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Review Article

New technologies in global burn care - a review of recent advances

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Abstract: There have been truly incredible strides in the standard of burn care. The mortality from burn injuries has more than halved since the 1950s, making it hugely unique among major diseases of the developed world. There can be no doubt technology and technological advances have driven this process, dramatically improved every aspect of burn care, from the intensive care management, the surgical management, management of the healing wound to the post burn sequelae, specifically scar management. This review aims to identify key technological advances in burns, in both the developed and developing world, and evaluate their influence in the continued strategy to improve the standards of global burn care.

Keywords: Technological advances, global strategy, burn care

Background

There have been truly incredible strides in the standard of burn care. The mortality from burn injuries has more than halved since the 1950s, making it truly unique among major diseases of the developed world [1]. There can be no doubt technology and technological advances have driven this process. Technological advances, have improved every aspect of burn care, from the intensive care management, the surgical management, approaches to wound healing and post burn sequelae specifically scar management. The assimilation of these improvements, in each constituent phase, has produced our current standard of care.

Despite impressive advances burns is still considered 'the forgotten global health crisis'. Currently 95% of burns injuries worldwide occur in low-income countries [2]. Whilst new advances are welcomed, there is undoubtedly a significant time lag before current health care systems can access and successfully utilise these technologies. In the developing world it is unlikely the benefits of recent advances will offer any measurable impact for decades. However certain aspects of burn care implemented globally have made a vital impact on outcomes, arguably on even a greater scale. Often overshadowed by more complex technologies, the role prevention campaigns, education and public health interventions have played should be not underestimated. This review aims to identify key technological advances in burns, in both the developed and developing world, and evaluate their influence in the continued strategy to improve the standards of global burn care.

Intensive care management of the burn patient

Reduced mortality rates in severe burn injuries have been attributed to improvements in critical care, specifically by improvement in fluid resuscitation, respiratory support nutrition and sepsis control [3, 4] (**Figure 1**). New techniques and technologies have had a definite role in these improvements although have not always successfully demonstrated influence on major outcomes for this patient population.

Resuscitation

The first intervention for the major burn patient is resuscitation. Adequate resuscitation is the critical therapeutic intervention in the management of the acute burn [5]. Without it burns of greater than 15-20% Total Surface Body Area

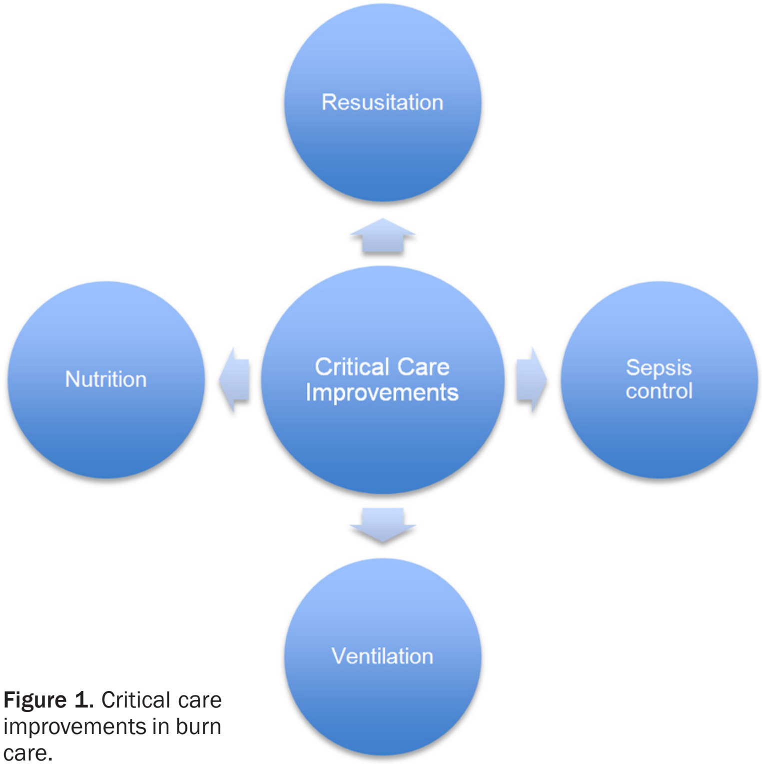

Figure 1. Critical care improvements in burn care.

