation (NPWTci) is non-cyclical. This method involves the continuous irrigation of solution into the foam and wound bed, while the suction action of NPWT is continuously applied at the same time.
- Although, there are no clinical case reports on NPWTi and NPWTci systems in burn injury, these advanced systems could play a beneficial role in future burn wound management via reducing number of treatment days, accelerated clearance of infection and wound closure.
- A study assessing NPWTi suggested that NPWTi may promote wound granulation rates compared to normal NPWT. When antimicrobial solutions were used in conjunction with NPWTi, a lower bioburden load was found when compared to standard dressings soaked with the same antimicrobial solution.

3. Burn wound infection: challenges and innovations

- Wound infection is a major challenge in burn care and is the most common cause of mortality after burn injury. With limited new antibiotics innovations enhancing the effectiveness of currently available topical and systemic antimicrobials is paramount to improve morbidity and mortality in burn patients.
- Gram negative bacteria cause most burn wound infections.
- Burn wound infection by Pseudomonas aeruginosa, Klebsiella pneumonia and Escherichia coli and the gram positive organism Staphylococcus aureus are independent predictors of mortality.
- Staphylococcus aureus is the major cause of gram-positive burn wound infections globally and a common cause of septicemia.

Topical antimicrobial agents

- Numerous innovative approaches have then been investigated in the past decade to achieve alternate topical antimicrobial treatment for burn wounds which do not compromised wound healing, require less dressing changes and induce minimal antibiotic resistance.
- Innovations generally involve new methods of delivering well-established antibiotics, alternative antimicrobials such as curcumin or synthetic antimicrobial agents such as LLKKK18 ,an antimicrobial peptide.
- Clinical trials comparing novel dressings containing LLKKK18 to the silver dressings in human burn cohorts will likely challenge conventional practice in the near future. Further investigation of the effectiveness of novel dressings against MDR bacteria is also required.

Systemic antibiotics

Currently, drug resistant organisms pose a difficult challenge. MRSA is the most common resistant organism encountered in burns and is normally treated with an ancient antibiotic, vancomycin.

- New antimicrobials including oxazolidiones, streptogramins, tigecycline, daptomycin, dalbavancin remain an important addition to the antibiotic armamentarium to combat such infection.
- Colistin, a polymyxin antibiotic, was once abandoned due to extensive side effects (neurotoxicity and nephrotoxicity) but has recently been reinvigorated to combat MDR gram-negative organisms. This new reliance on colistin has triggered various efforts to redevelop and re-engineer the antibiotic.

The dextrin-colistin conjugate:

- One such effort is the utilization of nano-antibiotic polymer therapeutics in which colistin is conjugated to dextrin. The dextrin-colistin conjugate exploits the enhanced permeability and retention effect enabling the molecule to be delivered preferentially to burn wounds and in a greater concentration for a prolonged duration with less systemic side effects.

- Critically illness patients post severe burn injuries have substantially altered physiology, which may profoundly lower antibiotic tissue concentrations culminating in therapeutic failure and the emergence of resistance.
- Methods to improve drug delivery involve regular monitoring of antibiotic concentrations and the delivery of antibiotics via continuous infusion rather than bolus regimes. For example a recent study demonstrated improved outcomes when P. aeruginosa infection was treated via extended infusions of piperacillin-tazobactam.

Anti-fungal infection

- The incidence of fungal infections is increasing with candida species being the most common. In the USA, fungi are responsible for approximately two thirds of invasive burn wound infections and is the fourth most common organism isolated in blood cultures.
- The most effective treatment for fungal infection is prevention via removal of burned tissue and closure of wounds.
- Positive fungal wound cultures and fungaemia particularly if Aspergillus spp. or other moulds are cultured, are generally indications for systemic therapy although specific indications for treatment remain unclear. Currently three classes of systemic antifungal drugs are available for treating fungal burn wound infection, including polyenes, azoles and echinocandins.

Polyenes:

- Polyenes such as amphotericin B are first line agents for the treatment of Candida, but its use is often limited by significant nephrotoxicity. Lipid soluble formulations of amphotericin B although causing less side effects, are substantially expensive.

Azoles:

- Of the azoles, fluconazole is the empiric choice for invasive candidiasis, although developing resistance is an issue.

