Update and Review of Acute Compartment Syndrome and Necrotizing Fasciitis

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Abstract:

This is a brief review of the etiology, diagnosis, treatment and outcome for patients with either acute compartment syndrome or necrotizing fasciitis. Both can be devastating to the extremities and can result in permanent impairment or amputation. Early diagnosis and treatment is the key to prevent permanent damage. Both can also affect the head or trunk of the body, but this review will focus primarily on the involvement of the extremities. Acute compartment syndrome (ACS) is a condition where osseofascial compartment pressures rise to a point that overcomes capillary perfusion pressure. The lack of tissue perfusion in ACS results in tissue ischemia and necrosis, which can lead to permanent loss of muscle function, nerve damage, limb amputation, and multisystem organ failure. Necrotizing fasciitis is a severe form of subcutaneous cellular infection with spread to and along the subcutaneous and fascial layers. Because of its location along the fascial plane and it is often polymicrobial nature, it can quickly progress in severity and become a life-threatening disease.

Introduction

Acute compartment syndrome (ACS) is a condition where osseofascial compartment pressures rise to a point that overcomes capillary perfusion pressure. The lack of tissue perfusion in ACS results in tissue ischemia and necrosis, which can lead to permanent loss of muscle function, nerve damage, limb amputation, and multisystem organ failure. Early diagnosis is essential for successful outcomes and is based on clinical findings and compartmental pressure measurements. Common etiologies of ACS include fracture, traumatic soft tissue injury, and non-traumatic increases in compartmental pressure. ACS most commonly occurs in the anterior compartment of the lower extremity following a tibial fracture, but can occur in the foot, thigh, forearm or hand [1]. Treatment consists of emergent surgical decompressive fasciotomy.

Etiology & Epidemiology

ACS is a common, yet difficult condition to diagnose. Effective diagnosis requires a thorough understanding of the etiology, epidemiology and risk factors. Two broad categories of etiology for ACS are :(1) increase compartment contents or -decrease compartment space [2].

Fractures are the most common cause of ACS, resulting in about 69% of all ACS cases and 76% of pediatric cases [3]. Not all fractures, however, impart the same level of risk. Tibial diaphyseal fractures comprise the leading cause of fracture-induced ACS at 40% of cases [1]. The next most common cause of ACS is soft tissue injury in the absence of a fracture, accounting 23% of all ACS cases [4]. Table 1 is a brief list of other causes:

Table 1: Brief List of Causes

INCREASED COMPARTMENTAL CONTENTS [2,5,6]	DECREASED COMPARTMENTAL SPACE [2,5]
Crush syndrome	Burns (circumferential)
Revascularization	Muscle hernia repair
Infiltrated fluid infusion	Casts
Arterial puncture	Circumferential dressings
Gunshot wound	Pneumatic antishock garments
Snake / venomous bite	Lithotomy surgical positioning
Nephrotic Syndrome	**MEDICAL COMORBIDITIES [2]**
Hematogenous osteomyelitis	Diabetes
Exercise (chronic compartment syndrome)	Coagulopathies

Age is one of the strongest predictors for ACS, where young males comprise the greatest risk [7]. The incidence of ACS is 3.1/100,000 people annually, but men are ten times more likely to develop ACS with an incidence of 7.3/100,000 [3]. The average age for ACS diagnosis is 32-years-old [3]. Patients younger than 35-years-old with tibial diaphyseal fractures are three times more likely to develop ACS than those over 35-years-old [3]. ACS is thought to be more common in younger patients due to presence of stronger fascia, increased muscle

volumes, and increased frequency of high-energy trauma [2].

Other risk factors for development of ACS include high-energy trauma and polytrauma [3]. Although it would seem like open fractures should decrease the risk of ACS, studies have shown no difference in the incidence of ACS in open versus closed fractures [2]. ACS can be iatrogenic during surgical procedure due to limb placement, traction, or intramedullary pinning [2,7].

Diagnosis

ACS can be difficult to diagnose and have poor outcomes when not recognized early in its course. The approach to diagnosing ACS is most frequently based on history and physical exam [1-3,5,6,8]. Some institutions also utilize intra-compartmental pressure (ICP) measurement techniques to aid in diagnosis. Regardless of approach, early diagnosis is necessary for successful early intervention [6]. The symptoms of ACS are progressive and therefore should be monitored over time in patients most at risk [5,8].

