Donnish Journal of Medicine and Medical Sciences. Vol 1(1) pp. 001-011 September, 2014.
http://www.donnishjournals.org/djmms

Review Paper

Microbiology Of Musculoskeletal Infections

Nidham M. Jamalludeen. M.Sc. PhD

Department of Microbiology, College of Medicine, University of Basrah, Basrah, Iraq.

Accepted 24th September, 2014.

There are several studies in the evaluation and description of musculoskeletal infections. However, the microbiology of these infections is very important in the isolation and identification of their aetiological agents. From literature surveys, we can identify microorganisms responsible for Osteomyelitis, Septic arthritis, Pyomyositis, and necrotizing fasciitis infections.

Keywords: Musculoskeletal, Osteomyelitis, Septic arthritis, Pyomyositis, Necrotizing fasciitis.

INTRODUCTION

Musculoskeletal infections may be considered as orphan conditions or diseases under any of the following medical disciplines; infectious diseases, orthopedic surgery and rheumatology. However, these infections are likely to grow in importance and prevalence in the Middle East and North America as the population within these regions ages and the risk factors such as underlying arthritis, diabetes mellitus, osteomyelitis and immunosuppression increase in prevalence.

As well, drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and /or emerging microorganisms are playing a greater role as pathogens in musculoskeletal infections which can enhance and complicate matters. For example, osteomyelitis, especially in diabetic patients, can literally threaten life and the limbs. Septic arthritis of both prosthetic and native joints can permanently hamper mobility and locomotion. The limited ability of musculoskeletal tissue to regenerate may make these infections permanently disabling. This review was aimed to highlight microbiological aspects of some musculoskeletal infections, including the important bacteriological agents associated with such infections.

MICROBIOLOGY OF OSTEOMYELITIS

Osteomyelitis is an infection of the bone and bone marrow generally through exposure of these tissues to pathogenic organisms during the course of bacteremia. Children younger than 5 years are highly susceptible, followed by adults. The most common form is acute hematogenous osteomyelitis (AHO) in the highly vascular bones [LaMont et al., 1987; Vaughan et al., 1987; Nelson, 1990]. Infection of the bone may occur in several ways, including hematogenous spread, direct inoculation, and contiguous spread from a local infection [Lew and Waldvogel, 1997; Lazzarini et al., 2004].

The vertebrae are the most common site of hematogenous infections in adults, but the long bones, pelvis, and clavicle may also be affected. Contiguous osteomyelitis may occur after a traumatic bone injury or as a result of the spread of infection from a nearby source such as soft tissue infection. Direct inoculation of bacteria into bone may occur during surgery or as a result of penetrating trauma, puncture wounds, or complex fractures [Frank et al., 2005]. *Staphylococcus aureus* is the most common pathogen that causes

Corresponding author: njovc@yahoo.com

pyogenic infections resulting in vertebral osteomyelitis in adults and the rate of this infection is between 40-45% of all cases. *Mycobacterium tuberculosis* on the other hand causes nonpyogenic (granulomatous) infection. In children, *S. aureus* is the most commonly identified organism causing osteomyelitis and accounts for 61% to 89% of all cases of AHO [Dich et al., 1975; Unkila-Kallio et al., 1994].

It has been reported [Ibia et al., 2003] that Group A β-hemolytic streptococci are the next most frequent pathogenic organism causing infection, and account for up to 10% of cases. Previously, *Haemophilus influenzae* had been reported as a causative pathogen accounting for 3% to 7% of cases [Dich et al., 1975;LaMont et al., 1987; Unkila-Kallio et al., 1994], but this organism was almost eliminated due to the effect of immunization [Bowerman et al., 1997; Ibia et al., 2003].

Patients with hematogenous osteomyelitis may also be infected with *Streptococcus pneumoniae*. It has been noted that *Kingella kingae* is a common cause of osteomyelitis in the Middle East, France and Israel and is being recognized increasingly in the United States [Yagupsky et al., 1993; Dartnell et al., 2012; Yagupsky, 2013; Yagupsky, 2014]. Infection with this organism occurs in young children after upper respiratory tract infections and stomatitis in the late summer through early winter [Yagupsky et al., 1993]. On the other hand, Gram-negative bacteria such as *Salmonella* spp. are also involved in causing acute hematogenous osteomyelitis (AHO), commonly in patients suffering from sickle cell disease. *Pseudomonas aeruginosa* is often identified in cases of osteochondritis after puncture wounds of the feet [Fitzgerald and Cowan, 1975; Raz and Miron, 1995]. *Escherichia coli*, another Gram-negative organism, is also reported as a causative agent of neonate osteomyelitis, and Group B *Streptococcus*, a Gram-positive micro-organism, is also incriminated [Edwards et al., 1978].

