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GUIDELINES

Wound, Pressure Ulcer, and Burn Guidelines (2023)–2: Guidelines for the Diagnosis and Treatment of Pressure Ulcers, Third Edition

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ABSTRACT

Guidelines for the diagnosis and treatment of pressure ulcers, third edition, is a fully revised guidelines drafted by the Japanese Dermatological Association Wound/Pressure Ulcer/Burn Guidelines Drafting Committee. They were developed in a systematic and transparent manner with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the four clinical questions with meta-analyses, debridement, topical medication, dressings, and negative-pressure wound therapy were weakly recommended in the treatment of pressure ulcers. General information on diagnosis, prevention, assessment, and unconventional treatment of pressure ulcers was also provided.

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Contents

1 | Chapter 1 General Information

1.1 | Background of the Drafting of Guidelines for the Diagnosis and Treatment of Pressure Ulcers, Third Edition

Guidelines are documents systematically prepared to support medical experts and patients for making appropriate judgments in particular clinical situations. The Japanese Society of Pressure Ulcers (JSPU) published the Guidelines for the Prevention and Management of Pressure Ulcers in February 2009, which has undergone revisions leading to the fifth edition in 2022. JSPU guidelines were intended not solely for physicians, but for nurses, nutritionists, pharmacists, physical therapists, occupational therapists, and other health care professionals, and emphasized the prevention and care over the treatment. For dermatologists and dermatology nurses who treat the pressure ulcers for themselves, the guidelines for the diagnosis and treatment of pressure ulcers, supported by the Japanese Dermatological Association (JDA), were prepared mainly on the treatment. Both JSPU and JDA guidelines share the same goal: presenting evidence-based recommendations to support clinical decisions in the prevention, care, and treatment of pressure ulcers, serving as a tool to improve the quality of diagnosis and treatment of pressure ulcer and improving the care of pressure ulcers in Japan.

1.2 | Position of Guidelines for the Diagnosis and Treatment of Pressure Ulcers, Third Edition

The Wound/Pressure Ulcer/Burn Guidelines Drafting Committee was composed of members delegated by the board of directors of JDA. The committee held the start-up meeting on June 3, 2018 and the following face-to face or online meetings, and drafted six skin wound-related guidelines, including the guidelines for the diagnosis and treatment of pressure ulcers, third edition, by taking into consideration the opinions of the scientific committee and the board of directors of JDA. The present guidelines reflect the current standards for diagnosis and treatment of pressure ulcers in Japan. The factors, which may affect the diagnosis and treatment of pressure ulcers, are more diverse than the other skin ulcers; not only the patient's conditions but the related conditions of his home, families, care providers, and communities may deeply affect the decision in the treatment of pressure ulcers. The optimal treatment designed for individual patient is usually different, if partly, from that recommended in this guidelines. Discordance from the guidelines should not be used in legal disputes. Also, it should be noticed that these guidelines have been often quoted in lawsuits in spite of the intention of the guideline committee.

1.3 | Major Update in the Third Edition

- In order to make recommendations in a systematic and transparent manner, we developed the guidelines according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, GRADE Handbook, updated October 2013.
- A quantitative systematic review (meta-analysis) was carried out with respect to four clinical questions, namely, surgical debridement, topical medication, dressings, and negative-pressure wound therapy, which the committee members considered as clinically most important.
- For the convenience of readers, outline of pressure ulcer diagnosis and treatment appeared at the top of the guidelines, and the details appeared in the following pages.

1.4 | Financial Support

All expenses required for drafting the guidelines were provided by JDA. Financial or any form of supports were not provided by organizations, enterprises, or pharmaceutical companies.

1.5 | Conflicts of Interest

According to the JAMS Guidelines on COI Management in Medical Research (https://jams.med.or.jp/guideline/index.html) published by the Japanese Association of Medical Sciences in March 2017, the

drafting committee members disclosed COI in previous 3 years to the publishing of guidelines. COI of the following were self-reported by the members to the committee; (1) the committee members and their spouses, (2) the first-degree relatives of the committee members and those who share the household with the committee members, and (3) organizations or departments, which the members belong to.

1.6 | Literature Search

The systematic review team for each clinical question (CQ) carried out a preliminary search according to the Minds Handbook for clinical practice guideline development 2020. The final literature search was carried out by the Japan Medical Library Association.

- Database search: PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society.
- Publication period: Between January1980 and December 2020.

1.7 | Systematic Review Methods

Systematic reviews were carried out according to the Minds Manual for Guideline Development 2020 ver. 3.0, with its working templates.

1.7.1 | Evaluation of Studies

The studies retrieved in the literature search were analyzed their effects and certainty of evidence by systematic review teams. The effects, prepared in risk ratio or risk difference, and certainty (strength) of evidence, determined by limitation in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias, were summarized in body of evidence, and grouped by outcomes. Randomized trials and observational studies were summarized separately.

1.7.2 | Overall Evidence

The body of evidence integrated across outcomes and the certainty of evidence were unified in overall evidence. Then, risk of bias and indirectness of evidence were reevaluated, and inconsistency of results, imprecision, and publication bias were assessed. Certainty of evidence was classified, as appeared in Table 1.

1.7.3 | Quantitative Systematic Review (Meta-Analysis)

When the several studies revealed the similar design and high-degree similarity in their Population, Intervention, Comparison, Outcome (PICO), meta-analysis was carried out to integrate results of the studies quantitatively. The results of meta-analysis served as factors to determine the certainty of evidence.

TABLE 1 | Certainty of evidence.

A (Strong)	We are very confident that the true effect lies close to that of the estimate of the effect
B (Moderate)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C (Weak)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
D (Very weak)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1.7.4 | Preparation of Summary of Findings Table

For each CQ, the results of the systematic reviews, certainty of evidence, and the balance of favorable effects (benefits) / unfavorable effects (risks and burdens) were summarized in summary of findings table, and presented to guideline panels.

1.8 | Determining Direction and Strength of Recommendations by Guideline Panels

Guideline panels re-evaluated the summary of findings table based on the importance of outcomes and certainty of evidence. Direction and strength of recommendation were voted anonymously for one of the following options:

- Strong recommendation for intervention.
- Weak recommendation for intervention (proposal or conditional recommendation).
- Weak recommendation against intervention (proposal or conditional recommendation).
- Strong recommendation against intervention.

Delphi method for voting was adopted. The recommendation was determined by agreement of more than 80% of the vote. If agreement of more than 80% was not reached in three consecutive voting, the result of voting was regarded as "no recommendation," and the voting panels may not express any recommendations.

Immediately before voting on each CQ, the presence or absence of COI was reconfirmed for the panel members. The voting count appeared along with the recommendations.

1.9 | CQ Modification in Preparing the Guidelines

Any of the CQ were not modified in preparing the guidelines.

1.10 | Time Course of Drafting the Guidelines

The Wound/Pressure Ulcer/Burn Guidelines Drafting Committee held the start-up meeting on June 3, 2018 and the following face-to face or online meetings, and drafted six skin wound-related guidelines during the COVID-19 pandemic era. Guideline panels held the online meeting on November 2, 2021, and voted for the direction and strength of recommendation. The drafts were prepared by the committee members, and evaluated by the members of JDA.

1.11 | Drafting Committee Members of the Diagnosis and Treatment of Pressure Ulcers, Third Edition

Refer to drafting committee member list in Appendix 1. COI of the members appeared in Appendix 2.

1.12 | Public Review Prior to Publication

Prior to the publication, public opinions for the guidelines were invited from the members of JDA between 2022 and 2023. The guidelines were revised through the discussion in the committee.

1.13 | Promotion of the Guideline After Publication

The guidelines was presented in the General meeting of JDA, and published in the Japanese Journal of Dermatology. The online version of the guidelines is freely downloadable from the JDA website. The publication of its English version is following.

Wound/Pressure Ulcer/Burn Guidelines Drafting Committee (Pressure Ulcer Group)

	Name	Affiliation	Contributions
Chairman of the supervising committee	Takao TACHIBANA	Department of Dermatology, Hoshigaoka Medical Center	Supervision
Vice-chairman of the supervising committee	Minoru HASEGAWA	Department of Dermatology, University of Fukui	Supervision
Vice-chairman of the supervising committee	Manabu FUJIMOTO	Department of Dermatology, Osaka University	Supervision
Supervising members	Yoshihide ASANO	Department of Dermatology, Tohoku University	Supervision
	Takeshi NAKANISHI	Department of Dermatology, Meiji University of Integrative Medicine	Supervision
	Takeo MAEKAWA	Department of Dermatology, Jichi Medical University Saitama Medical Center	Supervision
	Sei-ichiro MOTEGI	Department of Dermatology, Gunma University	Supervision
	Yuichiro YOSHINO	Department of Dermatology, Japanese Red Cross Kumamoto Hospital	Supervision
Representative of the drafting committee	Hiroshi FUJIWARA	Department of Dermatology, Niigata University	Systematic review, preparing manuscript, guideline panels
Drafting committee	Ryokichi IRISAWA	Department of Dermatology, Tokyo Medical University	Systematic review, preparing manuscript, guideline panels
	Masaki OTSUKA	Department of Dermatology, Chutoen General Medical Center	Systematic review, preparing manuscript, guideline panels
	Tomoko KAKO	Department of Dermatology, Mie Prefectural General Medical Center	Systematic review, preparing manuscript, guideline panels
	Tatsuya KAJI	Department of Dermatology, Hiroshima City Hiroshima Citizens Hospital	Systematic review, preparing manuscript, guideline panels
	Takafumi KADONO	Department of Dermatology, St. Marianna University School of Medicine	Systematic review, preparing manuscript, guideline panels
	Monji KOGA	Department of Dermatology, Fukuoka University	Systematic review, preparing manuscript, guideline panels

	Name	Affiliation	Contributions
	Kuninori HIROSAKI	Department of Dermatology, Hokkaido Medical Center	Systematic review, preparing manuscript, guideline panels
	Yoko NOKITA	Nurse, St. Marianna University School of Medicine, WOC	Guideline panels

	Systematic review team	Guideline panels
CQ1	Tomoko KAKO, Kuninori HIROSAKI	Ryokichi IRISAWA, Masaki OTSUKA, Tatsuya KAJI, Takafumi KADONO, Monji KOGA, Hiroshi FUJIWARA, Yoko NOKITA
CQ2	Ryokichi IRISAWA, Monji KOGA	Masaki OTSUKA, Tomoko KAKO, Tatsuya KAJI, Takafumi KADONO, Kuninori HIROSAKI, Hiroshi FUJIWARA, Yoko NOKITA
CQ3	Masaki OTSUKA, Tatsuya KAJI	Ryokichi IRISAWA, Tomoko KAKO, Takafumi KADONO, Monji KOGA, Kuninori HIROSAKI, Hiroshi FUJIWARA, Yoko NOKITA
CQ4	Takafumi KADONO, Hiroshi FUJIWARA	Ryokichi IRISAWA, Masaki OTSUKA, Tomoko KAKO, Tatsuya KAJI, Monji KOGA, Kuninori HIROSAKI, Yoko NOKITA

1.14 | Plans for Revision

The present guidelines are scheduled to be revised in 5 years. If necessary, the update will be presented in JDA website.

1.15 | Evaluation of the Effects of Guidelines

After the publication, usage and the clinical effect of the guidelines will be surveyed.

1.16 | Summary of Recommendations

CQ1 Is surgical debridement recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform surgical debridement in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

CQ2 Is the use of topical medication recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to use cadexomer iodine, bucladesine sodium or povidone-iodine sugar in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

CQ3 Is the use of dressings recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to use hydrophilic fibers, hydrocolloids, hydrogels or polyurethane foams in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

CQ4 Is negative-pressure wound therapy recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform negative-pressure wound therapy in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

2 | Chapter 2 Outline of the Diagnosis and Treatment of Pressure Ulcers (Figures 1 and 2)

2.1 | Diagnosis of Pressure Ulcers (Details Appeared in 5.1)

Pressure ulcer is defined as a wound caused by skin surface pressure-related ischemic damage of the tissue through the reduction of capillary blood flow in the soft tissue between the bone and skin (refer to glossary of terms and concepts). For

diagnosis of early pressure ulcers, glass or finger compression methods are useful (5.1.1). Differential diagnoses may include reactive erythema, peripheral arterial diseases associated with diabetes mellitus, irritant dermatitis by stool or urine, cutaneous candidiasis, contact dermatitis, burn caused by electric scalpel, and chemical burn of disinfectants (5.1.2).

2.2 | Prevention of Pressure Ulcers, Care, Assessment of Risk Factors, and Pain Control (5.2)

Assessment scales of risk factors for pressure ulcer development include the Braden Scale, the K Scale, the K Scale for home care, the OH Scale, and the pressure ulcer risk assessment sheet (Japanese Ministry of Health, Labour and Welfare) (5.2.1). At risk of developing pressure ulcers, application of moisturizing cream should be considered (5.2.2), body pressure-dispersion mattress should be used, the body position should be periodically changed (5.2.3) and energy, protein, amino acids, vitamins, and trace elements should be supplied (5.2.4).

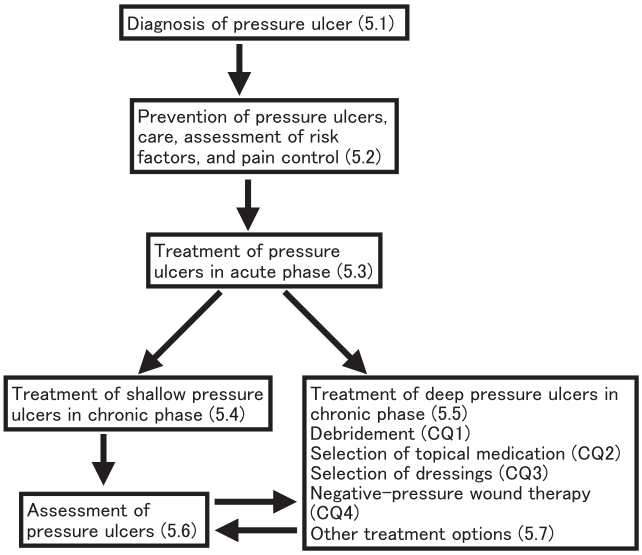


FIGURE 1 | The algorithm for diagnosis and treatment of pressure ulcers.

When the pressure ulcers were developed and the nutritional state is considered to be poor, it is recommended to consult with nutrition support team (NST) in hospital or nutrition specialists without delay (5.2.5).

Bathing is recommended for patients with pressure ulcers (5.2.6). To relieve the pain of pressure ulcers, anti-inflammatory or psychoactive medication, employing body pressure-dispersion mattress, and applying dressings are recommended (5.2.7).

Wheelchair seating and contact pressure checking are recommended for paraplegics and spinal cord injury patients with pressure ulcers (5.2.8).

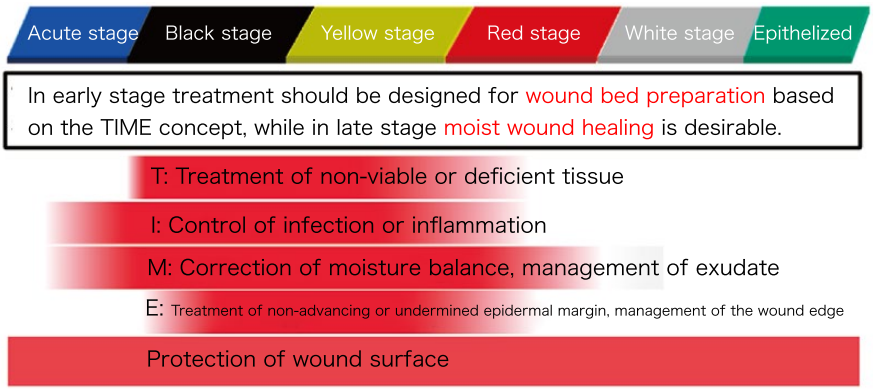
2.3 | Treatment of Acute Pressure Ulcers (5.3)

In the treatment of acute phase pressure ulcers the wound surface may be monitored applying a polyurethane film or translucent hydrocolloid dressings while decompressing. If topical medication be used, topical medication with lipids vehicle, such as petrolatum, zinc oxide, and dimethyl isopropyl azulene are recommended for protecting the wound surface, and silver sulfadiazine is recommended for prevention of infection. Topical medication with antibiotics may be applied for a short period (5.3.1).

If deep tissue injury (DTI) is clinically suspected, general body condition should be carefully monitored in addition to local decompression and monitoring the wound conditions, applying a polyurethane film or translucent hydrocolloid dressings (5.3.2). Imaging by magnetic resonance or ultrasound and blood examination should be performed (5.3.3).

2.4 | Treatment of Chronic Shallow Pressure Ulcers (5.4)

For chronic shallow pressure ulcers of Stage I or II, dressings, such as hydrocolloids, hydrogels, polyurethane foams and chitins, and topical medication with lipids vehicle, such as petroleum, zinc oxide, and dimethyl isopropyl azulene, are recommended for protecting the wound surface. Topical medication with antibiotics or granulation-promoting effect, such



Modified from Tachibana T, Miyachi Y: The mechanism of pressure ulcer treatment, Jpn J Cl in Nutr. 2003; 103(4): 353-356. Permission for reproduction and modification obtained from Ishiyaku Pub. Inc.

FIGURE 2 | The algorithm for treatment of deep pressure ulcers.

as bucladesine sodium and prostaglandin E1, is recommended. (5.4.1). Polyurethane films may be applied to uninfected and re-epithelizing shallow pressure ulcers (5.4.2).

2.5 | Treatment of Chronic Deep Pressure Ulcers (5.5, CQ1–CQ4)

For the treatment for deep pressure ulcers, wound bed preparation in the early phase based on TIME concept, and moist wound healing in the late phase should be considered. TIME is an acronym of "Tissue" (assessment and debridement of non-viable or necrotic tissue, biofilm or debris on the surface of the wound), "Infection/Inflammation" (assessment of the infection of wound, need for topical and/or systemic antibiotics, management of inflammation unrelated to infection), "Moisture imbalance" (assessment and management of wound exudate), and "Edge of wound" (assessment of non-advancing or undermined wound edge, and surrounded skin).

In order to improve in "T," tissue non-viable or deficient of TIME, surgical debridement of necrotic tissue is recommended as far as the patient's overall condition allows (CQ1). If the surgical debridement can not carry out, for some reason, application of cadexomer iodine, silver sulfadiazine, dextranomer, bromelain, or iodoform as a topical medication, or hydrogels as dressings, is recommended.

"I," infection or inflammation of TIME can be assessed by evaluation of the surface of the ulcer and surrounding skin (physical signs) with four cardinal signs of inflammation, that is, redness, heat, swelling and pain, systemic conditions, for example, fever, bacterial culture from the wound surface, and blood examination (5.5.1). Systemic administration of antibiotics is required not only with positive bacterial culture from the wound surface, but with inflammation in the surrounding skin, fever or increase in white blood cell count or C-reactive protein (5.5.2). Debridement of necrotic tissue is important for infection control. Other than the debridement, cadexomer iodine, silver sulfadiazine, povidone-iodine sugar, povidone-iodine gel, iodine ointment, or iodoform may be applied as topical medication (5.5.3), or silver-containing hydrophilic fibers or silver-containing polyurethane foams as dressings (5.5.4).

After the necrotic tissue is removed, topical medication (CQ2) or dressings (CQ3) may be applied in order to promote granulation and re-epithelization. "M," moisture imbalance of TIME, should be considered in choosing topical medication and dressings. Negative-pressure wound therapy may be effective in promoting granulation (CQ4).

If an edge of the ulcer is undermined, "E," edge of wound: non-advancing or undermined of TIME, povidone-iodine sugar, or tretinoin tocoferil may be effective (5.5.5). If not effective, surgical intervention should be considered (5.5.6).

Note: As of preparation of the guidelines, shipping of tretinoin tocoferil is suspended.

2.6 | Assessment of Pressure Ulcers (5.6)

For the assessment of pressure ulcers the DESIGN, DESIGN-R, DESIGN-R 2020, Pressure Sore Status Tool (PSST), and Pressure Ulcer Scale for Healing (PUSH) can be used.

2.7 | Other Treatment Options (5.7)

Surgical reconstruction with skin graft or skin flaps may be effective for pressure ulcers of Stage III or VI, however, indication of the surgery should be evaluated carefully. Infection control and surgical and/or chemical debridement should be performed in advance (5.7.1).

Topical application techniques of growth factors and autologous blood-borne cells have been developed (5.7.2).

Although not widely used in Japan, efficacy of hydrotherapy, infrared, visible light or ultraviolet light therapy, low-power LASER therapy, hyperbaric oxygen therapy, and electric stimulation therapy have been reported (5.7.3).

Indication of so-called "wrap therapy" requires a special attention. As the users are liable for the application of materials, such as kitchen cling film wrap, not intended for medical use, consent must be obtained from the patient and his family prior to start so-called "wrap therapy" (5.7.4).

3 | Chapter 3 Clinical Questions (CQs) and Recommendations

CQ1 Is surgical debridement recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence	voting count
We propose to perform surgical debridement in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak	7/7

3.1 | Background

Skin ulcer treatment has advanced with the development of new dressings and topical medication, but the surgical interventions for pressure ulcers of Stage III or IV, for example, debridement, reconstruction surgery with skin graft or flaps, may be required, occasionally. Surgical debridement is a procedure to remove necrotic or infected tissues with scalpels, electric scalpels or scissors. Recently, new medical devices for safe and accurate debridement, for example, hydraulic knife, ultrasonic equipment, have been developed.

3.2 | Objectives

In order to assess the efficacy of surgical debridement for pressure ulcers of Stage III or IV, a systematic review was carried out.

3.3 | Results

Two randomized controlled trials (RCT) [1, 2] of surgical debridement for pressure ulcers were retrieved.

Meta-analysis of these two reports revealed that the cure rate was slightly higher in the intervention group, although the difference was not significant with risk ratio: 1.07, 95% confidence interval: 0.88–1.30.

In the retrieved RCT, the cure rate of pressure ulcers was 100% in the intervention group and 90.3% in the control group; the difference was not significant, statistically. The incidence of adverse events was reported in one RCT [1]; the incidence of infection was lower in the intervention group. The healing speed (in days by Kaplan–Meier survival analysis) was reported in one RCT [2], and the pressure ulcers in control group, without surgical debridement, healed quicker.

