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Anthrax – an overview

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Summary

Anthrax, a disease of mammals (including humans), is caused by a spore-forming Gram-positive bacilli called *Bacillus anthracis*. Anthrax is one of the oldest threats to humanity, and remains endemic in animals in many parts of the world. The incidence of anthrax has decreased in developed countries, but it remains a considerable health problem in developing countries. The disease is transmitted to humans by contact with sick animals or their products, such as wool, skin, meat etc. Capsular polypeptide and anthrax toxin are the principal virulence factors of *B. anthracis*. Anthrax toxin consists of three proteins called protective antigen, edema factor, and lethal factor, each of which is nontoxic but acts synergistically. Human anthrax has three major clinical forms: cutaneous, inhalational, and gastrointestinal. The diagnosis is easily established in cutaneous cases, characterized by black eschar. Severe intoxication and collapse during the course of bronchopneumonia or hemorrhagic enteritis should prompt suspicion of anthrax. Treatment with antibiotics is mandatory. If untreated, anthrax in all forms can lead to septicemia and death. Recently, considerable attention has been focused on the potential for *B. anthracis* to be used in acts of biological terrorism. The ease of laboratory production and its dissemination via aerosol led to its adoption by terrorists, as shown by recent events in the USA. A good knowledge of anthrax, its epidemiology, pathogenesis, clinical forms and potential as a biological weapon is essential for timely prevention and treatment. This review summarizes the current knowledge on anthrax.

key words: **anthrax • *B.anthracis* • bioterrorism**

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BACKGROUND

Anthrax, a disease of mammals and humans, is caused by a spore-forming bacterium called *Bacillus anthracis* [1–3]. It has been an important disease throughout the history. The earliest known description of anthrax is found in the Book of *Genesis*, in which the fifth plaque (15th century B.C.) is reported to have killed the Egyptians' cattle [4]. There are numerous descriptions of anthrax in animals and humans in subsequent Hindu, Greek, and Roman literature [5]. In the 1600s, a pandemic of anthrax occurred in Europe, and the disease was called the 'black bane' [6]. With the industrialization of Europe, outbreaks of anthrax began to occur in factories where imported animal hides and hair were processed [7]. The disease is still enzootic in most developing countries, and occurs sporadically in many other countries [7]. The current problems with anthrax have given substance to the word bioterrorism [8].

EPIDEMIOLOGY

Anthrax is a zoonotic disease with a worldwide distribution [7–9]. The ability to form spores permits the organism to survive environmental and disinfective measures that destroy most other bacteria. Herbivores, the natural hosts, become infected by consuming the soil, and humans are incidentally infected by coming into contact with infected animals or their products [10]. 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 and processed [6,7]. West Africa is the most affected area of the world [7,11]. Anthrax is also a significant problem in other parts of Africa, Central America, Spain, Greece, Turkey, Albania, Romania, central Asia, and the Middle East [7,12–15]. Between 1979 and 1985, in association with civil war and the interruption of veterinary public health practices, Zimbabwe was the site of the largest outbreak of anthrax, with about 10,000 cases, almost all of which were cutaneous infections [11,16,17]. In experiments performed on Gruinard Island in 1942 and 1943 small bombs containing spores of *Bacillus anthracis* were suspended from a gantry and detonated, producing widespread contamination of the island's surface. As a result of the Gruinard test, the island was so badly contaminated that it has been completely sealed off to visitors. Over the years, there have been reports that the remaining animals of the island display prominent manifestations of genetic change [18–21].

Accidents are also possible, such as the one that occurred in 1979 after an explosion in a Soviet biological laboratory in former Sverdlovsk, which generated an aerosol causing 64 deaths [22–24]. Between 20,000 and 100,000 cases of anthrax have been estimated to occur worldwide annually [12]. Because anthrax remains a problem in developing countries, animal products imported from these areas continue to pose a risk. In economically advanced countries, where animal anthrax is controlled, it occurs only occasionally among humans. The incidence of infection has been reduced dramatically by the vaccination of high risk people and animals, along with improvements in industrial hygiene [25–27]. In the United States, the annual incidence was only 127 in the early part of the 20th century, and subsequently declined to less than 1 case per year — until the recent bioterrorist attacks.