Mycobacterium and fungi are rare causes of osteomyelitis [Raz and Miron, 1995]. However, *Bartonella henselae* is an atypical cause of osteomyelitis in patients with cat-scratch disease [Fernandez et al., 2000; Mirakhur et al., 2003]. Multimicrobial infection is not common and is seen mostly in cases of puncture wounds or other trauma [Frank et al., 2005]. Various organisms are responsible for osteomyelitis in different populations. The causative organism is related to the age, clinical history, and immune status of the patient (see Table 1). *S. aureus* is the most common cause in all cases.

PATHOGENESIS OF OSTEOMYELITIS

Acute haematogenous osteomyelitis is often seen in children and it is thought to occur in areas with rich vascular metaphyseal region [Gutierrez, 2005]. Children experience frequent episodes of bacteraemia, often with no apparent symptoms, leading to seeding and development of osteomyelitis [Conrad, 2010]. The total annual incidence rate of osteomyelitis was 13 per 100 000 and the incidence was higher in patients under the age of 3 than in older children. In addition, it was reported that the incidence of non-vertebral osteomyelitis was higher than the incidence of vertebral osteomyelitis (Riise et al., 2008). The pathogenesis of this process has been proposed, based on theoretical perceptions.

Inoculation of the metaphyseal vessels occurs at the transition point from the arteriolar vessels to the venous sinusoids, slowing blood flow and increasing vascular turbulence [Jansson et al., 2009]. These sites of turbulence may be predisposed to bacterial infection by providing an opportunity for local invasion. Untreated haematogenous osteomyelitis may cause chronic infection that may lead to devastating conditions including chronic sinuses with exposed bone, loss of structural integrity and growth disturbance [Beckles et al., 2010]. Trauma or direct injury to bone with bacteremia may significantly increase the rate of haematogenous osteomyelitis [Morrissy and Haynes, 1989; Kabak et al., 1999].

In vertebral osteomyelitis, infection of the spine is also caused by haematogeneous seeding of bacteremia into the vertebrae [Tay et al., 2002]. The venous anatomy and the unique vascular structures of the spine, allow retrograde flow from the pelvic venous plexus due to a lack of valvular structures, providing an opportunity for haematogenous deposition of bacteria [Batson, 1967]. Fine arteriolar structures surrounding the vertebral end plate may also represent a location at which bacteria can become trapped [Wiley and Trueta, 1959].

A different process of infection will occur in children depending on the anatomical development of the paediatric spine in which the blood vessels pass through the physeal cartilage and terminate within the intervertebral disc [Tay et al., 2002]. This orientation allows for seeding of infection from the osseous vasculature and results in a direct extension of infection into the disc, which is not seen in adult patients [Tay et al., 2002]. Osteomyelitis in adult patients often occurs due to inoculation from contiguous infection, and that can happen due to direct contamination at a site of injury, iatrogenic contamination at the time of an invasive procedure, or invasive infection from surrounding soft tissue [Mader et al., 1999]. The host inflammatory response provides a fertile environment for further bacterial invasion and progression as a result of small vessel obstruction due to coagulopathy and oedema in the tissues [Mader et al., 1999]. In diabetic foot patients, osteomyelitis represents the localized infection which includes peripheral neuropathy associated with superficial ulceration and peripheral vascular disease.

However, Lavery et al. [2009] in a large recent study reported no association of osteomyelitis with either peripheral neuropathy or vascular disease, but the history and physical examination findings support prior literatures, suggesting the clinical ability to infect bone directly in a diabetic ulcer diagnosed with underlying osteomyelitis [Grayson et al., 1995]. For further reading on pathophysiology and pathogenesis of osteomyelitis please read the review by Roy et al. [2012].

Table 1. A Summary Of The Common Organisms Implicated In Osteomyelitis In Different Patient Populations.

