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Clinical Guidelines for the Antibiotic Treatment for Community-Acquired Skin and Soft Tissue Infection

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Skin and soft tissue infection (SSTI) is common and important infectious disease. This work represents an update to 2012 Korean guideline for SSTI. The present guideline was developed by the adaptation method. This clinical guideline provides recommendations for the diagnosis and management of SSTI, including impetigo/ecthyma, purulent skin and soft tissue infection, erysipelas and cellulitis, necrotizing fasciitis, pyomyositis, clostridial myonecrosis, and human/animal bite. This guideline targets community-acquired skin and soft tissue infection occurring among adult patients aged 16 years and older. Diabetic foot infection, surgery-related infection, and infections in immunocompromised patients were not included in this guideline.

Key Words: Impetigo; Erysipelas; Cellulitis; Fasciitis; Pyomyositis

Introduction

1. Background of guidelines

Skin and soft tissue infection (SSTI) is a common infectious disease. Clinical physicians who care for patients with SSTI are responsible for determining the presence of an infection, identifying the extent of infection, ascertaining the causative microorganism, administering the appropriate antibiotics, and deciding on surgical treatments for purulent and necrotizing infections. Proper care by the clinical physician can promote speedy recovery in the patient, while also preventing severe complications such as skin deformation, body defect, and death and preventing the abuse and misuse of broad-spectrum antibiotics and expression of antibiotic-resistant bacteria. Development of clinical practice guidelines that provide scientific evidence for proper care by clinical physicians is very im-

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portant. Up to now, various practice guidelines for SSTIs have been developed by numerous academic societies outside of Korea. In 2012, a practice guideline was developed by the Korean Society of Infectious Diseases (KSID) and Korean Society for Chemotherapy (KSC). Revision of domestic guidelines for Korea was under consideration due to the accumulation of new data and knowledge and epidemiological changes in the causative microorganisms. We developed the present guideline with support from the Korea Centers for Disease Control and Prevention in the effort to inhibit expression of antibiotic-resistant bacteria through the proper use of antibiotics.

2. Target groups and diseases excluded in the guidelines

This guideline targets community-acquired SSTI occurring among adult patients aged 16 years and older. The following infections were excluded from the guideline: infections in immunosuppressed patients, such as patients who have recently undergone anticancer therapy, those currently taking immunosuppressants, and recipients of organ or bone marrow transplantation; surgery-related infection; and diabetic foot infection.

3. Recommended target groups for use of the guidelines

This guideline is intended for general practitioners, residents, and specialists responsible for inpatient, outpatient, and emergency room care in medical institutions of various sizes, including primary care institutions. The guideline was prepared so that it can be easily understood and referenced the user.

4. Revision of the guidelines

This guideline was prepared based on scientific articles published at the time of development. If new diagnostic and/or treatment methods are subsequently developed or important epidemiological changes in the causative microorganisms are found, revision of the guideline may be considered. Considering the rate of epidemiological changes in bacteria and the possible introduction of new antibiotics in Korea, it is expected that revision of this guideline may be needed in 4 to 5 years.

Summary of Recommendations

Recommendations	Recommendation level	Evidence level
KQ 1. What are the appropriate diagnoses and treatments for impetigo and ecthyma?		
1-1. Gram staining and bacterial culture testing are recommended for pus or exudate from lesion(s). However, typical cases can be treated without testing.	Strong	Moderate
1-2. Impetigo can be treated with oral antibiotics or antibiotic ointment. In cases of numerous lesions or in outbreaks of poststreptococcal glomerulonephritis due to specific *Streptococcus pyogenes* transmission, use of oral antibiotics is recommended. Ecthyma should be treated with oral antibiotics.	Strong	Moderate
1-3. For oral antibiotic therapy, amoxicillin/clavulanate, first-generation cephalosporins, or clindamycin are recommended. For topical antibiotic therapy with ointment, mupirocin, fusidic acid, or retapamulin are recommended.	Strong	High
1-4. If methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or confirmed, doxycycline, clindamycin, or trimethoprim/sulfamethoxazole are recommended for oral antibiotic therapy.	Strong	Moderate
1-5. Oral antibiotics should be used for 7 days and antibiotic ointment should be applied twice a day for 5 days.	Strong	High
KQ 2. What tests are needed for purulent SSTI?		
2-1. Gram staining and bacterial culture testing on pus samples from purulent SSTI are recommended. However, typical cases may be treated without testing.	Strong	Moderate
KQ 3. What is the appropriate treatment for purulent SSTI?		
3-1. Purulent SSTI can be treated by incision and drainage.	Strong	High

Recommendations	Recommendation level	Evidence level
3-2. Use of antibiotics is recommended in cases of extensive cellulitis near the purulent lesion, in patients with purulent SSTI presenting with systemic symptoms such as fever, or in immunosuppressed patients.	Strong	Low
KQ 4. What is the appropriate antibiotic therapy for purulent SSTI?		
4-1. First-generation cephalosporins, amoxicillin/clavulanate, or clindamycin are recommended as empirical antibiotics for purulent SSTI. Use of antibiotics active against MRSA may be considered in cases of previous MRSA infection, previous MRSA colonization, and failed primary treatment.	Strong	Low
KQ 5. What is the appropriate treatment for recurrent skin abscess?		
5-1. In cases where abscesses recur in the same area, it is necessary to look for the presence of foreign materials and to identify and correct other local factors, such as hidradenitis suppurativa and pilonidal cyst. Moreover, incision and drainage, together with pus culture testing, should be performed early on.	Strong	Moderate
5-2. Antibiotics should be used for 5–10 days against the isolated causative bacteria.	Weak	Low
5-3. For patients with recurrent skin abscess caused by *S. aureus*, intranasal application of mupirocin ointment (twice a day for 5 days, every month), a chlorhexidine bath, and washing of personal items (towels, sheets, clothes, and so on) may be considered.	Weak	Low
KQ 6. What tests are needed for diagnosis of erysipelas and cellulitis?		
6-1. Routine blood culture, aspiration culture, or punch biopsy culture for identification of the causative bacteria of erysipelas and cellulitis is not recommended. However, blood culture, aspiration culture, or punch biopsy culture may be considered for immunosuppressed patients, patients receiving anticancer therapy, patients with neutropenia, those with immersion injury, and patients with infection from an animal bite.	Strong Weak	Moderate Moderate
6-2. Radiological examination for diagnosis of erysipelas and cellulitis is not required in most cases. However, radiological examination may be required in cases suspected of involving osteomyelitis or difficulty in differentiating from necrotizing fasciitis.	Weak	Low
KQ 7. What is the appropriate treatment for erysipelas and cellulitis?		
7-1. The principal antibiotics recommended for treating erysipelas are penicillin and amoxicillin.	Strong	Low
7-2. Administration of first-generation cephalosporins, nafcillin, ampicillin/sulbactam, or amoxicillin/clavulanate is recommended for treating cellulitis. In addition, clindamycin may also be considered.	Strong	Moderate
7-3. Use of antibiotics against MRSA infection may be considered in cases of previous MRSA infection/colonization or failed primary antibiotic treatment.	Strong	Very low
7-4. For empirical therapy for severe cellulitis infection in severely immunosuppressed patients, combination therapy using vancomycin + piperacillin/tazobactam or vancomycin + imipenem or meropenem is recommended.	Strong	Moderate
7-5. The appropriate treatment duration for erysipelas and cellulitis without complications is 5 days. If there is no improvement or complications occur during this period, the treatment duration may be extended.	Strong	High
7-6. Raising the lesion area may help shorten the progression of cellulitis. If edema or skin disease that causes cellulitis is present, these must be treated.	Strong	Moderate
KQ 8. What are the appropriate evaluation and treatment for recurrent cellulitis?		
8-1. In patients with recurrent cellulitis, the presence of causative factors of cellulitis (edema, diffuse inflammation, eczema, venous insufficiency, and toe web abnormality) should be checked and any correctable factors should be modified.	Strong	Moderate
8-2. In patients with cellulitis recurring at least 3–4 times a year, prophylactic antibiotics may be administered. Oral amoxicillin or intramuscular (IM) benzathine penicillin G may be considered as a prophylactic antibiotic.	Strong	Moderate
KQ 9. How is necrotizing fasciitis diagnosed?		

