SYPHILIS FORUM

AN EDUCATIONAL PUBLICATION FROM KING PHARMACEUTICALS®, Inc.

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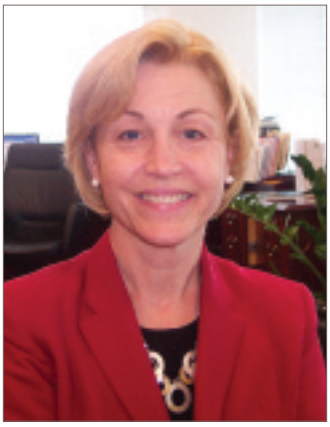
Notes from Dr. Wase

A Letter From Linda Wase, MD, Executive Vice President, Medical Affairs



Dear Colleagues,

As a new face on the King Pharmaceuticals®, Inc. management team, I welcome the opportunity to introduce myself to all of you in the syphilis treatment community through this third issue of Syphilis Forum. I recently joined King Pharmaceuticals® as Executive Vice President, Medical Affairs.

Before joining King, I served in a variety of senior medical roles over the last 20 years at Bristol-Myers Squibb, most recently Vice President Field Medical Science. I look forward to contributing my many years of healthcare industry experience and expanding my knowledge of the infectious disease area as I work with the Bicillin® team and clinicians such as you.

I am enthusiastic about continuing King's syphilis educational initiatives. This issue of Syphilis Forum will focus on some of the management and treatment questions that were asked during the June 2007 "State of Syphilis" audio conferences. These questions include: "How do I manage penicillin desensitization in select patient groups?" and "How do I understand/manage serofast titers in HIV-infected syphilis patients?" We believe that the following articles will help provide you with an effective treatment strategy for these patients.

Please watch for future letters inviting your participation in upcoming "State of Syphilis" audio conferences and other King initiatives. I welcome your comments, questions and/or suggestions.

Sincerely,

Linda Wase, MD
Executive Vice President, Medical Affairs, King Pharmaceuticals, Inc.

WHAT'S INSIDE

King Pharmaceuticals

New Bicillin® Web URL: www.bicillin.com

Please note that the Bicillin® Web site URL has changed and is now located at www.bicillin.com. We hope that you are finding this Web site to be a comprehensive and convenient resource about Bicillin® L-A (penicillin G benzathine injectable suspension) and Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension). Visitors will find details on specific indications, proper usage, and complete safety and prescribing information for both products. The Web site is frequently updated with new information and announcements, so we encourage you to visit often.

Please see important safety information on page 4 and accompanying full Prescribing Information which may also be obtained at www.bicillin.com.

When is Serofast, "Serofast?"

After effective syphilis treatment, the RPR* or VDRL* titer (non-treponemal test) usually becomes non-reactive or negative. In treating early syphilis such a response can occur in 6 months. In treating late syphilis that response can occur in 12 months or more.[1] HIV-infected patients generally have a slower decline in titers than HIV-uninfected patients.[2, 3, 4] Thus, most experts recommend determining the serological response to treatment at 6 and 12 months in HIV-uninfected patients with early and late syphilis respectively. Current CDC guidelines recommend clinical and serological post-therapy follow-up at 3,6,9,12 and 24 months in HIV-infected patients. Due to the slower serological response in HIV-infected patients some experts recommend determining treatment outcomes at 12 months for early syphilis and 24 months for late syphilis.[1, 2, 3, 4]

In up to 20% of patients, however, a reactive serologic titer may persist for more than 12 months (HIV-uninfected patients) or longer (HIV-infected patients).[5] A persistently reactive non-treponemal (RPR or VDRL) serologic test for syphilis after treatment for syphilis may represent treatment failure or a "serofast" reaction.[1, 2]

Determining whether a persistently reactive titer indicates treatment failure or the serofast reaction is one of the most challenging aspects in syphilis management. A 4-fold decrease in non-treponemal titer post-treatment is considered necessary to demonstrate therapeutic efficacy and the titer will usually become non-reactive with time; although, in some patients a low, serofast titer (less than or equal to 1:4) will remain for a long period of time or for life. Rising titers or persistent titers greater than or equal to 1:32 are more problematic and raise concerns about treatment failure, but in some cases could be a serofast reaction, in particular if the prior titer was substantially elevated (greater than 1:256) and the 1:32 represents at least a 4-fold decline.[1, 2, 6]

