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Ingestional (Oral Route/Enteric) Anthrax: Is It a Problem in Turkey?

Besin Kaynaklı (İntestinal) Şarbon: Türkiye İçin Sorun mu?

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SUMMARY

Anthrax is primarily a disease of herbivores that can be transmitted to humans. The disease occurs worldwide. Although the disease is well controlled in industrial and agricultural areas in western developed countries, it is still far from controlled in some developing countries. Currently, anthrax has assumed greater importance as a result of the potential use of Bacillus anthracis spores as an agent of bioterrorism and biological warfare. The infection in humans is correlated with the incidence of disease in domestic animals. Anthrax occurs primarily in three forms in humans: cutaneous, respiratory and ingestional. Sepsis and meningitis can develop rarely as a complication of primary infection. Ingestional anthrax has not received as much attention as cutaneous and inhalational anthrax in the last two decades; it is divided into two forms as oropharyngeal and gastrointestinal. Penicillin is still the drug of choice in the treatment of anthrax. In the therapy of oropharyngeal or intestinal anthrax, two or more antibiotic combinations with supportive therapy are suggested for 10-14 days. Surgical resection of advanced intestinal anthrax may be life-saving. Good veterinary practice in endemic areas, immunization of animals against anthrax and education of animal owners can be effective in controlling infection in endemic/hyperendemic areas.

Key Words: *Anthrax, Ingestion, Humans, Oropharynx, Agriculture*

ÖZET

Besin Kaynaklı (İntestinal) Şarbon: Türkiye İçin Sorun mu?

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Şarbon başlıca otobur hayvanların hastalığı olup insanlara da bulaşabilmektedir. Hastalık dünya genelinde görülür. Gelişmiş ülkelerde iyi kontrol edilmesine karşın bazı gelişmekte olan ülkelerde hala kontrol altına alınamamıştır. Günümüzde Bacillus anthracis sporlarının biyolojik savaş ve biyoterörizm ajanı olarak kullanım potansiyeli nedeniyle şarbona verilen önem artmaktadır. İnsanlardaki infeksiyon evcil hayvanlardaki hastalık insidansı ile ilişkilidir. Şarbon insanlarda başlıca üç formda meydana gelir: Kütanöz, respiratuar ve sindirim sistemi (intestinal). Primer infeksiyonun bir komplikasyonu olarak nadiren sepsis ve menenjit meydana gelebilir. Önceki 20 yılda kütanöz şarbon ve respiratuar şarbon kadar dikkat çekmeyen sindirim sistemi şarbonu orofarengeal ve gastrointestinal olmak üzere iki formda görülür. Penisilin şarbon tedavisinde halen iyi bir seçenektir. Orofarengeal veya intestinal şarbon tedavisinde destekleyici tedavi ile beraber 10-14 gün süreyle iki ya da daha fazla antibiyotik kombinasyonu önerilmektedir. İlerlemiş intestinal şarbonda cerrahi rezeksiyon hayat kurtarabilir. İyi veteriner uygulamaları; hayvanların şarbona karşı aşılanmaları ve hayvan sahiplerinin eğitimi endemik/hiperendemik bölgelerdeki infeksiyonun kontrolünde etkili olabilir.

Anahtar Kelimeler: *Şarbon, Sindirim, İnsan, Orofarenks, Çiftçilik*

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Anthrax is primarily a disease of herbivores that can be transmitted to humans. The disease occurs worldwide. Although the disease is well controlled in industrial and agricultural areas in western developed countries, it is still far from controlled in some developing countries. Currently, anthrax has assumed greater importance as a result of the potential use of *Bacillus anthracis* spores as an agent of bioterrorism and biological warfare. Several reports and reviews have recently focused on cutaneous and pulmonary manifestations of anthrax. The third form of anthrax, ingestional anthrax, has not received as much attention, and a limited number of papers have appeared on this topic. The aim of this paper is to present a general review of ingestional anthrax and a brief overview of the situation in Turkey.

