

Appendix D: BW Agents Vaccines, Prophylaxis, and Therapeutics

ANTHRAX

VACCINE/TOXOID	DEVELOPMENT
<p>Bioport BioThrax™ Anthrax Vaccine (AVA)</p> <p>Preexposure^(A): licensed for adults 18-65yr old, 0.5 mL SC @ 0, 2, 4 wk, 6, 12, 18 mo then annual boosters</p> <p>Postexposure^(IND): DoD Contingency Use Protocol for volunteer anthrax vaccination SC@ 0, 2, 4 wk in combination with approved and labeled antibiotics</p> <p>Pediatric Annex^{IND} for postexposure use.</p>	<p>Recombinant protective antigen (rPA) vaccine</p>
CHEMOPROPHYLAXIS	
<p>Ciprofloxacin^(A): 500 mg PO bid (adults), 15mg/kg (up to 500mg/dose) PO bid (peds)^(A), or</p> <p>Doxycycline^(A): 100 mg PO bid (adults), 2.2mg/kg (up to 100mg/dose) PO bid (peds < 45kg)^(A) or (if strain susceptible):</p> <p>Penicillin G procaine: 1,200,000U q 12 hr (adults)^(A), 25,000U/kg (maximum 1,200,000 unit) q 12 hr (peds)^(A), or</p> <p>Penicillin V Potassium: 500 mg q 6 hr (adults), or</p> <p>Amoxicillin: 500mg PO q 8 hr (adults and children>40kg), 15mg/kg q 8 hr (children<40kg), Plus, AVA (postexposure)^(IND)</p> <p>1. Fully immunized (completed 6 shot primary series and up-to-date on annual boosters, or 3 doses within past 6 mo): continue antibiotics for at least 30 days. 2. Unimmunized: 3 doses of AVA 0.5cc SQ at 0, 2, 4 weeks^(IND). Continue antibiotics for at least 7-14 days after 3rd dose. 3. No AVA used: continue antibiotics for at least 60 days</p>	
CHEMOTHERAPY	
<p>Inhalational, Gastrointestinal, or Systemic Cutaneous Disease:</p> <p>Ciprofloxacin : 400 mg IV 1 12 h initially then by mouth (adult)^(A) 15 mg/kg/dose (up to 400mg/dose) q 12 h (peds)^(A), or</p> <p>Doxycycline: 200 mg IV, then 100 mg IV q 12 h (adults)^(A) 2.2mg/kg (100mg/dose max) q 12 h (peds < 45kg)^(A), or (if strain susceptible),</p> <p>Penicillin G Procaine: 4 million units IV q 4 h (adults)^(A) 50,000U/kg (up to 4M U) IV q 6h (peds)^(A)</p> <p>PLUS, One or two additional antibiotics with activity against anthrax. (e.g. clindamycin plus rifampin may be a good empiric choice, pending susceptibilities). Potential additional antibiotics include one or more of the following: clindamycin, rifampin, gentamicin, macrolides, vancomycin, imipenem, and chloramphenicol.</p> <p>Convert from IV to oral therapy when the patient is stable, to complete at least 60 days of antibiotics.</p> <p>Meningitis: Add Rifampin 20mg/kg IV qd or Vancomycin 1g IVq12h</p>	<p>Anthrax Immune Globulin (AIG)</p>
COMMENTS	
<p>In 2002 the American Committee on immunization Practices (ACIP) recommended making anthrax vaccine available in a 3-dose regimen (0, 2, 4 weeks) in combination with antimicrobial postexposure prophylaxis under an IND application for unvaccinated persons at risk for inhalational anthrax.</p> <p>Penicillins should be used for anthrax treatment or prophylaxis only if the strain is demonstrated to be PCN-susceptible.</p> <p>According to CDC recommendations, amoxicillin prophylaxis is appropriate only after 14-21 days of fluoroquinolone or doxycycline and only for populations with contraindications to the other drugs (children, pregnancy)</p> <p>Oral dosing (versus the preferred IV) may be necessary for treatment of systemic disease in a mass casualty situation.</p> <p>Cutaneous Anthrax: Antibiotics for cutaneous disease (without systemic complaints) resulting from a BW attack involving BW aerosols are the same as for postexposure prophylaxis. Cutaneous anthrax acquired from natural exposure could be treated with 7-10 days of antibiotics.</p>	<p>AIG is serum from human AVA recipients with high anti-PA titers.</p>