CATEGORY OF OSTEOMYELITIS	POPULATION	CAUSATIVE ORGANISM
Hematogenous osteomyelitis	Patients of all ages	*S. aureus*
	Neonates	*Enterobacteriaceae*, group B streptococci
	Intravenous drug users	*S. aureus*, *Pseudomonas aeruginosa*, *Candida* species
	Patients with sickle cell disease	*Streptococcus pneumoniae*, *Salmonella* species
	HIV-infected patients	*Bartonella henselae*
	Patients with nosocomial infections	*S. aureus*, *Enterobacteriaceae*, *Candida* species, *Aspergillus* (in immunocompromised patients)
Vertebral osteomyelitis (hematogenous and contiguous focus)	Adults (most commonly)	*S. aureus*
	Patients with urinary tract infections	Aerobic gram-negative bacilli, *Enterococcus* species
	Intravenous drug users	*S. aureus*, *P. Aeruginosa*
	Patients undergoing spinal surgery	Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli
	Patients with infections of intravascular devices	*Candida* species, staphylococci
	Patients living in endemic regions	*M. tuberculosis*, *Brucella* species, regional fungi (*Coccidioides, Blastomyces, Histoplasmas*), *Coxiella burnetii* (Q fever)
Contiguous-focus osteomyelitis	Patients exposed to contaminated soil	*Clostridium* species, *Bacillus* species, *Stenotrophomonas maltophilia*, *Nocardia* species, atypical mycobacteria, *Aspergillus* species, *Rhizopus* species, *Mucor* species
	Patients with orthopedic devices	*S. aureus*, coagulase-negative staphylococci, *Propionibacterium* species
	Patients with decubitus ulcers	*Enterobacteriaceae*, *P. aeruginosa*, enterococci, anaerobes, *Candida* species
	Patients with a history of cat bites	*Pasteurella multocida*
	Patients with a history of human bites (including clenched-fist injury)	*Eikenella corrodens*, *Moraxella* species
	Patients with puncture injuries on the foot	*P. aeruginosa*
	Patients with periodontal infection	*Actinomyces* species
Osteomyelitis associated with vascular insufficiency	Patients with diabetes	Polymicrobial: *S. aureus*, β-hemolytic streptococci, *Enterococcus faecalis*, aerobic gram-negative bacilli

MICROBIOLOGY OF SEPTIC ARTHRITIS

The term septic arthritis refers to bacterial invasion of the joint space and subsequent inflammatory response, but also includes fungal infections. Septic arthritis due to bacterial pathogens is often a dangerous and destructive form of acute arthritis [Mathews and Coakley, 2008]. Most commonly, septic arthritis affects a single joint, but occasionally several joints are involved. The joints affected vary depending on the microbe causing the infection and the predisposing risk factors of the person affected. Septic arthritis is also called infectious arthritis [Margaretten et al., 2007].

Several predisposing factors have been reported to increase the onset of septic arthritis, such as age greater than 80 years, diabetes mellitus, rheumatoid arthritis, prosthetic joint, recent joint surgery, skin infection, cutaneous ulcers, IV drug abuse, alcoholism, and previous intra-articular corticosteroid injection. Each of these individual factors appears to have a modest impact on the risk of septic arthritis, however, combinations of independent risk factors substantially increase the risk [Margaretten et al., 2007; Mathews and Coakley, 2008]. Most septic joints develop as a result of hematogenous seeding of the vascular synovial membrane due to a bacteremic episode [Klein, 1988; Morgan et al., 1996].

Acute septic arthritis may also occur as a result of joint aspiration or local corticosteroid joint injection which happens to be a rare cause [Klein, 1988; Hunter and Blyth, 1999]. In addition, bacterial arthritis may arise secondary to penetrating trauma (such as human or animal bite or nail puncture) or after trauma to a joint without an obvious break in the skin. The direct

introduction of bacteria during joint surgery has increasingly been a source of bacterial arthritis, particularly in association with knee and hip arthroplasties.

MICROBES CAUSING SEPTIC ARTHRITIS

Septic arthritis can be caused by bacteria, viruses, and fungi. The most common causes of septic arthritis are bacteria, including Staphylococcus aureus and Haemophilus influenzae [Barton et al., 1987; LeDantec et al., 1996]. It has been reported historically that children younger than 2 years are mostly infected with Haemophilus influenzae, S. aureus, and group A Streptococci. A notable case of Haemophilus influenzae serotype a (Hia) septic arthritis in an immunized central Australian indigenous child has been recently increased and this serotype is taking over niche of Hib serotype [Fischer, 2014]. However, infection with Haemophilus influenzae as a causative agent of septic arthritis is decreasing as a result of using H. Influenzae type b (Hib) vaccine for children [DeJonghe and Glaesener, 1995].

A study of 165 cases of acute hematogenous osteomyelitis or septic arthritis treated in the years before and after the advent of the Hib vaccine demonstrated that musculoskeletal infections due to this bacterial species were reduced to nearly nonexistent levels [Bowerman et al., 1997]. On the other hand, several investigators [Yagupsky et al., 1992; Yagupsky et al., 1995; Lundy and Kehl, 1998; Luhmann and Luhmann, 1999] reported that the normal oropharyngeal resident of young children, Kingella kingae, may have taken the place of H. influenzae, specifically in patients younger than 2 years. Recently, Deng and Farricielli [2014] have reported that Lancefield group G streptococci (GGS) are a relatively less common cause of streptococcal infections, but the incidence of which has been reported to increase in the recent years.

