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Title: A systematic review of intervention studies demonstrates the need to develop a minimum set of indicators to report the presence of burn wound infection.

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ABSTRACT

Introduction: Burn wound infections (BWI) result in delayed healing and increased pain, scarring, sepsis risk and healthcare costs. Clinical decision making about BWI should be supported by evidence syntheses. Validity of evidence from systematic reviews may be reduced if definitions of BWI vary between trials. This review aimed to determine whether BWI is defined, and whether there is variation in the indicators used to define BWI across studies testing interventions for patients with burns.

Method: Searches were carried out in four databases (Ovid Medline, Ovid Embase, Cinahl, Cochrane Register of Trials) to identify studies evaluating interventions for patients with burns and reporting a BWI outcome. Pre-defined inclusion and exclusion criteria were systematically applied to select relevant studies. Data were systematically extracted and reported narratively.

Results: 2056 studies were identified, of which 72 met the inclusion criteria, comprising 71 unique datasets. 52.1% of studies were randomised controlled trials. Twenty-eight (38.0%) studies reporting a BWI outcome did not report how they had defined it. In the methods of included studies, 59 studies (83.1%) reported that they planned to measure BWI as an outcome. Of these, 44 studies (74.6%) described how they had defined BWI; 6 Studies (13.6%) reported use of a previously developed consensus-informed definition of BWI, and 41 studies (69.5%) described the specific indicators used to define it. Studies used between one (11 studies; 26.8%) and nine indicators (2 studies; 4.9%) to define BWI (median=3, Inter-quartile range=2). The most commonly used indicator was presence of bacteria in the wound (61.0% of studies). Only 13 studies (31.7%) defined BWI using the same indicators as at least one other study.

Discussion and Conclusions: Within intervention studies reporting BWI outcomes, a definition of this outcome is commonly not provided, or it varies between studies. This will prevent evidence synthesis to identify effective treatments for patients with burn injuries. Since there is no objective method for assessing BWI, expert consensus is needed to agree a minimum set of indicators (Core Indicator Set) reported in all trials reporting BWI as an outcome.

KEYWORDS: Burn wound infection, systematic review, outcome definition, diagnostic indicators

INTRODUCTION

Wound infections complicate recovery after burn injury and result in increased pain, scarring, risks of sepsis and increased healthcare costs [1]. In patients with burns of more than 40% body surface area (BSA), it is estimated that 75% of mortality is related to infections[2, 3]. To identify effective treatments to prevent, detect or treat BWI, evidence from systematic reviews is needed. Systematic reviews aggregate data from several trials of interventions, and are viewed as the best quality evidence upon which to base clinical decision making [4, 5]. Challenges with evidence synthesis include heterogeneity of outcome definitions across trials. If the definition of the outcome of interest varies between studies, or is not stated, the validity of the aggregated data may be compromised, because researchers may not be comparing like with like[6]. Variation in how the same outcomes are defined has been identified in a review of clinical outcomes reported in randomised trials of burn care interventions[7]. For example, the authors identified 166 ways of defining burn wound healing across 147 studies. It is unclear if a similar heterogeneity in the definition of BWI exists across burn care studies.

One reason for hypothesising that variations in the definition of BWI may exist is that there is no agreed objective method for diagnosing BWI. Diagnosis is typically based on clinician judgement, supported by data from clinical indicators. These include wound-related or systemic, patient-reported symptoms, observer-reported signs, non-specific laboratory tests indicating inflammation and wound microscopy to assess the quantity and type of microbes in the wound. Determination of wound colonisation typically takes 48 hours or longer. A decision about whether to treat BWI with superficial debridement or broad spectrum antibiotics is therefore commonly made before these data are available[8]. To support consistent diagnosis of BWI, consensus statements have been developed by the American Burns Association (ABA[3]), Center for Disease Control (CDC[9]) and European Wound Management Association (EWMA[10]). However, there are practical limitations that preclude their routine use in clinical care. For example, the ABA and CDC criteria require the use of a wound biopsy. It will be difficult to report data relating to this criterion where wound biopsy is not routinely used, due to risks of scarring and the need for anaesthesia. For example, in the UK wound biopsy is

rarely used to determine presence of BWI[11] The EWMA tool states sensitive, but rarely observed, wound-related signs as indicators for BWI (e.g. ecthyma gangrenosum), and without reference to systemic indicators of infection. These inherent difficulties with diagnosis of BWI are likely to lead to the use of varying definitions of BWI across trials in burn care.