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Brucellosis

VACCINE/TOXOID
None
CHEMOPROPHYLAXIS
Can try one of the treatment regimens for 3-6 weeks, for example: Doxycycline : 200mg po qd (adults) ^(A) , plus Rifampin: 600mg PO qd
CHEMOTHERAPY
Inhalational, Gastrointestinal, or SystemicCutaneous Disease Significant infection: Doxycycline: 100mg PO bid for 4-6 wks (adults) ^(A) , 2.2 mg/kg PO bid (peds), plus Streptomycin 1g IM qd for first 3 wks (adults) ^(A) , or Doxycycline ^(A) + Gentamicin (if streptomycin not available) Less severe disease: Doxycycline 100mg PO bid for 4-6 wks (adults) ^(A) , plus Rifampin 600-900 mg/day PO qd for 4-6 wks (adults) ^(A) , 15-20mg/kg (up to 600-900mg) qd or divided bid (peds) Others used with success: TMP/SMX 8-12mg/kg/d divided qid, plus Rifampin (may be preferred therapy during pregnancy or in children <8yrs), Or Ofloxacin + Rifampin Long-term (up to 6 mo) therapy for meningoenephalitis, endocarditis: Rifampin + a tetracycline + an aminoglycoside (first 3 weeks)
COMMENTS
Ideal chemoprophylaxis is unknown. Chemoprophylaxis not recommended after natural exposure. Avoid monotherapy (high relapse). Relapse common for treatments less than 4-6 weeks.

Glanders & Melioidosis

VACCINE/TOXOID
None
CHEMOPROPHYLAXIS
Can try one of the treatment regimens for 3-6 weeks, for example: Doxycycline : 200mg po qd (adults) ^(A) , plus Rifampin: 600mg PO qd
CHEMOTHERAPY
Severe Disease: ceftazidime (40mg/kg IV q 8hrs), or imipenem (15mg/kg IV q 6hr max 4 g/day), or meropenem (25mg/kg IV q 8hr, max 6g/day), plus , TMP/SMX (TMP 8 mg/kg/day IV in four divided doses) Continue IV therapy for at least 14 days and until patient clinically improved, then switch to oral maintenance therapy (see "mild disease" below) for 4-6 months. Melioidosis with septic shock: Consider addition of G-CSF 30ug/day IV for 10 days. Mild Disease: Historic: PO doxycycline and TMP/SMX for at least 20 weeks, plus PO chloramphenicol for the first 8 weeks. Alternative: doxycycline (100 mg po bid) plus TMP/SMX (4 mg/kg/day in two divided doses) for 20 weeks.
COMMENTS
Little is known about optimum therapy for glanders, as this disease has been rare in the modern antibiotic era. For this reason, most experts feel initial therapy of glanders should be based on proven therapy for the similar disease, melioidosis. One potential difference in the two organisms is that natural strains of <i>B. mallei</i> respond to aminoglycosides and macrolides, while <i>B. pseudomallei</i> does not; thus, these classes of antibiotics may be beneficial in treatment of glanders, but not melioidosis. Severe Disease: If ceftazidime or a carbapenem are not available, ampicillin/sulbactam or other intravenous beta-lactam/beta-lactamase inhibitor combinations may represent viable, albeit less-proven alternatives. Mild Disease: Amoxicillin/clavulanate may be an alternative to Doxycycline plus TMP/SMX, especially in pregnancy or for children <8yr old.

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Plague

VACCINE/TOXOID	DEVELOPMENT
	Recombinant F1-V Antigen Vaccines, DoD & UK
CHEMOPROPHYLAXIS	
Ciprofloxacin: 500 mg PO bid x 7 d (adults), 20mg/kg (up to 500mg) PO bid (peds), or Doxycycline: 100 mg PO q 12 h x 7 d (adults), 2.2 mg/kg (up to 100mg) PO bid (peds), or Tetracycline: 500 mg PO qid x 7 d (adults)	
CHEMOTHERAPY	
Streptomycin: 1g q 12hr IM (adults) ^(A) , 15mg/kg/d div q 12hr IM (up to 2 g/day)(peds) ^(A) , or Gentamicin: 5 mg/kg IM or IV OD or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV (adults), 2.5 mg/kg IM or IV q8h (peds). Alternatives: Doxycycline: 200 mg IV once then 100 mg IV bid until clinically improved, then 100 mg PO bid for total of 10-14 d (adults) ^(A) , or Ciprofloxacin: 400mg IV q 12 h until clinically improved then 750 mg PO bid for total 10-14 d, or Chloramphenicol: 25 mg/kg IV, then 15 mg/kg qid x 14 d. A minimum of 10 days of therapy is recommended (treat for at least 3-4 days after clinical recovery). Oral dosing (versus the preferred IV) may be necessary in a mass casualty situation. Meningitis: add Chloramphenicol 25mg/kg IV, then 15mg/kg IV qid.	FDA-approved therapeutics
COMMENTS	
Greer inactivated vaccine (FDA licensed) is no longer available. Streptomycin is not widely available in the US and therefore is of limited utility. Although not licensed for use in treating plague, gentamicin is the consensus choice for parenteral therapy by many authorities. Reduce dosage in renal failure. Chloramphenicol is contraindicated in children less than 2 yrs. While Chloramphenicol is potentially an alternative for post-exposure prophylaxis (25mg/kg PO qid), oral formulations are available only outside the US. Alternate therapy or prophylaxis for susceptible strains: trimethoprim-sulfamethoxazole Other fluoroquinolones or tetracyclines may represent viable alternatives to ciprofloxacin or doxycycline, respectively.	

