Journal of Bioterrorism & Biodefense

Expert Review Open Access

A Review of the Current Status of Anthrax Medical Countermeasures

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Abstract

Anthrax, the disease resulting from infection with the zoonotic bacterium Bacillus anthracis, has a high potential for use as an agent of biological terrorism and warfare, and has in fact been used for both. Given its relative high mortality rate in untreated humans, effective medical treatments and prophylactics are essential. This brief review will summarize the current state of medical countermeasures (MCM) for treating individuals exposed to anthrax as well as preventing the disease from manifesting.

Keywords: Anthrax; Vaccine; Monoclonal antibodies; Bioterrorism

Introduction

Background on Anthrax

The disease anthrax results from infection with the zoonotic, aerobic, gram-negative, endospore-forming bacterium *Bacillus anthracis*. Anthrax occurs primarily as cutaneous, gastrointestinal, and inhalational forms [1]. The cutaneous form is the most common natural infection (approximately 95% of human cases) and usually results from exposure to animals or animal products. Gastrointestinal anthrax is very rare, and inhalational anthrax accounts for approximately 5% of human cases. More recently, the much less common injection anthrax and welder's anthrax forms have been described [2].

Inhalational infection with B. anthracis occurs via introduction of the spores, followed by germination into the vegetative form of the bacterium which produces several characteristic toxins. The initial presentation (Stage I) of infection is characterized by nonspecific flu-like symptoms which last hours to days. Lacking treatment during Stage I, the disease progresses to a fulminant form of infection (Stage II) which is associated with fever, dyspnea, diaphoresis, massive lymphadenopathy, and stridor [3]. Chest X-rays at this stage show mediastinal widening (characteristic) and pleural effusion. Individuals with Stage II disease are unlikely to recover, with death resulting from massive organ failure [4].

B. anthracis produces three polypeptides which combine in binary form to produce lethal toxin (LT) or edema toxin (ET); the genes encoding all three antigens are found on the pXO1 plasmid. These toxins are responsible for the symptoms and lethality of anthrax. Protective antigen (PA) is the receptor binding component of both LT and ET and is responsible for delivery of these toxin complexes into the target cell. LT is a zinc metalloproteinase that cleaves the N-terminus of several mitogen-activated protein kinase kinases, and which induces an atypical vascular collapse (not endotoxin shock). ET is a calmodulin-dependent adenylate cyclase that affects many different cell-signaling pathways and is associated with hemorrhaging lesions in many organs [5]. The endospores of B. anthracis are extremely resistant to environmental degradation; this property, coupled with the rapidly virulent nature of the inhalational form of the disease as well as the initial non-specific signs which might be confused with less severe conditions, makes anthrax a near-ideal biological weapon (Goel, 2015). Consequently, anthrax has been utilized as a weapon or an agent of terrorism for several years and was a component of the biological warfare arsenals of multiple countries [6].

Anthrax medical countermeasures

Given the obvious importance of preventing and treating anthrax infections to human health and national security, a robust armamentarium of MCM to prevent and treat anthrax is necessary [7-10]. Also, the unique biology of *B. anthracis* (spore formation, elucidation of toxins, etc.) necessitates the use of multiple countermeasures, usually in some combination. Anthrax MCM can be roughly grouped into those that control the infection itself (generally antibiotics), those that prevent infection (vaccines) and those that prevent or mitigate the effects of the toxins (small molecule inhibitors, polyclonal antibodies, and monoclonal antibodies). We will briefly explore each of these in the following sections.

Antibiotics

Antibiotics are small molecule drugs used to treat bacterial infections and which work via several different mechanisms. Like most bacteria, B. anthracis is susceptible to select antibiotics. Four antibiotics are FDA-approved for use for PEP following exposure to aerosolized spores of B. anthracis: doxycycline, ciprofloxacin, levofloxacin, and parenteral procaine penicillin G. All these antibiotics were approved using animal data only since controlled exposure studies in humans are (obviously) unacceptable. For adults who have potentially been exposed to aerosolized spores of B. anthracis, the Centers for Disease Control and Prevention (CDC) recommends either ciprofloxacin (200-400 mg intravenously every 12 hours followed by 500-750 mg by mouth every 12 hours for up to 60 days post-exposure) or doxycycline (100 mg intravenously or by mouth every 12 hours for 60 days post- exposure), plus anthrax vaccine beginning as soon as possible following exposure. (Note that the extended duration of treatment with antibiotics is due to the durable anthrax spores, which can continue to germinate *in vivo* for an extended period.) Levofloxacin is recommended as a second-line agent since safety data are limited for its use in treatment for longer than 28 days. For children, ciprofloxacin or doxycycline also are used for first-line antimicrobial post-exposure prophylaxis (PEP). Because of the potential for serious adverse events, however, CDC recommends off-

