UDC 616-001

CLOSTRIDIAL MYONECROSIS IN 21TH CENTURY

G. Kirzhner, MD, PhD
Bogomolets National Medical University (Kyiv, Ukraine)

Summary. The emergence of a significant number of cases of Clostridial myonecrosis patients with war injuries requires a revision of the existing principles of early medical care, evacuation, early diagnosis and treatment of this disease.
***Key words*:** clostridial myonecrosis, evacuation, the use of a tourniquet, early diagnosis.
Резюме. Поява значної кількості випадків клострідіального міонекрозу у пацієнтів з бойовою травмою має призвести до перегляду тих принципів раннього надання медичної допомоги, евакуації, ранньої діагностики та лікування, що діють зараз.
Ключові слова: клострідіальний міонекроз, евакуація, використання джгута, рання діагностика.
Резюме. Появление значимого количества случаев клостридиального мионекролиза у пациентов с боевой травмой требует пересмотра действующих принципов раннего оказания медицинской помощи, эвакуации, ранней диагностики и лечения этого заболевания.
Ключевые слова: клостридиальный мионекроз, эвакуация, использование жгута, ранняя диагностика.

Clostridial myonecrosis remains an important cause of human morbidity and mortality worldwide. Although traumatic gas gangrene can be readily diagnosed from clinical findings and widely available technologies, spontaneous gas gangrene is more insidious, and gynecologic infections due to Clostridium sordellii progress so rapidly that death often precedes diagnosis. In each case, extensive tissue destruction and the subsequent systemic manifestations are mediated directly and indirectly by potent bacterial exotoxins. The management triumvirate of timely diagnosis, thorough surgical removal of necrotic tissue, and treatment with antibiotics that inhibit toxin synthesis remains the gold standard of care. Yet, despite these measures, mortality remains 30% to 100% and survivors often must cope with life-altering amputations. Recent insights regarding the genetic regulation of toxin production, the molecular mechanisms of toxin-induced host cell dysfunction, and the roles of newly described toxins in pathogenesis suggest that novel prevention, diagnostic, and treatment modalities may be on the horizon for these devastating infections.

Major advances in the treatment can be assimilated into a molecular and cellular model of pathogenesis which is initiated by direct toxin effects upon venous capillary endothelial cell function, leading to expression of pro-inflammatory mediators and adhesion molecules, and initiation of platelet aggregation. Toxin-induced hyperadhesion of leukocytes (see above section) with enhanced respiratory burst activity (due to toxins directly or to toxin-induced IL-8 or PAF synthesis by host cells) and toxin-induced chemotaxis deficits could result in neutrophil-mediated vascular injury. Direct toxin-induced cytopathic effects on EC may also contribute to vascular abnormalities associated with gas gangrene. Over prolonged incubation periods, PLC at sublytic concentrations causes EC to undergo profound shape changes similar to those described following prolonged TNF or interferon gamma exposure. In vivo, conversion of EC to this fibroblastoid morphology could contribute to the localized vascular leakage and massive swelling observed clinically with this infection. Similarly, the direct cytotoxicity of PFO could disrupt endothelial integrity and contribute to progressive edema both locally and systemically. Thus, via the mechanisms outlined above, both PLC and PFO may cause local, regional and systemic vascular dysfunction. For instance, local absorption of exotoxins within the capillary beds could affect the physiological function of the endothelium lining the postcapillary venules, resulting in impairment of phagocyte delivery at the site of infection. Toxin-induced endothelial dysfunction and microvascular injury could also cause loss of albumin, electrolytes, and water into the interstitial space resulting in marked localized edema. These events, combined with intravascular platelet

aggregation and leukostasis, would increase venous pressures and favor further loss of fluid and protein in the distal capillary bed. Ultimately, a reduced arteriolar flow would impair oxygen delivery thereby attenuating phagocyte oxidative killing and facilitating anaerobic glycolysis of muscle tissue. The resultant drop in tissue pH, together with reduced oxygen tension, might further decrease the redox potential of viable tissues to a point suitable for growth of this anaerobic bacillus. As infection progresses and additional toxin is absorbed, larger venous channels would become affected, causing regional vascular compromise, increased compartment pressures and rapid anoxic necrosis of large muscle groups. When toxins reach arterial circulation, systemic shock and multiorgan failure rapidly ensue, and death is common.

All researchers noted the role of tissue ischemia in the development of gas gangrene. Based on this effort in the prevention and treatment of gas gangrene were aimed at minimizing the use of tourniquets, organization of fast and non-traumatic evacuation, early surgical treatment of wounds and the rational use of antibiotics. Evidence of the effectiveness of specific serum is not obtained. The hyperbaric oxygenation using is debated.

Because of the relatively new measures are the use of X-ray computed tomography for early diagnosis of gas gangrene.

References

1. Awad MM, Bryant AE, Stevens DL, Rood JI. Virulence studies on chromosomal alpha-toxin and theta-toxin mutants constructed by allelic exchange provide genetic evidence for the essential role of alpha-toxin in Clostridium perfringens-mediated gas gangrene. Mol Microbiol 1995; 15:191.

2. MACLENNAN JD. The histotoxic clostridial infections of man. Bacteriol Rev 1962; 6:177.

3. Wang Y, Lu B, Hao P, et al. Comprehensive treatment for gas gangrene of the limbs in earthquakes. Chin Med J (Engl) 2013; 126:3833.

4. Centers for Disease Control and Prevention (CDC). Update: Clostridium novyi and unexplained illness among injecting-drug users--Scotland, Ireland, and England, April-June 2000. MMWR Morb Mortal Wkly Rep 2000; 49:543.

5. Stevens DL, Laposky LL, McDonald P, Harris I. Spontaneous gas gangrene at a site of remote injury--localization due to circulating antitoxin. West J Med 1988; 148:204.

6. McNee JW, Dunn JS. The method of spread of gas gangrene into living muscle. Br Med J 1917; 1:727.

7. Robb-Smith AHT. Tissues changes induced by C. welchii type a filtrates. Lancet 1945; 2:362.

8. Williamson ED, Titball RW. A genetically engineered vaccine against the alpha-toxin of Clostridium perfringens protects mice against experimental gas gangrene. Vaccine 1993; 11:1253.

9. Stevens DL, Titball RW, Jepson M, et al. Immunization with the C-Domain of alpha -Toxin prevents lethal infection, localizes tissue injury, and promotes host response to challenge with Clostridium perfringens. J Infect Dis 2004; 190:767.

10. Alouf JE, Geoffroy C. The Family of the Antigenically-Related, Cholesterol-Binding ("Sulphydryl-Activated") Cytolytic Toxins. In: Sourcebook of Bacterial Protein Toxins, Alouf JE, Freer JH (Eds), Academic Press, New York 1991. p.147.

11. Bryant AE, Bergstrom R, Zimmerman GA, et al. Clostridium perfringens invasiveness is enhanced by effects of theta toxin upon PMNL structure and function: the roles of leukocytotoxicity and expression of CD11/CD18 adherence glycoprotein. FEMS Immunol Med Microbiol 1993; 7:321.

12. Bryant AE, Stevens DL. Phospholipase C and perfringolysin O from Clostridium perfringens upregulate endothelial cell-leukocyte adherence molecule 1 and intercellular leukocyte adherence molecule 1 expression and induce interleukin-8 synthesis in cultured human umbilical vein endothelial cells. Infect Immun 1996; 64:358.