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GUIDELINE

The wound/burn guidelines – 2: Guidelines for the diagnosis and treatment for pressure ulcers

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ABSTRACT

The Wound/Burn Guidelines Committee consists of members commissioned by the Board of Directors of the Japanese Dermatological Association (JDA). It held several meetings and evaluations in writing since October 2008, and drafted five guidelines for the diagnosis and treatment including commentaries on wounds in general and the Guidelines for the Diagnosis and Treatment for Pressure Ulcers by taking opinions of the Scientific Committee and Board of Directors of JDA into consideration.

Key words: **body position changes, nutritional support, pressure ulcer, reactive erythema, skin care.**

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BACKGROUND OF THE DRAFTING OF THE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT FOR PRESSURE ULCERS

Guidelines are "documents systematically prepared to support medical experts and patients for making appropriate judgments in particular clinical situations".[1] and water content of the skin[7] Concerning pressure ulcers, the Guidelines for the Prevention and Management of Pressure Ulcers were issued by the Japanese Society of Pressure Ulcers in February 2009. However, the guidelines of the Japanese Society of Pressure Ulcers were for not only physicians but also nurses, dieticians, pharmacists, physical therapists and occupational therapists, and placed greater emphasis on the prevention and care than on the treatment. Therefore, the present guidelines were prepared by focusing more on treatment. The present guidelines are also designed to serve as a tool to improve the quality of the diagnosis and treatment of individual pressure ulcer patients and, further, to elevate the standards of care for pressure ulcers in Japan by systematically proposing evidence-based recommendations that help with clinical decisions for the prevention, care and treatment of pressure ulcer.

POSITION OF THE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT FOR PRESSURE ULCER

The Wound/Burn Guidelines Committee consists of members commissioned by the Board of Directors of the Japanese Dermatological Association. It held several meetings and evaluations in writing since October 2008 and drafted five guidelines for the diagnosis and treatment including commentaries on wounds in general and the Guidelines for the Diagnosis and Treatment for Pressure Ulcers by taking opinions of the Scientific Committee and Board of Directors of the Japanese Dermatological Association into consideration. Although the Guidelines for the Diagnosis and Treatment for Pressure Ulcers presented in this article show the current standards of the diagnosis and treatment in Japan, pressure ulcer patients vary in underlying diseases, severity of symptoms and background, including complications. Therefore, the physicians who conduct the diagnosis and treatment should determine the approaches to prevention, care and treatment with the patients, and their decisions are not required to be in complete agreement with the present guidelines. Also, the guidelines are not relevant for citation in lawsuits.

SPONSORS AND CONFLICTS OF INTEREST

All cost needed for drafting the Guidelines for the Diagnosis and Treatment for Pressure Ulcer has been borne by the Japanese Dermatological Association, and no fund has been received from particular organizations, enterprises, pharmaceutical companies or other sources. If any members of the committee participating in the drafting of the guidelines have been involved in the development of particular related drugs, and so forth, they were excluded from the evaluation of the recommendation level of the items in question. Each member of the committee has no other conflict of interest to disclose on drafting the present guidelines.

COLLECTION OF EVIDENCE

Databases used: Medline, PubMed, Japana Centra Revuo Medicina Web, and Cochrane database systematic reviews of ALL EBM Reviews. References obtained by manual search of each member were also added.

Search period: the published work that could be searched between January 1980 and December 2008 was reviewed. Recent published work of importance was added when considered appropriate.

Adoption criteria: priority was placed on systematic reviews of randomized controlled trials (RCT) and papers on individual RCT. If they were not available, papers on cohort studies, case–control studies and so forth were adopted. Although some papers on case series studies were also used as references, the published work on basic experiments was excluded.

CRITERIA FOR THE DETERMINATION OF THE EVIDENCE AND RECOMMENDATION LEVELS

The criteria adopted in the Guidelines for the Diagnosis and Treatment of Malignant Skin Tumors edited by the Japanese Dermatological Association mentioned below were used as references.

- Evidence levels:

  I Systematic reviews/meta-analyses.
  II One or more RCT.
  III Non-RCT (including before/after comparative studies with statistical analysis).
  IVa Analytical epidemiological studies (cohort studies).
  IVb Analytical epidemiological studies (case–control studies/ cross-sectional studies).
  V Descriptive studies (case reports and case series studies).
  VI Opinions of special committees and individual experts.

- Recommendation levels:

  A Strongly recommended (there is at least one piece of level I or good level II evidence indicating the effectiveness).
  B Recommended (there is at least one piece of inferior level II, good level III or very good level IV evidence).
  C1 Recommended as an option despite the lack of good evidence (there is inferior level III–IV evidence, several pieces of good level V evidence or level VI evidence endorsed by the committee).
  C2 (Presently) not recommendable due to the lack of sufficient evidence (there is no evidence indicating effectiveness or there is evidence indicating ineff ectiveness).
  D Disrecommended (there is good evidence indicating ineffectiveness or harmfulness).

The recommendation levels mentioned in the text are not necessarily in agreement with the above, because they were determined at some points according to the consensus of the committee (by showing evidence levels) in consideration of the international lack of evidence concerning the diagnosis and treatment of this condition, inappropriateness of directly applying overseas evidence to Japan and practicality of the guidelines.

REVIEWS BEFORE DISCLOSURE

Prior to the disclosure of the guidelines, progresses in drafting were presented at the Annual Meetings of the Japanese Dermatological Association from 2008 to 2011, opinions were invited from the association members and necessary revisions were made. The drafts were distributed to representatives, who were considered to be typical prospective users of the guidelines, their opinions were collected and summarized, and the results were reflected in the drafts.

UPDATING POLICIES

The present guidelines will be updated in 3–5 years. However, if partial updating becomes necessary, update information is presented on the website of the Japanese Dermatological Association when appropriate.

TERMINOLOGY

"Pressure ulcer": External force applied to the body reduces or blocks the blood flow of the soft tissue between bone and the superficial layer of the skin. If this condition continues for a period, the tissue sustains irreversible ischemic damage and develops pressure ulcer.

"Topical agents": Drugs that are applied through the skin or directly to skin lesions for topical treatment. They are prepared by compounding various drugs with a base.

"Dressing materials": Modern wound-dressing materials for creating a wet environment for wounds. Conventional sterilized gauze is excluded.

"Wound-dressing materials": Wound-dressing materials can be classified into dressing materials (modern dressing materials) and medical materials such as gauze (classic dressing materials) The former are medical materials aimed to provide conditions optimal for wound healing by maintaining a moist environment and must be used selectively depending on the state of the wound and amount of exudate. The latter allow drying of the wound and cannot maintain a moist environment if exudate is insufficient. Medical materials other than conventional gauze that provide an environment optimal for wound healing by covering the wound and maintaining moisture may also be called wound-dressing materials or dressing materials.

"Occlusive dressing": All dressing methods used to avoid drying of wounds for moist wound healing are called occlusive dressing. This is a collective term for dressing using modern wound-dressing materials other than conventional gauze dressing.

"Wet-to-dry dressing": Dressing aimed at debridement performed by applying gauze saturated with physiological saline to the wound and non-selectively removing foreign bodies and necrotic tissue adhering to dried gauze in changing gauze.

"Surgical treatments": Surgery, surgical debridement and invasive treatments of subcutaneous pockets.

"Physical agents": Treatments performed by applying stimulation to the body using physical means, which include physical energies such as heat, water, light, ultrashortwave, electricity, ultrasound, vibration, pressure and traction. Thermotherapy, cryotherapy, hydrotherapy, phototherapy, ultrashortwave therapy, electric stimulation therapy, ultrasound therapy, negative-pressure therapy, high-pressure oxygen therapy, and traction therapy are variations of physical agents. These physical agents are performed to mitigate pain, promote wound healing or increase the elasticity of tissues such as muscles and ligaments. Physical therapy is used as a general term for all these therapies, and the means for the treatment are conventionally called physical agents to avoid confusion.

"NPUAP pressure ulcer staging system": One of the classifications of the depth of pressure ulcers, a staging system proposed by the National Pressure Ulcer Advisory Panel (NPUAP) in 1989. Conventionally, pressure ulcers were classified as I, II, III and IV. Recently, however, the category of deep tissue injury (DTI) has been added on the basis of the concept that deep areas may be damaged even without damages to the skin surface. Therefore, by the new NPUAP pressure ulcer staging system issued in 2007, pressure ulcers are categorized into six stages: (suspected) deep tissue injury, stages I, II, III and IV, and unstageable (whether the depth of pressure ulcer is III or IV is impossible to determine).

"DESIGN": An assessment scale for the evaluation of the condition of pressure ulcer announced by the Japanese Society of Pressure Ulcers in 2002 and an assessment tool consisting of seven items: depth, exudate, size, inflammation/infection, granulation tissue, necrotic tissue and pocket. There are two types, one for severity classification representing severe and mild by capital and small letters, and the other for quantitative follow-up evaluations of the healing process. In the latter type, there are the 2002 version and 2008 revision (DESIGN-R with the "R" standing for "rating") modified for more accurate rating of the severity as well as evaluation of the course of pressure ulcers.

"Deep tissue injury (DTI)": The term used by the NPUAP in 2005, meaning a pressure ulcer without epidermal loss (stage I) in which damage to tissues deeper than subcutaneous tissue is suspected. In the NPUAP pressure ulcer staging system for pressure ulcers revised in 2007, "(suspected) deep tissue injury" was added as a new stage. It may be translated as "deep tissue damage" for damages other than pressure ulcers.

"Nutrition support team (NST)": The Japan Council for Nutritional Therapy (JCNT) calls nutritional management performed appropriately for individual patients and for the treatment of individual disorders "nutrition support" and defines a team of several professions including the physician, nurse, pharmacist, managerial dietician and clinical laboratory technician as an NST.

"Erosion": Cutaneous or mucosal defect not extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually cures without leaving a scar.

"Ulcer": Cutaneous or mucosal defect extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually leaves a scar after cure.

"Decompression": Reducing the contact pressure similarly to pressure reduction. Reducing the pressure to less than 32 mmHg, which was considered to be the internal pressure of the capillaries, used to be defined as decompression, and to 32 mmHg or above as pressure reduction, but this distinction is not made today.

"Body pressure-dispersion devices": Devices that reduce the pressure on a unit of body surface area by widening the area in contact with a supportive structure, such as the bed and chair, or reduce the pressure applied to the same area over a long period by shifting the area under pressure with time. Those used in the lying position include special beds, mattresses, overlay mattresses layered over a bottom mattress, and replacement mattresses to be substituted for conventional mattresses. Those used in the seated position include cushions for chairs and wheelchairs and pads used to adjust the body position. Materials used in body pressure-dispersion devices include air, water, urethane foam, gels and rubber.

"Wound bed preparation": Management of the wound surface environment to promote wound healing. Specifically, necrotic tissues are removed, bacterial load is reduced, drying of the wound is prevented, excessive exudate is controlled, and pockets and wound edges are treated.

"TIME": Practical principles of wound bed preparation based on the concept of evaluating factors that prevent wound healing from the viewpoints of tissue (T), infection or inflammation (I), moisture (M) and wound edge (E), and using the results for treatment and management.

"Moist wound healing": Maintaining the wound surface in a moist environment. This retains multinucleated leukocytes, macrophages, enzymes and cell growth factors contained in exudate on the wound surface. Such an environment promotes autolysis and removal of necrotic tissues and does not interfere with cell migration.

"Negative-pressure therapy": A variation of physical therapy. The wound is maintained in a closed environment and suction is applied to adjust the pressure to 125–150 mmHg, in principle. This directly eliminates bacteria and exotoxins released from them, promotes vascularization of granulation tissue and alleviates edema.

"Pocket": A wound cavity larger than a skin defect. The tissue covering a pocket is called the cover wall or cover lid.

"Washing": Removing chemical stimulants, infection sources and foreign bodies from the skin or wound surface using the hydraulic pressure or lysing effect of a liquid. Washing may be performed using physiological saline, tap water, or saline or tap water combined with a surfactant such as soap and detergent. The effect of washing may be derived from the flow volume or hydraulic pressure.

"Debridement": A therapeutic action to clean the wound by removing necrotic tissues that have ceased to react to stimulation by promoters of wound healing such as growth factors, foreign bodies and foci of bacterial infection, which are often associated with the above. Methods include: (i) autolytic debridement induced by occlusive dressing; (ii) mechanical debridement (e.g. wet-to-dry dressing, high-pressure washing, hydrotherapy and ultrasonic washing); (iii) debridement using proteolytic enzymes; (iv) surgical debridement; and (v) biological debridement using maggots.

"Critical colonization": Conventionally, the microbial environment of the wound was classified into infected and aseptic states, but the current trend is to understand the two conditions as continuous (the concept of bacterial balance). Infection of the wound is understood as continuous stages of contamination, colonization and infection, and infection is considered to occur depending on the balance between the bacterial burden on the wound and host resistance. Critical colonization is a stage between colonization and infection but tilted more to infection with the number of bacteria exceeding that of colonization.

"Biofilm": Bacteria that have colonized on the surface of a foreign body or in necrotic tissue may produce polysaccharides on their body surface. Polysaccharides around bacterial bodies gradually fuse and form a membrane-like structure, which wraps bacteria. This is called a biofilm. Bacteria wrapped in a biofilm is protected from antibiotics in general and leukocytes, and infection is likely to persist.

"Positioning": Maintaining the body of a person with motor dysfunction in a safe and comfortable position appropriate for performing a particular task by adjusting the relative relationships among parts of the body using cushions, and so on.

"Seating": A supportive skill to seat a person in a safe and comfortable posture using a cushion, based on physical evaluation in consideration of the effect of gravity. It particularly means helping those who cannot sit upright remain seated.

"Relieving the back": Relieving stress on the back by temporarily detaching it from the bed or wheelchair.

"Rule of 30": One way to remember a basic technique to disperse interface pressure. First, in lying a patient in a semilateral recumbent position to disperse the pressure on the greater trochanter, sacral and shoulder regions, compression of bone-protruding areas of the shoulder and buttocks can be mitigated by tilting the body to approximately 30° using a cushion, and, thus, increasing the contact area. Second, when the head side of the bed is elevated in the supine position, the angle of elevation should be restricted to 30° or less, and thighs should be elevated to approximately 30° before elevating the head, to prevent sliding down of the body and minimize the compression of the sacral region.

"Rule of 90": One way to remember a basic technique to disperse interface pressure. Adjusting the angles of the hip, knee, and foot joints at approximately 90° using cushions, and so on, to disperse interface pressure and prevent sliding of the body in a wheelchair or chair.

