

# Appendix M: Use of Drugs / Vaccines in Special or Vulnerable Populations in the Context of Bioterrorism.

(The pediatric patient, nursing mothers, pregnant patient and the immunocompromised)

## Pediatric patients

Management of pediatric patients exposed to BW agents may be problematic for several reasons. Some antimicrobials and vaccines are not licensed for use in children. Additionally, most investigational new drug (IND) applications do not include children in their subject groups. For example, the Anthrax Vaccine (AVA) is licensed only for pre-exposure use in people aged 18-65. While AVA may be effective in preventing anthrax in children as well, it has not been studied in pediatric populations. Smallpox vaccine can be used only in patients 6 months of age or older.

Some vaccines, even though licensed for use in children, are more problematic in children than in adults. Smallpox vaccine is much more likely to lead to postvaccinial encephalitis, an often-fatal condition, when given to young children. Yellow fever vaccine is more likely to cause severe encephalitis in young infants than it is in adults.

Some antimicrobials are relatively contraindicated in children due to real or perceived risks which do not appear to be present in adult populations. Tetracyclines and fluoroquinolones are the two classes of antibiotics that generate the most concern since they are the drugs of choice for treating or preventing many BW diseases.

**Tetracyclines.** This class of antibiotics is generally contraindicated in children less than 8 years old because the antibiotic and its pigmented breakdown products can cause permanent dental staining and, more rarely, enamel hypoplasia during odontogenesis. The degree of staining is proportional to the total dose received and is thus dependent upon both dose and duration of therapy. Thus, doxycycline, which is given only twice per day, represents a lower risk than other tetracyclines. Tetracyclines may also cause reversible delay in bone growth rate during the course of therapy. Despite these relative contraindications, the American Academy of Pediatrics (AAP) recommends tetracyclines for treating certain severe illnesses that respond poorly to other antibiotics (e.g. Rocky Mountain spotted fever and other rickettsial diseases), specifically including treatment or prevention of anthrax disease.

**Fluoroquinolones.** This class of antibiotics is generally contraindicated in patients less than 18 years old because it is associated with cartilage damage in juvenile animal models. While sporadic cases of arthropathy in humans have been reported, they have primarily been associated with adults and children receiving pefloxacin, a fluoroquinolone commonly used in France. Ciprofloxacin, which has been used extensively in children, has not thus far been associated with arthropathy and seems to be well tolerated. For this reason, the AAP

recognizes that fluoroquinolones may be used in children in special circumstances, specifically including treating or preventing anthrax. In fact, ciprofloxacin is specifically licensed by the FDA for postexposure prophylaxis against anthrax IN CHILDREN.

**General guidance.** In pediatric cases of suspected BW exposure or disease in which the empiric treatment of choice is a drug with limited pediatric experience, one may be left with few viable alternatives than to treat with such a drug. For example, if a 5-year-old child is suspected to have been exposed to an aerosol of *Bacillus anthracis* of unknown antibiotic susceptibility, the best initial choice of antibiotic may be ciprofloxacin or doxycycline (In fact, for this reason, the FDA and AAP recommend either of these drugs for empiric postexposure prophylaxis of inhalational anthrax). If the organism is later determined to be susceptible to penicillins, then one could switch to amoxicillin to complete the course of antibiotics. If the organism is not susceptible to penicillin but is susceptible to doxycycline and ciprofloxacin, then ciprofloxacin may represent a better choice for continued prophylaxis, as arthropathy from fluoroquinolones thus far has proved rare in children, whereas the necessarily prolonged course of doxycycline (perhaps 60 days) could lead to significant dental staining. If the same child was exposed to *Yersinia pestis* susceptible to both ciprofloxacin and doxycycline, doxycycline might be an equally good choice as ciprofloxacin, as the short (7 day) course of postexposure prophylaxis is unlikely to result in dental staining. Clinicians must use judgment in these cases, taking into account the organism's antibiotic susceptibilities, the available prophylaxis or treatment options, and the risk versus benefit to the individual patient. Antimicrobial doses are often different in children, and prescribed according to patient weight. Some representative antibiotics and their pediatric doses are included in Table 1.