EPIDEMIOLOGY

The infection is still endemic or hyper-endemic in both animals and humans in some areas in the Middle East, West Africa, Central Asia, South America, and Haiti. Soil is the reservoir for the infectious agent. The epidemiology of human anthrax has been described as agricultural and industrial. It is believed that the transmission of infection to animals generally occurs during grazing or browsing. Acquisition of anthrax through fly bites and inhalation of spores may also occur in animals. Today, anthrax infection is far from eradication in the world. Anthrax infection in animals and human is also endemic in Turkey as well as other Middle Eastern, Central Asian, West African and Latin American countries[1-4].

Infection in humans is correlated with the incidence of disease in domestic animals. In economically advanced countries, where animal anthrax has been controlled, it occurs only occasionally among humans. Human anthrax is most common in enzootic areas in developing countries, among people who work with livestock, eat undercooked meat from infected animals, or work in establishments where wool, goatskins, and pelts are stored or processed[1,2]. The main route of transmission is contact with or inhalation of *B. anthracis* spores. Human cases may occur in an agricultural or an industrial environment. In the agricultural setting, infection occurs from exposure to *B. anthracis* spores on the skin or the mucosal surfaces of the gastrointestinal tract. Primary infections of the respiratory tract are rare in an agricultural environment. Agricultural cases have occurred in individuals who came into contact with sick or dead animals in rural areas. In certain impoverished communities, livestock owners are forced to slaughter animals at the first sign of infection in order to salvage the meat, hair and hides due to the economic situation. Farmers, butchers, knackers, shepherds, and veterinarians are therefore the most frequently infected. Anthrax is also reported in women who spin wool with hand spindles and in carpet weavers[1-3]. Another route of infection is by ingestion of raw or undercooked meat from an infected carcass[5-8]. The disease is generally accepted as non-contagious; records of person-to-person transmission exist but are very rare. Occasionally, laboratory-acquired infections have occurred[1].

Anthrax occurs primarily in three forms in humans: cutaneous, respiratory and gastrointestinal. Sepsis and meningitis can develop rarely after the lymphohematogenous spread of *B. anthracis* from a primary lesion (cutaneous, gastrointestinal or pulmonary). The majority of cases reported are generally of cutaneous anthrax. We reviewed the reported cases between 1990-2008 from Turkey and details are provided in Table 1. The rate of cutaneous anthrax cases is given as 96.2%. Other clinical forms are given less frequently: 2.3% for ingestional and 1.3% for anthrax meningitis[3,8-10].

In the published reports in English, cases with gastrointestinal anthrax have been reported from Thailand, India, Iran, Gambia, Uganda, Lebanon, and Turkey[1,5-9,11]. Only two cases were reported from the United States, by the Centers for Disease Control and Prevention, in 2000[12]. The source of infection is generally noted as consumption of the local traditional dish made of raw or only slightly cooked meat. Despite the wide distribution of anthrax endemicity, there is no large series of pathologically described gastrointestinal anthrax cases. Based on the limited reports, the disease spectrum may range from asymptomatic to a fatal outcome, due to shock and sepsis. Cooking the meat may have prevented human cases[5-7]. To our knowledge, in the last three decades, 10 cases of ingestional anthrax have been reported from Turkey. Eight of these were oropharyngeal anthrax and two were gastrointestinal anthrax. The sources of infection were noted as consumption of food prepared with raw meat or improperly cooked beef or mutton[5,8,9,11,13].

Table 1. Clinical form of anthrax and outcome (an analysis of reported cases in Turkey between 1990-2008)*

	Cases		Death	
Clinical pictures	**Number of cases**	**%**	**Number of deaths**	**%**
• Cutaneous anthrax	413	96.3	4**	0.97
• Gastrointestinal anthrax	10	2.3	5	50
Oropharyngeal	8			
Intestinal	2			
• Anthrax meningitis	6***	1.4	6	100
• Total	429	100	15	3.5

* Summarized from references 3,8-10.
** 2 of 3 cases died due to sepsis and 2 cases also died as a result of airway obstruction, extensive edema and toxemia.
*** Meningitis originated from cutaneous lesion in 3 cases.