CONCEPTS OF PREVENTION, MANAGEMENT AND TREATMENT, AND ALGORITHM OF THE DIAGNOSIS AND TREATMENT

The basic principle for the prevention and management of pressure ulcer is to avoid applying unnecessary external force

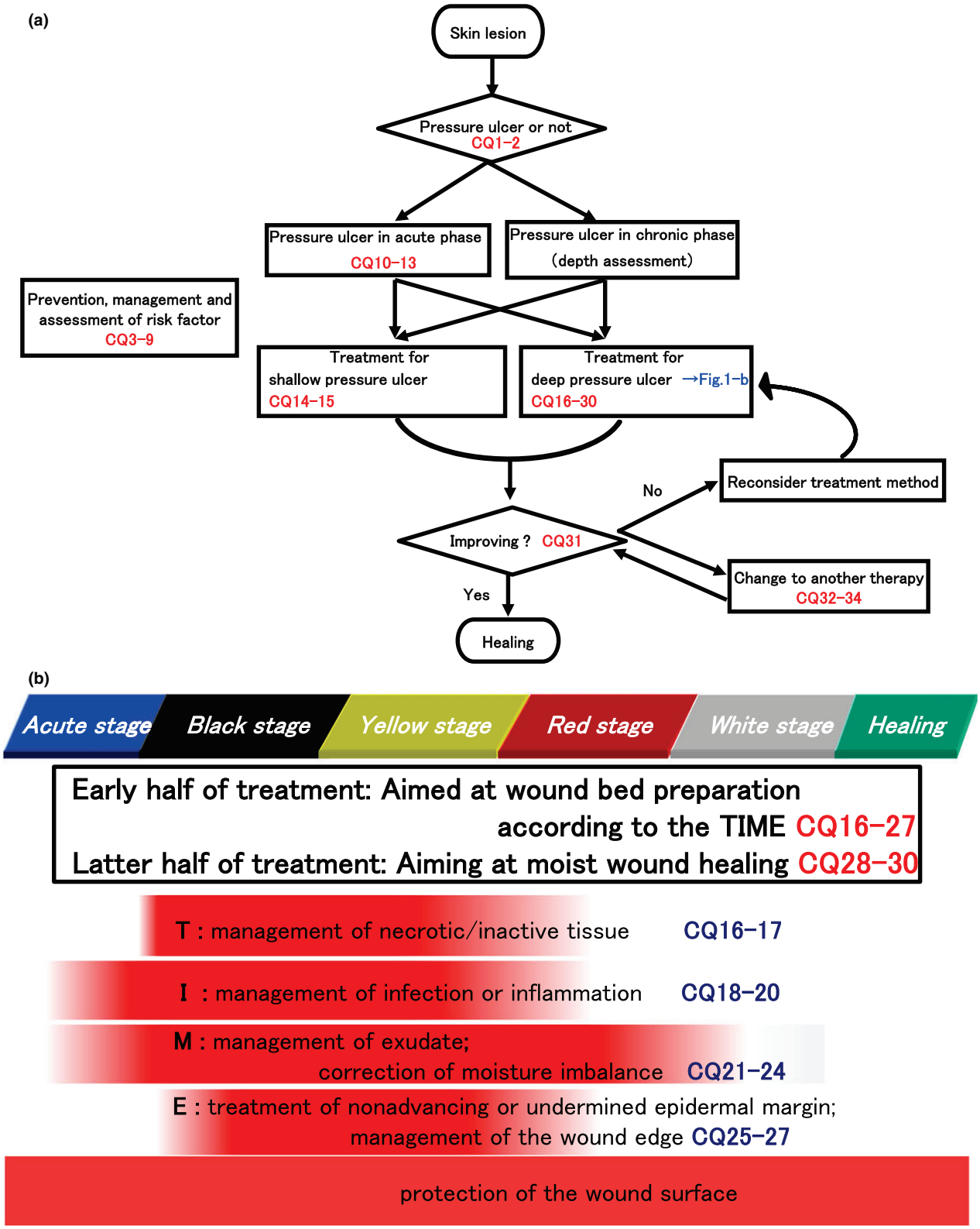

Figure 1. (a) Clinical algorithm for pressure ulcer (b) Clinical algorithm for deep chronic pressure ulcer (Modified from "T. Tachibana, Y. Miyachi: The mechanism of pressure ulcer heeling. Jpn J Clinical Nutrition 103 (4): 353–356, 2003").

such as compression and friction to the wound, that is, to protect the wound surface, similarly to the treatment for other wounds. If, unfortunately, a pressure ulcer has developed, the principle of treatment is wound bed preparation based on the TIME concept in the early half of treatment for a deep ulcer (black and yellow stages) and moist wound healing for a shallow ulcer and in the latter half of treatment for a deep ulcer (red and white stages). The TIME concept is an acronym for "tissue" (treatment of non-viable or deficient tissue; management of necrotic/inactive tissue), "infection or inflammation" (management of infection or inflammation), "moisture" (correction of moisture imbalance; management of exudate) and "edge of wound" (treatment of non-advancing or undermined epidermal margin; management of the wound edge).

Figure 1 shows the algorithm for the diagnosis and treatment prepared on the basis of the above concepts and clinical questions (CQ). The treatments were selected from all insurance-covered topical agents and dressing materials for skin traumas, namely, erosion and ulcer, standard surgical treatments and physical agents. However, while erosion and ulcer are indications for Vaseline-based ointments containing antibiotics, their use for the treatment of deep pressure ulcers in the chronic phase should be avoided because of the risk of the appearance of resistant strains on long-term use except when they are used for the treatment of shallow pressure ulcers in the acute or chronic phase in expectation of the wound-protecting effect of the Vaseline base. Also, while so-called "wrap therapy" including open moist therapy is not insured, it is included in the present guidelines, because the therapy is widely performed at home and is considered to fall within the responsibility of physicians.

"PRESSURE ULCER OR NOT": CQ1: HOW CAN GRADE I PRESSURE ULCER BE DISTINGUISHED FROM REACTIVE ERYTHEMA?

Remarks on recommendation: The transparent disk method or the finger compression method is recommended as an option.

Recommendation level: C1.

Comments:

- There is a case–control study evaluating the relative superiority between the transparent disk method and the finger compression method,[2] and its evidence level is IVb.
- In daily practice, the transparent disk method or finger compression method is used to distinguish between grade I pressure ulcer and reactive erythema. Concerning which of these methods is more preferable, there is a case–control study evaluating the interrater reliability, degree of agreement (Cohen's kappa), sensitivity, specificity, positive predictive value and negative predictive value.[1] While the transparent disk method showed a slightly higher sensitivity, no significant difference was noted between the two methods, and both are considered useful.
- In addition, attempts to distinguish them by comparing the blood flow using a laser Doppler technique,[3,4] skin temperature,[5] skin color using spectroscopy[6] and water content of the skin[7] have been made, but significant discrimination of grade I pressure ulcer and reactive erythemas not been achieved.

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CQ2: WHAT DISEASES, FOR EXAMPLE, NEED DIFFERENTIATION FROM PRESSURE ULCERS?

Remarks on recommendation: The inclusion of reactive erythema, peripheral arterial diseases due to diabetes, dermatitis due to irritation by stools or urine, cutaneous candidiasis, contact dermatitis, burns caused by the electric scalpel and chemical burns due to disinfectants in differential diagnoses is recommended as an option.

Recommendation level: C1.

Comments:

- Although there is a case–control study evaluating how accurately a grade I pressure ulcer can be discriminated from reactive erythema,[8,9] the evidence concerning all other diseases is expert opinions.[10] Their evidence levels are IVb and VI.
- Various conditions have been proposed as diseases that need differentiation from pressure ulcers. Reactive erythema is the most important, and the interrater reliability and degree of agreement were high when the diagnoses were made by those who underwent training of a certain level.[8,9] The diseases that require differentiation next are peripheral arterial diseases (PAD) due to diabetes which used to be known primarily as arteriosclerosis obliterans (ASO). Other diseases that need differentiation are considered to include dermatitis due to irritation by stools or urine, diaper dermatitis, cutaneous candidiasis, contact dermatitis, herpes zoster, and bullous diseases.

- Among postoperative conditions, there are burns caused by the electric scalpel and chemical burns due to disinfectants.[10] Burns due to the electric scalpel have become rare recently, but they are irregularly shaped, clearly circumscribed erythema caused by leakage of electricity. They occur from immediately after surgery in areas such as lateral to, or above, the gluteal cleft. Chemical burns due to disinfectants are primary irritant dermatitis caused by povidone iodine and are clearly-bordered, irregularly-shaped erythema occurring on surfaces that come into contact with the ground adjacent to the disinfected area including the gluteal region. It is noted 3 days after disinfection in some patients but can be detected immediately after surgery on close examination. On the other hand, pressure ulcer is vaguely-bordered erythema occurring immediately after surgery or with a delay. The site, size, and shape of the lesion are taken into consideration, but the differentiation based on these characteristics is difficult, and examination of the wound immediately after surgery contributes to the diagnosis.[10]

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EVALUATION OF PREVENTION, MANAGEMENT AND RISK FACTORS CQ3: WHAT SCALES ARE AVAILABLE FOR THE ASSESSMENT OF RISK FACTORS?

Remarks on recommendation: There are the Braden Scale, K Scale, OH scale, K Scale modified for home use, and pressure ulcer risk factor evaluation table presented by the Ministry of Health, Labor and Welfare as assessment scales for risk factors. Their appropriate use is recommended.

Recommendation level: B.

Comments:

- There is a systematic review comparatively evaluating the predictive validity of the multiple assessment scales.[11] Although the evidence level is I, the recommendation level was set as B, because the review did not include Japanese pressure ulcer patients. Also, there is a prospective cohort study evaluating the validity of the K scale regarding pressure ulcers in Japanese subjects, who show characteristics such as a low bodyweight and morbid bone protrusion.[12] Similarly, there are a case–control study concerning the OH scale[13] and a prospective cohort study regarding the K scale modified for home use.[14] As for the pressure ulcer risk factor evaluation table prepared by the Ministry of Health, Labor and Welfare, there is a retrospective cohort study.[15]
- The Braden Scale, K scale, OH scale, K scale modified for home use, and pressure ulcer risk factor evaluation table shown by the Ministry of Health, Labor and Welfare are known as assessment scales of risk factors. According to a systematic review comparatively evaluating the predictive validity of multiple assessment scales, the Braden Scale was superior to the Norton Scale, Waterlow Scale, and Nurses' clinical judgment when the validity, sensitivity, and specificity were assessed comprehensively.[11] However, Japanese patients characterized by a low bodyweight and morbid bone protrusion were not evaluated. Also, there is a study comparing the modified Braden, Braden, and Norton scales in Asian subjects and reporting that the predictive validity was highest in the modified Braden Scale.[16] While these assessment scales for the prediction of the occurrence of pressure ulcers may contribute to the intensification and improvement in the efficiency of preventive measures against pressure ulcer, there is as yet no RCT reporting that they significantly reduced the incidence of pressure ulcer.[17]
- Among studies in Japan, there are a prospective cohort study using the K scale in bed-ridden patients,[12] case–control study using the OH scale,[13] and retrospective cohort study using the pressure ulcer risk factor evaluation table of the Ministry of Health, Labor and Welfare,[15] and each has been shown to be useful. Concerning home-cared elderly people, there is a prospective cohort study using the K scale modified for home use,[14] and the scale is rated as useful in sensitivity, specificity, etc.

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CQ4: WHAT KIND OF SKIN CARE SHOULD BE PERFORMED TO PREVENT PRESSURE ULCER?

Remarks on recommendation: The use of moisturizing creams, etc. is recommended to protect the skin and to prevent pressure ulcers. Also, the application of a polyurethane film to bone

protruded areas for the prevention of pressure ulcers is recommended.

Recommendation level: B.

Comments:

- Regarding the protection of the skin by washing and prevention of pressure ulcers, there are 4 RCT using a squalene-containing cream, or hyperoxygenated fatty acid compounds[18–21] and their evidence level is II. Concerning the prevention using polyurethane films, there are three reports of RCT,[22–24] and their evidence level is II.
- As to whether or not skin care by washing or using a moisturizing cream is effective for the prevention of pressure ulcers, there have been 4 RCT using a squalene-containing cream, or hyperoxygenated fatty acid compounds, and a significant preventive effect was observed in three of them.[18–20] In addition, several reports have shown that the time until cure of pressure ulcers was shortened, and the cure rate was improved, by the use of a skin protective agent in addition to skin cleaning.[25–27] However, the regimen and cream used vary among reports. Also, many of them are not used in Japan, and, specifically, which component is the most effective is unknown.
- There have been 3 RCT concerning the prevention using polyurethane films, and each reported their usefulness.[22–24] When a polyurethane film was applied to bone protruded areas in elderly patients, the incidences of pressure ulcers[22] and persistent erythema[23] were significantly reduced. Also, by applying a polyurethane film to the sacral region to prevent the intraoperative onset of pressure ulcer, its incidence was significantly reduced.[24] Similarly, the incidence of the intraoperative occurrence of pressure ulcer was reported to be significantly reduced by the application of hydropolymer to the heel.[28]
- A polyurethane film is a film of polyurethane coated with a waterproof and low-allergenic acrylic or vinyl ether adhesive and can seal and occlude wounds. Since it is transparent or translucent, the wound can be observed through it. It is also waterproof and prevents the entry of water and bacteria but is semipermeable and allows the passage of gasses and vapor. Therefore, it not only maintains moist environment of the wound but also does not interfere with sensible or insensible perspiration. For this reason, the skin around the wound is not macerated, and the barrier function of the skin remains intact. However, it should not be used for infected wounds, because the possibility of rapid proliferation of bacteria in a moist environment has been suggested.

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CQ5: IS NUTRITIONAL SUPPORT EFFECTIVE FOR THE PREVENTION AND MANAGEMENT OF PRESSURE ULCER?

Remarks on recommendation: Nutritional support (energy, protein) is strongly recommended for the prevention and management of pressure ulcer. (A). Supplementation of amino acids, vitamins, and trace elements is recommended. (B)

Recommendation level: A and B for prevention, A and B for management.

Comments:

- There are two meta-analyses concerning nutritional support (energy, protein) in patients with, and at risk of, pressure ulcer.[29,30] In one of them,[29] nutritional support is found to be useful for the prevention and treatment, and the evidence level is I.
- There are two meta-analyses concerning supplementation of nutrients including amino acids, vitamins, and trace elements.[29,30] It was recognized as useful for the prevention and management in one[29] but not in the other.[30] There are also 2 RCT reporting the effectiveness of supplementation of trace elements for the management,[31,32] and the evidence level is II.
- A meta-analysis[29] shows that malnutrition is an important risk factor of pressure ulcer and that providing necessary nutrients (energy, protein) is effective for the management of pressure ulcer by preventing its occurrence in patients at risk and promoting its cure in those who have developed it, and it is recommended by guidelines in Japan, the United States, and Europe.[33–35] Particularly, supplementation of protein has been shown to be important for improving the wound condition.
- Since the resting energy expenditure is often increased in pressure ulcer patients, it is necessary to supplement energy and protein to balance this expenditure. The energy demand

is calculated by the formula, bodyweight × 25 (kcal) or basal energy expenditure (calculated by the Harris–Benedict equation) × activity index × stress index (kcal). Harris–Benedict equation: males, 66.5 + (13.8 × bodyweight) + (5.0 × height) − (6.8 × age); females, 655.1 + (9.6 × bodyweight) + (1.8 × height) − (4.7 × age).

For the treatment of pressure ulcer, an activity index of 1.2–1.3 and a stress index of 1.2–1.3 are considered appropriate. Also, a protein intake of 1.1–1.5 g/kg/day should be set as a target. For patients in whom intake of normal diet is insufficient or impossible, nutritional support using prescribable enteral nutrition products (L-6PM®, Elental®, Ensure Liquid®, Hepan® ED, Meibalance®, Renalen®) should be considered.

- The nutritional state should be comprehensively evaluated on the basis of body measurements, clinical findings, and blood chemistry test results.
- The bodyweight is an index that reflects the nutritional state. The diagnosis of overweight or underweight should be made by calculating the body mass index (BMI) from the results of body measurements. BMI: bodyweight (kg)/height (m^2) (22, standard bodyweight; <18.5, underweight; and >25, overweight).

  In addition, malnutrition is judged to be mild, moderate, and severe when the patient's bodyweight is 85–95, 75–84, and 74% or less, respectively, of his/her usual bodyweight (determined by inquiry to the patient or his/her family). According to the rate of bodyweight changes, malnutrition is considered possible if a loss of 2% or more in 1 week, 5% or more in 1 month, 7.5% or more in 3 months, or 10% or more in 6 months is observed. The following indices should be referred to in estimating the body muscle and fat masses.

  Triceps skinfold thickness (TSF): measured using calipers at the midpoint between the acromion and ulnar head of the non-dominant arm. Used to estimate the body fat mass.

  Arm circumference (AC): used to estimate the muscle mass.

  Arm muscle circumference (AMC: AC (cm) − π × TSF (mm)/10): an index of the systemic muscle mass and lean bodyweight. Although it can be measured even in patients in whom body measurements are difficult due to marked contracture, it is important to measure it serially and examine its changes, because there are errors of measurement.

- Subjective global assessment (SGA) is performed for clinical findings. SGA is an assessment method consisting of inquiry about the history of disease (bodyweight changes, changes in food intake, gastrointestinal symptoms, physical function levels, disease, and nutritional requirements) and physical examinations (fat mass, muscle mass, presence or absence of edema). While it is a subjective scale of the nutritional state, it is difficult to use for beginners as there is no scoring system. Therefore, if a patient is judged to have severe malnutrition, the NST or an expert in nutritional guidance should be consulted.
- On blood chemistry tests, the nutritional state is evaluated primarily according to the ability of the liver to synthesize proteins. Chronic and acute nutritional states are reflected by proteins with long and short half-lives, respectively. Serum albumin has a long half-life of 21 days, and patients with a serum albumin level of 3.5 g/dL or lower are considered to be at risk of malnutrition. In elderly patients, however, the serum albumin level is often below this level, and a criterion of 3.0 g/dL or below may be used. In chronic malnutrition, the serum albumin level may not decrease with the muscle mass or subcutaneous fat. Serum transthyretin (prealbumin) has a short half-life of 2 days, and as it decreases markedly in acute malnutrition, it serves as an index of the current nutritional state. Malnutrition is possible when it is 17 mg/dL or less. A serum transferrin level of 200 mg/dL or les, serum cholesterol level of 150 mg/dL or less, and total lymphocyte count of 1200/mm^3 may also serve as indices of malnutrition. [36,37]
- Regarding the administration of particular nutrients, there are RCT, though in a small number of patients, reporting that the cure of pressure ulcer was significantly accelerated by the administration of nutrients involved in the wound healing process such as arginine, zinc, and vitamin C.[31,32] Therefore, caution for their deficiency is needed.[38] Arginine, which is a conditionally essential amino acid, promotes hydroxyproline synthesis and, thus, increases collagen synthesis and plays an important role in wound healing. Vitamin C, which is necessary in the process of conversion of procollagen into collagen, is also important for wound healing. Vitamin B1 is a coenzyme involved in bridge formation of collagen, and as its reserve in the body is small, it is likely to become deficient. Zinc is an important trace element located in the active centers of many metalloenzymes. Both its intake and body content decrease in elderly people, and its deficiency causes cutaneous and mucosal symptoms and delay of wound healing. The supplements of such nutrients used in Japan include Isocal/Arginaid®, Abound®, Protein Max®, V CRESC®, and Tezon®. Liquid, gelatinous, and other preparation types can be selected depending on the swallowing ability.

