STUDY PROTOCOL

REVISED A scoping review protocol to identify clinical signs, symptoms and biomarkers indicative of biofilm presence in chronic wounds [version 2; peer review: 2 approved, 1 approved with reservations]

John D. Ivory[1-4], Akke Vellinga[2,5], James O'Gara[2,3,6], Georgina Gethin[1-3,7]

[1]School of Nursing & Midwifery, National University of Ireland, Galway, Galway, Galway, H91TK33, Ireland
[2]Alliance for Research & Innovation in Wounds (ARIW), National University of Ireland, Galway, Galway, Galway, H91TK33, Ireland
[3]CDA Diabetic Foot Disease: from PRevention to IMproved patient Outcomes (CDA DFD-PRIMO) Program, National University of Ireland, Galway, Galway, Galway, H91TK33, Ireland
[4]Irish Research Council, 3 Shelbourne Buildings, Crampton Avenue, Ballsbridge, D04 C2Y6, Ireland
[5]School of Medicine, National University of Ireland, Galway, Galway, Galway, H91TK33, Ireland
[6]Microbiology, School of Natural Sciences, National University of Ireland, Galway, Galway, Galway, H91TK33, Ireland
[7]School of Nursing and Midwifery, Monash University, Melbourne, Australia

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Abstract

Introduction: Wound healing is characterised by haemostatic, inflammatory, proliferative and remodelling phases. In the presence of comorbidities such as diabetes, healing can stall and chronic wounds may result. Infection is detrimental to these wounds and associated with poor outcomes. Wounds are contaminated with microbes and debris, and factors such as host resistance, bacterial virulence, species synergy and bioburden determine whether a wound will deteriorate to critically colonised/infected states. Biofilms are sessile microbial communities, exhibiting high-level antibiotic tolerance and resistance to host defences. Biofilm in critically colonised wounds can contribute to delayed healing. Little is known about clinical presentation and diagnosis of wound biofilms.
Objective: To identify from the literature clinical signs, symptoms and biomarkers that may indicate biofilm presence in chronic wounds.
Methods: This review will be guided by the Preferred Reporting Items for Systematic Reviews extension for Scoping Reviews (PRISMA-ScR), and the Joanna Briggs Institute Manual for Evidence Synthesis. Studies of any design in any language recruiting adult patients with venous, diabetic, pressure or mixed arterial-venous ulcers and reporting data on clinical signs/symptoms of biofilm are eligible. Searches of Medline, Embase, CINAHL, Cochrane Central and BASE will be conducted from inception to present. Reference scanning and contact with content experts will be employed. Title/abstract screening and

Open Peer Review

Approval Status ✓ ✓ ?

	1	2	3
version 2 (revision) 23 Nov 2021		✓ view	? view
version 1 08 Jul 2021	✓ view		

1. **Karen Ousey**, University of Huddersfield, Huddersfield, UK
2. **Gregory Schultz**, University of Florida, Gainesville, USA
3. **Luc Teot**, Montpellier University Hospital, Montpellier, France

Any reports and responses or comments on the article can be found at the end of the article.

full text selection will be executed by two reviewers independently. Discrepancies will be resolved by discussion between reviewers or through third party intervention. Data will be extracted by a single reviewer and verified by a second. Clinical signs and symptoms data will be presented in terms of study design, setting and participant demographic data.

Discussion: Understanding biofilm impact on chronic wounds is inconsistent and based largely on *in vitro* research. This work will consolidate clinical signs, symptoms and biomarkers of biofilm in chronic wounds reported in the literature.

Keywords

Chronic wound, Wound healing, Infection, Biofilm, Clinical signs and symptoms

Corresponding author: John D. Ivory (J.IVORY2@nuigalway.ie)

Author roles: Ivory JD: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Vellinga A**: Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **O'Gara J**: Conceptualization, Funding Acquisition, Investigation, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Gethin G**: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED **Amendments from Version 1**

One typographical error has been fixed in the inclusion criteria section: "any clinical any clinical signs, symptoms and/or biomarkers." has been changed to "any clinical signs, symptoms and/or biomarkers.

The sentence "Pay-per-view articles will not be included." has been removed from the exclusion criteria section.

The Medline search strategy was also updated.