The researchers have investigated a case of sepsis, migrating septic arthritis and diffuse myositis caused by β-haemolytic GGS which is an unusual case of diffuse β-haemolytic GGS myositis involving multiple muscle groups in a patient who demonstrated no skin lesions or sign of streptococcal toxic shock syndrome. Moraxella lacunata has been reported as a first case of causative agent of both endocarditis and bilateral septic arthritis [Nakayama et al., 2013]. The route of entry leading to bacteremia may be the oral cavity and this organism should be considered in bilateral septic arthritis in a patient with underlying heart abnormalities and /or with renal failure [Nakayama et al., 2013].

The representation of S. aureus is more pronounced in patients with either rheumatoid arthritis or diabetes [Ryan et al., 1997]. In certain "high-risk" individuals, other bacteria may cause septic arthritis, such as E. coli and Pseudomonas spp. in intravenous drug abusers and the elderly, Neisseria gonorrhoeae in sexually active young adults, and Salmonella spp. in young children or in people with sickle cell disease [Gregg et al., 1981; Fryden et al., 1990]. Other bacteria that can cause septic arthritis include; Mycobacterium tuberculosis and the spirochete bacterium that causes Lyme disease.

Viruses that can cause septic arthritis include hepatitis A, B, and C, parvovirus B19, herpes viruses, HIV (AIDS virus), HTLV-1, adenovirus, coxsackie viruses, mumps, and ebola [Sabella and Goldfarb, 1999; MiesRichie and Francis, 2003]. Fungi that can cause septic arthritis include histoplasma, coccidiomyces, and blastomyces [http://www.medicinenet.com/septic_arthritis/page2.htm.].

PATHOGENESIS OF SEPTIC ARTHRITIS

The incidence of septic arthritis is increased in patients with underlying joint disease, or prosthetic joints to approximately 30-60 per 100, 000 of the population per year [Smith et al., 2006; Favero et al., 2008]. There are two age groups that are particularly susceptible to septic arthritis; young children and the elderly. Others who have been reported as at risk groups include patients with diabetes, immunocompromised, patients who are on hemodialysis and intravenous drug users [Sharp et al., 1979; Gupta et al., 2001; Al-Nammari et al., 2008].

Any joint that carries underlying pathology, such as in rheumatoid arthritis, osteoarthritis or if a joint is prosthetic, has a significantly higher risk of developing intra-articular sepsis [Sharp et al., 1979; Weston et al., 1999; Gupta et al., 2001]. It has been noted that direct inoculation into the joint or hematogenous spread following septicemia or bacteremia is the main possible route by which pathogens can enter the joint. Haematogenous spread is more common, but the direct invasion of pathogens could occur as a result of orthopedic procedures and joint surgery, joint aspiration, intra-articular injection and via intra-articular extension from a nearby contiguous source [Kaandorp et al., 1997]. Kaandorp et al. [1997] also reported that cutaneous lesions are the most common focus of infection that leads to hematogenous spread and secondary joint involvement. Lower respiratory tract and urinary tract infections were the second and the third most common sources leading to secondary bacterial septic arthritis.

Experimental mouse models using staphylococcal and streptococcal infection have provided excellent evidence leading to understanding of the pathogenesis of septic arthritis [Hultgren et al., 1999; Mathews et al., 2010]. In one experiment [Hultgren et al., 1999] a pathogen was injected intravenously and the joints were thereby inoculated via hematogenous spread. As soon as bacteria invade the blood stream, various virulence factors, such as extracellular toxins, enzymes, adhesins, bacterial cell wall proteins, were produced, which initiate the inflammatory process via T-cell, B-cell and macrophage stimulation.

As a consequence, proinflammatory molecules including TNF-α, IL-1β and IL-6, immunomodulatory (IL-4, IL-12) and anti-inflammatory (IL-4 and IL-10) cytokines are produced by monocytes, macrophages and synovial fibroblasts [Hultgren et al., 1999]. The role of Toll-like receptors (TLR), a class of protein within the innate immune system, has been recently studied [Varoga et al., 2009; Papathanasiou et al., 2011] in the context of both Gram-positive and Gram-negative bacterial septic arthritis. The experiments showed that

there were higher levels of TLR-2 as compared with the normal controlled experimental models with a challenged one [Varoga et al., 2009; Papathanasiou et al., 2011].

PYOMYOSITIS

Pyomyositis is a purulent infection of skeletal muscle that arises from hematogenous spread, usually with abscess formation [Stevens et al., 2005]. It is common in tropical regions, but is rarely reported in temperate regions. Therefore, it is known as tropical myositis as most cases have been reported in patients living in tropical areas and, until recently, it was considered unusual in the temperate zone. However, reports from non-tropical areas have increased [Gibson et al., 1984; Andrew and Czyz, 1988; Hall et al., 1990; Patel et al., 1997].