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CQ6: ARE BODY POSITION CHANGES AND BODYWEIGHT DISPERSING DEVICES USEFUL FOR THE PREVENTION AND MANAGEMENT OF PRESSURE ULCER?

Remarks on recommendation: The use of a body pressure-dispersion mattress and periodic body position changes are strongly recommended for the prevention of pressure ulcer.

For the management, also, the use of a body pressure-dispersion mattress and periodic body position changes are strongly recommended.

Recommendation level: A for prevention, A for management.

Comments:

- Multiple systematic reviews[39–42] have shown that the incidence of pressure ulcer was reduced, and its cure was promoted, by using a bodyweight dispersing mattress and changing the body position compared with using a standard mattress or not changing the body position. The evidence level of all these reviews is I.
- Body pressure-dispersion mattresses can be classified by their specifications into those integrated with the bed frame (special beds), those to be substituted for usual mattresses (replacement mattresses), those layered over a standard mattress (overlay mattresses). Functionally, also, they can be classified into a type that prevents a high-pressure to be applied to the same site over a long time by dynamically changing the air pressure, i.e., the low-pressure-sustaining air mattress, and a type that statically deconcentrates the pressure. The latter includes urethane foam, gel, rubber, and air-pressure types.
- Since bodyweight dispersion mattresses can be selected using assessment tools appropriate for Japanese people such as the OH scale, this assessment should be performed in inpatients on admission. Generally, a low-pressure-sustaining air mattress should be selected with priority on pressure dispersion for those who cannot roll over without assistance (independence level of life: C2), and a low-pressure-sustaining air mattress that resists sinking of the body or static body pressure-dispersion mattress with priority on body position changes should be selected for those who can roll over alone (Ministry of Health, Labor and Welfare, independence level of daily living: C1). A very large number of studies have been carried out to compare products, but no particular product has been consistently rated high, and the results have not been conclusive.[39–42] Therefore, it is important to select bodyweight dispersion mattresses by taking the independence level, disease state, environment, and social life of the patient into consideration. Also, concerning patients who have developed pressure ulcer, a static body pressure-dispersion mattress should be selected for those who can lie in a body position that causes no compression of the ulcerated area, but a pressure-adjustable body pressure-dispersion mattress should be selected for those who cannot lie in a position that causes no compression of the ulcerated area, in principle.[42]
- Generally, as pressure ulcer is considered unlikely to occur if the contact pressure is 40 mmHg or less, the contact pressure of the sacral region with a body pressure-dispersion mattress should be checked using a simple interface pressure meter. If a simple interface pressure meter is unavailable, the contact pressure of the low-pressure-sustaining air mattress should be checked by examining the bottom-touch method.[43] By the bottom-touch method, the appropriateness of the air cell pressure is evaluated by inserting the fingers with the palm up under the low-pressure-sustaining air mattress and flexing the 2nd or 3rd finger. The pressure is considered to be appropriate when the bone protruded area can be touched lightly with the finger flexed to a height of about 2.5 cm.
- Even with the use of a adjustable body pressure-dispersion mattress, the body position should be changed at appropriate intervals.[39–43] There is an RCT reporting that the incidence of pressure ulcer was higher when a pressure-adjustable body pressure-dispersion mattress was used without changing the body position than when a static type was used with body position changes,[43] but the results appear to depend on the characteristics of the mattress model as mentioned below.
- The intervals of body position changes are recommended to be within 2 h if tolerated by the physical condition.[44] However, there are not only differences in function depending on the material and thickness of the static body pressure-dispersion mattress but also qualitative differences in the pressure-adjusting function of the low-pressure-sustaining air mattress. In addition, low-pressure-sustaining air mattresses with automated body position changing function (rolling function, multi-zone function) have been newly introduced. Therefore, it is difficult to discuss body pressure-dispersion mattresses in general, so there is presently no definite recommendation concerning the intervals of body position changes.[45]
- For patients who have developed pressure ulcer, a body position that minimizes compression of the ulcerated area should be selected. Back relieving in changing the body position and elevating the head side of the bed and the “rule of 30” in elevating the head side of the bed are measures useful for controlling friction and sliding. Attention to the

condition of the mattress cover or sheet including the hammock phenomenon (reducing the effect of the body pressure-dispersion mattress by covering it with a bed sheet with excessive tension like a tent), pressure setting of the low-pressure-sustaining air mattress (e.g., setting it at a level inappropriate for the patient's bodyweight), compression of the tubes, and disconnection of junctional parts is also necessary.[46]

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CQ7: CAN PRESSURE ULCER PATIENTS BATHE?

Remarks on recommendation: Bathing of patients with pressure ulcer is recommended.

Recommendation level: B.

Comments:

- There is 1 study comparing the cutaneous blood flow, bacterial mass, and pH between before and after bathing,[47] and its evidence level is IVb. However, as bathing is essential for skin care and is widely practiced in clinical settings, the recommendation level was set at B.
- Some textbooks favorably describe bathing of pressure ulcer patients, and there is a report indicating the effectiveness of bathing of elderly patients with pressure ulcer.[47] This report compares the cutaneous blood flow, bacterial mass, and pH between before and after bathing in patients with pressure ulcer and shows a significant increase in the cutaneous blood flow and a significant decrease in the bacterial mass after bathing. Also, there is a report that, when spinal cord injury patients with pressure ulcer were bathed, bacterial contamination of the bath tub was derived more from the intestine than from pressure ulcer and did not differ regardless of whether pressure ulcer was dressed or not.[48] However, effects of these findings on pressure ulcer are unknown.
- In bathing, it is considered useful to wash the skin particularly around pressure ulcer using soap.[49] Also, while neutral or acid soap with mild defatting power is often used, there is no particular problem in using usual alkaline soap if it is gently foamed on the skin without rubbing it with towel.[50]
- Although slightly different from bathing, foot bathing is often performed for the management of pressure ulcer on the heel. There are reports that it was useful[51] and that the ulcer size was significantly reduced by bathing in a whirlpool bath.[52]

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CQ8: WHAT PRECAUTIONS ARE NECESSARY IN USING A WHEELCHAIR FOR SPINAL CORD INJURY PATIENTS WITH PRESSURE ULCER?

Remarks on recommendation: Evaluating the seating of the wheelchair and checking the interface pressure are recommended as an option for spinal cord injury patients with pressure ulcer.

Recommendation level: C1.

Comments:

- Concerning the seating of the wheelchair, there is a before/after comparative study reporting that the tissue oxygen level recovered after alleviating compression by postural changes on the wheelchair,[53] and its evidence level is IVb. There is also a case report that pressure ulcers decreased by checking of the interface pressure on the wheelchair[54] with an evidence level of V.
- Remaining in the same posture on the wheelchair is considered to be a risk factor of pressure ulcer, but the tissue oxygen level of the compressed area has been reported to recover by relieving the compression for about 2 min by changing the posture or lifting the body.[53] Other than lifting the body, anterior leaning of the body to 45° or more is effective, and about 70% of the pressure can be relieved in this body position.[55] There is a report that pressure ulcer was reduced in spinal cord injury patient by consulting a rehabilitation specialist and having the interface pressure checked.[55]

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CQ9: CAN THE CURE OF PRESSURE ULCER BE PROMOTED BY IMPROVING THE NUTRITIONAL STATE?

Remarks on recommendation: To promote wound healing, prompt consultation with the NST or a specialist in nutritional guidance is strongly recommended for patients at high risk of, or with, pressure ulcer in a poor nutritional state.

Recommendation level: A.

Comments:

- Concerning the administration of nutrition to pressure ulcer patients, there are two systematic reviews[56,57] with an evidence level of II. There are also three studies comparing the nutritional state and incidence of pressure ulcer between before and after the introduction of the NST.[58–60]
- As to whether or not the nutrient administration to pressure ulcer patients is useful for the prevention and treatment of pressure ulcer, systematic reviews have shown that sufficient supplementation of protein and energy is effective for the prevention and treatment of pressure ulcer.[56,57]
- In evaluating the nutritional state and planning nutrient administration, it is necessary to consult the NST or a specialist in nutritional guidance. Indeed, there is a report that the occurrence of pressure ulcer after gastrointestinal surgery was reduced ($P = 0.051$) by the introduction of the NST probably due to shortening of the postoperative fasting period and an increase in the serum albumin level in the perioperative period.[58] There is another report that the incidence of pressure ulcer was reduced to about 1/3 after the introduction of the NST.[59] Intervention by the NST or a specialist in nutritional guidance has been reported to be effective in not only the perioperative but also chronic phase,[60] although no relevant literature concerning the timing of such intervention is known.
- As indices for nutritional assessment, the serum albumin level (3.0–3.5 g/dL is a provisional criterion of malnutrition), bodyweight loss (a marked loss during the past 2 weeks and losses of 5% in 1 month, 7.5% in 3 months, and 10% in 6 months are criteria for malnutrition), and eating rate (food intake rate: food intake of half the usual level or below over 2 weeks or longer is a criterion of malnutrition) are used.[61]
- The Subjective Global Assessment (SGA) is also frequently used by the NST or specialists in nutritional guidance. The SGA consists of inquiry about the disease history (bodyweight changes, changes in food intake, gastrointestinal symptoms, physical function levels, disease, and nutritional demands) and physical examinations (fat mass, muscle mass, presence or absence of edema) and is aimed to evaluate the subjective state of nutrition but is difficult to use for beginners for reasons such as that the findings are not scored. Therefore, if a patient is judged to have severe malnutrition, consultation with the NST or a specialist in nutritional guidance is desirable.

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PRESSURE ULCER IN THE ACUTE PHASE
CQ10: WHAT TOPICAL TREATMENTS OTHER THAN DECOMPRESSION SHOULD BE PERFORMED FOR PRESSURE ULCERS IN THE ACUTE PHASE?

Remarks on recommendation: If dressing materials are used in the acute phase, those that allow observation of the wound surface such as polyurethane film and hydrocolloid (HD) are recommended. If topical agents are used, white petrolatum or Vaseline-based ointments of dimethyl isopropyl azulene, and zinc oxide are recommended for protecting the wound surface, and silver sulfadiazine is recommended for preventing infection (B).

For short-term use in the acute phase, ointments containing antibiotics (antibacterial agents) are recommended as an option.

Recommendation level: B and C1.

Comments:

- There is no report other than expert opinions concerning the selection of dressing materials and topical agents for the acute phase,[62–66] and the evidence level is VI. However, as the use of dressing materials and Vaseline-based ointments for moist wound healing is an appropriate choice, and as they are used widely in clinical sittings, the recommendation level except ointments containing antibiotics (antibacterial agents), which may allow the development of resistant strains on long-term use, was set as B.

- Since pressure ulcer is unstable during the acute phase, the determination of the necrotic area is difficult, and tissue resistance to infection is weak. The discrimination between reactive congestion and grade I pressure ulcer is also difficult (See CQ1), and exacerbation in a short time is possible depending on the circumstances. Therefore, the point of topical treatment in this phase is to sufficiently observe the wound, protect it, and prevent infection.
- Dressing materials are often used to protect the wound surface. However, as the condition changes rapidly in the acute phase, it is important to select dressing materials that allow observation of the wound. Also, as the wound and skin around it are vulnerable, the use of dressing materials with mild adhesive force is desirable.
- A polyurethane film is a film of polyurethane coated with a waterproof and mildly allergenic acrylic or vinyl ether adhesive and can seal/occlude the wound. Since it is transparent or translucent, the wound can be observed through it. Also, as it is waterproof, it prevents the entry of water and bacteria, and as it is semipermeable, allowing the passage of gasses and vapor, it not only maintains a moist environment of the wound but also does not interfere with sensible or insensible perspiration. For this reason, it does not cause maceration of the skin around the wound and maintains the normal barrier function of the skin.
- HD retains moisture without adhering to the wound tightly, prevents the crust formation due to drying of the wound, promotes migration of epidermal cells by maintaining a moist wound environment, and promotes healing.[62] It also occludes the wound, prevents exposure of denuded nerve terminals to air, and, thus, mitigates the tingling characteristic of shallow wounds.[63]
- Commercially available HD materials, which are translucent and allow observation of the wound after application, include DuoACTIVE® ET. Visiderm® (a translucent and waterproof polyurethane film using HD in the layer adhering to the skin) and Remois® Pad (a transparent polyurethane film having a 3-layer structure with the layer adhering to the skin being HD compounded with moisture-retaining ceramide 2, supportive layer above it being a polyurethane film, and the outermost layer above it being very slippery nylon knit with a low friction coefficient) may also be used, though they are not medical materials.
- When topical agents are used, highly water-repellent white petrolatum or a Vaseline-based ointment of zinc oxide or dimethyl isopropyl azulene may be used to protect the wound surface.[64,65]
- If the prevention of infection is considered important, silver sulfadiazine with an emulsion ointment having an antibacterial activity and a strong penetrating property as the base should be used.[66] Since a Vaseline- base is used in ointments containing antibiotics (antibacterial agents) such as gentamycin-containing ointment, they may be used for a short period to protect the wound surface and to control or prevent infection, but they must be used cautiously because of the possibility of the development resistant strains on prolonged use.
- Silver sulfadiazine produces its infection controlling effect on the wound surface due to the antibacterial action of silver that it contains on the cell membrane and cell wall.[67,68] It controls the formation of biofilm of *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA).[69] Because of the emulsion base, it produces a debriding effect by causing softening and lysing of necrotic tissue. Also, its effect is attenuated when used concomitantly with povidone iodine. Its use in combination with other drugs, particularly, enzymatic debriding agents should be avoided.

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CQ11: HOW SHOULD PAIN OF PRESSURE ULCER IN THE ACUTE PHASE BE MANAGED?

Remarks on recommendation: Anti-inflammatory drugs or psychotropic drugs are recommended as an option to control pain of a pressure ulcer, particularly pain during its treatment. The use of body pressure-dispersion beddings and dressing materials is recommended as an option.

Recommendation level: C1.

Comments:

- Concerning the management of pain of pressure ulcers, there is a case–control study[70] and a case report,[71] and the evidence level is IVb.
- Of the patients with pressure ulcers, 37–66% were reported to have complained of pain at some point.[72] It has been reported that pain is related to the depth of pressure ulcer and that many patients felt pain during its treatment.[73]
- Anti-inflammatory drugs, psychotropic drugs, anti-anxiety drugs and anesthetics are used to control pain. Although they are usually effective to an extent, they are often ineffective.[70,71] There is also a report that body pressure-dispersion bedding and dressing with HD (which alleviates pain as it

maintains a moist environment without adhering to the wound and prevents exposure of denuded nerve terminals to air)[74,75] were effective for the control of pain.[70]
- Even if there is a wound, no intense acute pain is caused without stimulation of nerve terminals (mechanical stimulation, chemical stimulation by neutrophil proteinases and complements) except early after its development. Also, the effect of an anti-inflammatory drugs on chronic pain is limited (so the use of central nervous system agents and opioids is considered). The cause of pain should be analyzed, and if it is related to local/systemic infection or nutritional state, management of these causes should be the priority.

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CQ12: WHAT KIND OF EXAMINATION SHOULD BE PERFORMED IF DTI IS SUSPECTED?

Remarks on recommendation: For the diagnosis of DTI, imaging examinations (magnetic resonance imaging [MRI], ultrasound) and blood chemistry tests are recommended as an option.

Recommendation level: C1.

Comments:

- There are presently only case reports concerning examinations for the diagnosis of DTI,[76–78] and the evidence level is V.
- DTI is a term used by the National Pressure Ulcer Advisory Panel (NPUAP) in 2005 and means pressure ulcer without epidermal loss (stage I) showing signs of damage of tissues deeper than subcutaneous tissue. In the NPUAP staging of pressure ulcer revised in 2007,[79] a new stage called (suspected) deep tissue injury was added. However, pressure ulcers showing erosion (stage II) are also included in DTI if damage of tissues deeper than subcutaneous tissue is suspected. Also, it is a name given to conditions difficult to diagnose early on the basis of physical findings alone. What is the most important is management with the possibility of DTI in mind.
- Imaging examinations are expected to serve as supportive modalities for the diagnosis of deep lesions, but no examination has been shown to date to be consistently useful for the diagnosis of DTI. There is only a case report suggesting the possibility of predicting DTI by ultrasonography[76] and a case report in which deep injury could be visualized in an early stage by MRI, which can detect qualitative changes in muscles and soft tissues.[77]
- Imaging examinations may be useful for the differential diagnosis of pressure ulcer from other soft tissue infections (necrotizing fasciitis, gas gangrene, purulent myositis and osteomyelitis) and skin fistulas from retroperitoneal abscesses in elderly long-term bedridden patients. Also, plain X-rays of the pressure ulcer region are useful for the differential diagnosis from gas gangrene (air images) and osteomyelitis.
- DTI may be accompanied by damage of muscle tissue, and there is a case report indicating elevation of the serum levels of muscle-derived enzymes (creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, myoglobin).[78] Therefore, comprehensive evaluation including inflammatory reactions such as leukocytosis and C-reactive protein (CRP) and the urinary myoglobin level is necessary. Also, DTI is often caused by prolonged surgery and sudden disturbance of consciousness, and detailed history taking may contribute to the diagnosis. Skin biopsy may be useful for the diagnosis, because it may demonstrate necrosis of adipose tissue or sweat glands.