(TSBA) will result in hypovolemic shock, organ dysfunction and ultimately death [6]. The "Parkland" formula for fluid resuscitation remains the most widely used formula by burns units internationally [7, 8]. This formula, based on the patient's weight and percentage-burn, is used in conjunction with regular review physiological parameters and resuscitation end-points, specifically urine output. In the last decade concerns regarding its accuracy has prompted the burns community to re-evaluate the fluid resuscitation process, especially for elderly patients. The concept of over-resuscitation was highlighted by Pruitt's description of 'fluid creep' in 2000 [9]. This phenomenon of excess fluid loading usually results from a combination of inaccuracies in calculating fluid requirement, inattention to reducing unnecessary fluid infusions, the increased use of sedation and analgesic infusions and from the excess administration of crystalloid solutions [5]. In an attempt to improve the accuracy of fluid resuscitation, adjuncts in the form of modern-day minimally invasive devices have been introduced. These include pulmonary artery catheter, lithium indicator dilution and trans-pulmonary thermodilution allowing continuous measuring of mixed venous oxygenation, intra-thoracic blood volume, total blood volume index, and extravascular lung water [10]. However providers are cautioned that using these devices to correct surrogate markers for intravascular volume is challenging and may result in tissue oedema and resuscitation morbidity [7, 11]. In addition these devices have not as yet demonstrated significant evidence of a benefit of treatment as compared to standard care or an influence on major outcomes [12, 13]. Therefore despite our era of technological revolution the principle guide to adequate fluid resuscitation is still urine output. This also applies to low-income countries, where invasive monitoring is not readily available [14]. Technologies have been developed to support rather than replace this principle. A computerized decision-support program has been developed by the United States Army Institute of Surgical Research (USAISR). The technology interprets trends in urine output over a 3-hour period to make hourly fluid rate recommendations. This has been successful in both reducing excessive volumes of crystalloid resuscitation and consistently achieving target urine outputs [15].

Ventilation

Airway management and ventilator support are frequently required in major burns cases, particularly those with an inhalational injury. Ventilatory strategies to support respiratory failure in critically ill patients, including burns, have changed dramatically. The introduction of lung-protective ventilator strategies, have reduced the incidence of ventilator-associated lung injury. These strategies use low tidal volumes, avoid high peak inspiratory pressures and permit a degree of hypercapnia. They apply to patients in the absence of a diagnosis of Adult Respiratory Distress Syndrome (ARDS) [16]. Once ARDS is confirmed adjunctive protective strategies are often instigated including high-frequency percussive ventilation (HF-PV) and high-frequency oscillatory ventilation (HPOV) [17]. HPFV is a pressure driven mode of

Table 1. Modified and new techniques for burn assessment and surgery

Burn Assessment	
	Laser Doppler Imaging
	Active Dynamic Thermography
Burn Surgery	
	Meek skin grafting
	Fibrin sealant
	Cultured epithelial autografts (CEA)
	Integra
	Biogradable temporizing matix

ventilation that combines conventional cycles with high-pressure percussive breaths/min [18]. It has demonstrated specific benefits in inhalational injury namely improving pulmonary gas exchanges without haemodynamic compromise, assistance in clearing pulmonary debris and secretions and reducing infection rates [19].

High-frequency oscillatory ventilation (HFOV) is an unconventional form of mechanical ventilation, previously shown not to be of benefit in the general intensive, are population but has a suggested role in inhalation injuries and ARDS in the setting of burns. It is considered a rescue ventilator strategy for cases of oxygenation failure unresponsive to conventional ventilation [20]. It permits sufficient stabilization of these patients for early surgical debridement [20]. Non-ventilator adjuncts have also been described in this context including nitric oxide, inhaled prostacyclin, neuromuscular blockade with cisatracurium, fluid restriction and diuresis and prone ventilation [21]. Overall technological advances in the area of ventilation have demonstrated measureable improvements in outcomes for patients with severe burn and inhalational injuries.

