

# SOCIETY OF INFECTIOUS DISEASES PHARMACISTS



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## PRESIDENT'S COLUMN

### Charles Ballow, PharmD, FCCP

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Well, what an interesting year this is shaping up to be! As I prepare my first column as SIDP President, some of the recent news has been tragic and some of it positive, both affecting our Society. Since the terrible events of September 11, bioterrorism has gone from threat to reality. You are all also aware that our annual gathering at ICAAC has been postponed because of September 11. On the positive side, the Infectious Diseases Society of America (IDSA) appears to be interested in improved relations with SIDP. Wow, this is going to be fun!

First, let me state what an honor it is to serve as President of this vibrant Society. I am overwhelmed by the accomplishments of the membership and daunted by the tasks before us. Thank you for this great opportunity. In advance, I would like to thank an energetic Board of Directors for their support, commitment, and vision. When Dr. Peggy Carver sent out the call for committee volunteers, in July, I was amazed at the number of responses (over 50 within a month). The list of the committee members for the upcoming year appears on page 2. Thank you one and all.

In addition to our routine activities, there are at least two new initiatives that I would like SIDP to pursue over the next year. Now that bioterrorism has reached our shores, it is imperative that pharmacists become more familiar with these threats. This includes understanding the actual and potential infectious agents, helping to coordinate local and regional treatment regimens, educating the public and other health professionals about bioterrorism, and helping to mitigate the overuse of antimicrobial agents. To this end, we are organizing a working group of SIDP members with credentials in this arena. I envision newsletter articles and a continuing education program for pharmacists to evolve from this endeavor. Dr. Ben Lomaestro, the author of the enclosed anthrax article, has agreed to serve as the chair of this working group. Please let Ben or me know if you are interested in helping out.

For a variety of historical reasons, the IDSA and SIDP have never forged a bond, despite our common interests. In fact,

I would characterize the relationship between the primary organizations representing ID physicians and pharmacists as antagonistic or indifferent, at best. However, it is my view that we have far more in common than not. Patient care, the misuse of antimicrobial agents and resulting toxicities, resistance development, and the appropriate interpretation of clinical trial results are but a few of the areas where, I believe, we can find common ground. Probably every member of SIDP has worked in partnership with or owes a debt of gratitude to an IDSA physician. Moreover, I suspect that there are many IDSA members who feel similarly about the pharmacists in their institutions. I would like to see the two Societies forge a better relationship. Dr. David Gilbert, President of IDSA, has expressed a similar interest. Please share your thoughts (or concerns) with me as this initiative moves forward.

As usual, fund raising is a critical issue. I think that there are few professional societies of comparable size that are able to give back to the membership as much as SIDP does in terms of residency and grant support. Many thanks again to **Pfizer Pharmaceuticals** for their support of the research program, the Social Evening at ICAAC, and the newsletter. To date, I have received commitments from **Abbott Labs** and **Bayer Pharmaceuticals** for 2002. Despite hard economic times, I am encouraged that our funding will be as strong as ever. Although the deadline for residency applications has passed, I encourage all members interested in conducting research to submit an application for funding. One warning: you will be required to use the PHS 398 Forms this year. So, take a look at them early if you are unfamiliar with them. Thanks to Dr. David Nix and his Research Awards Committee for spearheading this initiative.

Finally, we will be considering a new Web master over the next few weeks. Please share any thoughts or ideas about the Web site with Dr. Russell Lewis or his Internet Committee members. Any suggestions about content, layout, links, etc., would be greatly appreciated. I think that this is one place where some "redecorating" is needed.

Please contact me anytime with questions, comments, concerns, or suggestions. I can be reached by phone at 716-885-3580, ext. 203, or by E-mail to [cballow@buffalocrc.org](mailto:cballow@buffalocrc.org). As I stated earlier, this year is going to be fun!

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## ANTHRAX AND BIOTERRORISM

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### Introduction

*Bacillus anthracis* is a Gram-positive, spore-forming soil organism.<sup>1,2</sup> Anthrax infection is initiated by endospores that do not divide and are resistant to drying, heat, ultraviolet light, gamma radiation and many disinfectants.<sup>2</sup> The virulence of this organism is dependent upon both its outer capsule and two exotoxins released by the bacilli.<sup>1</sup> The clinical presentation and associated mortality depends on the route of infection, patient immunologic status, size of the inoculum, and virulence of the infecting strain.<sup>1</sup>

### Types of Anthrax Infection

Three types of infection occur in humans: inhalational, cutaneous, and gastrointestinal. Gastrointestinal anthrax is uncommon and will not be discussed further in this article.