The condition is usually diagnosed late, and for this reason it is followed by increased morbidity and sometimes a significant mortality rate [Hall et al., 1990; Patel et al., 1997; Drosos, 2005]. Tropical pyomyositis primarily occurs in two age groups: children (age 2 to 5 years) and adults (age 20 to 45 years), with the majority of temperate pyomyositis cases occurring in adults. Males appear to be more commonly affected than females [Christin and Sarosi, 1992; Bickels et al., 2002]. Predisposing factors for pyomyositis include immunodeficiency, trauma, injection drug use, concurrent infection, and malnutrition [Schwartzman et al., 1991; Rodgers et al., 1993; Crum, 2004; Small and Ross, 2005].

In United States, most cases are associated with human immunodeficiency virus infection or other immunosuppressive conditions, including diabetes mellitus, cancer, connective-tissue diseases, and cirrhosis [Crum, 2004]. Christin and Sarosi [1992] observed that Staphylococcus aureus was the causative organism in 70 percent of cases, and that 31 percent of the patients had bacteremia [Christin and Sarosi, 1992]. Ansalonl and others [Horn and Master, 1968; Christin and Sarosi, 1992; Ansalonl et al., 1996; Miller et al., 2003] reported that HIV is a particularly important risk factor in pyomyositis and there was an association between this disease and HIV infection.

The mechanism of HIV infection in the predisposition to pyomyositis is unclear; factors may include immune compromise, primary HIV myopathy, antiretroviral therapy, and increased rates of staphylococcal carriage [Horn and Master, 1968; Holbrook et al., 1997; Miller et al., 2003; Crum, 2004]. Although any skeletal muscle can be involved, the disease has a predilection for the large muscle masses of the body [Chiedozi, 1979; Patel et al., 1997].

The most common site of involvement is the quadriceps muscle (65%), followed by the gluteal muscles (35%) [Lundy and Kehl, 1998]. Multiple muscle involvement occurs in 12-60% of patients [Levin, 1971; Chiedozi, 1979; Hall et al., 1990; Bickels et al., 2002].

MICROBES CAUSING PYOMYOSITIS

Staphylococcus aureus is the most common organism, responsible for 90-95% of the cases in tropical areas [Chiedozi, 1979; Christin and Sarosi, 1992]. In non-tropical areas, the frequency of staphylococcal infection is lower, about 60-70%, while other microorganisms are involved in about 40% of the cases [Gomez-Reino et al., 1994]. Other Gram-positive cocci have been reported such as Staphylococcus epidermidis [Yates et al., 1997], Streptococcus pneumoniae [Breton et al., 2001], Streptococcus pyogenes [Lawrentschuk et al., 2003], Streptococcus dysgalactiae [Woo et al., 2003].

Gram-negative bacilli were also reported and these were Proteus mirabilis [Chusid et al., 1998], Klebsiella oxytoca, Klebsiella pneumoniae [Schwab and Panwalker, 1986; Wang et al., 2001], Yersinia enterocolitica [Brennessel et al., 1984], Salmonella species [Lortholary et al., 1995; Collazos et al., 1999], Aeromonas hydrophila [Kratzke and Golenbock, 1987], Escherichia coli [Tumeh et al., 1988], Haemophilus influenzae [Hall et al., 1990], Citrobacter freundii [Fincher et al., 1990], and Stenotrophomonas maltophilia [Tsai et al., 2003]. Nocardia asteroides [Vilaseca Arroyo et al., 2000], a Gram-positive bacillus has also caused pyomyositis and Gram-negative cocci, Neissseria gonorrhoeae [Haugh et al., 1996] were also reported.

Anaerobic bacteria, such as Prevotella melaninogenica, Bacteroides fragilis, Eubacterium lentum [Calvo-Alen et al, 1995; Palomino-Nicas et al., 1996; Odeh et al., 2000] may rarely cause pyomyositis. Several researchers [Bonomo et al., 1995; del Giglio et al., 1997; Kim et al., 1999; Johnson and Herzig, 2000; Soler et al., 2001] have reported pyomyositis infection with Mycobacterium tuberculosis and [Lortholary et al., 1994] described one case with polymicrobial invasion. On the other hand, parasites such as Filaria, nematodes and viruses such as Herpes, Picornavirus, Coxsackie virus, Arenavirus, and Arbovirus, have also been involved [Shepherd, 1983; Christin and Sarosi, 1992]. Rayes et al. [2000] demonstrated a relationship between pyomyositis and toxocariasis. It has been noted that the main causative agent of pyomyositis in HIV patients is Staphylococcus aureus. However, Mycobacterium tuberculosis and one case of polymicrobial infection have also been reported in such patients with HIV [Christin and Sarosi, 1992].