Nutrition and sepsis control

Following a major burn injury the patient is in a hypermetabolic state resulting in protein loss, reduction in lean body mass and hyperglycemia. Hyperglycemia, particularly in the paediatric population, is associated with catabolism, bacterial and fungal infections and graft loss [22]. Failure to address the nutritional requirements of this hypermetabolic state and its resulting hyperglycemia, leads to impaired wound healing, susceptibility to infection, longer inpatient admissions, organ failure and death [23, 24]. Early enteral feeding, typically nasogastric or nasojejunal, with careful monitoring of carbohydrate and fat intake supplemented by vitamins, amino acids and insulin administration where required, has shown to decrease wound healing times [25]. Additional strategies include the use of oxandrolone. This anabolic agent has been proven to improve protein net balance and lean mass, and overall outcomes in the severely burned patient [26].

The prevention and early recognition of sepsis is a key component of critical care for the burns patient. Prevention strategies include topical antimicrobial dressings, early excision and grafting surgery and as discussed above, nutritional support [27, 28]. There remains no role for prophylactic antibiotics [29], however burns sepsis should be aggressively treated with systemic antibiotic therapy and where necessary antifungal agents. This is becoming increasingly more challenging due to the number of multidrug resistant organisms [30]. White cell count (WCC) and C-Reactive protein (CRP) are currently the most commonly used markers of sepsis although pro-calcitonin has been identified as an additional useful marker in adult population [31]. Strategies such as steroid administration have been investigated although at present have limited evidence to support their widespread use [32].

Surgical management of the burn patient

Early tangential excision and autologous split thickness skin grafting remains the standard of care in burn centers worldwide [28]. However major advances, in the form of new technologies and new modifications of established technologies are changing the practice of burn surgery (**Table 1**). Accurate assessment of burn depth is vital to ensure appropriate management of a burn injury. In 1993 Laser Doppler Imaging (LDI) was proposed as an adjunct to clinical assessment R and today is accepted as an accurate diagnostic tool with high sensitivity and specificity [33]. LDI measures the extent of disruption to dermal microvascular blood flow, accurately assessing the overall depth. Its use has resulted in reduced length of hospital stay, lower rates of operative interventions, shorter decision making times for grafting procedures, and overall cost reduction [34, 35]. Other techniques such as active dynamic thermography, where the measurement of burn wound temperature acts as an indicator of their depths, has also been described in this context but, as yet, remains limited to a research tool [36].

An important example of re-evaluating a previous technique is Meek skin grafting [37]. First described in 1958, it was soon eclipsed by Tanner's mesh technique [38]. In more recent decades, huge advances in both the resuscitation and intensive care management of major-burns have dramatically increased survival rates. As more and more patients are surviving the initial insult the focus has therefore shifted to rapid excision and wound closure. This is challenging in cases where extensive injuries have lead to a lack of autograft donor sites. In the 1990s Humeca worked in collaboration with the Red Cross to revive the Meek technique with their Humeca system. The technique successful produced widely expanded autografts (up to 1:9 ratios) with even small skin remnants [39]. The addition of an adhesive spray and pre-fabricated gauze aimed to improve effectiveness and efficiency of the technique. Favourable outcomes are well reported in terms of successful graft rate, cost-effectiveness, cosmetic results and infection rates [40-42]. The system has been used widely in developing world [43]. It has also shown promising results when used in combination with other new technologies such as skin substitutes [44]. Its revival may prompt us to revisit other previously established techniques in addition to developing current and evolving technologies.

A useful adjunct to autologous skin grafting has been the use of fibrin sealant. Fibrin is an insoluble fibrous protein formed in human plasma in response to tissue injury where it is essential to achieve hemostasis. Fibrin gel, manufactured from purified plasma fibrinogen and a thrombin solution rich in calcium to replicate this blood clot, can acquire a similar structure and mechanical properties [45]. In 2008 Artiss (Baxter) received FDA approval as skin graft adhesive [46]. A pivotal study has demonstrated it is safe and effective for attachment of skin grafts, with outcomes at least as good as or better than staple fixation [47]. It is also associated with improved patient-assessed outcomes, namely pain-related anxiety. As well as its function as a surgical adhesive, fibrin is a well-established delivery system for many agents and is under investigation as a vector for local anesthesia delivery. It has been suggested fibrin delivery of local anesthesia may have definite future potential in burns surgery, from the proposed dual function of augmenting skin graft adherence while releasing local anesthesia [48].