The aim of this systematic review was to determine whether BWI is defined as an outcome, and whether there is variation in indicators used to define BWI across studies testing interventions for patients with burns.

Method:

Methods for this review were specified in advance and the protocol registered on the PROSPERO database: REF CRD4201809664. We adhered to the PRISMA statement for reporting systematic reviews[12].

Study identification and selection:

Inclusion and exclusion criteria

We identified peer reviewed journal articles published between 1st January 2010 and 30th November 2016, in English, and meeting the following PICOS criteria (Population, Intervention, Control, Outcome, Study design):

i. *Participants*: studies reporting data from patients with acute burn wounds (before healing). Studies with mixed populations where patients had both burn and other traumatic injuries were excluded, unless data relating to patients with burns were presented separately.

ii. *Intervention and control groups:* Studies reporting any intervention to treat patients with burn injury and any comparator intervention or standard care were included.

iii. *Outcomes of interest*: Studies reporting BWI as an outcome in the abstract, methods, results or discussion were included. We accepted any study where the authors used the terms 'burn wound infection' or 'wound infection'.

iv. *Study design*: Studies were included if they employed a randomised controlled trial, controlled trial, observational study design, case control study or reported a protocol for a trial or observational study.

INSERT Table 1: Exclusion criteria for selection of studies

Electronic search

An electronic search of four databases was carried out to identify relevant studies: Cinahl, Ovid Embase, Ovid MEDLINE, Cochrane Register of Controlled Trials (CENTRAL). To identify studies that met the inclusion criteria, three groups of search terms were iteratively developed relating to burns, wound infection, interventions and trials. Medical Subject Headings (MeSH) were used where available. Synonyms for each term were combined using an OR term, and the groups of terms were combined using an AND term. Following piloting of the search strategy in two databases (Ovid Embase and Ovid MEDLINE), NOT terms were added to increase the specificity of the search, thus removing studies irrelevant to the topic (e.g. NOT Coxiella Burnetii, burnout). The search string used in Medline is presented in Table 2. This was modified for each database. The search terms were applied to the title, abstract and keywords where possible, to increase the specificity of the search.

INSERT Table 2: Search terms in Medline

Selection of papers for inclusion:

Search results were downloaded from each database and combined in an Endnote database (version 8), where records were manually reviewed to remove duplicates. Citations were exported to a

Microsoft Excel database for screening. First, titles and abstracts were reviewed against the exclusion criteria. Next, full text articles of retained citations were obtained and screened using the same criteria. For both screening stages a second researcher (FSJ) screened 20% of citations.

Data extraction

A proforma to standardise data extraction was developed in Microsoft Excel and piloted for comprehensiveness and clarity. Where the same dataset was reported across two or more studies, extracted data about the studies were combined as a single dataset. Data extraction from 20% of papers was checked by a second researcher (FSJ) to ensure reliability.

Extracted data to describe each study were: i) study identifiers (title, authors, date and citation), ii) study design, iii) intervention/s and control condition/s evaluated.

For each study, data were extracted about study methods and indicators used to define BWI. Data extracted were:

i) Whether BWI was defined in the study methods or results, ie. it reported a diagnostic tool (consensus statement) or the indicators used for diagnosis.

ii) A verbatim report of each indicator used to define BWI. We accepted author-defined BWI, whether the indicators were those typically used to define BWI or not. Each indicator wase categorised under a label to allow summary and comparison of data (see below). The number of indicators used to define BWI were noted for each study.

iii) Whether the same indicators were used to define BWI across studies.

iv) Whether numerical values were reported for indicators to determine presence of BWI

v) Whether a method for combining data from several indicators to determine presence of BWI was specified (e.g. a count of the number of indicators present or a weighted scoring system)

Categorising indicators

Examination of the verbatim data from (ii) to describe the BWI indicators used in each study demonstrated that for some indicators of BWI, terminology used to describe the same indicator varied across studies. To enable a count of the indicators used, and identify common indicators used across studies, a process was undertaken by two reviewers (AD, FSJ) to group such indicators under a consistent label. For example, if different studies had described an indicator as *'wound microscopy from swab'*,*'bacteria in wound identified using swab', 'swab of wound pus'*, these indicators were assigned the same label '*bacteria in wound swab identified from pus or exudate'*. Similarly, where studies had used the term '*spreading erythema'*, '*erythema*', '*redness in surrounding tissue'*, these were assigned the label *'spreading erythema'*.

