Periode	: Januari – Maret
Tahun	: 2024
Skema Penelitian	: Penelitian Dasar
Tema RIP Penelitian	: Kualitas Kesehatan, Penyakit Tropis, Gizi dan Kesehatan

LAPORAN AKHIR
PENELITIAN DASAR

Advancements in Managing Wound Biofilm: A Systematic Review and Meta-Analysis of Randomized Controlled Trials on Topical Modalities

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Fakultas Ilmu-Ilmu Kesehatan Program Studi Ilmu Keperawatan
Universitas Esa Unggul

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Lembar Pengesahan Laporan Akhir
Program Penelitian
Universitas Esa Unggul

1. Judul Kegiatan Penelitian : ADVANCEMENTS IN MANAGING WOUND BIOFILM: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS ON TOPICAL MODALITIES
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7. Periode/ Waktu Kegiatan : 1 Juni 2022 s/d 21 Desember 2023
8. Luaran yang Dihasilkan : Jurnal Internasional Bereputasi dan Berfaktor Dampak (Q1)
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IDENTITAS DAN URAIAN UMUM

1. Judul Penelitian : Advancements in Managing Wound Biofilm: A Systematic Review and Meta-analysis of Randomized Controlled Trials on Topical Modalities

2. Tim Peneliti

No	Nama	Jabatan	Bidang Keahlian	Instansi Asal	Alokasi Waktu (jam/minggu)
1	Adam Astrada	Ketua	Keperawatan Medikal Bedah	Universitas Esa Unggul	20 jam/ minggu
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3	Khoirul Rista Abidin	Anggota 2 (dosen)	Ilmu Biomedik	Politeknik ‘Aisyiyah Pontianak	4 jam/ minggu
4	Yusrika Fernandah	Anggota 3 (mahasiswa)	Ilmu Keperawatan	Universitas Esa Unggul	2 jam/ minggu

3. Objek Penelitian (jenis material yang akan diteliti dan segi penelitian):

   Objek pada penelitian ini adalah penelaahan sistematis disertai meta-analysis untuk mencari bukti terkait penggunaan terapi topikal dalam menangani masalah biofilm pada luka.

4. Masa Pelaksanaan

   Mulai : Juni tahun: 2022

   Berakhir : Desember tahun: 2023

5. Usulan Biaya: Tahun ke-1 : Rp -

6. Lokasi Penelitian (lab/studio/lapangan): Kantor.

7. Instansi lain yang terlibat (jika ada, dan uraikan apa kontribusinya)

   Politeknik ‘Aisyiyah Pontianak, dalam proses konsensus

8. Temuan yang ditargetkan (produk atau masukan untuk kebijakan)

   Hasil penelitian ini diharapkan dapat menemukan suatu bukti untuk penerapan *evidence-based practice* dalam penanganan masalah biofilm yang terdapat pada luka, selaku penyebab utama luka terinfeksi.

9. Kontribusi mendasar pada suatu bidang ilmu

   Penelitian ini didasari atas meningkatnya jumlah produk dan metode yang beredar di pasaran dengan klaim dapat membasmi biofilm, penyebab infeksi dan infeksi berulang, pada pasien dengan luka. Namun, masih belum ada penelitian yang berusaha menelaah bukti terkait klaim tersebut.

10. Jurnal ilmiah yang menjadi sasaran: Foot & Ankle Specialist

    Tahun : 2024

    Luaran HKI : -

DAFTAR ISI

DAFTAR TIM PELAKSANA DAN TUGAS

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BAB I

PENDAHULUAN

1. Latar Belakang

Biofilm has become a growing health concern since it contributes to 80% of human infections.(National Health Institute, 2002) Microorganisms living within a biofilm are up to 1,000 times more resistant to antibiotics than their planktonic forms.(Yan & Bassler, 2019) Biofilm attached to indwelled devices, such as implants, can cause early implant removal and surgical site infections. The absence of vascularization in implants creates a potential dead space that fosters microbial attachment and biofilm development. Biofilm-associated costs in wounds and surgery are estimated to reach several 3.3 billion US dollars in European countries.(Hrynyshyn et al., 2022) Moreover, a growing health threat by superbugs and multi-drug-resistant pathogens amplifies the need for therapeutic modalities to tackle biofilms, especially those associated with wounds.

2. Permasalahan

It is estimated that 78.2% of wounds present biofilms.(Malone et al., 2017) Since biofilm is ubiquitous in wounds, multi-modal approaches have been proposed and developed to combat this situation. Currently, more than 40 agents available on the market in various forms claim to have anti-biofilm effects.(Schwarzer et al., 2020) Yet, the evidence supporting this claim remains unclear.

3. Tujuan Penelitian

Therefore, this systematic review and meta-analysis aimed to provide pooled data on topical wound treatments such as cleansers, ointment, dressings, and therapeutic modalities and their immediate effects on biofilm elimination and wound healing in acute and chronic ulcers.