ETIOLOGY and PATHOGENESIS

B. anthracis, the causative agent of anthrax, is a gram-positive, aerobic or facultatively anaerobic, endospore-forming rod-shaped bacterium. The infected host sheds the vegetative bacilli onto the ground and these sporulate on exposure to the air. The spores can persist in the soil for decades until taken up by another host. When the spores enter the host body, they germinate, become a vegetative form and multiply, leading to infection[1,2].

Ingestion or oral route anthrax in humans occurs following ingestion of contaminated meat from an animal that died of the disease or ingestion of contaminated water. Infectious doses have not been established for human infection. Many data were generated from human experimentation in units 731 and Ei 1644 in Japan during the Second World War, but the published subcutaneous and oral minimum infectious doses (MID) of 10 and 50 mg, respectively, are hard to interpret without further information. No other information is found on infectious doses in humans by the oral route. Today, experimentation of anthrax infection in humans is not possible. For this reason, our knowledge is based on animal experimentation. It is noted that oral administration of 150 million spores proved fatal to most cattle. In a study on 50 pigs given doses of 10^7-10^{10} spores in feed containing grit, the majority showed clinical illness with recovery, and only two died with confirmed anthrax 6 and 8 days, respectively, after ingestion of spores; these were estimated to have received 1.6×10^7 and 7.7×10^7 spores, respectively[1]. When the spores reach the gastrointestinal tract and achieve access to Peyer's patches, the spores germinate inside the macrophages and the emergent vegetative forms are released, which multiply in the lymphatic system and enter the bloodstream, causing toxemia and sepsis[1,14].

Generally, the severity of anthrax infection depends on several factors, including route of infection, nutritional and other comorbid diseases of the infected person and virulence of the infecting strain[1,14].

B. anthracis has two principal virulence factors: the toxin complex and the polypeptide capsule. Both are plasmid-mediated. The genes for the toxin components and virulence gene regulators Atx A and PagR are located on a large (182 kb) plasmid designated pX01, and the genes for capsule synthesis and their regulators AcpA and AcpB are located on a smaller (95 kb) plasmid, pX02. Loss of either plasmid results in considerable reduction in virulence. Possibly also contributing to virulence are other proteins encoded on the chromosome or plasmids, such as cell surface S-layer extractable antigen 1 (EA1) and surface array protein (SAP), anthrolysin O, siderophores, and metal cation transport proteins[1,14,15].

The toxin complex consists of three synergistically acting proteins: protective antigen (PA, 83 kDa), lethal factor (LF, 90 kDa) and edema factor (EF, 89 kDa). LF in combination with PA (lethal toxin, LeTx) and EF in combination with PA (edema toxin, EdTx) are secreted during multiplication of the vegetative cells and are accepted as responsible for the characteristic signs and symptoms of anthrax. EdTx is a calmodulin-dependent adenylate cyclase that inc-

reases intracellular levels of cyclic adenosine monophosphate (cAMP) on entry into most cell types, leading to impaired maintenance of water homeostasis and characteristic edema. EdTx also inhibits macrophage activity by altering their cytokine production, decreases the circulating lymphocyte population and diminishes neutrophil function. LF is a zinc-dependent metalloprotease that cleaves the amino termini from mitogen-activated protein kinase kinases (MAPKKs), thereby disrupting signaling pathways with a range of resulting pathologic effects. LeTx kills or disrupts production and function of macrophages, dendritic cells, neutrophils, and some epithelial and endothelial cells, downregulates cytokine production, preventing induction of chemokines integral to responses to viral or bacterial infection, inhibits B-cell proliferation, and lowers B-cell production of immunoglobulin. Inflammatory mediators released in response to LeTx may also contribute to the sudden death characteristic of systemic anthrax, and its lethal effect on microvascular endothelial cells is presumed to be responsible for the also characteristic terminal hemorrhages[1,14-16].

