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A systematic review of quantitative burn wound microbiology in the management of burns patients

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ABSTRACT

Background: The early diagnosis of infection or sepsis in burns are important for patient care. Globally, a large number of burn centres advocate quantitative cultures of wound biopsies for patient management, since there is assumed to be a direct link between the bioburden of a burn wound and the risk of microbial invasion. Given the conflicting study findings in this area, a systematic review was warranted.

Methods: Bibliographic databases were searched with no language restrictions to August 2015. Study selection, data extraction and risk of bias assessment were performed in duplicate using pre-defined criteria. Substantial heterogeneity precluded quantitative synthesis, and findings were described narratively, sub-grouped by clinical question.

Results: Twenty six laboratory and/or clinical studies were included. Substantial heterogeneity hampered comparisons across studies and interpretation of findings. Limited evidence suggests that (i) more than one quantitative microbiology sample is required to obtain reliable estimates of bacterial load; (ii) biopsies are more sensitive than swabs in diagnosing or predicting sepsis; (iii) high bacterial loads may predict worse clinical outcomes, and (iv) both quantitative and semi-quantitative culture reports need to be interpreted with caution and in the context of other clinical risk factors.

Conclusion: The evidence base for the utility and reliability of quantitative microbiology for diagnosing or predicting clinical outcomes in burns patients is limited and often poorly reported. Consequently future research is warranted.

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1. Background

Infection is a significant complication for patients who survive an initial burn. Although there are a variety of infection routes which may lead to systemic infection and sepsis in the thermally injured patient, a key route of infection is *via* the breached and burnt areas of the skin. Here infection typically starts as bacterial colonisation (with bacteria contained in a biofilm), with the source bacteria easily introduced onto this exposed and vulnerable surface *via* a number of exogenous and endogenous routes. Colonisation may then progress to systemic infection, where mortality rates can be as high as 75% [1,2], with the majority of the mortality due to pneumonia, sepsis, urinary tract infections, and acute burn wound infections [2–5].

The longer the colonisation persists, the greater the likelihood of systemic infection [6]. Furthermore, it is believed that the risks of bacterial invasion and systemic infection increase in proportion to the size of the skin breach [1]. Consequently, microbiological assessment of burn wounds particularly when clinical signs of infection are present, or if the wound is deteriorating, or has changed in appearance, is important in patient management [7,8], and forms the standard of care in most burns units. This can be achieved with qualitative (bacterial presence/absence), semi-quantitative (some form of bacterial enumeration conducted), or quantitative (full bacterial count provided) microbiological methods. In the UK, assessment of burn wounds is generally qualitative and semi-quantitative, and utilises swab cultures [9]. We speculate that swabs are favoured owing to their non-invasive nature, and that qualitative and semi-quantitative methods are preferred owing to the likely substantial cost reductions for the clinical laboratory, both in terms of technical time, and media requirements.

Various authors [10,11] have suggested that qualitative and semi-quantitative methods should be replaced by fully quantitative bacteriology of biopsies in order to improve patient management. The use of burn wound biopsies for histological and quantitative assessment of the burn wound originates from Teplitz et al. [12], who stained and microscopically investigated tissue for bacteria, and provided an absolute measure of bacteria per unit of volume. Using a rat model, Teplitz et al. [12] found that increasing numbers of *Pseudomonas aeruginosa* on a burn wound were followed by invasion of the underlying viable tissue, and clinical infection.

A clinical method for quantitative biopsy in burns patients was first described by Loebl et al. [13], and subsequently modified [14,15]. Consequently, there now exist a variety of quantitative methods, but no universally accepted 'gold standard'. These methods differ in a number of ways, such as the method of sample collection, biopsy collection and processing, and timing of collection. There is most likely a difference in cost per biopsy type, although this information is not provided in the studies.

The evidence for the utility of quantitative burn wound culture is inconsistent. Some animal and *in vitro* studies suggest an association between high bacterial counts and infection [16], delayed wound healing [17], and poor skin graft take [18]. Some clinical studies were unable to demonstrate a relationship between bacterial counts and subsequent sepsis or graft loss [11,16].

The use of quantitative culture for the prediction of clinical outcomes is only one possible prognostic variable. Other prognostic factors could include the more traditionally used clinical factors, such as heart rate, temperature, and blood pressure [19], or newly developed novel tests such as neutrophil function [20]. The incremental utility of quantitative culture as a prognostic factor should therefore ideally be evaluated in the context of other known prognostic factors. Furthermore, any evidence on the prognostic utility of bacterial count (whether as a single prognostic factor or in conjunction with others), should ideally be evaluated in the context of the evidence on the accuracy and reliability of the counts obtained. Given the absence of quantitative burn wound microbiology in many burns centres, and the varied and sometimes conflicting evidence base, a comprehensive systematic review of all existing evidence was warranted.

2. Methods

A protocol detailing the methodology was registered (PROSPERO (CRD42015023903)) and published [21]. A summary of the methods is described here.

Bibliographic databases were searched to 3rd August 2015 (MEDLINE, PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus) using a combination of index and text words relating to the population (burns patients) and quantitative burn wound microbiology. There was no restriction by language, study design or outcome. A sample search strategy for MEDLINE is shown (Supplementary Fig. S1). ZETOC (British library) and the Science Citation Index (Web of Science) were searched for conference proceedings. Abstracts from national and international burns and microbiology conferences were searched from 2012 onwards. Clinical trial registries were searched for ongoing trials and relevant articles were citation checked.

Prospective studies using any method(s) of quantitative burn wound microbiology, in patients of any age with a burn were eligible. Relevant outcomes included any measures of reliability or repeatability of a single method for obtaining bacterial counts, measures relating to the agreement between two or more methods, clinical outcomes (such as sepsis or mortality), and their association with bacterial counts and resource related outcomes (e.g. length of hospital stay). Animal and *in vitro* studies, and studies only examining qualitative or semi-quantitative methods, were excluded.

Study selection, data extraction and quality (risk of bias) assessment were performed in duplicate by two independent reviewers using pre-specified criteria and standardised forms. Disagreements were resolved through discussion or referral to a third reviewer. Data was extracted on study aims and design, patient characteristics, methods and timings of sample collection and culture, length of follow-up and outcomes.

As the review encompassed a range of study designs with different study aims, it was necessary to include risk of bias criteria from different tools. Risk of bias assessment therefore included, where relevant for individual studies, elements from the 'COnsensus-based Standards for the selection of health

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