4. Manfaat Penelitian

5. Hasil yang Diharapkan

No	Jenis Luaran				Indikator Capaian		
	Kategori	Sub Kategori	Wajib	Tambahan	TS[1)]	TS+1	TS+2
1	Artikel ilmiah dimuat di jurnal[2)]	Internasional	√				
		Nasional terakreditasi			√		
		Nasional tidak terakreditasi					

2	Artikel ilmiah dimuat di prosiding[3)]	Internasional					
		Nasional					
3	*Invited speaker* dalam temu ilmiah[4)]	Internasional		√ (oral presentation)		√	
		Nasional					
4	Hak Kekayaan Intelektual (HKI)[6)]	Paten					
		Paten sederhana					
		Hak cipta					
		Merek dagang					
		Rahasia dagang					
		Desain produk industry					
		Indikasi geografis					
		Perlindungan varietas tanaman					
		Perlindungan topogarfi sirkuit terpadu					
5	Tehnologi tepat guna[7)]						
6	Model/Purwarupa/Desain/ Karya seni/ Rekayasa sosial[8)]						
7	Buku ajar (ISBN)						
8	Tingkat kesiapan teknologi (TKT)[10)]				1-2	3	

BAB II

RENSTRA DAN PETA JALAN PENELITIAN PERGURUAN TINGGI

Dalam penelitian ini, mengacu kepada RIP Universitas Esa Unggul yaitu Kualitas Kesehatan, Penyakit Tropis, Gizi & Obat-Obatan (*Health, Disease, Nutrition & Medicine).*

BAB III

TINJAUAN PUSTAKA DAN LANDASAN TEORI

1. Tinjauan Pustaka

Biofilm has become a growing health concern since it contributes to 80% of human infections.(National Health Institute, 2002) Microorganisms living within a biofilm are up to 1,000 times more resistant to antibiotics than their planktonic forms.(Yan & Bassler, 2019) Biofilm attached to indwelled devices, such as implants, can cause early implant removal and surgical site infections. The absence of vascularization in implants creates a potential dead space that fosters microbial attachment and biofilm development. Biofilm-associated costs in wounds and surgery are estimated to reach several 3.3 billion US dollars in European countries.(Hrynyshyn et al., 2022) Moreover, a growing health threat by superbugs and multi-drug-resistant pathogens amplifies the need for therapeutic modalities to tackle biofilms, especially those associated with wounds.

2. Tinjauan Teori

It is estimated that 78.2% of wounds present biofilms.(Malone et al., 2017) Since biofilm is ubiquitous in wounds, multi-modal approaches have been proposed and developed to combat this situation. Currently, more than 40 agents available on the market in various forms claim to have anti-biofilm effects.(Schwarzer et al., 2020) Yet, the evidence supporting this claim remains unclear. Therefore, this systematic review and meta-analysis aimed to provide pooled data on topical wound treatments such as cleansers, ointment, dressings, and therapeutic modalities and their immediate effects on biofilm elimination and wound healing in acute and chronic ulcers.

BAB IV
METODE PENELITIAN

1. Metode Penelitian

The search strategy was based on the research question of "To patients with acute or chronic ulcers (participants), do the topical wound treatments such as cleansers, ointment, dressings, and therapeutic modalities (intervention) provide anti-biofilm effects or eliminate biofilms compared to the standard of care or among the products (comparators)." The review protocol is reported according Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and registered in PROSPERO 2023 (ID: CRD42023407421), available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023407421

2. Waktu dan Tempat

Penelitian ini dilakukan di bulan Juni dan tahun 2022

3. Populasi dan Sampel

1.1 Eligibility Criteria

We aimed to find, assess and synthesize all randomized controlled trials, observational studies (all types), cohort (longitudinal) studies, or case-control studies containing all types of wounds (e.g., acute and chronic wounds, such as diabetic foot ulcers, venous ulcers, surgical site infections, etc.) or clinical studies and trials (e.g., randomized controlled trials, non-controlled interventional studies, observational studies involving human subjects). If they used the following interventions wound dressings, ointments, or techniques purposed to prevent, inhibit, or eliminate wound biofilms.

If biofilm elimination; absence or reduced biofilm structures as observed microscopically, and reduced wound size was reported, we included it as the primary outcome, while if complete wound closure; healed or unhealed or reduced signs of infection; erythema, oedema, warmth, pain, and dysfunction were reported we included them as the secondary outcomes. We included clinical studies conducted in all wound care settings, including in-patient and ambulatory facilities. Non-clinical studies (e.g., in vitro, product development involving subjects without wounds) were excluded.

1.2 Participants

Included participants were: all types of wounds (e.g., acute and chronic wounds, such as diabetic foot ulcers, venous ulcers, surgical site infections, etc.) or clinical studies and trials (e.g., randomized controlled trials, non-controlled interventional studies, observational studies involving human subjects). Participants were excluded if the articles were published in languages other than English or studies not related to wound biofilms.

1.3 Interventions

Studies were eligible if they evaluated: using wound dressing or ointment purposed to prevent, inhibit, or eliminate wound biofilms.

1.4 Comparators

We included: any topical wound interventions (e.g., topical agents or wound dressings, including normal saline, iodine, honey, etc.) deemed as the standard of care or among the products.

1.5 Outcomes

Studies with the following primary outcomes were included: biofilm elimination, absence or reduced biofilm structures observed microscopically, or reduced wound size. Secondary outcomes were: complete wound closure: healed or unhealed, or infections or signs of infection: erythema, oedema, warmth, pain, and dysfunction.

1.6 Setting

Studies were conducted in the following settings: all wound care settings, including in-patient and ambulatory facilities.