CLINICAL PRESENTATION

Ingestion of *B. anthracis* in contaminated food or drink may cause gastrointestinal anthrax. The lesion may localize from the oral cavity to the cecum. The incubation period is commonly varied between 3-7 days. In the literature, two clinical forms of ingestional anthrax are described as oropharyngeal anthrax and gastrointestinal anthrax[1,5-8,14].

Oropharyngeal Anthrax

Oropharyngeal anthrax is less frequently seen than the gastrointestinal form. The disease is generally underreported because only a limited number of physicians are familiar with and aware of the oropharyngeal form. We identified only seven publications, written in English, in MEDLINE and the other databases reporting anthrax lesions in the mouth or oropharynx[5,9,13,17-20]. Davies, described a major epidemic of anthrax involving over 9000 patients in Zimbabwe from 1978 to 1980[17]. The author noted only four cases in which lesions were on the tonsil and tongue but no clinical details were given. Sirisanthana and colleagues reported an outbreak of human anthrax after anthrax was found in water buffaloes in northern Thailand in 1982[18]. This outbreak included 52 cases with cutaneous anthrax and 24 cases with oropharyngeal anthrax. The authors described detailed clinical features of oropharyngeal anthrax in their paper published in 1984. All patients with oropharyngeal anthrax had recently eaten water buffalo meat. The mean incubation period was given as 42 hours (range 2-144 hours). All patients had sought medical attention because of painful neck swelling, and all but one complained of fever. Despite hospital admission and antibiotic treatment, 3 of 24 patients resulted in death, with a case fatality rate of 12.4%. In 1986, we described the same clinical pictures in six cases in our department when the author was working at Cumhuriyet University between 1981-1988. The case fatality rate was 50%[5]. Figure 1 shows a lesion covered with a gray pseudomembrane on the left tonsil and gram-positive bacilli on the smear taken from the lesion. Following that report, Onerci and Ergin reported one case in 1993 and Tas et al. also reported one case in 2008[9,13]. To our knowledge, a total of eight cases with oropharyngeal anthrax were reported between 1980 and 2008 from Turkey. Four of eight cases resulted in death, with a fatality rate of 50%. Table 2 shows the characteristics of cases with oropharyngeal anthrax reported from Turkey. The oropharyngeal lesion is generally localized in the oral cavity, especially on the buccal mucosa or tongue, the tonsils, and the posterior wall of the pharynx. In some cases, the lesion may be present in two or more places in the gastrointestinal system, oropharynx and intestine. The oral lesion is generally 2-3 cm in diameter and covered with a gray pseudomembrane surrounded by extensive edema. When infection is localized on the tonsils, the affected tonsil is also intensely edematous and covered with pseudomembrane. The main clinical features are sore throat, dysphagia, hoarseness, fever, and painful regional lymphadenopathy in the neck. The neck swelling is usually marked and caused by enlargement of cervical lymph nodes and soft tissue edema. The tonsillar lesions extend to the anterior and posterior pillar of fauces, the soft palate and uvula. In severe cases, the illness progresses rapidly, and edema develops around the lymph node and may extend to the upper anterior chest wall. Bacteremia may develop. The infection leads to toxemia and acute respiratory distress syndrome followed by shock and coma. In some ca-