Echinocandins:

- Echinocandins the newest antifungal agent introduced in 2001, are effective with a unique mechanism of action inhibiting the synthesis of β-1,3-D-glucan polymers and has a more favorable toxicity profile and pharmacokinetics.

4. Burn pain management: challenges and innovations

Issues of pain management

- Opioid reliance continues to define burn pain care. The side effects of opioid use include: nausea, vomiting, constipation, gastrointestinal dysmotility, dependence and tolerance. Severity of burn pain and duration of treatment also predisposes to tolerance, escalation of doses and high risk of addiction. Moreover, opioid can induce hyperalgesia, an additional overarching state of enhanced pain sensitivity along with increasing doses of opioid. Issues of opioid induced hyperalgesia presents a clinical challenge in the burn injury population.

Treatments for burn pain

Ketamine:

- Recent literature exhibited the capability of ketamine to reduce primary and secondary hyperalgesia; while also increasing thermal injury induced mechanical pain thresholds.
- Ketamine was first combined with benzodiazepines in attempt to reduce these adverse effects. A study reported the positive effects of this combination in burns patients, indicating that ketamine in combination with midazolam successfully reduces the side effects of ketamine.
- The range of pharmaceutics utilized in burn pain management provides opportunity to further investigate ketamine synergism, particularly in the areas of background and breakthrough pain which have not be studied in previous research.

Sedatives and anxiolytics:

- Benzodiazepines have no analgesic properties but are extensively utilized in burns patients as adjuncts for pain management.
- a2-agonists, similar to benzodiazepines, are used as sedatives and anxiolytics in burns. A clinical trial study of a2-agonists indicated the potential for an additional role in pain reduction

Neuropathic drugs and pruritus:

- Pregabalin and gabapentin are anticonvulsants used in the treatment of neuropathic pain of burn injury patients. A case series in 2010 established the efficacy of pregabalin in reducing post-burn neuropathic pain scores of outpatients.
- Subsequent randomized controlled trial demonstrated the role of pregabalin in both the acute and healing phases of burn injury ,demonstrating reductions of neuropathic pain during the first four weeks of treatment, while additionally reducing pain levels during procedural pain events.
- Another study found that pregabalin had positive effects in reducing post-burn pruritus, suggesting that pregabalin can be used in any patient with moderate to severe pruritus.

Neuropathic drugs and pruritus:

- Gabapentin has also received attention from burn pain investigators.
- Studies have shown positive results with gabapentin via reduction of mechanical allodynia in experimental partial thickness wounds. However, a randomized controlled trial study demonstrated that burn patients receiving gabapentin on day 1 of injury did not display any significant effects on either opioid consumption or acute burn pain.
- Similar to pregabalin, gabapentin shows favourable results in the management of post-burn pruritus.
- Subsequent studies further established gabapentin as a more effective alternative to antihistamine as monotherapy. Additionally, gabapentin was demonstrated as a first line therapy that leads to greater efficacy at each step up in therapy as part of a burns pruritus protocol.

5. Scarring and management

- With reduced mortality rates associated with severe burn injuries, the aim of burn wound care is shifting towards the management of burn scars.
- Burn scars can lead to causes many debilitating factors including pain, pruritus, dyspigmentation, heat intolerance, and limited range of motion due to scar contraction.

Stem cells

- Endogenous stem cells migrate to the site of injury during the initial inflammatory phase, where they elicit immunomodulation effects, followed by accelerated wound closure, angiogenesis and re-epithelialization.

Mesenchymal stem cells (MSCs):

MSCs are defined as self-renewing multipotent stem cells that can be differentiated into various lineages of mesenchymal origin. A number of studies have shown the positive effects of bone marrow-derived MSCs in reducing hypertrophic scarring via reduced expression of myofibroblast marker and the down-regulation of collagen I synthesis.