1.7 Study design

We included: randomized controlled trials, observational studies (all types), cohort (longitudinal) studies, cohort studies, or case-control studies. Only randomized controlled trials were included into the meta-analysis.

4. Teknik Sampel Penelitian

1.8 Search strategy

We included the following in the search string mesh or other subject terms, search filters, and text words. AA, a wound care expert, designed the search. The search was created with The Systematic Review Accelerator (https://pubmed.ncbi.nlm.nih.gov/32004673/).

Searches were done in PubMed, ClinicalTrials.gov, and Google Scholar with predefined keywords in MeSH terms. The dates searched were inception to 19th August 2022 (see Appendix 1).

We restricted our initial search to exclude certain publication types. Conference abstracts, theses, articles in press, books or book chapters, and reviews did not appear in our search results. Only articles published in English were included.

We manually checked the included studies' reference lists, performed a backward citation analysis, and had meta-analysis studies.

5. Teknik Analisis Data

1.9 Study screening and selection

1.9.1 Screening

Screening by title and abstract was conducted by AA and KRA independently. After identification and abstract screening, full texts were retrieved for the remaining articles. Two authors (AA and RAP) reviewed the full texts against the inclusion criteria. Discrepancies were resolved by consensus. Figure 1 shows the PRISMA flow diagram for the selection process.

1.9.2 Data extraction

We used a data extraction form for study characteristics and outcome data, piloted in Two studies in the review. Two study's authors (AA & RAP) extracted the following data from included studies:

- types: randomized controlled trials, observational studies (all types), cohort (longitudinal) studies, cohort studies, case-control studies
- methods: study authors, year, study design, duration of follow-up, setting
- participants: number of participants, wound type(s)
- interventions and comparators: type of intervention, method of delivery, how the intervention was provided, frequency, type of comparator, no treatment, placebo, usual care
- outcomes: biofilm elimination; absence or reduced biofilm structures as observed microscopically (primary outcomes) or reduced wound size, complete wound closure; healed or unhealed or infections/signs of infection: erythema, oedema, warmth, pain, and dysfunction; or bacterial load reduction (secondary outcomes). Table 1 describes the operational definition for each outcome.

Table 1. Operational definitions of the outcomes

Outcomes		Operational definition
Primary: anti-biofilm effects	Biofilm elimination (a)	Mean/median amount of biofilm eliminated from the whole wound bed, as observed quantitatively and objectively
	Presence of biofilm (b)	Absence or reduced biofilm structures as least 50%, as observed microscopically; dichotomous: present or absent
Secondary: wound healing and infection	Reduced wound size/score (c)	Mean/median of planar wound size or score reduction by the end of the study
	Complete wound closure (d)	Complete epithelization, dichotomous: healed or unhealed
	Infection/signs of infection (e)	Any presence of signs of infection: erythema, oedema, warmth, pain, and dysfunction; dichotomous: present or absent
	Bacterial load reduction (f)	Amounts of bacteria eliminated from the wound surface

1.9.3 Risk of Bias Assessment

Two review authors independently assessed the risk of bias for each study using the Cochrane Risk of Bias 2 tool.

1.10 Data analysis

The treatment/intervention effect was measured in Comprehensive Meta Analysis v3.7. The treatment/intervention effect was calculated using log odds ratios (LOD) for dichotomous outcomes. We undertook meta-analyses when at least two studies or comparisons reported the same outcome. We used a random effects model. The unit of analysis was individual patients. We did not contact investigators or study sponsors to provide missing data.

We used the τ^2 statistic to measure heterogeneity among the included trials. Publication bias / small studies effect was assessed using Funnel plot.

We did not perform subgroup analysis. Planned sensitivity analyses were: wounds receiving treatment for at least four weeks.

BAB V

HASIL PENELITIAN

A total of 1,964 records were identified by the systematic search, including 207 relevant searches in Google Scholar, grey literature, and articles found via reference tracing. Of those, 1,935 were excluded after the title and abstract screening and assessment of the eligibility criteria, as shown in Figure 1.

Of 28 articles, there are 13 RCTs (yielding 1,058 subjects), 3 case series, 8 interventional studies without controls, 3 observational studies, and 1 proof-of-concept interventional study. These studies include types of wound of post-surgical(Ceviker et al., 2015; Malizos et al., 2017), venous(Beele et al., 2010; Borges et al., 2018; Harding et al., 2016; Miller et al., 2010), diabetic foot ulcers (DFUs)(Astrada, Nakagami, Kashiwabara, et al., 2021; Malone et al., 2019, 2021; Rahma et al., 2022), leg ulcers(Albaugh et al., 2013; Miller et al., 2010; Patel et al., 2021; Yang et al., 2017), pressure ulcers(Koyanagi et al., 2021; Liu et al., 2019; Mori et al., 2019a), burns(Wattanaploy et al., 2017), and unspecified chronic and acute ulcers(Beele et al., 2010; De Francesco et al., 2022; Dryden et al., 2016; Gupta et al., 2019; Kim et al., 2018; Lenselink & Andriessen, 2011; D. Metcalf et al., 2016b; D. G. Metcalf & Bowler, 2020; Walker et al., 2015; Wolcott, 2015; Wu et al., 2022).