Any further responses from the reviewers can be found at the end of the article

Introduction

Wound healing occurs via a complex sequence of events which, under normal circumstances, proceed in an orderly fashion through haemostatic, inflammatory, proliferative and remodelling/maturation phases to restore cutaneous integrity and barrier function. However, in the presence of complicating factors such as diabetes or chronic venous insufficiency, the healing process can break down and the wound becomes chronic, failing to heal in a timely manner[1,2]. There is a lack of consensus regarding the definition of chronic wounds and they have for example, been described as 'wounds that have not proceeded through an orderly and timely reparation to produce anatomic and functional integrity after 3 months', 'wounds that lack a 20–40% reduction in size after 2–4 weeks of optimal treatment or when there is not complete healing after 6 weeks', or simply as 'wounds that fail to proceed through the normal phases of wound healing in an orderly and timely manner'[2,3]. Typically, these wounds include but are not limited to venous, diabetic and pressure aetiologies[4]. Chronic wounds of mixed aetiologies were estimated to have a pooled prevalence of 2.21 per 1000 population in a 2019 meta-analysis of three studies, while a second meta-analysis from the same year including nine studies estimated the pooled prevalence of chronic leg ulcers to be 1.5 per 1000 population[5]. Chronic wounds are burdensome to the individual in terms of finances and quality of life, and to healthcare systems. Unhealed diabetic foot ulcers (DFU), venous leg ulcers (VLU) and pressure ulcers (PU) cost the United Kingdom National Health Service (NHS) approximately £4 billion in 2017–2018, or an average of £6305 per patient[6,7].

Infection commonly affects chronic wounds and is associated with poor clinical outcomes[8]. The risk of hospitalisation for patients with a DFU is increased by a factor of 50 while the risk of lower-extremity amputation is 150 times higher if their wounds become infected. Development of infection in chronic wounds is a complex process. Multiple factors including virulence of colonising organisms, synergy between multiple microbial species, bioburden and host resistance interact with each other and determine whether a wound will progress from a non-threatening, contaminated/colonized state through to critically colonized or infected states[9].

Bacteria can manifest in wounds as a free-floating planktonic phenotype or as a sessile biofilm phenotype[10]. Biofilms occur when microbial cells organise themselves into aggregates or communities encased in a self-produced polymeric matrix which typically attach to surfaces. Biofilms exhibit high levels of tolerance to antimicrobial agents and host defences[11]. When they form in critically colonized chronic wounds, healing stalls and the wound remains stuck in the inflammatory phase[12–16].

In 2017, a panel of specialists, chosen for their expertise in chronic wounds and biofilms, for their scholarly activity and publication record, issued a consensus document[17]. The document aimed to clarify the role of biofilms in clinical practice, help clinicians to recognize biofilms in chronic non-healing wounds and optimise patient management. A modified Delphi process was used to achieve consensus on a series of statements formulated to address issues in ten areas relevant to management of non-healing chronic wounds. Five-point likert scales of agreement (1 = disagree strongly – 5 = agree strongly) and ranking (1 = not important – 5 = most important) were used to score the statements. There was strong agreement (mean 4.0, standard deviation [SD] 0.82) that specific clinical signs and symptoms should be used to confirm presence of biofilm in the absence of diagnostic bedside tests. Clinical features, such as a recurring gelatinous material on the wound edge, have been proposed as surrogate markers of wound biofilm but there was weak agreement (mean 3.6, SD 1.5) that the clinical signs and symptoms that could indicate the presence of biofilm. Little is known about presentation and diagnosis of wound biofilms and knowledge of their characteristics is limited[18]. Generally, biofilms are difficult to diagnose and currently no guidelines exist to help clinicians and microbiologists in diagnosis and treatment[19].

In addition, little quantitative work has been done with respect to clinical signs and symptoms of biofilm in chronic wounds, especially in human patients, and existing published research is mainly observational rather than incorporating more rigorous study designs[12,17,18,20,21].

For these reasons we suspect that a rigorous systematic review with a focused research question and strict criteria with respect to eligible study design may be too exclusive and fail to answer the research question.

A scoping review methodology will therefore be employed to identify any associated clinical signs and symptoms thought to determine the presence of biofilm in chronic wounds.

The research question for the study is: what clinical signs, symptoms and biomarkers are proposed within the literature to determine the presence of biofilm in chronic wounds?

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) statement, and the Joanna Briggs Institute Manual for Evidence Synthesis will guide this work[22,23].

Inclusion criteria

Eligible participants will be adults (18 years +). Eligible wound aetiologies will be venous leg ulcers (VLU), diabetic foot ulcers (DFU), pressure ulcers (PU) and/or mixed arterial/venous leg ulcers (MAVLU), treated in any setting.

Databases will be searched from inception to present without limits on language. Study designs including but not limited to systematic reviews, randomized controlled trials (RCTs), controlled clinical trials, cohort studies, case series, case reports, letters to the editor with relevant data and editorials will be included. These articles must report any clinical signs, symptoms and/or biomarkers, validated or otherwise, thought to be associated with the presence of biofilm in chronic wounds.