Q Fever

VACCINE/TOXOID	
Inactivated Whole Cell Vaccine (Preexposure) ^(IND) : DoD Laboratory Use Protocol using Australian Qvax TM vaccine in at-risk laboratory personnel.	
CHEMOPROPHYLAXIS	
Doxycycline: 100 mg PO bid x 5 d (adults), 2.2mg/kg PO bid (peds), or Tetracycline: 500 mg PO qid x 5d (adults) Start postexposure prophylaxis 8-12 d post-exposure.	
CHEMOTHERAPY	
Acute Q-fever: Doxycycline: 100 mg IV or PO q 12 h x at least 14 d (adults) ^(A) , 2.2 mg/kg PO q 12 h (peds), or Tetracycline: 500 mg PO q 6 hr x at least 14 d Alternatives: Quinolones (eg ciprofloxacin), or TMP-SMX, or Macrolides (eg clarithromycin or azithromycin) for 14-21 days. Patients with underlying cardiac valvular defects: Doxycycline plus Hydroxychloroquine 200mg PO tid for 12 months Chronic Q Fever: Doxycycline plus quinolones for 4 years, or Doxycycline plus hydroxychloroquine for 1.5-3 years.	
COMMENTS	
Q-Fever vaccine manufactured in 1970. Significant side effects if administered inappropriately; sterile abscesses if prior exposure/skin testing required prior to vaccination. Time to develop immunity – 5 weeks. Initiation of postexposure prophylaxis within 7 days of exposure merely delays incubation period of disease. Tetracyclines are preferred antibiotic for treatment of acute Q fever except in: 1. <u>Meningoencephalitis:</u> fluoroquinolones may penetrate CSF better than tetracyclines 2. <u>Children < 8yrs (doxycycline relatively contraindicated):</u> TMP/SMX or macrolides (especially clarithromycin or azithromycin). 3. <u>Pregnancy:</u> TMP/SMX 160mg/800mg PO bid for duration of pregnancy. If evidence of continued disease at parturition, use tetracycline or quinolone for 2-3 weeks.	

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Tularemia

VACCINE/TOXOID
Live attenuated vaccine (Preexposure) ^(IND)
DoD Laboratory Use Protocol for vaccine. Single 0.1ml dose via scarification in at-risk researchers.
CHEMOPROPHYLAXIS
Ciprofloxacin: 500 mg PO q 12 h for 14 d, 20mg/kg (up to 500mg) PO bid (peds), or
Doxycycline: 100 mg PO bid x 14 d (adults), 2.2mg/kg (up to 100mg) PO bid (peds<45kg), or
Tetracycline: 500 mg PO qid x 14 d (adults)
CHEMOTHERAPY
Streptomycin: 1g IM q12 h days x at least 10 days (adults) ^(A) , 15mg/kg (up to 2g/day) IM q12h (peds) ^(A) , or
Gentamicin: 5 mg/kg IM or IV qd, or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV q 8 h x at least 10 days (adults) ^(A) , 2.5mg/kg IM or IV q 8 h (peds), or
Alternatives:
Ciprofloxacin 400 mg IV q 12 h for at least 10d (adults), 15mg/kg (up to 400mg) IV q 12 h (peds), or
Doxycycline: 200 mg IV, then 100 mg IV q 12 h x 14-21 d (adults) ^(A) , 2.2mg/kg (up to 100mg) IV q 12 h (peds<45kg), or
Chloramphenicol: 25mg/kg IV q 6 h x 14-21 d, or
Tetracycline: 500 mg PO qid x 14-21 d (adults) ^(A)
COMMENTS
Vaccine manufactured in 1964.
Streptomycin is not widely available in the US and therefore is of limited utility. Gentamicin, although not approved for treatment of tularemia likely represents a suitable alternative. Adjust gentamicin dose for renal failure
Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; doxycycline and chloramphenicol are associated with high relapse rates with course shorter than 14-21 days. IM or IV doxycycline, ciprofloxacin, or chloramphenicol can be switched to oral antibiotic to complete course when patient clinically improved.
Chloramphenicol is contraindicated in children less than 2 yrs. While Chloramphenicol is potentially an alternative for post-exposure prophylaxis (25mg/kg PO qid), oral formulations are available only outside the US.