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Received: 03-July-2023, Manuscript No. jbtbd-23-105474; **Editor assigned:** 05-July-2023, PreQC No. jbtbd-23-105474 (PQ); **Reviewed:** 20-July-2023, QC No. jbtbd-23-105474; **Revised:** 24-July-2023, Manuscript No. jbtbd-23-105474 (R); **Published:** 31-July-2023, DOI: 10.4172/2157-2526.1000338

Citation: House RV (2023) A Review of the Current Status of Anthrax Medical Countermeasures . J Bioterr Biodef, 14: 338.

label use of amoxicillin as the preferred PEP agent if the anthrax strain is proven to be susceptible to that drug (Committee on Prepositioned Medical Countermeasures for the Public; Institute of Medicine, 2011). Since strains of anthrax have demonstrated resistance to these approved drugs, several other antibiotics are under investigation as potential MCM including moxifloxacin, linezolid, meropenem, and cyclic lipopeptides such as daptomycin; to date, none of these antibiotics have been approved by the FDA for treatment or PEP of anthrax [11].

Vaccines

While antibiotics represent the first line of MCM response to anthrax, their use is reactive rather than proactive; to adequately prepare for potential large-scale events involving anthrax dissemination, vaccines are required. Although anthrax had been used offensively in the past, following the so-called "Amerithrax" event of 2001, there was a renewed interest in developing and approving anthrax vaccines for the general population [12-13]. Currently, there are only two anthrax vaccines being administered in the West, namely Anthrax Vaccine Absorbed (AVA) which is approved in the United States and Anthrax Vaccine Precipitated (AVP) which is approved in the UK (Clark and Wolfe, 2020), although multiple investigators are evaluating additional anthrax vaccine candidates [14-15]. In addition, a modification of the AVA vaccine, Anthrax Vaccine Absorbed, Adjuvanted (AV7909) is in advanced development. These vaccines are described briefly below.

Anthrax vaccine absorbed (AVA; BioThrax®), emergent bio solutions

The only anthrax vaccine currently licensed in the US is AVA, more commonly known as BioThrax. It is manufactured as a cell-free filtrate from the culture of an avirulent, nonencapsulated strain of *B. anthracis* which are grown in a protein-free medium. This filtrate contains PA as well as other proteins; the mechanism of action is to induce the production of antibodies against the PA. Although antibodies against ET and LT may be induced, this has not been characterized. It is licensed for preexposure prophylaxis for adults aged 18–65 years; the approved dosage is 0.5 mL administered intramuscularly (IM) at 0, 1, and 6 months with boosters at 6 and 12 months after completion of the primary series and at 12-month intervals afterwards. AVA also is licensed for post exposure prophylaxis in combination with antibiotics for adults aged 18–65 years; the approved dosage for this indication is 0.5 mL administered subcutaneously (SC) at 0, 2, and 4 weeks [16]. BioThrax® was the first vaccine approved under the FDA's Animal Rule in November of 2015 [17-18].

Anthrax vaccine precipitated (AVP)

AVP comprises a cell-free filtrate of the acapsular, toxigenic *B. anthracis* Sterne 34F2 strain that is precipitated with alum [19]. AVP was developed at the Centre for Applied Microbiology and Research at Porton Down, and a UK product license was granted in 1979 [20]. The vaccine is manufactured by Porton Biopharma Ltd, UK. Unlike AVA, AVP contains all three toxin components, with roughly 7.9 μg/ml PA, 1.9 μg/ml LF, and detectable amounts of EF. It is administered via four intramuscular doses, administered at 0, 3, 6, and 32 weeks, with annual boosters [21].