A small number of studies reported defining BWI using an indicator that represented a group of signs or symptoms, for example '*clinical signs*', '*cellulitis*'. These indicators were labelled using their verbatim terminology. While it is acknowledged that these labelled indicators represent a group of signs and symptoms, since it is not known what signs and symptoms the authors referred to, they were counted as a single indicator.

Where studies reported use of a diagnostic tool (e.g. the ABA[3] or CDC[9] consensus statement), the indicators used in the tool were not reported as verbatim indicators and are excluded from the counts of indicators used to define BWI.

Data synthesis

No risk of bias assessment of studies or meta-analysis of outcome data was conducted, since this review aimed to report the indicators used to assess presence of BWI across studies and did not aim to assess the effectiveness of interventions. A narrative review of the data is presented.

RESULTS

Results of electronic search

The electronic search identified 4314 studies, of which 2258 were duplicates. Following the two screening stages, 72 studies, comprising 71 unique datasets met the inclusion criteria (Figure 1). Therefore, data from two studies were combined[13, 14].

INSERT FIGURE 1 HERE

Characteristics of included studies

Table 3 indicates the characteristics of included studies.

INSERT Table 3: Characteristics of included studies

i) Whether BWI was defined in the study

Fifty-nine studies (83.1%) described that BWI would be assessed as a study outcome in the methods. The remaining 12 studies (16.9%) did not describe that they planned to assess this outcome in their methods, despite reporting it in the results[15-26]. Forty-four of the 59 (74.6%) studies that stated that they planned to assess BWI as a study outcome provided a definition of BWI in the study methods or the study results. Therefore, 15 studies (25.4%) stated that BWI would be assessed, but did not describe the indicators used to define it [27-41].

Six studies (13.6%) reported that they had defined BWI using a consensus tool [42-47]. Four studies used the ABA consensus statement[3] (studies:[42, 45, 48, 49]). Two studies reported that they had used criteria developed by Peck and colleagues[50] (studies: [46, 47]). One study combined Peck and colleagues' criteria with criteria developed by Silla and colleagues[51] (study: [47]). Three of the studies using consensus statements also reported the use of additional specific indicators[42, 45, 47]. Therefore, 41 of the 59 studies (69.5%) that stated that they planned to assess BWI defined it using one or more indicators of BWI.

ii) Indicators used to define BWI within and across studies

The indicators used to define BWI in the 41 studies (69.5%) that reported the use of one or more specific indicators are presented in table 4. Twenty-seven different indicators were used to define BWI across all these studies. The number of indicators used within studies ranged between one (26.8% of studies) and nine (4.9% of studies; see figure 2). The median number of indicators used was 3 (inter-quartile range=2).

INSERT Figure 2: Number of indicators used across studies

The most frequently reported indicators used to define BWI were presence of bacteria in the wound, identified from swab of pus or exudate (n=25; 61.0% studies), change in colour or volume of exudate (n=25; 48.8%), spreading erythema (n=16; 39.0%), oedema (n=10; 24.4%), pyrexia and pain (n=9; 22.0% respectively).

Seven studies (17.0%) defined BWI using indicators that represented a group of signs and symptoms: Cellulitis was used as an indicator to define BWI in five studies[52-56] (12.2%), and 'clinical signs'[57] and 'biological markers'[57] in one study (2.4% respectively). Administration of antibiotics was used to define presence of BWI in two studies (4.9%)[58, 59].

