AMERICAN HEALTH CONSULTANTS

TB MONITOR™

The Monthly Report on TB Prevention, Control, and Treatment

September 2001 • Vol. 8, No. 9 • Pages 101-112

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New guidelines offer more nuances, treatment options

Extended therapy counseled for some

New TB treatment guidelines due out early next year will recommend lengthening treatment by an extra two to three months for patients who are still sputum-culture positive after two months' treatment.

For HIV-negative patients without cavitary disease, the new guidelines will also give the go-ahead to streamlining the continuation phase of treatment by substituting once-weekly rifapentine (RPT) and isoniazid (INH) for twice-weekly INH and rifampin (RIF).

Together, the two additions will provide a more nuanced approach to TB treatment, says **Rick O'Brien**, MD, chief of the research and evaluation branch of the Division of TB Elimination at the Centers for Disease Control and Prevention in Atlanta.

"That's probably the most important thing about this new treatment statement: the way it stratifies treatment based on patient characteristics," O'Brien says.

The last comprehensive treatment guidelines for adults and children date back to 1994. Like the older document, the new one was developed mainly by TB experts at the CDC working with their counterparts at the American Thoracic Society in New York City.

A handful of other professional organizations also supplied input, and for the first time, the Infectious Disease Society of America served as a co-sponsor of the new document. The guidelines are nearing final-draft form and should be completed by early winter. They will be published first in the *American Journal of Respiratory Care* and *Critical Medicine*, O'Brien adds.

In a recent meeting of the Advisory Committee to Eliminate Tuberculosis (ACET), O'Brien explained how data from Study 22 supported both the decision to recommend more therapy in some cases and the decision to allow a streamlined version in others.

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Study 22 was the TB Trial Consortium's clinical trial of rifapentine, a derivative of rifamycin with a half-life five times longer than that of rifampin. (The consortium is an agency at the CDC that conducts trials on promising TB drug candidates.)

As hoped, the study found that among patients with no radiographic evidence of cavitary disease, once-weekly RPT and INH were as safe, and almost as effective in preventing relapse or treatment failure, as twice-weekly RIF and INH. Across the United States, about 45% of patients fit the non-cavitary-disease category, CDC TB experts say.

In addition, the study turned up some unexpected findings. The 20% or so of patients in the study who were still sputum culture-positive after two months of therapy tended to have problems with both the experimental RPT/INH regimen and the standard twice-weekly regimen of INH and RIF. This means there were finally enough data to clinch what had been a long-standing hunch among experienced clinicians.

Then, O'Brien told his audience at ACET, CDC researchers went back and considered data from a much older study, a Hong Kong trial of patients afflicted with both TB and silicosis. Silicosis, a disabling lung condition related to exposure to industrial contaminants, impairs pulmonary immunity, making effective TB treatment much more difficult.

To determine whether longer treatment would help, the Hong Kong researchers gave six months of anti-TB treatment to one group of patients and eight months of treatment to the other. The two extra months of treatment resulted in much better outcomes. That suggested to CDC experts that two or three more months will probably work to reduce rates of relapse and failure in the sputum-culture positive group to acceptable levels.

Other new points in the forthcoming guidelines are expected to include:

- additional emphasis on the public-health dimension of TB treatment;
- discussions of the role of the fluoroquinolones in treating drug-resistant disease;
- detailed discussions of drug interactions and rifabutin's role in the treatment of HIV-positive TB patients;
- stronger recommendations for use of fixed-dose combination drugs;
- stronger emphasis on the use of directly observed therapy as an initial management strategy. ■

Phage work struggles for respect, funding

Still marred by a bad beginning

When a small biotech shop in Bothell, WA, announced last spring that it had expanded its work in TB research, there was scarcely a peep from mainstream scientific circles.

No wonder. In many places, confessing to an interest in phage therapy carries the same cachet as pulling out a membership card for the Flat Earth Society.

"Most scientists and academics think phage therapy is a lot of nonsense," says **Carl Merril**, MD, a senior staff member in biochemical genetics at the National Institutes for Health's intramural research program, and one of a small band of American microbiologists who are plugging away in phage therapy. "But that's a shame. There's a lot of potential there."