Anthrax vaccine adsorbed, adjuvanted (AV7909; NuThrax™), emergent bio solutions

AV7909 contains AVA bulk drug substance as a source of PA immunogen, aluminum hydroxide, and the Toll-like Receptor 9 (TLR9) agonist CPG 7909 [22]. It is being developed as a post-exposure prophylactic for a two-dose regimen, combined with antibiotics [23]. The CDC has submitted a pre–Emergency Use Authorization request to FDA to allow potential emergency use of AV7909; under the proposed EUA, AV7909 would be administered IM as two-dose series two weeks apart in conjunction with post-exposure antibiotics for adults aged 18–65 years [24]. Although this vaccine represents an improvement over AVA by decreasing the dosing schedule from three to two administrations, it is important to note that HHS has stated "Moving forward, BARDA will only invest in anthrax vaccine candidates that offer substantial improvements to concepts of operations for use of the vaccine. This would include those candidates that offer potential protection in a single dose. Emergent announced on September 30, 2021, that it had entered a contract with the US Government for development and procurement of AV7909, with a value of $399 million. AV7909 is intended to eventually replace AVA in the SNS. The Biologics License Application for AV7909 is currently under review by the FDA.

Antitoxins

Implicit in the term, antitoxins are MCM that focus on neutralizing the anthrax toxins directly, rather than being directed toward control of the infection. As noted previously, whereas antibiotics have been demonstrated to be effective for treating the infectious component of anthrax (that is, growth and survival of the bacterium), it is crucial to note that they are effective only at controlling the growth of the vegetative form of the bacterium itself and are not effective against the toxins (including PA). This is of particular importance when considering antibiotic-resistant forms of B. anthracis. Multidrug antibiotic resistance in naturally occurring B. anthracis infection has been reported in epidemiological samples [25]. In addition, Athamna et al. (2004) demonstrated that B. anthracis could readily acquire antibiotic resistance in vitro; suggesting that engineering this characteristic in weaponized anthrax would be relatively straightforward.

The CDC has recommended use of approved anthrax antitoxins in combination with antibiotics for treatment of inhalational anthrax [26]. Although initially the guidance was qualitative and no time windows for treatment were provided. Rubinson et al. (2017) sought to better understand define the critical period from anthrax exposure to successful treatment. The results indicated that administration of an antitoxin (in this case, Raxibacumab) concurrent with the initial dose of antibiotic would be expected to be beneficial if treatment was initiated within 7 days post spore exposure for ≥80% of subjects. These simulations also predicted that after 7 days an increasing number of subjects (and after 9 days most exposed individuals) would have inadequate toxin neutralization and would succumb to severe illness. Importantly, Rubinson et al. summarized their work: Our study suggests that intervention with antibiotic alone within 4 days after spore exposure is sufficient for survival for nearly all persons, and that use of anti-toxin together with antimicrobials extends this treatment window if administered within the first week. At later intervention times, the combination of antimicrobials with anti-toxin would not provide complete protection for all subjects. When it is not possible to utilize antimicrobials in combination with anti-toxin (e.g., an antibiotic-resistant strain), anti-toxin monotherapy within 6 days post spore exposure should neutralize toxin and promote survival of the patient's immune cells, allowing their immune system to prevent an infection from becoming established (emphasis added). Broadly speaking, antitoxins currently include 1) small molecule inhibitors of anthrax toxin activity and 2) passive immunization with antibodies. These are detailed below.

Small molecule inhibitors of anthrax toxin

Small molecule inhibitors of anthrax toxin have been under

development for several years; however, they are all still in early development and none have been approved for human use. Whereas many/most MCM for anthrax focus on PA, some investigators believe that this is short-sighted since the interaction of LT and ET are multifaceted. Accordingly, investigators are evaluating a wide variety of target including – but not limited to - inhibitors of binding domains on anthrax toxin receptors (TEM8 or CMG2), inhibitors of furin PA_{83} cleavage, inhibitors of PA_{63} oligomerization and prepore formation, inhibitors of LF and EF attachment to the PA oligomer, inhibitors of endosomal pore formation and translocation of LF and EF, and inhibitors of the intracellular enzymatic effects of LF [27, 28].