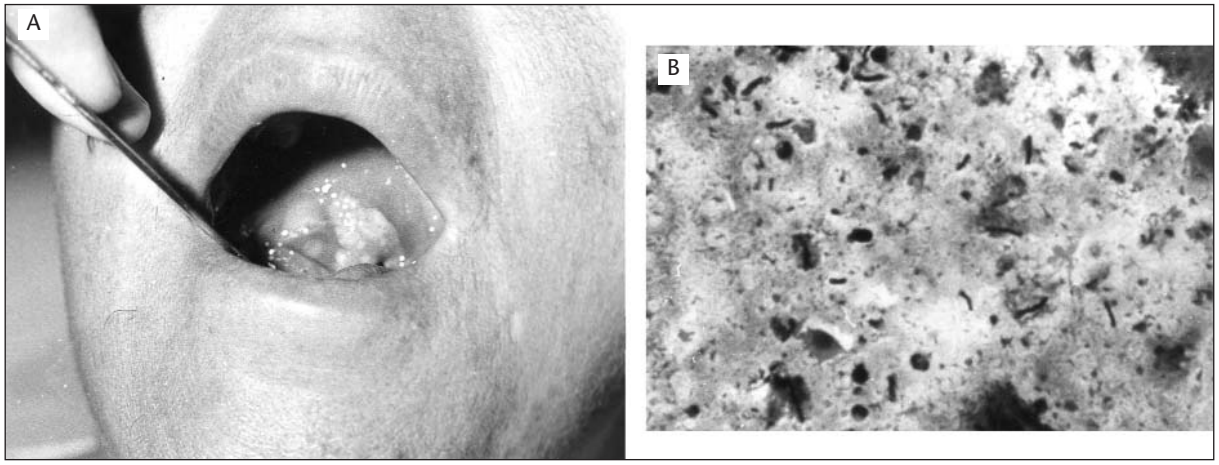

Figure 1. Oropharyngeal anthrax in a 26-year-old female. A. She applied with high fever (39°C) and sore throat. There was a lesion of 3 x 3 cm diameter covered with a grey pseudomembrane on the left tonsil and a painful mass on the left side of the neck. Source of infection was infected mutton eaten raw. B. Gram-positive bacilli are seen on the smear taken from the lesion.

Table 2. Characteristics of reported cases with oropharyngeal anthrax

Case no	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
• Reference	5	5	5	5	5	5	13	9
• Gender	F	F	F	F	F	F	M	F
• Age, year	18	26	40	46	35	16	46	70
• Source	Infected mutton	Infected mutton	NI	NI	Infected beef	Infected mutton	NI	NI
• Cutaneous lesion	-	-	-	-	-	-	-	-
• Site of lesion	Rt. tonsil	Base of tongue	Rt. tonsil	Rt. tonsil	Rt. tonsil	Rt. tonsil	Rt. tonsil	Soft plate-uvula
• Regional adenitis	+	+	+	+	+	+	+	+
• Fever	+	+	+	+	+	+	-	
• Hypothermia								+
• Sore throat	+	+	+	+	+	+	+	
• Toxemia	+	-	-	-	+	+		
• Respiratory distress	+	-	+	-	+	-		+
• Mucosal bleeding	-	-	-	-	+	-		
• WBC/µL	6000	5700	11.000	9000	6500	5000	?	14.800
• *Bacillus anthracis* isolation								
Lesion	+	+	+	+	+	+	+	
Blood	-	-	-	-	-	-	-	+
• Treatment	Pen + Gn	Pen	Pen	Pen	Pen	-	Pen	Cftr
• Outcome	Death	Survived	Survived	Survived	Death	Death	Survived	Death

NI: Not identified, WBC: White blood cells, Pen: Penicillin, Gn: Gentamicin.

