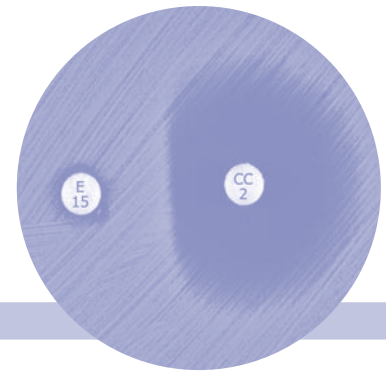


the d-zone

VOL. 36 SUPP. 2 JULY 2007



Reviews of the Month

• Hospital Practice

The incidence of invasive aspergillosis in the ICU is on the rise. Meersseman et al. discuss the challenges of diagnosis and treatment presented by this lethal disease.

Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis.* Jul 15 2007;45(2):205-216.

• Ambulatory Care

Acute otitis media seems to be caused by more *H. influenzae* and less penicillin-nonsusceptible *S. pneumoniae* these days. Should we think about changing our empiric therapies?

Block SL, Doern GV, Pfaller MA. Oral beta-lactams in the treatment of acute otitis media. *Diagn Microbiol Infect Dis.* Mar 2007;57 (3 Suppl):S19-30.

Quote of the Month

"Keep close to Nature's heart...and break clear away, once in awhile, and climb a mountain or spend a week in the woods. Wash your spirit clean."

-John Muir

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a monthly supplement to
Drug Therapy Topics
published by the UW
Drug Information Center

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also published online at
<http://uw.pnrx.org/therapyTopics.asp>

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Black D. Extensively Drug-Resistant
Tuberculosis (XDR-TB). *The D-Zone* 2007;
36(Suppl 2): S5-S8.

Extensively Drug-Resistant Tuberculosis (XDR-TB)

Introduction: from Koch to multidrug resistance

On March 24, 1882, Robert Koch announced his discovery of *Mycobacterium tuberculosis*. Approximately 125 years later, *M. tuberculosis* is recognized as one of the world's most successful pathogens, infecting about two billion people (one-third of the global population). Roughly two million deaths a year are credited to tuberculosis (TB).

The incidence of TB is stable or decreasing in most parts of the world except Africa, where HIV is fueling its rise.¹ During 1985-1992, after 30 years of decline, the number of TB cases reported in the United States (US) increased by 20%. Fortunately, a renewed emphasis on prevention and control reversed this trend. The rate of TB in 2005 was the lowest since 1953 when national reporting began.²

The specter of drug resistance has always been part of TB treatment. Indeed, the very first person treated with streptomycin in 1944 at the Mayo Clinic developed resistance to that drug.³ Some 45 years later, the emergence of multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampin, significantly complicated TB management. Treatment of MDR-TB is prolonged (18-24 months), toxic because of the need for multiple second-line drugs (SLDs), and expensive. In the 1990s, MDR-TB emerged as a significant threat in the US, but following the implementation of elements of the 1992 National Action Plan to Combat Multidrug-Resistant Tuberculosis, the number of cases of MDR-TB declined rapidly, as did the number of cases of TB overall. MDR-TB continues to be a problem worldwide; the World Health Organization (WHO) estimates the number of new cases of MDR-TB in 2004 as approximately 425,000, with 60% occurring in China, India, and the Russian Federation.³ Unfortunately, the global effort to control MDR-TB is inevitably associated with the risk of further drug resistance if the same factors that promoted its emergence are still present.

Locally, 127 cases of active TB were reported in King County in 2005, a 5% decrease from 2004. Ninety-five of the 127 cases (74.8%) occurred in foreign-born individuals. The rate of TB in King County (7.0 per 100,000 persons) is greater than the national rate (4.9 per 100,000 persons in 2004). Only two of the 127 cases of TB in 2005 (1.6%) were MDR-TB.

The recent misfortune of Andrew Speaker, a personal injury attorney from Atlanta, focused a great deal of national attention on what is now known as extensively drug-resistant tuberculosis (XDR-TB). The purpose of this article is to describe the history of XDR-TB, speculate on possible reasons for its emergence, and summarize the options for drug treatment.

XDR-TB: Extensively Drug-Resistant Tuberculosis (continued)

Early warning from Norway

In 1994, an HIV-negative patient in Norway with INH-resistant pulmonary TB began treatment. He did not receive directly observed therapy (DOT) and was soon lost to follow-up. A year later, the patient was admitted to the hospital with TB resistant to INH, rifampin, para-aminosalicylic acid, cycloserine, and thiacetazone (fitting the initial definition of XDR-TB, described below). Over the next 10 years, 23 patients were diagnosed with a strain of *M. tuberculosis* carrying the same IS6110 restriction fragment length polymorphism (RFLP) banding pattern and spoligotype, 15 of which were XDR. Thirty-seven cases of MDR-TB were diagnosed in Norway over the same time period; thus, XDR-TB represented 40% of the MDR-TB.^{4,5}

A disturbing aspect of this outbreak is that it occurred in a country thought to be in the elimination phase of TB. It also demonstrates the significantly detrimental effect that even one case lost to follow-up can have on public health.