Passive immunization

Passive immunization, also referred to (somewhat inaccurately) as "instant immunity" refers to protection against/treatment of infection by administering pre-formed antibody specific for antigens associated with the infection [29]. Passive immunization has the advantage of providing rapid (although perhaps not "instant") neutralization of the antigen of interest as compared with vaccination, which usually requires weeks to become fully protective. Moreover, as the antibodies are cleared from circulation this protection wanes until protection is no longer afforded to the host. Passive immunization may be mediated by either polyclonal antibodies or monoclonal antibodies. In 2015 the Centers for Disease Control and Prevention (CDC) conducted a review of the literature regarding the use of MCM in an anthrax mass casualty incident [30]. The use of antitoxins as part of a mass casualty event featured prominently in this review, particularly how they would be prioritized if required.

Polyclonal antibodies (pAb)

The term "polyclonal" refers to antibodies derived from multiple lineages of B-cells, as happens when humans are exposed to either single or multiple epitopes of a specific antigen (such as PA). They are made up primarily of IgG subclasses and may have differing affinities for the target antigen. Polyclonal antibodies used as therapeutics may be derived from various sources including convalescent serum from humans recovering from disease, hyperimmune serum from humans, serum from hyperimmunized animals, and serum from humanized animals. Although treatment with pAb is generally safe, treatment-related side effects are not uncommon (including flu-like symptoms, dermatological reactions, arrythmia, transfusion-related lung injury, renal impairment, hemolysis/neutropenia and electrolyte imbalance) but these reactions can usually be prevented or mediated by the rate of infusion.

Polyclonal antibodies for anthrax remain a viable MCM [31]. And one product, Anthrax Immune Globulin Intravenous has been approved for use in humans.

Anthrax immune globulin intravenous (AIGIV; Anthrasil®; Anthravig), emergent bio solutions

Anthrasil® is purified human polyclonal anti-PA IgG derived from the plasma of humans immunized with AVA [32]. AIGIV has the advantage of its composition reflecting a natural immune response and therefore likely able to induce a wide variety of immune effector mechanisms in the recipient. However, PAB have certain disadvantages, such as the limited availability of donor blood, batch-to-batch variation, and the risk of infectious disease transmission and the high cost of production [33]. AIGIV was approved by the FDA in March of 2015. To date, it is the only anthrax therapeutic that has been administered to humans with clinical anthrax [34]; however, the study was not controlled, and the patients had the relatively rare injectional form of anthrax. Interestingly, nonclinical (animal) studies have demonstrated that pre-administration of AIGIV suppresses the serum response to AVA, suggesting some form of immunological interference or modulation [35]. It is unknown if this interference would be true for mAb antitoxins (see below) but warrants future investigation.

Monoclonal Antibodies (mAbs)

Unlike pAbs which represent a wide diversity of specificities, mAbs are clonally derived from single B-cells and as such exhibit very high specificity for single (or an extremely limited number of) antigens. mAbs are generally considered to be superior to pAb due to their controlled manufacturing procedures and their reproducible affinity for specific target antigens. mAbs are imminently adaptable to protein engineering and recent advances in mAb technology allow the ability to exquisitely define antigen-antibody interactions, immune function enhancement, etc. [36-38]. Although several mAbs have been are being developed for treatment of anthrax [39]. Only two have been approved; namely, Raxibacumab and Obiltoxaximab, which are described below.

Raxibacumab (alternatively, ABthrax), emergent bio solutions

Raxibacumab is a recombinant fully human IgG1λ mAb that binds PA; it is produced by human scFv phage display library technology. It has a molecular weight of approximately 146 kDa [40]. It was originally developed by Human Genome Science/GlaxoSmithKline (GSK) and acquired by Emergent Biosolutions in 2017. Raxibacumab was the first anthrax antitoxin to be approved using the FDA Animal Rule (December 2012). It was approved for the treatment of adult and pediatric patients with inhalational anthrax in combination with appropriate antibiotics and for prophylaxis of inhalational anthrax when alternative therapies are not available or not appropriate [41]. Raxibacumab is administered as a single dose of 40 mg/kg as an infusion over 2 hours and 15 minutes In 2013 GSK was awarded a five-year, $196M BARDA contract to supply 60,000 doses of Raxibacumab to the US Government this contract was taken on by Emergent Biosolutions when they purchased the assets from GSK. Raxibacumab is included in the Strategic National Stockpile (SNS).