One of the most common pitfalls in the interpretation of follow-up syphilis test results is the failure to observe for an adequate amount of time. Syphilis titers represent an immunologic reaction to infection and take time-on the order of a year or two to decline. The immunologic titer response in long-standing infection usually takes longer to decline than the titer response in recently acquired infection.[5] If treatment failure, further CSF analysis should be considered to rule out neurosyphilis.[3, 5]

After the observation period, if there is doubt about whether the persistent titer represents treatment failure or a serofast response, many experts would err on the side of caution and re-treat the patient with a repeat course of therapy, usually a series of 3 injections of penicillin G benzathine (Bicillin® L-A) 2.4 MU intramuscular weekly for 3 weeks. If treatment failure, further CSF analysis should be considered to rule out neurosyphilis.[1, 4]

In late syphilis, which is usually diagnosed as late latent syphilis detected through a routine screening test and the non-treponemal serologic test titer is low (e.g., 1:2), a 4-fold decline in titer may take years. At two years should the titer not have declined 4-fold, and persists at 1:2 or 1:1, there are no clinical data to dictate best practice. Because at this stage less is known, some experts suggest continuing observation and others would re-treat with penicillin G benzathine 2.4 MU intramuscular once weekly for 3 weeks.[1]

It is important to remember that the syphilis titers one follows over time to evaluate the response to treatment are the **non-treponemal test titers**, the RPR or VDRL. The treponemal test titers (TPPA* or FTA-ABS*) once reactive usually remain reactive for the life of the patient. Although in primary syphilis, treponemal titers can become non-reactive (after 2-3 years) in about 15 to 25% of patients after successful treatment.[1]

**RPR = rapid plasma reagin*

VDRL = venereal disease research laboratory

TPPA = treponema pallidum particle agglutination

FTA-ABS = fluorescent treponemal antibody absorbed

1 Centers for Disease Control and Prevention, 2006 STD Treatment Guidelines. Syphilis Section. Available at www.cdc.gov/std.

2 Augenbraun, M. Syphilis. Lange, McGraw Hill. "Current Diagnosis & Treatment of Sexually Transmitted Diseases, Jeffrey D. Klausner; Edward W. Hook, III, 2007.

3 Rolfs, et al (1997). A randomized Trial of Enhanced Therapy for Early Syphilis Patients with and without Human Immunodeficiency Virus Infection. NEJM 337:307-314.

4 Zetola MZ, Engelman J, Jensen P, Klausner JD. Syphilis in the United States: An Update for Clinicians With an Emphasis on HIV Coinfection. Mayo Clin. Proc. September 2007;82(9):1091-1102.

5 Hook, EW. Principles of serological testing for syphilis; Lange, McGraw Hill, "Current Diagnosis & Treatment of Sexually Transmitted Diseases, Jeffrey D. Klausner; Edward W. Hook, III, 2007.

6 Zetola MZ, Klausner JD. Syphilis and HIV Infection: An Update.CID 2007:44 (1 May), HIV/AIDS.

Quick Reference for Penicillin Desensitization

King Pharmaceuticals

According to the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2006:[1]

- There are NO proven alternatives to benzathine penicillin G available for treating:
  - — Neurosyphilis
  - — Congenital syphilis
  - — Syphilis in pregnant women
- Pregnant women, infants and children with any stage of syphilis who are allergic to penicillin should be desensitized and treated with penicillin G
- Penicillin G is recommended for use, whenever possible, in HIV-infected patients. The efficacy of alternative non-penicillin regimens in HIV-infected patients has not been well studied.

DESENSITIZATION FACTS

- Patients who have a positive skin test to one of the penicillin determinants can be desensitized
- Desensitization can be performed via oral or intravenous (IV) administration
- Oral desensitization is regarded as safer and easier to perform
- Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur
- After desensitization, patients MUST be maintained on penicillin continuously for the duration of the course of therapy

1 Centers for Disease Control and Prevention, 2006 STD Treatment Guidelines. Syphilis Section. Available at www.cdc.gov/std <http://www.ded.gov/std> .