Adipose derived stem cells (ADSCs):

- An abundance of studies have supported the efficacy of fat grafting in both aesthetic and reconstructive cases, which has led to research into the utility of ADSCs in wound healing, regeneration of soft tissue, and reducing scarring by its remodeling capacity provided by the unique cytokine and growth factor profiles.
- ADSCs treatment can diminish established hypertrophic scars and keloids by the inhibition of transforming growth factor-beta 1 (TGF-β1) mediated fibroblast differentiation into myofibroblasts , and reducing collagen deposition by up-regulating matrix metallo-proteinases (MMPS), which are capable of remodeling collagen in the wound site.
- ADSCs have also been found to promote vascularization and wound healing through VEGF secretion and a decrease in TGF-β1 secretion in a mouse model.
- Sundew-inspired adhesive hydrogels combined with ADSCs was recently reported as an innovative method to deliver ADSCs and was found to promote a "suturing" effect to accelerate wound closure, although the effects on long term tissue remodeling or scar formation is not clear yet.

- Whether stem-cell-based therapies can be translated in clinical practice is still in debate. Furthermore, practical barriers associated with stem-cell-based therapies might restrict their utility in scarless wound healing post burn injury.
- Stem cell delivery along with an ECM patch can improve cell survival and proliferation, and significantly reduce fibrosis.
- Furthermore, practical barriers associated with stem-cell-based therapies might restrict their utility in scarless wound healing post burn injury. To address this limitation, conditioned media from umbilical cord-MSC cultures may be used to treat wounds.

- Dermal fibroblasts were found to exhibit characteristics comparable to fetal fibroblasts, showing low capacity to form myofibroblasts. Wounds treated with such umbilical cord-MSC-conditioned media healed faster with decreased collagen accumulation.
- Human amniotic-fluid-derived MSC-conditioned media also have the potential to inhibit the pro-fibrotic actions of TGF-β1 and even reverse the myofibroblasts phenotype to a fibroblast-like state in vitro. Taken together, innovations in stem cell studies provide more therapeutic options for treating burn scars.

Surgical approaches

- ***Fat grafting:***

Fat grafting as a surgical approach in treatment of burns has several documented benefits and is a rapidly evolving field for scar modulation. Functional and aesthetic improvements were shown in split-scar patients with reduced scar thickness and significantly better results in pain, colour, thickness, pliability/movement and shape/relief after 3 months.

A study on adherent burn scars showed a significant improvement in elasticity and maximal extension, and of the patient observer scales score at the 3-month follow up.In addition, colour difference remained unaffected.

Moreover, several case series have demonstrated great improvements in subjective patient ratings of burn scars, with improvements in texture, softness, thickness, colour, and wound healing which were also correlated histological findings.

- Fat grafting was also reported to enhance wound closure and improve neuropathic pain , and is further supported by a study that evaluated the effects of fat-grafting on burn-induced neuropathic pain in rat-models.
- ADSCs are believed to play a key role in fat grafting as they reduced collagen deposition and promoted vascularization and wound healing.

Laser therapy for scar modulation:

Keloid and hypertrophic scarring occurs by the loss of control mechanisms involved in biosynthesis and tissue degradation during the wound healing process, resulting in excessive collagen production and fibroblast proliferation.

Although contraction is part of the regular wound healing process, the contraction of healing burn wounds, grafts and scar tissue results in abnormal scar formation.

In addition, prolonged wound-healing and the inflammatory nature of burn wounds lead to hypertrophic scarring,followed by pigment alteration due to a dysbalanced amount of melanin or erythema.

Laser treatment may serve as a useful modality for the treatment of hypertrophic and keloid scars that have shown very encouraging results.Over the last decade, laser therapy has become increasingly popular and is increasingly a crucial part in reconstructive burn surgery.

Pulsed dye lasers (PDL) & neodymium-doped yttrium aluminiumgarnet (Nd:YAG) laser:

The mechanism of these vascular lasers still remains unclear, however, it has been postulated that selective photothermolysis by targeted vascular destruction leads to tissue hypoxia, collagen fiber heating, dissociation of disulfide bonds, catabolism and decreased cellular function, which consequently prevents excessive collagen deposition, and results in collagen fiber realignment and remodeling.

Histological analysis of scars treated with a 585-nm PDL revealed that thick hyalinized dermal collagen with haphazardly arranged fibroblasts became looser, with less coarse collagen fibers and a normal number of fibroblasts.

A meta-analysis including 28 well-designed clinical trials showed that the 585/595- nm PDL is effective in improving overall scar appearance and reducing both scar height and degree of erythema of hypertrophic scars.