Recommendations	Recommendation level	Evidence level
9-1. Necrotizing fasciitis should be suspected in SSTI if the following clinical symptoms or signs are present: (1) severe pain inconsistent with findings upon physical examination, (2) tense edema, (3) blisters, (4) ecchymoses or skin necrosis, (5) palpable crepitus, (6) localized skin hypoesthesia, and (7) manifestation of systemic toxicity with sudden deterioration.	Strong	Low
9-2. Computed tomography (CT) or MRI examination may be helpful in diagnosing necrotizing fasciitis. However, diagnosis and treatment decisions for necrotizing fasciitis should not be postponed until after radiological examination.	Strong	Low
9-3. Microbial tests should be performed on infected tissue or abscess samples to identify the causative bacteria.	Strong	Low
9-4. Blood culture tests are helpful for diagnosing the causative bacteria.	Strong	Low
KQ 10. What is the appropriate treatment for necrotizing fasciitis?		
10-1. As soon as necrotizing fasciitis is diagnosed, appropriate surgical treatment must be considered immediately.	Strong	Low
10-2. As empirical antibiotics, broad-spectrum antibiotics that target Gram-positive, Gram-negative, and anaerobic bacteria should be used and the use of antibiotics active against MRSA should be considered	Strong	Low
10-3. In cases that involve patients with liver cirrhosis or compromised liver function due to alcoholism who have recently eaten seafood or come in contact with seawater, combination therapy with third-generation cephalosporins such as cefotaxime or ceftriaxone and doxycycline or tetracycline should be used for suspicion of *Vibrio vulnificus* infection.	Strong	Low
10-4. Once the causative organism is identified, antibiotic administered should be switched to an effective antibiotic with a narrow spectrum based on the susceptibility test results.	Strong	Low
10-5. If streptococcal toxic shock syndrome is suspected, intravenous immunoglobulin (IVIG) may be considered as adjuvant therapy.	Weak	Very low
KQ 11. How is pyomyositis diagnosed?		
11-1. Pus and blood culture tests are should be performed to identify the causative bacteria.	Strong	Moderate
11-2. MRI is recommended as the radiological examination; CT may be useful as well.	Strong	Moderate
KQ 12. What is the appropriate treatment for pyomyositis?		
12-1. Antibiotics with active against Gram-positive and negative bacteria should be used as the empirical antibiotic.	Strong	Low
12-2. Once the causative bacterium is identified, antibiotics administered should be switched to an effective antibiotics with a narrow spectrum based on the susceptibility test results.	Strong	Low
12-3. Use of an antibiotics against MRSA infection may be considered in cases of previous MRSA infection or colonization and if primary treatment has failed.	Weak	Very low
12-4. Purulent material should be drained or removed early on.	Strong	Low
12-5. If there is no response to the treatment, radiological examination (MRI and/or CT) can be performed to evaluate whether the purulent material has been properly drained or removed.	Strong	Low
KQ 13. What is the appropriate treatment for clostridial myonecrosis?		
13-1. Surgical debridement of involved tissue should be performed early on and continued visual evaluation and removal of the infected area must be performed.	Strong	Moderate
13-2. Combination therapy with penicillin and clindamycin is recommended as the definitive antibiotic therapy.	Strong	Low
KQ 14. Is preemptive antibiotic therapy needed for prevention of infection from an animal or human bite?		
14-1. Preemptive antibiotic therapy is not recommended for mild bite wounds with low risk of infection.	Strong	Moderate

Recommendations	Recommendation level	Evidence level
14-2. Preemptive antibiotic therapy for 3–5 days is recommended in immunosuppressed patients and those with asplenism, severe liver disease, edema at the site of the bite, moderate to severe damage (especially to the hands or face), and damage extending to the periosteum or joint capsule.	Strong	Low
KQ 15. What is the appropriate antibiotic therapy for infection from an animal or human bite?		
15-1. Antibiotics active against both aerobic and anaerobic bacteria, such as amoxicillin/clavulanate, should be used.	Strong	Moderate
15-2. First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin should not be used alone.	Weak	Very low
15-3. As IV antibiotics, β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, piperacillin/tazobactam), second-generation cephalosporins such as cefoxitin, or carbapenem such as ertapenem can be used.	Weak	Moderate
KQ 16. Is post-exposure prophylaxis for tetanus needed after an animal or human bite?		
16-1. Depending on the wound condition, tetanus toxoid vaccine should be administered to anyone who has not been vaccinated for tetanus in the past 5 or 10 years. For patients who have not received tetanus-reduced diphtheria toxoid-acellular pertussis (Tdap) vaccine previously, Tdap is preferred over Td vaccination.	Strong	Low
KQ 17. When is post-exposure prophylaxis for rabies needed after an animal bite?		
17-1. Post-exposure prophylaxis for rabies may be needed when bitten by a wild animal or in an area where rabies is prevalent. Consultation with an infectious diseases specialist is recommended for deciding whether to begin vaccination.	Strong	Low
KQ 18. How is a bite wound treated?		
18-1. Delayed primary or secondary closure after thorough irrigation of the wound area and debridement is recommended.	Weak	Low
18-2. Primary wound closure is not recommended for wounds, with the exception of those to the face, which should be managed with copious irrigation, cautious debridement, and preemptive antibiotics.	Strong	Low
18-3. For a clenched-fist injury, a hand specialist should be consulted for examination of damage to the tendons, synovial membrane, joint capsule, and bones.	Weak	Low

Development process of diagnosis and treatment guidelines

1. Guidelines development committee

The development committee comprised a committee chairman (Sang-Ho Choi of the Ulsan University College of Medicine) and four committee members (Yee Kyung Kwak of Inje University College of Medicine, Seong-Ho Choi of Chung Ang University College of Medicine, Tark Kim of Soonchunghyang University College of Medicine, and Seong Yeon Park of Dongguk University College of Medicine), recommended by the KSC and KSID; one committee member (Soo-Hong Seo of Korea University College of Medicine) recommended by the Korean Dermatological Association; and one committee member (Min Bom Kim of Seoul National University College of Medicine) recommended by the Korean Orthopaedic Association.

2. Practice guidelines development methods and process

This guideline was developed by the adaptation process. The practice guideline adaptation process refers to a method whereby if high-quality evidence-based practice guidelines for the same topic or question have been developed already, a new guideline will be made by summarizing the information contained in those practice guidelines. Preparing a new practice guideline through collecting and analyzing all evidentiary studies requires a significant amount of time, effort, and cost; therefore, we took the approach of using existing high-quality practice guidelines and adapting them to suit conditions in Korea. In 2011, the Steering Committee for Clinical Practice Guideline of the Korean Academy of Medical Science developed a Korean version of the practice guideline adaptation process model, with the support of the Korean Ministry of Health and Welfare. The present guideline was developed

based on that model, using the following five steps.

1) Deriving the key questions

To derive the key questions, we attempted to include the key elements needed for the key questions, following the population, intervention, comparison, and outcome (PICO) principle. Population was defined as adults with community-acquired SSTI; intervention was defined as intervention needed for diagnosis or treatment; comparison was defined as the group being compared with a specific intervention method; and outcome was defined as usefulness of the diagnosis or treatment outcome. In the first round, we came up a total of 28 key questions.

2) Practice guidelines search

For the adaptation process, we searched practice guidelines published over 10 years between 2007 and 2016. Korean and non-Korean electronic databases used for the search included PubMed, National Guideline Clearinghouse, Guidelines International Network, National Library of Guidelines, the Cochrane Library, and KoreaMed. These databases were searched for practice guidelines and review articles using different combinations of the keywords "cellulitis," "erysipelas," "skin abscess," "soft tissue infection," "bites," "pyomyositis," "fasciitis," "clinical guideline," "practice guideline," "consensus," and "recommendation." Ultimately, a total of six practice guidelines were selected for review (Fig. 1). The six guidelines selected consisted of the Surgical Infection Society Guideline [1], Italian Society of Infectious Diseases and International Society of Chemotherapy Consensus Statement [2], KSID/KSC Clinical Practice Guidelines for Soft Tissue Infections [3], Infectious Diseases Society of America Guideline [4], World Society of Emergency Surgery Guideline [5], and Japanese Association for Infectious Diseases Guideline/Japanese Society of