MICROBIOLOGY

B.anthracis is an aerobic or optionally anaerobic, large, square-ended Gram-positive bacillus with a centrally located ellipsoidal to cylindrical spore. It is nonmotile, catalase positive, nonhemolytic on blood agar, and exhibits lysis by gamma-bacteriophage. The cells frequently occur in long chains, giving a bamboo appearance. The chains of virulent forms are usually surrounded by a capsule. Non-virulent forms are usually unencapsulated. Sporulation occurs in the soil and on culture media but not in living tissue, unless exposed to air. *B. anthracis* grows well on ordinary blood agar within 18 to 24 hours at 35°C. Typically the colonies are opaque, white to gray in color, flat and irregular, 4 to 5 mm in diameter, with a slightly undulate margin. Two potent exotoxins are produced. The two exotoxins are known as lethal factor (LF) and edema factor (EF). Both toxin molecules depend on a third protein called protective antigen (PA) for their biological activity.

Most *Bacillus* species encountered in the clinical laboratory are in group I of the Turnbull classification [28]. An approach to their identification is summarized in Table 1.

PATHOGENESIS

B. anthracis spores are highly resistant to UV light, temperature extremes, high pH, drying, high salinity levels, and routine methods of disinfection [10]. Inoculation of spores into the skin or contamination of preexisting abrasions leads to germination and vegetative reproduction. The resulting skin lesion is known as a malignant pustule, even though pus is not a hallmark of cutaneous anthrax unless there is secondary infection. Biopsy of cutaneous lesions reveals extensive tissue destruction with marked subepidermal edema, thrombosis of vessels, and hemorrhagic interstitium. Nonpitting edema around the lesion and a more generalized edema are thought to be due to toxin production [29,30]. Inhalation of a large number of spores leads to their phagocytosis by alveolar macrophages, after which they are transported to mediastinal lymph nodes, where they germinate. Mediastinal widening then ensues, usually followed by bacteremia [23,29]. Gastrointestinal anthrax results from the ingestion of contaminated meat containing large numbers of bacilli or spores. Points of entry into the submucosa appear, particularly in the oropharynx and the ileocecal region. Ulceration develops at the point of inoculation, and hemorrhage occurs in the draining lymph nodes along with local edema. Disease in bowel segments can be accompanied by hemorrhagic ascites [29,31]. Meningitis, when it occurs, is hemorrhagic and secondary to bacteremia, which may arise in any form of the disease [32].

Table 1. Some key characteristics for distinguishing between *B.anthracis* and other species of *Bacillus*.

Test	*B. anthracis*	*B.cereus*	*B.mycoides*	*B.thuringiensis*	*B.megaterium*	*B.subtilis*
B-hemolysis	–	+	–	+	–	**V**
Motility	–	+	V	+	V	**V**
Capsule	+	–	–	–	–	–
Urea hydrolysis	–	V	V	+	–	**V**
Nitrate reduction	**+**	**V**	**V**	**+**	–	**V**

(+) – >90% positive; (–) – <10% positive; v – 10% to 90% positive

Table 2. Common clinical forms of Anthrax.

Cutaneous: A skin lesion evolving during a period of 1 to 12 days from a papule, through a vesicular stage, to a depressed black eschar
Inhalational: A brief prodrome resembling a viral respiratory illness, followed by development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening
Gastrointestinal: Severe abdominal distress followed by fever and signs of septicemia, edema, and fever

The virulence of the organism is variable, determined by at least two factors: the polysaccaride capsule which prevents phagocytosis and an extracellular toxin [30,33,34]. Anthrax toxin is composed of three proteins: protective antigen (PA), edema factor (EF), and lethal factor (LF), each of which is nontoxic but interacts synergistically with at least one of the others [30,35,36]. The combination of PA and EF, edema toxin (ETx), causes edema, and has been demonstrated to decrease polymorphonuclear neutrophil function, suggesting that this is one of the ways that host susceptibility to infection with *B. anthracis* may be increased. Furthermore, a combination of PA and EF causes local edema, whereas the combination of PA and LF, lethal toxin (LTx), causes death when injected intravenously [30,36]. None of these three toxins, when administered alone, has any biologic effect in experimental animals [30]. Protective antigen is able to bind to cell-surface receptors, enabling them to be used by both EF and LF to reach the cytoplasma [35,37]. Recently, EF has been found to be a calcium- and calmodulin-dependent adenylate cyclase that causes dramatic increases in intracellular concentrations of cAMP [30,35,38]. Expression of these toxins takes place upon germination of spores within macrophages and vegetative growth of the bacilli, after they have been inoculated into a host.