In one RCT [2] the number of participants was small with a few dropout cases, and risk of bias was high. In the other report [1] because of the problems in randomization and blinding, risk of bias was high.

Based on these results, we propose to perform surgical debridement in the treatment of Stage III and Stage IV pressure ulcers with weak in strength of recommendation.

3.4 | Precautions for Clinical Use

We could not find a statistically significant difference in cure rate of Stage III or Stage IV pressure ulcers between the surgical debridement group and the control group. It may suggest that we can expect of the similar healing of pressure ulcers in with or without surgical debridement as far as the general and nutritional conditions of patients are preserved.

3.5 | Possibility of Future Research

In Piaggesi's report [1], the healing time after the surgical debridement was shorter than the control group. In Michailidis' report [2], the healing speed was evaluated after the randomization. The future randomized controlled trials to analyze overall healing time and incidence of adverse events may disclose a clearer answer for this CQ.

CQ2 Is the use of topical medication recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence	voting count
We propose to use cadexomer iodine, bucladesine sodium, or povidone-iodine sugar in the treatment of Stage III and Stage IV pressure ulcers.	Weak	Very weak	7/7

3.6 | Background

A wide range of topical medication for the treatment of pressure ulcers is available in Japan in comparison with in Europe or the United States. Moist wound healing is an important concept in the treatment of pressure ulcers though out all stages. With a precise choice of vehicles of topical medication with their water absorption properties, the optimal control of moisture condition can be achieved. Also, topical medication with antibiotic effects can control infectious conditions. In the late stage of treatment those with promoting the granulation or re-epithelization effects are useful. Although we consider that a proper topical medication with its chemicals and vehicles is useful in the treatment of pressure ulcers, the efficacy is remained to be clarified scientifically.

3.7 | Objectives

In order to assess the efficacy of topical medication for pressure ulcers of Stage III or IV, systematic reviews were carried out.

3.8 | Results

Systematic reviews of randomized controlled trials (RCT) were carried out to assess the efficacy of topical medication in the treatment of pressure ulcers of Stage III or IV. Three topical medication, cadexomer iodine (five RCT [3–7]), bucladesine sodium (two RCT [8, 9]), and povidone-iodine sugar (two RCT [10, 11]) were available for analyses of the cure rate or reduction rate of pressure ulcers.

Five RCT reported the efficacy of cadexomer iodine in the treatment of pressure ulcers [3–7]. Cure rate was analyzed in four RCT [3, 5–7]. 50% reduction rate was analyzed in four RCT [3–6].

The report by Moberg [3] compared cadexomer iodine with the treatment, composed by physiological saline dressing, enzyme-based debriding agents, and non-adhesive gauze dressing. In their report Stage II pressure ulcers were also included. The report by Anzai [4] compared cadexomer iodine with a vehicle control (dextrin polymer); Stage II pressure ulcers were also included. The report by Ishibashi [5] compared cadexomer iodine with dextranomer as a control; Stage II pressure ulcers were also included. The report by Kukita [6] compared cadexomer iodine with Elase-C, a chloromycetin-containing fibrinolysin, as a control; Stage II pressure ulcers were also included. The report by Raju [7] compared cadexomer iodine with the treatment, composed by physiological saline and absorbent cotton/gauze. Skin ulcers other than pressure ulcers were included. Furthermore, the stages of pressure ulcers were not clearly described. Meta-analysis of these four reports revealed that the cure rate was significantly higher in the cadexomer iodine group, with risk ratio: 2.48, 95% confidence interval: 1.63–3.78. 50% reduction rate was also significantly higher in the cadexomer iodine group, with risk ratio: 1.57, 95% confidence interval: 1.22–2.03.

Two RCT [8, 9] reported the efficacy of bucladesine sodium in the treatment of pressure. The report by Niimura (1990) [8] compared bucladesine sodium with a vehicle control, and Niimura (1991) [9] compared bucladesine sodium with lysozyme chloride ointment. Stage II pressure ulcers and skin ulcers other than pressure ulcers were also included. The reduction rate of size of the ulcers was significantly higher with bucladesine sodium in Niimura (1990) [8], but not in Niimura (1991) [9]. Meta-analysis of these two reports revealed that the reduction rate was significantly higher in the bucladesine sodium group, with risk ratio: 17.20, 95% confidence interval: 15.64–18.77.

Two RCT [10, 11] reported the efficacy of povidone-iodine sugar in the treatment of pressure. The report by Imamura [10] compared povidone-iodine sugar with lysozyme chloride ointment; Stage II pressure ulcers were also included. The report by KT-136 Skin Ulcers Comparative Study Group [11] compared povidone-iodine sugar with calf blood extract; Stage II pressure ulcers were also included. In the two reports a significant difference in the cure rate, but not in the 50% reduction rate was disclosed. Meta-analysis of these two reports revealed that reduction rate with risk ratio: 1.41, 95% confidence interval: 0.74–2.70, and 50% reduction rate with risk ratio: 1.40, 95% confidence interval: 1.00–1.97. They were significantly different between the povidone-iodine sugar and control.

3.9 | Further Information

A wide range of topical medication for the treatment of pressure ulcers is available in Japan in comparison with in Europe or the United States, and resulted in a different strategy in the treatment of pressure ulcers in Japan. Preparing the guidelines for the diagnosis and treatment of pressure ulcers, third edition, the drafting committee established the subject as pressure ulcers of Stage III or IV, the control as those treated without topical medication, and outcomes as cure rate or reduction rate of pressure ulcers. Only RCT were selected in the systematic review. Excluded were topical medication with only one RCT, studies without the cure rate or reduction rates in numerical values, studies in which topical medication served as a control and studies with topical medication unavailable in Japan, such as phenytoin and medical honey. Povidone-iodine solution was excluded because it aims not healing of pressure ulcers but disinfection [12–47]. Three Cochrane Database of Systematic Reviews [48–50] concerned with topical medication in the treatment of pressure ulcers, however, none of them were with topical medication available in Japan. The incidence of adverse events related to topical medication was small in all studies, and serious adverse events were not reported.

The cure rate and 50% reduction rate were adapted as an outcome for cadexomer iodine. A meta-analysis with four RCT of cadexomer iodine revealed a significantly high cure rate in cadexomer iodine groups. However, Morberg's study [3] included Stage II pressure ulcers, and its control treatment, consisted of physiological saline, non-adhesive gauze, and enzyme ointments, which are not available in Japan (suspicion of indirectness of evidence). The reports of Ishibashi [5] and Kukita [6] included Stage II pressure ulcers, and topical medication was used in the control groups (suspicion of Indirectness of evidence). The subjects of the report of Raju [7] included diabetic foot ulcers and venous leg ulcers in addition to pressure ulcers (indirectness of evidence). Its certainty of evidence was very weak, because of the suspicion of risk of bias and suspicion of publication bias. The guideline panels proposed to use cadexomer iodine in the treatment of Stage III or Stage IV pressure ulcers.

A meta-analysis with four RCT, Morberg [3], Ishibashi [5], Kukita [6], and Anzai [4], of cadexomer iodine revealed a significantly higher 50% reduction rate than controls. However, the report of Anzai [4] compared povidone-iodine sugar with dextrin polymer; shallow pressure ulcers were also included (suspicion of indirectness of evidence). Its certainty of evidence was very weak because of the suspicion of risk of bias and suspicion of publication.

The reduction rate was adapted as an outcome for bucladesine sodium. A meta-analysis with two RCT [8, 9] of bucladesine sodium revealed a significantly high reduction rate in bucladesine sodium groups. However, the reports of Niimura [8] and Niimura [9] included Stage II pressure ulcers. Niimura [8] used vehicle, and Niimura [9] used lysozyme chloride ointment as controls (suspicion of indirectness of evidence). Its certainty of evidence was very weak because of the suspicion of risk of bias, suspicion of imprecision, and suspicion of publication bias. The guideline panels proposed to use bucladesine sodium in the treatment of Stage III or Stage IV pressure ulcers.

The cure rate and 50% reduction rate were adapted as outcomes for povidone-iodine sugar. A meta-analysis with two RCT [10, 11] of povidone-iodine sugar did not reveal a significant difference in cure rate or 50% reduction rate between povidone-iodine sugar and control. The reports of both Imamura [10] and KT136 skin ulcer comparative study [11] included Stage II pressure ulcers. Its certainty of evidence was very weak because of the suspicion of risk of bias, suspicion of imprecision and suspicion of publication bias. The guideline panels proposed to use povidone-iodine sugar in the treatment of Stage III or Stage IV pressure ulcers.

The recommendations of either topical medication could not reach the strong recommendation, although cadexomer iodine showed the high cure rate with risk ratio: 2.48, 95% confidence interval: 1.63–3.78, and bucladesine sodium showed the high reduction rate with risk ratio: 17.2, 95% confidence interval: 15.64–18.77. Following factors contributed the very weak certainty of evidence. Most of the retrieved RCT were sponsored by pharmaceutical companies in Japan, included Stage II pressure ulcers, and used vehicles or conventional topical medication as a control (indirectness of evidence). Blinding was difficult, and many participants were missed with death or referral (risk of bias). Debridement was often incomplete.

3.10 | Precautions for Clinical Use

Ideal wound healing is achieved through the proper transition of inflammatory, proliferative and remodeling phases. Discourse from this process results in delayed healing of chronic skin ulcers. Moist wound healing is important in all of the three phases. Wound bed preparation is especially important in the transition from inflammatory phase to proliferative phase. An appropriate selection of topical medication, with its pharmaceutical effects and characteristics its vehicle, contributes to the wound bed preparation. Evaluation of wounds in TIME concept is useful in practice of wound treatment; namely, T, tissue non-viable or deficient, I, infection or inflammation, M, moisture imbalance, and E, edge of wound [51]. For "T," surgical or chemical debridement is the mainstay, however, autolysis of necrotic tissue accelerated with moisturizing condition is also important. For "I," under critical colonization, topical medication with antibacterial effect is desirable. For "M," an excessive amount of exudate, which contains inflammatory cytokines, should be removed properly. On the other hand, under the dry condition topical medication with moisture-removal properties should be avoided in order to maintain the activities of protease and various growth factors. For "E," topical medication with undermine-closing capacity should be applied.

The pharmaceutical effects of topical medication are mainly antibacterial or promoting the proliferation of cells. In order to achieve inflammation and infection control, cadexomer iodine, silver sulfadiazine, povidone-iodine gel, povidone-iodine sugar, iodine ointment, or iodoform, can be applied. To promote the granulation, trafermin, tretinoin tocoferil, bucladesine sodium, and prostaglandin E1 can be applied.

The vehicles of topical medication should be carefully selected considering the moisture and edema of wound surface. Conventional vehicles, such as lipids, emulsifiers, and polyethylene glycols (macrogols) and new-generation vehicles, such as hydrophilic polymers are available. Lipids are water-repellent and protects the wound surface, however, they do not directly moisten the wound surface. Emulsifiers can moisten the wound surface and can induce autolysis of necrotic tissues. Polyethylene glycols can absorb excess moisture from the wound surface, and hydrophilic polymers can absorb a bigger amount of excess moisture.

Selection of topical medication for pressure ulcers of Stage III or Stage IV lacking appropriate granulation.

- Pressure ulcers with necrotic tissue.

Cadexomer iodine, dextranomer, bromelain, or iodoform. Silver sulfadiazine can be applied on dry necrotic tissue.

- Pressure ulcers with inflammation or infection.

Cadexomer iodine, silver sulfadiazine, povidone-iodine sugar, povidone-iodine gel, iodine ointments, or iodoform can be applied. If local or systemic bacterial infection is suspected, systemic administration of antibiotics is required.

- Pressure ulcers with excessive exudates.

If exudates are excessive, cadexomer iodine, dextranomer, povidone-iodine sugar, or iodine ointments can be applied.

- Pressure ulcers with dry surface.

For the ulcers with dry surface, topical medication with lipids or emulsifiers as vehicles, such as zinc oxide, dimethyl isopropyl azulene, silver sulfadiazine, or petrolatum can be applied

- Pressure ulcers with undermined edge.

Surgical debridement and/or negative-pressure wound therapy may be considered. As a topical medication, povidone-iodine sugar for ulcers with excessive exudates, or trafermin or tretinoin tocoferil for ulcers with dry surface can be applied.

- Pressure ulcers with its surface fully covered with granulation.

Topical medication with lipids vehicle, such as, zinc oxide, dimethyl isopropyl azulene, trafermin, petrolatum, prostaglandin E1, or tretinoin tocoferil can be applied for ulcers with dry surface. Bucladesine sodium can be applied for ulcers with excess exudates or edematous wound surface.

Note: As of preparation of the guidelines, shipping of tretinoin tocoferil is suspended.

3.11 | Possibility of Future Research

Most of the RCT we retrieved in the systematic review adopted vehicles or other topical medication, not physiological saline, as a control, and were conducted with financial supports from pharmaceutical companies. The vehicles themselves may contribute to the moist wound healing. Unlike a comparison to physiological saline or dressings, comparison to vehicles enable us to design a double-blind studies. As what we want to know is not "the comparison of topical medication and physiological saline or dressings" but "which topical medication works in the treatment of pressure ulcers." Studies using vehicles as a control meet our requirement.

Among the retrieved RCT, the ulcer conditions, with/without necrotic tissues, significantly varied. If we can collect uniform pressures ulcers as a subject, we may obtain clearer information on the CQ.

CQ3 Is the use of dressings recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence	Voting count
We propose to use hydrophilic fibers, hydrocolloids, hydrogels, or polyurethane foams in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak	7/7

3.12 | Background

Dressings maintain a moist condition on the wound surface to provide appropriate environment for wound healing, and are often employed in the treatment of pressure ulcers. In addition to the basic dressings (i.e., saline gauze or similar non-bioactive dressings) [52], several "modern" dressings, such as hydrophilic fibers, hydrocolloids, hydrogels, and polyurethane foams, are available, and selected depends on the amount of exudate and the condition of wound surface.

3.13 | Objectives

In order to assess the efficacy of dressings for pressure ulcers of Stage III or IV, systematic reviews were carried out.

3.14 | Results

Systematic reviews of randomized controlled trials (RCT) were carried out to assess the efficacy of dressings in the treatment of pressure ulcers of Stage III or IV, adopting "cure rate" as an outcome. Two studies on hydrophilic fibers [53, 54], three on hydrocolloids [41, 55, 56], two on hydrogels [57, 58], and three on polyurethane foams [59–61] were retrieved.

Among two RCT [53, 54] on hydrophilic fibers, one RCT [53] adopted radiant heat dressing (localized hyperthermia with battery-powered heating equipment) as a control for Stage III or IV pressure ulcers. The other [54] adopted povidone-iodine gauze dressing as a control for surgical or trauma wounds, but not pressure ulcers. The two RCT [53, 54] did not revealed a significant difference between hydrophilic fibers and controls. Meta-analysis revealed that cure rate was not significantly different with risk ratio: 1.69, 95% confidence interval: 0.64–4.47.

Among three RCT on hydrocolloids [41, 55, 56] two RCT [41, 55] revealed a better cure rate in hydrocolloids than basic dressings, whereas another RCT [56] did not find a significant difference between hydrocolloids and basic dressings. In one RCT [41] the subjects included pressure ulcers of Stage I or II, but not Stage III or IV. Meta-analysis of these three reports revealed that cure rate was significantly higher in hydrocolloids with risk ratio: 1.98, 95% confidence interval: 1.39–2.82.

Two RCT [57, 58] on hydrogels did not revealed a significant difference between hydrogels and basic dressings. Meta-analysis revealed that cure rate was not significantly different with risk ratio: 1.42, 95% confidence interval: 0.75–2.69.

Among three RCT [59–61] on polyurethane foams, one RCT [60] included Stage II pressure ulcers, but not Stage III or Stage IV. The three RCT [59–61] did not revealed a significant difference between polyurethane foams and controls. Meta-analysis revealed that cure rate was not significantly different with risk ratio: 1.32, 95% confidence interval: 0.93–1.89.

3.15 | Further Information

We adopted cure rate as a sole outcome in this CQ3. Most of the retrieved studies in the systematic review adopted cure rate as an outcome. Among them not only basic dressings but other dressings were also adopted in control groups [62–66]. A few studies analyzed incidence of adverse events, and disclosed low incidence. Analysis of financial resources was not straightforward, because both laboring cost and material cost should be counted. Two studies [67, 68] reported a smaller cost of dressings than that of basic dressings because of the reduced number of dressing exchange, whereas another study [69] reported the similar cost. Meta-analysis was conducted with two RCT for each dressings.

Meta-analysis of two reports [53, 54] did not reveal a difference in cure rate between hydrophilic fibers and radiant heat dressing/basic dressings. In one RCT [53] radiant heat dressing, different from basic dressings, was adopted as a control. In the other RCT [54], the subjects did not include pressure ulcers but surgical or traumatic wounds. Certainty of evidence was very weak because of risk of bias, suspicion of Inconsistency of results and suspicion of imprecision. The guideline panels proposed to use hydrophilic fibers in the treatment of Stage III and Stage IV pressure ulcers.

Meta-analysis of three reports [41, 55, 56] revealed that cure rate was significantly higher in hydrocolloids than basic dressings. Certainty of evidence was very weak because of risk of bias and suspicion of inconsistency of results. The guideline panels proposed to use hydrocolloids in the treatment of Stage III and Stage IV pressure ulcers.

Meta-analysis of two reports [57, 58] did not reveal a difference in cure rate between hydrogels and basic dressings. Certainty of evidence was very weak because of risk of bias, suspicion of inconsistency of results and suspicion of imprecision. The guideline panels proposed to use hydrogels in the treatment of Stage III and Stage IV pressure ulcers.

Meta-analysis of three reports [59–61] did not reveal a difference in cure rate between polyurethane foams and basic dressings. Certainty of evidence was very weak because of risk of bias and suspicion of imprecision. The guideline panels proposed to use polyurethane foams in the treatment of Stage III and Stage IV pressure ulcers.

We proposed, not recommended, all four dressings for the treatment of Stage III and Stage IV pressure ulcers, although hydrocolloids showed a significant advantage over basic dressings. As the dressings and basic dressings, with an exception of one RCT [53] which used radiant heat dressing as a control, were compared, the blinding in treatment was almost impossible. Many participants were missed with death or referral to the other hospitals. The conditions of wound, such as the stage of pressure ulcers, size of the wound, necrotic tissue, and infection, differed among studies. Thus, the overall certainty of evidence was very weak over.

3.16 | Precautions for Clinical Use

In this CQ we did not conduct a comparison between each dressings or between dressings and topical medication, but between dressings and basic dressings.

Selection of dressings in Stage III and IV pressure ulcers of early stages.

- Pressure ulcers covered with necrotic tissue.

If the firm and dry necrotic tissues prevent an appropriate surgical debridement, hydrogels can be applied to soften and promote the autolysis of necrotic tissues.

- Pressure ulcers suspect of critical colonization.

If critical colonization is suspected, daily change of topical medication with antibacterial effect should be considered to observe the wound conditions. Silver-containing dressings, such as hydrophilic fibers, hydrocolloids or polyurethane foams are available. The selection of dressings depends on the amount of exudate from the wound surface. Hydrophilic fibers have the biggest capacity to absorb exudate, followed by polyurethane foams and hydrocolloids. Also, hydrogels containing polyhexamethylene biguanide (PHMB), which possess a broad antibacterial activity, were available in Japan since 2018.

- Pressure ulcers with local or systemic infection.

Prompt administration of systemic antibiotics is strongly recommend. If there, removal of dressings and exchange into topical medication with antibacterial effect should be considered.

- Pressure ulcers with excessive exudates.

Hydrophilic fibers, polyurethane foams, or polyurethane foam/soft silicone, which have a capacity to absorb exudate, can be applied.

- Pressure ulcers with moderate or small amount of exudates.

Hydrogels or polyurethane foams, which may closely cover the wound surface and maintain a moist environment, can be applied.

- Pressure ulcers with undermined edge.

Dressings are of little effect in undermine; surgical debridement is prompted. After the debridement hydrophilic fibers with hemostatic effects and a capacity to absorb exudate can be applied. In suspicion of critical colonization, silver-containing hydrophilic fibers can be applied.

Selection of dressings in Stage III and IV pressure ulcers of late stages.

- Pressure ulcers with moderate or small amount of exudates.

Hydrocolloids, hydrogels or polyurethane foams, which may closely cover the wound surface and maintain a moist environment, can be applied. Self-adhesive polyurethane foam/soft silicone has the advantage of minimizing pain and surface damage in removal, thus, it can be applied on the fragile skin.

- Pressure ulcers with excessive exudates.

Hydrophilic fibers, polyurethane foams, or polyurethane foam/soft silicone, which have a capacity to absorb exudate, can be applied.

Our analysis revealed that the cure rate of Stage III or IV pressure ulcers was not significantly different between dressings and basic dressings. As far as the general and nutritional conditions of patients are preserved, and necrotic tissues and infection are appropriately controlled, either dressings or basic dressings can promote wound healing.

3.17 | Possibility of Future Research

In this CQ we did not conduct a comparison between each dressings. Currently, topical medication is often applied for the treatment of pressure ulcers in Japan. RCT to analyze cure rate and incidence of adverse events, comparing between each dressings or between dressings and topical medication, may provide more information in the treatment of pressure ulcers.

CQ4 Is negative-pressure wound therapy recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence	voting count
We propose to perform negative-pressure wound therapy in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak	7/7

3.18 | Background

Negative-pressure wound therapy is one form of the physiotherapy. The wound is covered closely, and negative-pressure is applied at 75 or 125 mmHg. Negative-pressure wound therapy is effective through the removal of bacteria and its toxins, the promotion of angiogenesis in granulation tissues and improvement of tissue edema. It is often applied in treatment of chronic

ulcers, such as traumatic skin ulcers and diabetic skin ulcers. Pressure ulcers of Stage III or IV are often refractory to conventional treatment.

3.19 | Objectives

In order to assess the efficacy of negative-pressure wound therapy for pressure ulcers of Stage III or IV, a systematic review was carried out.

3.20 | Results

Three randomized controlled trials (RCT) [70–72] of negative-pressure wound therapy for pressure ulcers, adopting cure rate and incidence of adverse events, were retrieved.