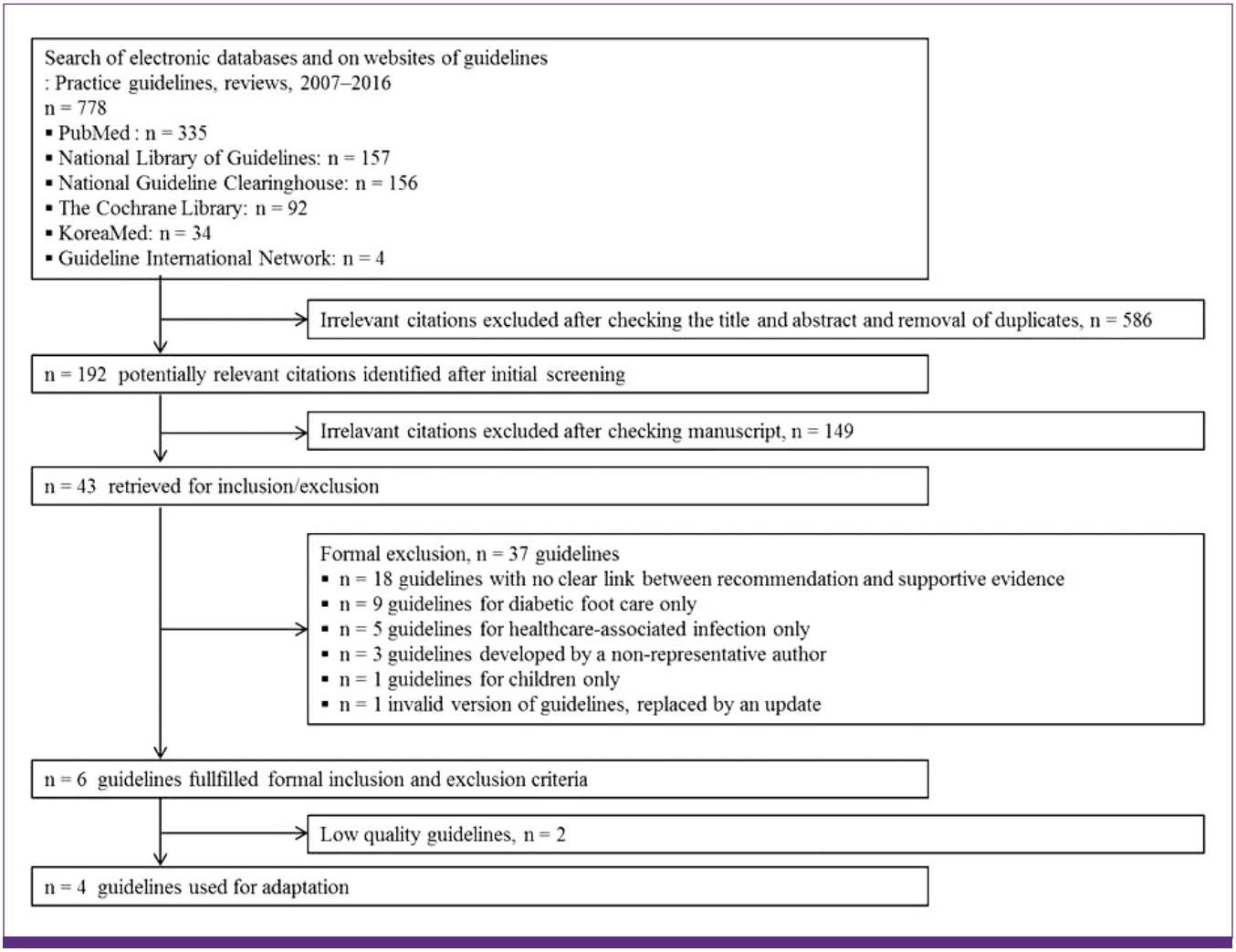

Figure 1. Selection of practice guidelines assessed.

Table 1. Definition of level of evidence [7]

High quality	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality	Any estimate of effect is very uncertain.

Chemotherapy Guideline [6].

3) Assessment and selection of practice guidelines

The quality of the six practice guidelines selected for the adaptation process were assessed by five development committee members using AGREE II, a guideline assessment scale. Standardized scores for six items (scope and purpose, stakeholder participation, developmental rigor, clarity and expression, applicability, and editorial independence) and overall assessment were calculated and the distributions of the scores were compared. Finally, the top four guidelines were selected (Surgical Infection Society Guideline, KSID Clinical Practice Guidelines for Soft Tissue Infections, Infectious Diseases Society of America Guideline, and World Society of Emergency Surgery Guideline).

4) Process of deriving the recommendations, strength of recommendation, and level of evidence

The recommendations were organized by each key question to construct a recommendation matrix. The most appropriate recommendations were derived by comparing the recommendations and by combining or deleting/revising them. The strength of recommendation and level of evidence were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method [7]. The strength of recommendation was divided into two types: strong or weak recommendation. Level of evidence was divided into four levels: high quality, moderate quality, low quality, and very low quality (Table 1). The type of strength of recommendation and the level of evidence were determined through assessment of the evidentiary literature supporting each recommendation and of the types and levels suggested in each guideline. A rough draft of recommendations was derived, with a total of 7 items and 18 key questions.

5) Expert consensus and opinion gathering for selecting the recommendations

The Delphi method was used for the process of consensus on the recommendations. A panel of 14 representative experts from the KSC and KSID were selected. The panel was requested to assess (via email) the 51 items in the rough draft of recommendations on a 9-point scale. Panel members were also encouraged to provide their opinions. A score of 7–9 points was considered to represent "agree"; 4–6 points, "unclear"; and 1–3 points, "do not agree." If 75% or more of the panel agreed on an item, a consensus on that item was considered to have been reached. A total of two rounds of surveys were conducted and the response rate in both the first and second surveys was 100%. Of a total 51 items, a consensus was reached on 48 items in the first round. Among the 3 items for which a consensus could not be reached, 1 item was deleted and a consensus reached on the other 2 items (1 item revised) in the second round, whereby a total of 50 items were ultimately selected.

Opinions were gathered from the 2017 Congress of the KSC and KSID (April 13, 2017) and KSID Training Lecture (July 8, 2017), attended by infection-related specialists, private practitioners, and residents.

Clinical guidelines by disease

1. Impetigo and ecthyma

Key question (KQ) 1. What are the appropriate diagnoses and treatments for impetigo and ecthyma?

Recommendations	Recommendation level	Evidence level
1-1. Gram staining and bacterial culture testing are recommended for pus or exudate from lesion(s). However, typical cases can be treated without testing.	Strong	Moderate
1-2. Impetigo can be treated with oral antibiotics or antibiotic ointment. In cases of numerous lesions or in outbreaks of post-streptococcal glomerulonephritis due to specific *Streptococcus pyogenes* transmission, use of oral antibiotics is recommended. Ecthyma should be treated with oral antibiotics.	Strong	Moderate

1-3. For oral antibiotic therapy, amoxicillin/clavulanate, first-generation cephalosporins, or clindamycin are recommended. For topical antibiotic therapy with ointment, mupirocin, fusidic acid, or retapamulin are recommended.	Strong	High
1-4. If methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or confirmed, doxycycline, clindamycin, or trimethoprim/sulfamethoxazole are recommended for oral antibiotic therapy.	Strong	Moderate
1-5. Oral antibiotics should be used for 7 days and antibiotic ointment should be applied twice a day for 5 days.	Strong	High

Impetigo is a bacterial infection that occurs on the epidermis and is manifested as two types: bullous and nonbullous impetigo [4]. In nonbullous impetigo, vesicles turn into pustules, and the pustules rupture and secrete purulent exudate, which forms a thick yellow eschar [3, 8]. In bullous impetigo, vesicles turn into inelastic bullae containing clear exudate; when the bullae rupture, a thin light brown eschar is formed [8]. Ecthyma is a deeper infection than impetigo. Ecthyma lesions are punched-out ulcers covered by greenish yellow crusts that extend deeply into the dermis and are often surrounded by elevated red margins. Even when treated, ecthyma may leave a scar [3, 4, 8].

Nonbullous impetigo is caused by streptococci or *S. aureus*, or it may be a polymicrobial infection involving both of these bacteria; bullous impetigo is caused by *S. aureus* [3, 4, 8]. Ecthyma can also be caused by streptococci or *S. aureus* or it may be a polymicrobial infection involving both of these bacteria [4]. A study conducted outside of Korea reported that the percentage of MRSA among *S. aureus*, the causative bacteria of impetigo, has been on the rise since 2000 [9].

When pus or exudate are present, the causative bacteria can be identified with Gram staining and bacterial culture testing, but typical lesions can be treated without testing, for microbial diagnosis. A drug that can treat both streptococci and *S. aureus* must be selected for treatment [10]. Amoxicillin/clavulanate, first-generation cephalosporins, or clindamycin may be used as an oral antibiotics whereas mupirocin, fusidic acid, or retapamulin may be used as an antibiotic ointment [10-12]. For impetigo, there is no known difference in treatment effect between antibiotic ointment and oral antibiotics [12]. However, oral antibiotics are recommended for patients with numerous lesions; oral antibiotics are also recommended for nephritogenic strains of *S. pyogenes* that cause subsequent poststreptococcal glomerulonephritis in community settings. Treatment of ecthyma is the same as for impetigo, except that oral antibiotics are recommended [13].