#### Cutaneous Anthrax

Cutaneous anthrax occurs following deposition of the organism into the skin, especially in the presence of previous cuts or abrasions.<sup>3</sup> Areas of exposed skin such as arms, hands, face, and neck are the most frequent points of entry.<sup>3</sup> In the last known large "outbreak," which occurred in 1979 in Sverdlovsk, Russia, cutaneous anthrax cases occurred up to 12 days after the original aerosol release.<sup>3</sup> As it is thought that this event occurred at a lab that was manufacturing and modifying pathogens for biologic warfare, the extrapolation of these data to the current bioterrorism in the United States is somewhat

suspect, but they are the best data currently available. The hallmark of this infection is an edematous, pruritic papule at the inoculation site that converts into an ulceration that is surrounded by vesicular lesions within only 2 days.<sup>4</sup> The ulceration later develops a centralized black necrotic eschar that eventually falls off leaving the patient with local scarring. Untreated, cutaneous anthrax has a mortality rate of approximately 20%. This rate decreases almost to nil with appropriate antibiotic treatment.

#### Inhalational Anthrax

Inhalational anthrax is not considered a true pneumonia, as there is usually no infection of the lungs. It usually has an unassuming initial phase (fever, malaise, myalgia, and a nonproductive cough) that resembles a low-grade lower respiratory tract infection. This phase is followed by an acute, severe phase (severe respiratory distress, meningitis, and shock) that is generally fatal within 5 to 7 days of the onset of the initial symptoms.<sup>1,2</sup> The endospores are engulfed by alveolar macrophages and transported to the mediastinal and peribronchial lymph nodes with spore germination en route.<sup>2</sup> The bacilli multiply in the lymph nodes, cause hemorrhagic mediastinitis, and subsequently spread throughout the body hematogenously.<sup>2</sup> Replicating bacteria release toxins that cause hemorrhage, edema, and necrosis of the tissues they have invaded including the pleura, gastrointestinal tract, and meninges.<sup>3</sup> Although during the Sverdlovsk outbreak the modal incubation time until symptom onset was 10 days (remember that these may have been virulence-enhanced isolates), the onset of symptoms occurred up to 43 days after the reported date of exposure.<sup>1,2</sup> In animals, death occurs once critical toxin production is reached, regardless of whether sterility of the bloodstream is attained with antimicrobials.<sup>3</sup>

## The Diagnosis of Anthrax

The diagnosis of anthrax depends on the recognition of an unusual radiological finding, identification in the microbiology laboratory, or recognition of specific pathologic findings.<sup>3</sup> The initial symptoms of inhalational anthrax are "flu-like" and nonspecific. If there has been a possibility of an exposure, it is necessary to maintain a high level of suspicion, because the only chance for a favorable prognosis relies on early recognition and treatment.<sup>2</sup> The sudden appearance of a large number of patients with an acute-onset, flu-like illness with short-term (1 to 2 day) case fatality rates of 80% or more, should raise a high suspicion of an anthrax or pneumonic plague outbreak.<sup>3</sup> A widened mediastinum on a chest radiograph in a previously healthy patient with evidence of overwhelming flu-like illness is pathognomonic for inhalational anthrax.<sup>3</sup> Though not historically very helpful because of poor techniques, currently the most useful microbiologic test is a blood culture that should show growth within 6 to 24 hours. A definitive diagnosis may require 1 or 2 more days.<sup>3</sup>

The first suspicion of anthrax should initiate immediate notifications to local, state, and federal authorities. Guidelines for testing *B anthracis* and the clinical evaluation of patients potentially infected with it are available on various Web sites (Table 1).

There is no evidence to suggest that patient-to-patient transmission of anthrax occurs. Therefore, standard barrier isolation precautions are recommended for hospitalized

patients with all forms of anthrax infection.<sup>3</sup> There is no need to immunize or dispense prophylaxis to patient contacts, unless they were also initially exposed.<sup>3</sup>

## What is the Susceptibility Pattern of the Latest Isolates of *Bacillus anthracis*?

Antimicrobial susceptibility has been determined for 11 *B anthracis* isolates from Florida, New York City, and Washington, DC (Table 2).<sup>5</sup> The data indicate the presence of a cephalosporinase in isolates of *B anthracis*. Additional studies have also identified other beta-lactamases. The organism tends to be resistant to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime; treatment with most other antibiotics such as fluoroquinolones, macrolides, tetracyclines, and penicillin has been possible.<sup>3</sup> Although the current strain that victims have been exposed to is broadly susceptible, it is important to test each isolate to assure that broad treatment options remain available and that the strain being spread has not been changed to a more resistant modified one.