11 of 41 studies (26.8%) studies reported the use of only one indicator[13, 14, 42, 45, 49, 55, 60-66]. Of these, four used bacteria in the wound identified from swab of pus or exudate [13, 62, 64, 65] and six used wound biopsy or tissue culture.[42, 45, 60, 61, 63, 66] The remaining study using describing the use of a single indicator to define BWI, defined it as cellulitis[55]; it should be noted that this represents a collection of signs and symptoms.

INSERT Table 4: Indicators used to define BWI in each study (n=41)

i) Whether the same indicators were used to define BWI across studies.

Thirteen studies (31.7%) had the same definition of BWI as at least one other study. In four of the 11 studies using a single indicator to define BWI, it was defined as presence of bacteria in the wound, identified from swabs of the wound or pus.[13] [62, 64, 65] In six of the 11 studies (54.5%) defining BWI with a single indicator, it was defined as bacterial presence indicated from wound biopsy or tissue culture,[42, 45, 60, 61, 63, 66] with three of these studies stating that wound infection was defined as $>10^5$ colony forming units per gram of tissue[14, 42, 45]. Of the nine studies using two indicators to define BWI, two (22.2%) used the same indicators to define it: presence of bacteria in the wound from swabs, and a change in colour or the quantity of exudate.[73, 74]

v) Numerical values for indicators used to determine presence of BWI

Of the 25 studies using presence of bacteria from wound swabs to define BWI, six (24.0%) described the numerical values used to determine presence of BWI ($>10^5$ microbes per gram of tissue[59] [47] [85] [65] [56, 75]). For tissue cultures, five of eight studies reported numerical values used to determine presence of BWI ($>10^5$ colony forming units per gram of tissue[45, 60] [42] [66]). The remaining studies did not report what numerical values were used for presence of bacteria in the wound. One of the nine studies (11.1%) using pyrexia reported the numerical values used to determine 'fever' and 'high fever' (>37.4°c and >38°c respectively[69]).

vi) Whether a method for combining data from several indicators to determine presence of BWI was specified (e.g. a count of the number of indicators present or a weighted scoring system)

Thirty-one studies (75.6%) used more than one indicator to define BWI. Of these, 10 (32.3%) reported a method for rating or combining data from the multiple indicators used to determine whether BWI was present. In four studies (40.0%) BWI was evaluated by counting the number of signs present.[56, 76, 78, 84]

DISCUSSION

This systematic review was undertaken to identify whether BWI is defined, and where defined, whether there is variation in the indicators used to define it across burn care studies. Of 71 included studies, 59 (83.1%) described that they planned to assess BWI as an outcome in the study methods. Of these 44 (62.0% of all studies) reported how they had defined BWI; six studies (13.6%) used a consensus tool, and 41 (93.2%) described the indicators used to define BWI. Twenty-seven different indicators of BWI were used across studies. Between one and nine indicators were used to define BWI across studies (median=3; IQR=2). Only 13 of 41 (31.7%) studies reporting the indicators that they used to define BWI used the same indictors as at least one other study.

There are two key findings from this review. The first is that in 38% of studies reporting data on BWI, it was not stated how this outcome was defined, and 16.9% of studies reported data about BWI without describing it as a study outcome in their methods. One quarter (25.4%) of studies describing BWI as an assessed study outcome failed to report how they had defined it. Where BWI was defined, a small number of studies used imprecise terms, including '*cellulitis*', '*wound signs*', and '*biological markers*'. These terms may represent numerous different indicators that were assessed. The lack of specificity identified in the some definitions of BWI in the current review replicates the findings of other systematic reviews in burn care[87], where poor-quality reporting of trial methodology has been identified. This lack of clarity of outcome definition will prevent reproducibility of a study's findings about intervention effectiveness[88].

The second finding is that across studies providing a definition of BWI, there was considerable heterogeneity in how it was defined. This variation in the indicators used to define wound infection has also been found in systematic reviews of surgical site infections[89] and healthcare associated infections[90]. This will limit the validity of evidence syntheses using data from these studies. If data from studies with varying outcome definitions are synthesised, the review's findings may not represent the 'truth' about the effectiveness of the intervention. This problem has been highlighted in recent Cochrane Reviews of the use of antibiotic prophylaxis[91], antiseptics[92], and

immunonutrition[93] for patients with burns, in which the authors reported that the validity of their findings was compromised due to limited reporting and varied indicators applied to define BWI.