Exclusion criteria

Patients with wounds resulting from burns, malignant fungating wounds, wounds secondary to conditions such as rheumatoid arthritis or pyoderma gangrenosum are ineligible for this study.

Search strategy

A search strategy will be developed in Medline, reviewed according to Peer Review of Electronic Search Strategies (PRESS) guidelines[24] and adapted for use in Embase, CINAHL, Cochrane Central and The Bielefeld Academic Search Engine (BASE).

Box 1. Search strategy for the Medline database

Medline
Run 23 Aug 21
1240 records

1. "wounds and injuries"/
2. Wound healing/
3. Skin ulcer/
4. Leg ulcer/
5. Varicose ulcer/
6. Foot ulcer/
7. Diabetic foot/
8. Diabetes Mellitus, Type2/co [Complications]
9. Diabetic neuropathies/
10. Peripheral nervous system diseases/
11. Peripheral arterial disease/
12. Pressure ulcer/
13. Wound infection/
14. Debridement/
15. Re-epithelialization/
16. (chronic adj3 ulcer*).tw.
17. (skin adj3 ulcer*).tw.
18. (vascular adj3 ulcer*).tw.
19. (varicose adj3 ulcer*).tw.
20. (venous adj3 ulcer*).tw.
21. (stasis adj3 ulcer*).tw.
22. (leg adj3 ulcer*).tw.
23. (foot adj3 ulcer*).tw.
24. (diabetic adj3 ulcer*).tw.
25. (neuropathic adj3 ulcer*).tw.
26. (isch?emic adj3 ulcer*).tw.
27. (neuro-isch?emic adj3 ulcer*).tw.
28. (neuroisch?emic adj3 ulcer*).tw.
29. (pressure adj3 ulcer*).tw.
30. (decubitus adj3 ulcer*).tw.
31. (arterial adj3 ulcer*).tw.
32. (mixed adj3 ulcer*).tw.
33. (care adj3 ulcer*).tw.
34. (heal* adj3 ulcer*).tw.
35. (nonheal* adj3 ulcer*).tw.
36. (non-heal* adj3 ulcer*).tw.
37. ("non heal*" adj3 ulcer*).tw.
38. (re-epitheliali* adj3 ulcer*).tw.
39. (reepitheliali* adj3 ulcer*).tw.
40. (surface adj3 ulcer*).tw.
41. ("lower extremit*" adj3 ulcer*).tw.
42. (lower-extremit* adj3 ulcer*).tw.
43. (debrid* adj3 ulcer*).tw.
44. (manag* adj3 ulcer*).tw.
45. (bed adj3 ulcer*).tw.
46. ("hard to heal" adj3 ulcer*).tw.
47. (hard-to-heal adj3 ulcer*).tw.
48. (infect* adj3 ulcer*).tw.
49. (chronic adj3 wound*).tw.
50. (skin adj3 wound*).tw.
51. (vascular adj3 wound*).tw.
52. (varicose adj3 wound*).tw.
53. (venous adj3 wound*).tw.
54. (stasis adj3 wound*).tw.
55. (leg adj3 wound*).tw.
56. (foot adj3 wound*).tw.
57. (diabetic adj3 wound*).tw.
58. (neuropathic adj3 wound*).tw.
59. (isch?emic adj3 wound*).tw.
60. (neuro-isch?emic adj3 wound*).tw.
61. (neuroisch?emic adj3 wound*).tw.
62. (pressure adj3 wound*).tw.
63. (decubitus adj3 wound*).tw.
64. (arterial adj3 wound*).tw.
65. (mixed adj3 wound*).tw.
66. (care adj3 wound*).tw.
67. (heal* adj3 wound*).tw.
68. (nonheal* adj3 wound*).tw.
69. (non-heal* adj3 wound*).tw.
70. ("non heal*" adj3 wound*).tw.
71. (re-epitheliali* adj3 wound*).tw.
72. (reepitheliali*adj3 wound*).tw.
73. (surface adj3 wound*).tw.
74. ("lower extremit*" adj3 wound*).tw.