## What Are the Recommended Treatment Guidelines for Anthrax ?

The Centers for Disease Control (CDC) recently published guidelines for both inhalational and cutaneous exposure to anthrax (Tables 3 and 4).<sup>5</sup> *The New England Journal of Medicine* also has an updated review of anthrax.<sup>6</sup> The risk for recurrence remains for at least 60 days because of the possibility of delayed germination of spores.<sup>3</sup> Once

**Table 1. Useful Web Sites**

Morbidity and Mortality Weekly Reports (MMWR)	<a href="http://www.cdc.gov/mmwr/">www.cdc.gov/mmwr/</a>
Johns Hopkins Center for Civilian Biodefense	<a href="http://www.hopkins-biodefense.org">www.hopkins-biodefense.org</a>
CDC health alerts and recommendations	<a href="http://www.bt.cdc.gov/">www.bt.cdc.gov/</a>
FDA updates on anthrax	<a href="http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html">www.fda.gov/oc/opacom/hottopics/bioterrorism.html</a>
American Society of Microbiology	<a href="http://www.asmusa.org/pcsrc/bioprep.htm">www.asmusa.org/pcsrc/bioprep.htm</a>
<i>Journal of the American Medical Association:</i> Several written consensus guidelines on the management of bioterrorist agents, including anthrax, are freely available	<a href="http://www.jama.ama-assn.org">www.jama.ama-assn.org</a>
US Army Medical Research Institute of Infectious Diseases	<a href="http://www.usamriid.army.mil/education/bluebook.html">www.usamriid.army.mil/education/bluebook.html</a>
New York City Department of Health anthrax update site	<a href="http://www.nyc.gov/html/doh/html/cd/anthrax.html">www.nyc.gov/html/doh/html/cd/anthrax.html</a>
American Hospital Association: Several useful documents, including hospital readiness and what to tell your community about anthrax	<a href="http://www.aha.org/emergency/readiness/madisasterB1003.asp">www.aha.org/emergency/readiness/madisasterB1003.asp</a>
New York State Office of the Professions: Guidance to pharmacists regarding dispensing antibiotics for prophylactic treatment of anthrax	<a href="http://www.op.nysed.gov/pharmanthrax.htm">www.op.nysed.gov/pharmanthrax.htm</a>
Medscape: Provides a regularly updated feature on bioterrorism with several useful links	<a href="http://www.medscape.com">www.medscape.com</a>
Biological and toxic weapons convention protocol can be downloaded from these sites	<a href="http://www.fas.org/bwc/">www.fas.org/bwc/</a> <a href="http://www.brad.ac.uk/acad/sbtwc/">www.brad.ac.uk/acad/sbtwc/</a> <a href="http://cns.miis.edu/research/cbw/">http://cns.miis.edu/research/cbw/</a>
American College of Physicians	<a href="http://www.acponline.org/bioterro/">www.acponline.org/bioterro/</a>
Association for Infection Control Practitioners	<a href="http://www.apic.org/bioterror/">www.apic.org/bioterror/</a>
Federal Register notice from FDA clarifying doxycycline and penicillin G procaine labeling	<a href="http://www.fda.gov/ohrms/dockets/98fr/cd01156.pdf">www.fda.gov/ohrms/dockets/98fr/cd01156.pdf</a>
Ciprofloxacin briefing document presented at FDA Advisory Committee Meeting, July 28, 2000	<a href="http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3632b1.htm">www.fda.gov/ohrms/dockets/ac/00/backgrd/3632b1.htm</a>

**Table 2. Published Susceptibility for Currently Identified Isolates**

Antimicrobial	MIC (mcg/mL)	Susceptibility: NCCLS Breakpoints for Staphylococci Used
Ciprofloxacin	≤ 0.06	S
Doxycycline	≤ 0.3	S
Chloramphenicol	4	S
Clindamycin	≤ 0.5	S
Tetracycline	0.06	S
Rifampin	≤ 0.5	S
Vancomycin	1–2	S
Imipenem	<0.12	S
Erythromycin	1	I
Azithromycin	2	S (borderline)
Clarithromycin	0.25	S
Penicillin	<0.06–0.12	S
Amoxicillin	<0.06	S
Ceftriaxone	16	I (using gram-negative interpretation)

S = susceptible; I = intermediate.