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CQ13: WHAT MEASURES SHOULD BE TAKEN WHEN DTI IS SUSPECTED?

Remarks on recommendation: Careful observation of the systemic condition and course of the lesion with local decompression is recommended as an option. As topical treatments, dressing of the wound surface using dressing materials that allow observation of the lesion such as a polyurethane film and translucent HD is recommended as an option.

Recommendation level: C1.

Comments:

- There are only expert opinions about measures to take when DTI is diagnosed, and the evidence level is VI.
- DTI is a lesion accompanied by ischemic injury of muscle or soft tissue, and the estimation of the affected area as well as qualitative diagnosis is important. When DTI has been

diagnosed, the patient should be placed in a body position to avoid compression of the lesion or, if it is impossible, the pressure on the lesion should be minimized using body pressure-dispersion devices.[80] Also, the possibility of exacerbation should be explained early to the patient and family while observing the skin surface (for bullae or purpura), carefully checking serum muscle-derived enzyme levels, signs of inflammation and urinalysis results, and sufficiently managing infusion to avoid renal failure due to myoglobin.

- If there is pain, the possibility of inflammation of the ulcer base is high, and treatments including surgery should be evaluated in addition to symptomatic treatments such as non-steroidal anti-inflammatory drugs. If the pulse is felt, and if necrosis is noted in the epidermis, treatment should be initiated as described in CQ16.
- There are no papers evaluating the use of a polyurethane film or translucent HD other than expert opinions, but maintaining a moist environment of the wound is expected to promote epithelial regeneration and wound healing. Also, as nerve terminals are remaining in pressure ulcers contained within the dermal level, exposure of denuded nerve terminals to air has been reported to cause pain, which, however, can be alleviated by covering the wound surface with a dressing material. [81–83]
- A polyurethane film is a film of polyurethane coated with a waterproof and mildly allergenic acryl or vinyl ether adhesive and can seal or occlude wounds. Because it is transparent or translucent, the wound can be observed through it. Also, as it is waterproof, it prevents the entry of water and bacteria, but as it is semipermeable, allowing the passage of gasses and vapor; it not only maintains a moist environment of the wound but also does not interfere with sensible or insensible perspiration. For this reason, the skin around the wound is not macerated, and the normal barrier function of the skin is maintained. However, caution is necessary as the possibility of rapid proliferation of bacteria has been suggested in infected wounds in a moist environment.
- HD maintains a moist environment without adhering to the wound and prevents crust formation due to drying of the wound. It also promotes migration of epidermal cells by maintaining a wet environment of the wound and accelerates healing. [82] It further occludes the wound, prevents exposure of denuded nerve terminals to air, and, thus, reduces the tingling characteristic of shallow wounds. [83]

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SHALLOW PRESSURE ULCERS
CQ14: IS POLYURETHANE FILM USEFUL FOR THE MANAGEMENT OF SHALLOW PRESSURE ULCERS?

Remarks on recommendation: For uninfected shallow pressure ulcers in the process of epithelization, the use of polyurethane film is recommended as an option.

Recommendation level: C1.

Comments:

- There are no papers evaluating the usefulness of a polyurethane film for the management of shallow pressure ulcers other than expert opinions, and the evidence level is VI.
- There are no papers evaluating the use of polyurethane film for shallow pressure ulcers within the dermal level (redness, bullae, erosion, shallow ulcers) other than expert opinions. If it is used for redness and bullae, it protects the wound from friction and sliding. Also, if it is used for erosion and shallow ulcers, it promotes epithelization and wound healing by maintaining moist environment of the wound. Since nerve terminals remain in pressure ulcers within the dermal level, exposure of denuded nerve terminals to air has been reported to cause pain, but this pain may be alleviated by covering the wound surface with a film.[84]
- A polyurethane film is a film of polyurethane coated with a waterproof and mildly allergenic acrylic or vinyl ether adhesive and can seal or occlude wounds. Since it is transparent or translucent, the wound can be observed through it. Also, as it is waterproof, it prevents the entry of water and bacteria, but as it is semipermeable, allowing the passage of gasses and water vapor, it not only maintains a moist environment of the wound but also does not interfere with sensible or insensible perspiration. For this reason, the skin around the wound is not macerated, and the normal barrier function of the skin is maintained. However, caution is necessary as the possibility of rapid proliferation of bacteria has been suggested in infected wounds in a moist environment.

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CQ15: WHAT TOPICAL TREATMENTS OTHER THAN REDUCING THE PRESSURE SHOULD BE PERFORMED FOR SHALLOW PRESSURE ULCERS?

Remarks on recommendation: Protection of the wound and maintaining an appropriate moist environment are necessary for the cure of shallow pressure ulcers within the dermal level (erosion, shallow ulcers). Therefore, dressing materials often play a primary role in the treatment. HD, hydrogel, polyurethane foam or chitin are recommended as options.

If external topical agents are used, white petrolatum or a Vaseline-based ointment of zinc oxide or dimethyl isopropyl

azulene is recommended for protecting the wound surface, or, for short-term use, Vaseline-based ointments containing antibiotics (antibacterial agents) are recommended, as an option. The use of granulation-promoting drugs such as bucladesine sodium and prostaglandin E1 is also recommended as an option.

Recommendation level: C1.

Comments:

- There are two RCT[85,86] and one systematic review[87] concerning topical treatment for shallow pressure ulcers (erosion, shallow ulcer) using HD, and the evidence level is I. While a significant difference was observed in the cure rate compared with saline gauze dressing, there was no significant difference compared with alginate, hydrogel or polyurethane foam. Therefore, the recommendation level was set similarly to other dressing materials shown below.
- There are three RCT using hydrogel,[88–90] and their evidence level is II. Because no significant difference was noted in the cure rate compared with saline gauze dressing,[88,89] HD[89] or povidone iodine,[90] the recommendation level was set at C1.
- There are five RCT using polyurethane foam,[91–95] and their evidence level is II. Since no significant difference was noted in the cure rate compared with saline gauze and polyurethane film,[91] HD,[92,93] hydrogel,[94] or hydropolymer,[95] the recommendation level was determined at C1.
- There is one case report using chitin,[96] and the evidence level is IVb. An epithelization effect has been reported.
- There are no papers concerning the use of topical agents for shallow pressure ulcers (erosion, shallow ulcer) other than expert opinions, and the evidence level is VI.
- Because it is necessary to protect the wound and maintain an appropriate moist environment for shallow pressure ulcers (erosion, shallow ulcers) within the dermal level, dressing materials are frequently used for their treatment. There are two RCT using HD for shallow pressure ulcers.[85,86] No significant difference was observed in the cure rate compared with saline gauze dressing.[85] Compared with saline gauze dressing and phenytoin cream,[86] the complete cure rate was significantly higher with HD. According to a systematic review summarizing these reports,[87] HD was used primarily for European Pressure Ulcer Advisory Panel (EPUAP) grade 2–3 pressure ulcers, and it was significantly superior to saline gauze dressing regarding the number of cured wounds, wound size reduction rate, period requiring dressing change, exudate absorbing capacity, pain during dressing change, adverse effects and cost, so HD is considered to have advantages over saline gauze dressing in the efficacy and cost. However, it was inferior to alginate, hydrogel and polyurethane foam in the number of cured wounds, time until cure, wound size reduction rate, ease of handling, period requiring dressing change, exudate-absorbing capacity and pain during dressing change. Particularly, it was significantly inferior to alginate in the wound size-reducing rate and pain during dressing change and to polyurethane foam in the period requiring dressing change, exudate-absorbing capacity and pain during dressing change. Concerning the cost, HD was more expensive than hydrogel or polyurethane foam. However, the difference in the efficacy compared with alginate, hydrogel or polyurethane foam was slight, and a clinical evaluation in a large number of patients is suggested to be necessary. Also, shallow pressure ulcers were not the only wounds evaluated in this review.
- HD maintains a moist environment without adhering to the wound and prevents crust formation due to drying of the wound. A moist environment of the wound promotes migration of epidermal cells and accelerates healing.[97] Also, HD occludes the wound, prevents exposure of denuded nerve terminals to air, and, thus, mitigates the tingling characteristic of shallow wounds.[98]
- There are three RCT of the use of hydrogel for shallow pressure ulcers.[88–90] No significant difference was observed in the cure rate compared with saline gauze dressing[88,89] or HD.[89] Compared with povidone iodine gauze,[90] there was no significant difference in the wound size-reduction rate, but epithelization was observed in 84% and 54% of the wounds dressed with hydrogel and povidone iodine gauze, respectively, with a significant difference, so hydrogel is considered to promote healing by accelerating epithelization. However, shallow pressure ulcers were not the only target lesions in any of these trials. There is a case report concerning the use of hydrogel for shallow pressure ulcers,[99] reporting its effectiveness for reducing the wound area, pain and surrounding redness.
- Hydrogel not only promotes granulation and epithelization by maintaining a moist environment but also alleviates pain by mitigating inflammation due to a rapid cooling effect.[100] Also, being transparent, it allows observation of the wound surface.[101]
- There are five RCT of the use of polyurethane foam for shallow pressure ulcers.[91–95] No significant difference was noted in the cure rate compared with saline gauze and polyurethane film[91] or hydrogel.[94] Compared with HD, there was also no significant difference in the cure rate,[92,93] but polyurethane foam was significantly more removable[92,93] and leakproof.[92] However, the time needed for change was 12.3 min for polyurethane foam, being significantly longer than 7.6 min for HD.[92] Compared with hydropolymer,[95] there was no significant difference in the cure rate, but damage, maceration and residue of the skin around the wound were significantly less with polyurethane foam. However, shallow pressure ulcers were not the only lesions evaluated in these trials.
- Polyurethane foam absorbs approximately 10 times its weight of exudate, maintains an appropriate moist environment, and promotes granulation and epithelization. It leaves no residue in the wound due to dissolution or detachment. Also, as the surface that comes into contact with the wound is made of a non-adhering polyurethane net, it is unlikely to rub off the newly formed epithelium even if it is displaced from the wound surface.[100]
- There is one case report of the use of chitin for shallow pressure ulcers.[96] Of the 32 pressure ulcer patients, the lesions were within the papillary layer of the dermis in 11. Chitin was also reported to show analgesic, exudate-control-

ling, granulation tissue-protecting and epithelization-promoting effects, and cure was observed in seven of the 11 patients. However, the chitin used was cotton-like chitin rather than unwoven chitin for wounds reaching the dermis.

- Chitin cotton is flexible and easy to apply to the wound surface and can protect it.[96] It absorbs liquid up to 25 times its weight.[102] It also promotes granulation, and the granulation tissue formed under it is reddish and of high quality. It can be used for pressure dressing and hemostasis after debridement.[102]
- When topical agents are used, Vaseline-based ointments, typically, highly water repellent white petrolatum, should be used for protecting the wound surface.[103] Vaseline-based zinc oxide and dimethyl isopropyl azulene ointments have the same effect and can be used for moist wound healing. Granulation promoters such as bucladesine sodium and prostaglandin E1 may also be used (see CQ28).
- Because ointments containing antibiotics (antibacterial agents) such as gentamycin-containing ointment are Vaseline-based, they may be used for a short period to protect the wound surface and control or prevent infection for shallow pressure ulcers in the acute or chronic phase. However, caution is necessary for the possibility of the development of resistant strains on long-term use.
- Many topical agents used for the treatment of skin ulcers fall in the category of granulation promoters, and most of them protect the wound surface or promote tissue repair and granulation by promoting the formation of matrix components (mucopolysaccharides) and fiber components (collagen) due to fibroblast proliferation, promoting angiogenesis, or improving the regional blood flow.[104]

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DEEP PRESSURE ULCERS EARLY HALF OF TREATMENT: AIMED AT WOUND BED PREPARATION ACCORDING TO THE TIME CONCEPT. CQ16–27 T: REMOVAL OF NECROTIC TISSUE CQ16: IS SURGICAL DEBRIDEMENT USEFUL FOR REMOVING NECROTIC TISSUE?

Remarks on recommendation: Surgical debridement of necrotic tissue after checking the hemorrhagic tendency is recommended if it is tolerated by the general condition.

Recommendation level: B.

Comments:

- There are no documents suggesting the usefulness of surgical debridement of necrotic tissue other than expert opinions, and the evidence level is VI. However, the procedure is essential for wound healing, and its importance is also emphasized by other guidelines.[105] Therefore, the recommendation level was set as B.
- No wound healing can be expected if necrotic tissue persists. Surgical debridement eliminates nests of infection and promotes wound healing. It also contributes to the accurate judgment of the wound depth.[105] However, as it is an invasive procedure, postoperative exacerbation of the general condition and even death is possible.[106] Therefore, sufficient evaluation of indications is necessary before its implementation.
- It is necessary to preoperatively check the general condition, blood test results (cell counts, clotting factors), and whether or not drugs such as antiplatelet agents and anticoagulants

have been used. Guidelines for cardiovascular diseases recommend minor operations in which hemorrhage can be controlled easily to be performed without using these drugs.[107] Guidelines for cerebral infarction mention that "oral administration of" warfarin "is desirable" and that antiplatelet therapy "may be continued".[108] However, as these treatments can be discontinued in some patients, it is desirable to first consult with the attending physician and manage the patients individually. If these treatments cannot be discontinued, debridement may be limited to necrotic tissue that does not bleed although this is insufficient as debridement (debridement within necrotic tissue is considered to cause little stress to the body including pain during the procedure).

- If there are clear signs of infection, and if it is causing cellulitis, necrotizing fasciitis or sepsis, surgical debridement is essential for saving the patient. However, if there is no urgency, autolysis may be promoted by topical agents or occlusive dressing, but careful examination of the wound for the presence or absence of deep infection is necessary.[105]
- Surgical debridement of limb ends (including the heel) should be performed carefully. Many patients have underlying PAD, and cure may be impossible even by surgical debridement. PAD was formerly called arteriosclerosis obliterans. Also, the infections mentioned above are absolute indications for surgical debridement. Amputation rather than debridement may contribute to the reduction of stress to the whole body.

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CQ17: WHAT TOPICAL TREATMENTS OTHER THAN SURGICAL DEBRIDEMENT SHOULD BE PERFORMED?

Remarks on recommendation: The use of cadexomer iodine is recommended for removing necrotic tissue of deep pressure ulcers (B).

The use of dextranomer or bromelain is recommended as an option. For dried necrotic tissue, the use of silver sulfadiazine is recommended as an option. Among dressing materials, the use of hydrogel is recommended as an option (C1).

Fradiomycin sulfate-crystalline trypsin cannot be recommended (at present) because of the lack of sufficient evidence. Also, wet-to-dry dressing cannot be recommended (at present) because of the lack of sufficient evidence (C2).

Recommendation level: B, C1 and C2.