Studies in Korea on the causative bacteria of impetigo are very rare [14, 15]; therefore, it is difficult to determine whether there has been a recent increase in MRSA infection in Korea. However, for lesions that do not respond to treatment, the possibility of MRSA infection can be considered and empirical oral antibiotics, such as doxycycline, trimethoprim/sulfamethoxazole, and clindamycin may be used. However, because studies are lacking in Korea on the frequency, genotypes, and susceptibility patterns of community-associated MRSA, it is necessary to perform microbial tests prior to using oral antibiotics. However, if such testing cannot be performed, it is necessary to verify the treatment effect after the antibiotic use.

2. Purulent SSTI

KQ 2. What tests are needed for purulent SSTI?

Recommendation	Recommendation level	Evidence level
2-1. Gram staining and bacterial culture testing on pus samples from purulent SSTI are recommended. However, typical cases may be treated without testing.	Strong	Moderate

Purulent SSTI includes cutaneous abscess, furuncle, carbuncle, and inflamed epidermoid cyst. Cutaneous abscess refers to pooling of pus within the dermis layer or further below. Furuncle refers to the infections of the hair follicle which causing the dermis and subcutaneous tissue to become purulent, resulting in formation of pustules on top of inflammatory nodules on the hair follicles. Carbuncle refers to infection spreading to a cluster of pilar cysts to form inflammatory nodules filled with pus [3, 4, 8]. Cutaneous abscess occurs from infiltration of nearby skin or mucosal cells; it may be a polymicrobial infection, but monomicrobial infection by *S. aureus* is most common [8]. The causative bacteria of furuncle and carbuncle are *S. aureus* [3, 4, 8]. Performing Gram staining and bacterial culture testing on pus collected from infected tissue

can help in choosing the right antibiotic, but typical cases may be treated without testing [8].

KQ 3. What is the appropriate treatment for purulent SSTI?

Recommendations	Recommendation level	Evidence level
3-1. Purulent SSTI can be treated by incision and drainage.	Strong	High
3-2. Use of antibiotics is recommended in cases of extensive cellulitis near the purulent lesion, in patients with purulent SSTI presenting with systemic symptoms such as fever, or in immunosuppressed patients.	Strong	Low

Purulent SSTI is treated by incision and drainage [1, 3-5, 8]. Although there is no evidence to support that administration of antibiotics can provide additional help, use of an antibiotic is recommended in cases of extensive cellulitis that remains even after drainage of the purulent lesion; in patients presenting with systemic symptoms, such as fever, chills, body ache, and general weakness; or in immunosuppressed patients [1, 3-5, 8].

KQ 4. What is the appropriate antibiotic therapy for purulent SSTI?

Recommendations	Recommendation level	Evidence level
4-1. First-generation cephalosporins, amoxicillin/clavulanate, or clindamycin are recommended as empirical antibiotics for purulent SSTI. Use of antibiotics active against MRSA may be considered in cases of previous MRSA infection, previous MRSA colonization, and failed primary treatment.	Strong	Low

First-generation cephalosporins, amoxicillin/clavulanate, or clindamycin that is effective against *S. aureus* may be used. Use of antibiotics against MRSA infection may be considered in cases of previous MRSA colonization or infection and in patients who do not respond to primary treatment. It has been reported that MRSA has been isolated in over 50% of emergency room patients with purulent SSTI in the US [16]; however, additional studies are needed in Korea as data from the country are almost nonexistent.

KQ 5. What is the appropriate treatment for recurrent skin abscess?

Recommendations	Recommendation level	Evidence level
5-1. In cases where abscesses recur in the same area, it is necessary to look for the presence of foreign materials and to identify and correct other local factors, such as hidradenitis suppurativa and pilonidal cyst. Moreover, incision and drainage, together with pus culture testing, should be performed early on.	Strong	Moderate
5-2. Antibiotics should be used for 5–10 days against the isolated causative bacteria.	Weak	Low
5-3. For patients with recurrent skin abscess caused by *S. aureus*, intranasal application of mupirocin ointment (twice a day for 5 days, every month), a chlorhexidine bath, and washing of personal items (towels, sheets, clothes, and so on) may be considered.	Weak	Low

In cases of recurrent skin abscess, it is necessary to look for the presence of foreign materials and identify and correct local factors that may cause recurring infection, such as hidradenitis suppurativa and pilonidal cyst [4]. For recurrent skin abscess, Gram staining and bacterial culture testing should be performed early on to verify the causative bacteria and antibiotics susceptibility, based on which the appropriate antibiotics can be selected and used for 5–10 days, together with incision and drainage [3, 4].

When recurrent skin abscess occurs as a mass outbreak in groups with close contact among its members, such as families and sports teams, the following methods may be considered: intranasal application of mupirocin ointment; baths using antimicrobial soap containing chlorhexidine; thorough washing of clothes, towels, and pajamas; and discouraging the shared use of towels and hygiene products [17-21].

3. Erysipelas and cellulitis

KQ 6. What tests are needed for diagnosis of erysipelas and cellulitis?

Recommendations	Recommendation level	Evidence level
6-1. Routine blood culture, aspiration culture, or punch biopsy culture for identification of the causative bacteria of erysipelas and cellulitis is not recommended.	Strong	Moderate
However, blood culture, aspiration culture, or punch biopsy culture may be considered for immunosuppressed patients, patients receiving anticancer therapy, patients with neutropenia, those with immersion injury, and patients with infection from an animal bite.	Weak	Moderate
6-2. Radiological examination for diagnosis of erysipelas and cellulitis is not required in most cases. However, radiological examination may be required in cases suspecteZd of involving osteomyelitis or difficulty in differentiating from necrotizing fasciitis.	Weak	Low

Erysipelas and cellulitis are characterized by spreading skin lesions with warmth and erythema that diffuse over a relatively wide area and infiltrate superficially. Erysipelas is a soft tissue infection that infiltrates the upper part of the dermis, with a distinct boundary between the lesion and surrounding normal tissue [22]. Cellulitis is an infection of the lower dermal area and subcutaneous fat layer; it has an ambiguous boundary with the surrounding area.

In typical cellulitis patients, the positive blood culture rate is below 5% [23]. It has been reported that the culture-positive rate can range between less than 5% and 40% with needle aspiration culture of the lesion area [24, 25] and between 20% and 30% with punch biopsy [24, 26]. It is a well-known fact that β-hemolytic streptococci or *S. aureus* are the causative bacteria in most cases of erysipelas and cellulitis. Therefore, blood culture or culture by aspiration or punch biopsy is not recommended for identifying the causative bacteria in typical erysipelas or cellulitis patients. However, it is relatively common to find that β-hemolytic streptococci or *S. aureus* are not the causative bacteria in cases involving immunosuppressed patients, patients receiving anticancer therapy, those with neutropenia, those with immersion injury, and patients with infection from an animal bite. For these cases, blood culture, lesion aspiration, or punch biopsy may be helpful [25].

In most cases, radiological examination is not required for diagnosis of erysipelas and cellulitis. However, in cases suspected of involving osteomyelitis or difficulty in differentiating from necrotizing fasciitis, radiological examination, such as magnetic resonance imaging (MRI), may be required [3].

KQ 7. What is the appropriate treatment for erysipelas and cellulitis?

Recommendations	Recommendation level	Evidence level
7-1. The principal antibiotics recommended for treating erysipelas are penicillin and amoxicillin.	Strong	Low
7-2. Administration of first-generation cephalosporins, nafcillin, ampicillin/sulbactam, or amoxicillin/clavulanate is recommended for treating cellulitis. In addition, clindamycin may also be considered.	Strong	Moderate
7-3. Use of antibiotics against MRSA infection may be considered in cases of previous MRSA infection/colonization or failed primary antibiotic treatment.	Strong	Very low
7-4. For empirical therapy for severe cellulitis infection in severely immunosuppressed patients, combination therapy using vancomycin + piperacillin/tazobactam or vancomycin + imipenem or meropenem is recommended.	Strong	Moderate
7-5. The appropriate treatment duration for erysipelas and cellulitis without complications is 5 days. If there is no improvement or complications occur during this period, the treatment duration may be extended.	Strong	High
7-6. Raising the lesion area may help shorten the progression of cellulitis. If edema or skin disease that causes cellulitis is present, these must be treated.	Strong	Moderate

According to the findings of studies conducted outside Korea, erysipelas is caused mostly by group A β-hemolytic streptococci (*S. pyogenes*); group C or group G β-hemolytic streptococci may also be the cause [27]. Kwak et al. investigated the causative bacteria in 144 patients with erysipelas from 10 sec-

ondary and tertiary hospitals in Korea. The causative agent was identified in only 3 patients (2.1%), *S. pyogenes* in 2 patients and group G β-hemolytic streptococci in 1 patient [28]. The principal antibiotic recommended for treating β-hemolytic streptococci infection, including *S. pyogenes*, is penicillin [3, 29]. When administered orally, penicillin V is used; however, because that drug cannot be used in Korea, amoxicillin, another oral penicillin, is used [3].