It was also found that to 585/595-nm PDL decrease scar pruritus [224,235], and may result in a synergistic action when combined with intralesional steroid or 5-fluorouracil injections.

Non-ablative and ablative fractional lasers:

Non-ablative fractional lasers (NAFL) are particularly effective for the treatment of atrophic, flat or mature scars.A clinical trial demonstrated that treatment of burn scars with NAFLs significantly improved scar quality over a 6-month follow-up, and through histological analysis collagen resembled normal skin.

However, it seems that treatment of burn scars with an ablative fractional laser (AFL) triggers a more vigorous reaction of neocollagenesis and tissue-rearrangement when compared to NAFL.

Histological analysis demonstrates that the distinct AFL injury promotes a cascade of heat shock proteins, matrix metalloproteinases, and inflammatory processes, which result in a rapid wound healing response with prolonged neocollagenesis and ensuing collagen remodelling.

Recent reports demonstrate that even one treatment with the AFL can lead to significant improvements in scar quality and symptoms (such as pruritus and neuropathic pain), heat-sensitivity, and a measured decrease in scar thickness, irrespective of the scar maturation status.

Laser-facilitated drug delivery combined with fractional resurfacing:

Laser-facilitated drug delivery combined with fractional resurfacing is another advanced technique to further enhance pliability and reduce thickness.

This combination can help to reduce adverse effects from the local accumulation of intralesional injected steroids or 5-fluorouracil by assisting the even distribution of the drug in dermis.

It can also be used before surgery to make scars more pliable, to potentially improve surgical outcomes or in scar rehabilitation to limit the development of contractures, promoting early mobility and thus accelerating the entire rehabilitative process.

6. Skin tissue engineering in treatment of burn injury

The ultimate goal of skin tissue engineering is to produce a 'living skin' which offers completely functional skin, including all skin appendages to replaces human skin in its entirety.

Researchers therefore pay their attentions into developing innovative biomaterials, advanced formulation technologies or new methods to incorporate autologous cells (e.g. keratinocytes, dermal fibroblasts, melanocytes) in order to increase the complexity of the skin substitutes.

The applications of skin tissue engineering are broad, ranging from basic scaffolds to aid the growth of the neodermis, to the delivery of biomolecules such as growth factors, and stem cells to enhance wound healing and skin regeneration with full functional skin.

Biomaterials in skin tissue engineering

Both natural polymers and synthetic polymers have been widely investigated in skin tissue engineering. Natural polymers are isolated from a variety of sources including animal (collagen, hyaluronic acid), seaweed (agarose, alginate) or bacteria.

Collagen and hyaluronic acid (HA) are two major components for skin regeneration and have been fabricated as sponges, films, matrices and gels to facilitate wound healing utilising the biodegradability and biocompatibility properties that make these polymers favourable.

Collagen scaffolds promote the strong attachment and proliferation of keratinocytes and dermal fibroblasts with various collagen based skin templates such as Biobrane™, MatriDerm®, Apligraf® and Integra® currently used in burn injury wound care.

Hyaluronic acid (HA) is a natural polysaccharide composed of N-acetylglucosamine and glucoronic acid sugar units. HA is a structural component of skin ECM and due to its low immunogenicity, it has been considered as an ideal biomaterial for wound repair.

However, poor physical properties of HA represent serious limitations for its medical application. Chemical modification with enhanced resistance to degradation has significantly improved physical properties of HA, resulting in two commercial products: Hyalomatrix and Hyalosafe that are currently used in burn treatment as dermal substitutes.

Elastin:

Elastin is an essential component of native human skin, providing structural and cell mediating functions.

Recent studies demonstrated that incorporation of elastin in skin substitutes can improve scar quality and enhances angiogenesis.

In a clinical study, collagen-elastin scaffolds were found to reduce wound contraction and improve scar tissue architecture.

The ability of elastin to enhance angiogenesis has led to the introduction of one-step procedures in burn surgery. Currently, many dermal skin substitutes involve two-step procedures as skin substitutes need time to be fully integrated with the wound bed and vascularized, prior to a secondary surgical step of split-thickness skin grafting. Otherwise, skin grafting will fail and result in skin graft loss and poor take.