Table 2. Aetiological Agents of Pyomyositis

Gram-Positive cocci	*Staphylococcus aureus* (Chiedozi, 1979; Christin and Sarosi, 1992) *S. epidermidis* (Yates et al., 1997) *Streptococcus pneumoniae* (Breton et al., 2001) *S. pyogenes* (Lawrentschuk et al., 2003) *S. dysgalactiae* (Woo et al., 2003)
Gram-negative bacilli	*Proteus mirabilis* (Chusid et al., 1998) *Klebsiella oxytoca* (Schwab and Panwalker, 1986) *K. pneumoniae* (Wang et al., 2001) *Yersinia enterocolitica* (Brennessel et al., 1984) *Salmonella spp.* (Lotholary et al., 1995; Collazos et al., 1999) *Aeromonas hydrophila* (Kratzke and Golenbock, 1987) *Escherichia coli* (Tumeh et al., 1988) *Haemophilus influenza* (Hall et al., 1990) *Citrobacter freundii* (Fincher et al., 1990) *Stenotrophomonas maltophilia* (Tsai et al., 2003)
Gram-positive bacilli	*Nocardia asteroides* (Vilaseca Arroyo et al., 2000)
Gram-negative cocci	*Neissseria gonorrhoea* (Haugh et al., 1996)
Anaerobic bacteria	*Prevotella melaninogenica* (Odeh et al., 2000) *Bacteroides fragilis* (Calvo-Alen et al, 1995) *Eubactterium lentum* (Palomino-Nicas et al., 1996) *Mycobacterium tuberculosis* (Kim et al., 1999; Johnson and Herzig, 2000; Soler et al., 2001)
Parasite	Filaria Nematodes Toxocariasis (Shepherd, 1983; Christin and Sarosi, 1992; Rayes et al., 2000)
Virus	Herpes, Picornavirus, Coxsackie virus, Arenavirus, and Arbovirus (Shepherd, 1983; Christin and Sarosi, 1992)
Fungus	*Candida albicans*

NECROTIZING FASCIITIS

Necrotizing skin infections were first described by Jones in 1871,but the term necrotising fasciitis was first used by Wilson (Wilson, 1952) in the 1950s to describe the most consistent feature of the infection such as necrosis of the fascia and subcutaneous tissue with relative sparing of the underlying muscle. Several synonyms have been mentioned to describe this disease such as necrotising soft tissue infection, Fournier's gangrene (necrotising fasciitis of scrotum or vulva), Ludwig's angina (necrotising fasciitis of submandibular space) (Anaya and Dellinger, 2007; Shimizu and Tokuda, 2010).

Necrotizing fasciitis is characterized by rapid destruction of tissue, systemic toxicity, and, if not treated aggressively, gross morbidity and mortality may result. The rate of mortality is ranged from 25% to 75% (Francis et al., 1993; McHenry et al., 1995). The disease is uncommon and the true incidence is not known.

However, more than 500 cases have been reported in North America and stated that men are slightly more affected than women (Francis et al., 1993; McHenry et al., 1995; Davies, 1996). Incidence of necrotizing fasciitis is increased in persons with diabetes, skin injury, including insect bite, trauma and surgical wounds, underlying conditions such as alcohol abuse, intravenous drug abuse, chronic liver or renal disease, peripheral vascular disease, malignancy, immunosuppression, and possibly, tuberculosis (Francis et al., 1993; Davies et al., 1996; Hefny and Abu-Zidan, 2010). In children, necrotizing fasciitis may follow varicella zoster infection (Bingol-Kologlu, 2007). It also occurs in young, previously healthy patients, including children. Mortality rates in children and previously healthy individuals tend to be much lower (Davies et al., 1996).

Necrotizing soft-tissue infections are classified as cellulitis, fasciitis, or myositis based on the principal soft-tissue layer involved with necrosis (McHenry and Malangoni, 1995). Whereas, aetiologically, NF infections have been classified into:

Type 1. Polymicrobial infection, with aerobic and anaerobic bacteria; usually in patients with immunocompromise or chronic disease (Shimizu and Tokuda, 2010; Machado, 2011).

Type 2. Monomicrobial infection or Group A streptococcus (GAS): occurs in any age group and in otherwise healthy people; occasionally accompanied by *Staphylococcus aureus* infection (Myslinski et al., 2003).

