Supplementary Material: Evidence Base Linking Anthrax Postexposure Prophylaxis and Treatment Recommendations to Data

Recommendation	Evidence
Tables of Preferred Antimicrobials and Antitoxins	
Tables of preferred (i.e., first-line) and alternative antimicrobials for adults, children, and pregnant persons are provided.	The recommended antimicrobials are preferentially ordered based on: 1) in vitro effectiveness against *B. anthracis* (1), 2) in vivo efficacy against *B. anthracis* exposures as demonstrated by odds ratios and confidence intervals for survival compared to no therapy or therapy with positive control (*2*), 3) the animal model used to generate efficacy data (nonhuman primate or rabbit models were preferred over mouse, guinea pig, or hamster models), 4) treatment outcomes for published human cases (*3*), 5) percent of patients expected to achieve microbiologic CSF cure at recommended antimicrobial dosing based on Monte Carlo simulation, 6) safety profiles of the antimicrobials (*4*), 7) logistical considerations (e.g., available formulations [including availability and palatability of liquid formulations], dosing intervals, cost, supply/availability patterns), and 8) expert opinion. Some antimicrobials are included for PEPAbx or treatment based on class efficacy (e.g., levofloxacin, moxifloxacin, ofloxacin) or for treatment based on demonstrated PEPAbx efficacy (e.g., minocycline).
Postexposure Prophylaxis	
Antimicrobial postexposure prophylaxis should be provided to persons exposed to *B. anthracis* by inhalation, ingestion, or cutaneous routes.	Meta-analyses and most individual animal studies that could not be combined into any of the meta-analyses showed a survival benefit for PEPAbx compared with no PEPAbx for ciprofloxacin, amoxicillin, amoxicillin/clavulanate (two of three studies), dalbavancin, oritavancin, daptomycin, doxycycline, minocycline, omadacycline, tetracycline, and imipenem. For the macrolide class, one of four studies showed a benefit (i.e., azithromycin) (*2*). In a human observational study conducted in the former Soviet Union, persons exposed to anthrax-affected animals were given PEPAbx. After exposure, 17% of 339 persons who did not receive PEPAbx developed anthrax. In contrast, only 1.7% of 287 persons who received a short course (i.e., 3 days) of PEPAbx developed anthrax ($p < 0.001$). Following this finding, when various antimicrobial postexposure prophylaxis (PEPAbx) regimens were

	used in 407 persons exposed to *B. anthracis*, none developed anthrax (*5*).
Treatment of Localized Cutaneous Anthrax	
Antimicrobial monotherapy may be used for treatment of localized cutaneous anthrax. Penicillin may be used as monotherapy if susceptibilities are known.	Of 605 patients hospitalized for anthrax, monotherapy, including penicillin monotherapy, resulted in high survival (98%) for adults with localized cutaneous anthrax (*3*).
Treatment of Systemic Cutaneous Anthrax Without Meningitis	
In patients who lack signs and symptoms of meningitis, systemic cutaneous anthrax may be treated like localized cutaneous anthrax.	For adults with systemic cutaneous anthrax without meningitis, survivorship was high if they received any treatment; only 1 patient in this category died. Survival with penicillin monotherapy was 89% for those with systemic illness without meningitis (*3*).
Treatment of Noncutaneous Systemic Anthrax	
Bactericidal antimicrobials are preferred over protein synthesis inhibitors (PSI) for the treatment of systemic anthrax, regardless of meningitis status.	After controlling for shock and altered mental status, odds of survival in systemically ill patients with anthrax were higher with bactericidal antimicrobial(s) alone than PSIs alone ($p < 0.05$) (*3*).
Noncutaneous systemic anthrax should be treated with one or more bactericidal antimicrobials, with or without a PSI.	For adults with systemic anthrax without meningitis, survivorship generally exceeded 70% if they received ≥1 antimicrobials with or without antitoxin/antiserum. PSIs by themselves had the lowest survival (64%). Most (82%) adults survived if given combinations with ≥1 bactericidal and ≥1 PSI antimicrobials (*3*).
Until meningitis is considered unlikely, patients with systemic anthrax, including those with inhalation anthrax, should be treated with two bactericidal agents plus a PSI or RNA synthesis inhibitor.	Meningitis complicates at least 33% of inhalation anthrax cases (*3*).For anthrax meningitis, neither antimicrobial monotherapy nor combination therapy were particularly effective (3/14 [21%] vs 3/18 [17%], respectively). However, they were more effective than no therapy. While there are no data to support three antimicrobials for treatment of anthrax meningitis, expert opinion is to use at least three different antimicrobial classes with activity against *B. anthracis.*
If meningitis is considered unlikely, inhalation anthrax may be treated with a single bactericidal agent in combination with a PSI, another bactericidal agent, or an RNA synthesis inhibitor.	Adults with inhalation anthrax lacking meningitis fared poorly with monotherapy: only 17% (1 of 6) survived compared to 70% (7 of 10) with combination therapy (*3*). Bactericidal agents have been shown to provide a survival benefit compared to other agents and are preferred over PSIs. However, rapidly reducing toxin production has proved beneficial for other toxin-producing pathogens (*6-8*) and provided survival benefit in one review of anthrax cases (*9*).