The first global study of extensively drug-resistant *M. tuberculosis*

In response to multiple reports of TB resistant to virtually all SLDs, the Centers for Disease Control and Prevention (CDC) and WHO surveyed a network of international TB laboratories to assess the frequency and distribution of XDR *M. tuberculosis*. XDR *M. tuberculosis* was defined as resistant to INH, rifampin, and three of the six classes of SLDs (see Table). Survey findings were published in the March 24, 2006 issue of the *Morbidity and Mortality Weekly Report* (MMWR).²

17,690 isolates (from 49 countries) tested for drug susceptibility to at least three second-line drugs (SLDs) were collected during 2000-2004. 3,520 (19.9%) were MDR, 347 of which (9.8%) were XDR. XDR was present in at least 17 countries on six continents. Note that interpretation of data collected in this manner is subject to referral bias (e.g., isolates are likely to be from the most complex cases).

The survey also provided more precise population-based data for South Korea (2004), the US (1993-2004), and Latvia (2000-2002). Of the 11,939 South Korean isolates, 1,298 were MDR, of which 200 (15.4%) were XDR. 2,689 (1.6%) of the 169,654 US isolates were MDR; 1,814 MDR isolates had susceptibility results for ≥ 3 SLD classes reported, and 74 (4.1%) met the criteria for XDR. The proportion of MDR cases in the US that were XDR increased slightly throughout the period (from 3.9% during 1993-1996 to 4.5% during 2001-2004) despite an overall decline in the incidence of MDR-TB. Patients with XDR-TB were 64% more likely to die during treatment than those with MDR-TB. Finally, of

the 605 MDR-TB patients in Latvia, 115 (19%) had XDR-TB. Patients with XDR-TB were 54% more likely to die or fail treatment than those with MDR-TB.

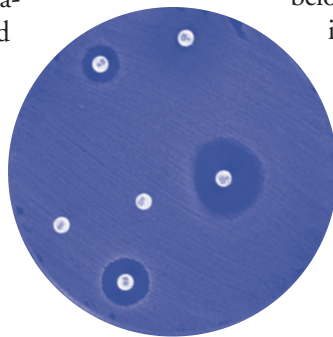
These data demonstrate that XDR-TB is widespread, that it has emerged in diverse areas including locations where TB control has been effective, and that treatment outcomes are worse than for MDR-TB.

Wakeup call: the chilling KwaZulu-Natal outbreak

The Church of Scotland Hospital in Tugela Ferry, a small town in KwaZulu-Natal Province, South Africa, serves a rural population with a high incidence of HIV. From January, 2005 to March, 2006, Gandhi et al. obtained sputum from 1,539 patients. Of 542 patients with positive cultures for *M. tuberculosis*, 221 were diagnosed with MDR-TB, and 53 of the 221 (24%) were found to have XDR-TB (using the currently accepted definition, described below). All 44 of the XDR-TB patients tested for HIV were found positive; median CD4 cell count at the time of sputum collection was 63 cells/mm.³ Sixty-four percent of the XDR-TB patients were hospitalized before the diagnosis of TB was made, whereas the remaining 36% were never hospitalized. Molecular typing revealed that 85% of the isolates were clonally related,

belong to the KZN family of strains first described in 1996.⁶ Fifty-two of the 53 XDR-TB patients died (median survival from sputum collection, 16 days), including all 15 HIV-coinfected patients receiving antiretroviral therapy and two HIV-coinfected healthcare workers.⁷

Since completion of this study, ten more patients in KwaZulu-Natal Province have been diagnosed with XDR-TB, and seven of them have died. XDR-TB has now been reported in all provinces of South Africa.¹



Revised definition of XDR-TB

On October 8-9, 2006, WHO held the first meeting of the Global XDR-TB Task Force in Geneva, Switzerland for the purpose of developing a rapid response to the emerging problem of XDR-TB.⁸ Important measures identified for halting the spread of XDR-TB included better access to rapid rifampin resistance testing (which would facilitate early detection and appropriate treatment of MDR-TB), increased availability of potent SLDs, and improved access to HIV testing and treatment. Laboratory experts attending the meeting asserted that with respect to testing *M. tuberculosis* for susceptibility to SLDs, only the fluoroquinolones and injectable agents (amikacin, kanamycin, and capreomycin) yield reproducible and reliable results. Moreover, resistance to fluoroquinolones and injectable SLDs has been associated with poor outcomes. Therefore, the definition of XDR-TB was modified to describe a strain of *M. tuberculosis* resistant to INH, rifampin, any fluoroquinolone, and an injectable agent.