75. (lower-extremit* adj3 wound*).tw.
76. (debrid* adj3 wound*).tw.
77. (manag* adj3 wound*).tw.
78. (bed* adj3 wound*).tw.
79. ("hard to heal" adj3 wound*).tw.
80. (hard-to-heal adj3 wound*).tw.
81. (infect* adj3 wound*).tw.
82. (diabetic adj3 foot).tw.
83. (diabetic adj3 feet).tw.
84. (pressure adj3 sore*).tw.
85. bedsore*.tw.
86. "bed sore*".tw.
87. bed-sore*.tw.
88. or/1-87
89. ("mixed etiolog*" adj3 ulcer*).tw.
90. ("mixed aetiolog*" adj3 ulcer*).tw.
91. ("mixed etiolog*" adj3 wound*).tw.
92. ("mixed aetiolog*" adj3 wound*).tw.
93. or/89-92
94. 88 or 93
95. Exp Biofilms/
96. biofilm*.tw.
97. "EPS matrix".tw.
98. "EPS matrices".tw.
99. "extracellular polymeric substance*".tw.
100. or/95-99
101. 94 AND 100
102. Exp Animals/ NOT (Humans/ and exp Animals/)
103. 101 NOT 102

This strategy will utilise controlled vocabulary and keywords associated with the concepts of biofilm and chronic wounds that are currently known to the authors and taken from eligible articles located through a preliminary search of PubMed and CINAHL. Boolean operators AND, OR and proximity operators will combine search terms in a manner that optimises efficiency of the strategy, ensuring that the maximum number of potentially eligible articles are captured, and that as much irrelevant material as possible is eliminated prior to screening.

Reference scanning. Reference lists of included articles will be scanned to locate subsequent, potentially relevant articles.

Content experts and organisations. Content experts and relevant organisations will be consulted to obtain information about unpublished or ongoing studies and where applicable, to request access to known but unavailable sources of evidence.

Search results will be exported to EndNote X9™ for storage and to RAYYAN[25] for screening against eligibility criteria.

Evidence screening and selection

Level 1 screening (title and abstract screening). Pairs of researchers will independently screen titles and abstracts for inclusion according to the pre-determined eligibility criteria. A single failed eligibility criterion will be considered sufficient to exclude a study from this review. Discrepancies will be resolved by discussion between researchers in a pair. In cases where disagreements cannot be resolved, a final decision on the discrepancy will be made by a third party.

The screening process will be pilot tested on a random sample of 50 titles and abstracts.

Level 2 screening (full text screening). Pairs of researchers will independently screen all located full text articles for inclusion into this review according to eligibility criteria. A single failed eligibility criterion will be considered sufficient to exclude a study from this review**.** Discrepancies will be resolved by discussion between researchers in a pair. In cases where disagreements cannot be resolved, a final decision on the discrepancy will be made by a third party.

This level of the screening process will be pilot tested on a random sample of 10 articles if available.

A chart of the screening and selection process detailing the flow of studies from the search to data extraction and including duplicate removal will be presented with the findings.

An appendix of excluded full -text articles will also be included along with reasons for exclusion.

Data extraction

A data extraction form will be developed *a priori* in Microsoft Excel (2016). The form will capture the following data:

- Study data including authorship, year of publication, article type/study design, country of origin, setting and study objective.
- Participant data including sample size, age, gender and wound aetiology.
- Study concept data i.e. reported clinical signs, symptoms and biomarkers of biofilm in chronic wounds.

Data will be extracted by a single researcher and verified by a second.

Critical appraisal/risk of bias assessment

The aim of this review is to collate a comprehensive list of signs, symptoms and biomarkers used to indicate presence of biofilm in chronic wounds regardless of their level of refinement. Relevant data may be found in articles that span the evidence hierarchy and range from systematic reviews to opinion/editorial

articles[21]. For these reasons, risk of bias assessment of included articles will not be necessary.

Data analysis, summary and presentation

Extracted data will be tabulated. Concept data will be presented in terms of country of origin, setting, study design, and in terms of participant data i.e. sample size, wound aetiology, age and gender. Data will be analysed with SPSS statistical package version 26. Demographic data will be presented descriptively in terms of mean and standard deviation or median and range.

Discussion

Little work regarding biofilms' impact on chronic wounds involving human subjects has been done and much of our clinical understanding is based on *in vitro* work. Clinician's knowledge of research data and of the importance of biofilms in the management of non-healing chronic wounds is inconsistent[17]. This review will for the first time, consolidate those signs, symptoms and biomarkers of biofilm in chronic wounds reported in the literature into one document which may serve to open an avenue for future clinical research in this area.

Dissemination

The findings of this scoping review will be published in a peer-reviewed medical journal.

The research team will also regularly update and disseminate project findings to key stakeholders, research colleagues, patient representatives and knowledge users.

Study status

The review has not yet initiated.

Data availability

No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ✔ ?

