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TB—CDC encourages docs to check for antibiotic resistance

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Tuberculosis (TB) can be effectively treated with combinations of oral antibiotics. The drugs for first-line treatment of TB include the following:

- isoniazid
- rifampin
- ethambutol
- pyrazinamide

Additional first-line agents include the following:

- rifabutin (Mycobutin) – sometimes prescribed in place of rifampin for HIV-positive people
- streptomycin – not commonly used in high-income countries

Resistance to therapy is an important issue in TB treatment for the following reasons:

- Antibiotics generally used for TB are several decades older than newer antibiotics routinely used for the treatment of other bacterial diseases. Not surprisingly, TB drugs have unpleasant side effects—factors that do not encourage regular pill taking.
- After a few weeks or months of TB treatment, people begin to feel better and may arrive at the mistaken conclusion that they are cured. Consequently, they might prematurely stop taking antibiotics.
- In some conditions, such as HIV co-infection, TB antibiotics may not be well absorbed.

Resistance

Shortly after the introduction of antibiotics in the 1950s, TB-causing bacteria began to develop resistance to one or more agents. Infection with drug-resistant TB bacteria can have serious consequences for affected people. Not only do regimens become more complex and expensive, but also the risk of death increases. For instance, researchers from Quebec have found that resistance to the antibiotic pyrazinamide is associated with an increased risk of death. Researchers with the U.S. Centers for Disease Control and Prevention (CDC) have found that people who have TB that is resistant to rifampin or rifabutin are also at increased risk of death.

Today, in such cases of drug-resistant TB, agents for second-line therapy are available. However, drugs used in second-line therapy are generally more toxic, may need to be injected and are less effective than first-line agents. Examples of drugs used for second-line therapy include the following:

- moxifloxacin, levofloxacin
- amikacin, capreomycin, kanamycin
- ethionamide
- cycloserine
- para-aminosalicylic acid
- thiacetazone

Third-line agents

Strains of TB-causing bacteria that are resistant to two or more antibiotics are called multiple drug resistant (MDR-
TB). In such cases, third-line agents are used, which include antibiotics such as linezolid (Zyvox, Zyvoxam), clofazimine and clarithromycin. They have not generally been tested in large clinical trials for the treatment of TB. Several drugs are being developed for the treatment of TB.

Strains of TB-causing bacteria that are resistant to at least isoniazid and rifampin, and at least moxifloxacin or levofloxacin and at least one second-line injectable antibiotic are called extremely drug-resistant (XDR-TB). Such strains of TB are very hard to treat and require prolonged courses of antibiotics.

Researchers at the CDC have reviewed data whereby fluid samples from TB patients were grown (or cultured) in labs to assess their potential for resisting antibiotics. The CDC review encompassed tests that were done across the U.S. between 1993 and 2008, using samples from 222,897 people with TB and focusing on test results from 14,770 people who had resistance testing before and at the end of therapy.

Key results were as follows:

- There were at least 1,864 (13%) cases of MDR-TB and 56 (less than 1%) cases of XDR-TB.
- Among 1,141 people whose bacteria were initially susceptible to ofloxacin and similar drugs, 32 (3%) became resistant to this and similar antibiotics (called fluoroquinolones) while on therapy.
- Among 2,274 people whose bacteria were initially susceptible to second-line injectable antibiotics (amikacin, kanamycin, capreomycin), 49 (2%) became resistant to this class of drugs while on therapy.

**Risk factors for developing resistance to second-line therapy**

Statistical analysis found that participants who became resistant to second-line injectable antibiotics while on treatment were likely to have the following profile:

- 25 to 44 years of age
- HIV positive
- had MDR-TB at initial antibiotic resistance screening
- received initial TB therapy with any second-line agent

**Risk factors for resistance to ofloxacin and similar antibiotics (fluoroquinolones)**

There were 32 people who became resistant to ofloxacin, nine of whom were HIV positive. The only risk factor found for developing this problem was having MDR-TB when initial resistance testing was done.

**Changes over time**

After 1993, fewer people developed resistance to the antibiotics mentioned in this report, as U.S. public health authorities were able to ensure adherence to medicines because of intensified directly observed therapy (DOT). However, the CDC researchers warn that despite these and other measures, patients are still acquiring resistance to antibiotics used for TB treatment.

**Imperfections**

The CDC research is imperfect. Although checking for resistance to first-line antibiotics prior to initiating anti-TB therapy is supposed to be done in the U.S. (and other high-income countries), checking for resistance to second-line therapy and for resistance during therapy is not routinely done and reported to public health authorities. Thus the CDC’s analysis only includes reported cases of antibiotic resistance.

**Forestalling resistance**

As resistance to second-line TB therapy complicates and reduces future treatment options, it is important to identify people at risk for the development of this problem and to help them and their health care providers take steps to minimize this problem from occurring. The CDC researchers encourage doctors and nurses caring for patients at high-risk for developing resistance to second-line TB therapy to do the following:

- prioritize these patients for fast-track antibiotic resistance testing (including rapid molecular drug resistance tests)
have patients strictly follow supervised treatment based on resistance testing results

By using at least these steps, the CDC research team hopes to slow the spread of drug-resistant TB.

**Resource**

*Tuberculosis & HIV—background information*

—Sean R. Hosein

**REFERENCES:**

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