Common causative bacteria of cellulitis are streptococci and *S. aureus* [30]. In a multicenter study from Korea that included 735 patients with cellulitis who were diagnosed between 2009 and 2011, the causative bacteria were identified in 7.8% (n = 57). Among them, the most common causative agent was *S. aureus* (44.0%, 26/57), followed by streptococci (27.1%, 16/57) [28]. A recent study in Korea that included 2,208 patients with cellulitis from 13 institutions identified the causative bacteria in 14.2% (n = 355); as in previous studies, *S. aureus* (45%, 162/355) and streptococci (24%, 85/355) were the most common causative agents [31]. Therefore, the principal antibiotics recommended for treating cellulitis are first-generation cephalosporins, such as cefazolin, and penicillinase-resistant penicillin, such as nafcillin, which are effective against *S. aureus* and streptococci [3, 4]. Intravenous (IV) ampicillin/sulbactam has similar efficacy as IV cefazolin [32]. The recommended antibiotics and doses for treating erysipelas and cellulitis are summarized by causative bacteria in Table 2.

The percentage of community-acquired cellulitis cases caused by MRSA is an important issue. According to a prospective study by a medical institution in the US, where the prevalence of CA-MRSA is known to be high, the treatment success rate of β-lactam class antibiotics such as cefazolin and oxacillin in cellulitis patients was 95.8%; based on serum test results, β-hemolytic streptococci represented the most common causative agent (73%) [33]. In other words, it is rare for MRSA to cause cellulitis and empirical MRSA treatment is not necessary. According to a recent Korean study, MRSA was isolated in 1.8% (n = 39) of 2,208 patients with community-onset cellulitis; when limited to only community-acquired cellulitis cases, the percentage was only 1.5% (29/1,977) [31]. These results indicate that MRSA as the cause of cellulitis is still very rare in Korea, accounting for less than 2% of cases. However, in cases of previous MRSA colonization/infection or failed

Table 2. Antibiotic therapy for erysipelas or cellulitis

Causative bacteria	Antibiotic	Adult dose
Streptococcus	Penicillin	2–4 million units q4–6 h IV
	Nafcillin	1–2 g q4–6 h IV
	Ampicillin/sulbactam	1.5–3 g q6 h IV
	Amoxicillin	500 mg q 12 h PO or 250 mg q8 h PO
	Cefazolin	1–2 g q8 h IV
	Cephalexin	500 mg q6 h PO
	Cephradine	500 mg q6 h PO
	Cefadroxil	500–1,000 mg q12–24 h
	Clindamycin	600–900 mg q8 h IV or 300–450 mg qid PO
Methicillin-susceptible *Staphylococcus aureus*	Nafcillin	1–2 g q4 h IV
	Cefazolin	1–2 g q8 h IV
	Cephalexin	500 mg q6 h PO
	Cephradine	500 mg q6 h PO
	Cefadroxil	500–1000 mg q12–24 h
	Clindamycin	600–900 mg q8 h IV or 300–450 mg qid PO
	Doxycycline	100 mg bid PO
	Trimethoprim/sulfamethoxazole	1–2 double-strength tablets bid PO
Methicillin-resistant *Staphylococcus aureus*	Vancomycin	15 mg/kg q12 h IV
	Linezolid	600 mg every 12 h IV or 600 mg bid PO
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid PO
	Doxycycline	100 mg bid PO
	Trimethoprim/sulfamethoxazole	1–2 double-strength tablets bid PO

IV, intravenous; PO, per os.

primary treatment with antibiotics, the possibility of MRSA should be kept in mind and use of antibiotics active against MRSA should be considered.

In a randomized study on cellulitis patients without complications, a 5-day course of antibiotic therapy was as effective as a 10-day course [34]. Although it is difficult to set a uniform treatment duration for cellulitis, 5-day therapy is recommended if improvement is seen within 5 days; if there is no improvement or complications occur during this period, the duration of antibiotic use may be extended [4].

Cellulitis occurs from microbial infiltration through damaged skin or when there is edema from venous or lymphatic obstruction [35, 36]. Skin damage may be due to trauma, as well as skin diseases such as impetigo or shingles, skin cracking between the toes, or tinea pedis. Obesity is also a well-known risk factor. When cellulitis occurs, the causative factors involved should be determined and any correctable factors should be modified [4].

KQ 8. What are the appropriate evaluation and treatment for recurrent cellulitis?

Recommendations	Recommendation level	Evidence level
8-1. In patients with recurrent cellulitis, the presence of causative factors of cellulitis (edema, diffuse inflammation, eczema, venous insufficiency, and toe web abnormality) should be checked and any correctable factors should be modified.	Strong	Moderate
8-2. In patients with cellulitis recurring at least 3–4 times a year, prophylactic antibiotics may be administered. Oral amoxicillin or intramuscular (IM) benzathine penicillin G may be considered as a prophylactic antibiotic.	Strong	Moderate

In patients with cellulitis of the lower extremities, the frequency of recurrence is about 8–20% [37-39]. Recurrence in the same area is common. Edema owing to venous or lymphatic obstruction, tinea pedis, or cracking between the toes are factors that increase the frequency of cellulitis recurrence [37-41]. Therefore, to prevent recurrence of cellulitis, the causative factors involved should be determined and any correctable factors should be modified [4]. When cellulitis recurs with lymphedema, the patient should be instructed to elevate the area affected by edema and prevent the skin from drying; the use of compression stockings is recommended when necessary [3].

If cellulitis recurs at least 3–4 times a year despite such measures, then prophylactic antibiotics may be administered. According to a randomized study, administering oral penicillin or erythromycin twice a day resulted in a significant decrease in the recurrence of erysipelas or cellulitis, as compared with the control group [42-44]. When 250 mg of oral penicillin was administered twice a day for 1 year in 274 patients with recurrent lower extremity cellulitis, the recurrence rate decreased significantly compared with the control group (22% *vs.* 38%); however, after discontinuing the prophylactic antibiotic, there was no difference in the recurrence rate [45]. In an observational study with monthly IM injection of 1.2 million units of benzathine penicillin, the recurrence rate decreased only in the patient group without risk factors of cellulitis recurrence [46]. In summary, administering oral amoxicillin or IM benzathine penicillin may be considered as a prophylactic antibiotic for patients with recurrent cellulitis. It is unclear as to how long an antibiotic should be administered as prophylaxis. The Infectious Diseases Society of America recommends that prophylactic antibiotic therapy should continue as long as the factors for cellulitis recurrence persist [4].

4. Necrotizing fasciitis

KQ 9. How is necrotizing fasciitis diagnosed?

Recommendations	Recommendation level	Evidence level
9-1. Necrotizing fasciitis should be suspected in SSTI if the following clinical symptoms or signs are present: (1) severe pain inconsistent with findings upon physical examination, (2) tense edema, (3) blisters, (4) ecchymoses or skin necrosis, (5) palpable crepitus, (6) localized skin hypoesthesia, and (7) manifestation of systemic toxicity with sudden deterioration.	Strong	Low
9-2. Computed tomography (CT) or MRI examination may be helpful in diagnosing necrotizing fasciitis. However, diagnosis and treatment decisions for necrotizing fasciitis should not be postponed until after radiological examination.	Strong	Low

9-3. Microbial tests should be performed on infected tissue or abscess samples to identify the causative bacteria.	Strong	Low
9-4. Blood culture tests are helpful for diagnosing the causative bacteria.	Strong	Low

Necrotizing fasciitis is a necrotizing soft tissue infection that invades the fascia that covers the muscles. Necrotizing fasciitis has a high mortality rate. A multicenter study in Korea among patients hospitalized during 2000–2012 reported that 21.2% (21/99) of patients died during hospitalization [47]. A recent multicenter study in Korea among patients hospitalized during 2012–2015 also reported that 23.2% (39/168) of patients died [48]. Therefore, early diagnosis and appropriate treatment of necrotizing fasciitis are very important.

The clinical features that raise suspicion of necrotizing fasciitis are as follows: (1) severe pain inconsistent with findings upon physical examination; (2) tense edema; (3) blisters; (4) ecchymoses or skin necrosis; (5) palpable crepitus; (6) localized skin hypoesthesia; and (7) manifestation of systemic toxicity, such as sepsis, with sudden deterioration [3, 49].

CT or MRI may be helpful in diagnosing necrotizing fasciitis. Fascial edema, fascial hypertrophy, fascial contrast enhancement, abscess, and gas formation may be observable by CT. With MRI, low signal intensity of soft tissues on T1-weighted images and high signal intensity of soft tissues and fascia, together with contrast enhancement on T2-weight images may appear [50]. CT alone is known to have a lower sensitivity of about 80%, comparing to MRI with a high sensitivity of 90-100% [51]. But there are concerns about overdiagnosis due to its lower specificity of MRI [52]. Above all, important decisions, such as surgical treatment, should not be postponed until after radiological examination(s).