The "6 P's" represent a helpful mnemonic for remembering the indicators associated with ACS: **pain** out of proportion to injury and pain with passive stretch, **paresthesia**, **pressure** on palpation, **pallor**, **paresis**, and **pulselessness** [1,2,5]. Collectively, these indicators have modest sensitivities, but high negative predictive values [2,3,8]. Patients with two positive indicators have a 25% probability of ACS, whereas patients with three positive indicators have a 93% of ACS [1].

Pain is recognized as the most prominent, reliable indicator of early ACS [1,2,5]. Pain in ACS is progressive and typically resistant to analgesic medications [2,8]. Patients may present early with paresthesia, or pressure on palpation [5]. More commonly, paresthesia and paresis are both late signs that only occur after a significant decrease in arterial blood flow [2]. Paresis is the result of longstanding nerve compression or irreversible muscle damage [5]. Pulselessness, pallor and slow capillary refill times are rare and more indicative of a vascular injury, although present as late signs in ACS [2,5]. It is therefore important to note that while the "6 P's" have a correlation with compartment syndrome, these signs and symptoms often present after cell death has already begun to occur. Making the diagnosis before the presentation of these late signs is much more ideal.

The clinical diagnosis to ACS has its limitations. Although pain is the most reliable indicator used by clinicians, it may occasionally be absent, especially in patients presenting with fully established ACS [5]. Pain can be masked by associated nerve injury, fracture, or the use of local or epidural anesthetics [2,3,8]. The utility of pain measurement is further limited by its subjectivity and variability among the population [3]. Obtaining information regarding pain can be especially challenging in certain patient populations: intoxicated patients, obtunded patients, patients with learning disabilities, or young children [1-3,5]. The variability of patient presentation, pain perception and the low positive predictive-values of the "6 P's" can sometimes make clinical diagnosis difficult or impossible.

Intra-compartmental pressure (ICP) monitoring offers a helpful alternative when clinical diagnosis is uncertain. As ACS develops, the pressure inside the compartment progressively increases. There is a critical point when the increased pressure inside the compartment inhibits vascular supply to the tissue causing necrosis. Therefore, when compartment syndrome is suspected, intra-compartmental pressures should be measured early and continued over time [5]. Pressure measurements allow clinicians to monitor possible progression to ACS and allow for early intervention.

Controversy exists regarding the minimum ICP for diagnosing ACS, ranging anywhere from 30 mmHg to 45 mmHg [1,2]. Symptoms of ACS begin to appear around ICP of 20-30 mmHg [2], and most sources define ACS at ICP measurements of greater than 30 mmHg [2]. Similarly, ACS is diagnosed when ICP measurements are within 30 mmHg (delta pressure) of the diastolic blood pressure [3-5].

Common techniques to measuring pressure within the compartment include slit catheter, slide port needle, fluid-filled catheter attached to an extracorporal transducer, simple needle manometry, or the infusion technique [1,5]. Pressure measurements should occur as close to the injury site as possible, and should be obtained in all compartments [6,8]. Some sources recommend both clinical and pressure monitoring during the first 48-hours after a fracture or surgical fixation [2]. Continuous pressure monitoring has been recommended by some to monitor for compartment syndrome in all tibial diaphyseal fractures [9].

Attempts have been made to incorporate imaging and biomarkers into the diagnostic workup for ACS. Near-InfraRed (NIR) spectroscopy is an imaging technique, based on the same principle as pulse oximetry, currently being developed and studied for determining muscle tissue oxygenation in ACS progression [1-4,8]. More large scale trials are needed before the efficacy of NIR spectroscopy can be determined [8]. Other imaging modalities such as MRI and Scintigraphy have shown limited diagnostic efficacy [2]. Biomarkers such as serum creatinine phosphokinase, erythrocyte sedimentation rate, white blood cells, and myoglobin can be elevated in ACS, but are not specific [2,5].

The key to successful treatment of ACS is early diagnosis [6]. The differential diagnoses include cellulitis, deep venous thrombosis, fracture, gas gangrene, necrotizing fasciitis, peripheral vascular injury rhabdomyolysis. The diagnostic approach to ACS utilizes information from patient history and physical exam, intra-compartmental pressure (ICP) measurements, or both. Currently, the use of imaging and laboratory biomarkers is inadequate for diagnosis. Clinicians should understand mechanism of injury, potential risk factors and maintain a high index of suspicion for at-risk patients [1,5].