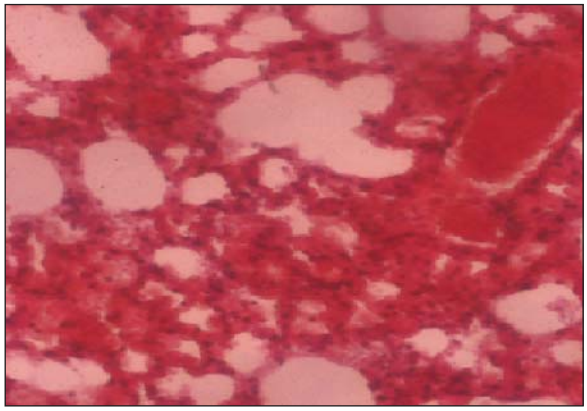

Figure 2. Histopathologic examination of the lung shows fill of erythrocytes in alveoli. Typical characteristic of hemorrhagic pneumonia due to anthrax sepsis originated from the tonsil lesion (HE 400x).

ses, toxemia leads to sudden death (Figure 2). Despite intensive medical therapy, the mortality is given between 12.4-50%[5,6,9,13,18,19].

In the differential diagnosis of oropharyngeal anthrax, diphtheria, complicated tonsillitis, streptococcal pharyngitis, Vincent angina, Ludwig angina, parapharyngeal abscess, and deep tissue infection of the neck should be considered[1,5,6]. A Gram-stained smear from the lesion shows numerous polymorphonuclear leukocytes and gram-positive bacilli. Diagnosis is confirmed by the isolation of *B. anthracis* from the cultures taken from oropharyngeal lesions and/or blood. Studies of serum antibody to anthrax antigens (PA, LF, EF) may be supportive for the diagnosis[20].

Gastrointestinal Anthrax

The gastrointestinal anthrax lesion localizes most commonly on the wall of the terminal ileum or cecum. The stomach, duodenum, upper ileum, and large bowel are occasionally affected. The character of the lesion is generally ulcerative, usually multiple and superficial, surrounded by edema. In cases with stomach infection, the lesion may bleed; hemorrhage may be massive and fatal in some cases. Intestinal hemorrhage, obstruction, perforation or any combination of these can be seen in intestinal anthrax. Massive ascites, shock and death sometimes follow these clinical pictures. In intestinal anthrax, pathological examination shows mucosal ulceration with edema and enlarged and hemorrhagic regional lymph nodes. Necrosis is sometimes present. Pulmonary and/or central nervous system involvement and sepsis can also be seen. The symptoms of intestinal anthrax are initially non-specific and include nausea, vomiting, anorexia, mild diarrhea, and fever. In this situation, patients are likely to not seek medical treatment, and even if they do, intestinal anthrax may not be considered in the differential diagnosis[1,6-8,11].

An outbreak of anthrax seen in 1982 in northeastern Thailand is noted as very informative. This outbreak originated from water buffaloes that died of anthrax. Of the 102 patients, 28 had cutaneous anthrax and 74 gastrointestinal anthrax. The only symptom in 67 of 74 patients with gastrointestinal anthrax was noted as acute diarrhea. The symptoms in the other seven cases were given as nausea, vomiting, abdominal distension, and severe abdominal pain. The case fatality rate was also given as 4%[6]. In some cases, the clinical picture may become more severe 24 hours after initiation of symptoms, and include acute diarrhea, nausea, vomiting, and abdominal pain. With the progression of the illness, abdominal pain, hematemesis, bloody diarrhea, and massive ascites occur, and signs suggestive of acute abdomen appear. Toxemia, sepsis and shock then develop, followed by death[1,6-8,11]. Patient history is very important for the suspicion of gastrointestinal anthrax. Travel to an endemic or hyperendemic area and consumption of traditional raw or improperly cooked food are the important clues for suspicion of ingestional anthrax. Physicians should consider a history of consumption of animal meat, which includes animals slaughtered before dying, in endemic or hyperendemic areas. Intestinal anthrax mimics food poisoning (in the early stages), acute abdomen of other causes and hemorrhagic gastroenteritis, particularly necrotizing enteritis due to *Clostridium perfringens*. The differential diagnosis in gastrointestinal anthrax includes food poisoning (in the early stage of intestinal anthrax), acute abdomen owing to other reasons, hemorrhagic gastroenteritis caused by other microorganisms, particularly necrotizing enteritis caused by *C. perfringens*, and dysentery (amoebic or bacterial)[1,6,7].