In a pilot study conducted by Ashby et al. [70], negative-pressure wound therapy ($n=6$) was compared with the standard treatment (dressings, $n=6$) for pressure ulcers of Stage III or IV. Before the treatment, median size of pressure ulcers was 3×5 cm with 4 cm in depth. One patient in the negative-pressure wound therapy group completely re-epithelized in 79 days, whereas none in the control group. Adverse events were observed in four of the six patients in the negative-pressure wound therapy group and in five of the six patients in the control group.

Ford et al. [71] compared negative-pressure wound therapy with Healthpoint System, a mixture gel product of Accuzyme, Iodosorb, and Panafil, on 41 pressure ulcers of Stage III or IV in 28 patients. Of 35 pressure ulcers evaluated for more than 6 weeks, complete re-epithelization was achieved in 2 of 20 lesions in the negative-pressure wound therapy group and in 2 of 15 lesions in the HealthPoint system group. Furthermore, the reduction rates at 6 weeks in the former and latter were 51.8% and 42.1%, respectively, which was not statistically significant ($p=0.46$). A serious adverse events, sepsis, occurred in one patient of negative-pressure wound therapy.

De Laat et al. [72] investigated 28 Stage IV pressure ulcers in 24 patients. Fifteen lesions were allocated for negative-pressure wound therapy and 13 lesions for control dressings, and 50% reduction rate was evaluated. After 6 weeks, 50% reduction was achieved in 24 of the 28 lesions in total. 50% reduction was achieved in 2.0 weeks on average in the negative-pressure wound therapy group and in 3.5 weeks in the control group ($p<0.001$). Adverse events were observed in three lesions in the negative-pressure wound therapy group and in three in the control group.

3.21 | Further Information

The retrieved two RCT [70, 71] did not reveal a difference in cure rate between the negative-pressure wound therapy and the control. In one RCT [72] 50% reduction of pressure ulcer size was achieved significantly quicker in the negative-pressure wound therapy group. Certainty of evidence was very weak because of Risk of bias and Indirectness of evidence. The retrieved three RCT [70–72] did not reveal a difference in incidence of adverse events between the negative-pressure wound therapy and the control. Difficulty in blinding resulted in risk of bias. Thus, the guideline panels proposed to perform negative-pressure wound therapy in the treatment of Stage III or Stage IV pressure ulcers.

3.22 | Precautions for Clinical Use

We adopted the cure rate and incidence of adverse event as outcomes. Other than the cure rate, obviously important, reduction rate of the size of ulcers and improvement of undermined edge can be important outcomes. Reduction of the size of pressure ulcer with negative-pressure wound therapy was reported in case–control studies [73, 74]. However, one RCT [75] and one non-RCT [76] did not revealed a significant difference between negative-pressure wound therapy and control. The application of negative-pressure wound therapy on undermined pressure ulcers was reported in a few case reports [77–80]. Careful consideration should be taken in the application of negative-pressure wound therapy, depends on the presented data as well the individual wound condition.

3.23 | Possibility of Future Research

We expect the difficulty in presenting a high cure rate of Stage III and IV pressure ulcers with negative-pressure wound therapy in a short period. Also, not only the wound conditions but the patient's general condition and social circumstances affect the wound healing, and make the inclusion criteria more complicated. It is almost impossible to perform negative-pressure wound therapy in a double-blind manner. Although it is difficult to plan an ideal study design, RCT comparing negative-pressure wound therapy and dressings may provide more information on this CQ.

4 | Chapter 4 Glossary of Terms and Concepts, Quoted From the Terminology List by the Terminology Committee of the Japanese Society of Pressure Ulcers

4.1 | Pressure Ulcer

Skin surface pressure reduces the capillary blood flow in the soft tissue between the bone and skin, and irreversible ischemic damage in the soft tissue may result in developing pressure ulcers.

4.2 | Topical Medication

Topical medication, a compound of chemical(s) mixed in vehicles, is applied directly on the skin or surface lesion for a local treatment.

4.3 | Dressings

Herein dressings refer to modern wound-dressings, excluding the conventional sterile gauze, to maintain an appropriately moist environment on the wound surface.

4.4 | Wound Dressings

Wound dressings can be divided into dressings (modern dressings) and conventional medical supplies such as gauze (classic dressings). The former aims to maintain an appropriately moist environment for wound healing, thus, it should be selected depending on the wound conditions and exudate. The latter dehydrates the wound surface, and may lead unwantedly dried condition on the wound with small amount of exudate. Only the former may be called wound dressings or dressings.

4.5 | Occlusive Dressing

All the dressings methods to maintain moisture condition for moist wound healing may be called occlusive dressings. It may refer to modern wound-dressings other than the conventional sterile gauze.

4.6 | Wet-to-Dry Dressing

Removing the dried gauze saturated with physiological saline eliminates the adhered foreign bodies or necrotic tissues non-selectively.

4.7 | Surgical Intervention

Reconstruction surgeries, surgical debridement, and opening the undermine are carried out in the treatment of pressure ulcers.

4.8 | Physical Therapy

Physical stimulation can be applied to reduce the pain, to promote wound healing, and to soften the soft tissue, such as muscles and ligaments. Physical therapies include thermotherapy, cryotherapy, hydrotherapy, phototherapy, ultrashort wave therapy, electric stimulation therapy, ultrasound therapy, negative-pressure therapy, high-pressure oxygen therapy, and traction therapy, stimulated by physical agents, such as heating, cooling, water, light, ultrashort waves, electric current, ultrasound, vibration, pressure, and traction.

4.9 | NPUAP Pressure Ulcer Staging System

The National Pressure Ulcer Advisory Panel (NPUAP) proposed a classification of depth of pressure ulcers in 1989. In addition to conventional Stages I through IV, new category, deep tissue injury (DTI), was added based on the concept that deep tissue may be damaged without the visible wound on the skin surface. The new NPUAP pressure ulcer staging system in 2007, proposed six stages of "suspected DTI," Stages I through IV and "U," unstageable to determine Stage III or IV.

4.10 | Deep Tissue Injury (DTI)

The National Pressure Ulcer Advisory Panel (NPUAP) proposed DTI for a pressure ulcer without surface wound (Stage I) in suspicion of damage to adipose tissue or deeper. In the NPUAP pressure ulcer staging system revised in 2007, "suspected DTI" was added as a new stage. NPUAP urges to use DTI strictly for pressure ulcers.

4.11 | Nutrition Support Team (NST)

The Japan Council for Nutritional Therapy (JCNT) calls nutritional support for individual patients and their disease conditions as "nutrition support," and a group to nutrition support composed of physician, nurses, pharmacists, nutritionists and laboratory technicians as "nutrition support team."

4.12 | Erosion

Damage of skin or mucous membrane, not exceeding the basement membrane in dermo-epidermal junction, or dermo-mucosal junction, usually heals without leaving a scar.

4.13 | Ulcer

Damage of skin or mucous membrane, exceeding the basement membrane in dermo-epidermal junction, or dermo-mucosal junction, usually heals leaving a scar.

4.14 | Decompression

Reducing the pressure on the skin prevents and improves pressure ulcers. Reducing the capillary pressure to less than 32 mmHg was formally called as "decompression," and to 32 mmHg or above as "pressure reduction."

4.15 | Body Pressure-Dispersion Devices

Body pressure-dispersion devices reduce the contact pressure from beds or chairs through the widening of the contact area or by shifting the pressure point occasionally. Cushions, elasticity of air, water, urethane foams, gels, or rubbers are used in designed beds, overlaying or replacement mattresses, chairs/wheelchairs cushions and pads for adjusting the body position.

4.16 | Wound Bed Preparation

In order to prepare the wound surface and promote wound healing, it is advisable to remove necrotic tissues, decrease the bacterial burden, moisten the wound surface while removing the excessive exudate, and treat the wound and undermine.

4.17 | Time

Practical principles and obstructing factors of wound bed preparation were summarized in T, tissue, I, infection or inflammation, M, moisture and E, wound edge.

4.18 | Moist Wound Healing

An appropriately moist condition on the wound surface retains enzymes and growth factors released in exudate from polynuclear leukocytes and macrophages, and promotes autolysis of necrotic tissues and migration of fibroblasts and endothels.

4.19 | Negative-Pressure Wound Therapy

The wound is maintained in a closed environment, and negative pressure of 125 or 150 mmHg is applied to eliminate bacteria and exotoxins, to promote capillary proliferation in granulation tissue, and to eliminate tissue edema.

4.20 | Undermine

A cavity or undermine may be formed under the overhang or coverlid.

4.21 | Washing

Water washing, with its pressure, volume and lysing effect, removes chemicals, infectious agents and foreign bodies from the wound surface and the surrounding skin. Physiological saline or tap water, occasionally combined with soap or detergent, can be used.

4.22 | Debridement

Necrotic tissues, aging tissues which does not react to growth factors, foreign bodies and bacterial foci should be removed and cleaned with autolysis under occlusive dressing, mechanical debridement, for example, wet-to-dry dressing, high-pressure washing, hydrotherapy and ultrasonic washing, proteolytic enzymes, surgical debridement, or maggot therapy.

4.23 | Critical Colonization

Not simply aseptic or infectious states, but in the bacterial burden concept, bacterial burden balanced with host immunity determines the consequence of infection, through the transitional states from contamination, colonization, critical colonization to infection.

4.24 | Biofilm

Bacteria colonized on the foreign bodies or necrotic tissues may produce polysaccharides, which fuse to form a membranous structures and forms biofilm. Bacteria within the biofilm is protected from antibiotics and leukocytes, and the infection may persist.

4.25 | Seating

A patient, especially who can not sit upright for himself, is supported to take a safe and comfortable seating position with cushions through the evaluation of his statue and gravity.

5 | Chapter 5 Guide for the Diagnosis and Treatment of Pressure Ulcers

5.1 | Diagnosis of Pressure Ulcers

5.1.1 | Glass Plate or Finger Compression Methods Are Useful for Differentiating Stage I Pressure Ulcers From Reactive Erythema

- A case–control study compared glass slide and finger compression methods in distinguishing Stage I pressure ulcers from reactive erythema [81]. Another case–control study evaluated incidence of pressure ulcers in glass plate or finger compression methods [82].
- In daily practice, either glass plate or finger compression methods are used to distinguish stage I pressure ulcers from reactive erythema. A case–control study evaluated interrater reliability, concordance rate in Cohen's kappa, sensitivity, specificity and positive and negative predictive values [81]. The glass plate method showed a slightly higher sensitivity without a statistically significant difference, and the both methods were considered useful. In addition, investigations on the incidence of pressure ulcer by glass plate and finger compression methods revealed that the former method was positive for a pressure ulcer in 3.9% of cases, while 7.1% in the latter [82]; the difference was not significant.
- In addition, measuring blood flow with LASER Doppler technique [83, 84], skin temperature [85], skin color spectroscopy [86], subepidermal moisture [87], or dermoscopy [88] could not discriminate Stage I pressure ulcer from reactive erythema.

5.1.2 | Differential Diagnoses May Include Reactive Erythema, Peripheral Arterial Diseases Associated With Diabetes Mellitus, Irritant Dermatitis by Stool or Urine, Cutaneous Candidiasis, Contact Dermatitis, Burn Caused by Electric Scalpel, and Chemical Burn of Disinfectants

Several conditions require to be differentiated from pressure ulcers. Among them reactive erythema is the most important; the interrater reliability and agreement were high when those who with a certain level of training [89, 90]. The second most important condition is peripheral arterial disease (PAD) associated with diabetes mellitus [91]. Other differential diagnoses include irritant dermatitis by stool or urine, cutaneous candidiasis,

contact dermatitis, burn caused by electric scalpel, and chemical burn of disinfectants.

Postoperative conditions which require to be differentiated from pressure ulcers include burn caused by electric scalpel and chemical burn by disinfectants [91]. Burn caused by electric scalpel has become rare in recent years. It is irregularly shaped, well-circumscribed erythema caused by electrical leakage. It occurs immediately after surgery in the buttock. Chemical burn of disinfectants is a primary irritant dermatitis caused by povidone-iodine; it appears as a well-circumscribed, irregularly shaped erythema on disinfected areas. It may appear a few days after the surgery or immediately after surgery in close examination. Conversely, pressure ulcer of surgery is poorly circumscribed erythema appears immediately or later. The location, size and shape of the ulcer are taken into consideration, but as the differentiation based on these characteristics is not always obvious, it is important to examine the skin conditions immediately after the surgery [92].

5.2 | Prevention, Care, Assessment of Risk Factors, and Pain Control of Pressure Ulcers

5.2.1 | Assessment Scales for Risk Factors Include Braden Scale, K Scale, K Scale for Home Care, OH Scale, Pressure Ulcer Risk Assessment Sheet (Japanese Ministry of Health, Labour and Welfare)

A systematic review [93] comparatively evaluated the predictive value of several assessment scales. A prospective cohort study [94] evaluated the validity of the K Scale in Japanese subjects with low body weight and bone protrusions [94]. A case–control study [95] assessed the OH Scale, a prospective cohort study [96] assessed the K Scale for home care, a multicenter cross-sectional study [97] assessed the Pressure Injury Primary Risk Assessment Scale for Home Care (PPRA-Home), and a retrospective cohort study [98] assessed the Pressure ulcer risk assessment sheet (Japanese Ministry of Health, Labour and Welfare).

In assessment of risk factors of pressure ulcers the Braden Scale, the K Scale, the K Scale for home care, the OH Scale, the PPRA-Home, and the Pressure ulcer risk assessment sheet (Japanese Ministry of Health, Labour and Welfare) may be useful. Braden Q Scale or Braden QD Scale can be applied for children. According to the systematic review [93] comparatively evaluating the predictive value of several assessment scales, the Braden Scale was superior to the Norton Scale, the Waterlow Scale, and the clinical judgment by nurses, comparing their sensitivity, specificity, and predictive comprehensively. Of note, Japanese patients with low body weight and bone protrusions were not included in this study. Also, a systematic review [99] compared the modified Braden Scale, the Braden Scale, and the Norton Scale in Asian subjects, and revealed that the predictive value was highest in the modified Braden Scale. A meta-analysis of pediatric pressure ulcer assessment scales [100] including the Neonatal Skin Risk Assessment Scale for Predicting Skin Breakdown, the Braden Q Scale, the Burn Pressure Skin Risk Assessment Scale, the Starkid Skin Scale, and the Glamorgan Scale did not reveal a superiority in any of them. While these assessment scales for the prediction of pressure ulcers may contribute to more effective and efficient preventive measures of pressure ulcers, it remains unclear whether they can truly reduce the incidence of pressure ulcers [101]. In a systematic review of pressure ulcer prevention and assessment scales for risk factors [102], the Waterlow Scale did not result in a significant reduction of the incidence of pressure ulcers, and because of the poor-quality of data, the results were conflicting with the Braden Scale and the Norton Scale.

A prospective cohort study [94] of the K Scale in bedridden patients, a case–control study [95] of the OH Scale, and a retrospective cohort study [98] of the Pressure ulcer risk assessment sheet (Japanese Ministry of Health, Labour and Welfare) on Japanese subjects revealed that all the methods mentioned were useful. For elderly people residing at home, a prospective cohort study [96] of the K Scale for home care and a multicenter cross-sectional study [97], with the PPRA-Home developed for home care by care managers, reported that the scales were useful in their sensitivity, and specificity.

5.2.2 | At Risk of Developing Pressure Ulcers, Application of Moisturizing Cream Should Be Considered

For washing and protection of the skin and prevention of pressure ulcers, five RCT [103–107] of squalene-containing cream, hyperoxygenated fatty acid compounds, and others were reported. In addition, there are three RCT [108–110] with polyurethane film and two with polyurethane foam [111, 112] for the prevention of pressure ulcers.

Five RCT reported the efficacy of skin washing or skin care with moisturizing cream in prevention of pressure ulcers. Three RCT [103–105] among the five with squalene-containing cream or hyperoxygenated fatty acid compounds revealed a significant preventive effect. Also, an increased cure rate and shortened treatment period were reported in several reports [113–115]. It should be noted that treatment methods and topical medication varied, and most of them are unavailable in Japan; it is unknown which ingredients were the most effective.

Three RCT [108–110] reported the efficacy of polyurethane films in prevention of pressure ulcers. Application of polyurethane films over bone protrusions in elderly significantly reduced the incidence of both pressure ulcers [108] and persistent erythema [109]. Also, application of polyurethane films over the sacral region clearly prevented intraoperative pressure ulcers [110]. One RCT [111] of polyurethane foam application on the heels reported a significant decrease in the prevalence of pressure ulcers. One RCT [112] of polyurethane foam/soft silicone application on the sacral region in cardiac surgery reported a significant decrease in the prevalence of pressure ulcers.

One observational study [116] of intraoperative polyurethane foam application on the heels reported a decrease in the prevalence of pressure ulcers.

Commercially available polyurethane films are formed as a film of polyurethane coated with a waterproof, hypoallergic and adhesive acrylic or vinyl materials. They can effectively seal and occlude wounds. With its transparency or translucency, the

wound conditions can be easily observed. They are waterproof and prevents the entry of water and bacteria from the outside; they are semipermeable and allow the vaporization. Therefore, they maintain moisture on the wound and do not interfere with perspiration or insensible water loss. Thus, the edge of pressure ulcers does not become macerated, and the barrier function of the skin remains intact. Polyurethane films should not be used for the wounds infected with bacteria; bacteria can rapidly proliferate in the moist environment.

5.2.3 | Body Pressure-Dispersion Mattress Should Be Used, and the Body Position Should Be Periodically Changed to Prevent Pressure Ulcers

Systematic reviews [117–120] revealed that the incidence of pressure ulcers decreased by bodyweight-dispersion mattress and changing the body position, in comparison with standard mattress or without changing the body position. A guideline [119] also reported their utility.

Body pressure-dispersion mattresses are classified into those integrated in bed frame (special beds), those to substitute a standard mattress (replacement mattresses) and those layered over the standard mattress (overlay mattresses). Functionally, the mattresses are classified into those changing the air pressure dynamically to prevent high pressure applied to the same body site for a long time, and those dispersing the pressure statically, such as urethane foams, gel, rubber, and air mattresses.

Body pressure-dispersion mattresses can be selected with the assessment tools developed for Japanese patients, such as the OH scale; the inpatients need be assessed on admission. General rules are as follows: a low-pressure sustaining air mattress are selected for those who can not roll over without assistance (daily life independence level: C2), mainly for pressure dispersion; a low-pressure sustaining air mattress with less body sinking, or a pressure-dispersion static mattress are selected for those who can roll over alone (daily life independence level: C1), in order not to disturb self-rolling. Many studies have compared the mattresses without the clear superiority in any of the products. It is important to select a body pressure-dispersion mattresses [117–122] considering the ability of the patient, the body condition and his social environment. Once pressure ulcers were developed, a static body pressure-dispersion mattress can be selected for those who can lie avoiding the compression on the ulcers, and a pressure-adjustable air mattress can be selected for those who can not [120].

In general, pressure ulcers will not develop with the contact pressure of less than 40 mmHg. It may be useful to measure the contact pressure on the sacral region while using a body pressure-dispersion mattress with pressure meter in preventing pressure ulcers. If pressure meter is not available, simple bottoming check may substitute [123]. The bottoming can be checked by inserting the observer's hand between the sacrum and mattress. If index or middle fingers directly touch the sacral bone, or impossible to bend the fingers, it is bottoming. If the fingers bended by 2.5 cm touch the sacral bone, the contact pressure is appropriate.

While using an adjustable body pressure-dispersion air mattress, the body position should be changed regularly [117–120]. An RCT [124] reported that the pressure ulcers may appear more while using a pressure-adjustable body pressure-dispersion air mattress without changing the body position than using a static mattress with a regular change of body position [124].

The body position is recommended to be changed every two hours, if the physical conditions allow [125]. However, the following factors should be considered; materials and thickness of static pressure-dispersion mattress, quality of pressure-adjustment of low-pressure-sustaining air mattress, novel functions, for example, motor-drive rolling function, pressure controlling in small fractions of air mattress. The appropriate interval of the change of body position is arguable.

Once pressure ulcers developed, a proper body positioning is important to minimize compression on the ulcers. To prevent the friction and unwanted change of body positions, relieving the wrinkles in clothes is useful in changing the body position or head elevation. The rule of 30, 30° laterally inclined and 30° head elevation, may be useful. A proper bedmaking is important to avoid the hammock phenomenon, that is, reduction of the effects of body pressure-dispersion mattress by the strong tension of bed sheet. The setting of air pressure of low-pressure-sustaining air mattress adjusted to the body weight, disconnection of air mattress tubing, and the position of urinary catheters should be monitored carefully [126].

5.2.4 | Energy, Protein, Amino Acids, Vitamins, and Trace Elements Should Be Supplied

Among two meta-analysis studies [127, 128] of nutritional support (energy, protein) in patients with or at risk of pressure ulcers, one [127] reported the usefulness of nutritional support in prevention and treatment of pressure ulcers. Among two meta-analysis studies [127, 128] of amino acids, vitamins and trace elements supplement, one study recognized the usefulness in the prevention and treatment of pressure ulcers, but the other [128] denied usefulness. Two RCT [129, 130] reported the efficacy of amino acids, vitamins, and trace elements in the treatment of pressure ulcers.

Malnutrition is an important risk factor in developing pressure ulcers. A meta-analysis report [127] revealed that providing necessary nutrients, energy and proteins may prevent pressure ulcers in patients at risk, and may be effective in the treatment of pressure ulcers. Supplementation of necessary nutrients was recommended by the guidelines in Europe, Japan, and the United States [125, 131, 132]. In particular, supplementation of protein in the treatment was emphasized in these guidelines.

5.2.5 | Once the Pressure Ulcers Were Developed and the Nutritional State Is Poor, It Is Recommended to Consult With Nutrition Support Team (NST) in Hospital or Nutrition Specialists Without Delay

The effect of nutrition for patients of pressure ulcers were reported in two systematic reviews [127, 128] of non-Japanese patients and in one RCT [133] of Japanese patients. Three observational studies [134–136] compared the nutritional state and

incidence of pressure ulcers in postoperative patients, before and after the involvement of hospital nutrition support teams.

Two systematic reviews [127, 128] reported that sufficient supplementation of protein and energy is effective for the prevention and treatment of pressure ulcers. One RCT [133] reported that a nutritional support was effective to significantly reduce the size of pressure ulcers in Japanese patients.