Of the RCTs, types of topical treatment sought for its anti-biofilm properties include 4 studies that used wound irrigation solution such as poly-hexamethylene biguanide (PHMB)(Borges et al., 2018; Ceviker et al., 2015; Romanelli et al., 2010) and sodium hypochlorite(Yang et al., 2017), 3 studies that used antibiotics(Kim et al., 2018; Malizos et al., 2017; Wolcott, 2015), 2 studies that used silver-based products(Beele et al., 2010; Miller et al., 2010), 4 studies that used gel-type ointments(Wattanaploy et al., 2017; Wolcott, 2015) and Iodosorb® (cadexomer iodine, Smith and Nephew, USA)(Malone et al., 2019; Miller et al., 2010), 1 study that used negative pressure wound therapy with instillation(Yang et al., 2017), and 2 studies that used the visual tool-guided wound cleansing(Astrada, Nakagami, Kashiwabara, et al., 2021; Rahma et al., 2022). The summary of each eligible articles is shown in Table 2.

1.11 Assessment of the Risk of Bias of the Included Studies

The risk of bias of all and individual RCTs are shown in Figures 2 and 3, respectively. All of the RCTs suggests high risk (70%) or some concern (30%) of bias (Figure 2), mostly due to the detection bias and randomization process (selection bias) (Figure 3). Studies by Borges, E *et al.* (2018) and Romanelli, M *et al* (2010) shows high risk of bias in all of the domains (Figure 3).

1.12 Anti-Biofilm Effects of the Treatments

As the first primary outcomes, the biofilm elimination is reported in one RCT by Astrada (2021)(Astrada, Nakagami, Kashiwabara, et al., 2021); three interventional

studies without controls by Lenselink *et al.* (2011)(Lenselink & Andriessen, 2011) and Metcalf (2016 & 2020)(D. Metcalf et al., 2016b; D. G. Metcalf & Bowler, 2020); and two observational studies by Mori *et al* (2019)(Mori et al., 2019a) and Koyanagi *et al* (2021)(Koyanagi et al., 2021) (Table 2). Since only one study was found for each primary outcome, the meta-analysis was not feasible.

Astrada et al. (2021) conducted a double-blinded randomized controlled trial in Indonesia, patients with diabetic foot ulcers (DFUs) were treated with standard of care (SOC) along with wound-blotting guided biofilm debridement and antimicrobial dressings. The study demonstrated significant anti-biofilm effects, with the intervention group showing a mean ± SD percentage of biofilm removed of 74.7% ± 5.33 at week 1, compared to 53.6% ± 5.42 in the control group ($p = 0.01$). By week 3, a significant reduction in the DMIST total score was observed in the intervention group (5.55 ± 0.33) compared to the control group (6.92 ± 0.33, $p < 0.01$), indicating improved wound healing outcomes.

In the study by Lenselink *et al.* (2011) the patients were treated with Suprasorb X dressings containing polyhexamethylene biguanide (PHMB). The study demonstrated 63% of the patients showing "good reduction" and 32% showing "moderate reduction" in biofilm presence. Additionally, two studies by Metcalf *et al.* (2016 & 2020) investigated the effectiveness of AQUACEL™ Ag^{+} (ConvaTec Ltd. UK), a hydrofiber wound dressing containing ionic silver, metal chelating agent, and surfactant in addition to SOC on stagnant or deteriorating chronic ulcers in 4 weeks of intervention shows. In their year 2020's study, they found that the 'unwanted' wound bed tissue, assumed as harbouring biofilm, changed from 92% to 40% (52% reduction). While in their 2016's study, they demonstrated 31% reduction of the wounds showing biofilm presence.

The observational studies by Mori et al. (2019) and Koyanagi *et al*. (2021) also highlighted the use of the wound-blotting method to evaluate biofilm elimination. In a cross-sectional and retrospective study conducted in Japan by Mori et al. (2019), two different studies evaluated the effectiveness of a biofilm-based wound care system in pressure ulcers. The intervention group showed significant anti-biofilm effects, with a higher proportion of biofilm removal (65.2% vs. 38.9%, $p = 0.009$) and an increased likelihood of 90-day wound healing (adjusted HR: 4.5, 95% CI: 1.3 - 15.0, $p = 0.015$) compared to the control group.

The second primary outcome, biofilm presence, is reported only in one RCT by Borges *et al.* (2018)(Borges et al., 2018) and one interventional study without control by Lenselink *at al* (2011)(Lenselink & Andriessen, 2011) (Table 2).

Borges et al. (2018) conducted an RCT in Brazil involving patients with venous leg ulcers. The intervention group received treatment with a PHMB cleansing solution, while the control group received a 0.9% NaCl solution. However, the study did not provide quantitative statistical findings on biofilm presence before and after treatment, thus the results regarding the effect of the intervention on biofilm presence is inconclusive.

Lenselink *et al.* (2011)(Lenselink & Andriessen, 2011), Metcalf *et al.* (2016 & 2020)(D. Metcalf et al., 2016b; D. G. Metcalf & Bowler, 2020), and Borges *et al.* (2018)(Borges et al., 2018) evaluated the primary outcomes only by surrogate or clinical cues such as the presence of necrotic tissue or visible gel-like materials found on wound surface (Table 2). Astrada *at al.* (2021), Mori *et al* (2019)(Mori et al., 2019a) and Koyanagi *et al.* (2021)(Koyanagi et al., 2021) used wound-blotting method to evaluate the primary outcomes (Table 2).