Pathogenesis

Extremity compartments are finite anatomic spaces formed by fascia, epimysium and skin [5,8]. Fascia is a low-compliance tissue that encases and separates muscle groups and their respective neurovascular supply. It provides sites for muscle attachment, and

offers mechanical support during muscle contraction by grouping muscles of similar function [8]. As fixed compartments, these spaces cannot accommodate large increases in fluid without a resulting increase in compartmental pressure. ACS is a situation whereby large hydrostatic pressures within the compartment space impede adequate tissue perfusion.

The basis for both primary ACS (compartment syndrome caused by trauma), and secondary ACS (non-trauma related compartment syndrome) is elevated hydrostatic pressure [8]. Physiologic conditions allow for cellular metabolism to take place at an oxygen tension of 5-7 mm Hg, achieved by a typical capillary perfusion pressure of 25 mm Hg and an interstitial pressure of 4-6 mm Hg [1]. Alterations in these pressures can initiate a cascade of detrimental physiologic and biochemical events resulting in ACS. The ischemic threshold of skeletal muscle, determined in canine models, is related to the difference between the compartment and mean arterial (<= 30) or diastolic pressure (<=20) [5]. Thus, the most important variable contributing to ACS is the difference between compartment pressure and blood pressure [5].

The progression of ACS begins with an inciting event (i.e. musculoskeletal trauma) where blood flow through the microvasculature does not meet the metabolic demand of the tissue [4]. This event causes both fluid extravasation into the compartment and mild tissue hypoxia. The hypoxic environment in the tissues stimulates release of vasoactive substances for precapillary vasodilation and increased vascular permeability [1,8]. The subsequent increased net filtration into the interstitial space creates a positive feedback loop, worsening the building compartmental pressure and tissue hypoxia.

High interstitial pressures eventually cause the thin-walled venules and veins to collapse. The ensuing elevation in venous pressure not only contributes to increased fluid extravasation, but also causes a significant decrease in the arteriovenous (AV) gradient and worsened perfusion. [5] These pressures can ultimately reach a critical level whereby the thicker-walled arterioles can spasm and close [1]. Critically high compartmental pressures and very low AV gradients overcome capillary perfusion pressures resulting in cessation vascular perfusion, nerve conduction slowing and ischemic tissue [5].

The central part of the muscle is the first to become ischemic [5]. The hypoxic cellular environment favors anaerobic metabolism over aerobic metabolism, resulting in decreased total ATP production [8]. The ATP scarcity manifests in an inability to maintain the Na/K ATPase exchange [8]. Thus, membrane potential and osmotic balance is lost leading to cellular swelling and necrosis [8]. Myocyte necrosis causes release of osmotically active particles that draws more fluid into the tissue [1].

Restoring blood flow to these ischemic or necrotic myocytes can result in a reperfusion injury. Ischemic myocytes may produce oxygen radicals, undergo lipid peroxidation and calcium influx upon blood flow restoration [8]. Mitochondrial dysfunction in oxidative phosphorylation and cell membrane damage are the immediate consequences [8]. Necrotic myocytes also

release myoglobin, potassium, and other inflammatory molecules [5]. Reperfusion will introduce these harmful molecules into circulation and cause renal failure or cardiac arrhythmias [5]. The duration and extent of the ischemia predicts the severity of systemic response upon reperfusion [5].

The pathophysiology of ACS is important for understanding the approach to diagnosis and the goals for treatment. The exact mechanism for the progression of ACS is debated, but the common final pathway of all compartment syndromes is tissue anoxia [5]. Many factors contribute to the development and severity of compartment syndrome including vascular tone, blood pressure, duration of elevated pressure, and the tissue metabolic demand [5].

Treatment

ACS is a surgical emergency that requires immediate decompressive fasciotomy of all affected compartments upon diagnosis [2,5]. Prior to surgery, attempts to decrease ICP should include prompt removal of casts and any other occlusive dressings [5]. The muscles affected should be placed at the level of the heart, but no higher as to maximize perfusion to the ischemic tissue [5]. Fasciotomy should be performed as early as possible following diagnosis. Fasciotomy is contraindicated if the diagnosis is suspected to be delayed over eight hours and if the patient has no apparent muscle function in any segment of the affected limb [5].