Comments:

- There are three reports of non-blinded RCT on the debriding effect of cadexomer-iodine,[109–111] and the evidence level is II.
  There is one report of a non-blinded RCT concerning the debriding effect of dextranomer,[112] and no significant effect was noted despite some improvements. However, there are three non-RCT without controls,[113–115] which showed improvements. The evidence level is III.
  There is one RCT evaluating the debriding effect of bromelain,[116] and the evidence level is II, but its recommendation level was determined at C1, because pressure ulcer was not included in the evaluated wounds.
  There are no papers evaluating the debriding effect of silver sulfadiazine other than expert opinions,[117,118] and the evidence level is VI.
  There is one RCT concerning the debriding effect of hydrogel applied to pressure ulcer patients with necrotic issue,[119] and the evidence level is II. However, as there was no significant difference in the necrotic tissue removal rate compared with dextranomer, the recommendation level was set at C1.
  Concerning fradiomycin sulfate-crystalline trypsin, there are expert opinions about removal of necrotic tissue, but the recommendation level was set at C2 because of the possibility of the development of resistant strains on long-term use.
  There are two reports on non-blinded RCT concerning the debriding effect of wet-to-dry dressing,[120,121] but no significant difference was noted in time until cure in either report. Also, as the treatment is time-consuming, and its economic efficiency is questionable, the recommendation level was set at C2.
- The removal of necrotic tissue can be accelerated and promoted by combining surgical debridement with other treatments including topical agents depending on the condition of the wound. If surgical debridement is impossible due to a poor general condition, also, debridement using topical agents is often selected. Debridement using topical agents includes chemical debridement using enzyme preparations and induction of autolysis by maintaining an appropriate moist environment.
- There are three papers on non-blinded RCT concerning the debriding effect of cadexomer-iodine.[109–111] No significant difference was noted in the studies comparing the treatment with dextranomer or dextrin polymer, a base material,[109,111] but cadexomer-iodine was significantly superior in reducing eschar (dried and hardened necrotic tissue) after 4- and 6-week treatment in a study comparing it with a drug containing fibrinolysin-deoxyrhibonuclease.[110]
- Cadexomer-iodine produces a bactericidal effect by slowly releasing iodine.[122] Dextrin polymer also absorbs not only exudate but also bacteria.[122–124] Therefore, it is useful for the treatment of wounds with a large amount of exudate or pus, but careful washing not to leave old polymer beads is necessary in changing the dressing, so it should not be used

for pockets that are difficult to wash.[117] If exudate is insufficient, the treatment may cause drying of the wound surface and delay wound healing. When used in a phase with well-developed granulation tissue, the treatment may damage it due to iodine. Also, caution for iodine allergy is necessary.[117]

- Concerning the debriding effect of dextranomer, there is one non-blinded RCT.[112] The improvement rate was reported to be 13% for saline dressing and 80% for dextranomer, but the difference was not significant. There are also three non-randomized comparative trials without a control group,[113–115] reporting that necrotic tissue was reduced by 91.3% after 4 weeks in three of the eight pressure ulcer patients,[113] that the improvement rate after 4 weeks was 84.1% in 93 patients with skin ulcer including 25 pressure ulcer patients,[114] and that the number of patients with a large amount of necrotic tissue was reduced from four to one after 1 week.[115]
- Dextranomer is reported to clean the wound surface by absorbing exudate.[125] It absorbs bacteria, as well as exudate.[126] There are powdery and paste preparations compounded with macrogol and purified water, and they are used as specified National Health Insurance medical materials. Because the preparations are water-absorbing, they are optimally indicated for patients with excessive/appropriate exudate, and caution for drying of the wound surface is necessary.
- Regarding the debriding effect of the proteolytic enzyme bromelain, there is one double-blind RCT.[116] A significant improvement compared with inactivated placebo was reported, but the trial was targeted to burn injuries, and pressure ulcer was not included. Concerning papers on pressure ulcers, there are two non-randomized comparative trials without a control group.[127,128] A mild or stronger debriding effect was observed in 14 of 16 patients (88%) in one and in 10 of 11 patients (91%) in the other.
- In using bromelain, caution for the frequent occurrence of pain is necessary. The normal skin around the ulcer must be protected with Vaseline-based ointments.[117] Also, as highly water-absorbing macrogol is used as the base, caution for attenuation of the debriding effect is necessary when exudate or wetness of the wound is decreasing.[117]
- Silver sulfadiazine is frequently used for dried necrotic tissue to induce autolysis, but there is no paper evaluating its debriding effect other than expert opinions.[117,118]
- Because silver sulfadiazine is prepared with an emulsion base with a high water content, it is frequently used for dried necrotic tissue to induce its autolysis.[118] Caution is necessary as it may induce edema of the wound surface if exudate is rich.[117] Its effectiveness is attenuated when used with povidone iodine. Its use with other drugs, particularly, external enzyme preparations, should be avoided.[117]
- There is one RCT concerning the debriding effect of hydrogel in pressure ulcer patients with necrotic tissue.[119] Compared with dextranomer, the wound size reduction rate on the 21st day was significantly greater with hydrogel, but no significant difference was noted in the necrotic tissue removal rate between the two materials.
- Hydrogel not only absorbs and retains exudate but, as it contains moisture, also macerates the wound and necrotic tissue and accelerates its removal.[129] Also, hydrogel does not cause pain, reddening or inflammation of the surrounding intact skin as observed in chemical debridement using enzyme preparations.[130] If necrotic tissue is found to be macerated at dressing change, surgical debridement should also be performed as much as possible.[130]
- There are no papers concerning the debriding effect of fradiomycin sulfate-crystalline trypsin other than expert opinions.
- Fradiomycin sulfate-crystalline trypsin is an external powdered preparation prepared by compounding the antibiotic fradiomycin sulfate and the proteolytic enzyme trypsin with a necrotic tissue-lysing effect. The permeation of the antibiotic into the wound focus is reported to be promoted, and the healing process to be accelerated, due to the wound cleaning effects of the two agents and the chemical debriding effect of the proteolytic enzyme.[131] However, when an ointment containing an antibiotic (antibacterial agent) is applied to deep pressure ulcers for the infection control, its use is often prolonged, possibly leading to microbial substitution (see CQ20).
- Concerning the debriding effect of wet-to-dry dressing, there are two non-blinded RCT.[120,121] In comparison with HD in 44 pressure ulcer patents, there was no significant difference in the cure rate or cure speed despite slightly faster cure with HD. Also, the time until cure was markedly longer, and the cost was significantly higher, for wet-to-dry dressing.[120] When compared with an original sustained negative-pressure therapy, also, the time until wound closure did not differ significantly, and the cost was higher for wet-to-dry dressing.[121]
- Wet-to-dry dressing, performed by applying gauze saturated with saline to the wound surface and non-selectively removing the foreign bodies and necrotic tissue adhering to dried gauze in dressing change, is employed for debridement. Although it has been used for centuries and can be performed readily using gauze and saline usually available at any medical facility, demerits such as pain on dressing change, necessity of 2–3 daily dressing changes, maceration of the surrounding normal skin due to excessive moistening of the wound, possibility of entry of contaminated external materials into the wound and detachment of newly formed granulation tissue with removal of dried gauze have been reported.[132,133]

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I: CONTROL/ELIMINATION OF INFECTION
CQ18: HOW SHOULD INFECTION OF PRESSURE ULCERS BE DIAGNOSED?

Remarks on recommendation: It is recommended to diagnose the presence or absence of infection by comprehensively evaluating local symptoms on the surface of the ulcer and surrounding skin (physical findings), namely, the four signs of inflammation (reddening, swelling, fever, pain), systemic symptoms, results of bacteriological tests of the wound surface, or the results of hematological and blood chemistry tests.

Recommendation level: B.

Comments:

- Regarding the diagnosis of the presence or absence of infection, there is only an expert opinion,[134] and the evidence level is VI, but the recommendation level was made B with consensus of the committee.
- Infection should be diagnosed on the basis of findings such as reddening, swelling, tenderness, pus discharge, an increase in effusion, and bad smell on the ulcer surface and surrounding skin.[134] Usually, some bacteria are attached to the surface of the pressure ulcer, but they do no cause infection. Recently, therefore, the concept of bacterial balance, namely, understanding the bacterial state of the wound continuously as contamination, colonization and infection, and infection to occur depending on the balance between the bacterial burden to the wound and resistance of the body, has replaced the conventional view of either an aseptic or infected state.[135] There is also the stage of critical colonization, which is a state between colonization and infection but tilted more to infection with an increase in the number of bacteria. When no improvement such as a decrease in the wound size or epithelialization is observed for 2 weeks is an example of critical colonization.[136]
- Examination and evaluation of the wound provide important information for the diagnosis of infection.[137] Once infection occurs, flabby pulse may be felt below black necrotic tissue, fine granular granulation tissue may enlarge to large edematous nodules, the color of granulation tissue may change from clear red to a darker color or the surface may become sticky. Also, exudate increases and becomes pussy or viscous in the event of infection but decreases and returns to slightly bloody or serous with its suppression.
- If infection is accompanied by systemic symptoms such as fever, it is also necessary to suspect systemic inflammation such as the peripheral white blood cell count and CRP. If the body temperature is high, sepsis should be suspected and a blood culture should be performed. In the event of infection, the causative microorganism must be identified by culturing, and susceptibility tests must be performed simultaneously. Resident bacteria such as *Staphylococcus epidermidis* are detected frequently from shallow pressure ulcers, but mixed infections of *Staphylococcus aureus*, pyogenic streptococci, or *Pseudomonas aeruginosa* with *Escherichia coli*, enterococci or *Proteus vulgaris* are often observed in deep pressure ulcers.[136,137]
- If the exudate is rich with an intense bad smell, an abscess under the wound should be suspected, and incision and

drainage should be performed. However, prior to such a procedure, the general condition, blood test results (cell counts, clotting factors), and medications such as antiplatelet agents and anticoagulants should be checked. According to the guidelines regarding cardiovascular diseases, the continuation of such medications is recommended for minor operations, in which bleeding can be readily controlled.[138] The guidelines concerning cerebral infarction also state that "continuation of oral warfarin is desirable" and that "antiplatelet therapy may be continued".[139] However, as these medications can be suspended in some patients, it is desirable to first consult with the attending physician and manage the patients individually. If bleeding due to treatment at home is expected, the patient should be referred to a facility capable of appropriate treatment.

- Soft tissue infections are often detected due to a complaint of pain. However, as many patients with spinal cord injury desensitized and do not complain of pain, infection is likely to be exacerbated,[140] and special attention is needed. Also, if there is infection, careful selection of topical agents is necessary (see CQ20).

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CQ19: IN WHAT SITUATIONS SHOULD ANTIBIOTICS BE ADMINISTRATED SYSTEMICALLY?

Remarks on recommendation: Systemic administration of antibiotics is recommended not only when bacterial cultures from the ulcer surface are positive but also when signs of inflammation are noted in the skin around the ulcer, or when fever, leukocytosis or enhancement of inflammatory reaction is observed.

Recommendation level: B.

Comments:

- There is no report on the effects of systemic administration of antibiotics for infection of pressure ulcers except an expert opinion,[141] and the evidence level is VI. However, as it is essential to control wound infection, and as systemic administration is widely performed in clinical settings, the recommendation level was set at B.
- Contamination of wounds in general should be managed first by careful washing with physiological saline, and surgical debridement should be performed if necrotic tissue is observed. If signs of inflammation such as reddening, swelling, fever and pain are still observed on the ulcer surface or the surrounding skin, systemic administration of antibiotics should be initiated.[141] Infections derived from pressure ulcer include cellulitis, fasciitis, osteomyelitis and sepsis, and systemic administration of antibiotics should be promptly initiated if systemic symptoms suggestive of these conditions such as fever, leukocytosis and elevation of CRP are observed.[141,142] Systemic administration of antibiotics should also be initiated promptly if a pressure ulcer patient has developed infection in areas other than the pressure ulcer such as the urinary tract, cardiac valves and paranasal sinus.[141]
- If there are signs of local infection, the microorganisms isolated from the wound are likely to be causing the infection. Antibiotics should be empirically selected for causative microorganisms expected from the site and local findings (see below) until the results of bacterial cultures become available. Once causative bacteria is identified, it is important to select drugs by limiting the spectrum on the basis of the results to prevent the development of resistant strains. If antibiotics are not effective, the causative microorganisms and their foci (e.g. is there an abscess below the ulcer, is there sepsis?) should be reevaluated. If MRSA infection is suspected, the drug should be promptly changed to an anti-MRSA drug. Resident bacteria such as *S. epidermidis* are detected frequently from shallow pressure ulcers, but mixed infections of *S. aureus*, pyogenic streptococci, or *P. aeruginosa* with *E. coli*, enterococci or *Proteus vulgaris* are often observed in deep pressure ulcers.[143]
- The smell of the wound and color of exudate attached to gauze are informative for estimating the causative microorganisms of infected pressure ulcers.[143] For example, lesions appear grayish white when infected by *S. epidermidis*, yellowish green when infected by *S. aureus* and greenish blue with a sweet–sour smell when infected by *P. aeruginosa*. Mixed infection with anaerobic bacteria causes a brownish color and a foul odor. In the event of systemic infection, its focus and causative microorganism must be identified.
- Patients with pressure ulcers are likely to become carriers. If resistant microorganisms such as MRSA, multidrug-resistant *P. aeruginosa* and multidrug resistant *Acinetobacter* are detected, a gown, mask, cap and gloves should be worn to prevent nosocomial infection. Also, all tools used should be changed to disposable ones, and surveillance cultures should be performed.[142]

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CQ20: WHAT TOPICAL TREATMENTS SHOULD BE PERFORMED TO CONTROL INFECTION?

Remarks on recommendation: The use of cadexomer-iodine, silver sulfadiazine and povidone iodine sugar is recommended for controlling infection of pressure ulcers (B).

The use of povidone iodine gel, iodoform or iodine ointment is recommended as an option. Alternatively, if a dressing material is used, silver-containing Hydrofiber® is recommended as an option (C1).

However, as there is no sufficient evidence for the use of an ointment containing an antibiotic (antibacterial agent), it is not recommended (at present) (C2).

Recommendation level: B, C1 and C2.

Comments:

- There are three RCT each concerning the infection control with cadexomer iodine,[144–146] silver sulfadiazine[147–149] and povidone iodine sugar,[150–152] and the evidence level is II for all.

  Concerning povidone iodine gel, there is one case report,[153] and the evidence level is V.

  There is no published work concerning the infection control with iodoform or iodine ointment other than expert opinions,[154,155] and the evidence level is VI.

  Concerning the infection control using silver-containing Hydrofiber, there is one RCT,[156] and the evidence level is II. While the treatment is reported to be useful when the wound is infected, the target wound was non-ischemic diabetic ulcers rather than pressure ulcers, and the number of patients was small. Therefore, the recommendation level was set at C1.

  Concerning the infection control using ointments containing antibiotics or antibacterial drugs, there are two RCT,[145,149] and the evidence level is II, but neither shows the effectiveness of the treatment. Also, as ointments containing antibiotics or antibacterial drugs are considered to be used often over a long period for deep pressure ulcers in the chronic phase and to likely to invite microbial substitution, the recommendation level was set at C2.

- Concerning the infection control using cadexomer iodine, there are two RCT,[144–146] and a significant difference was noted in the amount of pus compared with dextranomer.[144] Moreover, compared with dextrin polymer used as the base, cadexomer iodine was significantly superior in the bacterial disappearance rate and appearance rate of new bacteria in pressure ulcers.[146] Also, compared with a drug compounded with fibrinolysin-deoxyribonuclease (containing chloramphenicol), no significant difference was noted, and cadexomer iodine is expected to show clinical efficacy similar to that of chloramphenicol.[145]
- Cadexomer iodine produces a bactericidal effect by slowly releasing iodine.[157] Dextrin polymer absorbs not only effusion but also bacteria.[157–159] Therefore, it is useful for the treatment of wounds rich in exudate and pus, but old polymer beads must be completely washed off in dressing change, so the material should not be used for pockets difficult to wash.[154] If exudate is deficient, dextrin polymer may dry the wound surface and delay wound healing. In a phase with well-developed granulation tissue, iodine may damage the granulation tissue. Also, caution for iodine allergy is necessary.[154]
- Concerning the infection control using silver sulfadiazine, there are three RCT comparing it with povidone iodine solution, base and gentamicin sulfate.[147–149] Silver sulfadiazine showed a higher infection-controlling effect than povidone iodine solution.[147] On a double-blind trial comparing it with the base, it showed a significantly stronger effect.[148] On a double-blind trial comparing it with gentamicin sulfate cream, no significant difference was noted in the efficacy rate.[149]
- Silver sulfadiazine produces an infection-controlling effect on the wound surface due to the antibacterial action of the silver it contains on the cell membrane and cell wall[160,161] and suppresses the formation of biofilm by *S. aureus* including MRSA.[162] Because an emulsion base is used, necrotic tissue is softened and lysed, and this exerts a wound surface cleaning effect. Caution is necessary when it is used for wounds rich in exudate, because it may cause edema of the wound surface.[154] Its effectiveness is attenuated when used with povidone iodine. Also, its use with other drugs, particularly, external enzyme preparations, should be avoided.[154]
- Concerning the infection control using povidone iodine, there are three non-blinded RCT,[150–152] and it was found to be significantly superior compared with white sugar or calf blood extract. Also, it was superior to lysozyme chloride when compared in non-disinfected patients.
- Povidone iodine sugar produces an infection-controlling effect due to the antibacterial action of the iodine it contains.[163] White sugar inhibits the growth of bacteria and suppresses the formation of biofilm by *S. aureus* including MRSA.[164] It alleviates edema of the wound surface due to the water-absorbing effect, promotes collagen synthesis by fibroblasts, and, thus, induces satisfactory granulation.[165] However, in wounds deficient in exudate, it may dry the wound surface and delay healing.[154] In the red stage, when granulation tissue is well-developed, povidone iodine may damage granulation tissue. Caution for iodine allergy is also necessary.[154]
- Concerning the infection control using povidone iodine gel, there is one case report.[153] The skin lesions were pressure ulcers in two of the 20 patients. The treatment caused disappearance of *S. aureus* and *P. aeruginosa*, which did not disappear when treated with ointments containing antibiotics (antibacterial drugs).
- Povidone iodine gel produces an infection-controlling effect due to the antibacterial activity of iodine, and its bactericidal effect is stronger than that of povidone iodine sugar.[163,166] It exerts a strong killing (or inactivating) effect on not only bac-

teria including MRSA but also viruses.[167,168] It may cause transient hypothyroidism if used in large doses.[154] Caution for iodine allergy is necessary.[154]