Reprinted from Centers for Disease Control.<sup>5</sup>

susceptibility is known, it is recommended to use the most widely available, efficacious, and least toxic antibiotic.<sup>3</sup> Oral therapy may replace intravenous therapy as soon as a patient's clinical condition improves. Although the treatment of cutaneous anthrax is typically 7 to 10 days, the risk of simultaneous inhalation of spores during the current bioterrorism attack is high. Therefore, persons with cutaneous exposure should also be treated for 60 days.<sup>5</sup>

Ciprofloxacin is recommended in pediatric patients, with a penicillin substitution when susceptibilities are known. Although doxycycline is not recommended in children under the age of 9 years, the serious risk of this infection supports the consensus recommendation for its use if other agents are not readily available.<sup>3</sup> Ciprofloxacin has also been recommended in pregnant women because of a paucity of animal data suggesting teratogenicity in humans and the gravity of this illness.<sup>3</sup>

Because of the mortality associated with inhalational anthrax, 2 or more antimicrobial agents are recommended for empiric or documented infection, despite the lack of controlled studies to support a multiple-drug approach.<sup>5</sup> The CDC recommendation<sup>5</sup> suggests adding to ciprofloxacin or doxycycline agents including rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, and clarithromycin. Amoxicillin/clavulanate is thought to be no better than amoxicillin, despite its beta-lactamase protection, because of the overwhelming number of organisms likely to be present.<sup>5</sup> Combination therapy for cutaneous anthrax has also been recommended.<sup>5</sup>

Aggressive forms of the disease may also require replacement of fluid and electrolytes.<sup>1</sup> Corticosteroids may be considered for extensive edema or the swelling of the head and neck region associated with cutaneous anthrax.<sup>5</sup> Toxemia may require hydrocortisone 100 to 200 mg per day because of exhaustion of the adrenal function.<sup>1</sup>

### What Are the Recommendations for Initiating Prophylaxis?

Although tetracycline, doxycycline, minocycline, and penicillin have approved labeling by the Food and Drug Administration (FDA) for disease associated with *B anthracis*, none of these agents is approved for postexposure prophylaxis for disease caused by inhaled *B anthracis*.<sup>7</sup> The data used to support ciprofloxacin's indication for the prevention of inhalational anthrax comes from a primate (macaque) model.<sup>8</sup> In this model, mortality was merely delayed if prophylaxis was administered for 5, 10, or 20 days. At 30 days, results in survival rates began to approximate the "best-case" results. Furthermore, data from the outbreak in Sverdlovsk in 1979 show that 1 patient developed the disease 43 days after the presumed exposure.<sup>9</sup> Persons with an exposure or contact with an item or environment known or suspected to be contaminated with *B anthracis* should be offered antimicrobial prophylaxis.<sup>3,5</sup> Prophylaxis can be achieved with a 6-week course of therapy. If the suspected dose of spores is high, a longer course is warranted to assure total pulmonary clearance of spores that are not affected by antimicrobials.<sup>2</sup> Exposure or contact, regardless of laboratory test results, is the basis for initiating therapy (Table 5).<sup>5</sup>

The anthrax vaccine in the United States is an inactivated cell-free product made from the cell-free filtrate of a nonencapsulated attenuated strain of *B anthracis*.<sup>3</sup> It is manufactured by Bioport Corporation and is to be administered as a 6-dose series of 0.5 mL subcutaneous injections at 0, 2, and 4 weeks and at 6, 12, and 18 months.<sup>2</sup> Chemoprophylaxis should continue for at least 4 weeks until at least 3 doses of the vaccine have been received by all exposed.<sup>1</sup> Vaccination is not practical after an attack because of the length of time it takes until immunity develops. Edema, erythema, warmth, tenderness, and nodules at the injection site are reported by approximately a third of those vaccinated.<sup>1</sup> A human,

live, attenuated vaccine is produced and used in countries of the former Soviet Union.<sup>3</sup> Existing supplies of the US vaccine are used to immunize all military personnel.<sup>2</sup>

### What Are Potential Problems Associated With These Guidelines?

Recommendations for prophylaxis and treatment are based on animal data, an understanding of *B anthracis* resistance potential and patterns, and the possible logistics of treating large numbers of patients.<sup>3</sup> Of prime importance is the knowledge that a delay of even a few hours may greatly lessen the chances for a favorable treatment outcome.<sup>3</sup> This, combined with the difficulty of diagnosing anthrax, implies that all patients with fever or evidence of systemic disease in

an area with evidence of anthrax should receive treatment until the disease is excluded.<sup>3</sup> Difficulty in establishing a quick diagnosis, combined with patient anxiety over the current bioterrorism threat, has created an environment in which large numbers of patients are being treated empirically for suspected anthrax. There is also a fear of widespread resistance in more common pathogens because of the indiscriminate use of antimicrobials for anthrax prophylaxis.<sup>10</sup>

The NY State Department of Health has recently published a "Dear Pharmacist" letter that attempts to provide guidance regarding the dispensing of antibiotics for prophylactic treatment of anthrax and other organisms. The letter can be found on the Web site [www.op.nysed.gov](http://www.op.nysed.gov).

