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Original article

Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection?

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ABSTRACT

Objectives: The aim of this study was to determine whether assessment of wound infection differs when culture results from wound biopsy versus wound swab are available in clinical practice.
Methods: For 180 eligible patients, a swab and biopsy were taken from one wound during a regular appointment at a wound care facility in eastern Netherlands. Culture results from both methods were supplemented with clinical information and provided to a panel of six experts who independently assessed each wound as infect or not, separately for swab and biopsy. Assessments for biopsy and swab were compared for the complete expert panel, and for individual experts.
Results: The complete expert panel provided the same wound assessment based on (clinical information and) culture results from wound biopsy and wound swab in 158 of 180 wounds (87.8%, kappa 0.67). For individual experts, agreement between biopsy and swab varied between 77% and 96%. However, there were substantial differences between experts: the same assessment was provided in 62 (34.4%) to 76 (42.2%) wounds for swab and biopsy respectively.
Conclusions: Assessment of infection does not significantly differ when culture results from swabs or biopsies are available. The substantial variability between individual experts indicates non-uniformity in the way wounds are assessed. This complicates accurate detection of infection and comparability between studies using assessment of infection as reference standard. **M. Haalboom, Clin Microbiol Infect 2019;25:629.e7–629.e12**

Introduction

Wound infection is a major challenge in wound care. It is often defined as a complex phenomenon in which microorganisms outcompete the host immune system and therefore are able to invade, disseminate and cause further damage to the wound and its surrounding tissues [1]. Wound infection does not only delay wound healing; it can also cause hospitalization and, in the worst cases, sepsis leading to death. Early and accurate detection of wound infection enables the start of appropriate treatment in a timely manner and prevents further complications. On the other hand, the ability to accurately rule out infection prevents unnecessary use of antibiotics [2]. However, it is still a matter of debate how to detect wound infection, particularly in chronic wounds.

Traditionally, quantitative culture of wound biopsies was considered to be the reference standard with wound infection being defined as a load of $>10^5$ bacteria per gram of tissue [3]. However, this reference standard is rarely used in routine clinical practice and its value for the detection of infection has been

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questioned by many experts in recent years [3–7]. The presence of a certain 'critical level' of specific microorganisms in a wound is not necessarily related to wound infection, as certain combinations of microorganisms either mitigate or exacerbate effects because of factors such as toxin production, biofilm formation, and interspecies competition [1,3]. Therefore, wound care providers often rely on clinical signs and symptoms of wound infection such as pain, erythema, oedema, heat, and pus. These signs and symptoms are, however, not always clearly related to wound infection [8–10]. Especially in patients with arterial or venous insufficiency and diabetes, signs and symptoms of wound infection are often missing [2,7,11,12]. In addition, in many cases wound infection is at an advanced stage (e.g., cellulitis) by the time clinical signs and symptoms are clearly visible [8]. Therefore, diagnosis of wound infection is often based on a combination of clinical judgement and microbiological culture. The question remains as to what sampling method for microbiology should be used to appropriately aid the detection of wound infection. Some studies claim that wound biopsies yield the most accurate culture results, whilst others have shown that non-invasive wound swabs can provide similar results [2–5,10,13–18]. These studies have mainly focused on comparability of microbiological culture results, but what is missing is an answer to the question 'Does the use of different sampling methods result in a different assessment of wound infection in clinical practice?'. Therefore, we designed a study to compare the assessment of wound infection by different experts based on their own clinical judgment between the situation in which they were provided with culture results from wound biopsy versus wound swabs.

Methods

This study was designed as prospective multicentre study, performed in four different hospitals and one homecare facility in eastern Netherlands. The study was approved by the Twente Medical Ethics Committee and conducted conform the ethical guidelines of the Declaration of Helsinki. Between May 2013 and October 2015, patients with open chronic wounds (break through dermis and epidermis, existing for $\geq$3 weeks, without a clear tendency towards healing) were included after providing informed consent. Patients were eligible for participation if their wound was suitable for both wound biopsy and wound swab, thus excluding patients with a wound bed completely consisting of exposed bone or with a wound size <3 mm (diameter punch biopsy), malignant or fully necrotic wounds with no possibility of necrotectomy or completely dry wounds. In addition, we excluded patients who were hypersensitive to lidocaine when local anaesthesia was deemed necessary, and patients who used antibiotics in the 5 days prior to study participation. To prevent uncontrolled bleeding during or after wound biopsy, we excluded patients with a known high risk for uncontrolled bleeding. Patients using anticoagulation medication were only included if their international normalized ratio (INR) was $\leq$4.