Identifying the causative bacteria of necrotizing fasciitis is necessary for selecting the appropriate antibiotic, determining the prognosis, and switching the oral antibiotic. Culture testing of abscess or tissue samples should be performed to identify the causative bacteria of necrotizing fasciitis; blood culture tests are helpful as well. According to a Korean multicenter study, the causative bacteria were identified in 64.1% (66/103) of cases, for which testing of specimens obtained during surgery (48.5%, 32/66) and blood culture testing (43.9%, 29/66) were useful [47]. Similar results were also found in a recent Korean multicenter study [48].

KQ 10. What is the appropriate treatment for necrotizing fasciitis?

Recommendations	Recommendation level	Evidence level
10-1. As soon as necrotizing fasciitis is diagnosed, appropriate surgical treatment must be considered immediately.	Strong	Low
10-2. As empirical antibiotics, broad-spectrum antibiotics that target Gram-positive, Gram-negative, and anaerobic bacteria should be used and the use of antibiotics active against MRSA should be considered	Strong	Low
10-3. In cases that involve patients with liver cirrhosis or compromised liver function due to alcoholism who have recently eaten seafood or come in contact with seawater, combination therapy with third-generation cephalosporins such as cefotaxime or ceftriaxone and doxycycline or tetracycline should be used for suspicion of *Vibrio vulnificus* infection.	Strong	Low
10-4. Once the causative organism is identified, antibiotic administered should be switched to an effective antibiotic with a narrow spectrum based on the susceptibility test results.	Strong	Low
10-5. If streptococcal toxic shock syndrome is suspected, intravenous immunoglobulin (IVIG) may be considered as adjuvant therapy.	Weak	Very low

If necrotizing fasciitis is suspected, an empirical antibiotic should be administered immediately. Various pathogen may cause necrotizing fasciitis and it is common for necrotizing fasciitis to be caused by a mixed infection involving multiple bacterial strains. A Korean multicenter study reported that among 66 patients with confirmed causative bacteria, Gram-positive bacteria, such as streptococci and staphylococci, were identified in 63.6% (42/66) of patients and Gram-negative bacteria were identified in 42.4% (28/66). In addition, anaerobic bacteria were identified in approximately 5% of cases; however, this value was much lower than that of other countries and it is estimated that mixed infections with anaerobic bacteria may be more common in Korea [47]. A recent

Table 3. Antibiotic therapy for necrotizing fasciitis

Disease classification	Antibiotic	Adult dose
Empirical therapy	Teicoplanin or	6–12 mg/kg q24 h IV
	vancomycin or	15 mg/kg q12 h IV
	linezolid	600 mg q12 h IV
	plus	
	piperacillin/tazobactam or	3.375–4.5 g q8 h IV
	ertapenem or	1 g q24 h IV
	meropenem or	1 g q8 h IV
	imipenem or	500 mg q6 h IV
	cefepime	2 g q8 h IV
	plus	
	metronidazole	500 mg q8 h IV
Streptococcus	Penicillin	2-4 million units q4–6 h IV
	plus	
	clindamycin	600–900 mg q8 h IV
Methicillin-susceptible *Staphylococcus aureus*	Nafcillin or	1–2 g q4 h IV
	cefazolin	1–2 g q8 h IV
Methicillin-resistant *Staphylococcus aureus*	Vancomycin or	15 mg/kg q12 hr IV
	teicoplanin or	6-12 mg/kg q24 h IV
	linezolid	600 mg q12 h IV
Aeromonas hydrophilia	Ciprofloxacin or	400 mg q12 h IV
	cefotaxime or	2 g q8 h IV
	ceftriaxone	2 g q24 h IV
	plus	
	doxycycline	100 mg bid PO
Vibrio vulnificus	Cefotaxime or	2 g q8 h IV
	ceftriaxone	2 g q24 h IV
	plus	
	doxycycline	100 mg bid PO

IV, intravenous; PO, per os.

Korean multicenter study showed similar results, where mixed infection accounted for 19.2% of patients with confirmed pathogens [48]. Therefore, for the initial empirical antibiotics for necrotizing fasciitis, a broad-spectrum antibiotic that targets Gram-positive, Gram-negative, and anaerobic bacteria should be selected.

SSTI guidelines in the US recommend selecting an antibiotic active against MRSA for empirical therapy of necrotizing fasciitis [4]. This is because MRSA is a common cause of necrotizing fasciitis in the US, where a multicenter study reported that MRSA was identified in 35% of monomicrobial infections [53]. A Korean multicenter study among patients hospitalized during 2000–2010 reported that MRSA was isolated in 3.9% (4/103) of patients [47]; the proportion increased to 6.1% (10/165) in a recent multicenter study among patients hospitalized during 2012–2015 [48]. It is still too early to view MRSA as a major cause of necrotizing fasciitis in Korea. However, considering the serious progression and high mortality rate associated with necrotizing fasciitis, using antibiotics active against MRSA as an empirical antibiotic should be considered.

For Gram-negative and anaerobic bacteria, combination therapy with cefepime and metronidazole can be used; piperacillin/tazobactam and carbapenems may be considered as well (Table 3) [4]. For patients with liver cirrhosis or compromised liver function due to alcoholism who have recently eaten seafood or come in contact with seawater, *Vibrio vulnificus* infection must be considered. Therefore, for empirical therapy for necrotizing fasciitis in these patients, combination therapy with third-generation cephalosporins such as cefotaxime or ceftriaxone and doxycycline or tetracycline should be considered [3].

Once the causative organism is identified, the empirical antibiotics administered should be switched to effective antibiotics with a narrow spectrum based on the susceptibility test results (Table 3). Cefazolin or nafcillin are recommended an-

tibiotics for methicillin-susceptible *S. aureus*. If the causative bacterium is identified as group A β-hemolytic streptococci, combination therapy with penicillin and clindamycin is recommended. The reason why combination therapy is recommended is because clindamycin can suppress toxins and is reported to have superior efficacy compared with penicillin [54, 55]. However, because group A β-hemolytic streptococci may develop resistance to clindamycin, it is not recommended to use clindamycin alone [56].

Once necrotizing fasciitis is diagnosed, surgical treatment must be administered as soon as possible. There are several reports indicating that if surgical treatment is not administered early on, the mortality rate of necrotizing fasciitis increases [57-59]. In particular, Wong et al. reported that whether surgical treatment was administered within 24 h was associated with the prognosis [57]. Therefore, if necrotizing fasciitis is clinically suspected, both medical and surgical treatment must be administered simultaneously and organically.

IVIG therapy uses IgG subclass immunoglobulins from healthy adults to neutralize toxic factors or toxins, inhibit superantigen-elicited T-cell activation, and facilitate opsonization of bacteria [60]. Some observational studies on streptococcal toxic shock syndrome have reported that IVIG administration reduces the mortality rate [61, 62]. However, in a blinded controlled study, the group that received IVIG tended to show a lower mortality rate, but the difference was not statistically significant [63]. Although additional studies are needed on the efficacy of IVIG, but it can be considered as an adjuvant therapy for patients who are critically ill owing to necrotizing fasciitis.

5. Pyomyositis

KQ 11. How is pyomyositis diagnosed?

Recommendations	Recommendation level	Evidence level
11-1. Pus and blood culture tests are should be performed to identify the causative bacteria.	Strong	Moderate
11-2. MRI is recommended as the radiological examination; CT may be useful as well.	Strong	Moderate

Pyomyositis is an acute infection that infiltrates the muscles, which often leads to muscle abscess. It often occurs in hematogenic form and it can also occur from the spread of nearby infection, such as pyogenic arthritis and osteomyelitis. When possible, identification of the causative bacteria of pyomyositis is needed for selecting the appropriate antibiotic, determining the prognosis, and switching to an effective oral antibiotics. Blood culture testing is useful, with a positive rate of 5–30%; abscess or tissue culture testing is also recommended [4]. A recent multicenter study in Korea reported that the causative bacteria were identified in 70.7% of cases, with 39.2% (55/140) identified from culture specimens obtained during surgery and 24.4% (34/140) from blood culture tests [64].

Among radiological examinations, MRI is the most effective for pyomyositis. In T2-weighted images, high signal intensity appears throughout the muscle, and strong high signal intensity appears inside the abscess [65]. MRI has the advantages of being able to identify intramuscular abscess and confirm the presence of purulent arthritis or osteomyelitis. With CT, the flat surface of the muscles is lost, fluid retention inside the muscle is observed, and contrast enhancement in the surrounding area is seen [66]. CT can be performed more easily than MRI, but CT has lower sensitivity than MRI and provides less anatomical information.

