

Azzopardi. EA., Duncan RT, Kearns M., et al. Cost-benefit analysis of cutaneous laser surgery in secondary burn reconstruction. In: Veeramani S., Odili. J., Eds. BAPRAS Winter Conference Monaco2019. [http://www.bapras.org.uk/docs/default-source/bapras-event-documents/scientific-meetings/v2\\_bapras-winter-19-programme.pdf?sfvrsn=2](http://www.bapras.org.uk/docs/default-source/bapras-event-documents/scientific-meetings/v2_bapras-winter-19-programme.pdf?sfvrsn=2)

Thermal disease presents a major burden to individual patient morbidity, healthcare cost as well as to over all economy. Burns also also represent a significant per-patient utilisation of finite healthcare resources. Secondary complications in these patients, such as multiple drug resistant organisms, may have a devastating effect. Laser surgery has recently come of age as an optimal tool in the secondary reconstruction of burn injury, that is able to simultaneously address significant sheet scar tightness, hypertrophic, atrophic, and keloid complications, pruritus, microstomia, ectropion, skin graft honeycombing, and improve range of movement whilst reducing the risk of infection to <1%. Yet, cutaneous laser surgery is often underutilised due to the perceived concerns about the sustainability of a new service with relatively high startup cost. We present a dual methodology to explore this concern: an evidence-based background review of the last 5 years of current best evidence, and a 22-year cost-analysis comparison at an established, high volume UK Centre of reconstructive surgery. We report that fiscal viability for laser surgery services for secondary burn reconstruction is supported by: level 2 (one systematic review) level 4 evidence (2 studies) and level 5 evidence (expert reports). Evidence over 22 years from an established super-regional NHS laser centre shows that introduction of this service led to sustained and substantial cost saving, producing excellent surgical results at a fraction of the cost of traditional surgery. Analysis of the potential dollar-effect of these advantages to the general population supports state investment in expertise and capital equipment as a medium to long-term cost saving strategy, which may also aid re-integrating patients into the workforce

making a meaningful contribution to the economy.

## Summary

Multidrug resistant surgical infection is a global threat to the practice of surgery. This work is the first to describe a characteristic spectrum of Gram-negative bacteria to infect burn wounds, establish a clinically viable mechanism for passive drug accumulation and “smart release” at any infected soft tissue site. This work subsequently established an entirely novel class of macromolecular antibiotics.

Burn wound infections in different centres were traditionally thought to be caused by differing sets of organisms. However, our metanalysis of standardised bacterial incidence rates confirmed *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacter* spp., *Proteus* spp. and *Escherichia coli* as characteristic Gram-negative burn wound pathogens ( $F(4,20)=1.1$ ,  $p=0.3797$ ;  $r^2=9.84$ ). We subsequently identified a common biochemical cascade instigated by these bacteria, *Streptococcus* and *Staphylococcus aureus* which is bradykinin-controlled, leading to local vascular permeability enhancement (VPE).

The mechanism leads to accumulation of macromolecules around the site of infection.

Conventional “small molecule” antibiotics cannot target specifically an infected area-distributing to unintended sites, facilitating toxicity. This work therefore utilised the mechanisms heretofore discussed in custom-designing a prototype polymer-antibiotic conjugate that allows targeting to, and controlled release at, an infected site. I employed the biodegradable, naturally-occurring polymer, dextrin, and a “last-line” antibiotic, colistin, as the first model combination.

Colistin’s toxic multiple amine groups, were eliminated through the formation of peptide bonds, to dextrin, facilitating linkage whilst reducing toxicity. The colistin was therefore “masked” in transit to the target site through chemical bonding and the steric hindrance of a

large dextrin chain. The reaction was feasible, predictable and reproducible ( $r^2 = 0.96$ ,  $p < 0.0001$ ).

Exposed to normal levels of amylase activity ( $\leq 100$  IU/L), minimally modified low molecular weight dextrin, conjugated to colistin, exhibited an ideal “masking” profile. Ex vivo, this lead compound also rapidly “unmasked” at infected sites. The resulting bioactivity was comparable to the current clinical formulation of colistin (Colimycin) against a clinical library of MDR *A. baumannii*, *K. pneumoniae* and *E. coli*. However the compound suppressed bacterial growth fourfold longer than the equivalent dose of Colimycin ( $p < 0.05$ ).

An ex vivo ( $n=6$ ) series of human infected burn wound fluid samples confirmed a significantly higher amylase activity around wounds than in plasma. Upon incubation, colistin was easily “unmasked” at the infected site, supporting the notion of locally-triggered, enzymatically-mediated unmasking. An in vivo ( $n=32$ ) Sprague Dawley rat model reported optimisation of pharmacokinetic parameters (plasma half-life doubled, clearance decreased 6-fold). In contrast to colistin, no clinical toxicity was observed at the highest protocol dose. This study is the first to establish the pathogens responsible for the majority of Gram-negative burn wound infections. The EPR mechanism is dependent on human bradykinin release in response to non-specific bacterial infection; the accumulated amylase is human, emphasising the applicability of this proof of concept for target antibiotics to most soft tissue infections, achieving controlled release whilst minimising adverse effect. This approach provides an effective clinical tool for the treatment of surgical soft tissue infection.