Chapter 2-5-3a. Anaerobic infections (individual fields):
skin and soft tissue infections

Introduction

The skin and underlying soft tissues are comprised of the epidermis (in external contact), dermis, subcutaneous fat (adipose) tissue, fascia and muscles. Since anaerobes are bacteria that grow in oxygen-free (anaerobic) environments, as to skin and soft tissue infections, these bacteria are involved in infections of fascia and muscle at deep sites of the skin, where oxygen concentrations are lower than in superficial sites.

Pathogenesis

No definite systematic classification of skin and soft tissue infections with anaerobic bacteria has yet been established. In a narrow sense, however, these infections are classified into two types according to the presence/absence of aeroisis, i.e., gas gangrene and necrotizing fasciitis. The former condition is classified into infection with Clostridium (clostridial type) versus bacteria other than Clostridium (non-clostridial type) [1]. Necrotizing fasciitis is classified into type I (polymicrobial necrotizing fasciitis), i.e., mixed infections with anaerobic bacteria, and type II due to group A β-hemolytic Streptococcus (Table 1). In actuality, there are some cases with both gas gangrene and necrotizing fasciitis (double cases). The main causative bacteria are C. perfringens, Peptostreptococcus anaerobius and Bacteroides fragilis. Cultures yielding a single type of anaerobic bacteria are rare. Genus Staphylococcus and genus Streptococcus show symbiosis with anaerobic bacteria, and mixed infection of either genus Staphylococcus or genus Streptococcus with anaerobes occurs in most cases.

Necrotizing fasciitis is described in detail in other sections.

Classification

Infection with gas-generating anaerobes (gas gangrene)

Gas gangrene is classified into infections with Clostridium (clostridial type) and those with bacteria other than Clostridium (non-clostridial type) [2]. The frequency of clostridial gas gangrene was previously high, but in recent years that of non-clostridial gas gangrene has tended to increase [3].

Clostridial gas gangrene This disease is a clostridial infection with gas-generating clostridia, and is also called “clostridial myonecrosis” [4]. There are 6 species of causative bacteria: C. perfringens (Welch bacillus), C. novyi, C. histolyticum, C. sporogenes, C. septicum and C. fallax. The incidence of infection with C. perfringens is the highest (80–95%) [2].

With regard to predisposing factors, the majority of these diseases are due to trauma; the disease manifests secondary to an operative, dermal sutures removal or contaminated wound, and also after tonsillectomy or abortion [3]. The latent period is 6 h to 2 days. The common sites of occurrence are the lower extremities. These infections can also develop in the upper extremities, gluteal region, external pudendal region and the neck.

Clinical symptoms include severe pain at the affected site as a local finding, redness, swelling, dark purple discoloration, necrosis, fluctuation and blistering. Subcutaneous crepitation is palpable. When gas is present at a shallow skin site, rattles and fine crackles are recognizable.
When the wound is incised, serous and/or bouillon-like pus is recognized. It has a specific strong putrid flesh smell. Remarkable generalized symptoms, as follows, are associated with this disease: hyperthermia, arthralgia, muscle pain, nausea/vomiting, general malaise, delirium and shock. The clostridial type produces exotoxins leading to thrombus formation, and can cause disseminated intravascular coagulation (DIC) and shock.

On examination, gas bubbles in tissue are demonstrated by X-ray or computed tomography (CT). Gas bubbles in the deep muscle layer produce a feather-like invasion pattern on X-ray images [2]. Clinical laboratory data show leukocytosis with a nuclear shift to the left, extremely increased C-reactive protein (CRP), increased blood sedimentation, and liver dysfunction. The spread of inflammation from fascia to muscles lead to increasing CPK or aldorase value, and sepsis, DIC and shock may develop from renal failure due to rhabdomyolysis [5].

To investigate causative bacteria, Gram staining and microscopy of smear preparations from pus and necrotic tissue must be conducted immediately as bacteriological tests. The presence of spores with Gram-positive bacilli strongly suggests the clostridial type. Since anaerobic culture takes several days, treatment should be started early without waiting for culture results.

Some reports have shown the mortality rate to be 7–25% [2, 4].

Non-clostridial gas gangrene This is gas gangrene due to non-clostridial infections with anaerobes. The causative bacteria are obligate anaerobes including B. fragilis, Porphyromonas asaccharolytica, Peptostreptococcus aerobius and Eggerthella lenta. In mixed infections with facultative anaerobes, Streptococcus pyogenes, Escherichia coli, Klebsiella species, Proteus species and Staphylococcus aureus are included.
Diabetes mellitus is associated with diseases due to these pathogens in many cases, with a frequency of 60% among all cases. Other conditions associated with these pathogens include decubitus ulcers, carcinomas, pilonidal sinus and hidradenitis suppurativa [6]. These infectious diseases also develop in many patients with liver cirrhosis.