It is important to consult with nutrition support team (NST) or nutrition specialists in evaluating the nutritional state and in planning nutrition support. An observational study [134] reported that the intervention of NST significantly decreased incidence of pressure ulcers in the patients after gastrointestinal surgery ($p = 0.051$), by shortening of the postoperative fasting period or an increase in the serum albumin level in perioperative period. The other observational study [135] reported the reduced incidence of pressure ulcers approximately in one-third after the intervention of NST. Intervention of NST or nutrition specialists is useful both in perioperative periods and chronic phase of pressure ulcers [136]. The appropriate timing of NST intervention is yet to be disclosed.

The serum albumin level (less than 3.0 or 3.5 g/dL regarded as malnutrition), bodyweight loss (a marked bodyweight loss in 2 weeks, bodyweight loss of 5% in 1 month, 7.5% loss in 3 months, or 10% loss in 6 months regarded as malnutrition) and dietary intake (less than half of the usual level over 2 weeks or longer regarded as malnutrition) are the criteria for general nutrition state [137].

NST and nutrition specialists often use the subjective global assessment (SGA) for the evaluation of nutritional state. The SGA consists of history interview (bodyweight changes, changes in dietary intake, gastrointestinal symptoms, physical function levels, underlying disorders, and nutritional demands) and physical examinations (fat and muscle volumes and edema). It represents subjective nutritional states. It is not a numerical score or suitable for beginners. When severe malnutrition is suspected, consultation with the NST or nutritional specialists is recommended.

5.2.6 | Bathing Is Recommended for Patients With Pressure Ulcers

One observational study [138] reported cutaneous blood flow, bacterial load, and pH before and after bathing. Bathing is essential for skin care and is widely practiced in clinical settings.

Bathing of pressure ulcer patients is favorably accepted in general. One observational study [138] indicated the efficacy of bathing in elderly patients with pressure ulcers. In this study, increased cutaneous blood flow and decreased bacterial load after bathing were reported, comparing cutaneous blood flow, bacterial load, and skin surface pH before and after bathing. The cultured bacteria of exercising pool water, after the bathing of spinal injury patients with pressure ulcers, regardless of covering the wounds or not, was mainly not from pressure ulcers but from facultative aerobic bacteria of intestine [139]. The bacterial flora on pressure ulcers were of little chance to contaminate the bath water, and the patients should not be prohibited bathing.

Cleansing the surrounding skin of pressure ulcers with a pH-balanced cleanser promoted the healing of pressure ulcers [140]. Washing with acidic or neutral detergents, or foaming alkaline soap without rubbing the surface of ulcers would not delay the healing of pressure ulcers [141].

The efficacy of foot bathing, not the body bathing, for the pressure ulcers of the heels was reported [142], and it is often practiced in the management of them. A whirlpool bathing may promote a quick healing of pressure ulcers [143].

5.2.7 | To Relieve the Pain of Pressure Ulcers, Anti-Inflammatory or Psychoactive Medication, Employing Body Pressure-Dispersion Mattress, and Applying Dressings Are Recommended

One case–control study [144] and one case report [145] reported the management of pain in pressure ulcers. It should be noticed that not only the ulcers themselves but bacterial infection may cause pain.

Of the patients with pressure ulcers, 37%–66% patients complained of pain at some point [146]. The intensity of the pain was related to the depth of the pressure ulcer, and was worsened during the dressing change of pressure ulcers [147].

Anti-inflammatory or psychoactive medication is often prescribed to relieve the pain, however, their effects were often limited [144, 145] Body pressure-dispersion mattresses and hydrocolloid dressings, which maintain the moisture without adhering to the wound surface and protect the nerve endings from exposure [148, 149], were effective for relieving the pain [144].

Treatment of pressure ulcers itself may cause the pain [150]. Application of soft silicone [151], hydrogels or hydrophilic fibers may be less painful [152].

Should the ulcers exist, other than in the acute phase, the patient may not feel the strong acute pain if not the stimulation of nerve endings by mechanical stimulation, or chemical stimulation by neutrophil proteinases or complements. The effect of anti-inflammatory medication on chronic pain is limited, prescription of psychoactive or opioid medication should be considered. It is important to treat the local or systemic infections or to improve the nutritional conditions, in case they may relate to the pain.

5.2.8 | Wheelchair Seating and Checking Contact Pressure Are Important for Paraplegics and Spinal Cord Injury Patients With Pressure Ulcers

One retrospective cohort study [153] reported that intervention of pressure clinics decreased the incidence of pressure ulcer recurrence in spinal cord injury patients.

An observational study [154] reported that tissue oxygen levels recovered in 111 s (mean) after unloading the body pressure in patients with spinal cord injuries. A case report [155] disclosed a small incidence of pressure ulcers with the intervention of pressure clinics measuring the contact pressure in the patients with spinal cord injuries.

Although tipping the wheelchair back to 65° or leaning the subject forward with chest toward thighs significantly relieved the ischial pressures, tipping the wheelchair back to 35° was of little effect [156].

5.3 | Treatment of Acute Pressure Ulcers

5.3.1 | In the Treatment of Acute Phase Pressure Ulcers the Wound Surface May be Monitored Applying a Polyurethane Film or Translucent Hydrocolloid Dressings While Decompressing. If Topical Medication be Used, Topical Medication With Lipids Vehicle, Such as Petrolatum, Zinc Oxide, and Dimethyl Isopropyl Azulene Are Recommended for Protecting the Wound Surface, and Silver Sulfadiazine Is Recommended for Prevention of Infection. Topical Medication With Antibiotics May be Applied for a Short Period

Application of dressings and topical medication in the treatment of acute pressure ulcers was mentioned in five review article [148, 149, 157–159]. Covering the wound surface with lipids or appropriate dressings promotes moist wound healing, and is widely practiced in clinical settings.

The wound conditions and the depth of necrotic tissue in acute pressure ulcers are difficult to evaluate; acute pressure ulcers are prone to bacterial infection. It is also difficult to discriminate temporary erythema from Stage I pressure ulcers, which may rapidly exacerbate. The acute pressure ulcers require careful observation and protection of wound surface, and prevention of bacterial infection.

In this phase, dressings are often applied to protect the wound surface. The conditions of pressure ulcers may change rapidly, and transparent dressings should be applied to observe the wound surface. To protect the vulnerable wound surface and surrounding skin, weakly adhesive dressings are desirable.

Commercially available polyurethane film products are polyurethane films coated with waterproof and hypoallergenic acrylics or vinyl ether adhesives. They can seal and occlude the wound surface. They are transparent or translucent and the wound surface can be easily observed. They are waterproof and prevent the entry of water and bacteria. At the same time they are semipermeable and allow the passage of air and vapor. They may maintain moist environment and may not interfere with sweating and insensible perspiration. They may prevent maceration and maintain barrier function of the skin.

Hydrocolloids retain moisture without tightly adhering to the wound surface, and they can promote migration of keratinocytes and healing of the wound [148]. They occlude the wound surface, prevent exposure of denuded nerve endings to the air, and relieve the pain [149].

Translucent hydrocolloid products are available, such as DuoActive ET, Remois Pad (a mixture of hydrocolloids and ceramide NG covered with a transparent polyurethane film and slippery nylon knit layers), and Visiderm (hydrocolloids covered with a translucent waterproof polyurethane film); the latter two are not covered by health insurance in Japan.

Topical medication of lipids vehicle, such as dimethyl isopropyl azulene, petrolatum, and zinc oxide, can be applied to protect the wound surface [157, 158].

Silver sulfadiazine with emulsifiers vehicle has a strong penetrating property and antibacterial effect [159]. Topical antibiotics with lipids vehicle, such as gentamycin ointments, can be applied for a short period to protect the wound surface and to control or prevent bacterial infection. Note the possibility of developing antimicrobial resistant bacteria in prolonged use.

Silver sulfadiazine with its silver ion can destroy bacterial cell membrane and cell wall, and show antibiotic effect [160, 161]. It inhibits the formation of biofilm derived from methicillin-sensitive or methicillin-resistant *Staphylococcus aureus* (MRSA) [162]. Its emulsifiers vehicle can soften and lyse the necrotic tissue, and debride the wound surface. Its effect is attenuated when used concomitantly with povidone-iodine. Concomitant use of silver sulfadiazine with other topical medication, especially that of enzymatic activity, should be avoided.

5.3.2 | If Deep Tissue Injury (DTI) is Clinically Suspected, General Body Condition Should Be Carefully Monitored in Addition to Local Decompression and Monitoring the Wound Conditions, Applying a Polyurethane Film or Translucent Hydrocolloid Dressings

Currently, RCT for DTI was not reported, and DTI was discussed only in review articles.

DTI is an ischemic lesion of the muscle or soft tissue. The diagnosis of DTI and its extension is problematic. After the diagnosis of DTI is established, compression of the DTI lesion should be avoided with a proper body position or with body pressure-dispersion mattresses [163]. Also, the possibility of exacerbation should be noticed to the patient and his family while closely observing the skin conditions, appearance of bullae or purpura, monitoring the serum creatine kinase and C-reactive protein level, and the urinalysis, and providing the extracellular fluid to avoid renal failure with myoglobinemia.

An acute pain is suggestive of deep tissue inflammation and prompts to prescribe non-steroidal anti-inflammatory drugs for pain relief and to prepare for a surgical intervention. The fluid retention beneath the necrotic tissue requires the surgical intervention for bacterial infection in pressure ulcers.

Application of polyurethane films or translucent hydrocolloids was discussed in a few review articles [148, 149, 164]. These dressings can maintain the moist environment, promote re-epithelization, and lead the wound healing. In Stage II pressure ulcers the nerve endings expose to the air and cause pain. Covering the wound surface with dressings may relieve the pain.

Commercially available polyurethane film products are polyurethane films coated with waterproof and hypoallergenic acrylics or vinyl ether adhesives. They can seal and occlude the wound surface. They are transparent or translucent and the wound surface can be observed. They are waterproof and prevent the entry of water and bacteria. At the same time they are semipermeable and allow the passage of air and vapor. They may maintain moist environment and may not interfere with sweating and insensible perspiration. They may prevent maceration and maintain barrier function of the skin. Of note that bacterial infection may exacerbate under the polyurethane films.

Hydrocolloids retain moisture without tightly adhering to the wound surface, and can promote migration of keratinocytes and healing of the wound [148]. They occlude the wound surface, prevent exposure of denuded nerve endings to the air, and relieve the pain [149].

5.3.3 | Imaging by Magnetic Resonance or Ultrasound and Blood Examination Should Be Performed

Four case reports [165–168] discussed the diagnostic examinations for DTI. A systematic review [169] in 2010 disclosed a lack of consensus in diagnosis and treatment of DTI.

DTI was defined by the National Pressure Ulcer Advisory Panel, NPUAP, in 2005 referring a stage I pressure ulcers with subcutaneous or deeper tissue involvement. In the NPUAP pressure ulcer staging revised in 2007 [170], DTI appeared as a new stage called "suspected deep tissue injury." In the current practice, Stage II pressure ulcers with epidermal damage and suspected damage in subcutaneous or deeper tissue are also called DTI. DTI is difficult to diagnose on objectively; it is important to keep in mind the possibility of DTI.

In spite of the expectations, none of the diagnostic imaging is proved useful in the diagnosis of DTI. A case report [165] suggested a predicting value of ultrasonography for DTI. Another case report [166] suggested an early detection of damage in deep tissue by magnetic resonance imaging.

Diagnostic imaging may be useful in differentiating pressure ulcers from other soft tissue infections, such as necrotizing fasciitis, gas gangrene, pyomyositis and osteomyelitis, and fistula connected to the retroperitoneal abscesses in bedridden elderly patients. Plain x-ray picture may be helpful in detecting gas gangrene and osteomyelitis.

DTI may damage the underlying muscle tissue, and serum levels of muscle enzymes, such as aspartate aminotransferase, creatine kinase, and lactate dehydrogenase and myoglobin may increase [167]. These levels and white blood cell count, serum C-reactive protein and urinary myoglobin levels may be helpful in diagnosis of underlying muscle damage. DTI often appears in prolonged surgery or sudden disturbance of consciousness. Detailed medical history may contribute to the diagnosis of DTI. Necrosis of adipose tissue or sweat glands in skin biopsy may be suggestive of DTI.

5.4 | Treatment of Chronic Shallow Pressure Ulcers

5.4.1 | For Chronic Shallow Pressure Ulcers of Stage I or II, Dressings, Such as Hydrocolloids, Hydrogels, Polyurethane Foams and Chitins, and Topical Medication With Lipids Vehicle, Such as Petroleum, Zinc Oxide, and Dimethyl Isopropyl Azulene, Are Recommended for Protecting the Wound Surface. Topical Medication With Antibiotics or Granulation-Promoting Effect, Such as Bucladesine Sodium and Prostaglandin E1, Is Recommended

Two RCT [41, 55] and one systematic review [171] disclosed that the cure rate of pressure ulcers, not limited to shallow ulcers, and treatment with hydrocolloids was significantly higher than that with saline gauze dressing. Hydrogels did not show a significant difference from hydrophilic fibers or polyurethane foams.

Three RCT [58, 172, 173] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with hydrogels was not significantly different from that with saline gauze dressing [58, 172], hydrocolloids [172], and povidone-iodine [173].

Four RCT [59, 64, 66, 175] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with polyurethane foams was not significantly different from that with saline gauze dressing [59], hydrocolloids [64, 175] and hydrogels [66], while in one RCT [174] polyurethane foams was superior to hydrocolloids in the treatment of shallow ulcers.

In one case report [176] chitin may contribute to re-epithelization.

It is important to protect and maintain an appropriate moist environment of wound surface in the treatment of shallow pressure ulcers, and dressings is often applied on the wound surface. One RCT [55], not limited to shallow ulcers, reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with hydrocolloids was not significantly different from that with saline gauze dressing. Another RCT [41] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with hydrocolloids was significantly higher than that with saline gauze dressing or phenytoin cream [41]. One systematic review [171] stated "(h)ydrocolloids were most frequently used on pressure ulcers grade 2 or 3. Hydrocolloids are more effective than gauze dressings to decrease the wound size. The absorption capacity, the time needed for dressing changes, the pain during dressing changes and the side effects were in favor of hydrocolloids in comparison with gauze dressings. (H)ydrocolloids seemed to be less expensive compared with collagen-, saline-, and povidone iodide-soaked gauze but more expensive compared to hydrogel, polyurethane foam, and collagenase."

Hydrocolloids retain moisture without tightly adhering to the wound surface; thus, they can promote migration of keratinocytes and healing of the wound [148]. They occlude the wound surface, prevent exposure of denuded nerve endings to the air, and relieve the pain [149].

Two RCT [58, 172] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with hydrogels was not significantly different from that with saline gauze dressing [58, 172] and hydrocolloids [172]. One RCT [173] reported that the cure rate was not significantly different between hydrogels and povidone-iodine gauze dressing, but the wound healing rate(cm^2/days) was significantly larger with hydrogels. One case report [177] suggested the efficacy of hydrogels in decreasing the wound size, pain and erythema around the wounds.

Hydrogels promotes granulation and epithelization by maintaining a moist environment and relieve the pain with improving the inflammation by rapid cooling effect [177]. Transparency of hydrogels allows a clean view of the wound surface [178].

Two RCT [59, 66] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with polyurethane foams was not significantly different from that with saline gauze dressing [59] and hydrogels [66]. One RCT [174] reported that polyurethane foams group had a higher percentage of healed pressure ulcers at 8 weeks and a shorter average healing time compared with hydrocolloids group in the treatment of shallow pressure ulcers, while other two RCT [64, 175] reported that the cure rate of pressure ulcers, not limited to shallow ulcers, treated with polyurethane foams was not significantly different from that with hydrocolloids. Polyurethane foams were easier to remove [64, 175] and quicker to change [64].

Polyurethane foams can absorb exudate of approximately 10 times of its weight, maintain an appropriate moisture, and promote the granulation and re-epithelization. It leaves no residues on the wound surface. Polyurethane foams does not adhere to the wound surface, In addition, as the surface that comes into contact with the wound is made of a non-adhesive polyurethane net, and shear force does not result in the detachment of newly formed epidermis [177].

One case report [176] described the application of chitin, not a sheet product approved for shallow pressure ulcers by health insurance in Japan, but non-approved cotton type for the treatment of pressure ulcers [176]. In 32 patients, 11 patients were of pressure ulcers limited to the papillary dermis; the pressures were healed in 11 patients. Chitin may relieve pain, absorb exudate, protect granulation tissue, and promote re-epithelization.

Chitin fibers are soft, closely attach and protect the wound surface [176]. They can absorb fluid of up to 25 times of its weight [179]. They may promote granulation rich in blood vessels [176]. They allow compression hemostasis after the surgical debridement [179].

Currently no RCT was published targeting only shallow pressure ulcers treated with topical medication. Five RCT [3–7] of cadexomer iodine, one RCT [17] of silver sulfadiazine, one RCT [35] of trafermin, two RCT [25, 26] of tretinoin tocoferil, two RCT [8, 9] of bucladesine sodium, two RCT [29, 30] of prostaglandin E1, and two RCT [10, 11] of povidone-iodine sugar reported their efficacy in cure and reduction rates of Stage II–IV pressure ulcers, albeit of small number of Stage II pressure ulcers. Application of topical medication with lipids vehicle, such as petrolatum, zinc oxide, and dimethyl isopropyl azulene, is often practiced to protect and maintain the moist condition of wound surface [158]. Bucladesine sodium [180] and prostaglandin E1 [181, 182] may also promote re-epithelization. Should the critical colonization be suspected, cadexomer iodine, silver sulfadiazine, povidone-iodine sugar, or iodine ointments can be applied (Refer to 5.5.3).

Bucladesine sodium, with hygroscopic polyethylene glycols (macrogols) vehicle, can be applied to exudative or edematous wounds. It may overly dry the wound, if applied to already dry surface.

Prostaglandin E1, with liquid paraffin vehicle, can applied to moderate or less exudative wound. The application to exudative or edematous wounds is not recommended.

Cadexomer iodine, iodine ointments and povidone-iodine sugar can be applied to shallow ulcers suspected of critical colonization. They may lead an over-dehydration.

Silver sulfadiazine can be applied to shallow ulcers suspected of critical colonization. It may lead edema of the wounds and maceration of the surrounding skin.

Topical antibiotics with lipids vehicle, such as gentamycin ointment, can be applied for a short period to protect the wound surface and to control or prevent bacterial infection of acute or chronic shallow pressure ulcers. Antimicrobial resistant bacteria may appear in prolonged use.

Note: As of preparation of the guidelines, shipping of tretinoin tocoferil is suspended.

5.4.2 | Polyurethane Films May Be Applied to Uninfected and Re-Epithelizing Shallow Pressure Ulcers

A case report [164] recommended the application of polyurethan films to shallow pressure injuries, that is, erythema, bullae, erosion, or shallow ulcers. Polyurethan films may protect wound surface from shear force. It can maintain the moist environment, promote re-epithelization and wound healing. In Stage II pressure ulcers the nerve endings expose to the air and cause pain. Covering the wound surface with dressings may relieve the pain.

Polyurethan films are waterproof and prevent the entry of water and bacteria. At the same time they are semipermeable and allow the passage of air and vapor. They may maintain moist environment and may not interfere with sweating and insensible perspiration. They may prevent maceration and maintain barrier function of the skin. Of note that bacterial infection may exacerbate under the polyurethane films. Commercially available polyurethane films are formed as a film of polyurethane coated with a waterproof, hypoallergic and adhesive acrylic or vinyl materials. They can effectively seal and occlude wounds. With their transparency or translucency, the wound condition can be easily observed. They are semipermeable and allow the vaporization. Therefore, they maintain moisture on the wound and do not interfere with perspiration or insensible water loss. Thus, the edge of pressure ulcers does not become macerated, and the

barrier function of the skin remains intact. Polyurethane films should not be used for the wounds infected with bacteria; bacteria can rapidly proliferate in the moist environment under the polyurethan films.

5.5 | Treatment of Chronic Deep Pressure Ulcers

5.5.1 | Infection of Pressure Ulcers Is Assessed by Evaluation of the Surface of the Ulcer and Surrounding Skin With Four Cardinal Signs of Inflammation, That Is, Redness, Heat, Swelling and Pain, Systemic Conditions, for Example, Fever, Bacterial Culture From the Wound Surface, and Blood Examination

A meta-analysis [183] on the diagnosis of infection in pressure ulcers, with 15 studies and 985 patients, reported that the positive likelihood ratio for pain as a predictor of infection was high at 11–20, and was statistically significant. The negative likelihood ratio of 0.64–0.88, other clinical symptoms or examinations were not significant statistically. As a review article [184] stated, some patients do not complain of pain despite the presence of infection, and it is important to assess the infection through a comprehensive evaluation of clinical symptoms and signs along with the results of examinations.

Infection of pressure ulcers should be assessed by the combination of color, swelling, tenderness, pus discharge, an increase in exudate, and unpleasant odor of the ulcer and surrounding skin [184]. As a rule certain amount of bacteria can be detected from the wound surface, but they are not always harmful. The concept of bacterial balance, is now in mainstream. Not either septic or aseptic but the balance between bacterial burden, that is, contamination, colonization, and infection, and individual immune function decide the infection [185]. "Critical colonization" is a transitional state from colonization to infection, by bacteria increase on the wound surface. It may appear as a delay of wound healing or re-epithelization for 2 weeks [119].

Careful examination and evaluation of the wound provide important information for the diagnosis of infection [141]. The fluid retention beneath the necrotic tissue, enlargement of fine granular granulation into large edematous granylation, change of the color of wound surface from clear red to dark red and viscous exudate are the signs of infection. Infection makes the exudate suppurative, viscous and increased in volume. Once the infection is controlled the exudate decrease in volume and becomes serous or less bloody.

Fever and other systemic signs of infection prompt blood examination, such as CBC and C-reactive protein. Sudden high fever is a suspicious sign of sepsis, and blood bacterial culture should be performed. Bacterial culture should identify the pathogens and their antimicrobial susceptibilities. Bacterial culture of shallow pressure ulcers often identifies normal bacterial flora, such as *Staphylococcus epidermidis*; that of deep pressure ulcers often identifies concurrent infection of *S. aureus, Streptococcus pyogenes, Pseudomonas aeruginosa*, and *Escherichia coli, Enterococci* or *Proteus vulgaris* [119, 141].