Data and sample collection

For each patient, one wound was included. After removal of the dressing, the wound was assessed by an experienced ($\geq$10 years) wound care nurse or nurse practitioner for signs and symptoms of wound infection by filling in the Clinical Signs and Symptoms Checklist [9,19] (Table S1). At the bottom of the checklist, they had to provide their own assessment of wound: infected or not infected. Subsequently, the wound was cleansed with sterile saline and a sterile cotton swab (ESwab, Copan, Murrieta, CA, USA) was rotated with a small amount of pressure on a 1-cm^2 area of viable tissue in the wound. This technique, also known as the Levine technique [20], is believed to be the most accurate way of taking wound swabs for microbiological culture [4,14,17]. A wound tissue sample was taken from the same location in the wound, under sterile conditions (sterile gloves, cloth) with a 3-mm sterile punch biopsy. To prevent contamination, the skin surrounding the wound was cleaned with chlorhexidine digluconate 0.5% in alcohol prior to wound biopsy. If deemed necessary, the wound was anaesthetized by directly applying drops of lidocaine (HCL 20 mg/mL) to the wound bed. The wound tissue and swab were stored in a monitored refrigerator (4°C) until transportation to the microbiological laboratory. Both samples were inoculated onto Columbia agar with 5% sheep blood, chocolate agar, Columbia blood agar with nalidixic acid, 8-cystine-lactose-electrolyte deficient agar for 24–48 h at 36 ± 2°C and at 5% carbon dioxide for the detection of aerobic bacteria. Brain–heart infusion was inoculated with an incubation time of 14 days at 36 ± 2°C, ambient air. For the detection of anaerobic bacteria, CDC anaerobe 5% sheep blood agar with phenylethyl alcohol, Schaedler CNA agar with 5% sheep blood and Schaedler agar with nalidixic acid and vancomycin were used as media for 24–48 h at 36 ± 2°C in anaerobic jars. Isolated pathogens were identified using MALDI-TOF (Bruker, Billerica, MA, USA) [15].

Assessment of wound infection

A panel of 6 experts was asked to independently assess each wound as infected or not. The panel consisted of three microbiologists, with 5–35 years of experience in clinical microbiology and wound infection, and three clinicians of whom two were vascular surgeons (10 years' experience) and one nurse practitioner (14 years' experience in wound care). Each expert was provided with two separate files: one with culture results from wound biopsy for each wound separately and the other with culture results from wound swab. In addition to the culture results, information was provided about the age and sex of the patient, wound type, location and duration, and the presence of clinical signs and symptoms of wound infection as registered on the Clinical Signs and Symptoms Checklist at time of inclusion. To enable independent assessment, all wounds were ordered differently between the files for wound biopsy and wound swab and between experts.

Statistical analyses

Descriptive analyses (IBM SPSS Statistics, version 24) were used to analyse demographic data. Wound assessments based on (clinical judgement and) culture results from wound biopsy were compared to the assessments based on culture results from wound swabs by calculating observed agreement i.e. the percentage of wounds in which both sampling methods resulted in the same assessment. In addition, Cohen's kappa was calculated together with a 95% confidence interval (95% CI). We calculated these parameters for the assessments provided by the complete expert panel (defined as the assessment given by the majority of experts), as well as for the different professions (microbiologists versus clinicians) and individual experts. Sub-analyses were performed for the three most frequently cultured microorganisms and for the different wound types. Exploratory analyses were performed to compare assessment of wound infection based solely on clinical information versus the combination of clinical information and culture results. Therefore, we compared the assessment of wound infection as provided by the experienced wound care nurse or nurse practitioner at time of inclusion to the assessments provided by the expert panel. The assessments provided by the expert panel were based on the same clinical information as used by the wound care nurse or nurse practitioner, as they registered their observations and this information was included in the files provided to the

expert panel. However, the expert panel did have additional access to the culture results from wound swab and biopsy (separately).