Obiltoxaximab (ETI-204, Anthim®), Elusys therapeutics, Inc.

Obiltoxaximab is a humanized and affinity-enhanced (deimmunized) mAb used for prevention and treatment of anthrax [42,43]. It is produced by hybridoma technology and is a chimeric IgG1 kappa mAb binding PA; it has an approximate molecular weight of 148 kDa [44]. The approved therapeutic dose of Obiltoxaximab is 16 mg/kg administered intravenously, which was extrapolated from animal studies demonstrating efficacy [44]. It was originally developed by Elusys Therapeutics, Inc. and was acquired by Heat (subsequently Nighthawk Biosciences) in 2022. Intravenous Obiltoxaximab was approved in the USA for the treatment (in combination with appropriate antibacterial drugs) and prophylaxis of inhalational anthrax in March of 2016 [45]. And marketing authorization valid throughout the European Union was issued on November 18, 2020.

In January of 2022, Heat Biologics announced the award of a contract with the Department of Health and Human Services to supply Obiltoxaximab to the US Strategic National Stockpile. The contract consists of a base period of performance, valued at $50 million, which has been fulfilled. The contract also includes options valued up to $31 million; if all options are exercised, the total contract value will be $80,864,000 with completion of the contract expected by the first half

of 2023. Obiltoxaximab is supplied to the SNS in the US. In addition, in April 2022 Heat Biologics announced that it had finalized a contract with the Canadian government to deliver ANTHIM® to Canada's National Emergency Strategic Stockpile under a procurement contract totaling CAD $7.9 million.

At present, Raxibacumab and Obiltoxaximab are the only mAbs approved for treatment and PEP of anthrax and are likely to remain so. In 2021 a Justification and Approval for Other Than Full and Open Competition stated: "FDA does not anticipate another product entering the market in the next 5-10 years as there is no market outside of the USG for such which dissuades vendors from investing hundreds of millions of dollars with no potential return." The justification further states: "Due to the expense and intensive time investments needed to bring a new anthrax antitoxin to market, it is not anticipated that the USG will invest in the creation of an additional anthrax antitoxin in the near future." [Award of Anthim (Obiltoxaximab) 600mg/6ml for Injection (Accessed from SAM.GOV Oct 24, 2022. Although both mAbs have been approved by the FDA using the Animal Rule (and Obiltoxaximab was approved by the European Union), neither has been used to treat inhalational anthrax following human exposure. Studies are ongoing by various investigators to further elucidate the full effectiveness of these MCM [46-48].

Anticipated ongoing and future investments in MCM for anthrax

United States

Barda

In May of 2022, BARDA published its Strategic Plan 2022-2026: Fortifying the Nation's Health Security. Although this Strategic Plan lays out a wide-ranging series of goals for BARDA, there is sparce mention of acquisition of MCM, including those for anthrax. However, the Department of Health and Human Services' 2022 Justification of Estimates for Appropriations Committee included line items for Anthrax ($10 million), stating that "FY 2022 funding will support assessment of delivery approaches that may enable a next-generation anthrax vaccine that can provide protection after a single dose." Additionally, a line item for Anthrax Antitoxins ($1 million) was included to "support ongoing analytical studies designed to evaluate extended stability of existing anthrax antitoxins.

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Strategic national stockpile (SNS)

In 1998 Congress appropriated funds for the CDC to acquire a stockpile of vaccines and pharmaceuticals to address biological and chemical threats. The program was originally called the National Pharmaceutical Stockpile (NPS) program; however, as the program evolved to include additional medical and emergency supplies, on March 1, 2003, it was renamed the Strategic National Stockpile (SNS). The program is currently overseen by HHS/ASPR.

The SNS contains multiple products for preventing and treating anthrax; in fact, from fiscal years 2015 through 2021, HHS obligated nearly $2.3B (approximately 50% of the total allocated for the SNS) specifically for anthrax MCM. (Smallpox MCM was second at $1.1B or 24% of the total.) In 2022 the US Government Accountability Office conducted an assessment of the SNS and their reviews shows the SNS "contained most medical countermeasure types recommended, but often not in the recommended quantities. HHS officials noted that gaps in quantities are due to budget constraints and acknowledge these gaps present risks" [PUBLIC HEALTH PREPAREDNESS HHS Should Address Strategic National Stockpile Requirements and Inventory Risks. Accessed Oct 21, 2022. It was unclear from the report if anthrax-specific MCM recommended quantities were deficient, although this seems unlikely.