- There is no published work concerning the infection-controlling effect of iodine ointment other than an expert opinion,[155] according to which the treatment is considered appropriate for infected wounds.[169]
- Iodine ointment shows an iodine-release property similar to that of cadexomer iodine and a bactericidal effect similar to that of cadexomer iodine, with no growth of any of the bacterial species examined, including MRSA, being observed.[170] By gelatinizing, it is expected to contribute to a decrease in the stress during treatment.[155] Its water-absorbing capacity is 7.3 mL of purified water/g,[170] which ranks highest among various preparations. Therefore, it is appropriate for wounds rich in exudate, but, in wounds deficient in exudate, it is difficult to gelatinize,[171] and caution for drying of the wound surface is necessary. Caution for iodine allergy is also necessary.
- There is one RCT of the use of silver-containing Hydrofiber for the treatment of non-ischemic diabetic ulcer of the foot requiring infection control.[156] Compared with alginate, no significant difference was noted in the cure rate or the number of dressing changes, but the improvement in the depth of ulcer associated with improvement in granulation was significantly greater. When 12 patients treated with silver-containing Hydrofiber and eight patients treated with alginate were compared among patients with infected wounds treated using antibiotics, the cure rate was significantly higher in the silver-containing Hydrofiber group despite the small number of patients.
- There is one RCT using a silver-containing dressing material (silver-containing alginate) other than silver-containing Hydrofiber for the treatment of lower leg venous ulcer and pressure ulcer requiring infection control.[172] The wound infection rate was 33% with silver-containing alginate and 46% with usual alginate, being low for silver-containing alginate, although the difference was not significant. The cure rate after 4-week treatment was significantly higher with silver-containing alginate. Algisite Ag, which is a silver-containing alginate dressing material, has been marketed since January 2011.
- Hydrofiber absorbs approximately 30 times its weight of water.[173] With this water-absorbing capacity, which is approximately two times higher than that of alginate, it maintains a moist environment optimal for healing over a long period and promotes granulation.[173] It suppresses horizontal spread of the exudate it has absorbed and prevents maceration of the normal skin around the wound.[173] It also retains exudate-containing bacteria, and prevents its reflux to the wound. Because silver is released in this state, bacteria contained in exudate can be rapidly and efficiently eradicated.[174–176]
- There are two RCT concerning ointments containing antibiotics (antibacterial drugs).[145,149] A trial of gentamicin sulfate (cream-based) versus silver sulfadiazine[149] was performed by the double-blind design, and no significant difference was noted in changes in the bacterial count during a 2-week evaluation period. In a trial of a fibrinolysin-deoxyribonuclease compounded drug (containing chloramphenicol) versus cadexomer-iodine,[145] the disappearance rate of *P. aeruginosa* after 4 weeks was higher in the first group, but the appearance rates of new bacteria after 4 and 6 weeks did not differ significantly. Also, in a large-scale RCT of white petrolatum versus bacitracin-containing ointment for surgical wounds, there was no significant difference in the infection rate, but as contact dermatitis occurred in a small number of patients treated with bacitracin-containing ointment, white petrolatum is concluded to be safer.[177] None of these studies presented evidence indicating superiority of ointments containing antibiotics (antibacterial drugs), and, as mentioned in reference[6], ointments containing antibiotics (antibacterial drugs), the use of which for controlling infection of deep pressure ulcer tends to be prolonged, should be avoided, considering the possibility of microbial substitution. The use of fradiomycin sulfate-crystalline trypsin is also disrecommended for the same reason.

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M: MAINTAINING MOIST ENVIRONMENT (CONTROL/ELIMINATION OF EFFUSION)

CQ21: What topical agents should be used for topical treatment of pressure ulcers in the black-yellow stages with excessive effusion?

Remarks on recommendation: The use of cadexomer-iodine, dextranomer and povidone iodine sugar is recommended in a period with excessive exudate (B).

The use of iodine ointment is also recommended as an option (C1).

Recommendation level: B and C1.

Comments:

- Concerning the control of exudate using cadexomer-iodine, dextranomer and povidone iodine sugar, there are three,[178–180] one[181] and one[182] RCT, respectively, and the evidence level is II.
- There is no published work concerning the control of exudate using iodine ointment other than expert opinions,[183,184] and the evidence level is VI.
- Exudate is often excessive in pressure ulcers in the yellow stage, and its control is also desirable from the viewpoint of wound bed preparation. Also, frequent change of dressing is disadvantageous from the viewpoints of manpower and cost. However, the use of a strong hygroscopic material may cause drying of the wound surface and interfere with moist wound healing. Therefore, wounds must be carefully observed with the possibility of decrease in exudate with improvement in the state of wound surface in mind, and change of treatment must be evaluated according to the algorithm if a tendency to drying is observed.
- Concerning the control of exudate using cadexomer-iodine, there are three RCT.[178–180] Compared with dextranomer, the amount of exudate was significantly improved with cadexomer iosine.[178] Exudate was also significantly reduced with cadexomer-iodine compared with a fibrinolysin-deoxyribonuclease compounded drug.[179] Also, the exudate-absorbing effect of cadexomer-iodine did not differ significantly compared with dextrin polymer, which was the base, alone on an RCT.[180] Therefore, it is derived from dextrin polymer.
- Cadexomer-iodine produces a bactericidal effect by slowly releasing iodine.[185] Dextrin polymer absorbs not only exudate but also bacteria.[185–187] Therefore, it is useful for the treatment of wounds rich in exudate and pus, but old polymer beads must be washed off completely at dressing changes, and it should not be used for pockets that are difficult to wash.[188] If exudate is deficient, the treatment may dry the wound surface and delay wound healing. In a stage with well-developed granulation tissue, it may be damaged by iodine. Also, caution for iodine allergy is necessary.[188]
- There is a non-blinded RCT concerning the exudate control using dextranomer.[181] The amount of exudate was significantly improved in terms of the improvement rate compared with physiological saline dressing.

- Dextranomer is reported to clean the wound surface by absorbing exudate.[189] It absorbs not only exudate but also bacteria.[190] It is available in the forms of powder and paste prepared by the addition of macrogol and purified water, and they are used as specified materials covered by the National Health Insurance. Because they are water-absorbing preparations, patients with excessive to appropriate exudate are their good indications, and caution for drying of the wound surface is necessary.
- There is one non-blinded RCT concerning the control of exudate using povidone iodine sugar.[182] Povidone iodine sugar showed significantly higher improvement rates in both serous and pussy secretions compared with lysozyme chloride.
- The exudate-absorbing effect of povidone iodine sugar did not differ significantly compared with white sugar, which is a primary component, alone,[191,192] so this effect is considered to be derived from white sugar. If exudate is deficient, the treatment has been reported to dry the wound surface and delay the healing.[188] Similarly, in a phase with well-developed granulation tissue, granulation tissue may be damaged by povidone iodine gel. Also, caution for iodine allergy is necessary.[188]
- There is no published work concerning the control of exudate using iodine ointment other than expert opinions.[183,184] By compounding a gelatinizing agent such as partially neutralized polyacrylic acid with macrogol as the base, the preparation is designed to gelatinize when it absorbs exudate.
- When gelatinized, iodine ointment is expected to contribute to a reduction in stress during treatment.[193] Its water-absorbing capacity is 7.3 mL of purified water/g,[194] which ranks best among various preparations. Therefore, it is appropriate for wounds rich in exudate but is difficult to gelatinize in wounds deficient in exudate, and caution for drying of the wound surface is necessary.[183] Caution for iodine allergy is also necessary.

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CQ22: WHAT DRESSING MATERIALS SHOULD BE USED FOR TOPICAL TREATMENT OF PRESSURE ULCERS IN THE BLACK-YELLOW STAGES WITH EXCESSIVE EXUDATE?

Remarks on recommendation: The use of alginate or polyurethane foam with a high water-absorbing property is recommended in a stage with excessive exudate (B).

The use of chitin, Hydrofiber (including silver-containing dressings) and hydropolymer is recommended as an option (C1).

Recommendation level: B and C1.

Comments:

- Concerning alginate, there are two RCT comparing it with dextranomer and HD for deep pressure ulcers,[195,196] and the evidence level is II. Concerning the exudate-absorbing property of polyurethane foam, there is one RCT comparing it with HD,[197] and the evidence level is II.
- There are case reports concerning the effusion-absorbing properties of chitin, Hydrofiber and hydropolymer,[198–201] and the evidence level is IVb.
- There are two RCT using alginate for deep pressure ulcers requiring the control of exudate.[195,196] The cure rate was significantly higher compared with dextranomer.[195] Also, when pressure ulcers were treated with alginate for the first 4 weeks and with HD for the next 4 weeks, with controls treated with HD alone for 8 weeks, the ulcer size reduction rate was significantly higher compared with the control group.[196]

- Alginate absorbs 10–20 times its weight of liquid.[202] It gelatinizes by absorbing a large volume of exudate and promotes healing by maintaining a moist environment on the wound surface.[203] Also, exchange of calcium ion in alginate and sodium ion in blood or body fluid occurs on its interface with the wound, and calcium ion diffuses in the capillaries due to the concentration gradient, producing a hemostatic effect.[204]
- There is one RCT concerning the exudate-absorbing property of polyurethane foam.[197] It was significantly superior to HD in the water-absorbing property and ease of detachment, but no significant difference was noted in the dressing period.
- Polyurethane foam absorbs approximately 10 times its weight of exudate and promotes granulation and epithelization by maintaining an appropriate moist environment and leaves no residue due to lysis or detachment of the dressing material. Also, as its surface that comes into contact with the wound is made of a non-adhering polyurethane net, it is unlikely to cause detachment of the newly formed epithelium even when it is displaced from the wound surface.[202]
- There are two case reports concerning the exudate-absorbing property of chitin.[198,199] However, it has been reported both to have[198] and not to have[199] an exudate-controlling effect.
- Because chitin cotton is flexible, it can be readily applied to the wound surface for its protection.[198] It absorbs 25 times its weight of liquid.[199] It also promotes granulation, and granulation tissue that develops under it is reddish and of high quality.[198] Because it can be used for pressure dressing, it is useful for hemostasis after debridement.[199]
- There is one case report concerning the exudate-absorbing property of silver-containing Hydrofiber,[200] reporting an improvement in exudate. It was used in 30 chronic ulcer patients (including four patients with pressure ulcer) with delayed cure or in a state of critical colonization, and decreases in the wound size, mitigation of maceration around the wound, a debriding effect and satisfactory granulation were reported. There is also one case report concerning the exudate-absorbing property of Hydrofiber,[205] reporting an improvement in exudate, but the subjects did not include pressure ulcer patients.
- Hydrofiber absorbs approximately 30 times its weight of liquid.[202] It has approximately two times higher water-retaining capacity compared with alginate, maintains a moist environment optimal for cure and promotes granulation.[202] It prevents horizontal spread of exudate that it has absorbed and prevents maceration of the normal skin around the wound.[202] Also, silver-containing Hydrofiber retains exudate containing bacteria, and prevents its reflux to the wound. Because silver ion is released in this state, bacteria contained in the exudate can be rapidly and efficiently eradicated.[206–208]
- There is one case report on the use of hydropolymer for deep pressure ulcers requiring the control of exudate.[201] Satisfactory absorption of exudate was reported.
- Hydropolymer absorbs exudate, and its exudate-disposing ability is enhanced by active evaporation of the absorbed exudate.[201] The adhesive is water-based polyurethane gel, which partly accounts for the low irritativity of this dressing material to the skin.[201] It swells by absorbing exudate and fits into the depression of the ulcer.[202] Because it does no gelatinize, it leaves no residue.[209]

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CQ23: WHAT TOPICAL AGENTS SHOULD BE USED FOR TOPICAL TREATMENT OF PRESSURE ULCERS IN THE BLACK-YELLOW STAGE WHEN EXUDATE IS DEFICIENT?

Remarks on recommendation: The use of silver sulfadiazine is recommended in a period with low exudate (B).

The use of Vaseline-based ointments such as white petrolatum, zinc oxide, and dimethyl isopropyl azulene is recommended as an option (C1).

Recommendation level: B and C1.

Comments:

- There is no published work on topical agents to be used in the yellow stage when exudate is deficient other than expert opinions,[210–212] and the evidence level is VI. However, the

recommendation level of silver sulfadiazine was set at B, because it can be used simultaneously for debridement and infection control.

- In deep pressure ulcers, drying of the wound surface leads to delay of healing.[210] To maintain the wound in an appropriate moist environment, it is necessary to use a drug with an appropriate water content or Vaseline-based ointment with a wound surface-protecting effect. Particularly, in the yellow stage, a preparation with debriding and infection-controlling effects as well as water-retaining effect is optimal.
- Because silver sulfadiazine preparations are emulsion-based, they produce a wound surface cleaning effect by providing moisture to the wound and softening, and inducing autolysis of, necrotic tissue. In the phase with margins of the black necrotic tissue detached from the wound, these preparations are considered to facilitate surgical debridement and control infection of the wound surface by the antibacterial action of the silver that they contain on the cell membrane and cell wall.[211] Caution is necessary when the exudate is rich as they may induce edema of the wound surface.[212] Also, their efficacy is attenuated when they are used with povidone iodine. Their concomitant use with other drugs, particularly external enzyme preparations, should be avoided.[212]
- Ointments with Vaseline-base, typically highly water-repellent white petrolatum (e.g. zinc oxide and dimethyl isopropyl azulene ointments), are useful when exudate is deficient, because they protect the drying wound surface,[212] but they have no infection-controlling or debriding effect on the wound surface. While ointments containing antibiotics (antibacterial agents) are also Vaseline-based, their use for deep pressure ulcers in the chronic phase should be avoided, in principle, considering the possibility of the appearance of resistant strains (see CQ20).

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CQ24: WHAT DRESSING MATERIALS SHOULD BE USED FOR TOPICAL TREATMENT OF PRESSURE ULCERS IN THE BLACK-YELLOW STAGE WHEN EXUDATE IS DEFICIENT?

Remarks on recommendation: The use of hydrogel is recommended as an option when dried necrotic tissue adheres to the wound and exudate is deficient.

Recommendation level: C1.

Comments:

- There is one RCT concerning the debriding effect of hydrogel in pressure ulcer patients with necrotic tissue,[213] and the evidence level is II. Although the wound size reduction rate was significantly higher with hydrogel compared with dextranomer, the necrotic tissue removal rate showed no significant difference between the two materials. Therefore, the recommendation level was set at C1.
- Hydrogel not only absorbs and retains exudate but also macerates the wound and necrotic tissue because of the water it contains and promotes its removal.[214] Also, hydrogel causes no pain, redness or inflammation of the surrounding normal skin unlike chemical debridement using enzyme preparations.[215] If necrotic tissue is found to be macerated at dressing change, surgical debridement should be also performed as much as possible.[215]

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E: MANAGEMENT OF WOUND EDGE (RESOLUTION AND ELIMINATION OF POCKETS)

CQ25: WHAT TOPICAL TREATMENTS SHOULD BE PERFORMED WHEN THERE IS A POCKET?

Remarks on recommendation: If there is much exudate in the pocket on the wound surface, the use of povidone iodine sugar is recommended as an option.

If exudate is deficient, the use of trafermin or tretinoin tocopherol is recommended as an option.

However, if no improvement is observed with these treatments, surgical treatments or physical agents should be evaluated.

Recommendation level: C1.

Comments:

- There is one each non-randomized comparative trial on the treatment of pockets with povidone iodine sugar and trafermin,[216,217] and the evidence level is III for both.
- There is no published work concerning treatment of pockets with tretinoin tocopherol other than an expert opinion,[218] and the evidence level is VI.
- Because necrotic tissue is likely to persist in deep parts of a pocket, generation of new granulation tissue is prevented, and infection control is difficult. Moreover, drainage of exudate tends to become insufficient, causing an excessively moist condition. Also, a pocket is displaced readily with body movements and is likely to be enlarged further. Therefore, these problems should be identified, and management appropriate for individual patients should be performed to eliminate compression and friction causing pockets. However, if the pocket does not disappear even after elimination of its causes by sufficient management, treatment with

topical agents should not be continued as a routine practice, and surgical treatments or physical agents such as negative-pressure wound therapy (NPWT) should be considered.