Results

The wounds of 180 patients were assessed for infection by the expert panel. The characteristics of these patients are presented in Table 1.

Forty-one wounds (22.8%) were assessed as infected by the complete expert panel when culture results from wound biopsy were provided (in addition to clinical information) versus 47 (26.1%) when culture results from wound swab were provided.

Differences between wound biopsy and wound swab

In 87.8% of all wounds, the assessment of wound infection by the expert panel did not differ when provided with culture results from wound biopsy or wound swab (Table 2). Assessments did not significantly differ when specific microorganisms were cultured (Table S2) nor for different wound types (Table S3). Microbiologists had higher agreement between assessments for wound biopsy and wound swab than clinicians. When wound assessments were compared for each individual expert, observed agreement varied between 77.2% and 92.2%. Kappa varied between 0.54 and 0.87, with the exception of one expert (microbiologist 3) who had an extremely low kappa between both sampling methods due to a low number of wounds assessed as infected. Exclusion of this expert from the panel gave similar results: observed agreement and kappa were 84.4% and 0.68 (95% CI 0.57–0.78).

Differences between experts

All experts provided the same assessment in 62 (34.4%) to 76 (42.2%) wounds for swab and biopsy respectively. Within the professional groups, wound assessments differed significantly less. Clinicians assessed more wounds as infected than microbiologists did, irrespective of whether they were provided with culture results from wound biopsy or swab (Table 3). Kappa between microbiologists and clinicians was 0.39 and 0.23 for wound biopsy and swab respectively. Wound assessments did not only differ between professional groups, but also between individual experts (Fig. 1).

Exploratory analyses

Initially, 29 wounds were assessed as infected by the wound care nurse or nurse practitioner at the time patients were included in the study (Table 4). The expert panel assessed more wounds as infected when they were provided with both clinical information and culture results. In 32 (biopsy) and 34 (swab) wounds, the expert panel provided a different assessment than initially was provided based on clinical information alone at time of inclusion.

Discussion

This study assessed whether the availability of culture results from wound biopsies versus wound swabs would lead to a different assessment of wound infection in clinical practice. In our earlier published manuscript [15], we already demonstrated fair agreement in microbiological discovery for the two methods in the same study population. In this manuscript, we also demonstrated a fair observed agreement (87.8%) and kappa (0.67) between actual assessment of wound infection by an expert panel for the situation in which culture results from wound biopsies versus wound swabs were available. A limitation in the expert assessments was the inability to visually assess the wound, for instance by using wound pictures. However, this would have complicated independent assessments between swab and biopsy as experts would recognize wounds and provide consistent assessments over both methods, irrespective of other information provided.

In clinical practice, wounds are often assessed by one individual expert. Therefore, we assessed whether the assessment of wound infection differed for individual experts. Individual experts were quite consistent in their own assessments of wounds when they were provided with either culture results of wound swab or wound biopsy; observed agreement between the sampling methods varied

Table 1
Characteristics of the study population ($n = 180$)

		Frequency (%)	Median (range)
Sex	Male	115 (63.9)	
	Female	65 (36.1)	
Age in years			68.0 (28–95)
Wound type	Venous leg ulcer	19 (10.6)	
	Arterial leg ulcer	11 (6.1)	
	Diabetic foot ulcer	64 (35.6)	
	Pressure ulcer	17 (9.4)	
	Postoperative wounds	16 (8.9)	
	Traumatic ulcers	42 (23.3)	
	Other[a]	11 (6.1)	
Wound duration in weeks			14.1 (2.7–1021.7)
Clinical signs and symptoms of wound infection	Increased pain	15 (8.3)	
	Redness	46 (25.6)	
	Oedema	47 (26.1)	
	Warmth	31 (17.2)	
	Purulent exudate	19 (10.6)	
	Serous exudate	99 (55.0)	
	Delayed wound healing	110 (61.1)	
	Discoloration of granulation tissue	57 (31.7)	
	Friable granulation tissue	31 (17.2)	
	Pockets of granulation tissue	32 (17.8)	
	Odour	22 (12.2)	
	Damaged epithelium	24 (13.3)	
	Fever (related to the wound)	7 (3.9)	

