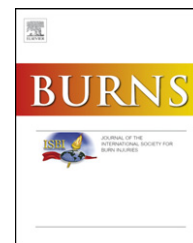


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## Review

## The year in burns 2010

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## ABSTRACT

For 2010, roughly 1446 original burn research articles were published in scientific journals using the English language. This article reviews those with the most impact on burn treatment according to the Editor of one of the major journals (*Burns*) and his colleagues. As in previous reviews, articles were divided into the following topic areas: epidemiology, demographics of injury, wound characterisation and treatment, critical care, inhalation injury, infection, metabolism and nutrition, psychological considerations, pain and itching management, rehabilitation and long-term outcomes, and burn reconstruction. Each selected article is mentioned briefly with editorial comment.

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## 1. Introduction

Research to advance burn care is an ongoing process which is reflected in the published literature from year to year. Many laboratories throughout the world, both clinical and basic, are active in investigating the science of burns and testing treatments; all of this is done in an effort to improve

the lot of patients with this injury. However, to gain widespread acceptance of new findings, publication in the scientific literature is usual (and optimal) for two reasons, (1) peer-review of methods, results, and conclusions to confirm study novelty/validity and to filter findings to only those that stand scrutiny and (2) proliferation of findings throughout the scientific community to engender further

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discussion and investigation, and potentially change practice.

In 2007–2008, one of the authors reviewed the burn literature for those articles he felt was most important to burn care going forward [1,2]. As follow-on, we now review the literature for 2010 in a similar fashion. To increase generalisability, more authors were added to provide more diverse opinion. The following review is of course based on the views of the authors with intimate knowledge of the literature; however, introduced bias is likely based on individual experience, and this review should be seen in that light. Further, this is only a very brief rendition on each paper and the reader is encouraged to view the entire article if his or her interest is piqued. As in previous years, works not mentioned are not to be diminished; all published work is important in its own right, and all authors in the burn literature are to be congratulated for their contributions in this field.

The search of the literature was done using Scopus® with the following limits: burns (article title, abstract, keywords); year (2010); Life Sciences, Health Sciences, and Social Sciences and Humanities (Medicine, Biochemistry, Genetics and Molecular Biology, Nursing, Pharmacology, Toxicology, and Pharmaceutics, Health Professions, Social Sciences, Engineering, Immunology and Microbiology, Neuroscience, Psychology, Business Management and Accounting, Materials Science, Arts and Humanities, Multidisciplinary, Economics, Econometrics and Finance, Computer Science, and Mathematics); original articles and conference papers; and English language. For the year 2010, 1446 papers met these criteria, which was a slight increase over the previous year (Fig. 1). In examining the figure from the graph, burn related articles are increasing at about 75 per year.

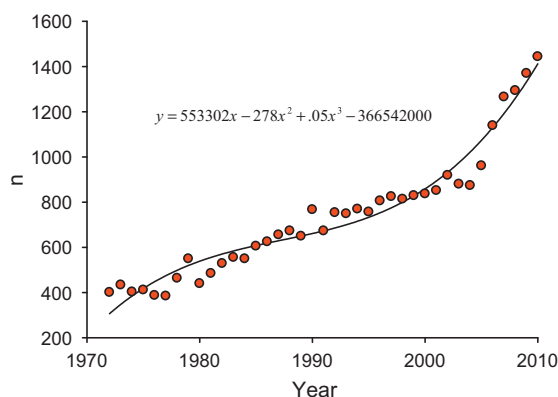
This article will review approximately 100 of those publications from 2010 which were determined by the authors to be the most important in terms of burn care. The selected articles were distributed by best fit into 10 areas of interest: epidemiology of injury, wound and scar characterisation,

critical care, inhalation injury, infection, metabolism and nutrition, psychological considerations, pain and itching management, rehabilitation and long-term outcomes, and burn reconstruction.