Version 2

Reviewer Report 18 February 2022

https://doi.org/10.21956/hrbopenres.14586.r31438

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Luc Teot
Department of Plastic and Reconstructive Surgery and Wound Healing, Montpellier University Hospital, Montpellier, France

The eligibility criteria no. 1 may avoid the inclusion of a group of articles where biofilm is not mentioned in the abstract, even if in the full text there is a part concerning biofilms. On the contrary "optimistic" colleagues pretending that more than 90% of the wounds are contaminated by a biofilm may be considered as an extrapolation on which it will be difficult to define a clear opinion. 'Biofilm' is a very fashionable word.

The inclusion criteria defines the usual chronic wounds but exclude most of the well known biofilm colonised wounds like the post trauma, post infection, malignant fungating wounds or post burn wounds.

Another potential criticism concerns the rejection of a rigorous systematic review, replacing it by a scoping review methodology which is not well defined. Is it a score like for local infection signs or is it a list of signs, symptoms and biomarkers? All together or dissociated? Which ponderation will be applied to each of them?

Is this research sponsored by a company and which one?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Wound healing

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 15 February 2022

https://doi.org/10.21956/hrbopenres.14586.r31436

Gregory Schultz
Department of Obstetrics and Gynecology, College of Medicine, University of Florida, Gainesville, FL, USA

The study proposal addresses an important issue for the field of chronic wound care, specifically, how can clinicians reliably assess if a chronic wound contains bacterial biofilm communities as part of the bacterial bioburden in the wound bed. The proposed methods and data analysis techniques are sufficiently described and adequate to address the key questions and objectives. The results of the research will be published in a peer-reviewed medical journal and will make a substantial contribution to the field of clinical care for chronic skin wounds. Funding is recommended with high level of enthusiasm.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: I am a co-inventor of a rapid, point-of-care detector that localizes bacterial biofilms in chronic wounds beds. This is not in conflict with assessing if a subset of clinical signs and symptoms can be used to also determine if biofilms are present in wounds.

Reviewer Expertise: bacterial biofilms in chronic wounds and point-of-care detectors for biofilm in wound beds

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 14 July 2021

https://doi.org/10.21956/hrbopenres.14477.r29794

Karen Ousey
Institute of Skin Integrity and Infection Prevention, School of Human and Health Sciences, University of Huddersfield, Huddersfield, UK

A clear well, written, and structured scoping review. The area of biofilms is relevant to clinical practice and will be of interest to the multi-disciplinary team. I am sure the outcome of the review will identify areas for future research. The rationale and objectives are described coherently and supported by an appropriate study design. The methods suggested will allow for replication. I am surprised the authors have decided to exclude pay to view papers as I am worried this will preclude a lot of papers that will be relevant to the review.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Skin integrity, wound infection

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 Aug 2021

John Ivory, National University of Ireland, Galway, Galway, Ireland

Dear Professor Ousey,

Many thanks for taking the time to review this protocol and for the valuable feedback.

We will change our eligibility criteria to admit pay-per-view articles.

Competing Interests: No competing interests were disclosed.

Comments on this article

Version 2

Author Response 26 Nov 2021

John Ivory, National University of Ireland, Galway, Galway, Ireland

The literature search strives to maximize comprehensiveness of returns while simultaneously screening out irrelevant material. It provides the evidence base for a review thus making it a foundational aspect whose integrity can influence the review's findings. Structured peer review of search strategies can locate errors and suggest improvements to improve sensitivity and specificity (McGowan 2016).
The version 1 strategy was peer reviewed in accordance with Peer Review of Electronic Search Strategies (PRESS) guidelines (McGowan 2016) by a librarian experienced in developing searches for systematic reviews, and revised according to her recommendations.

In addition, we decided to remove Scopus, Web of Science and Google scholar from the strategy for this review post-consultation.
Scopus carries more journals, but topics outside that of biomedicine are included and so its value is considered to be limited. In addition, its interface cannot manage searches with the level of complexity typical of systematic/scoping reviews.
Similarly, Web of Science has a limited search interface and the literature does not provide any evidence that either database adds to the results of a search strategy that includes Medline, Embase and CINAHL.

Google scholar has been shown to lack transparency with respect to scope or coverage. It fails to demonstrate comprehensiveness in terms of basic medical citations (e.g. the database will retrieve some but not all relevant PubMed records) and is not as comprehensive or precise as native interfaces. It demonstrates unreliability of advanced search functions and it lacks capability to search controlled vocabulary. There is no authority control for journal or author names. Some

retrieved material is not scholarly and there is a lack of transparency with respect to how scholarly is defined.
In addition, duplicate citations may be included in results and it is not current, with testing showing it to be about 6 months behind (Shultz 2007).

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