Type 3. Gram-negative monomicrobial infection: This includes marine organisms such as *Vibrio* spp. and *Aeromonas hydrophila*, which can occur following seawater contamination of wounds, injuries involving fish fins or stings, and raw seafood consumption; particularly in patients with chronic liver disease. These marine infections are particularly virulent and can be fatal within 48 hours (Goodell et al., 2004; Bross et al., 2007).

Type 4. Fungal infection: This is caused by fungal infection such as *Aspergillus* or *Zygomycetes* after traumatic wounds or burns. *Candida* infection is rare but can be seen in immunocompromised patients and can be rapidly progressive with high mortality (Cook et al., 1990; Jain et al., 2006). *Mucor* and *Rhizopus spp*. are affecting immunocompetent patients after sever trauma and are responsible for almost 32% of necrotizing fasciitis in type 3 cases (Jain et al., 2006).

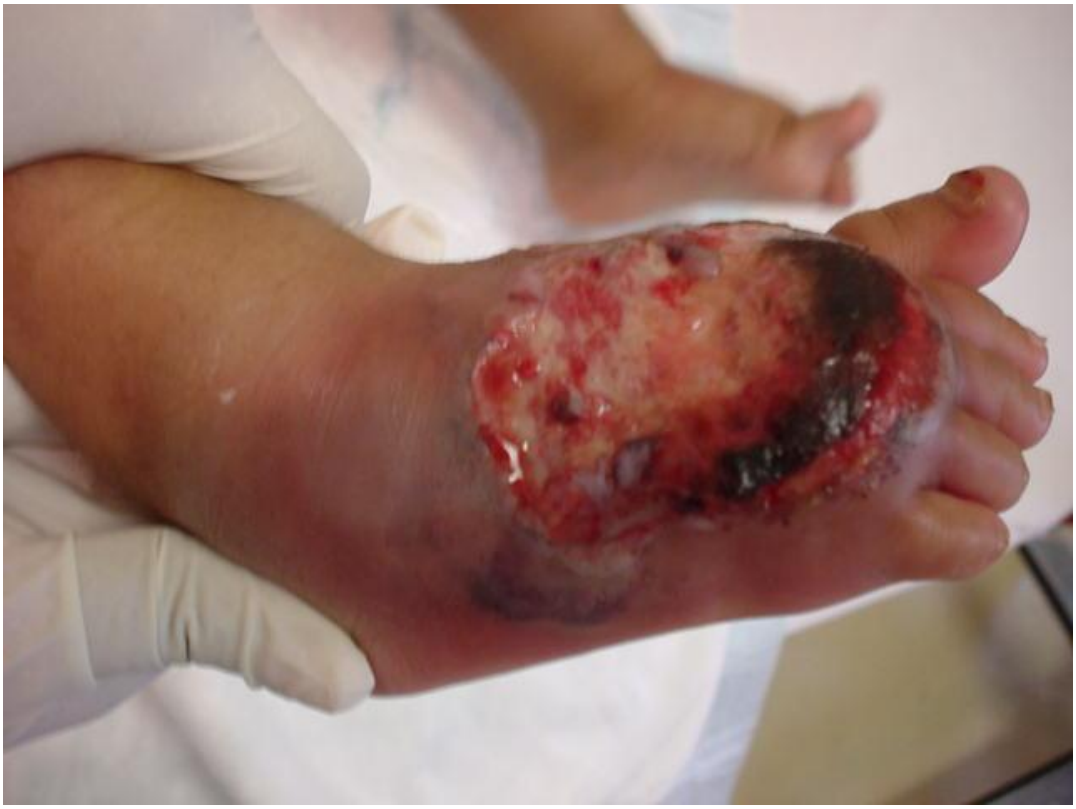

Fig. 1. Necrotizing fasciitis involving dorsum of the foot of a three-year-old child following a recent Herpes Zoster infection; Image adapted from Machado [2011].

MICROBIOLOGY OF NECROTIZING FASCIITIS

Most studies have shown that necrotising fasciitis is polymicrobial in origin, with most cultures yielding a mixture of aerobic and anaerobic organisms (McHenry et al., 1995; Eke, 2000; Elliot et al., 2000). These infections typically occur in the perineum and trunk. The isolates reflect normal skin commensalism found adjacent to the site of infection. Pathogenic Gram-positive organisms such as Staphylococcus aureus, S pyogenes, and enterococci are the aetiological isolate of Necrotizing fasciitis, and Gram-negative aerobes such as Escherichia coli and Pseudomonas species. In addition, anaerobic organisms are also isolated from NF infection such as Bacteroides or Clostridium species (such as C. Perfringens, C. Histolyticum, C. Septicum) which results for gas gangrene and occur often secondary as a result to trauma or crush injury (Sudarsky et al., 1987; McHenry et al., 1995; Miller et al., 2005). But overall, streptococcus is the most common causative organism reported in NF.