1.13 Wound Healing

For the secondary outcomes, the reduced wound size/score is reported in 6 RCTs(Astrada, Nakagami, Kashiwabara, et al., 2021; Beele et al., 2010; Miller et al., 2010; Rahma et al., 2022; Romanelli et al., 2010; Wolcott, 2015), in 6 case series or non-controlled interventional studies(De Francesco et al., 2022; Harding et al., 2016; Lenselink & Andriessen, 2011; Liu et al., 2019; D. Metcalf et al., 2016a; Walker et al., 2015), and in 2 observational studies(Albaugh et al., 2013; Mori et al., 2019b). However, the meta-analysis for this outcome could not be performed due to the poor data report(Romanelli et al., 2010) and data was ununifiable(Astrada, Nakagami, Kashiwabara, et al., 2021; Beele et al., 2010; Miller et al., 2010; Rahma et al., 2022; Wolcott, 2015).

An RCT conducted by Romanelli et al. (2010) in Italy assessed the efficacy of Prontosan® wound irrigation solution compared to normal saline in treating chronic leg ulcers. After a 4-week duration, no significant difference in wound size reduction was observed between the groups.

In a 3-arm RCT conducted by Wolcott *et al.* (2015) in the USA, the effectiveness of different treatments on acute and chronic ulcers was evaluated. Arm-1 represented the control group, receiving standard of care (SOC) management. Arm-2 received Lipogel (Sanguitec gel, USA) containing antibiofilm (hammamelitannin, xylitol, gallium) and antibiotics, and Arm-3 received SOC along with Lipogel containing personalized antimicrobial. The study included 15 subjects in each arm, and after 4 weeks of weekly debridement, Arm-3 demonstrated the highest improvement in wound size reduction (72%) compared to Arm-1 (47%) and Arm-2 (62%), with statistical significance.

Two multicenter RCTs investigated the silver-based products. Miller *et al.* (2010) conducted a multicenter RCT in Australia to compare the effects of nanocrystalline silver and cadexomer iodine treatments on lower leg ulcers, the majority of which were venous ulcers. After 2 weeks of treatment with antimicrobial dressings, the mean wound size reduction was 2.12 ± 2.94 cm^2 in the silver group and -0.22 ± 8.18 cm^2 in the iodine group. Beele *et al.* (2010) in Belgium and the Netherlands, investigated the efficacy of silver alginate/carboxymethylcellulose dressing compared to non-silver calcium alginate fiber dressing in venous leg and pressure

ulcers. After a 4-week duration, the intervention group showed a wound size reduction of 11.9%, whereas the control group exhibited an increase 31.7% (p<.05).

While, in the same category of silver-based products, interventional studies without control by Walker *et al.* (2015), Metcalf *et al.* (2016), and Harding *et al.* (2016) investigated the effectiveness of AQUACEL™ Ag^+ (ConvaTec Ltd. UK) in addition to SOC on stagnant or deteriorating chronic ulcers in 4 weeks of intervention. They found that a mean of wound reduction ranged 54% to 89%. Additionally, Francesco *et al.* (2022) investigated the used of cream containing SSD and hyaluronic acid in chronic wounds for 4 weeks and found 65% wound size reduction (mean reduction 4.85 cm^2) in 80% ± 4% of wounds, p<.05.

Two visual tool-guided RCTs were conducted by Astrada *et al.* (2021) and Rahma *et al.* (2022).(Rahma et al., 2022) Astrada *et al.* (2021)(Astrada, Nakagami, Kashiwabara, et al., 2021) conducted a double-blinded RCT in Indonesia to evaluate the impact of wound-blotting guided biofilm debridement and antimicrobial dressings on diabetic foot ulcers (DFUs) compared to standard of care (SOC). After a 3-week duration, there was no significant difference in absolute wound size reduction between the groups. However, the intervention group showed a significant reduction in the DMIST(Oe et al., 2020) total score by week 3 (p<.01), indicating improved wound characteristics. While Rahma *et al.* (2022) conducted an RCT in the UK to assess the efficacy of autofluorescence imaging-guided wound treatment using MolecuLight i:X compared to SOC in DFUs. After 12 weeks, the intervention group exhibited a median percentage wound reduction of 91.3% (IQR=47.3–100%), while the control group had a median reduction of 72.8% (IQR=22.3-100%).

The use of antibiotic-based is demonstrated in a within-group control case series conducted by Albaugh *et al.* (2013)(Albaugh et al., 2013). They employed the application of 1-gram vancomycin-impregnated cellulose dressing on chronic wounds for 3 weeks and showed mean ± SD = 24.6% ± 13.59 of wound size reduction in the intervention group while in the control group the size seems to increase by 14.5% ± 71.91 (p=.014).

Furthermore, a Chinese Medicine-based product by Liu *et al.* (2019) is presented in a non-randomized controlled study on 60 pressure ulcers, 30 each for intervention and control groups. They investigated the application of paste containing lyophilized Yunnan Baiyao (YB Group Co. Ltd., China) aqueous extract in addition to debridement and 20 – 30 minutes of infrared therapy. They found a significant difference in wound size reduction in the intervention group mean difference of 4.1 cm^2 after 3 weeks.