- There is one non-randomized comparative trial with no control group concerning povidone iodine sugar,[216] reporting improvements in pockets. In 36 patients with skin ulcers complicated by diabetes (including six with pressure ulcers), response or complete response was observed in eight (88.9%) of the nine patients with pocket-forming ulcers.
- Advantages of povidone iodine sugar include an excellent infection-controlling effect as well as promotion of adequate granulation due to absorption of exudate and suppression of edema.[218] However, if exudate is deficient, it may dry the wound surface and delay the healing.[218] In a phase with well-developed granulation tissue, povidone iodine may damage granulation tissue. Caution for iodine allergy is also necessary.[218]
- There is one non-randomized comparative trial concerning the effectiveness of trafermin for the treatment of pockets.[217] Comparison of various topical agents with a granulation-promoting effect showed that trafermin accelerates the cure of pockets but not significantly. There are also case reports that pocket size was reduced by the use of trafermin.[219,220] While there are case reports of inserting chitin sprayed with trafermin into pockets to transport the drug to deep parts[221] and of the concomitant use of trafermin with NPWT,[222] the evaluation is difficult as trafermin was not used alone.
- Because trafermin has strong angiogenic and granulation-promoting actions,[223–225] it is expected to be effective for closing pockets. Its use in combination with other topical agents and dressing materials is recommended to fill dead spaces and retain moisture.[218]
- There is no published work concerning the treatment of pockets using tretinoin tocopherol other than an expert opinion.[218]
- Tretinoin tocopherol promotes granulation and angiogenesis due to promotive effects on fibroblast migration, cell migration and cell proliferation.[226–229] Because an emulsion base with a water content of 70% is used, the drug is appropriate for wounds showing a strong tendency to dry[218] but not for wounds rich in exudate or showing marked edema, surgical debridement should be also performed as much as possible.[218]

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CQ26: HOW SHOULD POCKET EXCISION BE PERFORMED?

Remarks on recommendation: Pocket excision with adequate control of bleeding is recommended as an option. Either partial incision or total removal of the pocket lid is also recommendable.

Recommendation level: C1.

Comments:

- There are two case reports on the procedure of Pocket excision,[230,231] and the evidence level is V.
- Infection inside a pocket causing exacerbation of the general condition is an absolute indication of pocket excision (see CQ16). Pocket excision is performed using an electric scalpel, with caution for bleeding. The general condition, blood test results (cell counts, clotting factors), and the presence or absence of medications such as antiplatelets and anticoagulants must be checked before surgery. The guidelines concerning cardiovascular disorders recommend continuation of the administration of these drugs in minor operations in which bleeding can be controlled readily.[232] The guidelines concerning cerebral infarction also state that "continuation of the oral administration" of warfarin "is desirable", and antiplatelet therapy "may be continued".[233] However, as suspension of the administration of these drugs is possible in some patients, it is desirable to consult with the attending physician first and determine the management of patients individually.

- Whether the pocket should be incised partially or the pocket lid should be removed completely must be determined in consideration of the subsequent treatments and nursing. Factors that should be taken into consideration include:

  1. Is there infection or necrotic tissue in the pocket, or is there a pocket in pocket? (All these conditions are indications of total removal of the pocket lid).
  2. After excision, will conservative therapy be continued, will reconstruction be performed using skin grafts or skin flaps, or will NPWT be performed? (Unless NPWT is performed, remaining pocket lid often interferes with epithelization).
  3. Will management after excision be performed by a physician, ward nurses, home-care nurses or family members? (If examination inside the pocket is difficult, leaving the pocket lid is dangerous).

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CQ27: HOW SHOULD NPWT FOR PRESSURE ULCERS WITH POCKETS BE PERFORMED?

Remarks on recommendation: NPWT can be performed using either the VAC® system or custom-made instruments, and both are recommended as an option.

Recommendation level: C1.

Comments:

- There are four case reports regarding the efficacy of NPWT,[234–237] and the evidence level is V.
- The VAC system has also been marketed in Japan since April 2010. Until then, negative-pressure therapy had been performed using custom-made instruments prepared by combining an occlusive dressing material and a syringe or continuous aspirator. Both methods are effective according to case reports. However, coverage by the insurance can be demanded only when the treatment is performed using the VAC system as topical negative-pressure therapy.
- Payment for materials of topical negative-pressure therapy can be demanded concerning both the occlusive dressing material and sponge to be inserted into the wound only when they are used as part of the negative-pressure therapy system of KCI (Kinetic Concepts, Inc., Tokyo, Japan). Although sponge is inserted into the wound by VAC system, a method by applying a negative pressure without inserting a material into the wound is also employed in Japan.
- Whichever method may be selected, appropriate control of necrotic tissue and infection is the principle of wound treatment, and careful observation, appropriate surgical debridement and improvement in the general condition are necessary.

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LATTER HALF OF TREATMENT: AIMING AT MOIST WOUND HEALING
CQ28–30
CQ28: WHAT TOPICAL AGENTS SHOULD BE USED FOR TOPICAL TREATMENT FOR PRESSURE ULCERS IN THE RED-WHITE STAGES?

Remarks on recommendation: The use of trafermin or prostaglandin E1 is recommended for wounds with appropriate/deficient exudate. The use of tretinoin tocopherol is recommended for wounds with deficient exudate. The use of bucladesine sodium is recommended for wounds with excessive exudate or marked edema (B).

The use of lysozyme chloride, calf blood extract, white petrolatum, zinc oxide and dimethyl isopropyl azulene is recommended as an option for wounds with appropriate/deficient exudate. The use of aluminum chlorohydroxy allantoinate (Alcloxa) is recommended as an option for wounds with excessive exudate or marked edema (C1).

Recommendation level: B and C1.

Comments:

- There are two, one, two and two RCT concerning the granulation promoting and wound size reducing effects of trafermin,[238,239] prostaglandin E1,[240] tretinoin tocopherol[241,242] and bucladesine sodium,[243,244] respectively, and the evidence level is II for all.
- There are three non-blinded RCT of lysozyme chloride about its effects on granulation and ulcer size,[245–247] and the evidence level is II, but the recommendation level was made C1 because of defects in the study design.
- There is no published work other than expert opinions[248] concerning calf blood extract, white petrolatum or Vaseline-

based ointments of zinc oxide, and dimethyl isopropyl azulene, and the evidence level is VI.
  - There are two RCT regarding aluminum chlorohydroxy allantoinate,[249,250] and it significantly promoted granulation compared with the base or calf blood extract. However, as it is an old drug, and the frequency of its use has decreased with the development and marketing of new drugs, the recommendation level was made C1.
- In the latter half of treatment, the wound enters the red stage, and the risk of infection decreases. In this period, it is most important to maintain an appropriate moist environment. As adequate granulation tissue is formed, the wound begins to shrink. Therefore, the point of treatment is to select topical agents that protect the wound surface, promote granulation and reduce the wound size. In Japan, multiple topical agents with a granulation promoting effect have been developed, and they should be selected according to the amount of exudate and the presence or absence of edema on the wound surface. For implementing a study design incorporating the concept of moist wound healing, it is necessary to focus on patients with pressure ulcer in the red stage in the latter half of treatment, but such reports are few.
- There is one RCT comparing the wound size-reducing effect of trafermin with that of granulocyte macrophage colony-stimulating factor (GM-CSF),[238] and the wound size reduction rate was reported to be significantly higher with trafermin. There is also an RCT using povidone iodine sugar as a control,[239] and the ulcer depth reduction rate was reported to be significantly greater with trafermin, but the use of povidone iodine sugar as a control drug in the red period is considered questionable.
- Trafermin promotes wound healing due to its angiogenic and granulation-promoting actions.[251–253] While its wound healing effect is strong, moist environment of the wound is difficult to maintain with a spray type preparation of this drug alone, and the concomitant use of other topical agents or dressing materials is recommended.[248] Also, while trafermin is expensive, there is a case–control study concerning the cost-effectiveness of a dressing material alone versus trafermin plus a dressing material.[254] Although there was no difference in the cost of materials used until cure, the period until cure was markedly shortened with trafermin plus a dressing material, so the treatment was concluded to be economically advantageous considering the charges for treatments and hospitalization.
- Concerning prostaglandin E1, there is one non-blinded RCT comparing it with lysozyme chloride[240] and reporting significant decreases in the area and depth of pressure ulcer.
- Prostaglandin E1 promotes wound healing due to its cutaneous blood flow increasing[255] and angiogenesis-promoting[256,257] actions. It also acts on fibroblasts to promote their proliferation[256,257] and stimulates keratinocyte proliferation by increasing the release of interleukin-6 from fibroblasts.[258,259] Because oleaginous plastibase is used as the base, the drug is appropriate for wounds with appropriate/deficient exudate but not for exudate-rich or markedly edematous wounds.
- There are two non-blinded RCT comparing tretinoin tocopherol with lysozyme or ointment containing bendazac.[241,242] Significant differences were observed in granulation and the ulcer size reduction rate compared with lysozyme chloride. Compared with bendazac-containing ointment, there was no significant difference in the ulcer size reduction rate, but a significant difference was noted in granulation.
- Tretinoin tocopherol promotes granulation and angiogenesis by stimulating fibroblast migration, cell migration and cell proliferation.[260–263] Because an emulsion base with a water content of 70% is used, the preparation is appropriate for wounds showing a marked tendency to dry[248] but not for exudate-rich or markedly edematous wounds.
- Concerning bucladesine sodium, there is a non-blinded RCT comparing it with lysozyme chloride.[243] While it showed improvements in the ulcer size and granulation in intractable ulcers in general, there was no comparison in pressure ulcers alone, and the evaluation of its effectiveness is impossible. However, there is one double-blind RCT comparing it with the base macrogol,[244] and a significant decrease in the ulcer size was noted. There are also three non-randomized comparative trials with no adequate control group,[264–266] indicating promotion of granulation in pressure ulcers.
- Bucladesine sodium promotes wound healing by improving the regional blood flow and promoting angiogenesis, granulation and epidermis formation.[267–270] Because the base macrogol is hygroscopic, the preparation should be used for wounds with excessive exudate or marked edema. However, caution for drying is necessary in its use for wounds deficient in exudate.
- Concerning lysozyme chloride, there are three non-blinded RCT evaluating its effects on granulation and ulcer size.[245–247] Improvements were observed by treatment with lysozyme chloride, but no statistical analysis was performed in any of them. Also, in all these trials, the control drug was povidone iodine sugar, which is considered questionable as a control drug in the red stage, as it is a topical agent that promotes drying.
- Lysozyme chloride has promotive effects on epidermal cell and fibroblast proliferation and promotes wound healing by stimulating mucopolysaccharide synthesis.[271–274] Because a base with water content of 23% is used, its primary effect on the wound is protection rather than supply of moisture.
- There is no published work except an expert opinion[248] concerning the granulation-promoting or wound size-reducing effect of calf blood extract.
- Calf blood extract reportedly accelerates wound healing by activating tissue functions and promoting fibroblast proliferation, and thus promoting granulation and vascular regeneration.[275–277] Because an emulsion base with a water content of 25% is used, the preparation is appropriate due to its protective effect for wounds in which exudate is appropriate to deficient but not for exudate-rich or markedly edematous wounds.

- There is no published work concerning Vaseline-based ointments such as white petrolatum, zinc oxide and dimethyl isopropyl azulene other than an expert opinion.[248]
- Ointments with Vaseline base, typically highly water repellent white petrolatum, such as those of zinc oxide and dimethyl isopropyl azulene have wound-protecting effect and promote shrinking of the wound by maintaining a moist environment.[248] Therefore, they are appropriate for wounds in which exudate is appropriate or deficient but not for exudate-rich or markedly edematous wounds. Although ointments containing antibiotics (antibacterial drugs) such as gentamicin are also Vaseline-based, they are usually not used, because there is no need for infection control in the red stage, and because the advent of resistant strains is possible on long-term use (see CQ20).
- There is one double-blind RCT of aluminum chlorohydroxy allantoinate,[249] and significant promotion of granulation was noted compared with the base. Also, there is one non-blinded RCT using calf blood extract as the control drug,[250] and significant granulation-promoting and wound size-reducing effects were observed. Although the evidence level is II, the recommendation level was made C1, because it is an old drug, commercial distribution of which began in 1984, and because the frequency of its use has decreased with the development and marketing of new drugs.
- Aluminum chlorohydroxy allantoinate is considered to promote angiogenesis, drying of the wound surface, granulation, epidermal regeneration and reduction of the wound size.[278] There are powdered and gelatinized preparations, but as the bases of both preparations are hygroscopic, they should be used for wounds with excessive exudate or marked edema, and their use for dry wounds should be avoided.

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CQ29: WHAT DRESSING MATERIALS SHOULD BE USED FOR TOPICAL TREATMENT FOR PRESSURE ULCERS IN THE RED-WHITE STAGES?

Remarks on recommendation: The use of HD, hydrogel, hydropolymer or polyurethane foam is recommended as an option for wounds with appropriate/deficient exudate. The use of alginate or chitin is recommended as an option for wounds with excessive exudate or marked edema.

Recommendation level: C1.

Comments:

- There are three RCT[279–281] and one systematic review[282] concerning the use of HD for pressure ulcers in the red-white stages, and the evidence level is I. Because a significant difference was observed in the cure rate compared with saline gauze dressing but not compared with alginate, hydrogel or polyurethane foam, the recommendation level was set similarly to that of the other dressing materials shown below.
- There are three RCT using hydrogel,[283–285] and the evidence level is II. Because no significant difference was noted in comparison with saline gauze dressing,[283,284] HD[284] or povidone iodine gauze,[285] the recommendation level was set at C1.
- There are two RCT using hydropolymer,[286,287] and the evidence level is II. Since no significant difference was noted in the cure rate in comparison with HD,[286,287] the recommendation level was set at C1.
- There are five RCT using polyurethane foam,[288–292] and the evidence level is II. Because no significant difference was noted in the cure rate compared with polyurethane film with saline gauze,[288] HD,[289,290] hydrogel[291] or hydropolymer,[292] the recommendation level was set at C1.
- There is one case report each of the use of alginate and chitin,[293,294] and the evidence level is IVb.
- The principle of moist wound healing is an appropriate water balance at the wound, and not only drying due to marked deficiency of exudate but also excessive exudate delays wound healing. Because dressing materials to be used in the black-yellow stages with excessive (CQ22) and deficient (CQ24) exudate were mentioned above, pressure ulcers in the red-white stages with appropriate exudate are discussed in this section.
- There are three RCT concerning the use of HD for pressure ulcers in the red-white stages.[279–281] No significant difference was observed in the cure rate compared with saline gauze dressing.[279,281] The complete cure rate was significantly higher with HD than with saline gauze dressing or phenytoin cream.[280] According to a systematic review summarizing these trials,[282] HD has been used primarily for EPUAP grade 2–3 pressure ulcers, and the number of wounds cured, wound size reduction rate, period requiring dressing change, exudate-absorbing capacity, pain on dressing change, adverse effects and cost were significantly more favorable compared with saline gauze dressing, concluding that HD is superior in effect and cost to saline gauze dressing. However, compared with alginate, hydrogel and polyurethane foam, HD is rated as inferior in the period requiring dressing change, exudate-absorbing capacity and pain on dressing change. Concerning the cost, also, HD is reportedly more expensive than hydrogel and polyurethane foam. However, the difference in the effect compared with alginate, hydrogel or polyurethane foam is slight, and a large-scale clinical trial is suggested to be necessary. However, the target wounds were not restricted to pressure ulcers in the red-white stages in any of these trials.
- There is one RCT using clear and absorbent acrylic dressing material (Tegaderm™ Absorbent Clear Acrylic Dressing; TAAD) and HD (DuoDERM® CGF) for pressure ulcers in the red-white stages.[295] On comparison of comfortableness, duration of application and wound healing, no significant difference was observed in wound healing, but TAAD was rated significantly higher in comfortableness. The mean duration of application was 5.7 days for TAAD and 4.7 days for HD, and the difference is ascribed to the avoidance of unnecessary dressing change because of the transparency of the material. In Japan, DuoActive® ET is marketed as

translucent HD preparations allowing observation of the wound after the application.