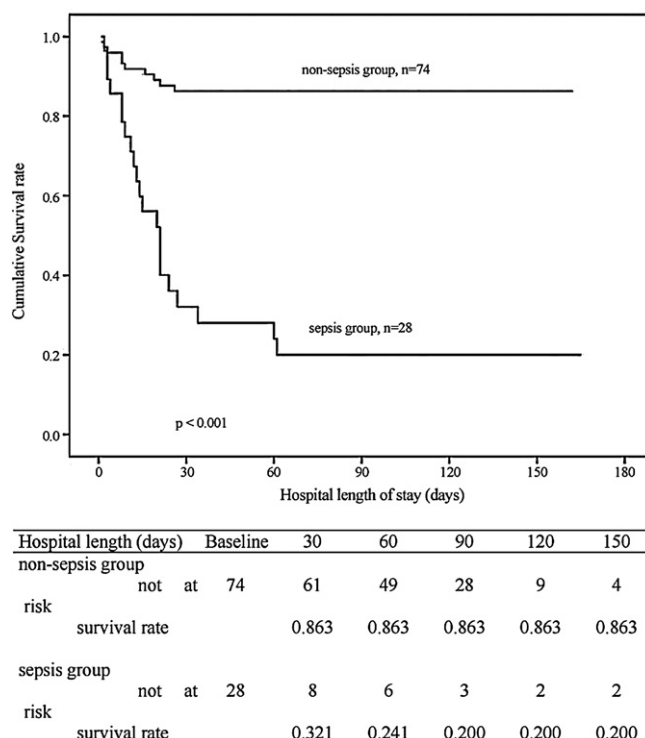
## 2. Epidemiology

In this section, we review articles describing characteristics of those who are burned. Some of these are descriptions of regional incidence, and others are factors associated with outcomes after injury. Perhaps one of the best studies recently in the epidemiology of burns comes from Bangladesh where investigators showed in a nested case-control study that children in households without a separate kitchen, a kitchen without doors, or those that use kerosene lamps for lighting are at greater risk for receiving significant burns. Furthermore, restricted use of kerosene lamps significantly improved risk [3]. This is a follow on to a very important paper from these authors in 2009 showing the true epidemiology of paediatric burns in a developing country in a labour intensive door-to-door investigation, and has shown conclusive methods of prevention; these series of studies are a model for such efforts. Another study from Iran on outpatient burns showed in a 1-year cross-sectional survey of outpatient burns that non-intentional scalding remained the most common form of injury regardless of age or gender, but perhaps the most preventable were in women and children as these were most commonly seen with kitchen incidents [4]. This study reiterates that most burns are preventable and are most likely amenable to simple preventative efforts. Interestingly, a systematic search of the literature for the epidemiology of burns in Europe from 1985 to 2009 revealed a similar population prevalence for burns, mostly males, children, and scald, flames, and contact as the major causes. Mortality decreased over time. Burn size and age remained the principal associations with mortality [5]. An interesting study from Germany compared patients who were injured in civilian gas explosions to their general population. This was engendered by an interest in potentialities from a terrorist attack. They found that mortality and outcomes correlated with burn size and age and that the severity of injury was similar as well, as expected, but interestingly they found that mortality was significantly higher in the explosion group [6]. Reasons for this were not clear, and might be the focus of further investigation. The last in this group investigated the impact of socioeconomic factors in burn incidence and severity in a developed country, New Zealand. These investigators found that the rate of admissions to their burn unit increased in proportion with diminishing socioeconomic status [7]. These findings are in line with those above in that those with the least available resources are at the greatest risk of injury. Prevention of burns then has as much association with raising socioeconomic well-being as providing specific prevention technologies [8].

Three papers for the year analysed factors associated with mortality. The first from China reported 30% mortality for adults with greater than 70% TBSA burns. Associated factors were burn size, severe inhalation injury, serum creatinine, inotropic support, thrombocytopaenia, sepsis, and ventilator dependency. With multiple variable modeling, only sepsis,



**Fig. 1 – Burn publications per year using the specified criteria search. Cubic regression yields a formula with an  $r^2$  value of 0.95, indicating a high correlation. Burn publications have been increasing with an acceleration inflection point in about 2003 coincident with a shift to more electronic publication. Publications are recently increasing at about 75/year.**



**Fig. 2 – Kaplan–Meier plot survival analysis comparing cumulative survival rate in sepsis and non-sepsis patients (total = 102) with extensive burns over 2 months of follow-up. Reprinted with permission from Wang et al. [9].**

ventilator dependency, and thrombocytopaenia remained as significant contributors. Sepsis diagnosis was highly associated with mortality (Fig. 2) [9]. These findings are similar to those found in a paediatric population in the US a decade before [10] but these data are still a testament to the improvements in care of massive burns. Another paper showed the utility of the APACHE III-j score in predicting mortality [11]. Both of these studies show that data in addition to burn size that are gathered during a course of care make the prediction of death from injury more certain, and should receive consideration in any decisions on the utility of treatment.

An interesting paper described populations and predictors of intensive care unit stay in the severely burned. It described techniques to predict ICU stay, and found that linear regressions based on injury characteristics were not as accurate as support vector machine regression, which is an artificial intelligence technique incorporating data gathered after admission [12]. This is conceptually the same as the conclusions for mortality prediction described above, in that predictions become more accurate when response to treatment is integrated into the model. This implies that some treatment is necessary to ‘test’ whether further treatment will be effective, and should be incorporated into decision matrices in clinical care.

A series of papers investigated the role of patient individuality (genetic background) in the prediction of mortality. The first used the structure of longitudinal gene expression from blood in severely burned patients to predict survival time. They found that the most important genes were those associated with the inflammatory response and the

immune system. They also found that prediction method was superior to those with individual time point gene expression or pooling across time [13]. This paper again shows the role of data analysis in relation to previously collected data to define the course and trajectory of response. A second study evaluated the role of ‘pathway genetic load’ in predicting the response to injury. This technique uses analysis of a number of alleles on the DNA that are associated with a single pathway, which in this study were those associated with TLR4 signaling and response. These authors showed that this method was able to assign increased probability for complicated sepsis and death in the severely burned [14]. This is a new approach to analyse multiple alleles simultaneously on the genetic code of patients to predict outcomes. These same authors showed that some particular alleles for interleukin-10 were associated with decreased risk of death in the severely burned [15]. We expect that further work will be done in this area with the push for ‘individualised medicine’ and treatments.

The next series of papers is in regards to burn centre criteria and outcomes. The first examined outcomes between verified burn centres and non-verified centres in the US. They found that only 22% of patients with burn codes were treated at verified centres [16]. Another statewide study in the US reported that 52% of burned patients were treated in burn centres, and that among those treated at non-burn centres, 48% had injury criteria suggesting burn centre care for optimal management by the American Burn Association [17]. Both of these studies found that burn centres had a higher preponderance of younger (non-Medicare insured) patients, hand

burns, and those with inhalation injury. The same also appears to be true in the UK, as investigators reported that 74% of patients meeting criteria were not referred. Of interest though is that only 4% of this group eventually received care in a burn centre [18]. For outcomes between verified and non-verified centres, investigators found that mortality was highest in non-verified self-designated burn centres, followed by verified burn centres, and was lowest in other centres. These authors did emphasise that they could not include known stratifying risks, making interpretation of these data and data like it difficult [19]. One could then presume that the most seriously injured were cared for at verified centres, but this could not be validated. Studies from this year indicate that many burned patients are not cared for in burn centres, but perhaps there is a higher preponderance of those with the highest severity and/or low reimbursement status. Further analysis seems to be necessary. We also wonder whether administrative databases will be sufficient for this task, and whether more uniform disease-oriented (not charge oriented) databases will be more useful for true answers.