The local findings and general symptoms are generally similar to those of clostridial gas gangrene; the disease spreads rapidly to reach the deep fascia. Superficial swelling, fine crackles and crepitation manifest. When the wound is incised, gas bubbles are revealed. The discharge obtained by incision and drainage is purulent. In the case of infection with \textit{B. fragilis}, the discharge smells like feces. In the case of infection with \textit{P. anaerobius}, the discharge is a yellowish pus which smells like fetid mud [3].

Examination findings of the disease are also similar to those for clostridial gas gangrene, but gas bubbles rarely spread to muscles in non-clostridial gas gangrene. Mixed infections with \textit{Streptococcus} species may lead to the rapid spread of phlegmon and cause streptococcal gangrene.

In a manner similar to that for clostridial gas gangrene, Gram staining and microscopy of smear preparations from pus and necrotic tissue must be conducted immediately to identify the causative bacteria. When the causative bacteria are members of genus \textit{Bacteroides}, which are small Gram-negative bacilli, being overlooked is likely because they blend into the background [7]. Since culture takes at least 2 days, treatment should be started immediately in suspected cases without waiting for culture results.

The prognosis of this disease is considered to be worse than that of clostridial gas gangrene; the morbidity rate is believed to be 30–40%.

### Anaerobic infections without characteristic gas generation

**Necrotizing fasciitis (for details, refer to other sections)** This is the most serious infection leading to necrosis of the skin and soft tissue with cardiovascular disturbances. It is classified into type I (polymicrobial fasciitis: causative bacteria are obligate and facultative anaerobes) and type II [streptococcal gangrene: severe infection with group A \(\beta\)-hemolytic \textit{Streptococcus} leading to sudden septic shock, DIC, adult respiratory distress syndrome (ARDS), and multiple organ failure] [1, 8].

### Causative bacteria

The main causative bacteria of skin and soft tissue anaerobic infections are listed in Table 2.

\textit{Bacteroides} species includes small anaerobic Gram-negative bacilli. \textit{B. fragilis} is an anaerobe with relatively high aerotolerance, and even when left untreated for 3 days, some cells remain alive [7]. This resistance to oxygen (the aerotolerant state) is considered to be related to the pathogenicity of \textit{Bacteroides} species.

\textit{Clostridium} species includes obligate anaerobic Gram-positive bacilli. They exist in soil and animal feces, and most are non-pathogenic. Most infections with these bacteria develop after injury. The bacteria frequently cause infections from the gastrointestinal tract and skin at the injury site. Infections with these bacteria develop from intramuscular injections, surgical and dermal sutures-out wounds, after abortion, with rectal cancer, and from foreign bodies in the rectum [4]. Six species of clostridia, \textit{C. perfringens} (Welch bacillus), \textit{C. novyi}, \textit{C. histolyticum}, \textit{C. sporogenes}, \textit{C. septicum} and \textit{C. fallax}, are believed to possess pathogenicity. \textit{C. perfringens} is among the resident flora of the lower gastrointestinal tract.

<table>
<thead>
<tr>
<th>Anaerobic bacteria other than \textit{Clostridium} species</th>
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<tbody>
<tr>
<td>\textit{C. perfringens} (Welch bacillus)</td>
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<tr>
<td>\textit{C. novyi}</td>
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<td>\textit{C. histolyticum}</td>
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<td>\textit{C. sporogenes}</td>
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<td>\textit{C. septicum}</td>
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<td>\textit{C. fallax}</td>
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<td>\textit{Bacteroides fragilis}</td>
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<td>\textit{Porphyromonas asaccharolytica}</td>
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<td>\textit{Peptostreptococcus anaerobius}</td>
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<td>\textit{Feingoldia magna}</td>
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<td>\textit{Eggerthella lenta}</td>
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<td>\textit{Prevotella} species</td>
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<td>\textit{Fusobacterium} species</td>
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produces exotoxins, i.e., toxins $\alpha$, $\kappa$, $\mu$ and $\theta$ (phospholipase C, hemolytic action, collagenase, hyaluronidase), and thereby induces hemolysis, hematogenous disorders and tissue damage. The most important exotoxin is toxin $\alpha$ [4].

$P$. anaerobius is a Gram-positive anaerobic coccus.