Botulinum Toxins

VACCINE/TOXOID	DEVELOPMENT
Pentavalent Toxoid Vaccine ^(IND) (Preexposure use only)	DoD rBONT Heptavalent Vaccine
HBIG, DoD pentavalent human botulism immune globulin, types A-E ^(IND) . IND for pre-exposure prophylaxis for high risk individuals only.	
CHEMOPROPHYLAXIS	
DoD equine antitoxins ^(IND) In general, botulinum antitoxin is not used prophylactically. Under special circumstances, if the evidence of exposure is clear in a group of individuals, some of whom have well defined neurological findings consistent with botulism, treatment can be contemplated in those without neurological signs.	
CHEMOTHERAPY	
CDC trivalent equine antitoxin for serotypes A, B and E. A and B are licensed and E is a CDC IND Product. BabyBig™, California Health Department, types A and B Human lyophilized IgG ^(A) HE-BAT, DoD heptavalent equine botulism antitoxin, types A-G ^(IND) HFabBAT, DoD de-speiciated heptavalent equine botulism antitoxin, types A-G ^(IND)	Monoclonal antibodies
COMMENTS	
Pentavalent Toxoid Vaccine failed potency testing for Serotypes D and E. FDA has concerns about all of the other Serotypes potency. Must initiate series 13 weeks before potential exposure for optimum protection. Skin test for hypersensitivity before equine antitoxin administration.	

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Ricin Toxin

VACCINE/TOXOID	DEVELOPMENT
	Formalin treated toxoid vaccine; De-glycosylated A-chain vaccine
CHEMOPROPHYLAXIS	
CHEMOTHERAPY	
COMMENTS	
Inhalation: supportive therapy G-I: gastric lavage, superactivated charcoal, cathartics.	Availability of ricin vaccine contingent upon transition of candidate to advanced development and upon availability of funds.

Staphylococcus Enterotoxins

VACCINE/TOXOID	DEVELOPMENT
	DoD recombinant SEB Vaccine
CHEMOPROPHYLAXIS	
CHEMOTHERAPY	
COMMENTS	
Supportive care including assisted ventilation for inhalation exposure.	Currently insufficient funding for JVAP development to IND product.

Encephalitis Viruses

VACCINE/TOXOID	DEVELOPMENT
JE live attenuated vaccine ^(A) VEE Live Attenuated Vaccine ^(IND) (DoD Laboratory Use Protocol for Preexposure) TC-83 strain, for initial immunizations VEE Inactivated Vaccine ^(IND) (DoD Laboratory Use Protocol for Preexposure) C-84 strain, for booster immunizations EEE Inactivated Vaccine ^(IND) (DoD Laboratory Use Protocol for Preexposure) WEE Inactivated Vaccine ^(IND) (DoD Laboratory Use Protocol for Preexposure)	VEE (V3526) Vaccine.
CHEMOPROPHYLAXIS	
None	
CHEMOTHERAPY	
No specific therapy. Supportive care only.	
COMMENTS	
VEE TC-83 vaccine manufactured in 1965. Live, attenuated vaccine, with significant side effects. 25%-35% of recipients require 2-3 days bed rest. Time to develop immunity – 8 weeks. VEE TC-83 reactogenic in 20%. No seroconversion in 20%. Only effective against subtypes 1A, 1B, and 1C. VEE C-84 vaccine used for non-responders to VEE TC-83. Must be given prior to EEE or WEE (if administered subsequent, antibody response decreases from 81% to 67%). EEE vaccine manufactured in 1989. Antibody response is poor, requires 3-dose primary (one month) and 1-2 boosters (one month apart). Primary series yields antibody response in 77%; 5%-10% of non-responders after boosts. Time to immunity – 3 months. WEE vaccine manufactured in 1991. Antibody response is poor, requires 3-dose primary (one month) and 3-4 boosters (one month apart). Primary series antibody response in 29%, 66% after four boosts. Time to develop immunity – six months. EEE and WEE inactivated vaccines are poorly immunogenic. Multiple immunizations are required.	