[a] Other wound types consisted of wounds after split skin graft (SSG), bursitis, impetigo bullosa, erysipelas, erythema nodosum bulleus, removal of an infected continuous ambulatory peritoneal dialysis (CAPD) catheter, pyoderma gangrenosum, and mixed arterial and venous leg ulcers.

Table 2
Assessment of wound infection by the whole expert panel, and by the group of microbiologists and clinicians separately, when provided with culture results from wound biopsy versus wound swab

		Expert panel assessment with culture results of wound biopsy			Observed agreement	Kappa (95% CI)
		Infection	No infection	*Total*		
Expert panel assessment with culture results of wound swab	Infection	33	14	47	87.8%	0.67 (0.54 −0.80)
	No infection	8	125	133		
	Total	41	139	180		
		Microbiologists assessment with culture results of wound biopsy			Observed agreement	Kappa (95% CI)
		Infection	No infection	Total		
Microbiologists assessment with culture results of wound swab	Infection	24	4	28	94.4%	0.79 (0.67 − 0.92)
	No infection	6	146	152		
	Total	30	150	180		
		Clinicians assessment with culture results of wound biopsy			Observed agreement	Kappa (95% CI)
		Infection	No infection	Total		
Clinicians assessment with culture results of wound swab	Infection	62	18	80	78.9%	0.57 (0.45 −0.69)
	No infection	20	80	100		
	Total	82	98	180		

Table 3
Inter-rater variability between microbiologists and clinicians when culture results of wound biopsies or wound swabs are provided for the assessment of wound infection

		Microbiologists assessment with culture results from wound biopsy			Observed agreement	Kappa (95% CI)
		Infection	No infection	Total		
Clinicians assessment with culture results from wound biopsy	Infection	30	52	82	71.1%	0.39 (0.27–0.50)
	No infection	0	98	98		
	Total	30	150	180		
		Microbiologists assessment with culture results from wound swab			Observed agreement	Kappa (95% CI)
		Infection	No infection	Total		
Clinicians assessment with culture results from wound swab	Infection	22	58	80	64.4%	0.23 (0.11 −0.35)
	No infection	6	94	100		
	Total	28	152	180		

between 77% and 96% per expert. Kappa varied between 0.54 and 0.87 for each expert. These results suggest that both group-based and individual assessments of wound infection differ minimally between the situation in which culture results from wound swabs or wound biopsies are available. Therefore, we would recommend clinicians to initially use a wound swab in case microbiological culture results are deemed relevant because this is a non-invasive, relatively-easy-to-perform method to collect a sample for culturing. In addition, wound swabs pose a significantly lower burden on the patient in terms of fear and pain.

The question might be raised as to what the added value from culture results is for the assessment of wound infection. Although we did not design this study to answer this question, we performed exploratory analyses to compare the results from wound assessment based on clinical information alone (by an experienced wound care nurse/nurse practitioner at time of inclusion) to the assessment of the expert panel based on clinical information and culture results. We found that the availability of culture results does influence assessment of wound infection. However, these results have to be confirmed in a study designed to answer this question as assessments based on clinical information alone versus clinical information in addition to culture results were not carried out by the same persons in our study.

As demonstrated, variability in the assessment of wound infection between individual experts can be substantial. This variability was partly due to differences in profession. For instance, clinicians assessed substantially more wounds as infected than microbiologists did. Kappa between clinicians and microbiologists was therefore low; 0.39 and 0.23 respectively when wound biopsy and wound swab culture results were available. However, we still observed some variability between individual experts within the same profession. This indicates that there is no reference standard for the detection of wound infection, which complicates one of the important aims of wound care; to appropriately and timely detect, or rule out, wound infection [21,22]. It also complicates the comparability between scientific studies that use clinical judgement of wound infection as reference standard.