The Washington biotech shop — Phage Therapeutics International — is working on a way to enable phages, which are basically viruses that invade and kill bacteria, to get at TB microbes that are already sequestered inside macrophages. That's a harder target than, say, a staphylococcus circulating in the bloodstream, and is one of the biggest challenges in TB phage therapy research.

"Our technology for delivering phages to mycobacteria sequestered in the intracellular space isn't what I'd call polished yet, but we're developing a means for doing it," says **Richard Honour**, PhD, chief executive officer of Phage Therapeutics. "Not only are we getting the phage inside the macrophage, but also into the phagosome itself, where the bacilli reside."

The work so far has proceeded only in the lab, but collaborators abroad are due to start animal trials soon, Honour adds.

The real problem is how to get the phages deep inside the lungs, where most of the invaders are hiding out. "It's not as if the bugs are just sitting there on the surface of the lung, waiting to be attacked," says **Clif Barry**, PhD, a senior investigator in TB research at the National Institutes of Health in Bethesda, MD. "They're deep within lung tissue; what are you going to do, inject them? That's what I call a real delivery problem."

Honour is nonplussed. "Maybe we'll use some sort of inhalation therapy," he says. Besides, he adds, phage therapy could still help by attacking microbes that are circulating, thus lowering the overall bacterial burden. "Especially in developing countries, TB is such a complex disease, with so many phases," he says. "It's a problem that will take lots of different approaches to solve. I think we can have an impact."

Honour also has a request for the public-health community. To build phages lethal to multidrug-resistant strains of TB, his company is assembling a library of drug-sensitive and drug-resistant TB isolates, and also needs old phage-typing collections. "The isolates would be very useful in screening, and some of the old genetic material from the phages might turn out to be very valuable," he adds.

At first glance, it's tough to see why more entrepreneurs like Honour, with his 10-person fledgling company, aren't tinkering with phages. After all, phages are found everywhere there are bacteria; they are cheap and easy to work with; and once inside their target microbe, they multiply exponentially, swiftly wiping out entire bacterial populations — without the side effects of antibiotic therapy. Because each phage type is very specific in its choice of microbial host, phages aren't prone to doing incidental damage to benevolent bacteria dwelling in the host animal, either.

According to Merril, the trouble is that phage research (which dates back to 1916, when phages were first discovered) has been haunted by poor judgment, plus some awful luck.

Seminal work in phage research has always been centered in, of all places, Tbilisi, the capital of the former Soviet republic of Georgia. (That's where one of the two co-discoverers of phages decided to set up shop.) Even phage skeptics concede that Tbilisi researchers have produced some truly spectacular successes. The trouble is that because of the hit-and-miss quality of the work — the old Soviet Union never bought into the system of clinical trials — almost none of the successes have been replicable.

Here in the United States, meanwhile, phage therapy's early boosters made preposterously inflated claims for the new therapy, managing in the process to convince several big drug companies to invest heavily in the new technology.

The claims never panned out. Then, in a near-fatal blow, a professional medical association pronounced phage therapy to be worthless humbuggery. "That really put the kibosh on things," sighs Merril.

Worst of all, though, was timing. Once penicillin and other early antibiotics were discovered, U.S.

medical researchers began devising the system of clinical trials — the very discipline that might have rescued phage therapy and set it on a more rigorous course. But it was too late. American medical researchers had already turned their backs on phage therapy; now, they turned all their attention to antibiotics.

It's not surprising, then, that most scientists simply shrug when the subject comes up. "Sure, phage therapy sounds great," says Barry. "But in truth, we're nowhere near having an effective therapy."

Along with all the problems specific to TB phage-therapy, the field in general is hindered by the fact that the phages' microbe-targets can mutate, an act that can render the bugs immune to phage attack. Of course, phages might well match that with mutations of their own. But that conjures up the untidy specter of a clutter of serial phage mutations, all of which would have to be painstakingly patented, Barry notes.

Merril denies that mutations are a problem. For one thing, seminal work published decades ago (and painstakingly replicated in two subsequent experiments) found that phage therapy actually provokes fewer mutations in target microbes than antibiotic therapy, he says.