Monomicrobial infections are less common than the polymicrobial types. These typically occur in the limbs and afflict healthy patients with no implicative comorbidities. There is often a history of trauma. S pyogenes and S aureus are the usual pathogens; this type of infection might be associated with toxic shock syndrome (Anaya and Dellinger, 2007). Recently, much concern has arisen with the emergence of toxic shock strains of streptococcus (group A haemolytic streptococci) leading to fasciitis with organ dysfunction. Moreover, Community-acquired methicillin–resistant S aureus (MRSA) has increasingly been described in NF and considered one-third of cases at the recent study (Miller et al., 2005). Vibrio spp. are less common aetiological agents of necrotizing fasciitis which enter through skin lesions that have been exposed to seawater or marine animals (McHenry et al., 1995).

PATHOGENESIS OF NECROTIZING FASCIITIS

Necrotizing fasciitis is a rapidly progressing bacterial infection of the soft tissue that destroys the subcutaneous fat and fascia. In most cases, the deep fascia and the muscle are spared from destruction by the infection, but myonecrosis can occur due to a compartment syndrome (Bisno and Stevens, 1996). The incidence of necrotizing fasciitis has been reported to be between 500 and 1500 cases per year in the United States and the mortality rates have been reported to range from 8% to 65% averaging 21.9% (Stoneback and Hak, 2011).

The typical patient who has contracted a type of necrotizing fasciitis usually has an underlying illness that has weakened the immune system and has often incurred a disruption in the skin caused by a cut, ulcer, or even an insect bite. This opening in the skin serves as a portal of entry for the bacteria. Males and the

elderly are at a higher risk for contracting the disease (Brook and Frazier, 1995; Brothers, 1998). Diabetes remains one of the most common illnesses that weaken the immune system. Other predisposing factors include peripheral vascular disease, end-stage kidney disease, chemotherapy for cancer treatment, and immunosuppression due to organ transplant. In most of the NF cases, the immunocompromised male or elderly patient with a skin disruption allowed the entry of bacteria. On the other hand, many cases of necrotizing fasciitis in young, healthy individuals has been found with no break in the skin to serve as an area of entry. Bacteria of group A streptococcus could cause such infection and it seems this bacteria has become more virulent which usually cause outbreak in winter months (Drake et al., 1997; Weiss and Laverdiere, 1998). This bacteria is commonly found in the nose and throat of healthy individuals. The group A streptococci produce a variety of so-called virulence factors that permit them to evade the defense mechanisms of the host and thus cause disease.

These factors include polysaccharide capsules and M proteins that impede phagocytosis, enzymes that degrade host tissues, and toxins that overstimulate the immune system, causing fever and shock. Organisms spread from the subcutaneous tissue along the superficial and deep facial planes, facilitated by bacterial enzymes and toxins. This deep infection causes vascular occlusion, ischemia, and tissue necrosis. Superficial nerves are damaged, producing the characteristic localized anesthesia. Septicemia ensues with systemic toxicity (Schwartz 2004).

Bacterial factors M-1 and M-3 surface proteins increase the adherence of the streptococci to the tissues and protect the bacteria against phagocytosis by neutrophils. Streptococcal pyrogenic exotoxins (SPEs) A, B, C are directly toxic and tend to be produced by strains causing NF. These exotoxins, together with streptococcal superantigen (SSA), lead to release of cytokines and produce clinical signs such as hypotension. The poor prognosis in NF has been linked to infection with certain streptococcal strains (Schwartz 2004). Facultative aerobic organisms grow since polymorphonuclear (PMN) leukocytes exhibit decreased function under hypoxic wound conditions. This growth further lowers the oxidation/reduction potential, enabling the more anaerobic proliferation and, thus, accelerating the disease process. Carbon dioxide and water are the end products of aerobic metabolism. Hydrogen, nitrogen, hydrogen sulfide, and methane are produced from the combination of aerobic and anaerobic bacteria in a soft tissue infection. These gases, except carbon dioxide, accumulate in tissues because of reduced water solubility (Maynor 2004)

CONCLUSION

Microbiology of musculoskeletal infections should be considered in patients in order to obtain an early diagnosis. Highly sensitive and specific methods should be suggested for the evaluation of such infections. For example, pyomyositis is not common but patients with muscle pain, fever, leucocytosis, elevated ESR and CRP, in tropical and non-tropical countries should be considered for infection. As well, necrotizing fasciitis is a rare but devastating infection of the fascia and subcutaneous tissue and the presentation of the disease is variable. Delay in recognition and effective treatment increases the mortality, therefore early diagnosis and management are essential for a better outcome.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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