**Table 3. Latest Treatment Guidelines for Inhalational Anthrax<sup>a,b</sup>**

Category	Initial Therapy (Intravenous) <sup>c,d</sup>	Duration
Adults	Ciprofloxacin 400 mg every 12 hrs <sup>e</sup> or Doxycycline 100 mg every 12 hrs <sup>f</sup> and One or two additional antimicrobials <sup>d</sup>	IV treatment initially. <sup>e</sup> Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID Continue for 60 days (IV and po combined) <sup>g</sup>
Children	Ciprofloxacin 10–15 mg/kg every 12 hrs <sup>h,i</sup> or Doxycycline: <sup>i</sup> >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs and One or two additional antimicrobials <sup>d</sup>	IV treatment initially. <sup>e</sup> Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10–15 mg/kg po every 12 hrs <sup>i</sup> or Doxycycline: <sup>i</sup> >8 yrs and >45 kg: 100 mg po BID >8 yrs and ≤45 kg: 2.2 mg/kg po BID ≤8 yrs: 2.2 mg/kg po BID Continue for 60 days (IV and po combined) <sup>g</sup>
Pregnant women <sup>k</sup>	Same for nonpregnant adults (the high death rate from the infection outweighs the risk posed by the antimicrobial agent)	IV treatment initially. <sup>e</sup> Switch to oral antimicrobial therapy when clinically appropriate. <sup>b</sup> Oral therapy regimens same for nonpregnant adults
Immunocompromised persons	Same for nonimmunocompromised persons and children	Same for nonimmunocompromised persons and children

<sup>a</sup> For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.

<sup>b</sup> Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.

<sup>c</sup> Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.

<sup>d</sup> Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.

<sup>e</sup> Initial therapy may be altered based on clinical course of the patient: one or two antimicrobial agents (eg, ciprofloxacin or doxycycline) may be adequate as the patient improves.

<sup>f</sup> If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.

<sup>g</sup> Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.

<sup>h</sup> If intravenous ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1–2 hours after oral dosing but may not be achieved if vomiting or ileus is present.

<sup>i</sup> In children, ciprofloxacin dosages should not exceed 1g/day.

<sup>j</sup> The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).

<sup>k</sup> Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

Reprinted from Centers for Disease Control.<sup>5</sup>

**Table 4. Latest Treatment Guidelines for Cutaneous Anthrax**

Category	Initial Therapy (Oral) <sup>a</sup>	Duration
Adults <sup>b</sup>	Ciprofloxacin 500 mg BID <b>or</b> Doxycycline 100 mg BID	60 days <sup>c</sup>
Children <sup>b</sup>	Ciprofloxacin 10–15 mg/kg every 12 hrs (not to exceed 1g/day) <b>or</b> Doxycycline: <sup>d</sup> >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs	60 days <sup>c</sup>
Pregnant women <sup>b,e</sup>	Ciprofloxacin 500 mg BID <b>or</b> Doxycycline 100 mg BID	60 day <sup>c</sup>
Immunocompromised persons <sup>b</sup>	Same for nonimmunocompromised persons and children	60 days <sup>c</sup>

<sup>a</sup> Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin 500 mg po TID for adults or 80 mg/kg/day divided every 8 hours for children is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.

<sup>b</sup> Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended (see Table 3).

<sup>c</sup> Previous guidelines have suggested treating cutaneous anthrax for 7–10 days, but 60 days is recommended in the setting of this attack, given the likelihood of exposure to aerosolized *B anthracis*.

<sup>d</sup> The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).

<sup>e</sup> Although tetracyclines or ciprofloxacin is not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

Reprinted from Centers for Disease Control.<sup>5</sup>

**Table 5. Latest Prophylaxis Recommendations**

Category	Initial Therapy	Duration
Adults (including pregnant women and immunocompromised persons)	Ciprofloxacin 500 mg po BID <b>or</b> Doxycycline 100 mg po BID	60 days
Children	Ciprofloxacin 10–15 mg/kg po every 12 hrs <sup>a</sup> <b>or</b> Doxycycline: >8 yrs and >45 kg: 100 mg po BID >8 yrs and ≤45 kg: 2.2 mg/kg po BID ≤8 yrs: 2.2 mg/kg po BID	60 days

<sup>a</sup> In children, ciprofloxacin dosages should not exceed 1 g/day .