The diagnosis is confirmed by blood culture, examination of ascites fluid by smear, culture, and/or toxin tests and/or polymerase chain reaction. In those who survive, serology may be supportive for retrospective diagnosis. Where anthrax has not been suspected prior to death and postmortem, dark hemoly-

zed unclotting blood, enlarged hemorrhagic spleen, petechial hemorrhages throughout the organs, and dark edematous intestinal tract, ulcerated or with areas of necrosis, are the characteristic histopathological signs of intestinal anthrax[1,6,7].

TREATMENT

In vitro, human clinical isolates of *B. anthracis* are susceptible against a wide range of antibiotics: penicillins, aminoglycosides, macrolides, quinolones, carbapenems, tetracyclines, vancomycin, clindamycin, rifampin, cefazolin, and linezolid[1,21]. To our knowledge, a penicillin-resistant human isolate has not been reported from Turkey. However, the rate of penicillin resistance reached 11.5% in a French study that tested 96 isolates of *B. anthracis* (28 isolates from animal and 67 from environmental sources)[22].

Penicillin G is still the drug of choice in the therapy of naturally occurring anthrax. Currently, doxycycline and ciprofloxacin are alternative choices. In the therapy of oropharyngeal anthrax, supportive therapy and antibiotic treatment are given together. Physicians should be aware of airway obstruction in oropharyngeal anthrax. In the situation of respiratory difficulties due to tracheal obstruction, tracheotomy and ventilatory support may be required. The new World Health Organization (WHO) guidelines suggest two or more antibiotic combinations in the treatment of systemic anthrax[1]. Our suggestion is a combination of intravenous (IV) penicillin G (total 20-24 million units per day divided into 4-6) and clindamycin (600-900 mg IV every 6-8 hours) in the therapy of oropharyngeal anthrax. The combination of ciprofloxacin and clindamycin may also be given alternatively.

Clinical pictures of gastrointestinal anthrax may have a large range from a mild gastroenteritis to a severe form including abdominal pain, bloody diarrhea, hematemesis, severe toxemia, severe sepsis, shock, and massive ascites, etc. Patients having mild diarrhea generally escape medical attention. Many patients undergo abdominal surgery because of acute abdomen and are diagnosed during abdominal laparotomy or in the post-operative period after cultures and histopathological examination results. The diagnosis is sometimes made post-mortem. Physicians should be aware of this clinic form of anthrax in endemic areas, and the treatment should consist of:

1. Initiation of appropriate IV antibiotic treatment.

2. Replacement of fluid, electrolytes and protein losses.

3. Wide resection of the infected and necrotic parts of the intestine into seemingly healthy tissues with primary anastomosis in patients who do not improve with medical therapy.

4. Continuous drainage of the ascites, as fluid will continue to accumulate for several days after surgery[1,7,11].

A combination of penicillin G with an aminoglycoside (streptomycin is preferable) is recommended according to the WHO guidelines in the treatment of gastrointestinal anthrax. An alternative antibiotic treatment may be a combination of ciprofloxacin and streptomycin[1].

Duration of therapy is suggested as 10-14 days in ingestional anthrax. In spite of therapy, mortality may be high[1].

PREVENTION and CONTROL

Anthrax is an endemic disease in some parts of world including Turkey. Foods made of raw meat are still traditionally consumed in developing countries. People living in endemic areas should be educated regarding the health hazards associated with such a custom. Animal owners should give attention to ensure that sick animals are not slaughtered or butchered for consumption of the meats.

Controlling anthrax in humans depends on controlling the infection in animals. Good veterinary practice in endemic or hyperendemic areas involves close surveillance, burying or cremation of animal carcasses, and decontamination and disinfection procedures. Immunization of animals against anthrax and education of animal owners may control infection in these areas[1,3,7].

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