The next series of papers are in regards to care management and costs in the severely burned. The first describes a method of case management that provides wider access and directed allocation of resources for massively burned patients. They showed in a series of severe burns in workman's compensation cases (mean TBSA burned 28%) that such a model was used to achieve final outcomes in 20 months; at the beginning of outpatient management, 47% received total assistance, but at termination 84% were completely independent, and 73% had returned to work [20]. These data are testament to the finding that burned patients after wound closure generally improve dramatically with time; whether this particular programme drove these improvements or made the course of improvement more manageable should be addressed with a randomised study to address causation. A second study measured resource utilisation for the severely burned in order to assess resources to provide such care in a mass casualty. They found that 0.3 operating theatre visits and 23 min of time occurred for each %TBSA burned, and length of hospitalisation was 1.1 days/%TBSA burned. Each of these increased exponentially with increasing burn size. Operative time was greatest early in the course while personnel time for nursing and rehabilitation was constant [21]. These data are expected we think, but actual enumeration of the times is useful to guide resource allocation in the event of a mass casualty. An interesting study from Australia compared costs for burn ICU patients to non-burn ICU patients, and they found no differences between the groups in overall per day costs. Differences that were found were more physiotherapy and dressings in the burned group with more costs for radiology in the non-burn group [22]. Other investigators showed in paediatric burns that total costs for a 30–40% TBSA burn averaged £63,157, which was significantly above the tariff rate reimbursement of £17,797 [23]. All these studies show that burn care is an expensive business but is comparable to other conditions, and that the needs can be reasonably predicted with more intensity early in the course.

The last two papers in this section describe the burn literature itself. The first analysed BURNS for the proper use of statistics, and found that 22% of the examined studies were

randomised controlled trials, 35% cohort studies, 22% case-control studies, and 22% case series. In these studies, the majority of data reporting was proper with some perceived deficiencies in naming the statistical programme used and the particular significance level assigned [24]. The next by the same author team assessed the quantity and quality of research evidence in burn journals. They found that case reports and case series dominated this literature, but that the proportion of trials and controlled studies was increasing with time [25]. We hope that these continue to increase.

### 3. Wound/scar characterisation

This section reviews this year's most important papers on wound characterisation and description of treatments. The first series of papers is on describing wounds using imaging technologies. Investigators in Australia showed (again) that the use of laser Doppler imaging decreased time to definitive treatment [26]. Furthermore, other investigators showed that this technique could be reliably used for decision-making in regards to treatment even after 48 h from the injury [27,28]. Finally, investigators in the Netherlands described a technical advancement in imaging speed, thus alleviating one of the drawbacks to the use of this technique [29]. These papers and many others through the literature document the usefulness of laser Doppler imaging in burn care. Based on these and other findings, we question how this technique cannot be considered the standard of care for burns of indeterminate depth on physical exam?

Investigators in the US described microarray gene changes in partial thickness wounds from 48 patients. They were able to segregate extensive gene responses (2286 genes significantly changed in expression) into three time groupings: 1–3 days, 4–6 days, and 7–18 days. They concluded that these findings might initiate identification of molecular markers of healing [30]. It is interesting that these groupings fit neatly into time-honoured phases of wound healing, but perhaps these changes might be used to identify wounds that deviate from the 'normal' path of healing.

The next group of papers described wound treatments. The first mentions the efficacy of cold water irrigation in partial thickness wounds for 20 min in a pre-clinical model, and showed improved rate of epithelialisation and decreased scarring. Furthermore, they showed that treatment for as little as 10 min or within an hour of injury also showed improvement compared to untreated controls [31]. This same group also retrospectively analysed their data on Acticoat, Jelonet, and Solosite gel on deep partial thickness burns. They found that epithelialisation was faster in Jelonet and Solosite compared to Acticoat, but that infection/colonisation was controlled best with the silver containing agent. Their primary insight, however, was the observation of significant variability in their measurements even in this controlled pre-clinical model [32]. This is an important study in that it shows that wound healing is difficult to measure because of variability in responses and has many contributors to its 'quality'. The 'best' dressing will then be dependent on what is sought; faster epithelialisation, easier handling, decreased infection, etc. with tradeoffs between methods.

In other dressing studies, investigators in the UK examined healing times in ambulatory burned patients with the use of silver-based dressings with historical controls dressed with paraffin-based products. They found that use of silver-based dressings were increasingly used but found no advantage in healing times for superficial burns, whereas they did find an advantage for deeper wounds. This was a relatively large study (347 subjects) with a reasonable analysis [33]. Other investigators canvassed the literature for other evidence of advantage for the silver-based fabric dressings, and found only one good trial showing better anti-microbial activity, but other findings of improved healing, etc. were not as well demonstrated [34]. Regardless, it seems that in 2010, silver-based fabric dressings are very commonly used throughout the world primarily because of ease of use for both providers and patients; as described above, wounds and quality of wound healing is highly variable, and to claim superiority in any of these domains is a daunting prospect. Perhaps it is better to focus upon ease of use and pain relief instead?

For wound treatments, an interesting paper from investigators in Turkey revealed in a pre-clinical comb-burn model that activated protein C treatment preserves the zone of stasis as measured by laser Doppler [35]. This is an interesting finding that could easily be applied to clinical practice. Another study showed that amnion-derived cellular supernatant and delivery of the cells themselves increased epithelialisation in a pre-clinical partial thickness burn model [36]. These data were compelling enough to support institution of a clinical trial; we await the results. Another study investigated the effects of platelet-derived growth factor gene transfection with liposomal delivery in porcine burn wounds. They found that gene transfection into wound cells occurred at a 34% rate, was greatest between days 2 and 4 after treatment, and that treatment was associated with accelerated wound epithelialisation [37]. These data are of interest probably for all wounds, and we look forward to further work in this field. The last of this series was a paper investigating effects of extracorporeal shock wave therapy on wound healing. Investigators found that a single dose of this treatment to donor sites in anaesthetised patients at the time of skin harvest improved time to healing by 17% [38]. This is an intriguing finding, and if follow-on studies have similar results this treatment should be highly considered. The mechanism of effect, however, is not clear.

