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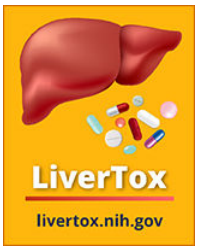

Antituberculosis Agents

Updated: September 22, 2017.

OVERVIEW

Infection with mycobacterium tuberculosis remains an uncommon, but clinically important problem in the United States despite sustained public health efforts and the availability of effective antituberculous therapy for more than 50 years. An estimated 12,000 to 15,000 cases of active tuberculosis occur yearly in the United States and account for at least 600 deaths annually. Worldwide, tuberculosis is a major cause of morbidity and mortality, ranking among the top five most fatal infectious diseases.

The modern era of antituberculosis medications began in 1944 with the development of streptomycin for which Selman Waksman received the Nobel Prize. Subsequently, more potent agents with wider activity and better tolerability were developed including p-aminosalicylic acid (PAS) in 1949, isoniazid in 1952, pyrazinamide in 1954, ethambutol in 1962, rifampin in 1963 and cycloserine in 1964. The development of chemotherapy for tuberculosis is one of the great achievements of biomedical research in the 20th Century.

Importantly, however, the major first line antituberculosis medications have hepatotoxic potential, including clinically apparent acute liver disease as well as acute liver failure and death or need for emergency liver transplantation. Furthermore, combination therapy which is required for the therapy of active tuberculosis appears to be associated with a higher rate of hepatotoxicity than occurs with the individual agents by themselves.

The current recommended therapy of active tuberculosis is the combination of at least two potent antimycobacterial agents for 6 to 9 months, examples being isoniazid, rifampin, pyrazinamide and ethambutol (the two latter agents often given in a 4-drug regimen for the first 2 months in patients with suspected drug resistant disease). PAS (p-aminosalicylic acid) is now rarely used, because of poor tolerance and its known hepatotoxicity. Ethambutol is used in instances of suspected or proven multidrug resistance. Other agents similar to rifampin which have activity against mycobacterium tuberculosis and several of the atypical mycobacteria include rifabutin and rifapentine. Second line agents, used in situations of toxicity of the first line agents or for multidrug resistance, include amikacin, azithromycin, capreomycin, cycloserine, ethionamide, levofloxacin, moxifloxacin, and streptomycin which in general have lower rates of hepatotoxicity.

Therapy is also recommended for latent tuberculosis or the finding of a positive protein derivative skin test (PPD), particularly in a high risk individual, after known exposure or with known skin test conversion. The primary regimen recommended for latent tuberculosis is a 9 month course of isoniazid, daily or twice weekly. The twice weekly regimen is appropriate for "directly observed therapy" (DOT), which helps in compliance and early detection and management of adverse reactions including hepatotoxicity. Alternative approaches include a 6 month course of isoniazid daily or twice weekly (DOT), a 4 month course of rifampin daily, and a 3 month course of isoniazid and rifapentine once weekly (DOT). The previous recommendation for using a 4 month

course of rifampin and pyrazinamide is no longer recommended because of the potential for severe hepatotoxicity.

Regularly updated recommendations on the diagnosis, prevention and therapy of tuberculosis are available from the Centers for Disease Control and Prevention at: http://www.cdc.gov/tb/.

First line medications used in the therapy of tuberculosis include ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifapentine. Second line medications include streptomycin, capreomycin, cycloserine, ethionamide, amikacin, levofloxacin, moxifloxacin, and para-aminosalicylic acid (PAS) (the latter is not discussed on this website). Finally, bedaquiline, the first new medication specifically for treatment of tuberculosis in more than forty years, was approved for use in the United States in 2012. Bedaquiline is currently limited in availability and is recommended only as directly observed therapy of multidrug resistant tuberculosis when an effective treatment regimen cannot otherwise be provided.

The following antituberculosis medications are discussed individually:

- Bedaquiline
- Capreomycin
- Cycloserine
- Ethambutol
- Ethionamide
- Isoniazid
- Pretomanid
- Pyrazinamide
- Rifabutin
- Rifampin
- Rifapentine
- Streptomycin