During surgery, the goal is to decompress the compartments to allow reestablished blood flow to the tissues [5]. All visibly necrotic tissue must be debrided [2]. Following fasciotomy, the wounds are typically placed underneath a vacuum-assisted wound device to allow ICP to continue to normalize [2,5]. Primary wound closure may be completed once swelling has decreased and may require a split-thickness skin graft.

There is no successful alternative to decompressive fasciotomy. Adjunctive therapy may include blood pressure management and hydration to increase tissue perfusion pressure [1]. Oxygen supplementation has also been recommended to maximize saturation and oxygen delivery to ischemic tissue [6].

Outcomes & Complications

Untreated, ACS leads to muscle necrosis, fibrosis and contracture [5]. A late presentation may result in total loss of muscle function and require amputation [5]. Muscle necrosis will cause release of myoglobin and potassium, which can lead to renal failure or cardiac arrhythmias, respectively [5]. Multisystem organ failure and death are other possible sequelae [5].

Early fasciotomy, on the other hand, can allow for complete limb recovery if the diagnosis occurs within six hours of symptom onset [1]. Irreversible nerve damage occurs after 12 hours [1]. Fasciotomy that occurs in a delayed fashion will cause an increased risk of infection, sepsis, amputation, renal failure and death [1]. The use of vacuum-assisted wound devices and prophylactic antibiotics have decreased post-operative complication rates [1].

Although the consequences of untreated ACS are devastating, decompressive fasciotomy is not risk-free. Potential adverse postoperative outcomes include infection, need for split-thickness skin grafting, and poor cosmetic appearance [1,5]. Only 68% of fasciotomies performed within 12 hours of symptom onset resulted in complete recovery of muscle function, and only 8% if performed after 12 hours [7].

ACS is a condition that causes significant morbidity and potential mortality if undiagnosed or untreated. Even if the diagnosis is made early and decompressive fasciotomy is performed, some patients sustain significant morbidity from the surgical procedure. Patients must be educated on both the complications of ACS and the potential complications of surgery.

Necrotizing Fasciitis

Incidence and Etiology

Necrotizing fasciitis is a severe form of subcutaneous cellular infection with spread to and along the subcutaneous and fascial layers. Because of its location along the fascial plane and it is often polymicrobial nature, it can quickly progress in severity and become a life-threatening disease [10]. Prompt diagnosis is essential, and emergent surgery is indicated in the case of progressive disease.

The development of necrotizing fasciitis in children is rare, with an incidence of approximately 0.8 in every one million children [11]. The clinical picture of the disease is distinct from the usual presentation of necrotizing fasciitis in adults. While typically presenting in adults that are immunocompromised have a chronic disease, necrotizing fasciitis in children may be found in otherwise healthy patients without any known susceptibilities for infection [12]. Moss *et al*. reported that 95% of 20 children with necrotizing fasciitis were previously healthy, and Fustes-Morales *et al.* reported half of their 39 children with necrotizing fasciitis had no predilection for infection, though there was a strong association with malnutrition [12][13].

The process of deep bacterial seeding within the fascia is not thought to be different from that of adults. Minor and major trauma creating an entry-way for bacteria seems to be a common etiology. Excoriations during courses of varicella infection have been the most common cause among small children [13]. In newborns, cases of omphalitis and infected surgical wounds from circumcision have led to several cases [13]. Another common initiating factor is the infection of wounds from surgery or trauma, but in some cases the etiology cannot be determined [14]. Over 50% of pediatric cases present in the extremities, though other common locations include the trunk and neck [13].

Clinical Presentation and Diagnosis

Delayed diagnosis is one reason for high mortality rates among patients with necrotizing fasciitis [15]. Early in its course, necrotizing fasciitis may appear clinically indistinguishable from cellulitis or other more mild dermal infections. For one to two days patients may have no indication of severe disease, presenting with only dermal induration and erythema accompanied by a fever [16]. On days 3 to 4, hemorrhagic blisters or bullae may develop, and the skin will typically start to appear shiny, and the fulminant infectious process leads to severe localized pain [12]. In the following days, thrombosis of superficial nutrient vessels in the subcutaneous tissue leads to devitalized and friable subcutaneous tissue as well as

skin necrosis [12]. It is important to note that skin necrosis is a late finding, and the extent of subcutaneous tissue destruction is always more extensive than that which may be perceived externally by the necrotic skin margins [17]. Beyond the local involvement of the disease, the natural history of the disease ultimately leads to multi-organ systemic dysfunction. Disseminated intravascular coagulation was a major contributor to mortality in one study, leading to 28% of the study's deaths [13]. As septicemia develops, fluid third-spacing and autonomic vascular dysfunction can lead to hemodynamic instability and demise [18]. Lastly, infection can easily spread to multiple organs and may result in organ failure.