The next paper describes a novel experience with grafting of cultured epithelial autografts upon engrafted allodermis in 88 severely burned patients over a 20-year period. The authors showed a final take rate of 73% with 91% surviving. Common complications were shearing/blistering (31%), and wound contracture (66%) [39]. These are the common complications associated with this treatment, however, these are impressive data regarding the potential application of this technology, and give us data to focus upon for improvement.

In terms of scarring, an important paper from this year described a new method of burn scar assessment, spectrocutometry, which is based on estimated concentration change of haemoglobin and melanin in scars. The authors found that intraclass correlation coefficients were higher for spectrocutometry than Vancouver Scar Scale or an independent observer scar assessment scale, indicating better reliability of

this measure than the others [40]. One of the problems with scar assessment is measurability, and perhaps this gives us another tool to do this, particularly for researchers into treatments.

A potentially important paper on donor site scarring came from Brazil which showed that the use of the scalp as a donor site was not associated with any incidence of hypertrophic scarring in 295 patients; healing was generally in 7 days, and the principal complication noted was alopecia, which occurred in 2% of patients [41]. This is often an overlooked donor site which should be given consideration for greater use.

The last series of papers in this section are findings of studies with dermal equivalents. Investigators in Korea showed that the use of AlloDerm® in the acute stage of grafting was associated with decreased scar thickness, and decreased erythema one year from injury [42]. Other investigators showed that elasticity measured by cutometry was not different than normal skin if Integra was used one year after injury, while in the areas without Integra use no such correlation was seen [43]. Another material was used by authors in Germany, who showed that Matriderm® improved range of motion when used on the dorsum of the hand compared to within-subject controls [44]. These three papers get us closer to understanding whether clinical advantage is present for the use of dermal equivalents in acute wound management, which appears to be building, but the definitive answer is still forthcoming.

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#### 4. Critical care

The next section reviews papers in critical care. The first group was in regards resuscitation and early treatment. Investigators in Switzerland used confocal microscopy to evaluate the microcirculation during burn shock and resuscitation. They found that burn shock significantly reduced blood cell flow in normal skin to 60% of controls; resuscitation restored flows to normal after 24 h. Skin thickness was assessed through measures of basal layer and epidermal thickness, which was found to slightly less than controls at admission, and after resuscitation was increased by 25–50% [45]. This would be consistent with oedema. This was a very important paper in that it showed visually what occurs during resuscitation, and how the physiologic state is dynamic in the first 24 h which should probably dictate different strategies depending upon the hour into treatment. We expect to see more work along these lines in the near future. Another paper regarding emergency treatment assessed the impact of hypothermia upon arrival to the hospital. They found that this was more common in massive burns, and was highly associated with mortality [46]. This is further evidence for keeping burned patients warm, especially early in the course. The last of this group was an important report of a survey of resuscitation practices among experts in the field throughout the world. The investigator found that large variations in practice exist all the way from fluids selected as well as rates, monitors, etc. [47]. This shows that either the specific practice of burn resuscitation has little impact on outcomes other than one of many treatments is sufficient, or alternatively that the 'best' practice is elusive or not yet known. Further research will then be



necessary to address the latter possibility with knowledge that the former contention may in fact be true.

The next set of papers addressed physiologic changes with severe burn. Investigators in Iran found that hypophosphataemia was relatively common in the severely burned which increased with increasing burn size. Impact on outcomes was not assessed [48]. Other investigators examined the coagulation system longitudinally after injury, and found that burns <10% TBSA had little effect, while those with greater size injuries developed hypercoagulability which evolved to consumptive coagulopathy with >40% TBSA burned [49]. This is an interesting observational study that should clearly be expanded with the understanding that these are *in vitro* data, the interpretation of which must be seen in light of clinical findings and outcomes. Finally, a paper from Sweden showed that glomerular filtration measured by iohexol clearance was increased by 32% at 24 h after injury compared to controls. Over time, this dissipates, but shows that glomerular filtration function increases after severe burn [50]. This is rarely considered it seems during clinical practice.

The next study measured levels of proteosomes in the blood after injury. These authors found that 20S, but not 26S proteosomes, were elevated after injury which was proportional to burn size as well as presence of inhalation injury. They concluded that 20S proteosome abundance after burn is a measure of tissue injury. This is already mostly evident on physical exam except for inhalation injury, and might be useful as an adjunct for the diagnosis of severity of this particular injury [51].

The next grouping of papers was in regards to the characterisation of sepsis. The first was a survey of regulatory T-cell activity in severe burns. They found that cell activity and cytokine production increased with increasing severity of injury, and was further increased with sepsis. Most interestingly though, they found that non-survivors did not have such increases, and thus the 'negative' finding of no increase in response to stimulus (at least for regulatory T-cells) might be an indication of someone who will have a poor outcome [52]. This questions the utility of looking for some inflammatory markers as indicators of complications, as it may be those who have no response and thus no signal who are the most vulnerable to poor outcomes. This notion is further elucidated with such findings as no effect of high body temperature and white blood cell count on the detection of sepsis in the severely burned [53]. This notion was supported by another paper this year that reported decreased levels of granzyme A, a serine protease expressed in cytotoxic cells, in burned patients who were septic and did not survive [54]. Lastly, a very important paper describing changes in lung water in relation to procalcitonin, PEEP, and a sepsis scale was found. They found that extravascular lung water index correlated with all of these at *r* values of approximately 0.5 and an area under a receiver operating curve of 0.76, indicating that increasing lung water is associated with the development of sepsis. Most importantly they found that with antibiotic treatment, a decline in lung water was seen in survivors but not in non-survivors; procalcitonin declines in both groups suggesting better prediction of poor outcome with no change in lung water [55].