Several efforts have been made to help clinicians to diagnose wound infection in a more standardized manner, like the Clinical Signs and Symptoms Checklist of Gardner et al. [9,19], the Infectious Diseases Society of America (IDSA) clinical practice guideline for the diagnosis and treatment of diabetic foot infections, the criteria developed during an international expert consensus meeting in 2007 [23,24], and the criteria proposed by Cutting and White in 2004 [8]. However, there still is no universally accepted reference standard for diagnosing infection [2,25]. This not only leads to sub-

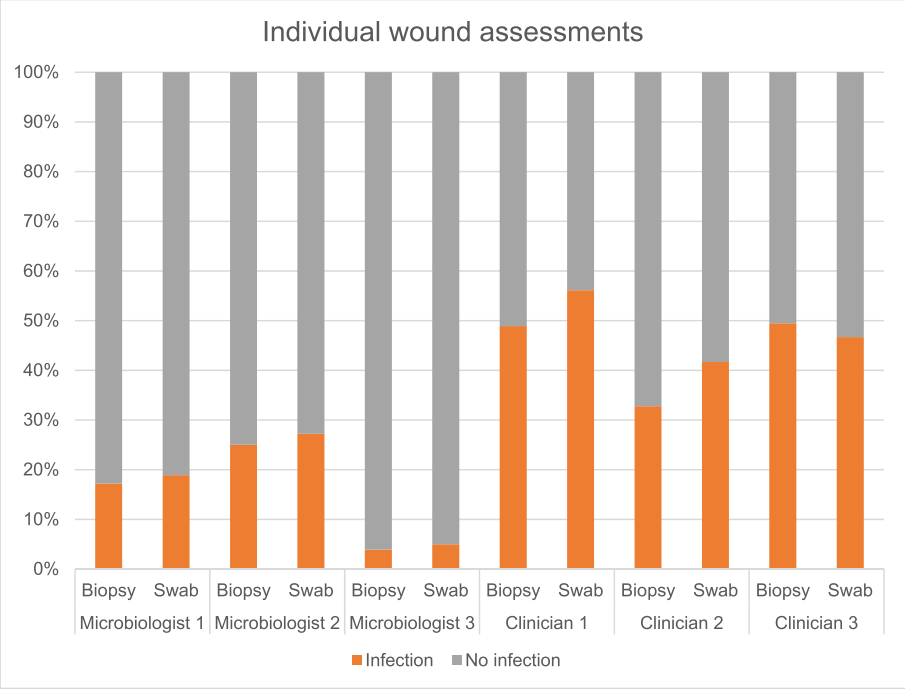

Fig. 1. Percentage of wounds assessed as infected or not by each individual expert.

Table 4
Assessment of wound infection solely based on clinical information versus the assessment of wound infection based on the combination of clinical information and culture results

		Assessment solely based on clinical information[a]		Total
		Infection	No infection	
Assessment based on clinical information and biopsy culture results[b]	Infection	19	22	41
	No infection	10	129	139
Assessment based on clinical information and swab culture results[b]	Infection	21	26	47
	No infection	8	125	133
	Total	29	151	

[a] Assessment of wound infection was provided by one experienced wound care nurse, nurse practitioner or physician at the time of inclusion.
[b] Assessment of wound infection was provided by the expert panel ($n = 6$).

optimal wound care practices, it also leads to the inappropriate use of antibiotic treatment which in turn favours development of antibiotic resistance [2,26]. Possible reasons for the non-uniformity in diagnosing infection are the subjectivity in assessment of clinical signs and symptoms of wound infection and the different manifestations of these signs and symptoms in patients with a variety of wound types and comorbidities [8,25]. One way to overcome these problems is to increase knowledge about the exact mechanisms behind wound infection and use this knowledge to find objective markers related to wound infection. In the past few years, several studies have shown promising results by targeting enzymes, proteins and metabolites related to the human immune response during wound infection [27]. These methods still need to be appropriately validated in clinical practice. Until then, one must be aware of the differences that exist between experts both for clinical practice and scientific research.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.08.012.

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