Antitoxins should be provided as adjunctive therapy for all patients with systemic anthrax, particularly those with underlying comorbidities.	In animal models, survival benefit has been shown for antitoxins compared to no treatment but not when added to antimicrobials: Animal data show that postexposure prophylaxis with any of the anthrax antitoxins (i.e., anthrax immune globulin intravenous [AIGIV; polyclonal], raxibacumab, obiltoxaximab [both monoclonal]) provided a significant survival benefit compared to no treatment, with the greatest benefit obtained with the earliest administration (*10-13*). Although monotherapy with either of the monoclonal antitoxins provided a significant survival benefit compared to no treatment in animal models, adding either monoclonal antitoxin to antimicrobials did not significantly improve survival over antimicrobials alone (*10-13*). Diabetes, obesity, hypertension, and chronic obstructive pulmonary disease were associated with severe anthrax in patients with cutaneous anthrax (p<.01 for all) (*14*).
The monoclonal antitoxins raxibacumab and obiltoxaximab are preferred over AIGIV.	A head-to-head comparison of the three antitoxins for treatment following aerosol exposure to *B. anthracis* demonstrated a survival benefit compared to placebo. There were no differences seen in survival benefit between the monoclonal antitoxins raxibacumab and obiltoxaximab; however, both monoclonals were significantly more effective than the polyclonal antitoxin, AIGIV (*15*).
Ancillary Treatment of Anthrax Meningitis	
For anthrax meningitis, consider including antimicrobials with potential neuroprotective benefits in vivo (e.g., minocycline, doxycycline, clindamycin, beta-lactam antimicrobials) for combination therapy for anthrax meningitis.	Minocycline is a highly lipophilic second-generation tetracycline that readily crosses the BBB and has been shown in vivo to have neuroprotective effects against SAH (*16-20*), intracerebral bleeding (*16, 19, 21-27*), and blood brain barrier disruption (*16, 19, 20, 22, 27-35*). Theoretically, minocycline might be beneficial for the treatment of anthrax meningitis because of its anti-inflammatory, anti-apoptotic, and antioxidant effects (*36-38*). Other antimicrobials with in vivo neuroprotective effects for some meningitides include beta-lactams (*39*), clindamycin (*40*), and daptomycin (*41, 42*).
Mannitol or hypertonic saline should be considered for patients with anthrax meningitis and evidence of cerebral edema.	When looking specifically at adults with anthrax meningitis, patients who received mannitol had higher odds of survival than those who did not (OR, 24.00; 95% CI, 1.66-347.85) (*3*). In bacterial meningitis, preclinical animal studies suggest a

	beneficial effect of hypertonic saline for the treatment of symptomatic cerebral edema. Liu et al reports that 3% hypertonic saline reduces intracranial pressure, improves cerebral perfusion pressure, inhibits aquaporin-4 expression, reduces cerebral edema, and attenuates neuronal injury (43).
Other therapies that target intracranial bleeding and swelling, such as nimodipine, have been shown to improve outcomes in aneurysmal subarachnoid hemorrhage and intracerebral hemorrhage and may be applicable to the treatment of hemorrhagic anthrax meningitis.	Subarachnoid and intracerebral hemorrhage are common in patients with anthrax meningitis. Subarachnoid hemorrhage was detected by lumbar puncture in 43% of 132 patients with anthrax meningitis (*44*). In one study, hemorrhages within the brain parenchyma were noted in 31% of nonhuman primates with inhalation anthrax (*45*). Nimodipine reduces the incidence of poor neurological outcome in subarachnoid hemorrhage by 40% (*46*) and is Food and Drug Administration (FDA) approved for aneurysmal subarachnoid hemorrhage.
Ancillary Treatment of Fluid Collections in Systemic Anthrax	
Patients with systemic anthrax, particularly those with inhalation anthrax, should be evaluated for pleural effusions. Early and aggressive drainage of any clinically or radiographically apparent pleural effusions is recommended.	Pleural effusions are a common complication of inhalation anthrax (76%) and may be observed in patients with ingestion (3%) or injection (8%) anthrax or primary anthrax meningitis (10%) (*47*). In 2006 and again in 2011, mass spectroscopy of pleural fluid from patients with inhalation anthrax demonstrated the presence of anthrax lethal factor (LF). In both patients, pleural fluid LF levels exceeded concurrently measured plasma / serum levels (*48, 49*). Draining pleural fluid from patients with such collections should reduce the amount of LF and decrease morbidity.
Peritoneal fluid collections that occur with systemic anthrax, particularly ingestion anthrax, should be drained.	Ascites was observed in 52% of patients with ingestion anthrax, but also in 4% of those with inhalation anthrax and in 1 person each with injection anthrax and primary anthrax meningitis(*47*). Ascites might serve as a reservoir for LF. Hypothetically, draining peritoneal fluid from patients with such collections could reduce the amount of LF and decrease morbidity.

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