Oral Desensitization Protocol for Patients with a Positive Skin Test*

Observation period: 30 minutes before parenteral administration of penicillin

Interval between doses: 15 minutes

Cumulative dose: 1.3 million units

Penicillin V Suspension Dose*	Amount§ (units/mL)	mL	Units	Cumulative Dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

+ Elapsed time is 3 hours and 45 minutes;
§ The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

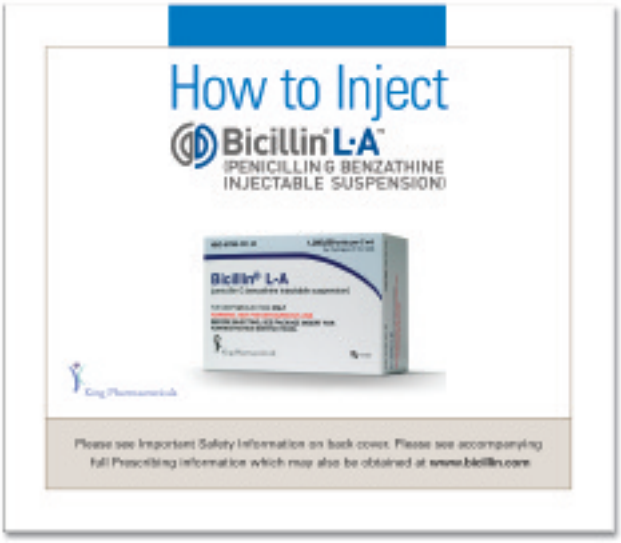
** Reprinted with permission from the New England Journal of Medicine.*
SOURCE: Wendel GO Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin Allergy and Desensitization in Serious Infections During Pregnancy. New England Journal of Medicine 1985; 312: 1229-32§

Free "How-To-Inject" Bicillin® L-A Video Now Available

King Pharmaceuticals®, Inc. is now offering healthcare providers a free CD or DVD copy of its newly developed "How-to-Inject" Bicillin® L-A (penicillin G benzathine injectable suspension) video. The video was developed through a collaboration between King Pharmaceuticals and the San Francisco Department of Public Health.

Narrated by syphilis expert Dr. Jeffrey D. Klausner, Director, STD Prevention and Control Services, San Francisco Department of Public Health, the short program provides step-by-step instructions on proper injection of Bicillin® L-A and suggested tips on patient comfort and safety information. In addition, the video stresses that Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) should not be substituted for Bicillin® L-A in the treatment of syphilis. Bicillin® C-R is not approved for the treatment of syphilis.

To obtain your free copy, please e-mail your request to Jan Madura at jan.madura@cstratinc.com. Please specify your format preference (CD or DVD) and mailing address.



BICILLIN L-A (penicillin G benzathine injectable suspension) is indicated in the treatment of infections due to penicillin G sensitive microorganisms that are susceptible to the low and very prolonged serum levels provided by this particular dosage form. These include mild-to-moderate upper respiratory tract infections due to susceptible streptococci (including streptococcal pharyngitis), syphilis, yaws, bejel, and pinta. It is also indicated as prophylactic treatment for rheumatic fever and glomerulonephritis.

BICILLIN C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is indicated in the treatment of moderately severe infections due to penicillin-G-susceptible microorganisms that are susceptible to serum levels common to this particular dosage form. These include upper respiratory tract infections, scarlet fever, erysipelas, skin and soft-tissue infections due to susceptible streptococci, and pneumonia and otitis media due to susceptible pneumococci. **NOTE: This formulation should not be used in the treatment of venereal disease, including syphilis.**

Important Safety Information for BICILLIN L-A and BICILLIN C-R

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardio-respiratory arrest and death.

Penicillin G is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins and BICILLIN C-R in patients with a history of hypersensitivity reaction to procaine. Before use, identify previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If allergic reaction occurs, discontinue use and initiate appropriate therapy.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening.

Give only by deep intramuscular injection. Do not inject into or near nerves or arteries; severe neurovascular or other damage may occur. Adverse reactions include but are not limited to: gastrointestinal, hypersensitivity, central nervous system, dermatologic, hematologic, and injection site reactions.

Please see accompanying full Prescribing Information.

If you would like more information about this newsletter, or would like to receive it via e-mail, please contact **Jan.Madura@cstratinc.com or visit www.bicillin.com**

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