KQ 12. What is the appropriate treatment for pyomyositis?

Recommendations	Recommendation level	Evidence level
12-1. Antibiotics with active against Gram-positive and negative bacteria should be used as the empirical antibiotic.	Strong	Low
12-2. Once the causative bacterium is identified, antibiotics administered should be switched to an effective antibiotics with a narrow spectrum based on the susceptibility test results.	Strong	Low
12-3. Use of an antibiotics against MRSA infection may be considered in cases of previous MRSA infection or colonization and if primary treatment has failed.	Weak	Very low
12-4. Purulent material should be drained or removed early on.	Strong	Low
12-5. If there is no response to the treatment, radiological examination (MRI and/or CT) can be performed to evaluate whether the purulent material has been properly drained or removed.	Strong	Low

S. aureus is a well-known cause of pyomyositis [67]. In a recent multicenter study in Korea, *S. aureus* was the most common causative bacteria, accounting for approximately 50% of all bacteria identified. However, Gram-negative bacteria also accounted for approximately 30% of the causative bacteria identified [64]. Therefore, a broad-spectrum antibiotics active against Gram-positive bacteria (such as *S. aureus*) and Gram-negative bacteria should be selected as the empirical antibiotic for pyomyositis (Table 4).

In the US, MRSA is a major cause of pyomyositis; therefore, the use of an antibiotic active against MRSA is recommended as the empirical antibiotics [4, 68]. However, a recent multicenter study in Korea found that MRSA was the causative bacteria in only 2.9% (4/140) of all patients [64]. Therefore, use of empirical antibiotics against MRSA should be considered in limited cases of pyomyositis with a history of previous MRSA infection or colonization and failed primary treatment.

Once the causative bacteria is identified, the antibiotic administered should be switched to an effective antibiotic with a narrow spectrum based on the susceptibility test results (Table 4). The use of cefazolin or nafcillin is recommended for *S. aureus* that shows susceptibility to methicillin. Combination therapy with penicillin and clindamycin is recommended for *S. pyogenes* infection [34].

If purulent material is identified in pyomyositis, early drainage or surgical removal is recommended [4]. If there is no response to the treatment despite the use of an appropriate antibiotics, CT or MRI should be performed to determine whether the purulent material is still present [4].

KQ 13. What is the appropriate treatment for clostridial myonecrosis?

Recommendations	Recommendation level	Evidence level
13-1. Surgical debridement of involved tissue should be performed early on and continued visual evaluation and removal of the infected area must be performed.	Strong	Moderate
13-2. Combination therapy with penicillin and clindamycin is recommended as the definitive antibiotic therapy.	Strong	Low

Clostridial myonecrosis, also referred to as gas gangrene, is a very rapidly progressing muscle infection. It is caused by *Clostridium* species and *C. perfringens* is the most common causative bacterium. It can occur from contamination of the wound area after a trauma. In immunosuppressed patients, it can also occur as a complication of bacteremia, without any trauma. In trauma-related cases, progression of myonecrosis begins 2–3 days after the trauma. Clostridial myonecrosis has similar clinical features as necrotizing fasciitis and symptoms include severe pain and altered consciousness, as well as hypotension, shock, and organ failure that can even lead to death. Findings from physical examination also show tense edema, fetor, and palpable crepitus, similar to necrotizing fasciitis.

Clostridial myonecrosis is a fulminant infection that requires intensive care and immediate and extensive surgical removal of the infected area [4, 69, 70]. The initial treatment

Table 4. Antibiotic therapy for pyomyositis

Disease classification	Antibiotic	Adult dose
Empirical therapy	Ampicillin/sulbactam or	3 g q6 h IV
	cefepime or	2 g q8 h IV
	piperacillin/tazobactam or	3.375–4.5 g q6–8 h IV
	ertapenem	1 g q24 h IV
Streptococcus	Penicillin	2–4 million units q4–6 h IV
	plus	
	clindamycin	600–900 mg q8 h IV
Methicillin-susceptible *Staphylococcus aureus*	Nafcillin or	1–2 g q4 h IV
	cefazolin	1–2 g q8 h IV
Methicillin-resistance *Staphylococcus aureus*	Vancomycin or	15 mg/kg q12 h IV
	teicoplanin or	6–12 mg/kg q24 h IV
	linezolid	600 mg q12 h IV

IV, intravenous; PO, per os.

should be administration of broad-spectrum antibiotics, just as with necrotizing fasciitis. For confirmed cases of clostridial myonecrosis, combination therapy with penicillin 2-4 million units q4-6 h IV and clindamycin 600–900 mg q8 h IV is recommended. The reason why combination therapy is recommended is because animal studies have reported that combination therapy with clindamycin plus penicillin is most effective [71] and that *C. perfringens* may be resistant to clindamycin [72].

6. Animal or human bite

KQ 14. Is preemptive antibiotic therapy needed for prevention of infection from an animal or human bite?

Recommendations	Recommendation level	Evidence level
14-1. Preemptive antibiotic therapy is not recommended for mild bite wounds with low risk of infection.	Strong	Moderate
14-2. Preemptive antibiotic therapy for 3–5 days is recommended in immunosuppressed patients and those with asplenism, severe liver disease, edema at the site of the bite, moderate to severe damage (especially to the hands or face), and damage extending to the periosteum or joint capsule.	Strong	Low

Most bite wounds occur as a result of being bitten by a mammal, such as a human, dog, or cat [73, 74]. In patients who visit a hospital early after being bitten by an animal or human (within 8 h), wound infection may not yet have occurred; however, in 85% of cases, potential pathogens may be found in the bite wound. However, it is difficult to accurately predict whether a wound will progress to an infection. The infection rate of bite wounds may vary depending on the causative animal, severity of the bite wound, and the location of the wound. There is a low risk of infection associated with a bite from an animal other than a human and a bite wound that does not involve the hands, with an infection rate below 2%. By contrast, a deep human bite to the hand may develop into an infection in over 50% of cases [1]. Generally, the risk of infection is high in cases that involve a deep puncture, crush injury, devitalized tissue, and heavy contamination [74]. A human bite typically has a higher risk of infection than that from a dog or a cat [74]. A hand bite has a high risk of infection and complications can increase the risk of long-term functional impairment. A hand bite wound should be examined carefully as the deep tissue may be inoculated with a large number of bacteria that can cause tissue destruction and damage. Moreover, deep hand infection may progress along the fascia and tendon sheath. Therefore, the fact that a hand wound has a high risk of infection should be kept in mind even if the wound does not appear to be severe [1].

Whether preemptive antibiotics should be used for bite injuries is debatable, but they should be considered based on the location of the wound, causative animal, severity of the wound, and immune status of the patient. Regarding mammal bites, a Cochrane review has reported that use of prophylactic antibiotics was associated with a statistically significant reduction of infection rate only after human bites and hand injuries [74]; however, the number of patients included in that study was small (range, 12-190). A significant difference was found only in one study among 48 patients with a human bite on the hand [75]. In a randomized study of 127 cases of low-risk human bite wounds, excluding hand bite, prophylactic antibiotics administration showed no benefit [73]. A meta-analysis of 8 randomized studies on dog bites showed that the cumulative infection rate after a dog bite was 16% and preemptive antibiotic therapy lowered the infection rate of only high-risk wounds [76]. In patients with an animal bite that occurred at least 9 h earlier, administration of amoxicillin/clavulanate reduced the infection rate.

In summary, preemptive antibiotic therapy seems to provide marginal benefit for wounds with a low risk of infection that are reported with 12–24 h after injury (those that are not associated with puncture wounds, those in patients who are not immunosuppressed or not taking immunosuppressants, and wounds not involving the face, hand, or foot) [77-80]. In general, preemptive antibiotic therapy is advocated for 3–5 days for uninfected animal bites in moderate-to-severe injuries, especially those to the hand or face, deep injuries penetrating bone structures, in the presence of edema, and in immunocompromised hosts.

KQ 15. What is the appropriate antibiotic therapy for infection from an animal or human bite?