If exudates are abundant with an intensely poor odor, a surgical incision and drainage should be performed for the deep tissue infections. Prior to the procedures, the patient's general condition and prescribed medication, such as antiplatelet agents and anticoagulants, should be checked. Surface surgery, such as incision of undermine, is classified in low-risk. The Japanese Circulation Society recommended aspirin to be continued, $P2Y_{12}$ receptor antagonists, such as clopidogrel, to be reconsider depends on the risk of thrombosis, and anticoagulants, such as direct oral anticoagulant (DOAC) and warfarin, to be continued [186]. The Japan Stroke Society recommended antiplatelet agents and anticoagulants to be continued [187]. Consultation to the attending physician is recommended prior to the suspension of antiplatelet agents or anticoagulants with the risk of hemorrhage. If surgical interventions with a risk of hemorrhage are required at home care, reference to a facility providing appropriate treatment is recommended.

Soft tissue infections are often noticed by its pain. Spinal cord injury patients may not recognize the pain, and their infection may be noticed after deterioration [188]; the close observation is required. Application of topical medication is difficult for the treatment of infection in spinal cord injury patients.

5.5.2 | Systemic Administration of Antibiotics Is Required Not Only With Positive Bacterial Culture From the Wound Surface, but With Inflammation in the Surrounding Skin, Fever or Increase in White Blood Cell Count or C-Reactive Protein

A guideline [119] mentioned efficacy of systemic administration of antibiotics for infection of pressure ulcers. Systemic administration of antibiotics is often employed in the treatment of wound infection.

In general, wounds should be cleansed with tap water or physiological saline. Necrotic tissue should be surgically removed. If inflammation signs, such as redness, swelling, heat, and pain are still observed in the ulcer or surrounding skin, systemic administration of antibiotics should be considered [119]. Cellulitis, fasciitis, osteomyelitis and sepsis may occur following the infection of pressure ulcers. If symptoms and signs suggestive of these conditions are observed, such as fever, leukocytosis, and elevated C-reactive protein levels, systemic administration of antibiotics should be initiated promptly [119, 163] In case urinary tract infection, infectious endocarditis or sinusitis appear in pressure ulcer patients, systemic antibiotics should be administered [119].

If systemic or local infection are suspected, bacterial flora should be cultured from pressure ulcers. Starting from broad-spectrum antibiotics, the antibiotics should be de-escalated depends on the result of the bacterial culture. If the antibiotics were not effective, infectious foci, such as abscess or sepsis, and the causative microorganisms should be reevaluated. Administration of anti-MRSA antibiotics may be required. Bacterial culture of shallow pressure ulcers often identifies normal bacterial flora, such as *S. epidermidis* and that of deep pressure ulcers often identifies concurrent infection of *S. aureus, S. pyogenes, P. aeruginosa,* and *E. coli, Enterococci* or *P. vulgaris* [141].

The odor and color of the exudates may be helpful to predict the result of bacterial culture [141]. *S. epidermidis* may appear in gray, *S. aureus* in lime green, and *P. aeruginosa* in bright green with a sweet–sour odor. Mixed infection with anaerobes may appear in brown color with a foul odor.

Patients with pressure ulcers often become carriers of multidrug-resistant *Staphylococcus, Pseudomonas and Acinetobacter*. In order to prevent spreading the multidrug-resistant strains, disposable gown technique should be applied. Disposable forceps and other devices may be used. Bacterial surveillance should be done [163].

5.5.3 | Cadexomer Iodine, Silver Sulfadiazine, Povidone-Iodine Sugar, Povidone-Iodine Gel, Iodine Ointment, or Iodoform May Be Applied as Topical Medication for Infectious Pressure Ulcers

Three RCT [4–6, 10–12, 15, 17, 19] reported treatment of skin ulcers with cadexomer iodine, silver sulfadiazine, or povidone-iodine sugar. Cadexomer iodine was superior to dextranomer and its vehicle, dextrin polymer. Silver sulfadiazine was superior to povidone iodine and its vehicle. Povidone-iodine sugar was superior to sucrose and calf blood extract. One case report [189] mentioned povidone-iodine gel in the treatment of skin ulcers. Two review articles [190, 191] mentioned iodoform and iodine ointment gel in the treatment of skin ulcers.

One RCT [5] of cadexomer iodine reported a significant reduction of discharge compared with dextranomer. One RCT [4] reported a significant reduction of bacterial burden and re-emergence. The other RCT [6] reported no difference compared with a mixture of fibrinolysin, deoxyribonuclease, and chloramphenicol.

Cadexomer iodine shows a bactericidal effect by releasing the iodine slowly, and its vehicle dextrin polymer absorbs not only exudates but also bacteria [192–194]. It is useful in the treatment of wounds rich in bacteria and exudates, however, polymer beads must be completely washed off in dressing change. Cadexomer iodine should not be used in undermine in which washing is difficult [190]. Application of cadexomer iodine may make the dry wound surface drier and may disturb wound healing. It may damage the granulation tissue or may lead iodine allergy [190].

One RCT [12] of silver sulfadiazine reported a significantly reduction of bacterial load compared to povidone-iodine solution, but not significant compared to physiological saline. One RCT [15] reported a significantly superior effect to its vehicle. The other RCT [17] reported no difference compared with gentamicin sulfate cream.

Silver sulfadiazine with its silver ion can destroy bacterial cell membrane and cell wall, and show antibiotic effect [160, 161]. It inhibits the formation of biofilm derived from methicillin-sensitive or methicillin-resistant *Staphylococcus aureus* [162]. Its emulsifiers vehicle can soften and lyse the necrotic tissue, and debride the wound surface, however, the emulsifiers vehicle may provide too much hydration on the wound surface [190]. Its effect is attenuated when used concomitantly with povidone-iodine. Concomitant use of silver sulfadiazine with other topical medication, especially with that of enzymatic activity, should be avoided [190].

Three non-blinded RCT [10, 11, 19] of povidone-iodine reported a significantly superior effect to sucrose, calf blood extract and lysozyme chloride.

The effect of povidone-iodine sugar derived from both povidone-iodine and sugar. Povidone-iodine is bactericidal [195]. Sugar suppresses bacterial growth and biofilm formation of *S. aureus* [196]. Sugar absorbs exudate from the edematous wound surface, and promotes collagen synthesis by fibroblasts and granulation [197]. Application of povidone-iodine sugar may make the dry wound surface drier to disturb wound healing [190]. Povidone-iodine sugar may damage the granulation tissue. It may cause iodine allergy [190].

In a case report [189] povidone-iodine gel could erase *S. aureus* and *P. aeruginosa* in ulcers intractable to antibiotics ointments in the skin lesions, with two pressure ulcers in total of 20 patients.

The effect of povidone-iodine gel derived from povidone-iodine, and its bactericidal effect is stronger than that of povidone-iodine sugar [195, 198]. It exerts strong antiseptic or inactivating effects not only on bacteria including MRSA but on viruses [199, 200]. It may cause transient hypothyroidism if used in large doses, or iodine allregy [190].

A review article mentioned a bactericidal effect of iodoform, which derived from iodine [190].

Iodoform exerts a bactericidal effect through the iodine released into exudates. It may reduce odor, exudates and pain of a wound [201]. It may exert iodine poisoning or allergy [190].

A review article mentioned a bactericidal effect of iodine ointment [191].

Iodine ointment could release a similar amount of iodine to cadexomer iodine. Its bactericidal effect is also similar to that of cadexomer iodine, and it can inhibit bacterial growth, including MRSA [202, 203]. Softened in application on wound surface, it may ease the pain in treatment [191]. One gram of iodine ointment can absorb 7.3 mL of purified water [203], the largest capacity among the topical medication for wound treatment. Thus, it is appropriate for wounds rich in exudate, but if applied in wounds poor in exudate, it may make the dry wound surface drier to disturb wound healing. Iodine allergy may appear.

A double-blind RCT [17] revealed that the bacteria count was not significantly different in 2 weeks between gentamycin sulfate in emulsifiers' vehicle and silver sulfadiazine. One RCT [6] reported a superior effect of a mixture of fibrinolysin, deoxyribonuclease and chloramphenicol in erasing *P. aeruginosa* in 4 weeks to cadexomer iodine, but the recurrence rates in 4 or 6 weeks was similar among them. The other RCT [204] reported that the infection rate of surgical wounds was not different between bacitracin ointment and petrolatum, but contact dermatitis occurred in bacitracin ointment group. None of these studies presented superiority of an antibiotics among them. The

long-term use of antibiotics ointment for deep pressure ulcers may lead microbial substitution.

5.5.4 | Silver-Containing Hydrophilic Fibers or Silver-Containing Polyurethane Foams Dressings May Be Applied for Infected Pressure Ulcers

One systematic review [205] reported the antibacterial effect of silver-containing hydrophilic fibers and silver-containing polyurethane foams in infected chronic wounds. In total, 1285 patients with 210 pressure ulcers were analyzed and three studies reported an antibacterial effect.

Another systematic review [206] reported the similar efficacy of silver-containing hydrophilic fibers and silver-containing polyurethane foams in the healing of infected open wounds in 4 weeks. One RCT [207] reported superiority of silver-containing polyurethane foams to conventional polyurethane foams, in reduction of wound area and control of exudates, odor and pain. Another RCT [208] of silver-containing hydrophilic fibers reported a quick reduction of wound area, although infection index was not different from the control group.

Among two RCT [207, 208] of silver-containing hydrophilic fibers on infected chronic wounds [207, 208], one RCT [207] did not disclose a difference between silver-containing and conventional hydrophilic fibers. Another RCT [208] reported a greater reduction of wound size in silver-containing hydrophilic fibers group.

Hydrophilic fibers dressing is divided in Hydrofiber and alginate. Hydrofiber can absorb exudate of approximately 30 times over its own weight, which is roughly a double of aliginate. Hydrofiber may maintain a moist environment to promote granulation. It may prevent leakage of exudate and maceration of the surrounding sskin [177]. Silver-containing Hydrofiber absorbs exudate and bacteria, and may reduce the bacterial burden on wound surface. Released silver ions from silver-containing Hydrofiber may show an antibacterial efect [211–213].

Alginate can absorb exudate of 10–20 times over its own weight [177]. Absorbing exudates, a wet alginate may maintain a moist environment to promote wound healing [178] In addition, alginate works in hemostasis through its calcium ion which exchange with sodium ion in the blood and exudate, and spread in the capillaries [214]. Absorbing exudate, silver-containing alginate release silver ion and show antiseptic effect. Silver-containing alginate may be effective for wounds susceptible for infection.

Polyurethane foams absorb can absorb exudate of approximately 10 times over its own weight. Absorbing exudates, polyurethane foams may maintain a moist environment to promote granulation and re-epithelization. It may not be adhesive and protect the re-epithelized fragile wound surface from sheer force [177]. Silver-containing polyurethane foams may be effective for wounds susceptible for infection by antiseptic silver ions.

Polyhexamethylene biguanide (PHMB)-containing hydrogel has been available in Japan since 2018. PHMB shows a broad antimicrobial activity and may eliminate biofilms [215]. It has been used over 20 years world-widely, and recognized its safety profile. At the preparation of the guidelines RCT of PHMB for pressure ulcers is not available.

5.5.5 | Povidone-Iodine Sugar or Tretinoin Tocoferil May Be Effective for Undermined Pressure Ulcers

Treatment of undermined pressure ulcers was reported in one observational study of povidone-iodine sugar [216], one non-randomized study of trafermin [217] and one review article of tretinoin tocoferil [218]. In the undermine the removal of necrotic tissue and the control of bacterial infection are difficult to achieve. The insufficient drainage of exudates leads an excessively moist condition. Shear force from the outside results in further enlargement of undermine. Evaluation of the individual condition to eliminate compression and shearing is warranted, however, if the undermine is not resolved, surgical opening and/or negative-pressure wound therapy should be considered.

One observational study of povidone-iodine sugar [216] reported a beneficial effect in the treatment of undermined ulcers. In 36 diabetics of skin ulcers, among them six were pressure ulcers, eight out of nine (88.9%) undermined ulcer improved with povidone-iodine sugar.

Advantages of povidone-iodine sugar are absorbing exudate, improving tissue edema, promoting granulation, and controlling bacterial infection. Application of povidone-iodine sugar may make the dry wound surface drier to disturb wound healing. It may damage the granulation tissue or lead iodine allergy [218].

One non-randomized study [217] could not demonstrate the superiority of trafermin over other topical medication. Two case reports [219, 220] mentioned a size reduction of undermine with trafermin treatment. Attempts to insert a chitin sprayed with trafermin to deliver the drug into undermine [221] and combination of trafermin with NPWT [77] were reported in case reports. Strong effects of angiogenesis and fibrogenesis may reduce the size of undermine [222–224]. The combination with other topical medication or dressings is recommended to fill the dead spaces and to retain the moisture condition in undermine [218].

Tretinoin tocoferil promotes migration and proliferation of fibroblasts and endothel, and granulation [225–228]. Its emulsifiers vehicle with 70% water make tretinoin tocoferil suitable for dried ulcers, but not for wet and edematous ulcers.

Note: As of preparation of the guidelines, shipping of tretinoin tocoferil is suspended.

5.5.6 | Surgical Intervention Should Be Considered for Undermined Pressure Ulcers

One prospective cohort study [229] reported that after 4 weeks of surgical intervention the DESIGN-R value was improved significantly in 39 out of 162 undermined pressure ulcers [229]. Also, there are four case reports [230–233] of the surgical intervention to undermined pressure ulcers.

In case the bacterial infection in undermine affects and worsen the general condition, the immediate surgical intervention is required. As the immediate handling of post-operative bleeding may not be available, a proper hemostasis with electrical scalpels during the surgery should be considered. Prior to the procedures, the patient's general condition and prescribed medications, such as antiplatelet agents and anticoagulants, should be checked. Surface surgery, such as incision of undermine, is classified in low risk. The Japanese Circulation Society recommended aspirin to be continued, $P2Y_{12}$ receptor antagonists, such as clopidogrel, to be reconsider depends on the risk of thrombosis, and anticoagulants, such as direct oral anticoagulant (DOAC) and warfarin, to be continued [186]. The Japan Stroke Society recommended antiplatelet agents and anticoagulants to be continued [187]. Consultation to the attending physician is recommended prior to the suspension of antiplatelet agents or anticoagulants with the risk of hemorrhage.

The choice of procedures, removal of whole overlay or simple incision, depends on the subsequent treatments and care. The following conditions should be considered:

Infection in the undermine, existence of firm necrotic tissue or complex structure within the undermine these are indications for the removal of whole overlay.

Plans after the simple incision; topical treatment with dressings or topical medication, reconstruction surgery, skin graft or flaps, or negative-pressure wound therapy.

Other than negative-pressure wound therapy, remaining overlay is useless, and even harmful.

Personnel to treat the pressure ulcers; physicians, nurses in the hospital, homecare nurses, or patient's family members.

In case the family members can not clean inside of the undermine, the removal of whole overlay is advisable.

5.6 | Assessment of Pressure Ulcers

5.6.1 | For the Assessment of Pressure Ulcers the DESIGN, DESIGN-R, DESIGN-R 2020, Pressure Sore Status Tool (PSST), and Pressure Ulcer Scale for Healing (PUSH) Can Be Used

Analyses on the assessment scales of pressure ulcers were reported in a case–control study of PSST [234], three prospective cohort studies of PUSH [235–237], a case–control study of DESIGN [238], and three cohort studies of DESIGN-R [239–241].

The interrater reliability of PSST was 0.91 [234], but it is difficult to use in clinical situations because of its large number of parameters. The National Pressure Ulcer Advisory Panel developed PUSH to overcome this shortcoming. The PUSH score decreased in healing pressure ulcers but not in those intractable. The PUSH score was correlated with the size of pressure ulcers and the PSST score [235–237]. Principal components analysis confirmed that the parameters in PUSH accounted for 58%–74% of the wound healing variance over a 10-week period [245]. A survey of the PUSH reported its reliability, although its usefulness was questionable [246].

DESIGN was developed by the Japanese Society of Pressure Ulcers in 2002. Its interrater reliability was 0.98 with clinical pictures and 0.91 with on-site patients. It was strongly correlated with the PSST score [238]. DESIGN was useful in evaluating the longitudinal course of pressure ulcers, however, it could not compare the severity of pressure ulcers among the patients. DESIGN-R [239, 244] was developed in 2008 to compare the severity of pressure ulcers among the patients with weighted parameters [247]. The DESIGN-R score was correlated with the improvement of pressure ulcers [240], and healing period [241]. In 2020, “suspected deep tissue injury (DTI)” and concept of critical colonization were included in DESIGN-R2020 [248].

5.7 | Other Treatment Options

5.7.1 | Surgical Reconstruction With Skin Graft or Skin Flaps May Be Effective for Pressure Ulcers of Stage III or VI, However, Indication of the Surgery Should Be Evaluated Carefully. Infection Control and Surgical and/or Chemical Debridement Should Be Performed in Advance

Surgical reconstruction with skin graft or skin flaps may be effective for pressure ulcers of Stage III or VI, but the indication should be evaluated carefully. Infection control and surgical and/or chemical debridement should be performed in advance.

Surgical interventions for pressure ulcers were reported in retrospective cohort studies [249–254] and a case report [255].

Surgical reconstruction with skin graft or skin flaps may induce a rapid healing for deep pressure ulcers recalcitrant to conservative therapies with topical medication and dressings. Surgical reconstruction, especially muscle and musculofascial flaps, is an invasive procedures [249], and its indication requires a careful evaluation. Prior to the procedures, the patient’s general condition and prescribed medications, such as antiplatelet agents and anticoagulants, should be checked. Surface surgery is classified in low-risk procedures. The Japanese Circulation Society recommended aspirin to be continued, $P2Y_{12}$ receptor antagonists, such as clopidogrel, to be reconsider depends on the risk of thrombosis, and anticoagulants, such as direct oral anticoagulant (DOAC) and warfarin, to be continued [186]. The Japan Stroke Society recommended antiplatelet agents and anticoagulants to be continued [187]. Consultation to the attending physician is recommended prior to the suspension of antiplatelet agents or anticoagulants with the risk of hemorrhage.

The factors, which underlie in developing pressure ulcers, such as frail, poor nutrition, cardiopulmonary dysfunction, are usually persist before and after the surgeries. Attentive care, such as frequent body repositioning and a body pressure-dispersion mattress, is usually employed during the hospital stay, however, it is often not the case in home-care settings. Prior to discharge from the hospital, the home care settings should be evaluated; otherwise, the pressure ulcers may recur, and the surgeries may

fall into a mere self-satisfaction of the surgeons. The postoperative recurrence rate may exceeded 70% [250–253].

The details of the surgical reconstruction procedures are beyond the focus of these guidelines; for details of the procedures we recommend to refer the surgical textbooks. Also, we advise the proper wound bed preparation, with surgical or chemical debridement with topical proteinases, at least a few weeks prior to the surgery, and selecting the procedures, split-thickness or full-thickness skin grafts, musculofascial, perforator or muscle flaps, foreseeing the weight bearing and constriction in the surgical site. The musculofascial flaps may be superior to muscle flaps [254]. The urinary tract diversion or ostomy may be useful in some situations [255].

5.7.2 | Topical Application Techniques of Growth Factors and Autologous Blood-Borne Cells, Have Been Developed

The applications of growth factors and autologous blood-borne cells for the treatment of chronic wounds have been explored. Basic fibroblast growth factor (bFGF) is commercially available in Japan. Vascular endothelial growth factor (VEGF) [256], platelet-derived growth factor (PDGF) [257] and granulocyte-macrophage colony-stimulating factor (GM-CSF) [258] are available in some countries. Efficacy of PDGF is reported in one RCT [258] with a significant reduction in treatment period.

Peripheral blood cells and their culture supernatant are rich in growth factors; the activated platelet supernatant [259] and red blood cells [260] are used in the treatment of chronic skin ulcers. The autologous hematopoietic stem cells contain vascular endothel precursor and they are injected in the ischemic limb lesions to promote angiogenesis [261]. Clinical studies for pressure ulcers were yet to be reported.

A clinical study of allogeneic cultured dermal substitute composed of spongy collagen with fibroblasts applied to pressure ulcers was reported [262]. The applications of a substrate filled with bone marrow cells [263] or bFGF [264] to the skin ulcers were also reported.

5.7.3 | Hydrotherapy, Infrared, Visible or Ultraviolet Light Therapy, Low-Power LASER Therapy, Hyperbaric Oxygen Therapy, and Electric Stimulation Therapy Have Been Reported to Be Effective in the Treatment of Pressure Ulcers, However, They Are Not Widely Employed in Japan

One RCT of hydrotherapy [143] on pressure ulcers reported a significant decrease in wound area compared with saline gauze dressing as a control [143]. The mechanism of its effect is not discussed. In general hydrotherapy stimulates whole body in Hubbard tank or a part of the body with whirlpool water at 35.5°C–36.6°C.

Infrared therapy for pressure ulcers was reported in several literatures. One RCT [265] reported a significantly faster healing compared with the control group. The wavelength of infrared light is varied by the apparatus. The exact effective wavelength is yet to be determined. One RCT [266] of low-power LASER therapy did not reveal a superiority to the control. One blinded RCT [268] of ultraviolet light therapy, with Kromayer lamp, revealed a promotion of wound healing. Both intervention [266] and control groups were consisted with eight subjects, and the irradiation, twice a week, was started at 2.5 minimal erythema dose, and was gradually increased to maintain erythema. One systematic review [272] concluded that they were very uncertain in the effect of phototherapy in treating pressure ulcers.

Hyperbaric oxygen therapy places a patient in a chamber with elevated oxygen pressure. It is applied to carbon monoxide poisoning or anaerobic bacterial infection. A few case reports [267, 278] could not prove its efficacy on pressure ulcers.

A meta-analysis [269] of electric stimulation therapy reported its efficacy on pressure ulcers. One double-blind RCT [270] reported a quick decrease of wound size on Day 45, but not on Day 147. Electric stimulation therapy promotes wound healing by the electric current between the wound and surrounding skin attached with electrode. The negative electrode gathers sodium ions with high pH; with low pH. The change in acidity may affect bacterial infection and vasodilation. Also, negatively charged cells, such as macrophages and neutrophils, migrate toward the positive electrode, and positively charged cells, such as fibroblasts, migrate toward the negative electrode (electrotaxis).

One meta-analysis [269] of electric stimulation of the gluteus maximus muscle revealed a significant improvement in pressure ulcers in spinal cord injury patients. In addition to the electrotaxis, electric stimulation may reduce the contact pressure in sitting [273–276] and increase the cutaneous blood flow [277].