Renal failure is an issue in the severely burned. Papers addressing this topic included a meta-analysis of outcomes from acute kidney injury in this population. They found that diagnosis of acute kidney injury (AKI) by RIFLE criteria was associated with a 3–6 fold higher mortality. AKI was found in 25% of those with severe burns. Interestingly, they found that outcomes in patients affected with AKI were improving with time. They concluded that AKI remains prevalent in the severely burned which is associated with increased mortality [56]. Another paper described risk factors for the development of AKI, again by RIFLE criteria. These authors found that extra-renal SOFA score, nephrotoxic drugs, increased fluid administration, and sepsis were associated with progression of renal failure [57].

The next series of papers deals with treatment of sepsis in the severely burned. The first examined pre-morbid statin use, and found that statin use before injury was associated with an 83% reduction in odds of death after burn compared to non-treated controls [58]. This does not provide much insight into how to treat once injured though. Perhaps treatment after injury will have an effect, but this can only be answered with a defined well-controlled experiment. The next study examined the use of therapeutic plasma exchange during burn resuscitation. These investigators chose this treatment when resuscitation fluids exceeded 3.6 cc/kg/%TBSA burned, and compared treated patients with contemporaneous controls. They found that therapeutic plasma exchange was used mostly in those with high serum lactate determined post hoc, and that the treatment significantly improved blood pressure, urine output, decreased resuscitation fluids, and decreased serum lactates by 50% [59].

The next papers are on acute resuscitation after injury. The first retrospectively described effects of colloid administration during resuscitation. They found that approximately half of their major burns over 40% TBSA had some decline in urine output associated with increasing crystalloid administration (but half did not...) which was alleviated by administering albumin as part of the resuscitation once this was identified. They concluded that colloid administration during resuscitation reduces fluid administration and ameliorates fluid creep [60]. These are interesting data, but as others have shown, the biology of fluid shifts, etc. changes dramatically in the first 24 h after injury with improvement in urine output, etc. at about 13 h after injury in the majority [61]. Was albumin given systematically shortly before this time (at the nadir of urine output if it was going to occur) that could explain this finding? The contribution of colloid administration relative to the time from injury should probably be more closely examined. The next paper described a 65% increase in resuscitation volumes over time since 1975 that was linearly associated with an increase in opioid administration [62]. Could this be a major contributor to the increases seen in resuscitation fluids? Further studies are warranted.

The next papers were on ventilation techniques in the severely burned. A very important study compared standard ventilation using ARDSnet criteria and high-frequency percussive ventilation (HFPV) in burned patients. They found no differences in ventilator-free days, but did find that the number of subjects undergoing 'rescue' therapy with another mode of ventilation was higher in the standard group,

intimating that HFPV is more beneficial to at least one subset of burned patients, perhaps those with the most serious injuries [63]. A personal interpretation of these data are that standard ventilation techniques are sufficient for mild to moderate airway and lung problems in burns, while those with severe injuries will be best treated with alternative modes. What is needed now is some estimate of what is mild, moderate, and severe from the outset. The next paper described long-term outcomes of burned patients with tracheostomy. These authors found that laryngeal pathology was common in these patients even long after de-cannulation. This was associated with impairment in hyoid mobility. This should be considered prior to tracheostomy in burned patients [64].

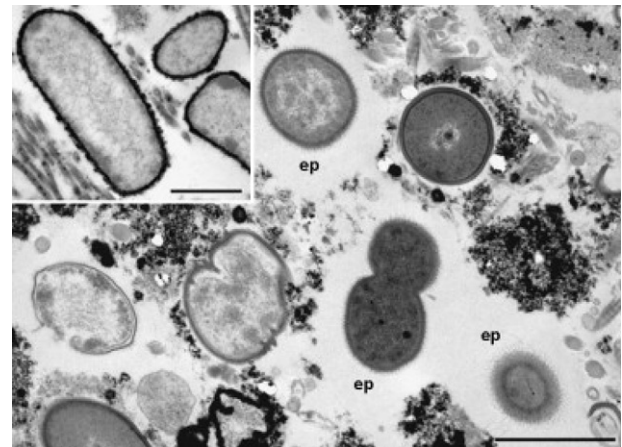
The last papers in this section are in regards to early excision and grafting and systemic effects in pre-clinical models. Investigators in Taiwan found that earlier excision was associated with linearly decreasing cytokine expression in a pre-clinical model [65]. A similar effect was seen on measures of insulin resistance in another study [66]. These data further define the beneficial effects of early excision, and show that indeed the earlier the better seems to be the case.

## 5. Inhalation injury

Three papers in regards to inhalation injury are included. The first was a retrospective study assessing the severity of inhalation injury, not just the presence, on outcomes. These authors found that bronchoscopic findings correlated with mortality, however, when age, burn size, and P/F ratio were included in a multivariate model, the bronchoscopic findings fell out [67]. This is common it seems in that inhalation injury is always included as a predictive variable, but when seen in relation to other variables often loses its significance. We wonder whether this is due to inclusion of relatively minor injuries not adequately excluded by bronchoscopy thus diluting the effects in those with real injuries. What is needed to solve the conundrum is a validated scoring system of severity of this injury. The next two studied effects of smoke inhalation in a well-known pre-clinical model. These investigators found that inhaled treatment with a muscarinic receptor antagonist, tiotropium bromide, improved ventilator pressures, pulmonary dysfunction, and upper airway obstruction measures both with pre-injury and post-injury treatment. They concluded that this may be a useful treatment in patients [68]. Another study showed that a modified tetracycline given intravenously as a matrix metalloproteinase inhibitor significantly improved haemodynamics and ventilation in a combined burn and smoke inhalation model, which was associated with improved survival and lung pathology [69]. Perhaps these might be a reasonable adjuncts to treatment in those with smoke inhalation injury.