Skin substitutes are a heterogeneous group of wound coverage materials that aid in would closure where autologous skin grafts are either unavailable, i.e. in extensive burns, or undesirable i.e. in full thickness burns with significant loss of dermis [49]. In addition to rapid wound closure they act to increase the dermal component of healed wound, reduce or remove inhibitory factors of wound healing, reduce the inflammatory response and therefore subsequent scarring [50]. Kumar provided a useful classification-Class I: temporary impervious dressing materials, Class II: Single layer durable epidermal or dermal substitutes and Class III: Composite skin substitutes either skin graft or tissue engineered skin [51]. Class II and III substitutes have been particularly important in the evolution of burns surgery, offering reconstruction options in injuries previously considered unreconstructable.

The culture of keratinocytes or epithelial autografts (CEA), a class II epidermal substitute, was an important advance in the burn care. First reported in 1981, cultured epithelial autografts (CEA) produces a large surface area of keratinocytes obtained from a relatively small skin biopsy from the patient. The autologous keratinocytes are isolated, cultured and expanded into sheets over periods of 3-5 weeks [52]. The technique of suspension in fibrin glue has reduced the time for clinical use to 2 weeks [53]. The ReCell system, pioneered by Professor Fiona Woods of the Royal Perth Hospital, further refined this technique and successfully demonstrated similar results to classic skin grafts for the treatment of deep partial thickness burns [54]. While eliminating need for autologous skin grafting its use was previously limited by fragility of the technique, unpredictable take rate and high costs [55]. Its potential is now being re-investigated as part of a two-stage strategy to completely replace the autologous skin graft [42].

Integra® artificial skin, a class III agent, is currently the most widely accepted artificial skin substitute for management of acute deep partial-thickness and full-thickness burns [56]. It is a bilayer consisting of a temporary epidermal substitute layer of silicone and a dermal replacement layer consisting of cross-linked bovine tendon collagen and glycosaminoglycan. The outer silicone layer works as a temporary epidermis controlling moisture loss from the wound [57]. The collagen dermal replacement layer serves as a matrix for the infiltration of fibroblasts, macrophages, lymphocytes, and capillaries derived from the wound bed [58]. After approximately 21-30 days there is adequate vascularization of the dermal layer and the temporary silicone layer is removed. A thin split-skin autograft is then placed over the vascular "neodermis". The main limitations to its use are a reported risk of infection from possible accumulation of seromas and haematomas and its high-cost [59]. Despite these limitation successful clinical use is well reported for a range of complex burns reconstructions [60-62].

Potentially the most exciting contribution to burns surgery in the past decade is the work of Professor John Greenwood of the Royal Adelaide Hospital. His proposal to offer a two-stage skin graft replacement strategy essentially combines the technologies previously developed for class II and III substitutes. The rationale for this replacement strategy is to facilitate immediate and complete excision of extensive burns, therefore improving survival outcomes, but also improving functionality and overall cosmetic outcomes in the reconstructed burn patient. The technique involves initial application of a recently developed biogradable temporizing matrix (BTM) to the excised wound bed (NovoSorb™). In addition to temporizing the wound bed it will allow integration of vascular tissue to create a neodermis, capable of sustaining either a skin graft or once successfully developed cultured composite skin (CCS). The overall aim is to reduce wound contraction during the remodeling phase [63]. Unlike current existing dermal replacement technologies such as Integra®, it does not contain any biological molecules such as collagen, potentially offering a greater resistance to infection [64]. It is also considered more cost-effective than existent technologies suggesting it will be economically viable to use outside of high-income countries. Successful integration and split-skin graft take has been demonstrated in animal models and more recently in clinical studies addressing reconstruction of free flap donor sites [65]. Development of autologous cultured composite skin (CCS) is ongoing although has been achieved in a porcine model [66]. Major funding and research grants have been secured hopefully suggesting that successful clinical application of this strategy is on the horizon. These efforts have and will continue to rapidly accelerate progress and development in the field of burn surgery.