XDR-TB: Extensively Drug-Resistant Tuberculosis (continued)

Table 1. Antituberculous agents

FIRST LINE AGENTS	DOSE*
Ethambutol	15–25 mg/kg/day PO
Isoniazid	5 mg/kg/day PO
Pyrazinamide	25–30 mg/kg/day PO
Rifampin	10 mg/kg/day PO
SECOND LINE AGENTS	DOSE*
Aminoglycosides <i>Amikacin</i> <i>Streptomycin**</i>	7.5–10 mg/kg/day IM/IV 15 mg/kg/day IM/IV
Capreomycin (polypeptide)	15 mg/kg/day IM/IV
Cycloserine	15 mg/kg/day PO (divided bid–qid)
Ethionamide	15–20 mg/kg/day PO (divided qd–tid)
Fluoroquinolones <i>Ciprofloxacin</i> <i>Levofloxacin</i> <i>Moxifloxacin</i>	750 mg PO bid 500–1000 mg PO qd 400 mg PO qd
Para-aminosalicylic acid	200 mg/kg/day (divided bid)
REINFORCING AGENTS***	DOSE*
Amoxicillin/clavulanic acid	1000 mg (amoxicillin) PO bid
Clarithromycin	500 mg PO bid
Clofazimine	100 mg PO qd
Linezolid	600 mg PO bid

* administered as one dose per day unless otherwise indicated

** listed as a first-line agent by some authorities

*** drugs with antimycobacterial activity *in vitro*; optimum dosing unestablished

The current situation in the US

In the March 23, 2007 issue of the MMWR, CDC updated the US situation using the revised case definition of XDR-TB and two more years of data.⁹ During 1993–2006, 49 cases of XDR-TB from nine states (3% of MDR-TB) met the revised definition. Thirty-two (65%) of these cases were reported during 1993–1999, the remainder during 2000–2006. Twenty-seven of the cases were from New York State, mainly New York City (19 cases). Of the 29 cases in whom HIV status was known, 16 (55%) were HIV-positive. Compared to 1993–1999, cases from 2000–2006 were more likely to have occurred in foreign-born persons and less likely in persons infected with HIV. Among the 41 patients with XDR-TB and known outcome, 12 (29%) died; 10 of the 12 were infected with HIV and two were of unknown HIV status.

Such surveillance data unfortunately do not provide adequate information as to how cases of XDR-TB arise. For example, it would be useful to judge the importance of person-to-person transmission of XDR-TB relative to the consequences of inadequate antituberculous therapy.

Why did XDR-TB emerge?

The following determinants probably play (or played) a role in the emergence of XDR-TB, although there are insufficient data to assign relative weights:

1. Failure of general tuberculosis control strategies (such as drug shortages, shortened treatment regimens, and insufficient patient supervision);
2. Inappropriate treatment of MDR-TB (due to insufficient treatment duration, or poor-potency SLDs);
3. Suboptimal infection-control practices (such as overcrowded hospitals and inadequate isolation of appropriate patients);
4. High prevalence of HIV;
5. Widespread use of certain SLDs, such as fluoroquinolones for respiratory tract infection, contributing to the development of resistance (the phenomenon known as collateral damage).

Drug treatment of XDR-TB

Effective treatment of XDR-TB is a daunting task. New WHO guidelines for management of drug-resistant TB recommend four or more active drugs, which means that the treatment of patients with XDR-TB is unlikely to meet international standards.¹⁰

The most advantageous treatment approach to XDR-TB has not been established. Furin suggests the following general strategy for approaching treatment of MDR-TB and XDR-TB.¹¹ Eighteen to 24 months of therapy (preferably directly observed) is required.

1. Use any first-line agent to which susceptibility has been documented;
2. Include an injectable drug for a minimum of six months of negative cultures (will probably not be possible with XDR-TB);
3. Use a fluoroquinolone whenever possible (not possible with XDR-TB);
4. Add SLDs to which the isolate is susceptible up to a minimum of four or five total drugs, if possible;
5. In the event of severe parenchymal damage or clinically advanced disease, consider the use of reinforcing agents.

XDR-TB: Extensively Drug-Resistant Tuberculosis (continued)

Looking to the future

Successful management of XDR-TB will require an aggressive multidisciplinary approach including the development of drugs with novel mechanisms of action. Unfortunately, there has not been a new antituberculous drug developed in four decades.¹ Two compounds under development deserve brief mention. PA-824 is a nitroimidazopyran derivative with substantial mycobactericidal activity against both actively multiplying bacilli and so-called “persisters” in the population (capable of surviving months of combination

drug therapy).¹² R207910, a diarylquinoline, is an inhibitor of mycobacterial ATP synthase with bactericidal activity against *M. tuberculosis* and several other mycobacterial species.¹³ Besides being useful for treatment of resistant disease, such drugs could be used to enhance the potency of first-line regimens. This could potentially shorten treatment duration, increase the overall likelihood of success, and help prevent emergence of resistance in the first place.

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