While for the complete wound closure, it is reported in 8 RCTs(Beele et al., 2010; Ceviker et al., 2015; Kim et al., 2018; Malizos et al., 2017; Malone et al., 2019;

Miller et al., 2010; Rahma et al., 2022; Wolcott, 2015), in 8 case series or non-controlled interventional studies(Dryden et al., 2016; Gupta et al., 2019; Harding et al., 2016; Lenselink & Andriessen, 2011; D. Metcalf et al., 2016a; D. G. Metcalf & Bowler, 2020; Patel et al., 2021; Walker et al., 2015), and in 1 observational study(Wu et al., 2022). Studies by Kim *et al.* (2018)(Kim et al., 2018) and Miller *et al.* (2010)(Miller et al., 2010) were not included into the analysis because the unreported number of events of the wounds reaching closure.

The six RCTs included into the pooled analysis yielding n=439, including the studies by Malizos *et al.* (2017)(Malizos et al., 2017), Malone *et al.* (2019)(Malone et al., 2019), Wolcott *et al.* (2015)(Wolcott, 2015), Beele *et al.* (2010)(Beele et al., 2010), Ceviker *et al.* (2015)(Ceviker et al., 2015), and Rahma *et al.* (2022)(Rahma et al., 2022).

Two antibiotic-based studies investigated this outcome was by Malizos *et al.* (2017) and Wolcott *et al.* (2015). Malizos *et al.* (2017) conducted a multi-center RCT across Italy, France, and Belgium, focusing on surgical site post-osteosynthesis for closed fractures. The intervention group (n=126) used the coating of osteosynthesis implants with antibiotic-loaded hydrogel (DAC®), while the control group (n=127) received un-coated osteosynthesis implants. After 2 weeks; wound closure in the intervention group was 96.0% (121 of 126), while in the control group was 94.5% (120 of 127), p=.76, no significant difference observed between groups. On the other hand, in a study by Wolcott *et al.* (2015), they found that groups receiving Lipogel in combination with antibiotics and antibiofilm shows 80% to 93% of wounds achieved closure, while the control group only 53%, although there was no estimation of statistical difference provided.

The silver-based product study by Beele *et al.* (2010) also showed there was not significant difference between groups in terms of wound closure.

Malone et al. (2019) conducted an RCT in Australia focusing on the effectiveness of 6-week vs. 2-week treatment with Iodosorb® (cadexomer iodine, Smith and Nephew, USA) on DFUs. The study involved 8 subjects in the intervention group and 10 subjects in the control group. After 12 weeks, the incidence of DFU complete closure was observed in 2 of 10 subjects (20%) in the intervention group, compared to 5 of 8 subjects (62.5%) in the control group. However, the difference between the groups was not statistically significant (p=.145).

Ceviker et al. (2015) conducted an open-label RCT in Turkey, focusing on coronary bypass post-surgical wounds. The intervention group (n=15) received 0.5% PHMB (Actolind) for irrigation and topical application (soaked gauze), while the control group (n=16) received Ringer Lactate Solution (Neoflex) for irrigation and topical application (soaked gauze). After a 3-week duration, the complete wound closure,

was 66.7% (10 of 15) in the intervention group and 43.8% (7 of 16) in the control group, with significant difference between groups.

The visual-guided wound intervention study by Rahma *et al.* (2022) shows that by week 12, wounds receiving the autofluorescence imaging-guided wound treatment had the number of wounds healed 13 of 29 (45%, 95% CI 26–64%), while in the control group 6 of 27 (22.2%, 95% CI 9–42%). There was no statistical significance estimated.

Figure 4 shows forest plot of the pooled random effects of 6RCTs for this outcome with log odds ratio (LOD) 0.03 (95% CI: -1.02 – 1.09). The between-study heterogeneity variance was estimated at τ^2=1.09 (SE: 1.10; Q=14.33, *p*=.014). Funnel plot of this outcome is shown in Figure 5.

1.14 Inflammation/Infection

The presence of inflammation/infection was reported in 4 RCTs(Beele et al., 2010; Ceviker et al., 2015; Malizos et al., 2017; Wattanaploy et al., 2017) and 1 non-controlled interventional study(De Francesco et al., 2022). Of 4 RCTs, 2 studies (Wattanaploy *et al.*, 2017 & Beele *et al.*, 2010) were not included into the meta-analysis due to reporting zero events of inflammation/infection in both groups, therefore giving no weight in the analysis. The pooled analysis yields n=284 from Malizos *et al.* (2017)(Malizos et al., 2017) and Ceviker *et al.* (2015)(Ceviker et al., 2015) studies.

The use of coating of osteosynthesis implants with antibiotic-loaded hydrogel (DAC®) in a study by Malizos *et al.* (2017) showed a significant difference between groups where the incidence of inflammation/infection was 0% (0 of 126) in the intervention group, whereas the control group exhibited an incidence of 4.7% (6 of 127).

The treatment of PHMB-based product as irrigation solution and topical application in the study by Ceviker *et al.* (2015) demonstrated that after a 52-week observation, the infection rate on coronary bypass post-surgical wounds, as identified by culture, was 40% in the intervention group and 37.5% in the control group. However, there was no significant difference between the groups (p=0.886).

The pooled estimate of this outcome for those studies is LOD -0.95 (95% CI: -3.54 – 1.64) while the between-study heterogeneity variance was estimated at τ^2=2.32 (Q=2.71, *p*=.10) (Figure 6).