The pathophysiology of wound healing

The advancement of burn care has been associated with a deeper understanding of the pathophysiology of burn wound healing. Similar to the healing of any wound, it requires the collaborative efforts of many different tissues and cell lineages that contribute to inflammation, proliferation, migration, matrix synthesis and contraction phases [67]. Burn healing is a dynamic process in which these phases overlap [68]. Understanding key concepts at each phase has let to developments in wound care. The initial inflammatory phase brings neutrophils and monocytes to the site of injury vial localized vasodilation and fluid extravasation, preventing infection and allowing degradation of necrotic tissue [24]. Following this the release of inflammatory mediators, including cytokines, lipids and kinins, provide immune signals to recruit leukocytes and macrophages to initiate the proliferative phase. In the overlapping proliferate phase, activated keratinocytes and fibroblasts migrate to, re-epitheliase and restore the vascular network of the wound, essential for wound healing [69]. In the final remodeling phase, collagen and elastin are deposited and continuously reformed by the conversion of fibroblasts to myofibroblasts. This conversion results in high contractile force necessary for tissue contracture and scar maturation [70].

The attempted modification of these pathways has led to a number of advances in wound healing. Excessive or prolonged inflammation has been targeted however the use of anti-inflammatory treatments can potentially delay wound healing. This makes the identification and application of the beneficial effects challenging [71]. The use of NSAIDS in this context demonstrated impaired wound healing. However steroid use has shown a reduction in proinflamma-

Table 2. Current, novel and future therapies for management burn scarring

Current techniques	
	Massage
	Silicone
	Intra-lesional corticosteroid injection
	Pressure therapy
Novel therapies and future therapies	
	Fluorouracil, mitomycin C and bleomycin
	Autologous fat grafting
	Laser therapy
	Stem cells

tory cytokines associated with shorter hospital admissions [72]. The information yielded form understanding the pathophysiology of wound healing has been applied to develop 'intelligent' dressings capable not just of controlling bioburden, but also accelerating the healing process itself. Silver has been used in burn care since the introduction of topical silver sulfadiazine (SSD) preparation in the 1970's. More recently, nanocrystalline silver dressings have become widespread in clinical use. These dressings utilise nanotechnology to release clusters of extremely small and highly reactive silver particles and have been found to have anti-inflammatory effects [73]. The cost of nanocrystalline dressings has limited their use in economically-strained environments. In underfunded, under-resourced facilities silver sulfadiazine has been the major component of wound care due to its practicality, effectiveness, affordability and associated high compliance rates [74]. In these environments there is understandably a compromise to be made between most overall effectiveness and cost-effectiveness. Recent studies have highlighted the benefit of honey-based dressings over SSD [75]. Honey based dressings, previously shown to have anti-inflammatory properties, have traditionally had a role in wound care in the developing world [76]. As nanocrystalline dressings may not be feasible, this recent evidence may shift the focus to honey-based preparations, securing their role in the future wound care strategies.

As discussed previously the engineering of autologous keratinocytes is currently under development. Cultured epithelilal keratinocytes aim to promote keratinocyte migration in the proliferative phase, and subsequent epithelisation, angiogenesis and wound closure. Although some benefit has been demonstrated in terms of comparability with split-skin grafts in wound closure this technique has yet to translate into clinically viable options [77].

Excessive myofibroblast driven contractile force in the remodeling phase can result in extensive and hypertrophic scarring. The functional and psychosocial sequelae of burns scars remain a major rehabilitative challenge, decreasing quality of life and delaying reintegration into society. Despite extensive research this is arguably the area that has demonstrated the least measurable clinical outcomes compared to other aspects of burn care.