Consensus statements have been developed to standardise the diagnosis of BWI. However, only six of the 71 included studies (8.5%) reported their use. This may relate to practical limitations of these tools. These include the use of wound biopsy[3] [9], which is costly,may cause scarring, and is infrequently used in some health care systems such as the UK NHS. Further potential limitations are the inclusion of indicators that are sensitive signs of infection but rarely observed in patients[10], and a focus on wound-related signs without reference to key systemic signs of infection (e.g. pyrexia, leucocytosis)[10].

A further funding from this this review is a potential over-reliance on non-quantitative and quantitative bacterial counts from wound swabs and tissue sampling. Many of the studies defining BWI using wound swabs and tissue sampling used quantitative microbiological assessment of the wound, commonly as the *only* indicator of BWI. Furthermore, many of the included studies defined BWI as $>10^5$ bacteria/ colony forming units per gram of tissue. Clinically relevant infection that requires treatment should not be identified without referring to other clinical signs and symptoms of BWI. A recent systematic review of human studies investigating the reliability of wound swabs and biopsies found that more than one sample of the wound may be needed to obtain an accurate estimate of bacterial load, correlation between swabs and biopsies is frequently poor, and that clinical signs and symptoms should be referred to in addition to quantitative microbiology, since 13 studies found no correlation of biopsy findings with clinical outcomes. A further literature review supports the view that quantitative microbiology should not be used without reference to clinical signs and symptoms, and is suggestive that the 10^5colony forming units/gram of tissue cut-off is arbitrary, particularly since clinically relevant infection is more likely to be found at higher bacterial concentrations. [94, 95]. These data suggest that quantitative microbiology alone may be an unreliable indicator of BWI and may overstate the incidence of BWI, since bacteria are frequently present in burn wounds without being clinically relevant[1] (wound colonisation).

This review employed a systematic approach to the identification and selection of studies reporting BWI as an outcome. The use of four databases to identify RCTs, observational studies, case control studies and protocols provides a comprehensive review of how BWI has been defined across studies. Limitations include the exclusion of studies published before 2010. This limit was placed to ensure that we identified reports relating to current BWI diagnostic practices. Studies that were not published in English were excluded due to funding constraints. While unpublished literature was requested from interested parties, no additional studies or work in progress reports were put forward.

Clinical decision-making about effective treatments for BWI requires that evidence is synthesised across relevant studies. Inconsistent definition and measurement of BWI creates 'noise' in the data which may obscure the true effect of interventions, whereby interventions that are effective may not be identified. There is a need to improve the consistency of how BWI is defined, and for this to be reported in the study methods and results. However, identification of a consistent definition is difficult as there no agreed objective diagnostic method for determining presence of clinically relevant BWI. Until an objective method for diagnosing BWI is available, agreement about a minimum set of indicators to be reported when assessing BWI as an outcome is necessary to allow comparison and collation. One means to do this is to use published literature and expert consensus to identify a minimum set of BWI indicators (a Core Indicator Set) that are considered important to report in future research trials, and that are most suggestive of BWI infection. This consensus methodology has been used to identify diagnostic indicators in other infection domains, such as bone and joint infections, and renal cyst infections[96, 97]. By defining a Core Indicator Set, BWI outcomes and the indicators used to define it can be compared across burn care trials to reliably synthesise the data and identify effective treatments for patients.

CONCLUSIONS

This systematic review of how BWI is defined in trials of interventions for patients with burns has shown that 38% of included studies did not report how they defined BWI, that there is considerable heterogeneity in the indicators used, and limited use of consensus tools. This inconsistency in definition of BWI will limit the validity of evidence syntheses, preventing the identification of the most effective treatments for patients with burns. Until there is an objective method to diagnose clinically relevant BWI, development of a minimum core set of indicators (CIS) to standardise reporting in trials reporting a BWI outcome is needed.

Ethical approvals: No ethical approval was required to conduct this systematic review.

Declaration of interest: none

Author contributions: AY conceived the project; AD conducted all data extraction and analysis with assistance from FSJ; the manuscript was drafted by AD and AY with editorial input from FSJ and ATAJ.

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