Reprinted from Centers for Disease Control.<sup>5</sup>

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# 41ST INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)— A REVIEW OF SELECTED ABSTRACTS

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Over the past decade, SIDP members have contributed significantly to the body of scientific data presented at the American Society for Microbiology's Annual Meeting on infectious diseases (Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC]). This year was to be no exception. The reason I say "was to be" is that we are all painfully aware of the heartrending circumstances surrounding the postponement of this year's ICAAC. As such, I welcomed the opportunity to carefully review the programs and abstracts of the 41st Annual ICAAC in preparation for this article; it was a pleasant distraction from the events of the world.

Collectively, 71 SIDP members had poster and/or platform presentations that numbered 156! In fact, many SIDP members co-authored or presented multiple abstracts and presentations. Indeed, 7 individuals appeared as authors on at least 6 abstracts: they include Drs. Ellie Hershberger, James Johnson, Russell Lewis, David Nicolau, Charles Nightingale, Michael Rybak, and George Zhanel (who had 11!). Out of this sizeable body of outstanding science, it was a difficult task to decide which abstracts to include in this review (obviously, space limitations precluded an in-depth review of all 156!). That having been said, this article focuses on 10 diverse abstracts that will hopefully be of interest to the majority of SIDP members. I tried to include "a little bit of everything." My apologies go to all the authors whose abstracts could not be included.

In what is sure to capture the attention of clinicians everywhere, Joe Bertino and colleagues<sup>1</sup> reported 4 cases of torsades de pointes (TdP)/ventricular fibrillation (VF) among patients receiving gatifloxacin. Previously, only 1 case of TdP had been reported in an estimated 1.9 million gatifloxacin recipients. Patients were 60 to 81 years of age (3 females; 1 male) and were receiving gatifloxacin 400 mg daily (3 intravenously and 1 orally). Two patients developed TdP/VF after the initial oral dose, and 2 after 3 days of oral or intravenous therapy. Underlying cardiovascular disease, renal impairment, duration of gatifloxacin therapy, and concomitant medications were all hypothesized to contribute to cardiotoxicity with gatifloxacin. In the words of the authors, the results of this report "raise serious questions" concerning the utility of certain information (eg, QTc prolongation) to predict cardiotoxicity a priori with antibiotics such as gatifloxacin.

On a more uplifting note, the group including Joseph Kuti, Charles Nightingale, and David Nicolau reported on the pharmacoeconomic impact of a pharmacist-managed automatic intravenous (IV) to oral (PO) conversion program for levofloxacin.<sup>2</sup> These authors compared economic and clinical outcomes between the "standard of care at their institution" with that of an active pharmacist-conversion program. The criteria for switching from IV to PO levofloxacin were developed before the study was initiated. Results showed that the average day of conversion from IV to PO levofloxacin for the pharmacist-conversion program was 3 days compared to 7 days in the standard-of-care group ( $P=.009$ ). Of note, patients met the criteria for conversion on day 2 in both groups. Although the length of hospital stay was similar between cohorts, the cost per patient for levofloxacin treatment was \$158.00 in the standard-of-care group versus \$90.00 in the pharmacist-conversion group ( $P=.002$ ). The clinical outcome did not differ between groups. This study contributes to the growing body of literature that supports the beneficial impact of clinical pharmacists on economic outcomes—an important point to consider in this age of managed care.

Some additional interesting pharmacoeconomic data were presented in a poster that included Gail Itokazu among its authors.<sup>3</sup> In this study, antibiotics with redundant antimicrobial spectra were prospectively identified by an infectious diseases pharmacist and simplified when indicated. Redundant drug costs were determined, and the potential savings from interventions were calculated. A total of 137 cases of antibiotic combinations with redundant antimicrobial spectra were identified in a chart review over a 5-week period. Physician-prescribing errors and lapses in the hospital drug ordering and distribution system were largely responsible for antibiotic combinations with redundant spectra. Interventions were accepted in 96% of the cases and the potential and actual cost savings exceeded \$10,000. These results further suggest that a pharmacist's review and correction for antibiotic regimens with redundant spectra offer an effective means of reducing in-patient antibiotic costs.