CLINICAL FORMS OF ANTHRAX

The disease can occur in different forms (Table 2). The vast majority of cases of naturally acquired anthrax [95%] are cutaneous anthrax, followed by inhalational anthrax, gastrointestinal anthrax and other rare forms.

Cutaneous Anthrax

In most cases, there will be a history of occupational contact; more rarely, infection may have been transmitted by biting flies that previously fed on anthrax-infected carcasses [39]. The incubation period generally ranges from 1 to 12 days. Most of the cases occur in exposed skin areas on the arms and hands, followed by the face and neck [40,41]. The disease may remain localized, but some patients experience systemic symptoms. Cutaneous anthrax begins at an early stage with a painless, pruritic papule that appears at the site of inoculation. Several days later the papule progresses to a vesicle, then erodes to a highly characteristic necrotic ulcer with a black central eschar. A major diagnostic characteristic is the development of edema around the lesion. Perilesional edema may be extensive, especially if the lesion is located on the face, neck or upper chest. In these more severe forms, clinical findings include high fever, toxemia, regional painful adenomegaly and extensive edema; shock and death may ensue [42,43]. Healing usually results in scar formation, and reconstructive surgery may be required [41,44]. Antibiotic therapy does not appear to change the natural progression of the lesion itself; however, it will decrease or inhibit development of edema and systemic symptoms. The case fatality rate is 20% without, and less than 1% with, antibiotic treatment [45–47].

Inhalational Anthrax

Inhalational anthrax is the most lethal form of anthrax. It results most commonly from inhalation of pathogenic endospores. The minimal infectious dose has not been established, but the U.S. Department of Defense estimates that the lethal dose for humans is approximately 8,000–10,000 spores. The illness is biphasic; after inhalation of large numbers of spores, patients often complain of a 'flu-like' illness with a nonproductive cough suggestive of upper respiratory infection. After several days and often after an apparent improvement from the primary phase, there is a sudden onset of rapidly progressive respiratory failure, acute dyspnea, circulatory collapse, cyanosis, signs of pleural effusion and fever. The patient usually dies of toxemia and suffocation within 24 hours of the onset of this second stage. The mortality rate is very high, despite supportive care including appropriate antibiotics [48–51]. On chest x-rays, patients with pulmonary anthrax are found to have mediastinal widening (70%), pulmonary infiltrates (70%), or pleural effusion (80%), whereas most patients with influenza-like illnesses do not [52,53].

Gastrointestinal Anthrax

Gastrointestinal anthrax, although extremely rare in developed countries, has an extremely high mortality rate, estimated to be 25 to 60 percent [31,54]. Gastrointestinal anthrax may present after an incubation period of 1–7 days following ingestion of *B. anthracis* in contaminated food or drink. An oropharyngeal and an intestinal form of the disease have been described. Oropharyngeal lesions are present at the base of the tongue, and dysphagia, fever, and regional lymphadenopathy can be seen [55]. The intestinal form is manifested by severe abdominal pain, fever, nausea, vomiting, and bloody diarrhea [54]. Unless treatment commences early enough, toxemia and shock develop, followed by death [31,48].

Other clinical forms

Meningitis due to *B.anthracis* is a very rare complication that may result from a primary infection elsewhere [32,56]. This hemorrhagic meningitis results from hematogenous or lymphatic spread of bacilli to the central nervous system. Symptoms include nuchal rigidity, fever, headache, seizure, agitation and delirium. The case fatality rate is almost 100% [32,57].

Anthrax sepsis develops after the lymphohematogenous spread of *B. anthracis* from a primary lesion. Clinical features are high fever, toxemia and shock, with death following in a short time.

Renal anthrax and *ophthalmic anthrax* have also been described but are extremely rare [58–60].