Of note here is the Department of Health and Human Services Fiscal Year 2023 Public Health and Social Services Emergency Fund Justification of Estimates for Appropriations Committee, which references the SNS. Specifically, the budget justification includes $975 million for the SNS to procure products transitioning from Project Bio Shield support and prioritizes funding for sustainment of current product lines and procurement of several products previously supported by BARDA that lack a significant commercial market. These items include procurement of sufficient quantities of a domestically manufactured, FDA approved, smallpox antiviral, procurement enough bandages to treat an estimated 14,000 people impacted by a radiological/nuclear incident, and limited quantities of anthrax therapeutics.

Non-US

Canada

The National Emergency Strategic Stockpile in Canada is managed by the Public Health Agency of Canada. Among its assets are pharmaceuticals and vaccines for various infectious disease emergencies, including medicines for anthrax. As with the SNS in the US, details of specific requirements are not publicly available, although as previously noted Obiltoxaximab has been purchased for the NESS.

European Union

The European Health Emergency Preparedness and Response Authority (HERA) is a European equivalent to BARDA in the US. HERA's objective is "to strengthen Europe's ability to prevent, detect, and respond rapidly to cross-border health emergencies by ensuring the development, manufacturing, procurement, and equitable distribution of key medical countermeasures when a health emergency hits." HERA was launched by the European Commission in September 2021 in response to feedback that the EU had failed to match the US in terms of response to COVID-19 and was adopted by the EU on October 24, 2022. The HERA Work plan 2022 proposes 1.3 B € to address current and expected infectious disease emergencies, of which almost 700 M € would be earmarked for acquisition/stockpiling of medical countermeasures, although the types and quantities are not specified.

Other considerations

It is unquestionable that anthrax will remain a bioterrorism/biowarfare threat, likely indefinitely. Accordingly, the requirement for effective and readily available MCM is unlikely to diminish. As described earlier in this review, antibiotics will almost certainly be a necessary component of treatment for control of the bacterial infection, with an understanding that *B. anthracis* may at some point evolve antibiotic resistance [49]. However, antibiotics alone are insufficient to treat anthrax once the bacterium has expressed its characteristic toxins. Thus, a combination of antibiotics/antimicrobials and antitoxins will be the most effective approach, particularly in a mass casualty situation [50]. Moreover, the antitoxin of choice should be a monoclonal antibody due to considerations of source material, consistency, ease of manufacturing, and costs.

Unfortunately, due to industry consolidations and the lack of a commercial market for most MCM, bottlenecks can occur. For example, according to a report by the Mitre Corporation Consolidation of many important assets into a single or small handful of companies creates substantial risk since it creates the potential for a single-point of failur.

In addition, as the COVID-19 pandemic demonstrated, disruptions in the supply chain and issues with manufacturing can have profound effects on the availability of MCM when most needed [51].

In a third quarter Earnings Call in November of 2021; Emergent announced that it had reached mutual agreement with BARDA to terminate the Center for Innovation and Advanced Development and Manufacturing (CIADM) contract which was awarded in 2012. Further, in a March 29, 2022, Earnings Call they stated their intent to technology transfer Raxibacumab manufacturing to their Bay view facility, but that the COVID-19 pandemic had "put those plans on hold [52]. There is currently no open-source information available on when EBSI intends to restart production of Raxibacumab. The uncertainty in supply was cited in a Justification and Approval for Other Than Full and Open Competition for awarding a Obiltoxaximab contract in which the US Government stated: "This situation makes it even more critical to not only award this contract to Elusys to maintain the SNS stockpile inventory but also to maintain Elusys as it is currently the only operational business in the anthrax antitoxin industrial base. Award of Anthim (obiltoxaximab) 600mg/6ml for Injection (Accessed from SAM.GOV Oct 24, 2022. The importance of having a reliable source of anti-anthrax monoclonal antibody antitoxin cannot be overstated, and the dependability of supply chain should be of paramount importance to US and foreign governments to protect their citizens against the ongoing and likely perpetual threat of anthrax.

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