The LRINEC score has been proposed as one potential diagnostic tool based on objective laboratory data [19]. This scoring system has not yet been validated in the pediatric population, but it has shown to have a positive predictive value of 92% when the high risk score criteria are met [19]. Not all adult data may be extrapolated to children, but the LRINEC scoring system may have a role in diagnosing pediatric necrotizing fasciitis.

In patients with an equivocal diagnosis of necrotizing fasciitis, the "finger test" or "cut down test" may be performed. This test involves making a small incision over the suspect area under local anesthesia. If "dishwater pus" presents, or if the subcutaneous tissue overlying the fascia lacks normal resistance to blunt dissection, then necrotizing fasciitis is diagnosed [20]. This test, in combination with histopathological analysis of a specimen of tissue from this cut down are the gold standard for confirming the diagnosis.

Treatment

Early diagnosis, hemodynamic resuscitation and early extensive surgical debridement are the keys to successful treatment of necrotizing fasciitis. One study showed that when surgery was delayed more than 24 hours the mortality rate was twice as high compared to those treated surgically within 24 hours [21]. Surgical debridement must include sufficient excision of all involved skin, subcutaneous tissue and fascia to be effective [22]. As noted previously, the extent of necessary debridement of necessity must extend far beyond the border of the skin necrosis. The excision should extend until healthy vascularized borders are achieved at the fascial, subcutaneous and cutaneous layers [20]. The wounds should be examined frequently, and most cases will require more than one operating room procedure as further necrotic tissue eventually declares itself. Care should be taken to salvage all healthy soft tissue for coverage. In the extremities, justification for amputation may be found in patients that have high anesthetic risk, vascular insufficiency, unresolvable hemodynamic instability, or a significantly large infectious burden in the extremity [22].

Negative-pressure wound vacuums may be helpful in wound management until coverage can be achieved through skin flaps or grafts [20]. Nutritional monitoring and supplementation is critical during the wound healing period. Coagulation profiles and basic metabolic profiles must be monitored closely as clotting factors and electrolytes are often depleted [23]. Careful hemodynamic monitoring should continue in the post-debridement period.

Concomitant antibiotic treatment is essential with broad spectrum aerobic and anaerobic coverage. However, in isolation, pharmacologic treatment is insufficient as

there is no way for the antibiotics to effectively reach to hypovascular, necrotic tissue [24]. Antibiotic treatment may be narrowed based on the results of specimen cultures and sensitivities. Other supplemental treatments may include hyperbaric oxygen, intravenous immunoglobulin, and kallistatin administration [25][26]. However, the efficacy of these treatments is still controversial.

Outcomes

Outcome data in children is sparse than the literature describing adult outcomes. In the few pediatric studies looking at outcomes, the average mortality rate has ranged from 10-60%, with a mean among all studies of approximately 20% [22]. In the largest pediatric case series found in the literature, mortality was 18% [22]. Most deaths were due to infectious spread to vital organs or hemodynamic compromise. The presence of hemodynamic instability before surgery and pre-existing immune--compromised state were significant risk factors for mortality in children. Among survivors, scars and deformity were the primary complaints of survivors (72% and 56%, respectively). Skin and fascial contractures resulted in significant loss of joint range of motion in 20% of patients [22].

Summary

With acute compartment syndrome or necrotizing fasciitis the most important factor in determining outcome is early diagnosis and treatment. Patients can present in a number of clinical settings making it important for clinicians in all specialties to be aware of the basic signs and symptoms. It is better to send a patient to the emergency department for further evaluation and treatment even if they do not have acute compartment syndrome or necrotizing fasciitis. Missing either diagnosis can be devastating and limb/life threatening.