MatriDerm® is the first commercialized skin substitute containing elastin. MatriDerm® has been proven to be applicable in one-step procedures without a reduction in skin graft taken rate and it was also found effective in a range of acute and reconstructive burn wounds.

Silk:

Silk is composed of two proteins, fibroin and sericin.In skin tissue engineering, silk was found to promote collagen synthesis from dermal fibroblasts and 3D silk scaffolds are being optimized as a new generation of skin substitutes.

A recent study showed that scaffold incorporation of silk and hair-derived keratin as a dermal substitute, resulted in better cell adhesion and proliferation of fibroblasts, and increased collagen protein expression .

The advantages of using silk in skin tissue engineering are further expanded in combination with keratin, collagen, elastin, chitosan, fibronectin and synthetic materials.

Advanced technologies in skin tissue engineering

Recombinant proteins:

A variety of recombinant proteins are currently being investigated, such as tropoelastin, a precursor to elastin. Our research team recently investigated the effects of tropoelastin incorporated into Integra®, and found that tropoelastin has a comparable function to bovine derived elastin.

Tropoelastin incorporated Integra® significantly increased angiogenesis in both mouse and porcine wound repair models compared to skin grafting only.

The production of recombinant collagen is limited by the lack of an animal-cell-specific, post- translational enzyme system. Although the gram-positive bacterium, Streptococcus pyogenes, has been found to produce a stable and thermal resistant collagen, it lacks specific binding sites native to human collagen.

Electrospinning:

Electrospinning was developed over 30 years ago but has attracted new interest in the last decade. Using this technique, nano-scale fibers can be produced to mimic ECM in native human skin. A major advantage of electrospinning technology is the ability to spin both natural polymer and synthetic materials or copolymer together.

Research attempts to combine various natural and synthetic materials to enhance the biocompatibility as well as the mechanical strength of scaffolds. In order to overcome poor infiltration of cells into electrospin scaffolds due to low porosity and small pore size, many advanced methods have been developed, including leaching of selective water-soluble fibers and cell-nanofiber fabrication.

A successful approach involved repeatedly seeding fibroblasts layer-by layer into electrospin scaffolds until the desired number of cell-nanofiber layers were achieved.

Three-dimensional (3D) bioprinting:

Bioprinting technology has the potential to directly create graded macroscale architectures to better mimic the natural ECM, thereby augmenting cell attachment and proliferation.

3D bioprinting of skin is receiving great attention as it can rapidly produce an even landscape by allowing an increasingly controlled and precise deposition of cells into a predefined tissue structure.

Various biomaterials have been evaluated for bioprinting skin such as collagen, bovine gelatin, chitosan and silk fibrin, also synthetic biopolymers being PCL, poly (lactic acid) PLA, poly (lactide-coglycolide) PLGA and PLLA or human plasma.

A recent study successfully demonstrated the deposition of 20 layers of fibroblasts and 20 layers of keratinocytes, respectively, in collagen using laser-based bioprinting.

The results showed the presence of cadherin and connexin 43 in the epidermis, which are fundamental for tissue morphogenesis and cohesion.

Furthermore, a 3D bioprinted skin using keratinocytes and fibroblasts in collagen showed good graft take, and blood vessel formation/growth in the surrounding wound area in nude mice at 11 days post transplantation.

The integration of pilosebaceous units, with hair follicles and sebaceous glands in skin substitutes remains an unsolved challenge.

7. Conclusion

Significant advancements have been made in burn injury management and research in the past decade, including developments in novel skin substitutes; application of new antimicrobial wound dressings and enhanced systemic drug delivery for wound infection; testing new pharmacological interventions and finding new targets for wound pain control; together with advanced surgical approaches such as laser therapy, fat grafting, skin grafting and coverage options.

As a result, the survival rate of severe burn injury patients has been improved with significantly reduced hospital stay, resulting in decreased costs to patients and medical providers. However, several challenges still need to be solved to continue to improve current burn care. In particular, investigating how to accelerate wound healing, attenuate burn induced hypermetabolic-catabolic conditions, control systemic infection and reduce the overall time for functional recovery, should be prioritized.

Further research will continue to optimize current treatment paradigms and identify novel targets in burn care to ultimately enhance the outcome for severe burn injury patients.

Thanks For Your Attention