Laboratory Diagnosis

Accurate, timely diagnosis of anthrax is essential, and the range of differential diagnosis is extensive. Specimens from patients suspected to have anthrax should be stained by both Gram's stain and polychrome methylene blue. A direct Gram-stain of any tissue or fluid will reveal large numbers of the characteristic bacilli. *B. anthracis* is seen as large, nonspore-forming rods in Gram's stain. Polypeptide capsules are revealed by polychrome methylene blue. The spores appear as unstained areas within the bacterial cells in Gram-stained preparations; however, they are best demonstrated after the organisms have grown on artificial media. *B. anthracis* can be cultured on sheep's blood agar from blood, ascitic fluid, pleural effusions, or skin lesions. The colonies of *B. anthracis* are normally large (4 to 5 mm), opaque, white to gray in color, raised, and irregular, with a curled margin. Blood cultures are typically positive in the acute phase of inhalational anthrax, and bacteria may be demonstrable in peripheral smears, due to the high titered bacteremia typical of septicemic anthrax [61]. Antibiotic susceptibility testing should be done on all isolates, especially if biologic warfare or terrorism is a possibility, because strains can be mutated to be resistant to some antibiotics.

The anthraxin skin test, performed by subdermal injection of an attenuated strain, can diagnose both acute and prior infections. The skin test will be positive in 82% of cases 1–3 days after the onset of symptoms and in 99% of cases at the end of 4 weeks [62].

Serologic diagnosis is possible, but most tests are useful retrospectively, because acute and convalescent samples are needed [63,64]. An enzyme–linked immunosorbent assay (ELISA) is available [65]. The newest diagnostic modality, which is becoming the preferred method, is polymerase chain reaction (PCR). PCR can amplify specific markers of *B. anthracis* and specific virulence plasmid markers carried by different strains [66].

Treatment

Prompt clinical suspicion and rapid administration of effective antimicrobials are essential for treatment of anthrax. Supportive therapy should also be initiated to prevent septic shock, fluid and electrolyte imbalance, and loss of airway patency. Although *B. anthracis* can be expected to be highly sensitive to penicillin, being cheap and readily available in most of the world, penicillin should not be used as monotherapy, because the strain implicated in the most recent outbreak, as well as multiple historical strains, produces an inducible β-lactamase [67–72]. *B. anthracis* may appear highly susceptible to penicillin in vitro but in patients with high microbial load, as with inhalational anthrax, penicillin therapy might induce the β-lactamase and result in penicillin resistance in vivo [46,71,72]. Also, there are published reports that *B.anthracis* can be resistant to penicillins [69,70,73]. Therefore ciprofloxacin (400 mg intravenously twice daily) and possibly other quinolones or doxycycline (200 mg intravenously twice daily) should be used for initial therapy until antimicrobial susceptibility and β-lactamase test results are known [4,46, 48,74] (Table 3). This is important, since penicillin is still frequently cited in textbooks and antibiotic pocket-guides as first-line treatment of choice for anthrax infections. Ciprofloxacin also has some practical and theoretical advantages, in that similar peak serum levels can be obtained with oral and intravenous dosing, and it has a wide volume of distribution. Recommendations for antibiotic therapy of inhalational anthrax include use of ciprofloxacin or doxycycline with combination therapy, which includes 1 of these 2 antibiotics plus 1–2 additional antibiotics that are known to be active *in vitro* against *B. anthracis* [68,75]. Other agents with in vitro activity against *B. anthracis* include rifampicin, vancomycin, imipenem, chloramphenicol, aminoglycosides, penicillin, ampicillin, clindamycin and clarithromycin [45, 76]. It is resistant to cefuroxime, extended spectrum cephalosporins such as cefotaxime and ceftazidime, aztreonam, trimethoprim and sulfamethoxazole. Penicillin is recommended as a combination therapy with either ciprofloxacin or doxycycline [45,46,74,77].

The approach to therapy is guided, in part, by whether the disease is naturally occurring or related to a bioterrorist attack. The duration of treatment for inhalational anthrax should be 60 days [46,48,74]. For cutaneous anthrax, treatment should continue for 60 days in the context of bioterrorism, as opposed to 7 to 10 days in

Table 3. Anthrax treatment protocol.