5.7.4 | Indication of So-Called "Wrap Therapy" Requires a Special Attention. As the Users Are Liable for the Application of Materials, Such as Kitchen Cling Film Wrap, Not Intended for Medical Use, the Consent Must Be Obtained From the Patient and His Family Prior to Start So-Called "Wrap Therapy"

One RCT [279] on Stage II or Stage III pressure ulcers did not reveal a difference between so-called "wrap therapy" ($n = 35$) and control ($n = 31$) groups in the wound size or DESIGN-R and PUSH scores. The other RCT [280, 281] reported that so-called "wrap therapy" was superior in DESIGN [280] or medical expenses [281]. However, a case series study [282] reported severe systemic infection after so-called "wrap therapy" in Stage IV pressure ulcers; some fell in fatal outcomes. Thus, the guidelines committee urges that the indication of this treatment requires a special attention.

Occlusive dressings intend to avoid drying of the wound surface to achieve moist wound healing. Occlusive dressings is a general term for a dressing method using modern dressings, such as hydrocolloids to occlude the wound surface and create a moist environment, hydrogels to moisten the dried wound

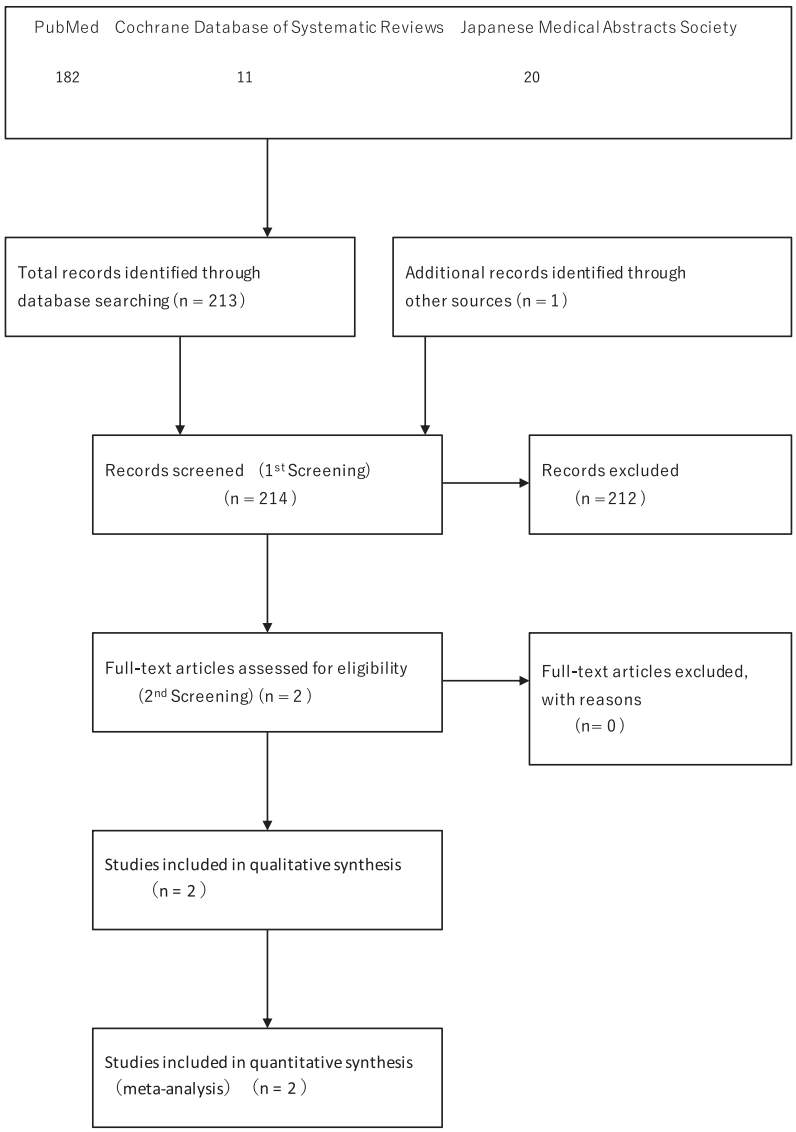
surface, hydrophilic fibers, chitin, hydropolymers, and polyurethane foams to absorb and retain exudates, and polyurethane film as a secondary dressing, over the conventional gauze dressing [283].

If a wound dressing prevents the entry of liquids, oxygen and bacteria into the wound from outside, and leakage or evaporation of exudate from the wound, it can be classified in an occlusive dressing, but more accurately in a closed or sealed dressing. By contrast, dressings that allow the passage of vapor and oxygen are classified in semi-occlusive or semipermeable dressings. Their boundary is not always distinct, thus, they are often referred to as occlusive dressing methods without making such a distinction [283].

Wrap therapy is a dressing method using polychlorovinylidene kitchen cling film wrap with low permeability to oxygen and water vapor. Unlike polyurethane films of semi-occlusive characteristics, it can be truly occlusive without adhering and sealing the wound surface [280, 281, 283]. Advocates of so-called "wrap therapy" call it "open wet dressing," as excess exudates can escape from the incomplete sealing [283, 284].

There are variations in so-called "wrap therapy" or open wet dressing; no established protocols exist. Therefore, it is impossible to evaluate so-called "wrap therapy" as a whole. It may be effective if the procedure is carried out strictly adhering to the methods mentioned in the RCT [280], which reported the efficacy of polychlorovinylidene dressing without increasing the incidence of infection.

Kitchen cling film wrap is not approved for a medical use. Physicians who instructed wrap therapy must be aware that they are responsible for any damage caused by the wrap therapy, such as infection. Explaining the efficacy and risk of wrap therapy to the patient and his family, an written consent must be obtained.



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 3 | CQ1 Flow chart of literature search.

6 | Chapter 6 Data and Analyses of CQs

CQ1 Is surgical debridement recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform surgical debridement in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

6.1 | Literature Search

For the third edition of the guidelines for the diagnosis and treatment of pressure ulcers, the Japan Medical Library Association searched the electronic databases, PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society, to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

Results: RCT of surgical debridement solely on pressure ulcers were not found. With a modified search one RCT of surgical debridement partly on pressure ulcers, and another RCT on general ulcers were retrieved. These two RCT proceeded for further analysis.

6.2 | Outcome

The systematic review team selected Cure rate (Importance: 5) as an outcome. Incidence of adverse events was not selected as an outcome as it was reported in only one study. The relative importance of outcome was voted by all drafting committee members, with 100% agreement.

6.3 | Literature Screening

The first screening with "all ulcers including pressure ulcers AND surgical debridement" as the query was performed, and 213 studies were retrieved. In addition, one RCT was retrieved with "surgical debridement" as the query. The second screening filtered for RCT retrieved two studies referring cure rate, which proceeded for further analysis. Flow chart of literature search appeared in Figure 3.

6.4 | Evaluation of Certainty of Evidence

The effects, prepared in risk ratio or risk difference, and certainty (strength) of evidence, that is, limitation in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias, were analyzed based on the Minds Manual for Guideline Development 2020 ver. 3.0. As

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
A. Piaggesi 1998	22	22	23	24	87.8%	1.04 [0.93, 1.17]	1998
L. Michailidis 2018	5	5	5	7	12.2%	1.33 [0.79, 2.26]	2018
Total (95% CI)		**27**		**31**	**100.0%**	**1.07 [0.88, 1.30]**	
Total events	27		28				

Heterogeneity: Tau² = 0.01; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 0.71 (P = 0.48)

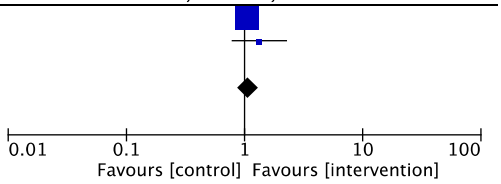


FIGURE 4 | CQ1 Forest plot.

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	debridement
Controls	conventional therapy

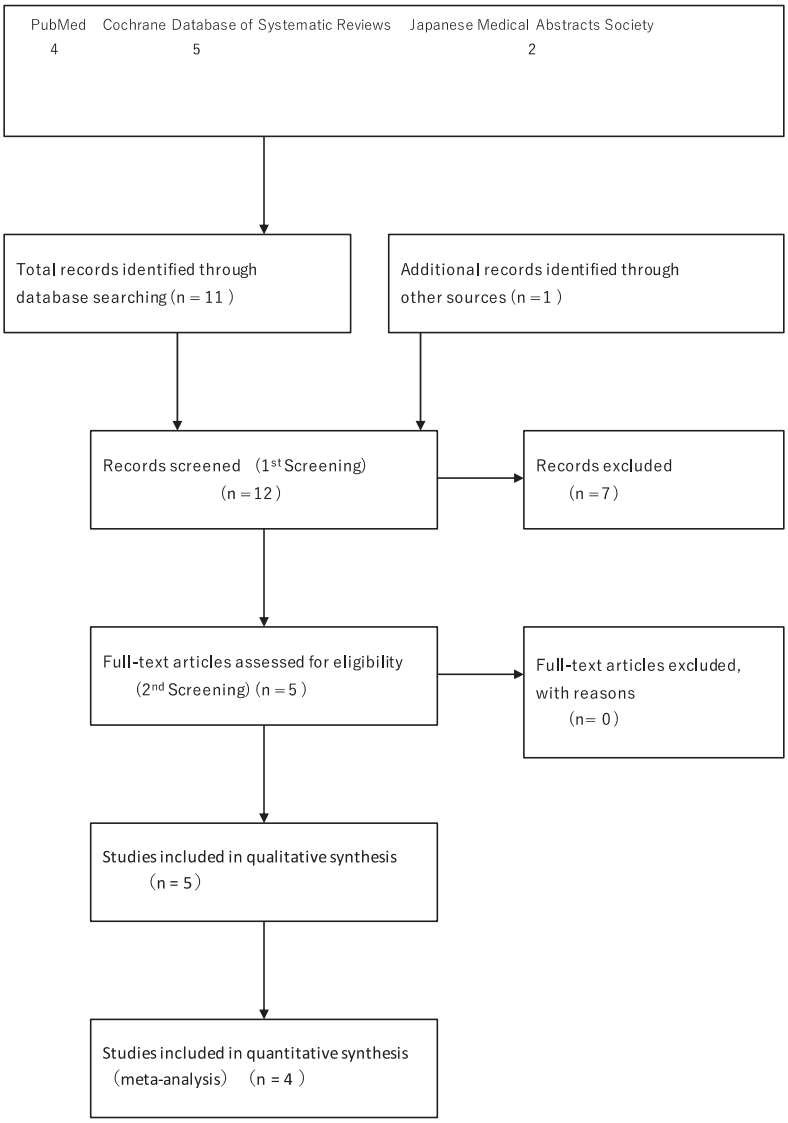
The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Number of participants, Absolute effects: Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Cure rate	RCT/2	-1	0	-2	-1	0	0	31	28	90.3	27	27	100	RR	1.07	0.88-1.30	Very weak	5

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

FIGURE 5 | CQ1 Overall evidence.



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 6 | CQ2 Cadexomer iodine flow chart of literature search.

the surgical debridement could not perform in blind fashion, certainty of evidence were lowered in risk of bias and imprecision.

6.5 | Evaluation of Outcome

A meta-analysis was performed for respective outcome in relative effect and 95% confidence interval with Review Manager Version 5.4, The Cochrane Collaboration, 2020.

6.6 | Results

Outcome: cure rate; relative effect: 1.07; 95% confidence interval: 0.88–1.30; certainty of evidence: very weak (D).

Forest plot and overall evidence appeared in Figures 4 and 5. Evidence profile in Supporting Information can be obtained from the Japanese Dermatological Association. Summary of findings table was presented to guideline panels.

CQ2 Is the use of topical medication recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to use cadexomer iodine, bucladesine sodium or povidone-iodine sugar in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

6.7 | Literature Search

For the third edition of the Guidelines for the diagnosis and treatment of pressure ulcers the Japan Medical Library Association searched the electronic databases, PubMed, Cochrane Database

of Systematic Reviews, and Japanese Medical Abstracts Society, to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

All the topical medication approved in Japan for the treatment of skin ulcers, prostaglandin E_1, bromelain, bucladesine sodium, cadexomer iodine, dextranomer, dimethyl isopropylazulene, gentamicin, iodoform, povidone-iodine sugar, fusidic acid, silver sulfadiazine, trafermin, and tretinoin tocoferil, were screened for preliminary search, and a systematic review was conducted for cadexomer iodine, bucladesine sodium, and povidone-iodine sugar. For cadexomer iodine, the search in PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society retrieved 4, 5, and 2 studies, respectively, and another study in a relevant search. For bucladesine sodium only the search in Japanese Medical Abstracts Society retrieved four studies. For povidone-iodine sugar, the search in PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society retrieved 1, 1, and 7 studies, respectively, and two studies in a relevant search.

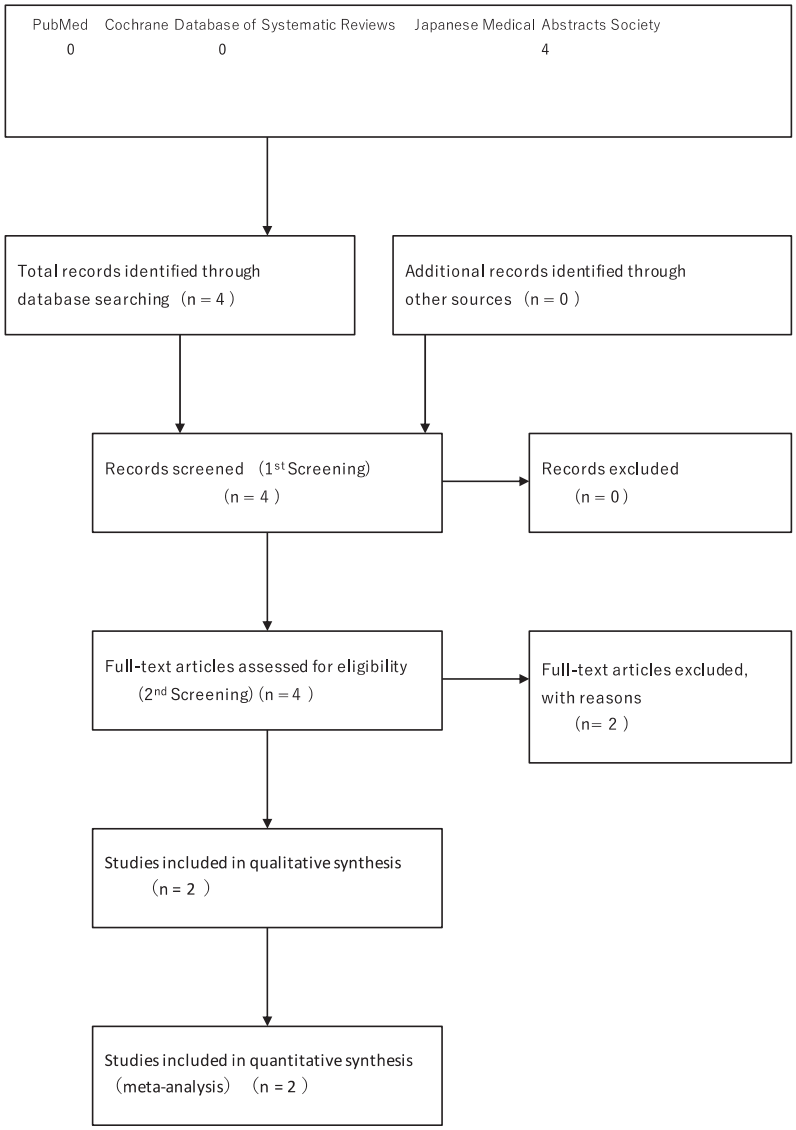
Note: As of preparation of the guidelines, shipping of tretinoin tocoferil is suspended.

6.8 | Outcome

The systematic review team selected cure rate (Importance: 5), reduction rate (Importance: 5), 50% reduction rate (Importance: 4), and incidence of adverse events (Importance: 4) as outcomes. The relative importance of outcome was voted by all drafting committee members, with 100% agreement.

6.9 | Literature Screening

Cadexomer iodine: The first screening for the above outcomes retrieved 12 studies. The second screening filtered for RCT



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 7 | CQ2 Bucladesine sodium flow chart of literature search.

retrieved 5 studies, which proceeded for further analysis. Flow chart of literature search appeared in Figure 6.

Bucladesine sodium: The first screening for the above outcomes retrieved 4 studies. The second screening filtered for RCT retrieved 2 studies, which proceeded for further analysis. Flow chart of literature search appeared in Figure 7.

Povidone-iodine sugar: The first screening for the above outcomes retrieved 11 studies. The second screening filtered for RCT retrieved 2 studies, which proceeded for further analysis. Flow chart of literature search appeared in Figure 8.

6.10 | Evaluation of Certainty of Evidence

The effects, prepared in risk ratio or risk difference, and certainty (strength) of evidence, that is, limitation in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias, were analyzed based on the Minds Manual for Guideline Development 2020 ver. 3.0. Most of the clinical trials published in Japan were financially sponsored by the manufactures; thus, certainty of evidence were lowered in other bias.

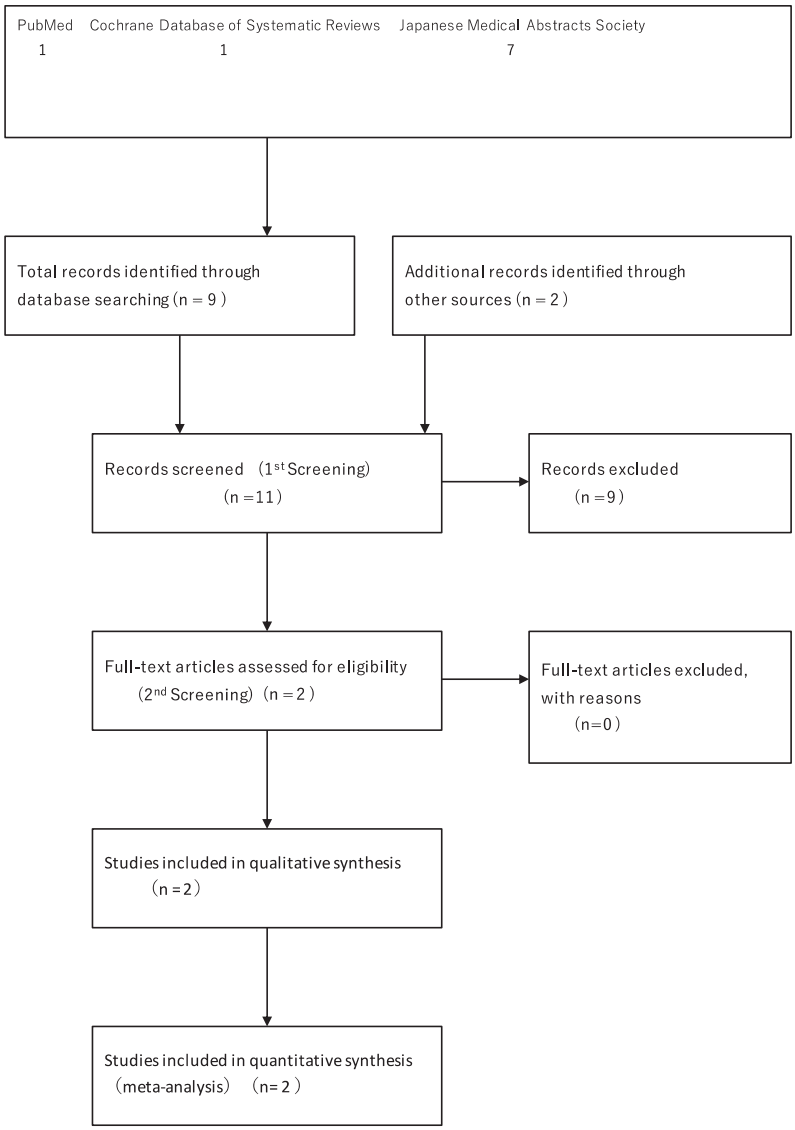
6.11 | Evaluation of Outcome

A meta-analysis was performed for respective outcome in relative effect and 95% confidence interval with Review Manager Version 5.4, The Cochrane Collaboration, 2020.

6.12 | Results

6.12.1 | Cadexomer Iodine

Outcome: cure rate; relative effect: 2.48; 95% confidence interval: 1.63–3.78; certainty of evidence: very weak (D).



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 8 | CQ2 Povidone-iodine sugar flow chart of literature search.

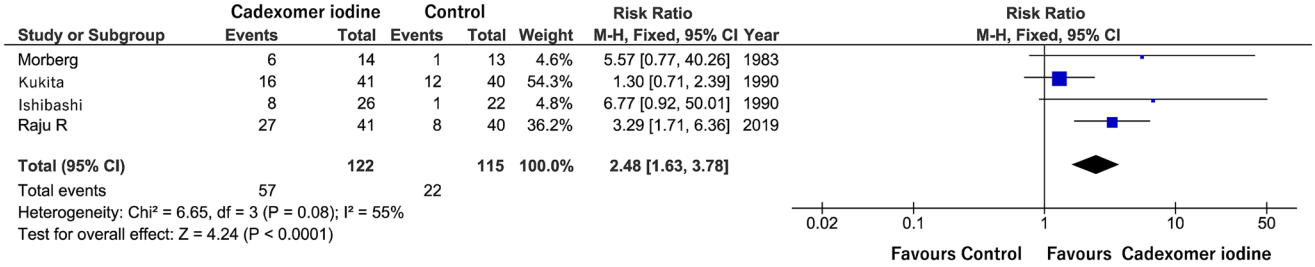


FIGURE 9 | CQ2 Cadexomer iodine cure rate forest plot.

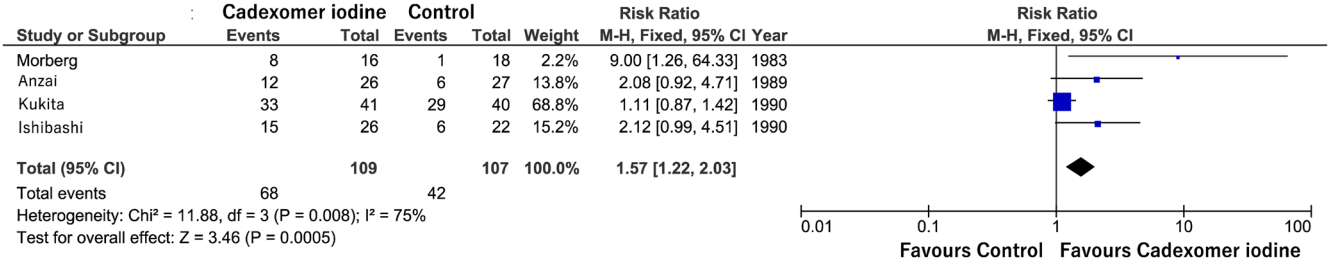


FIGURE 10 | CQ2 Cadexomer iodine 50% reduction rate forest plot.