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Hemorrhagic Fever Viruses

VACCINE/TOXOID	DEVELOPMENT
Yellow Fever live attenuated 17D vaccine ^(A) AHF vaccine ^(IND) (x-protection for BHF) RVF inactivated vaccine ^(IND) (DoD IND for high-risk laboratory workers)	Adenovirus vectored Ebola Vaccine Ebola DNA vaccine
CHEMOPROPHYLAXIS	
Lassa fever and CCHF: Ribavirin 500mg PO q 6 hr for 7 days (Not FDA approved for this use)	
CHEMOTHERAPY	
Ribavirin (CCHF/Lassa/KHF): 30 mg/kg (up to 2g) IV initial dose; then 16 mg/kg (up to 1g) IV q 6 h x 4 d; then 8 mg/kg (up to 500mg) IV q 8 h x 6 d (adults) ^(IND) <u>Mass Casualty Situation (Arenavirus, Bunyavirus, or VHF of unknown etiology. Not FDA-approved or IND)</u> Ribavirin: 2000mg PO; then 600mg PO bid (if > 75kg), or 400mg PO in am and 600mg PO in PM (if < 75kg) for 10 days (adults), 30mg/kg then 15mg/kg divided bid for 10 days (peds)	Passive antibody for AHF, BHF, Lassa fever, and CCHF.
COMMENTS	
Aggressive supportive care and management of hypotension and coagulopathy very important. Human antibody used with apparent beneficial effect in uncontrolled human trials of AHF. Human experience with postexposure ribaririn use for VHF exposure is limited to a few cases exposed to CCHF and Lassa. Any use for this purpose should be ideally under IND. Consensus statement in JAMA from 2002 suggests using Ribavirin to treat clinically apparent hemorrhagic fever virus infection of unknown etiology using doses from CCHF/Lassa/KHF IND.	Ebola DNA vaccine in human trials at NIH

Smallpox

VACCINE/TOXOID	DEVELOPMENT
Wyeth Dryvax™ (1:1) (Preexposure) ^(A) Aventis Pasteur Smallpox Vaccine (APSV) (Preexposure) ^(IND) Cell Culture derived Vaccines (all NYCBOH strain): - Dynport Vaccine (Preexposure) ^(IND) - Acambis/Acambis-Baxter Vaccines (ACAM1000 and ACAM2000) (Preexposure) ^(IND)	Attenuated Vaccinia Vaccines: Acambis Modified Vaccinia Ankara (MVA) VaxGen LC16m8 strain
CHEMOPROPHYLAXIS	
Wyeth Dryvax™ (1:1) (Postexposure) ^(IND) Use of Smallpox Vaccine in Response to Bioterrorism: Wyeth Dryvax™ (1:5 dilution) ^(IND) CDC IND. If Dryvax™ (1:5) used up, not available, or need both vaccines, then use: APSV (1:5 dilution) ^(IND)	DoD IND for APSV (1:5) Contingency Use
CHEMOTHERAPY	
Cidofovir for treatment of smallpox ^(IND) : - Probenecid 2g PO 3 h prior to cidofovir infusion. - infuse 1L NS 1 h prior to cidofovir infusion - Cidofovir 5mg/kg IV over 1 hr - repeat probenecid 1g PO 2 h and again 8 h after cidofovir infusion completed. For Select Vaccine Adverse reactions (Eczema vaccinatum, vaccinia necrosum, ocular vaccinia w/o keratitis, severe generalized vaccinia): 1. VIG IV (Vaccinia Immune Globulin – intravenous formulation). 100mg/kg IV infusion. 2. VIG-IM (Vaccinia Immune Globulin – intramuscular formulation). 0.6ml/kg IM. 3. Cidofovir 5mg/kg IV infusion (as above).	Oral formulations of cidofovir derivatives Monoclonal Vaccinia Immune Globulins
COMMENTS	
Dryvax™ - Wyeth calf lymph vaccinia vaccine 100 dose vials undiluted: 1 dose by scarification. Greater than 97% take after one dose within 14 days of administration. Dryvax™ is effective (either preventing or attenuating resulting disease) up to at least 4 days post exposure. Dryvax™ (1:1) FDA license approved 25 Oct 2002. APSV is also known as the Salk Institute (TSI) vaccine, a frozen, liquid formulation using the NYCBOH vaccine strain via calf-lymph production also used in the Dryvax™ Pre and post exposure vaccination recommended if > 3 years since last vaccine. Recommendations for use of smallpox vaccine in response to bioterrorism are periodically undated by the Centers for Disease Control and Prevention (CDC), and the most recent recommendations can be found at http://www.cdc.gov .	

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