Moving from economics to fungi, Debra Goff collaborated with investigators from several institutions in a multicenter, matched, case-control study to identify risk factors for nosocomial candidemia in surgical intensive care unit (SICU) patients.<sup>4</sup> Forty-three patients who acquired nosocomial candidemia in the SICU were matched with 79 control subjects. Compared with the controls, the SICU patients had higher APACHE II scores, were significantly more likely to have renal dysfunction, central venous catheterization, pulmonary artery catheterization, digestive tract surgical procedures, and to have received total parenteral nutrition, intravenous lipids, third-generation cephalosporins, and drugs with potent antianaerobic activity. A multivariate analysis revealed that pulmonary artery catheterization (odds ratio (OR), 17.8; 95% confidence interval (CI), 3.0–104.9) and total parenteral nutrition (OR, 18.7; 95% CI, 3.3–105.8) were independent predictors for nosocomial candidemia. As the authors note, efficacy studies of empiric antifungals among these high-risk SICU patients are warranted.

Russell Lewis and Randall Prince were collaborators on an interesting abstract that found that itraconazole attenuated the efficacy of increasing amphotericin B doses in a murine

model of invasive pulmonary aspergillosis.<sup>5</sup> Mice (pretreated and untreated with itraconazole) with pulmonary *Aspergillus fumigatus* received amphotericin B at 4 different doses. At amphotericin B doses >1 mg/kg, fewer itraconazole pretreated mice versus untreated mice were alive at 96 hours (0% to 20% versus 60% to 80%, respectively). The fungal burden in the lung (CFU/mL and chitin assay) was also higher at all time points in the group of mice pretreated with itraconazole than in those that were untreated ( $P<.05$ ). The authors showed that amphotericin B's mycological efficacy was poorer in mice pretreated with itraconazole. Moreover, high-dose amphotericin B did not reverse this antagonism. If these results adequately reflect the pharmacodynamic interaction between itraconazole and amphotericin B in humans, there may be clinical implications in patients with *Aspergillosis*; further investigative study in humans is necessary.

In another compelling investigation, Elizabeth Coyle, Raymond Cha, and Michael Rybak reported the comparative antibacterial effects of linezolid, penicillin, and clindamycin alone and in combinations on virulent group A streptococcus (GAS) and pyrogenic exotoxin A (SpeA) production.<sup>6</sup> An in vitro pharmacodynamic model was used to emulate infection with a known SpeA-producing GAS isolate. Treatment with linezolid, clindamycin, and combination regimens revealed significantly lower SpeA release at 1 hour compared to that for penicillin alone and control ( $P<.05$ ). The authors note that the reduction of early SpeA-release by linezolid and clindamycin, alone and in combination with penicillin, may optimize treatment of GAS infections. This is welcome data that has the potential to impact a rapidly progressing, often fatal infection. Although studies confirming the usefulness of these protein synthesis inhibitors (linezolid and clindamycin) in humans would be ideal, they would be most difficult to conduct.

Bacterial resistance continues to be a widespread concern among the health care community, yet the source of resistant organisms can often be difficult to trace. Several researchers, including Ellie Hershberger, established information on prevalence rates in Michigan for resistant enterococci in food and animals and their potential roles as reservoirs.<sup>7</sup> Fecal samples from 12 beef, 12 dairy, 12 swine, 8 turkey, and 7 chicken farms were evaluated. Of note, vancomycin resistance was not found in any of the farms. However, dairy and swine farms using gentamicin showed greater resistance than did dairy and swine farms with no gentamicin use. Beef farms did not use gentamicin, and resistance was 0%. In turkey farms, the use of virginiamycin was associated with a higher prevalence of *Enterococcus faecium* resistance to quinupristin-dalfopristin (Synercid). Similarly, ciprofloxacin resistance rates were higher in dairy farms (mean 76%) and turkey farms (mean 54%) that used the fluoroquinolone enrofloxacin. Collectively, these data suggest that animals may comprise a significant reservoir of antibiotic resistance.

Another study, with more encouraging results, addressed the issue of bacterial resistance among *Streptococcus pneumoniae* in Canada.<sup>8</sup> The Canadian Respiratory Organism Susceptibility Study (CROSS) Group, including George Zhanel, reported results from an ongoing national surveillance study

to determine the incidence of penicillin nonsusceptible *Streptococcus pneumoniae* in Canada over a 4-year period; they also assessed antibiotic use during this period. Twenty-three medical centers, representing 9 out of 10 Canadian provinces, provided up to 100 respiratory tract isolates of *S pneumoniae* each year. The isolates were tested against 25 antibiotics. The investigators found that the percentage of penicillin-resistant isolates decreased steadily from 21.2% in 1997–1998 (1180 isolates tested) to 15.1% in 2000–2001 (865 isolates tested). Interestingly, beta-lactam prescriptions in Canada decreased by 20.3% from the years 1996 to 2000, and total antibiotic use decreased by 14.2% over this same time period. Results from this study suggest that antimicrobial resistance may be impacted over a large geographical area in a short period of time with changes in antibiotic use.