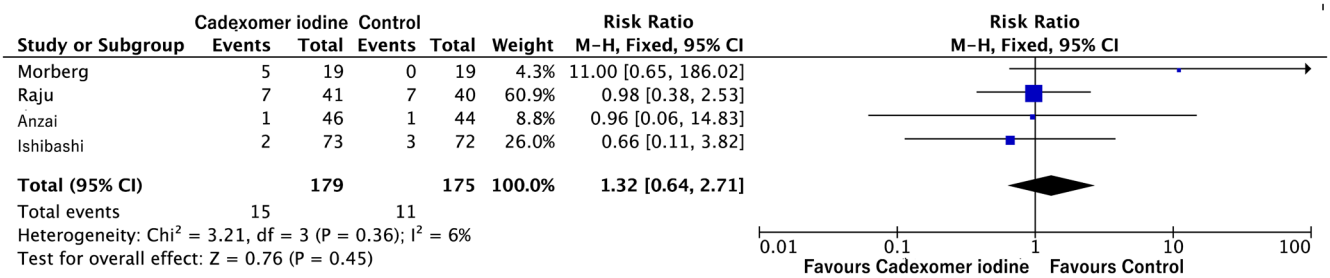


FIGURE 11 | CQ2 Cadexomer iodine incidence of adverse events forest plot.

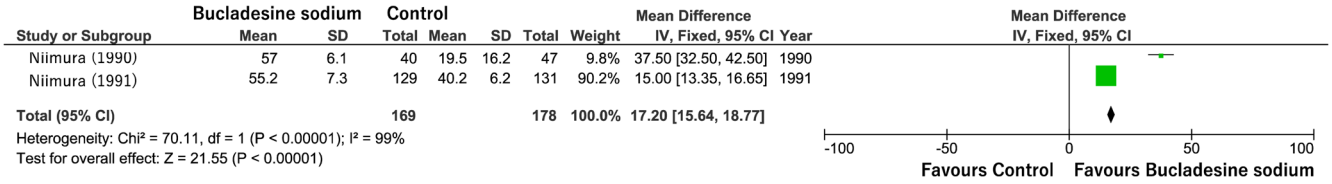


FIGURE 12 | CQ2 Bucladesine sodium reduction rate forest plot.

FIGURE 13 | CQ2 Bucladesine sodium incidence of adverse events forest plot.

Outcome: 50% reduction rate; relative effect: 1.57; 95% confidence interval: 1.22–2.03; certainty of evidence: very weak (D).

Outcome: incidence of adverse events; relative effect: 1.37; 95% confidence interval: 0.61–3.06; certainty of evidence: very weak (D).

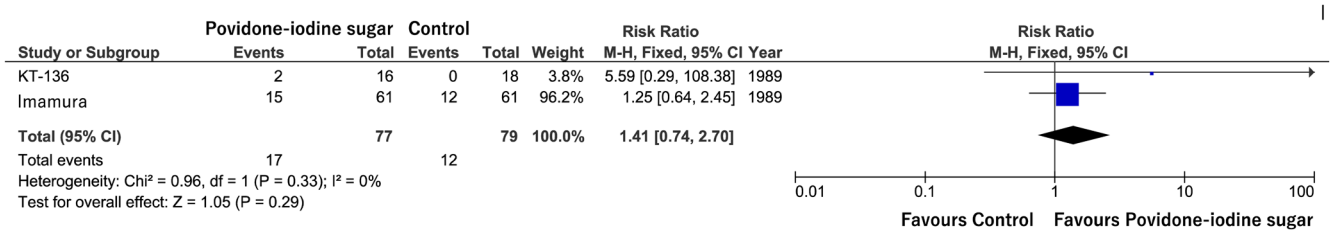


FIGURE 14 | CQ2 Povidone-iodine sugar cure rate forest plot.

FIGURE 15 | CQ2 Povidone-iodine sugar reduction rate forest plot.

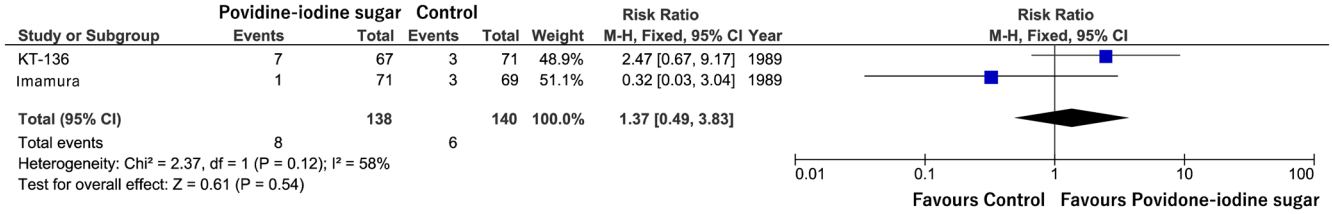


FIGURE 16 | CQ2 Povidone-iodine sugar incidence of adverse events forest plot.

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	Cadexomer iodine
Controls	treatments without topical medication

The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Number of participants, Absolute effects: Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Cure rate	RCT/4	-1	0	0	-1	-1	0	115	22	19.1	122	57	47	RR	2.48	1.63-3.78	Very weak	5
50% reduction rate	RCT/4	-1	0	0	-1	-1	0	107	42	39.2	109	68	62	RR	1.57	1.22-2.03	Very weak	4
Incidence of adverse events	RCT/4	-1	0	-1	-1	-1	0	175	11	6	170	15	9	RR	1.37	0.61-3.06	Very weak	4

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

FIGURE 17 | CQ2 Cadexomer iodine overall evidence.

6.12.2 | Bucladesine Sodium

Outcome: reduction rate; relative effect: 17.2; 95% confidence interval: 15.64–18.77; certainty of evidence: very weak (D).

Outcome: incidence of adverse events relative effect: 0.91; 95% confidence interval: 0.45–1.86; certainty of evidence: very weak (D).

6.12.3 | Povidone-Iodine Sugar

Outcome: cure rate; relative effect: 1.41; 95% confidence interval: 0.74–2.70; certainty of evidence: very weak (D).

Outcome: 50% reduction rate; relative effect: 1.40; 95% confidence interval: 1.00–1.97; certainty of evidence: very weak (D).

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	Bucladesine sodium
Controls	treatments without topical medication

The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Number of participants, Absolute effects: Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Reduction rate	RCT/2	-1	-1	0	0	-1	0	178			169			MD	17.2	15.64-18.77	Very weak	5
Incidence of adverse events	RCT/2	-1	0	-1	-1	-1	0	223	15	6.7	215	13	6	RR	0.91	0.45-1.86	Very weak	4

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio; MD: mean difference

FIGURE 18 | CQ2 Bucladesine sodium overall evidence.

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	Povidone-iodine sugar
Controls	treatments without topical medication

The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Number of participants, Absolute effects: Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Cure rate	RCT/2	-1	0	-1	-1	-1	0	79	12	15.1	77	17	22.1	RR	1.41	0.74-2.70	Very weak	5
50% reduction rate	RCT/2	-1	0	-1	-1	-1	0	78	30	38.4	77	42	54.5	RR	1.4	1.00-1.97	Very weak	4
Incidence of adverse events	RCT/2	-1	0	-1	-1	-1	0	140	6	4.3	138	8	5.8	RR	1.37	0.49-3.83	Very weak	4

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

FIGURE 19 | CQ2 Povidone-iodine sugar overall evidence.

Outcome: incidence of adverse events; relative effect: 1.37; 95% confidence interval: 0.49–3.83; certainty of evidence: very weak (D).

Forest plot and overall evidence appeared in Figures 9–19. Evidence profile in Supporting Information can be obtained from the Japanese Dermatological Association. Summary of findings table was presented to guideline panels.

CQ3 Is the use of dressings recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to use hydrophilic fibers, hydrocolloids, hydrogels or polyurethane foams in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

6.13 | Literature Search

For the third edition of the Guidelines for the diagnosis and treatment of pressure ulcers the Japan Medical Library Association searched the electronic databases, PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society, to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

RCT of hydrophilic fibers, hydrocolloids, hydrogels, and polyurethane foams were screened for preliminary search. A relevant search was also performed.

6.14 | Outcome

The systematic review team selected Cure rate (Importance: 5) as an outcome. Incidence of adverse events and cost of

treatment were listed as candidates, however, their clinical importance was inferior to that of cure rate; therefore, they were not adopted for the outcome. The relative importance of outcome was voted by all drafting committee members, with 100% agreement.

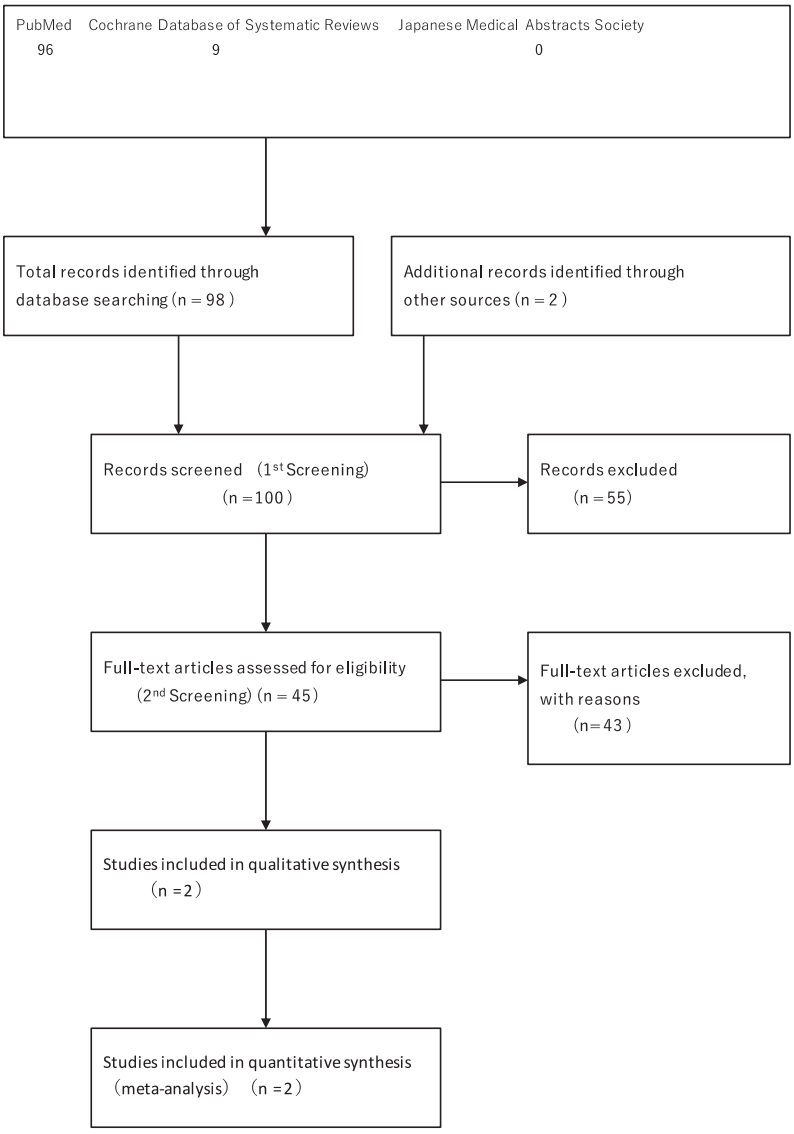
6.15 | Literature Screening

Hydrophilic fibers: The first screening with "ulcer AND (hydrofiber OR alginate)" as the query was performed, and 100 studies were retrieved. Seven duplicated studies were excluded. Two relevant studies were included. The second screening filtered for RCT retrieved 45 studies, and among them 2 studies referred to cure rate, which proceeded for further analysis. Flow chart of literature search appeared in Figure 20.

Hydrocolloids: The first screening with "ulcer AND hydrocolloid" as the query was performed, and 251 studies were retrieved. Sixteen duplicated studies were excluded. The second screening filtered for RCT retrieved 112 studies, and among them 3 studies referred to cure rate, which proceeded for further analysis. Flow chart of literature search appeared in Figure 21.

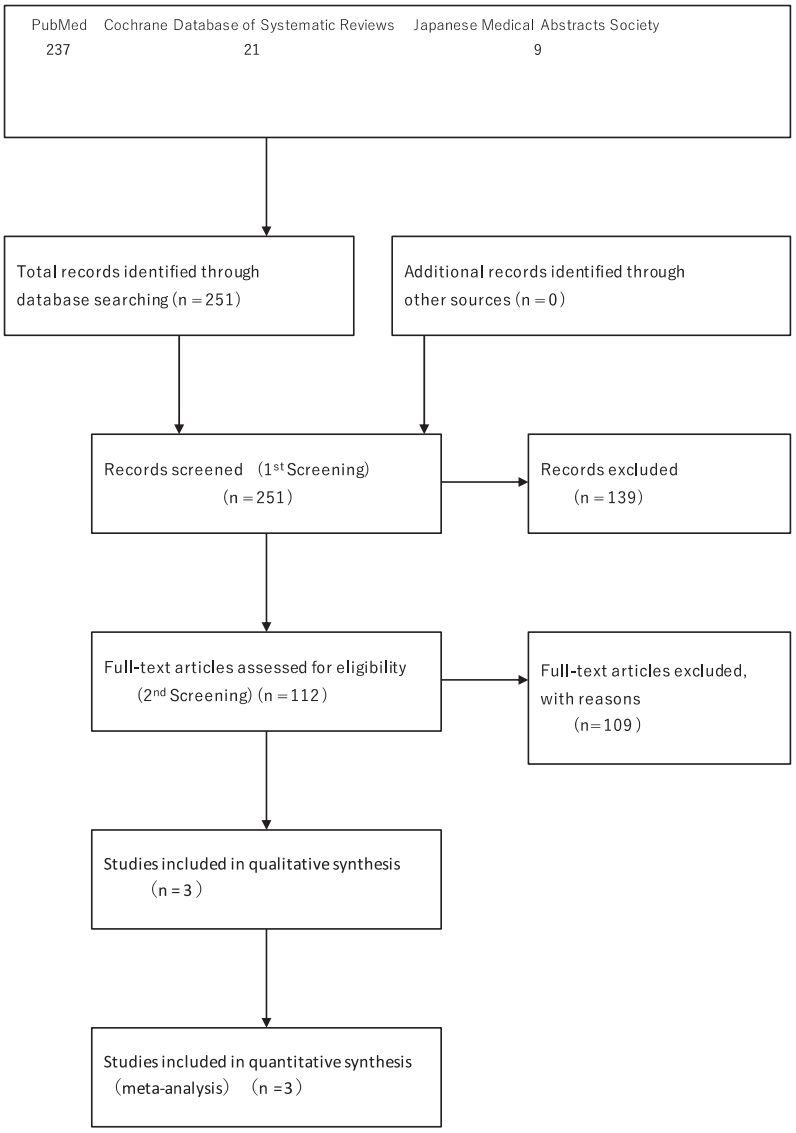
Hydrogels: The first screening with "ulcer AND hydrogel" as the query was performed, and 99 studies were retrieved. Six duplicated studies were excluded. The second screening filtered for RCT retrieved 44 studies, and among them 2 studies referred to cure rate, which proceeded for further analysis. Flow chart of literature search appeared in Figure 22.

Polyurethane foams: The first screening with "ulcer AND polyurethane" as the query was performed, and 52 studies were



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 20 | CQ3 Hydrophilic fibers flow chart of literature search.



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 21 | CQ3 Hydrocolloids flow chart of literature search.

retrieved. Four duplicated studies were excluded. Two relevant studies were included The second screening filtered for RCT retrieved 25 studies, and among them 3 studies referred to Cure rate, which proceeded for further analysis. Flow chart of literature search appeared in Figure 23.

6.16 | Evaluation of Certainty of Evidence

The effects, prepared in risk ratio or risk difference, and certainty (strength) of evidence, that is, limitation in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias, were analyzed based on the Minds Manual for Guideline Development 2020 ver. 3.0. As dressings could not be applied in blind fashion, certainty of evidence were lowered in risk of bias. Furthermore, number of participants were lost in death or transfer to the other hospitals in several studies, and certainty of evidence was lowered in attribution bias (risk of bias).

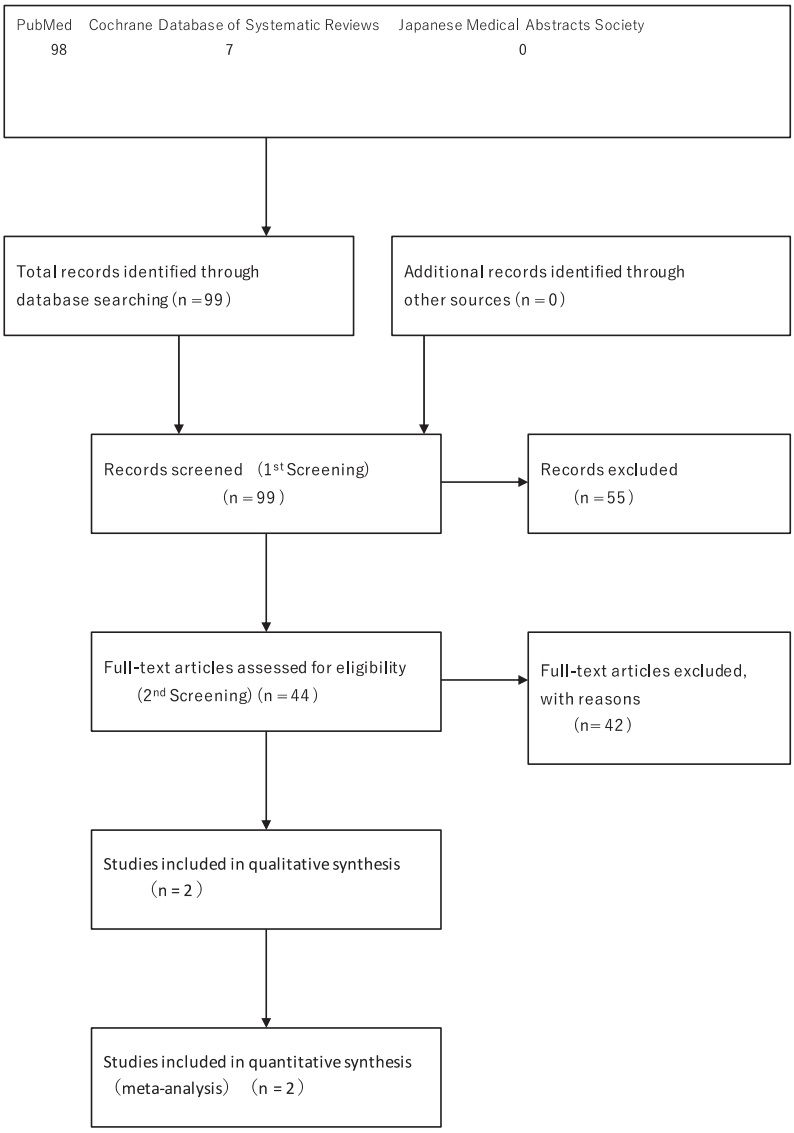
6.17 | Evaluation of Outcome

A meta-analysis was performed for respective outcome in relative effect and 95% confidence interval with Review Manager Version 5.4, The Cochrane Collaboration, 2020.

6.18 | Results

6.18.1 | Hydrophilic Fibers

Outcome: cure rate; relative effect: 1.69; 95% confidence interval: 0.64–4.47; certainty of evidence: very weak (D).



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 22 | CQ3 Hydrogels flow chart of literature search.

6.18.2 | Hydrocolloids

Outcome: cure rate; relative effect: 1.98; 95% confidence interval: 1.39–2.82; certainty of evidence: very weak (D).

6.18.3 | Hydrogels

Outcome: cure rate; relative effect: 1.42; 95% confidence interval: 0.75–2.69; certainty of evidence: very weak (D).

6.18.4 | Polyurethane Foams

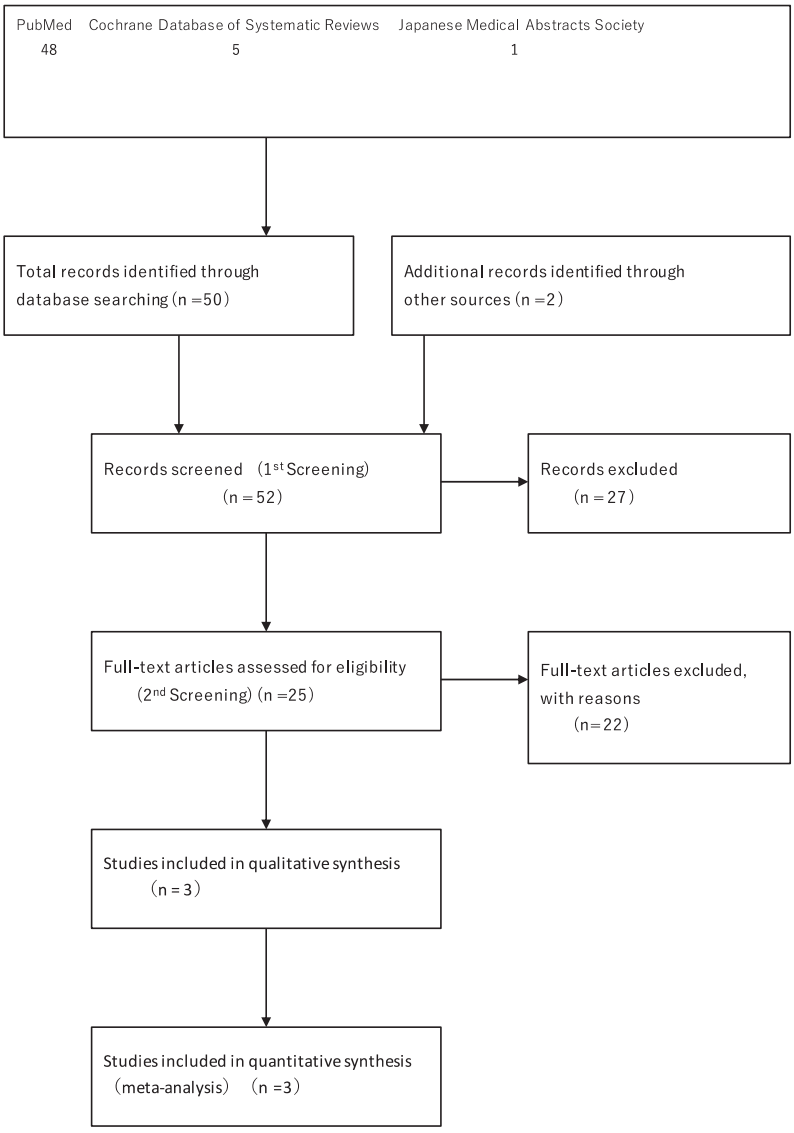
Outcome: cure rate; relative effect: 1.32; 95% confidence interval: 0.93–1.89; certainty of evidence: very weak (D).