New technologies in scar management

Successful approaches to modulate the scar remodeling process, minimise the development of scarring, specifically hypertrophic scarring, have yet to be established. Proposed beneficial effects of novel surgical techniques, discussed above, are awaited. Meanwhile scar management remains a formidable challenge for the burn community. Currently the most commonly used techniques are pressure garments, with and without silicone and injected corticosteroids [78]. Evidence has been conflicting with studies showing modest to no improvements with use of these techniques [79-81]. Numerous novel therapies have been introduced, but to date, have not made the anticipated impacts (**Table 2**).

The influence of intralesional injections of chemotherapeutic agents such as 5-fluorouracil, mitomycin C and bleomycin has been extensively evaluated. These therapies are challenging to administer, often requiring multiple repeat injections and have shown only modest overall effect primarily on scar height [82]. Autologous fat grafting, the revolutionary technique of reconstructive and aesthetic surgery, has been proposed as an intervention to improve mature burn scars. Recent studies failed to demonstrate differences in scar pigmentation, vascularity and height post-treatment [83]. Lasers were proposed as a revolutionary new tool for treatment hypertrophic and erythematous burn and donor site scars with moderate success. Photodynamic lasers have a role for early erythematous scars and fractional lasers in treatment of hypertrophic scars, surface irregularities, pigmentary abnormalities, hypertrophy, pruritis, and contraction. Randomized, prospective multi-institutional studies are needed to accurately define and describe optimal uses of laser for burn reconstruction [84].

The future of wound healing and scar modulation is thought to hinge on our growing understanding of progenitor and stem cells and from development of these novel therapies [85]. Several studies have suggested bone marrow derived stem cells, such as mesenchyme stem cells (MSCs) and progenitor cells such as endothelial progenitor cells, may be involved in skin repair and regeneration [86, 87]. MSCs in particular have been shown to enhance wound healing through increased angiogenesis, reepithelialization, and granulation tissue formation [88]. While the true mechanism of action of MSCs is not fully understood, the current evidence suggests they provide the necessary cues for wound healing through the release of inflammatory mediators, cytokines and growth factors. In addition the cells themselves participate in the process of wound healing, ultimately differentiating into the cell types required for closure of the wound. Adult stem cells are an exciting source for future wound healing applications, owing mostly to their relative ease of harvest and the ability to yield large quantities of cells.

Technological aids in the developing world

As discussed, the majority of advances described in the various aspects of burn management, are not feasible in economically strained environments. Unfortunately these are the very environments where improvements are urgently needed. Currently 95% of burns injuries worldwide that require medical attention occur in low-income countries [2]. It is worthwhile to reconsider how we define technology and how this definition might apply to the developing world. Education programs and strategies targeting primary prevention, first aid and early presentation have been identified as key components necessary to implement effective standards of care [89]. These strategies were instrumental in reducing mortality in the developed world from the 1960's. The benefit of primary prevention in particular should not be underestimated in low-income countries, owing to the challenges and lack of resources in secondary and tertiary management [90]. Childhood supervision in the community, parental education and caution against storage and use of flammable liquids, have been identified as important risk factors [91]. Educational programs addressing these risk factors can have a significant impact on burn morbidity, especially in children [92]. Other important education strategies include the challenging cultural beliefs so that immolation is not used as form of punishment by communities or self-inflicted, the education and training of healthcare professionals in burn care and the implementation of clinical standards, guidelines and protocols in daily clinical practice [93].

Conclusion

Technological advances have, without doubt, revolutionized all aspects of burn care in both the developed and developing world. From this review we propose our current stand of care is the not the result of individual key advances but the cumulation of multiple advances in each constituent phase of burn management.

Despite these advances we must strive for the continued improvements survival and scarring in burns. Further reductions in morbidity and mortality, faster and improved wound healing and reduced scarring, are goals that can and must be achieved internationally. This review identifies the key strategy to achieve these goals; by incorporating new and evolving techniques into clinical practice but also re-evaluating and bringing forward lessons gained from techniques previously established. Future technological advances should be developed to support rather than replace, as no new technology can substitute for the care and experience of the multi-disciplinary burns team.

Disclosure of conflict of interest

None.

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