Well-controlled prospective studies evaluating HMG-CoA-reductase inhibitor (statin) therapy for the management of hyperlipidemia among protease inhibitor recipients are lacking. Susan Chuck and coworkers described the efficacy and safety of pravastatin in patients with protease inhibitor-associated hyperlipidemia.<sup>9</sup> National Cholesterol Education Program (NCEP) guidelines were used to manage patients who were assessed for efficacy and safety at week 12. Pravastatin was dosed at 20 mg daily with the option to increase to 40 mg daily after 4 weeks if the LDL cholesterol goal was not met. Skeletal muscle toxicity and liver function tests were used to assess safety. Seventeen patients completed the study. In 9 patients, whose LDL cholesterol could be calculated, the mean LDL cholesterol decreased from 216 to 158 mg/dL ( $P<.003$ ). Of note, in those patients whose elevated triglycerides precluded calculation of LDL cholesterol, 50% reached the LDL goal at week 12. Excluding an outlier with an 80% increase, the mean percent-change in triglycerides was -26% ( $P=.009$ ). No toxicities attributable to pravastatin were reported, nor were any deleterious effects on HIV-RNA or CD4+ cell counts observed. In patients with protease inhibitor-associated hyperlipidemia, pravastatin resulted in both statistically and clinically significant reductions in LDL, total cholesterol, and triglycerides at week 12. The relative efficacy and safety of pravastatin in this study is welcome information. A large prospective multicenter trial involving pravastatin for the use of protease inhibitor-associated hyperlipidemia is currently underway.

Drug interactions between methadone and antiretrovirals have been the source of much interest over the past several years, with several antiretrovirals being implicated in precipitating methadone withdrawal (eg, nevirapine and efavirenz). In addition, ritonavir has been shown to reduce methadone levels. Mark Shelton, Lori Esch, and colleagues<sup>10</sup> assessed the influence of a once-daily saquinavir and ritonavir combination (1600 mg and 100 mg, respectively) on the pharmacokinetics of methadone. HIV-negative volunteers on stable methadone were assessed for unbound R-methadone plasma concentrations before (on day 0) and after 14 days of directly observed ritonavir-saquinavir exposure (day 14). The day 14/day 0 geometric mean ratio (95% CI) for unbound R-methadone was 0.92 (0.87–0.98). The investigators also measured alpha<sub>1</sub>-acid-glycoprotein (AAG) before and after administering the protease inhibitor; the day 14/day 0 geometric mean ratio (95% CI) for AAG was

0.92 (0.87–0.98). Thus, once-daily ritonavir–saquinavir treatment was associated with a clinically insignificant reduction in unbound R-methadone, perhaps because of an increase in AAG.

A second aspect of this study assessed steady-state saquinavir and ritonavir concentrations in these volunteers. Ten of 12 subjects had saquinavir  $C_{min}$  values greater than the saquinavir  $EC_{50}$  (50 ng/mL); this was lower than expected (despite 100% adherence and adequate ritonavir exposure). The authors concluded that further population-based studies of a combination of saquinavir and ritonavir once daily are needed to determine factors associated with suboptimal saquinavir exposure.

Lastly, by the time that this review appears in print, we will have been treated to what I'm sure will be outstanding treatises by Joe Bertino, on pharmacogenetics and drug disposition,<sup>11</sup> and by Angela Kashuba, on metabolism interactions to improve systemic exposure.<sup>12</sup> Again, SIDP members have contributed readily to the body of science comprising the 41st ICAAC, and we look forward to all their contributions in the future.

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## POST-ICAAC FOLLOW-UP

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Three notable events occurred at ICAAC that I think are worth highlighting:

1. Dr. Rybak and I met with Drs. David Gilbert (President) and Mike Scheld (President-Elect) of IDSA to discuss improved relations between our Societies. We had a very honest exchange of viewpoints and I came away from the meeting with a sense that the current leadership of IDSA is sincerely interested in improved relations. The IDSA Executive Committee and the SIDP Board of Directors will be considering what positive steps can be taken over the next few months to forge a better working relationship. Again, let me hear from you on this!
2. Dr. Matthew Dolan delivered an outstanding State-of-the-Art Lecture on bioterrorism at the Annual Meeting. The lecture was very timely and informative. I can't remember so many members remaining until the end of the meeting. Many thanks to Dr. Tom Hardin and his colleagues at **Ortho-McNeil Pharmaceuticals** for their support of Dr. Dolan's lecture.
3. Past President Dr. Steve Barriere delivered an outstanding and entertaining overview of SIDP's first decade at the Social Event. All in attendance had a great time. Thanks, Steve!