Recommendations	Recommendation level	Evidence level
15-1. Antibiotics active against both aerobic and anaerobic bacteria, such as amoxicillin/clavulanate, should be used.	Strong	Moderate

15-2. First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin should not be used alone.	Weak	Very low
15-3. As IV antibiotics, β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, piperacillin/tazobactam), second-generation cephalosporins such as cefoxitin, or carbapenem such as ertapenem can be used.	Weak	Moderate

A bite wound infection may involve bacteria rarely found in other infections and tends to be a polymicrobial infection in most cases [1]. Most bite wound infections involve an average of five types of bacteria, with a mixture of both aerobic and anaerobic bacteria. Staphylococci and streptococci are common aerobic bacteria whereas *Bacteroides* spp., peptostreptococci, *Fusobacterium* spp., and *Prevotella heparinolytica* are common anaerobic bacteria in bite wounds. *Pasteurella* spp. and *Capnocytophaga canimorsus* are considered bite-specific causative bacteria, which can cause rapidly progressing sepsis that can be fatal. *Pasteurella* spp. is especially common in dog (50%) and cat (75%) bite wounds. These bacteria are Gram-negative coccobacilli, oral resident bacteria found in

Table 5. Pathogens most commonly associated with animal and human bites, in decreasing order of frequency [73]

Rank	Causative bacteria	Causative animal
1	*Pasteurella multocida*	Dog, cat
2	*Capnocytophaga canimorsus*	Dog
3	*Eikenella corrodens*	Human
4	*Streptococcus*	All species
5	*Staphylococcus aureus*	All species
6	*Staphylococcus intermedius*	Dog
7	Anaerobes	Most species

Table 6. Empirical antibiotic therapy for bite wound infection

Classification	Antibiotic	Adult dose (normal kidney function)
Drug of choice	Amoxicillin/clavulanate	875/125 mg bid PO
	Ampicillin/sulbactam	1.5–3.0 g q6–8 h IV
	Piperacillin/tazobactam	3.375–4.5 g q6-8 h IV
	Ceftriaxone or	2 g q24 h IV
	Cefotaxime	1–2 g q6–8 h IV
	plus	
	Metronidazole or	500 mg q8 h IV or 250–500 mg tid PO
	Clindamycin	600 mg q6–8 h IV or 300 mg tid PO
Alternatives	Cefoxitin	1 g q6–8 h IV
	Ertapenem	1 g q24 h IV
	Moxifloxacin	400 mg q24 h IV or PO
	Doxycycline	100 mg bid PO
	Ciprofloxacin or	400 mg q12 h IV or 500–750 mg bid PO
	Levofloxacin or	750 mg q24 h IV or PO
	Trimethoprim-sulfamethoxazole or	TMP 5–10 mg/kg/day IV or 160–800 mg bid
	Cefuroxime	1 g q12 h IV or 500 mg bid PO
	plus	
	Metronidazole or	500 mg q8 h IV or 250–500 mg tid PO
	Clindamycin	600 mg q6–8 h IV or 300 mg tid PO

PO, per os; IV, intravenous.

Table 7. Preventative measures for tetanus based on tetanus vaccination history and wound condition

Vaccination history	Clean and small wound		Other wounds	
	Td	TIG	Td	TIG
Unknown or <3 times	Yes	No	Yes	Yes
≥3 times				
≥10 years since last vaccination	Yes	No	Yes	No
5–9 years since last vaccination	No	No	Yes	No
<5 years since last vaccination	No	No	No	No

Td, tetanus-diphtheria toxoid; TIG, tetanus immunoglobulin.

many animals. *Haemophilus* spp. and *Eikenella corrodens* are common aerobic bacteria in human bite cases (Table 5).

Purulent wounds from an animal bite usually involve a polymicrobial infection with both aerobic and anaerobic bacteria whereas in non-purulent wounds, staphylococci and streptococci are commonly isolated [81, 82]. While *Pasteurella* spp. is commonly isolated in non-purulent wounds and abscesses, non-purulent wound infection may also be a polymicrobial infection [82]. Based on such information, amoxicillin/clavulanate is the appropriate oral antibiotic against aerobic and anaerobic bacteria in bite wounds (Table 6). Alternatively, second- or third-generation cephalosporins plus antianaerobic agents (metronidazole or clindamycin) may be administered. Moxifloxacin, doxycycline, or a carbapenem such as ertapenem may be used as well. When administering trimethoprim/sulfamethoxazole or levofloxacin, anaerobic coverage with metronidazole or clindamycin should be added. Unless there is no other possible substitute, macrolides should be avoided since they have unreliable antimicrobial activity against *Pasteurella multocida* and *Fusobacterium*. For pregnant women, tetracycline and fluoroquinolones administration is prohibited, but trimethoprim/sulfamethoxazole can be prescribed safely, except during the third trimester [81-86].

The causative bacteria involved in human bites are complex but include various anaerobic bacteria such as *Fusobacterium*, *Peptostreptococcus, Prevotella,* and *Porphyromonas* spp., as well as aerobic bacteria such as streptococci, *S. aureus*, and *Eikenella corrodens*. *E. corrodens* is resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides. Therefore, treatment with amoxicillin/clavulanate, ampicillin/sulbactam, or ertapenem is recommended. For patients with hypersensitivity to β-lactam, administration of ciprofloxacin or levofloxacin plus metronidazole, or moxifloxacin alone is recommended. A human bite may transmit various viruses including herpes virus, hepatitis B and C viruses, and human immunodeficiency virus (HIV) [3].

KQ 16. Is post-exposure prophylaxis for tetanus needed after an animal or human bite?

Recommendations	Recommendation level	Evidence level
16-1. Depending on the wound condition, tetanus toxoid vaccine should be administered to anyone who has not been vaccinated for tetanus in the past 5 or 10 years. For patients who have not received tetanus-reduced diphtheria toxoid-acellular pertussis (Tdap) vaccine previously, Tdap is preferred over Td vaccination.	Strong	Low

Tetanus is a severe disease that can be fatal at times and can be prevented by vaccination (3 vaccinations during childhood and additional vaccination every 10 years). Although there are no recent reports of tetanus from a bite, a wound from animal or human bite may cause the disease [87, 88] Vaccination for tetanus to prevent infection from the wound is determined by how clean the wound is and history of previous diphtheria-tetanus-acellular pertussis (DTaP) or tetanus-diphtheria toxoid (Td) vaccination (Table 7). Tetanus vaccine should be administered if 5 years have passed since the last tetanus vaccination for a dirty wound and 10 years for a clean wound. When vaccinating to prevent tetanus, Tdap is recommended over Td vaccination if the patient does not have a history of Tdap vaccination [89].

KQ 17. When is post-exposure prophylaxis for rabies needed after an animal bite?

Recommendations	Recommendation level	Evidence level
17-1. Post-exposure prophylaxis for rabies may be needed when bitten by a wild animal or in an area where rabies is prevalent. Consultation with an infectious diseases specialist is recommended for deciding whether to begin vaccination.	Strong	Low

Measures for preventing rabies should be considered if bitten by a wild animal or in an area where rabies is prevalent. Prevention of rabies should involve timely administration of rabies immunoglobulin and vaccine (0, 3, 7, 14, and ± 28 days) [90, 91]. In cases where a patient with no previous history of rabies vaccination is bitten by a wild animal or an animal that cannot be observed, post-exposure prophylaxis for rabies should be administered [90]. When it is difficult to assess the condition of the animal, post-exposure treatment must be determined based on epidemiological and clinical requirements. Consultation with an infectious diseases specialist is recommended [4].

KQ 18. How is a bite wound treated?

Recommendations	Recommendation level	Evidence level
18-1. Delayed primary or secondary closure after thorough irrigation of the wound area and debridement is recommended.	Weak	Low
18-2. Primary wound closure is not recommended for wounds, with the exception of those to the face, which should be managed with copious irrigation, cautious debridement, and preemptive antibiotics.	Strong	Low
18-3. For a clenched-fist injury, a hand specialist should be consulted for examination of damage to the tendons, synovial membrane, joint capsule, and bones.	Weak	Low

Initial wound care is important for treating a bite wound. For a bite wound, the wound should be washed thoroughly using a 19-gauge needle with at least 150 mL of sterile saline or Ringer's solution [3]. Debris on the epidermis must be removed, but it is not necessary to use solution containing iodine or antibiotics. Devitalized or contaminated tissues should be removed according to the rules for debridement.

Randomized controlled studies on wound closure after a bite are limited. When primary closure is performed for laceration or perforation from a dog bite, the reported infection rate is below 1% [92]. However, closure of a hand wound has a higher infection rate than wounds of other locations [93]. In a study on 345 cases of bite wounds, the infection rate was higher for puncture wounds and sutured wounds [94, 95]. Therefore, when possible, primary closure is not recommended initially for bite wounds. Delayed primary or secondary closure after washing the wound, performing debridement when necessary, and approximating the margins of the wound are recommended for bite wounds [3]. Wound closure of large and extensive facial wounds should not be delayed for cosmetic and functional reasons; therefore, primary closure may be used after copious irrigation and preemptive antimicrobial therapy. Keeping the wound area elevated for several days after the injury can help the healing process; elevation is even more necessary when edema is present.

In cases of clenched-fist injury, careful examination is necessary as even a small wound may spread deep into the hand tissue [3]. After a hand puncture injury, residual joint stiffness may occur, which may cause long-term functional impairment of the hand.

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Conflicts of Interest

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Supplementary material

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