## 6. Infection

The next series of papers is in regards to infection, a common condition in burned patients, and specific treatment. One of the most interesting was a qualitative study on the presence of



**Fig. 3 – Low power transmission electron micrograph of a mixed bacterial biofilm consisting of rods and cocci, some of which are degenerate (arrows). Bar = 10  $\mu$ m. Reprinted with permission from Kennedy et al. [70].**

biofilm on organisms found in burn wounds. These investigators found that biofilm was commonly found on organisms in wounds older than 7 days which was clearly associated with chronicity of the wound (Fig. 3) [70]. This is consistent with observations that wounds early in the course have bacteria that are relatively easy to eradicate, but this advantage diminishes with time. Perhaps development of biofilms is the reason. In another study, investigators in Belgium found interestingly in a pairwise-matched cohort study that blood-stream infection in burned patients was associated with more use of vasopressors, longer hospitalisation, and more mechanical ventilation but no difference in mortality or use of renal replacement therapies [71]. We suppose that these results might be expected, but the finding of no difference in mortality is of interest in this relatively large study ( $n = 179$ ), intimating that perhaps the impact of bacteraemia is not as large as expected. The next two studies were sequential, and described isolated bacteria from burn patients at a single centre over a five year period (2003–2008), and found that the most prevalent organisms were *Acinetobacter baumannii* and *Staphylococcus aureus* which were more common early in hospitalisation (<15 days). Later, *Pseudomonas* and *Klebsiella* were more common. Bigger burns had more *Pseudomonas* isolates [72]. The second study examined those organisms that were multidrug-resistant (MDRO) over the same period, and found that over half of *A. baumannii* isolates met these criteria with lower rates for MRSA (34%), *Klebsiella* (17%), and *Pseudomonas* (15%). Respiratory cultures were more likely to grow MDROs than from the blood (24% vs 9%). Resistance for *A. baumannii* increased with length of hospitalisation which was not true for other organisms. The authors recommended that these findings should be used when choosing empiric antibiotics; culture site and time in the hospital might affect organism resistance [73]. Interestingly, antibiotic pressure had little discernable effect. The last from this section examined risk factors for pneumonia in older burned patients. Investigators found that in those over 55 years old and burned, 9% developed pneumonia which was associated with larger burn

size, inhalation injury, and presence of co-morbidities. Development of this complication was associated with an adjusted odds ratio for death of 1.9 [74].

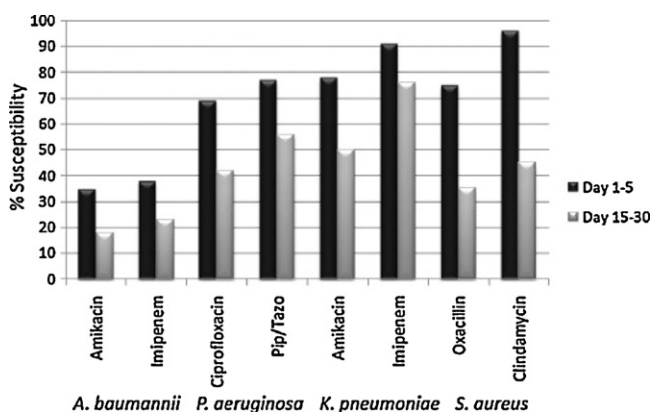
The next series of papers are in regards to particular organisms. Investigators were interested in risk factors for *Candida* bloodstream infection in the severely burned and found that about 10% of their patients had *Candida* isolates, but only 1% had candidaemia. This was associated with prior colonisation which increased with number of sites, larger burn sizes and longer hospitalisation, use of parenteral nutrition, and certain antibiotics (vancomycin, amikacin, ceftriaxone). Attributable mortality with candidaemia was 15% [75]. Another study examined attributable mortality for bacterial and viral causes. They found that bacteria were the identified cause of death in 25% of autopsies, and 5% for virus. Bloodstream infection was the most common cause associated with bacteria followed by pneumonia and wound infection. Fatal viral infections involved the lower respiratory tract, and were either cytomegalovirus or herpes simplex virus [76]. Other investigators examined *Pseudomonas* bacteraemia in particular, and found that this was present in 25% of gram-negative bacteraemia episodes, and the antibiotic susceptibility could be determined in 75% by previous isolates from the wound or lungs (Fig. 4) [77]. The last study of this section examined the impact of MDRO *Klebsiella* infection in the severely burned. These investigators found that patients with isolation of this organism had higher injury severity, and in a multivariate analysis found that the most predictive factor for death in this burn unit was isolation of an MDRO *Klebsiella*, with an odds ratio of 4.0 [78]. This is somewhat striking, and isolation of this organism should incite immediate attention.

Further studies were done on treatment of infections. The first to be mentioned was a meta-analysis of prophylactic antibiotics in burned patients. This study found that antibiotic use 4–14 days after admission showed a significant reduction in all cause mortality (risk ratio 0.54 [0.34,0.87]), which is quite substantial, and a number needed to treat to alleviate one death at 8. Rates of pneumonia, wound infection, and isolation of *S. aureus* were lower in the treatment group as well. The authors noted that the quality of the studies, however, was