Other bacteria, which are involved in the pathogenesis of this disease, include Finegoldia (Finegoldia magna), Parvimonas (Parvimonas micra, previously Micromonas), Peptoniphilus (Peptoniphilus asaccharolyticus), Prevotella species and Fusobacterium species.

**Treatment**

The important therapeutic methods for skin and soft tissue infections with anaerobic bacteria are: ① Management of general condition; ② wound opening and removal (debridement) of necrotic tissue; and ③ administration of antimicrobial agents. The antimicrobial agents will be described later.

**Management of general condition**

At the intensive care unit (ICU), etc., where general conditions can be managed, a route is secured for fluid replacement. Vital signs are checked, and respiration, heartbeat and blood pressure are constantly monitored.

**Wound opening and removal (debridement) of necrotic tissue**

When progression is rapid and the patient’s general condition is poor, surgical treatment by debridement is performed under anesthesia in the operating room to rapidly counter this condition. Debridment begins with a longitudinal incision [9]. According to the affected sites and depths of infection, plastic surgery, surgery and orthopedic, as well as dermatology, consultations are required. It is important to remove the environment fostering anaerobic multiplication and to thoroughly remove the necrotic tissue, pus and any foreign bodies in the wound. Administration of antimicrobial agents, regional cleansing with physiological saline solutions including antiseptic solutions, and discharge with a drain inserted are necessary for wound management. When the wound is stable, skin grafting is undertaken at the affected site 1–2 weeks after these procedures.

**Administration of antimicrobial agents**

Details of antimicrobial drug administration will be described later.

Oxygen under high pressure (OHP) therapy

Since anaerobic bacteria are harmed by oxygen, oxygen is very effective for gas gangrene. Oxygen is essential for the treatment of clostridial gas gangrene, while it is less effective for non-clostridial gas gangrene [4]. Transportation of patients with clostridial infections to institutions equipped with OHP should also be considered.

**Antimicrobial therapy**

When causative bacteria are identified by Gram staining and anaerobic culture, the antimicrobial drugs used are re-examined, and changed to other agents to which the isolated bacteria are susceptible. With regard to skin and soft tissue infections with anaerobic bacteria, it is rare for these infections to involve a single type of anaerobe. Most of these infections involve multiple bacteria. It is therefore desirable to administer antimicrobial drugs with broad spectra, covering these bacteria [10]. Skin and soft tissue infections with anaerobic bacteria are serious diseases with a high possibility of taking a fatal course. The drugs are frequently administered by non-approved dosage regimens.

Fundamentally, many anaerobic bacteria isolated from skin and soft tissue infections are sensitive to the penicillins. Therefore, penicillins are effective against these bacteria. High dose administration of PCG is suggested. In actual clinical settings, piperacillin (PIPC) is administered at a dose of 2 g, 4 times, and a tazobactam/piperacillin (TAZ/PIPC) combination, at a dose of 4.5 g, also 4 times.

In the presence of mixed infections, second-generation cephems with broad antibacterial spectra are used additionally.

**Clostridial gas gangrene**

PIPC (2 g $\times$ 4/day) and a TAZ/PIPC combination (4.5 g $\times$ 4/day) are administered intravenously. For $C$. perfringens infections, ampicillin (ABPC) (2 g $\times$ 4/day) or sulbactam/ampicillin (SBT/ABPC) combination (3 g $\times$ 4/day) is administered intravenously.

**Non-clostridial gas gangrene**

For $P$. anaerobicus infections, PIPC (2 g $\times$ 4/day) and a TAZ/PIPC combination (4.5 g $\times$ 4/day) are administered intravenously. $B$. fragilis shows natural resistance to aminoglycosides and cotrimoxazoles, and the efficacy of fluoroquinolones is also low when these bacteria are the causative microorganisms. Therefore, SBT/ABPC (3 g $\times$ 4/day), as well as cefmetazole (CMZ), flomoxef
(FMOX) and ceftazidime (CAZ), administered at a dose of 2 g, 3–4 times a day, are effective.

As combined therapy, clindamycin (CLDM) (600 mg × 4/day) or minocycline (MINO) (200 mg × 2/day) is also administered intravenously.

Regardless of the types of causative bacteria, carbapenem, i.e., a combination of imipenem/cilastain (IPM/CS) (0.5 g × 2–3/day or 1 g × 3/day), is administered intravenously for severe cases. Meropenem (MEPM) is administered intravenously (0.5 g or 1 g × 3/day).

When infection with methicillin-resistant Staphylococcus aureus (MRSA) is suspected, vancomycin (VCM) is administered (1 g × 2/day) [11].

References