### **Nursing mothers**

Some medications are excreted in breast milk (see Table 1), and thus may be ingested by nursing infants. Such medications, if contraindicated in infants and orally absorbed, should also be avoided by breastfeeding mothers if possible. It is generally recommended that fluoroquinolones, tetracyclines, and chloramphenicol be avoided in nursing mothers. Obviously, these drugs may represent the treatment of choice for many BW agents; thus, practitioners must again weigh the risks of administering these drugs with the potential adverse consequences of using a less effective medication. In some cases, temporary cessation of nursing while on the offending drug may be necessary. Antibiotics generally considered safe during nursing are aminoglycosides, penicillins, cephalosporins, and macrolides.

### **Pregnant patients**

Some medications that are useful and safe for treating diseases in women may nonetheless pose specific risks during pregnancy. FDA has developed the following pregnancy risk categories. **A:** studies in pregnant women show no risk; **B:** animal studies show no risk but human studies are not adequate or animal toxicity has been shown but human studies show no risk; **C:** animal studies show toxicity, human studies are inadequate but benefit of use may exceed risk; **D:** evidence of human risk but benefits may outweigh risks; **X:** fetal abnormalities in

humans, risk outweighs benefit. Pregnancy risk categories for representative therapeutics are included in Table 1.

Again, tetracyclines and fluoroquinolones must be addressed, as they are empiric treatments of choice for many BW diseases yet relatively contraindicated in pregnancy. Animal studies indicate that tetracyclines can retard skeletal development in the fetus; embryotoxicity has also been described in animals treated early in pregnancy. There are few adequate studies of fluoroquinolones in pregnant women; existing published data, albeit sparse, do not demonstrate a substantial teratogenic risk associated with ciprofloxacin use during pregnancy. In cases for which either ciprofloxacin or doxycycline are recommended for initial empiric prophylaxis (e.g., inhalational anthrax, plague, or tularemia), ciprofloxacin if tolerated may represent the lower risk option; then, after antibiotic susceptibility data are gained, antibiotics should be switched to lower risk alternatives if possible.

While most vaccinations are to be avoided during pregnancy, killed vaccines are generally considered to be of low risk. While live vaccines (e.g., measles-mumps-rubella) are contraindicated during pregnancy, a notable exception is the administration of the smallpox vaccine (vaccinia) to pregnant women after a known or highly suspected exposure to the smallpox virus during an outbreak.

### **The immunocompromised patient**

While immunocompromised individuals may be more susceptible to BW disease or may develop more severe disease than immunocompetent patients, consensus groups generally recommend using the same antimicrobial regimens recommended for their immunocompetent counterparts. The most obvious difference in management of these patients concerns receipt of live vaccines, such as the currently licensed smallpox vaccine, or the LVS tularemia vaccine. Generally, it is best to manage these individuals on a case-by-case basis and in concert with immunologists and/or infectious disease specialists.