poor and the absence of definitive evidence must be emphasised. This was a methodologically sound study with quite shocking results [79]. The next two studies examined pharmacokinetics of antibiotics in burned patients. These studies found that vancomycin and meropenem were cleared faster, while the volume of distribution did not change for vancomycin but did increase for meropenem [80,81]. In general, half-life for drugs is faster for burned patients, and larger doses may be needed to address distribution for optimal effect. Another paper from India described the use of citric acid as an antimicrobial. This was formulated into a 3% gel and compared to silver sulfadiazine. They showed that organisms treated in their burn centre were sensitive to citric acid, and further that the 3% gel was associated with better completion of wound healing than conventional treatment [82]. This is an interesting finding and certainly of interest for containing cost. Two other groups investigated the effects of photodynamic therapy on control of microbial growth. This treatment consists of application of a dye to wounds with irradiation of the wound with a particular wavelength of light (just regular light from a special lightbulb...). One group found that a *Pseudomonas* species on a rat burn wound model was decreased by two orders of magnitude with 2 h of light therapy [83]. Another found that bacteraemia associated with wound inoculation with *Pseudomonas aeruginosa* in a mouse burn model using a similar therapy was not only delayed, but decreased. This is a very interesting alternative to eradicate or control wound bacterial growth, at least temporarily, that is not associated with application of an antibiotic [84]. I wonder whether this might be of use as a temporary treatment of heavily contaminated wounds in severely septic patients or alternatively in those with chronic non-healing wounds not responsive to traditional treatments? What about those with heavy biofilm formation? These studies should be done.

## 7. Metabolism and nutrition

The next series of studies is in regards to the metabolic condition of severe burns and treatment with nutrition and nutritional adjuncts. The first paper is a significant one that describes a non-invasive method to analyse protein kinetics in burned children. A non-radioactive tracer is given as a drink, and whole-body protein synthesis and breakdown are calculated from urine samples. The investigators found that protein turnover was increased by 50% in severely burned children (measured while outpatients) compared to controls which was associated with increased protein synthesis (not decreased...). This is an interesting technique with potential for wider application to measure the effects of nutrition and rehabilitation in the severely burned without tissue samples [85]. Another study examined the quantity and quality of 'wound fluid' collected with Vacuum-Assisted Closure (VAC) devices commonly used in the treatment of burn wounds. These investigators found that protein concentration of the fluid obtained from open abdomens and wounds was 2.9 g/dL with an average of 300 cc/day collected [86]. Protein losses are then in g/day with this treatment, which should be considered in nutritional provision. Another study along these lines evaluated the contribution of muscle protein to whole-body



**Fig. 4 – Antibiotic susceptibility by days of hospitalisation for the 2 most active agents for the 4 most common bacteria—total isolates ( $p < 0.05$ ). Piperacillin/tazobactam (Pip/Tazo).**

Reprinted with permission from: Keen et al. [73].



protein loss after severe burn. They showed that only 7% of protein loss was attributable to muscle, and during convalescence was actually similar to normal subjects [87]. This is a wide diversion from what is commonly believed, and should be followed with more in-depth studies if for no other reason than to repeat the experiment to confirm the findings. Most of the rest of the literature is in direct opposition to these findings.

The next two papers are from an important series of studies from the group in Galveston in regards to insulin treatment in the severely burned. This group has consistently found beneficial effects of this treatment, most recently showing that intensive insulin treatment in a randomised trial decreased the incidence of infection and sepsis, improved biochemical markers of inflammation, and decreased the catabolic response [88]. This group also showed through mathematical modeling techniques that blood glucose values less than 130 mg/dL were associated with better outcomes, and suggested that this should be the target for insulin therapies in burned children [89].

The next is a very interesting paper from Iran, which was a clinical trial randomising children to receiving intravenous resuscitation for the first 48 h after injury versus another group which received enteral nutrition volume as part of the resuscitation within 6 h of injury. Group demographics were similar between groups, but time of hospitalisation was shorter in the fed group, and mortality was also improved. These are somewhat striking data showing that early nutritional intervention may have significant effects on mortality [90].

## 8. Psychological considerations

The next group of papers considers findings from psychologic investigations, with the emergent theme of significant morbidity among the severely burned. The first study included showed that most burned patients (61%) have at least one lifetime psychiatric disorder (axis I or II), among them substance abuse (47%), psychotic disorders (10%), and personality disorders (23%) [91]. These incidences might be expected by experienced providers, but seeing them concretely presented in print is certainly revealing. Another group who had previously shown that pre-existing psychiatric diagnosis was associated with longer hospital stay and more treatment (more surgical operations) for similar injuries showed similar findings for high levels of psychologic distress [92]. This indicates then that psychologic co-morbidities significantly affect wound outcomes and treatments. Another study investigated the impact of personality type and coping on the development of depression after severe burn. This group found that depression occurred in approximately 20% of subjects with no correlation to burn severity or demographics, which is in keeping with previous findings from other groups. However, they did find that neuroticism and avoidant coping were associated with depression [93].

The next was a very interesting study examining the trajectory of distress recovery in burned patients. This study found that a four-class model representing high, sub-threshold, mild, and minimal symptom severity described

the measured burn population well. Covariates of pre-existing illness, etc., significantly affected prediction of group assignment and slope of recovery, intimating that psychological distress remain stable over time in burned patients (they don't change too much), and are significantly affected by non-injury related variables [94].

Delirium during acute hospitalisation is a significant problem in burns. Investigators in the USA found that symptoms of delirium were found in 77% of ventilated burned patients which was highly associated with the use of benzodiazepines, but the use of opioids in particular methadone, was protective [95]. These are some interesting empirical data that should engender further studies to decrease this complication in our patients. The last paper in this section addresses the effects of post-traumatic stress disorder (PTSD) and pain on functional outcomes after injury. These investigators found that higher PTSD symptom severity was associated with poorer functioning and higher disability, however, this diminished with time. Severe pain, however, was correlated with ongoing difficulties with social functioning [96].