References

1. Tzioupis, C., Cox, G., & Giannoudis, P. V. Acute compartment syndrome of the lower extremity: an update. *Orthopaedics And Trauma*, 2009;*23*(6), 433-440.
2. Babak, Matthew, David, Gregg, Claude, Paul. *Current thinking about acute compartment syndrome of the lower extremity*. Canadian Medical Association. 2009
3. McQueen, M. M., & Duckworth, A. D. The diagnosis of acute compartment syndrome: a review. *European Journal Of Trauma And Emergency Surgery*. 2014
4. Elliott, K. G., & Johnstone, A.J. DIAGNOSING ACUTE COMPARTMENT SYNDROME. *Bone & Joint Journal*, 2003;85-B(5), 625-632. A
5. Olson SA, & Glasgow RR. Acute compartment syndrome in lower extremity musculoskeletal trauma. *The Journal Of The American Academy Of Orthopaedic Surgeons*, 2005;*13*(7), 436-44.
6. Singh, S., Trikha, S. P., & Lewis, J. Acute compartment syndrome. *Current Orthopaedics*, 2004;*18*(6), 468-476.
7. Schmidt AH. Acute Compartment Syndrome. *The Orthopedic Clinics Of North America*, 2016;*47*(3), 517-25.
8. von Keudell, A. G., Weaver, M. J., Appleton, P. T., Bae, D. S., Dyer, G. S. M., Heng, M., ... Vrahas, M. S. Diagnosis and treatment of acute extremity compartment syndrome. *The Lancet*, 2015;*386*(10000), 1299-1310.
9. Mcqueen MM, Christie J, Court-brown CM. Acute compartment syndrome in tibial diaphyseal fractures. J Bone Joint Surg Br. 1996;78(1):95-8.
10. Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. Am J Surg. 1977;134:52-57.
11. Laupland KB, Davies HD, Low DE, Schawartz B, Green K, McGeer A, and the Ontario Group A Streptococcal Study Group. Invasive group A streptococcal disease in children and associateion with varicella-zoster virus infection. Pediatrics. 2000;105:e60.
12. Moss RL, Musemeche CA, Kosloske AM. Necrotizing Fasciitis in Children: Prompt recognition and aggressive therapy improve survival. J Pediatr Surg. 1996;31:1142-1146.
13. Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, et al. Necrotizing fasciitis: report of 39 pediatric cases. Arch Dermatol 2002;138(7):893-9.
14. Rea WJ, Wyrick WJ, Necrotizing fasciitis. Ann Surg. 1970;172:957-964.
15. Voros D, Pissiotis C, Georgantas D, et al: Role of early and aggressive surgery in the treatment of severe necrotizing soft issue infections. Br J Surg 1993; 80:1190–1191.
16. Meleney FL. Hemolytic streptococcus gangrene. Arch Surg. 1924;9:317-364.
17. Stone DR, Gorbach SL. Necrotizing fasciitis: The changing Spectrum. Dermatol Clin. 1997;15:213-220.
18. Misago N. Narisawa Y, Ryu S, et al. Necrotizing fasciitis due to group A streptococci: a clinicopathological study of six patients. J Dermatol. 1996;23:876-882.
19. Wong CH1, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004 Jul;32(7):1535-41.
20. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas

A. Current Concepts in the Management of Necrotizing Fasciitis. Front Surg. 2014; 1: 36.
21. Freischlag JA, Ajalat G, Busuttil RW. Treatment of necrotizing soft tissue infections. The need for a new approach. Am J Surg. 1985 Jun;149(6):751-5.
22. Tang WM, Ho PL, Fung KK, Yuen KY, Leong JC.. Necrotising fasciitis of a limb. J Bone Joint Surg Br (2001) 83:709–14.
23. Farrell LD, Karl SR, Davis PK, et al: Postoperative necrotizing fasciitis in children. Pediatrics 82:874-879, 1988.
24. Wilson HD, Haltalin KC. Acute necrotizing fasciitis in childhood: report of 11 cases. AJDC. 1973;125:591-595.
25. Anaya DA, Dellinger EP.. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis (2007) 44:705.
26. Lu SL, Tsai CY, Luo YH, Kuo CF, Lin WC, Chang YT, et al. Kallistatin modulates immune cells and confers anti-inflammatory response to protect mice from group A streptococcal infection. Antimicrob Agents Chemother (2013) 57:5366.