	Therapy	Description
Pulmonary anthrax	Initial therapy	Ciprofloxacin i.v.[1] or doxycycline i.v.[1] plus 1–2 additional antibiotics[2]
	Prolonged therapy[3]	Switch to oral antimicrobial therapy when the patient is clinically stable (Ciprofloxacin p.o.[4] or doxycycline p.o.[4]) Continue for 60 days (IV and oral combined)
Cutaneous anthrax	Initial therapy	Ciprofloxacin i.v.[1] or doxycycline i.v.[1] plus 1–2 additional antibiotics[2] (Systemic involvement, extensive edema, lesions of head and neck) Ciprofloxacin p.o.[4] or doxycycline p.o.[4] (Localized disease without complication)
	Prolonged therapy[2]	Continue for 7–10 days in naturally acquired disease Continue for 60 days in the context of bioterrorism
Other forms	Initial therapy	Treat as inhalational anthrax
	Prolonged therapy[3]	

Treatment of pregnant women and immunocompromised persons is the same for nonpregnant and nonimmunocompromised persons.

[1] – Dosage for adults: Ciprofloxacin 400 mg q12h, Doxycycline 100 mg q12h, Dosage for children: Ciprofloxacin 10–15 mg/kg q12h (Ciprofloxacin dose should not exceed 1 g per day in children), Doxycycline: >8 years and >45 kg:100 mg q12h, >8 years and ⩽45 kg: 2.2 mg/kg q12h, ⩽8 years: 2.2 mg/kg q12h;

[2] – Other agents with in vitro activity against *B. anthracis* includes rifampisin, vancomycin, imipenem, chloramphenicol, aminoglycosides, penicillin, ampicillin, clindamycin and clarithromycin;

[3] – Antimicrobial susceptibility and β-lactamase test results should be taken under consideration. In case the isolate is susceptible to penicillin and is a non β-lactamase producer, penicillin is a cheap and effective agent for prolonged therapy;

[4] – Dosage for adults: Ciprofloxacin 500 mg q12h, Doxycycline 100 mg q12h Dosage for children: Ciprofloxacin 10–15 mg/kg q12h (Ciprofloxacin dose should not exceed 1 g per day in children), Doxycycline: >8 years and >45 kg: 100 mg q12h, >8 years and ⩽45 kg: 2.2 mg/kg q12h, ⩽8 years: 2.2 mg/kg q12h

Table 4. Recommendations for Anthrax prophylaxis.

Category	Therapy	Duration
Adults (including pregnant women and immunocompromised persons)	Ciprofloxacin, 500 mg p.o. q12h or doxycycline, 100 mg orally twice daily	60 days
Children	Ciprofloxacin 10–15 mg/kg p.o. q12h or doxycycline: >8 years and >45 kg: 100 mg p.o. q12h, >8 years and ⩽45 kg: 2.2 mg/kg p.o. q12h, ⩽8 years: 2.2 mg/kg p.o. q12h	60 days

naturally acquired disease [39,46,78] (Table 3). Therapy with a multidrug regimen is recommended if signs of systemic involvement, extensive edema, or lesions on the head and neck are present. For gastrointestinal and oropharyngeal anthrax, the same regimens used for inhalational anthrax is recommended [4,74]. Corticosteroid therapy should be considered for patients with inhalational anthrax associated with meningitis or for patients who have severe extensive edema [68]. If meningitis is suspected doxycycline may be less optimal because of poor central nervous system penetration.

Prevention and post-exposure prophylaxis

The best measure to eliminate human anthrax is control in domestic animals by effective surveillance and by immunization of animals in endemic areas. Prevention of anthrax is possible by immunization of persons at high risk with a cell-free vaccine prepared from protective antigen from an attenuated, nonencapsulated strain of *B. anthracis* absorbed to aluminium hydroxide gel [79,80]. The vaccine is administered at 0, 2 and 4 weeks and again at 6,12, and 18 months. Annual boosters are necessary to maintain immunity. No serious adverse events related to its use have been reported [81,82].