## 9. Pain and itch management

The first paper in this section describes a study in multi-modal distraction for pain in burned children. The investigators found in a prospective randomised trial that a programme in distraction which included a game to describe treatment before dressing change as well as distraction during the procedure led to improved reported pain scores and decreased time for dressing changes when compared to use of a standard video game platform or to standard distraction [97]. This is a potential breakthrough in outpatient (and inpatient) care we think to not only improve patient perception of pain, but also to improve throughput and stress on providers. More work is needed in this area. Another study demonstrated that analgesic programmes that include tramadol, ketamine, and dexmedetomidine were superior to more standard regimens including only ketamine or benzodiazepines [98].

In terms of itching, two papers of note were published this year. The first addressed the use of combined agents to affect itch. These investigators found that monotherapy was more ineffective with high initial itch scores, and that a combination of centrally acting agents such as gabapentin and peripherally acting antihistamines were more effective. Further, they showed that failure of monotherapy was more likely with decreasing age and increasing burn size [99]. Another study from the same group showed in a survey study that itching was generally not addressed in a systematic approach in burns, with a reliance of antihistamines rather than central actors or non-pharmacologic approaches. These two studies are important in that they show some marginal benefits from non-standard therapies in our patients. These are more likely to be beneficial if used in children and those with bigger burns. We think that part of the problem with itching after burn is the relative lack of effect of some of our standard treatments (anti-histamines); new agents and approaches are needed.

## 10. Rehabilitation and long-term outcomes

The first two papers in this section are in regards to measurement of scars and function. Investigators in the USA surveyed experienced burn therapists for their preferred method to measure scar contracture, and could find no agreement or consensus. Most methods used were not objective nor could these be tested for reliability. The authors concluded, rightly, that standard reliable and objective protocols to measure scar contracture are necessary to improve outcomes [100]. We look forward to the development of these tools. Another group from Australia sought to do just that, in a way, with assessment of the reliability and validity of measures of lower limb function after severe burn. They found that a Timed Up-and-Go and Tandem Walk Forward (but not backward) were valid and reliable measurements of recovery, and provided additional information for burn specific health [101].

Pressure garments and silicone have long been used for scar management in burned patients; two papers addressing benefits are included this year. The first from Hong Kong showed in a prospective randomised trial of 6 months of treatment with pressure garments, silicone gel dressing, or both. The combined therapy decreased scar thickness at 2 and 6 months while pressure garments alone decreased scar thickness at 6 months. Silicone gel dressings decreased pain and itching with no effect on scar appearance. This study provides more evidence in favour of pressure garments and improved outcomes with the addition of silicone gel [102]. Another study used laser Doppler to measure blood flow with pressure on facial scars. They found that application of pressure decreased blood flow significantly which was not altered by changes in facial expression. Further, they showed that removal of the mask was associated with hyperaemia which was present for at least 30 min after removal [103]. This information is probably applicable to all pressure therapy, and should be considered in treatment paradigms.

Several interesting papers were found in relation to long-term functional outcomes. The first was another measurement study which showed that the SF-36, a commonly used outcome measure in many different conditions, was as valid as the more cumbersome Burns Specific Health Scale [104]. This should be considered in further outcome study designs. The next study investigated the impact of hand burns on functional outcomes in burned children, and found that only upper extremity function was decreased long-term. However, when used in conjunction with burn size it was a predictor of increased resource utilisation [105]. Investigators in Australia found that outcomes in children whose parents had high state anxiety in combination with ineffective coping strategies seemed most at risk for non-adaptive outcomes after severe burn [106].

The effects of severe burn can be quite prolonged. Investigators in the USA found that in burn survivors with a mean 57% TBSA burned and 17 years from injury continued to have issues with temperature sensation, sensory loss, and itching even long after the injury. The fragility of scarred skin was reported to increase with time from injury even after maturation [107]. This is interesting in that the clinical dogma states that the scarred skin is stable and relatively normal after scar maturation. This should be considered in long-term follow-up plans.

Finally, an important paper on access to rehabilitation is included. Investigators posited that burned patients with health insurance and lack of social support were more likely to receive inpatient rehabilitation after their injury. They found that this was indeed the case; patients with adequate social support were 44 times more likely to return directly home from the hospital, and those without insurance were also 7 times more likely to return home [108]. This appears to us more of an indictment of economic factors of whom will receive inpatient rehabilitation after burn than injury. It would seem that inpatient rehabilitation should be used in whom it is most effective, not in who meets socioeconomic criteria. Access to health care is important, but is only one of the issues and contributes less than other variables.

## 11. Burn reconstruction

The first of this series is a description of a technique for scalp alopecia treatment after burn. These authors used a combination of scalp tissue expanders to address areas of alopecia initially followed by hair transplantation to address 'thinning', with reasonable results in 62 patients [109]. This elucidates another treatment modality for those with alopecia. The next was a study showing that tissue expansion for breast reconstruction in the burned chest was successful with comparable complications to a group with congenital breast deformities [110]. This is another technique that should be considered in those affected. Investigators in China showed that donor skin taken from previously scarred areas on the back was effective in use in covering defects during reconstruction or other scars. They overgrafted the donor site in all cases without increases in complications [111].

The last paper is an important one addressing long-term scar formation in areas treated with a dermal substitute compared to standard skin grafting. This was from subjects with truly long-term assessment (>5 years). They divided subjects into dermal substitute use in acute wound closure and reconstructive wound closure. They found that surface roughness was improved with dermal substitution in reconstructive wound closure, and several subjective measures were improved in both acute and reconstructive treated scars. Finally, in acute wounds closed with widely meshed skin and dermal substitution, elasticity was improved [112]. These results are important in that they show some improvements, alas mostly subjective, and not particularly impressive. This questions the benefit in relation to significant effort and costs. This study shows the measured benefits are primarily subjective, which is of course subject to significant bias. It has been almost 30 years now since these products have been available with only marginal demonstration of benefit for scar. Shouldn't we see a definitive trial in this area to finally answer the question of whether (not can...) these products should be used?

## 12. Conclusion

We look forward to next year where we hope to see further advances in burn research and publication.

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