**Table 1. Antimicrobials in Special Populations**

Class of Drug	Pregnancy category	Drug name	breast milk	Pediatric Oral Dose	Pediatric parenteral dose
Aminoglycosides	C	Gentamicin	(+) small		3 - 7.5 mg/kg/day in 3 doses (IV or IM)
	D	Amikacin	(+) small		15 - 22.5 mg/kg/day in 3 doses (max 1.5g/day) (IV or IM)
	D	Streptomycin	(+) small		30 mg/kg/day in 2 doses (max 2g/day)(IM only)
	D	Tobramycin	(+) small		3 - 7.5 mg/kg/day in 3 doses (IV or IM)
Carbapenems	C	Imipenem	(?)		60 mg/kg/day in 4 doses (max 4g/day) (IV or IM)
	B	Meropenem	(?)		60-120 mg/kg/day in 3 doses (max 6g/day) (IV)
Cephalosporins	B	Ceftriaxone	(+) trace		80 - 100 mg/kg in 1 or 2 doses (max 4g/day) (IV or IM)
	B	Ceftazidime	(+) trace		125-150 mg/kg/day in 3 doses (max 6g/day) (IV or IM)
	B	Cephalexin	(+) trace	25-50 mg/kg/day in 3-4 doses	
	B	Cefuroxime	(+) trace	20-30 mg/kg/day in 2 doses (max 2g/day)	100-150 mg/kg/day in 3 doses (max 6g/day) (IV or IM)
	B	Cefepime	(+) trace		150mg in 3 doses (max 4g/day) (IV or IM)
Chloramphenicol	C		(+)	50-100 mg/kg/day in 4 doses (formulation not avail in US)	50-100 mg/kg/day in 4 doses (max 4g/day) (IV)
Fluoroquinolones	C	Ciprofloxacin	(+)	30 mg/kg/day in 2 doses (max 1.5g)	20-30 mg/kg/day in 2 doses (max 800mg/day)(IV)
Glycopeptides	C	Vancomycin	(+)		40-60 mg/kg/day in 4 doses (max 4g/day) (IV)
Lincosamides	B	Clindamycin	(+)	10-20 mg/kg/day in 3-4 doses (max 1.8g/day)	25-40 mg/kg/day in 3-4 doses (max 2.7g/day) (IV or IM)
Lipopeptides	B	Daptomycin	(?)		4 mg/kg once daily (IV)
Macrolides	B	Azithromycin	(+)	5-12 mg/kg/day once daily (max 600mg/day)	
	C	Clarithromycin	(?)	15 mg/kg/day in 2 doses (max 1g/day)	
	B	Erythromycin	(+)	30-50 mg/kg/day in 2-4 doses (max 2g/day)	15-50 mg/kg/day in 4 doses (max 4g/day) (IV)
Monobactams	B	Aztreonam	(+)trace		90-120 mg/kg/day in 3-4 doses (max 8g) (IV or IM)
Oxalodinones	C	Linezolid	(+)	20-30 mg/kg/day in 3 doses (max 800/mg/day)	20-30 mg/kg/day in 3 doses (max 1200/mg/day)(IV)
Penicillins	B	Amoxicillin	(+) trace	25-9 0mg/kg/day in 3 doses (max 1.5g/day)	
	B	Ampicillin	(+) trace	50-100 mg/kg/day in 4 doses (max 4g/day)	200-400 mg/kg/day in 4 doses (max 12g/day) (IV or IM)
	B	Penicillin G	(+) trace		25000-400000U/kg/day in 4-6 doses (mag 24milU/day) (IV or IM)
	B	Nafcillin	(+) trace		100-150 mg/kg/day in 4 doses (max12g) (IV or IM)
Rifampin	C		(+)	10-20 mg/kg/day in 1-2 doses (max 600mg/day)	10-20 mg/kg/day in 1-2 doses (max 600mg/day)
Streptogramins	B	Dalfopristin-Quinupristin	(+)		22.5 mg/kg/day in 3 doses (IV)
Sulfonamides	C	Trimethoprim/Sulfamethoxazole	(+) trace	8-12 mg/kg/dayTMP in 4 doses (max 320 mg/day TMP)	8-12 mg/kg/dayTMP in 4 doses (IV)
	D	Doxycycline	(+)	2-4 mg/kg/day in 1-2 doses (max 200mg/day)	2-4 mg/kg/day in 1-2 doses (max 200mg/day)(IV)
	D	Tetracycline	(+)	20-50 mg/kg/day in 4 doses (max 2g)	10-25 mg/kg/day in 2-4 doses (max 2g) (IV)
Cidofovir	C		(?)		5mg/kg once with probenecid and hydration
Osetamivir	C		(+)	1-12 years old: ≤15 kg: 30 mg twice daily; 15-23 kg: 45 mg 2X/day; 23-40kg: 60mg 2X/day; >40kg: adult dose	
Ribavirin	X		(?)	30 mg/kg once, then 15 mg/kg/day in 2 doses (VHFs)	Same as for adults, dosed by weight (IV)

Note: (1) The above dose are for children outside of the neonatal period. Neonatal doses may be different

Note: (2) Pediatric antibiotic doses included in this table represent generic doses for severe disease. They may not accurately reflect expert consensus for treatment of some specific BW diseases (anthrax, plague, tularemia). For those diseases, refer to the specific chapter for recommendations.