- HD maintains moist environment without adhering to the wound and prevents crusting due to drying of the wound. By maintaining a moist environment of the wound, it promotes migration of epidermal cells and accelerates healing.[296] HD also occludes the wound and prevents exposure of denuded nerve terminals to air, thus, mitigating the tingling characteristic of shallow wounds.[297]
- There are three RCT using hydrogel for pressure ulcers in the red-white stages.[283–285] No significant difference was observed in the cure rate compared with saline gauze dressing[283,284] or HD.[284] Compared with povidone-iodine gauze,[285] no significant difference was noted in the wound size reduction rate, but as epithelization was noted significantly more frequently in the hydrogel (84%) than povisone iodine gauze (54%) group, hydrogel is considered to promote cure by accelerating epithelization. However, the target wounds were not restricted to pressure ulcers in the red-white stage in any of these trials.
- Hydrogel not only promotes granulation and epithelialization by maintaining moist environment but also controls inflammation and mitigates pain due to its rapid cooling effect.[298] It also allows observation of the wound surface due to its transparency.[299]
- There are two RCT using hydropolymer for pressure ulcers in the red-white stages.[286,287] Although no significant difference was noted in the cure rate compared with HD,[286,287] the cost,[286] leakage of exudate[287] and mitigation of smell[287] were rated significantly more favorably for hydropolymer. However, the target wounds were not restricted to pressure ulcers in the red-white stages in any of these trials.
- Hydropolymer enhances the exudate-disposing ability by not only absorbing exudate but also actively evaporating the absorbed exudate.[300] Hydropolymer, using water-based polyurethane gel as the adhesive, is a dressing material minimally irritative to the skin.[300] It also absorbs exudate and fits into the depression of ulcers.[298] Because it does not gelatinize, it leaves no residue.[301]
- There are five RCT regarding the use of polyurethane foam for pressure ulcers in the red-white stages.[288–292] No significant difference was observed in the cure rate compared with polyurethane film with saline gauze[288] or hydrogel.[288] Compared with HD,[290,291] no significant difference was noted in the cure rate, but polyurethane foam was rated significantly more favorably in the ease of detachment[289,290] and leakage.[289] However, the time needed for dressing change was significantly longer for polyurethane foam (12.3 min) than for HD (7.6 min).[289] Compared with hydropolymer,[292] there was no significant difference in the cure rate, but damage or maceration of the skin around the wound and residue were observed significantly less frequently with polyurethane foam. However, the target wounds were not restricted to pressure ulcers in the red-white stages in any of these trials.
- Polyurethane foam promotes granulation and epithelization by absorbing approximately 10 times its weight of exudate and maintaining an appropriate moist environment. It leaves no residue at the wound due to dissolution or detachment. It is also unlikely to cause detachment of the newly formed epithelium even if it is displaced from the wound surface, because its surface that comes into contact with the wound is made of a non-adhesive polyurethane net.[298]
- There is one case report of the use of alginate for pressure ulcers in the red-white stages.[293] It was used for 50 each patients with International Association for Enterostomal Therapy (IAET) grade II and III pressure ulcers and showed a wound size-reducing effect. All grade II pressure ulcers cured with a mean treatment period of 17.9 days. Grade III pressure ulcers cured in 32 patients (64%) with a mean treatment period of 55.7 days. However, the target wounds were not restricted to pressure ulcers in the red-white stages in this study.
- Alginate can absorb 10–20 times its weight of liquid.[298] It promotes healing by absorbing a large volume of exudate as it gelatinizes, thus maintaining a moist environment over the wound surface.[299] Also, calcium ion contained in alginate is exchanged for sodium ion in blood/body fluid across the interface with the wound, and calcium ion diffuses in the capillaries due to its concentration gradient, producing a hemostatic effect.[302]
- There is one case report of the use of chitin for pressure ulcers in the red-white stages.[294] It was used in 32 patients with pressure ulcer (to the papillary layer of the dermis in 11 and deeper in 21) and was found to be effective for controlling exudate, protecting granulation tissue, promoting granulation and inducing epidermal formation. However, the target wounds were not restricted to pressure ulcers in the red-white stages.
- Chitin cotton is flexible and easy to apply to the wound surface for its protection.[294] It absorbs 25 times its weight of liquid.[303] It also promotes granulation and induces the formation of reddish, high-quality granulation tissue.[294] It can be used for pressure dressing and is useful for hemostasis after debridement.[303]

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CQ30: IS NPWT USEFUL FOR THE TREATMENT OF RED-STAGE PRESSURE ULCERS?

Remarks on recommendation: Negative-pressure therapy is recommended as an option for treating grade III or severer pressure ulcers in the red stage. Careful observation is necessary if the wound is infected.

Recommendation level: C1.

Comments:

- There are two RCT concerning negative-pressure therapy for grade III or severer pressure ulcers in the red stage,[304,305] and the evidence level is II. However, the recommendation level is set at C1, because its efficacy was only comparable to that of conventional surgical therapy.
- In one RCT, the period until the wound area decreased to one in two was compared with wet-to-dry dressing using Ringer's solution as the control treatment, and it did not differ significantly between negative-pressure therapy (27 days) and the control treatment (28 days).[304] In the other, the cure rate and wound size reduction rate after 6-week treatment were compared using Healthpoint System of wound gel products (a combination of cadexomer iodine and an enzyme preparation) as a control. No significant difference was observed in the cure rate (2/20 in the NPWT group, 2/15 in the control group) or wound size reduction rate (51.8% and 42.1%, respectively).[305]
- The VAC system (KCI) has been marketed also in Japan since April 2010. Until then, negative-pressure therapy was performed in Japan using custom-made instruments prepared by combining an occlusive dressing material and a syringe or continuous aspirator. Both methods are effective according to case reports. However, negative-pressure therapy is covered by the National Health Insurance system only when it is performed using the VAC system. Also, payment for the occlusive material and sponge to be inserted into the wound can be demanded from the National Health Insurance system only when they are used as part of the negative-pressure therapy system of KCI.
- Grade II or milder pressure ulcers are not indications of negative-pressure therapy. There is a report that early implementation of negative-pressure therapy is advantageous when it is applied to grade III or severer pressure ulcers,[306] but the efficacy or cure rate is not compared in this report. There are many reports of negative-pressure therapy performed in patients with pockets.
- There is no report of detailed evaluation of negative-pressure therapy applied to infected pressure ulcers. There is the opinion that infection can be controlled by applying a negative pressure, but, generally speaking, frequent direct observation and dressing change are recommended for infected wounds. Also, attempts to control infection by continuous washing with water have been made, but such attempts including treatment of necrotic tissue in the wound should be performed carefully.

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ARE THERE IMPROVEMENTS?
CQ31: HOW SHOULD PRESSURE ULCERS BE ASSESSED?

Remarks on recommendation: The use of the DESIGN, Pressure Ulcer Scale for Healing (PUSH) or Pressure Sore Status Tool (PSST) is recommended for the assessment of pressure ulcers.

Recommendation level: B.

Comments:

- There is one case–control study concerning the PSST as a method for the assessment of pressure ulcers,[307] and the evidence level is IVb. Concerning the PUSH, as there is one prospective cohort study,[308] the evidence level is IVa. For the DESIGN, there is one case–control study,[309] and the evidence level is IVb, but the recommendation level was set at B, because the assessment of the wound is essential for its management.
- The PSST,[307] PUSH,[308] Pressure Ulcer Healing Process (PUHP),[310] DESIGN[311] and DESIGN-R as its revised version[312] are known as methods for the assessment of pressure ulcers.
- The interrater reliability of the PSST has been reported to be high at 0.91,[307] but it is difficult to use in clinical situations due to the large number of evaluation items. The PUSH was devised to overcome this shortcoming. Concerning the PUSH, the score decreased significantly in healing pressure ulcers but did not in those that did not heal. The PUSH score was also closely correlated with the area of pressure ulcer and PSST score.[308] Also, principal component analysis showed that 58–74% of the changes observed in wound healing during a 10-week period could be explained by PUSH items.[313] Another report of an investigation of the use of the PUSH rated the system to be practically usable and reliable in clinical settings.[314]
- The DESIGN is an assessment tool for pressure ulcers developed and disclosed by the Japanese Society of Pressure Ulcers in 2002. Its interrater reliability was very high at 0.98 according to judgments using photographs and 0.91 in actual patients, and its score was strongly correlated with the PSST score.[309] Although the DESIGN was useful for following up the course of treatment for a particular pressure ulcer, it could not be used for comparison between multiple pressure ulcers. Therefore, it was supplemented in 2008 with the DESIGN-R,[312] in which each item of the DESIGN is weighted[315] to make comparison of the severity of multiple pressure ulcers possible according to the score.

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SELECTION OF OTHER TREATMENTS
CQ32: WHEN SHOULD SURGICAL TREATMENTS FOR PRESSURE ULCERS BE PERFORMED?

Remarks on recommendation: Surgical treatment is recommended as an option for grade III or severer pressure ulcers, but it should be performed after careful evaluation of the general condition and indications. Also, measures for infection control and surgical and/or chemical debridement should be performed in advance.

Recommendation level: C1.

Comments:

- There are retrospective cohort studies[316–321] and a case report[322] as the published work concerning surgical treatments, and the evidence level is IVa.
- Skin grafting and flap surgery are surgical procedures effective for inducing early cure of pressure ulcers that are not expected to be cured by non-surgical treatments or require long-term treatment. Because they are invasive procedures, and because musculocutaneous and fasciocutaneous flap surgery, in particular, is markedly invasive, careful evaluation of indications is necessary.[316] Also, preoperative checking of the general condition, results of blood tests (cell counts, clotting factors), and the presence or absence of medications including antiplatelets and anticoagulants is important. Guidelines concerning cardiovascular disorders recommend continuation of these medications in minor operations in which bleeding can be controlled readily[323]. Guidelines concerning cerebral infarction also state that, “continuation of oral administration of warfarin is desirable, and antiplatelet therapy may be continued”. [324] However, as such mediations can be suspended in some patients, it is desirable to consult with the attending physician first and manage the patients individually.
- Pressure ulcers do not occur without a cause. Conditions of patients such as restriction of locomotion, nutritional state and cardiopulmonary function often persist after surgery. Also, if intensive management including frequent repositioning and the use of pressure redistribution mattresses in the body position and the use of body pressure-dispersion beddings may be possible during hospitalization, the manage-

ment often reverts to the original low level after discharge. Without sufficient assessment with the patient of his/her environment at home after discharge, recurrence is likely, and the treatment may end up with self-content of the medical staff ("cured only during hospitalization"). Possibly reflecting such a situation, the postoperative recurrence rate exceeded 70% in some reports.[317–320] Also, there are situations in which surgery is inevitable for early closure of the wound even when recurrence is expected.

- Consult with appropriate references for surgical procedures in detail. The principle is to perform wound bed preparation by surgical debridement or chemical debridement using an enzyme preparation (a few weeks before reconstructive surgery, if possible) and then select the procedure from split-thickness skin grafting (can be performed at the bedside under local anesthesia), full-thickness skin grafting, fasciocutaneous flap surgery and musculocutaneous flap surgery according to the prospect of weight-bearing and scar contracture. There is a report that the results of fasciocutaneous flap surgery were more favorable than those of musculocutaneous flap surgery.[321] Some patients may require urinary tract diversion or ostomy.[322]

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CQ33: CAN SO-CALLED "WRAP THERAPY" BE PERFORMED FOR PRESSURE ULCERS?

Remarks on recommendation: So-called "wrap therapy" is recommended as an option. However, as the user is liable for the use of a material unapproved for medical use such as kitchen wrap, consent must be obtained from the patient and family before treatment.

Recommendation level: C1.

Comments:

- There are two non-randomized comparative trials reporting that so-called "wrap therapy" significantly contributes to improvements in the wound condition,[325,326] and the evidence level is III.
- Occlusive dressing is a dressing method used to avoid drying of the wound in expectation of moist wound healing. It is a general term for dressing methods using modern wound-dressing materials rather than conventional gauze dressing. It means dressing using materials that occlude the wound surface and create a moist environment such as HD, those that moisten dried wounds such as hydrogel, those that absorb and retain exudate such as alginate, chitin, Hydrofiber, polyurethane foam or secondary dressing materials such as polyurethane film.[327]
- Wound-dressing methods that prevent the entry of liquids, oxygen and bacteria into the wound from outside, and leakage or evaporation of exudate from the wound, are occlusive dressing methods, but they may be called closed or sealed dressing methods in more exact terms. In contrast, dressing methods that allow the passage of vapor and oxygen are semi-occlusive or semi-permeable, but both are usually called occlusive dressing methods without making clear distinction, because their border is unclear.[327]
- So-called "wrap therapy", namely, a dressing method using polychlorovinylidene kitchen wrap with low permeability to oxygen and water vapor, can be occlusive dressing unlike semi-occlusive dressing using a polyurethane film but does not seal the wound, because the material is not adhesive.[325–327] Advocates of so-called "wrap therapy" call the method "open wet dressing" as excessive exudate escapes from the wound due to incomplete sealing.[327,328]
- There are various dressing methods so-called "wrap therapy" or open wet dressing, and there is no established protocol. Therefore, it is difficult to judge whether or not so-called "wrap therapy" is valuable as a whole. However, a non-randomized comparative trial showed that dressing using polychlorovinylidene significantly improved pressure ulcers compared with conventional treatment and that no significant difference was noted in the occurrence of infection.[325] The method appears effective when it is performed as in this trial.
- Because kitchen wrap is not approved as a medical material, physicians must be aware that they are responsible for health damages if they are caused by the treatment and should perform it with consent of the patients and their families.

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CQ34: WHAT TOPICAL TREATMENTS ARE PERFORMED OTHER THAN SURGICAL TREATMENT AND SO-CALLED "WRAP THERAPIES"?

Remarks on recommendation: Electric stimulation therapy, phototherapy (ultraviolet therapy, infrared-visual light therapy, low-power laser therapy), hydrotherapy and hyperbaric oxygen therapy are recommended as an option.

Recommendation level: C1.

Comments:

- There is a meta-analysis[329] and RCT[330] concerning electric stimulation therapy, blinded RCT[331] concerning ultraviolet therapy, RCT[332,333] concerning infrared therapy, RCT concerning hydrotherapy,[334]and case report[335] concerning hyperbaric oxygen therapy. Although the evidence levels of these studies are I–V, the recommendation level was set at C1, because they are not widely performed in Japan.
- Electric stimulation therapy has been reported to be effective by meta-analysis.[329] However, there is also a multicenter collaborative double-blind RCT (63 cases) reporting that the wound area decreased more rapidly until 45 days of follow up but that there was no significant difference in the wound area decrease rate, cure rate or period until cure at the endpoint (147th day).[330] This therapy, which is not well-known and is performed infrequently in Japan, is aimed to promote wound healing by flowing electric currents between the wound and electrodes attached around it. Because sodium ion gathers at the anode, the pH of the area near it becomes alkaline, and the area near the cathode becomes acidic. These changes in the pH near the electrodes are considered to affect bacterial infection or vasodilation at the wound. Also, when electricity is applied, negatively charged cells such as macrophages and neutrophils migrate toward the cathode, and positively charged cells such as fibroblasts migrate toward the anode. Such a phenomenon of particular cells attracted to electrodes is known as electrotaxis. Therefore, it is necessary to change the electrodes at the wound every 1–3 days.
- There is one meta-analysis showing a significant improvement in pressure ulcers in spinal cord injury patients by electric stimulation of the gluteus maximus muscle.[329] As for its mechanism, there are some reports of a decrease in the pressure on the buttocks in the seated position due to muscle contraction induced by electric stimulation in addition to the above.[336–339] An increase in the regional cutaneous blood flow aftercompared with before electric stimulation with an associated significant decrease in the pressure on the buttocks in the seated position has also been reported in patients with spinal cord injury.[340]
- Concerning ultraviolet therapy, healing was shown to be significantly accelerated in a group irradiated at 2.5–10 minimum effective dose (MED) by a blinded RCT,[331] but the number of patients was small (n = 16), and irradiation was made at 10 MED, which is higher than the usual dose. Concerning infrared therapy, there are many reports suggesting its effects on wound healing. There is also an RCT targeted to pressure ulcer reporting significant acceleration of wound healing compared with a non-irradiated group.[332] However, the instruments used varied among reports, and no conclusion has been reached as for which infrared frequency range is effective. Concerning low-power laser therapy, an RCT reported no difference in the healing of pressure ulcers between irradiated and non-irradiated groups.[333] Thus, the action mechanism of phototherapy may vary depending on the wave length, but an increase in the blood flow at the wound and activation of fibroblasts on the wound surface are common effects of phototherapy.[333]
- There is an RCT concerning hydrotherapy,[334] and while the wound area is reported to have decreased significantly compared with the control saline gauze dressing, its mechanism is not discussed. This therapy is performed by applying physical stimulation with water warmed to an indifferent temperature (35.5–36.6°C) or a vortical flow to the whole body (Hubbard tank therapy) or part of the body (whirlpool therapy).
- Hyperbaric oxygen therapy is performed by placing the patient in a chamber with an elevated oxygen pressure for the treatment of carbon monoxide intoxication or anaerobic bacterial infection. There are case reports of its use for the treatment of pressure ulcer,[335,341] but there is no evidence that it is more useful than usual therapies.
- Other than the above therapies, treatments for chronic wounds such as the administration of an angiogenic or cell growth factor or the administration of autologous cells are recently being developed. As for drugs, vascular endothelial growth factor,[342] platelet-derived growth factor (PDGF),[343] and GM-CSF,[344] as well as basal fibroblast growth factor (bFGF; see CQ28), which is already in clinical use, are employed. They are administrated topically or as a plasmid by i.m. injection. There is a study, an RCT using a small number of patients, of topical administration of PDGF for pressure ulcer, showing significant shortening of the treatment period.[344] Presently, in the USA, clinical trials of treatment for stasis ulcer using virus vectors are in progress.
- Because blood and blood cells include cell growth factors, a solution prepared from platelets[345] or heparinized preserved blood[346] is topically applied with sealed dressing to treat wounds. Also, to induce angiogenesis, autologous hematopoietic stem cells are administrated primarily for conditions associated with limb ischemia,[347] because the vascular endothelium is derived from bone marrow cells. No clinical study has been conducted concerning the administration of any stem cell for pressure ulcer, and future evaluation is awaited.
- Healing of skin ulcers is considered to be promoted by applying cultured dermal substitute prepared by culturing

human fibroblasts in collagen sponge, and its usefulness has been reported in a report of five cases of pressure ulcer.[348] Applying bone marrow cells[349] or bFGF[350] diffused in a gelatinous matrix has also been attempted.

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