If a biological warfare attack is threatened or may have occurred, prophylaxis of unimmunized persons is recommended [48,75,83]. Post-exposure prophylaxis is indicated to prevent inhalational anthrax after a confirmed or suspected exposure to anthrax aerosol. When the antimicrobial susceptibility of the implicated strain of *B. anthracis* is unknown, initial therapy with ciprofloxacin or doxycycline is recommended for post-exposure prophylaxis [46,48]. The recommended dosage of ciprofloxacin is 500 mg orally, twice a day, and 100 mg orally twice a day for doxycycline [46,48] (Table 4). It is possible that other quinolones with a similar spectrum of activity would have similar success in prevention and treatment. Penicillin or amoxycillin should be substituted for prolonged treatment course in patients with a contraindication to ciprofloxacin or doxycycline, including children, pregnant women, and lactating women, in case the given strain of *B. anthracis* is susceptible. Should an anthrax attack be confirmed, chemoprophylaxis should be continued for at least 60 days [45,75,84].

Anthrax as a bioterrorist weapon

In considering bioterrorism agents, one characteristic that perpetrators look for is an agent known for causing morbidity, possible mortality, and perhaps a disease that

is difficult to diagnose and to treat. Other qualities include accessibility, short incubation period, reproducibility, stability, and dispersibility.

Anthrax is classified as a category A biological weapon (most dangerous, along with smallpox, plague, tularemia, *Clostridium Botulinum* toxins, filovoviruses and arenaviruses) [85].

The attractiveness of anthrax as a bioweapon was recognized by scientists very early. In 1915, attempts were purportedly made by German secret agents against the allies. In 1937, Japan used *B. anthracis* as a biowarfare weapon against the Chinese. Other countries, specifically the USA, the UK, and the Soviet Union, also started developing *B. anthracis* as a weapon before and during World War II, but ultimately did not utilize biological weapons. More recently, Iraq has been implicated as having an active biological warfare program, utilizing a number of agents, including *B. anthracis* [15].

The most recent bioterrorist attack took place shortly after the attack on the World Trade Center and the Pentagon on 11 September 2001, when four or five letters containing spores of *B. anthracis* were sent to media companies and politicians in various parts of the USA. As a result, 11 persons contracted pulmonary anthrax, and another seven the cutaneus form of the infection. Five of those with pulmonary anthrax died [46,75,86].

B. anthracis has many biological, technical and virulence characteristics that make it attractive as a bioweapon. *B. anthracis* is relatively easily obtained from a variety of sources. Once obtained, it is relatively easy to grow and process. The weaponized agent can be easily stored after production. It can be prepared with minimal technology, and, as the recent outrage has shown, it is easily delivered and engenders great public panic. When used as a weapon of mass destruction, the agent is dispersed in particles less than 5μm in diameter, a size that allows penetration into the pulmonary alveoli. Aerosol dispersion can expose the greatest number of people over time. The World Health Organization estimated that 50 kg of weapon-grade anthrax spores released by an aircraft over an urban population of 5 million would result in 250,000 cases of predominantly inhalational anthrax. The economic impact was estimated at $26.2 billion per 100,000 persons exposed. This of course does not take into account the public panic; paralysis of transport, social, and economic activities; and the add-on costs of loss of activity of valuable antimicrobial agents [4].

Conclusions

Anthrax, a disease of mammals and humans, is caused by a spore-forming bacterium called *B. anthracis*. Herbivores, the natural hosts, become infected by consuming the soil and humans are incidentally infected by coming into contact with infected animals or their products. In its spore form it can persist in nature for prolonged periods, possibly years. The distribution of anthrax is worldwide. The three virulence factors of *B. anthracis* are edema toxin, lethal toxin and capsular antigen. The incidence of anthrax has decreased in developed countries, but it remains a considerable health problem in developing countries.

The disease occurs primarily in three forms: cutaneous, respiratory, and gastrointestinal. If untreated, anthrax in all forms can lead to septicemia and death. Early treatment of all forms is important for recovery. *B. anthracis* has also been exploited as a biological warfare agent, and concern exists that it could be used as biological agent by terrorists. Post-exposure prophylaxis is indicated to prevent inhalational anthrax, and therapy with ciprofloxacin or doxycycline is recommended for adults and children for 60 days. The same agents are also advocated for the treatment of anthrax. Understanding the epidemiologic, pathophysiologic and bioterrorism principles of anthrax are the clinician's best means of early detection and appropriate treatment of cases.

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