1.15 Bioburden

The effect of bacterial load reduction was reported in 4 RCTs(Borges et al., 2018; Kim et al., 2018; Malone et al., 2019; Yang et al., 2017) and 5 case series or non-controlled interventional study(De Francesco et al., 2022; Dryden et al., 2016; Gupta et al., 2019; Malone et al., 2021; Patel et al., 2021). However, the pooled analysis of the RCTs was not feasible due to poor data report (Borges *et al.*, 2018 & Kim *at al.*, 2018)(Borges et al., 2018; Kim et al., 2018) and ununifiable outcomes (Yang *at al.*, 2017 & Malone *et al.*, 2019)(Malone et al., 2019; Yang et al., 2017). The five case series were conducted by Gupta *et al.* (2019)(Gupta et al., 2019), Patel *et al.* (2021)(Serena et al., 2021), Malone *et al.* (2021)(Malone et al., 2021), Dryden *et al.* (2016)(Dryden et al., 2016), and Francesco *at al.* (2022)(De Francesco et al., 2022).

Case series by Gupta *et al.* (2019)(Gupta et al., 2019) and Patel *et al.* (2021)(Serena et al., 2021) studied the used of topical bacteriophage therapy which isolated from different water sources (pond, rivers, and sewers). Using a convenient sample of 20 and 48 chronic non-healing wounds, respectively, they showed that after a 2-week post intervention all wounds became sterile.(Gupta et al., 2019; Patel et al., 2021)

Malone *et al.* (2021)(Malone et al., 2021) studied the application of surfactant gel Plurogel®in addition to the standard of care and showed that 7 of 10 wounds had a Log10 reduction in bioburden.

Dryden *et al.* (2016)(Dryden et al., 2016) studied the application of Surgihoney RO™ (Matoke Holdings Ltd., UK), a pure honey-derived gel with enhanced reactive oxygen species, on acute and chronic ulcers. After 4 weeks of application 98% of the wounds exhibited a bacterial load reduction as evaluated via semiquantitative culture, but there is no statistical significance estimation provided.

While Francesco *at al.* (2022)(De Francesco et al., 2022) utilized the topical application of hyaluronic acid in combination with silver sulfadiazine on complicated chronic wounds and showed a significant Log10 bacterial load reduction 4 weeks after the baseline.

BAB VI

PEMBAHASAN

This systematic review and meta-analysis aimed to elucidate the effectiveness of various interventions in targeting biofilms and their impact on wound healing outcomes on clinical studies. According to our review, the effect of any intervention aimed for biofilm elimination and complete biofilm's presence eradication could not be clarified at the present time due to lack of clinical trials available. However, we could estimate its pooled effect on the secondary outcomes: complete wound closure and presence of inflammation/infection. Still, we found that all the products claimed to have the anti-biofilm properties show no significant effect in achieving complete wound closure and reducing the inflammation/infection as compared to the control treatment.

Clinical trials we found involving techniques of visual-guided wound cleansing including wound-blotting guided debridement and autofluorescence imaging camera, silver-based products, PHMB dressing and irrigation solution, NPWT with instillation of sodium hypochloride, cadexomer iodine, and antibiotic-impregnated gels. One interesting approach is the use of topical bacteriophage cocktail studies by Gupta *et al.* (2019)(Gupta et al., 2019) and Patel *et al.* (2021)(Serena et al., 2021)in case series studies. Although after the treatment all the wound became sterile, this might suggest that the treatment might prevent the development of biofilm in the first place.

Problems with studies included is that there was lack of consensus on how to evaluate the biofilm objectively. Studies included in this review still rely on the conventional culture method or surrogate end-point such as clinical signs and symptoms. Studies by Beele *et al.* (2010) use clinical signs and symptoms to identify biofilm such as continuous pain, edema, warmth, moderate to heavy exudate, and the presence of slough at least 50% of the wound surface, foul odor, or necrotic plaques. Studies by Yang *et al.* (2017)(Yang et al., 2017), Miller *et al.* (2010)(Miller et al., 2010), Wolcott *et al.* (2015)(Wolcott, 2015), were also claiming the evaluation of intervention on the biofilm matrix. However, these studies fell short of presenting data regarding the objective evaluation of the biofilm's presence itself. Rather, they focused on colony forming unit count and exploring its influence on the wound healing process. Only studies by Borges *et al.* (2018)(Borges et al., 2018) and Malone *et al.* (2019 & 2021)(Malone et al., 2019, 2021) were reporting objective evaluation of biofilm using scanning electron microscopy, DNA sequencing and real-time quantitative polymerase chain reaction (qPCR). Yet this technique was used only to confirm the biofilm presence at the baseline, not used as a quantitative evaluation at the end of intervention.

The skill of wound care clinician seems the most important factors in the biofilm management. This may include the cleansing technique, ability to locate the highly

susceptible wound bed for the development of biofilm, exudate management, and antimicrobial selection, and adherence to the timely dressing change.