Forest plot and overall evidence appeared in Figures 24–28. Evidence profile in Supporting Information can be obtained from the Japanese Dermatological Association. Summary of findings table was presented to guideline panels.

CQ4 Is negative-pressure wound therapy recommended for the treatment of pressure ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform negative-pressure wound therapy in the treatment of Stage III and Stage IV pressure ulcers	Weak	Very weak

Negative-pressure wound therapy is one of important advances in the history of wound treatment [285]. It may be effective for pressure ulcers, but few studies have analyzed its efficacy for



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 23 | CQ3 Polyurethane foams flow chart of literature search.

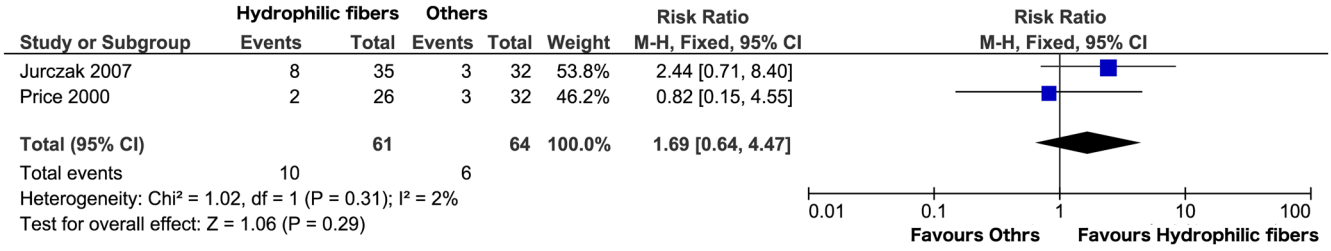


FIGURE 24 | CQ3 Hydrophilic fibers forest plot.

pressure ulcers. The Cochrane Database of Systematic Reviews [286] in 2015 reported that the efficacy for pressure ulcers could not be concluded because conference abstracts, in which the details were unclear, were included for analysis, and because a review of adverse events was insufficient. In CQ4, to clarify the efficacy of negative-pressure wound therapy for pressure ulcers, a systematic review and a meta-analysis were carried out, and the results were presented to guideline panels.

6.19 | Literature Search

For the third edition of the guidelines for the diagnosis and treatment of pressure ulcers, the Japan Medical Library Association searched the electronic databases, PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society, to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search

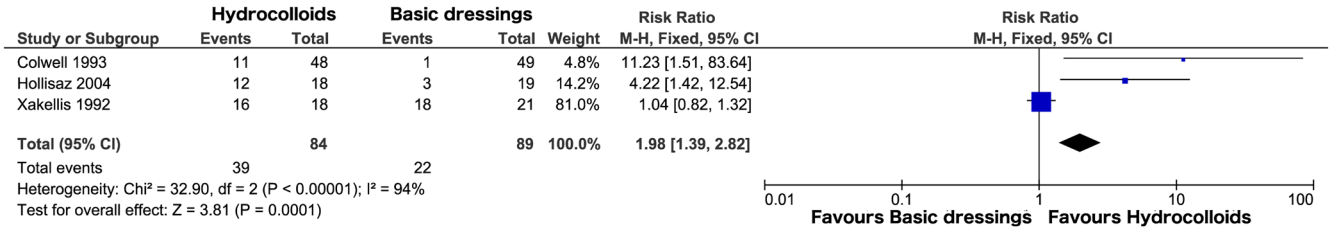


FIGURE 25 | CQ3 Hydrocolloids forest plot.

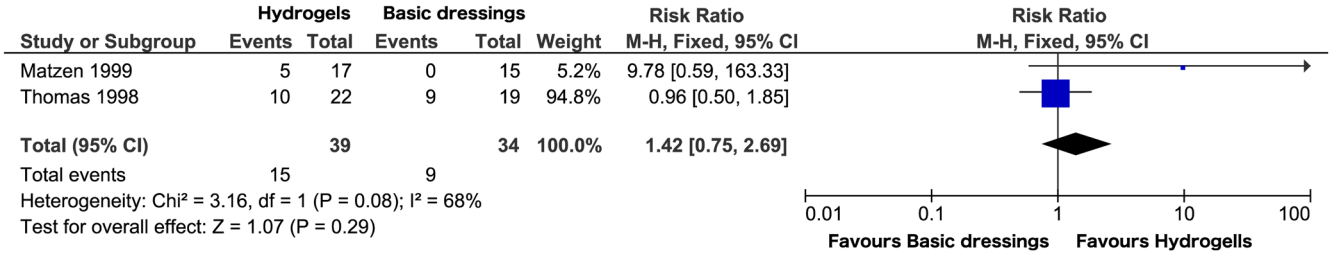


FIGURE 26 | CQ3 Hydrogels forest plot.

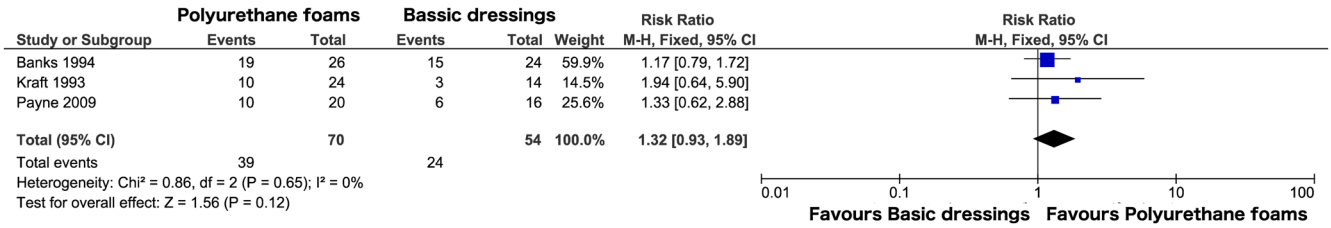


FIGURE 27 | CQ3 Polyurethane foams forest plot.

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	dressings
Controls	basic dresssings

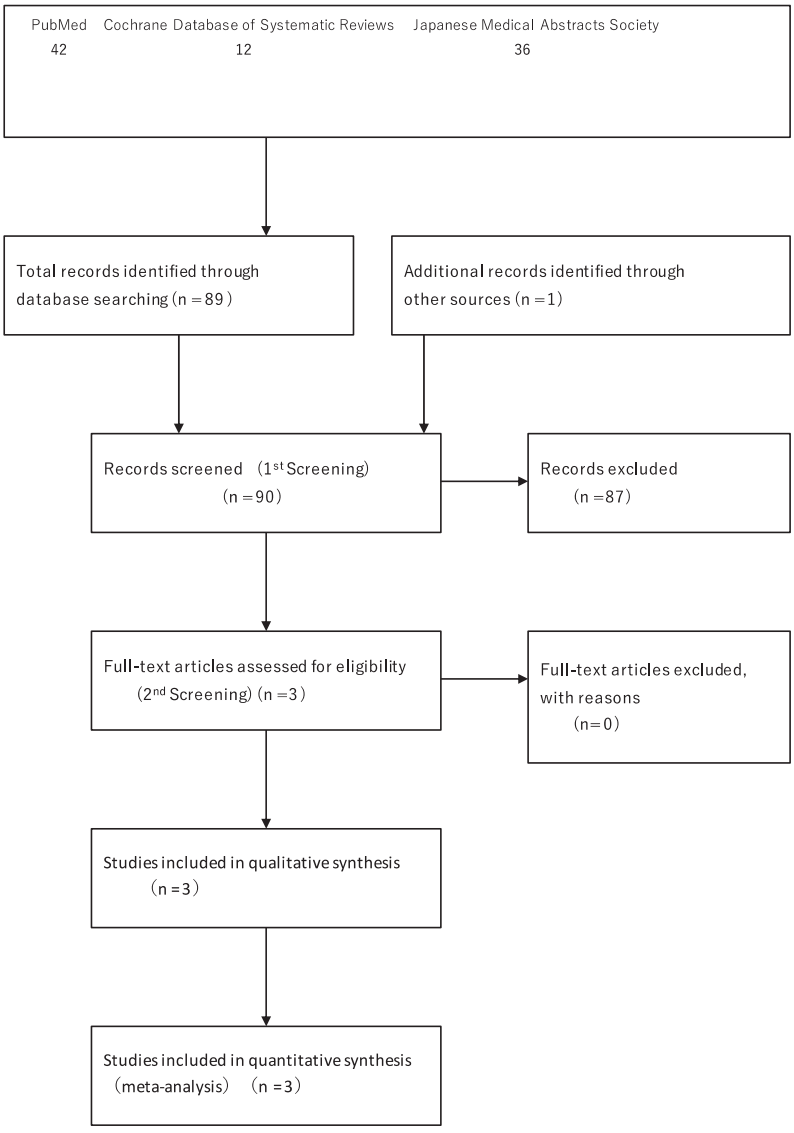
The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

								Number of participants, Absolute effects										
Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Hydropholic fibers Cure rate	RCT/2	-2	-1	-1	-1	0	0	64	6	9.3	61	10	16.4	RR	1.69	0.64-4.47	Very weak	5
Hydrocolloids Cure rate	RCT/3	-2	-1	0	0	0	0	89	22	24.7	84	39	46.4	RR	1.98	1.39-2.82	Very weak	6
Hydrogels Cure rate	RCT/2	-2	-1	-1	0	0	0	34	9	26.5	39	15	38.5	RR	1.42	0.75-2.69	Very weak	5
Polyurethane foams Cure rate	RCT/3	-2	0	-1	0	0	0	54	24	44.4	70	39	55.7	RR	1.32	0.93-1.89	Very weak	6

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

FIGURE 28 | CQ3 Overall evidence.



Prepared with a template in the Minds Handbook for clinical practice guideline development 2020.

FIGURE 29 | CQ4 Flow chart of literature search.

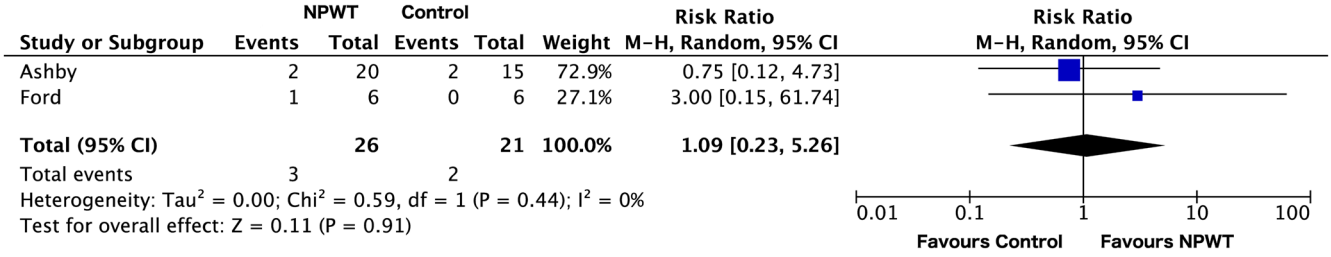


FIGURE 30 | CQ4 Cure rate forest plot.

appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

RCT of negative-pressure wound therapy and a relevant search were retrieved.

Results: The search in PubMed, Cochrane Database of Systematic Reviews, and Japanese Medical Abstracts Society retrieved 42, 12, and 36 studies, respectively.

6.20 | Outcome

The systematic review team selected cure rate (Importance: 5) and incidence of adverse events (Importance: 4) as outcomes. The ulcer reduction rate and wound infection were listed as candidates, but their clinical importance was inferior to that of cure rate or Incidence of adverse events; therefore, they were not adopted. The relative importance of outcome was voted by all drafting committee members, with 100% agreement.

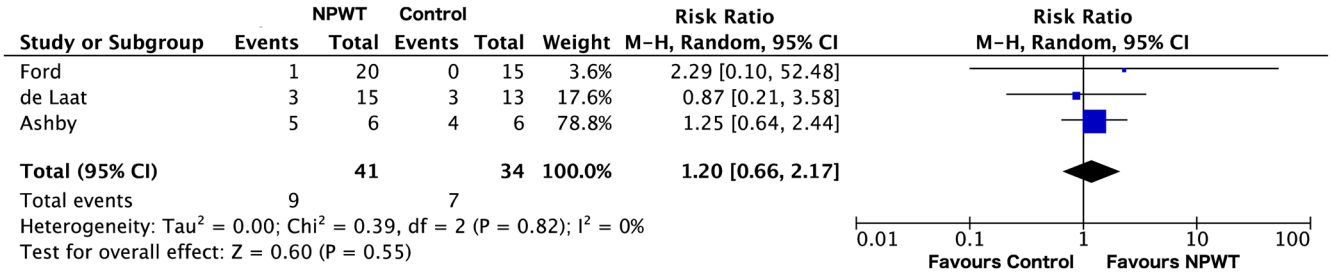


FIGURE 31 | CQ4 Incidence of adverse events forest plot.

Guidelines	Pressure ulcer guidelines, 3rd ed.
Subjects	Pressure ulcers, stages III or IV
Intervention	negative pressure wound therapy
Controls	topical medication

The highest certainty of evidence for RCT is High (A); for obsevational study, Weak (C).
*: Each domain appears in High risk (-2), Medium risk or suspicius (-1), or Low risk (0).
**: Factors that can increase the quality of the evidence appear in High (+2), Medium (+1), or Low (0).
***: Certainty of evidence appears in Strong (A), Moderate (B), Weak (C), or Very weak (D).
****: Outcome importance: 9 (highest) - 1 (lowest).

Ovderall evidence

								Number of participants, Absolute effects										
Outcome	Study designs, Number	Limitations in study design or execution (risk of bias)*	Inconsistency of results*	Imprecision*	Indirectness of evidence*	Others, e.g. Publication bias*	Factors that can increase the quality of the evidence**	Control group, Total	Control group, Outcome Achieved	(%)	Intervention group, Total	Intervention group, Outcome achieved	(%)	Effect measure	Relative effect	95% CI	Certainty of evidence***	Outcome importance ****
Cure rate	RCT/2	-1	0	0	0	0	0	21	2	9.5	26	3	47	RR	1.09	0.23-5.26	Very weak	5
Incidence of adverse events	RCT/3	-1	0	0	-2	0	0	34	7	20.6	41	9	22	RR	1.2	0.66-2.17	Moderate	4

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

FIGURE 32 | CQ4 Overall evidence.

6.21 | Literature Screening

The first screening with "negative-pressure wound therapy AND pressure ulcer" as the query was performed, and 90 studies were retrieved. One duplicated study was excluded. One relevant study was included. The second screening filtered for RCT retrieved 3 studies, which proceeded for further analysis. Flow chart of literature search appeared in Figure 29.

6.22 | Evaluation of Certainty of Evidence

The effects, prepared in risk ratio or risk difference, and certainty (strength) of evidence, that is, limitation in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias, were analyze. based on the Minds Manual for Guideline Development 2020 ver. 3.0. As negative-pressure wound therapy could not perform in blind fashion, certainty of evidence were lowered in risk of bias and imprecision.

6.23 | Evaluation of Outcome

A meta-analysis was performed for respective outcome in relative effect and 95% confidence interval with Review Manager Version 5.4, The Cochrane Collaboration, 2020.

6.24 | Results

Outcome: cure rate; relative effect: 1.09; 95% confidence interval: 0.23–5.26; certainty of evidence: moderate (B).

Outcome: incidence of adverse events; relative effect: 1.20; 95% confidence interval: 0.66–2.17; certainty of evidence: very weak (D).

Forest plot and overall evidence appeared in Figures 30–32. Evidence profile in Supporting Information can be obtained from the Japanese Dermatological Association. Summary of findings table was presented to guideline panels.

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Appendix 1

Wound/Pressure Ulcer/Burn Guidelines Drafting Committee Member List

Supervising Committee

Chairperson: Takao TACHIBANA (Hoshigaoka Medical Center).

Vice-chairperson: Minoru HASEGAWA (University of Fukui), Manabu FUJIMOTO (Osaka University).

Members: Yoshihide ASANO (Tohoku University), Takeshi NAKANISHI (Meiji University of Integrative Medicine), Hiroshi FUJIWARA (Niigata University), Takeo MAEKAWA (Jichi Medical University Saitama Medical Center), Sei-ichiro MOTEGI (Gunma University), Yuichiro YOSHINO (Japanese Red Cross Kumamoto Hospital).

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Appendix 2

Declarations of Interest

Conflict of interest (COI) reporting criteria for participants in the Wound/Pressure Ulcer/Burn Guidelines Supervising and Drafting Committees, participation/non-participation criteria, and a list of the COI disclosed [Prepared in reference to JAMS Guidelines on COI Management in Medical Research (in March 2017, Japanese Association of Medical Sciences, https://jams.med.or.jp/guideline/index.html)].

Criteria for Judgment of COI Disclosure

Participants

1. Presence or absence of officers and advisors in companies and for-profit organizations and the amounts of their remunerations.

Classification of pension amounts: (1) equal to or more than1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than10 million yen/company/year.

2. Ownership of stocks and profits derived from the stocks (profits for the previous year presented in this format).

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

3. Royalty payments for patents by companies and for-profit organizations.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

4. Remunerations, such as daily allowances and lecture fees, paid by a company and for-profit organization for attending a conference (presentations, advice).

Classification of amount: (1) equal to or more than 0.5 million yen/company/year, (2) equal to or more than 1 million yen/company/year, (3) equal to or more than 2 million yen/company/year.

5. Fees paid by a company and for-profit organization for the creation of pamphlets, roundtable discussion articles.

Classification of amount: (1) equal to or more than 0.5 million yen/company/year, (2) equal to or more than 1 million yen/company/year, (3) equal to or more than 2 million yen/company/year.

6. Research funds (industry-academia collaborative research, contract research, clinical trials) provided by a company and for-profit organization.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 10 million yen/company/year, (3) equal to or more than 20 million yen/company/year.

7. Donations for scholarships and incentives offered by a company and for-profit organization.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

8. Employed by organizations or departments sponsored by companies, with donations of equal to or more than 1 million yen.

9. Other remunerations (e.g., travel grant, not directly related to research, gifts).

Classification of amount: (1) equal to or more than 50 thousand yen, (2) equal to or more than 200 thousand yen, (3) equal to or more than 200 thousand yen.

Spouses or First-Degree Relatives of Participants, Those Who Share Income or Property Interests With Participants

1. Presence or absence of officers and advisors in companies and for-profit organizations and the amounts of their remunerations.

Classification of pension amounts: (1) equal to or more than1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than10 million yen/company/year.

2. Ownership of stocks and profits derived from the stocks (profits for the previous year presented in this format).

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

3. Royalty payments for patents by companies and for-profit organizations.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

Organizations or departments that participants belong to:

1. Research funds (industry-academia collaborative research, contract research, clinical trials) provided by a company and for-profit organization.

Classification of amount: (1) equal to or more than 10 million yen/company/year, (2) equal to or more than 20 million yen/company/year, (3) equal to or more than 40 million yen/company/year.

2. Donations for scholarships and incentives offered by a company and for-profit organization.

Classification of amount: (1) equal to or more than 2 million yen/company/year, (2) equal to or more than 10 million yen/company/year, (3) equal to or more than 20 million yen/company/year.

Criteria for exclusion from the committee: Members of the guideline drafting committee, their spouses, first-degree relatives, or those who share income or property interests if they fall under any of the following:

1. Incomes of the officers and advisors of companies and for-profit organizations equal to or exceeding 1 million yen/company/year.

2. Ownership of stocks and profits generated from the stocks equal to or exceeding 5% of total stocks of the company or 1 million yen/company/year.

3. Receipt of patent royalties from companies and for-profit organizations equal to or exceeding 1 million yen/company/year.

4. Employed by organizations or departments sponsored by companies and for-profit organizations.

Criteria that should be met by the chairperson of the guideline drafting committee

Both individual and organizational COI are classified into Category (1) or below.

Criteria that should be met by the members of the guideline supervisory and drafting committees

Both individual and organizational COI are classified into Category (2) or below. However, the number of persons in Category (2) shall not exceed half of the guideline drafting committee.

List of the COI

Ryokichi IRISAWA (member of the guideline drafting committee), financial COI, Maruho Co. Ltd. (Category (2) or below).

Takeo MAEKAWA (member of the guideline supervisory committee), financial COI, Ono Pharmaceutical Co. Ltd. (Category (2) or below), Sun Pharma Japan Ltd. (Category (2) or below), Taiho Pharmaceutical Co. Ltd. (Category (2) or below), Maruho Co. Ltd. (Category (2) or below), Mitsubishi Tanabe Pharma Corporation (Category (2) or below), Eisai Co. Ltd. (Category (2) or below), Leo Pharma K.K. (Category (2) or below).

Minoru HASEGAWA (member of the guideline supervisory committee), financial COI, Maruho Co. Ltd. (Category (2) or below), Ono Pharmaceutical Co. Ltd. (Category (2) or below).

Manabu FUJIMOTO (member of the guideline supervisory committee), financial COI, Maruho Co. Ltd. (Category (2) or below).

Non-Financial COI

Takafumi KADONO is the editor-in-chief of Journal of Dermatology and a co-author of this article. He is excluded from editorial decision-making related to the acceptance and publication of this article.

Minoru HASEGAWA is an editorial board member of Journal of Dermatology and a co-author of this article. To minimize bias, he is excluded from all editorial decision-making related to the acceptance of this article for publication.

Mari KISHIBE and Hideki FUJITA are the Editorial Board Members of the Journal of Dermatology and are acknowledged in this article. They are excluded from editorial decision-making related to the acceptance and publication of this article.