The use of visual-guided wound cleansing approach may offer solution at the clinician's best interest more objectively. Techniques such as the wound-blotting and autofluorescence-guided imaging may offers a promising approach for assessing biofilm presence and monitoring the effectiveness of interventions in real-time. Wound-blotting technique could visualize the wound surface biofilm by attaching a piece of nitrocellulose membrane on wounds for 10 seconds then stained by Alcian Blue to highlight parts of wound that still harbour biofilms. This technique has the sensitivity of 100% as shown in *in vivo* study.(Astrada, Nakagami, Minematsu, et al., 2021) An RCT by Astrada *et al.* (2021) and observational studies by Mori *et al.* (2019)(Mori et al., 2019a) and Koyanagi *et al*. (2021)(Koyanagi et al., 2021) shows that wound blotting could help clinicians to determine the effectiveness of the wound cleansing in real-time as well as improving wound healing. While in The Fluorescence imaging Assessment and Guidance (FLAAG) study, a multi-center diagnostic accuracy study by Le *et* al. (2022)(Le et al., 2021) on 350 patients with chronic wounds, shows that the autofluorescence imaging technique could detect $>10^4$ CFU/g in 82% of biopsied wound tissue which mostly missed by direct inspection of the clinical signs and symptoms. The study shows that this technique has a moderate sensitivity (61,0%) but with high specificity (84%).(Le et al., 2021) A study by Rahma *et al.* (2022)(Rahma et al., 2022) is the first RCT conducted for to evaluate this technique and but it is still as a pilot study. Regardless, the use of this technique could change 69% of treatment plans and influenced 85% of wound bed preparation, and improved overall 90% of patient care by 20 clinicians in those centers.(Le et al., 2021) Additionally, a study by Wu *et al.* (2022)(Wu et al., 2022) attempted to compare the both techniques i.e. wound-blotting and autofluorescence imaging, in predicting healing in chronic wounds in 90 days. They found that wound blotting shows a significantly strong correlation coefficient of Kendall's tau value = 0.563, $p<.001$ to complete wound healing, while MolecuLight i:X exhibited no significant association ($p=.184$). This indicates that wound blotting may be more beneficial for wound healing prognosis, because the wound blotting detects the actual biofilms, while the autofluorescence bacterial visualization detects both in planktonic and biofilm forms, but cannot distinguish between the two.(Astrada, Nakagami, Minematsu, et al., 2021) Future research is needed to focus on standardized methods for biofilm assessment and to assess the long-term effects of biofilm elimination on wound healing outcomes considering the clinical implications of biofilm elimination in improving patient well-being.

Limitations

There is high risk of bias in almost of clinical trials included in the meta-analysis. The main source of bias is the lack of consensus on how to objectively evaluate the biofilm.

There is also risk of selection bias because studies included into the pooled estimation did not distinguish types of modalities due to lack number of clinical trials eligible.

BAB VII
KESIMPULAN DAN SARAN

A. KESIMPULAN

This study indicates that there is currently inadequate evidence to support the claims of any topical treatments having an anti-biofilm effect on the healing of acute and chronic wounds. The skill of treating clinicians seem to offer the main contribution in eliminating biofilm and improving wound healing which can be optimized via the visual-guided wound cleansing such as wound blotting and autofluorescence imaging techniques. More rigorous clinical trial studies are needed to clarify the benefit of those techniques.

BAB VIII

BIAYA DAN JADWAL PENELITIAN

A. Anggaran Biaya

A. Jadwal Penelitian

No	Jenis Kegiatan	Bulan ke-											
		1	2	3	4	5	6	7	8	9	10	11	12
1													
2													
3													
4													
6													
7													
8	Pembuatan laporan												
9	Seminar												
10	Publikasi												

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Lampiran 1. Surat Pernyataan Ketua Pelaksana

Surat Pernyataan Ketua Pelaksana
Penelitian

Yang bertadatangan di bawah ini:

Nama	: Adam Astrada, Ns., MHS, CNS, DHSc., FACCWS
NIDN/NIK	: 1101059201
Fakultas/ Prodi	: Ilmu-Ilmu Kesehatan
Jabatan fungsional	: Lektor (200)

Dengan ini saya menyatakan bahwa proposal program penelitian yang diajukan dengan judul:

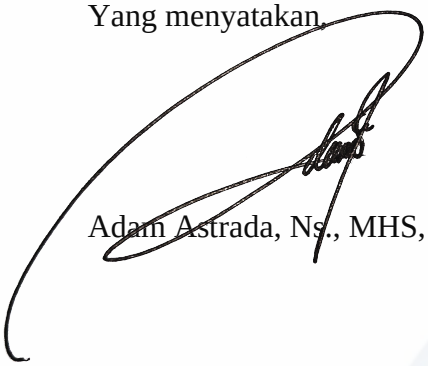
"Advancements in Managing Wound Biofilm: A Systematic Review and Meta-analysis of Randomized Controlled Trials on Topical Modalities"

Yang saya usulkan dalam skema penelitian mandiri tahun 2023 bersifat original dan belum pernah dibiayai oleh lembaga/ sumber dana lain.

Bilamana diketahui dikemudian hari adanya indikasi ketidakjujuran/ itikad kurang baik sebagaimana dimaksud di atas, maka kegiatan ini dibatalkan dan saya bersedia mengembalikan dana yang telah diterima kepada pihak Universitas Esa Unggul melalui LPPM.

Demikian pernyataan ini dibuat dengan sesumgguhnya dan dengan sebenar-benarnya.

Jakarta, 31 Mei 2022
Yang menyatakan,



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Lampiran 2. Biodata Pengusul dan Anggota

Biodata Pengusul