The real challenge, he adds, is the way animal hosts tend to clear phages from circulation before they get the chance to attack target microbes. Merril has published work showing that by successively selecting phages that remain in a mouse after a period of time, a phage can be cultured that will stay in circulation for long periods of time.

More recently, Merril says he's tackled the problem of how to give phages (which are very picky in their choice of target) a broader spectrum of killing activity. To do so, he's equipped phage tails with extra enzymes, so the viruses can break through varying compositions of pathogen cell walls. That makes them effective against a broader range of strains of a pathogen — a finding that has potential applications for TB.

"In some situations, phages can be life-saving," concludes Merril. "We need to set aside these theoretical arguments about what phages can or can't do, and start doing some real work." ■

ACET group eyes deportee dilemma

Drug resistance, recidivism probes under way

By the time the year is over, the Immigration and Naturalization Service (INS) probably will have deported about 250,000 people. One of those already deported is a multidrug-resistant tuberculosis (MDR-TB) patient from Mexico. Deported last month, he'd been convicted of a crime and had done time in a federal prison in Springfield, MO. After an appearance in immigration court, the deportation wheels began to turn.

By the time **Jeannie Laswell**, RN, heard about the man with MDR-TB, he was back home in Mexico, the central-line catheter through which he'd been getting drugs still dangling from his neck.

Laswell, who works for a cross-border TB referral program called TB NET, frantically began working the phone lines and soon managed to locate both the patient and a free supply of the expensive medications he needs to finish treatment. But there was a problem: Though the drugs and the treatment would be free, they weren't available in the man's hometown. He and his family would have to pack up and move far away.

Across the miles and the language barrier, Laswell fought to convey the importance of finishing treatment. (She also found a clinic nurse in Mexico who took out the dangling catheter.) But as of late last month, the man had simply disappeared; not even his family knew where he was.

"I haven't given up," says Laswell, explaining that she's just gotten off the phone from talking with the man's sister. "I've got lots of my fingers crossed. He may turn up yet."

Physicians who work for the Division of Immigration Health Services (DIHS), the medical arm of the INS, say the scenario is not rare. What's more, they say, some as-yet-unknown proportion of INS deportees with active TB are slipping back across the border into the United States again, continuing to expose others to disease in this country.

Like Laswell's MDR-TB patient, many deportees — again, there are only preliminary estimates of how many — have some degree of drug-resistant disease.

The deportation issue has prompted a working group of the federal Advisory Committee to Eliminate Tuberculosis (ACET) to begin a search for information and solutions. At a recent ACET meeting in Atlanta, the group reported preliminary

findings and conclusions. They include:

• Some deportees with TB return, still untreated, to the United States.

• Because many countries lack the resources, many other deportees with TB fail to get proper treatment in countries to which they return.

• INS detainees with TB who are deported before completing treatment are, therefore, an "international public-health hazard."

Working-group members are trying to arrange a meeting with U.S. Health and Human Services (HHS) chief Tommy Thompson to air the issue. Finding a solution that addresses all the various issues, they concede, will be tough.

From a public-health perspective, the ideal answer would probably be a policy change that lets the DIHS hold detainees with TB instead of deporting them so they can complete treatment of their TB. (Current policy allows DIHS to hold and treat patients only until they are noninfectious.)

Such a policy change would need to be brokered, at the very least, between the Department of Justice (which oversees the INS) and the HHS (which oversees the DIHS). More likely, it would take an act of Congress, says INS spokeswoman **Karen Kraushaar**.

Plus, there are human rights and foreign-policy ramifications to the situation. Can the United States hold the citizen of another country simply for TB treatment? Practical matters also loom large. Who will pay for treatment? Where will detainees be housed?

At least the numbers look manageable

As far as the expense is concerned, preliminary information-gathering by the ACET working group suggests the numbers of TB patients netted prior to being deported may be manageable, despite the big public-health headaches they cause.

TB screening carried out at nine INS service processing facilities (SPFs) and two detention facilities found 97 cases (both suspect and confirmed) in the year 2000. Of the 97, 57 were culture-confirmed. For 1999, the comparable figures were 80 cases or suspect cases, with 55 culture-confirmed, the working group reported.

Even though 81% of deportees last year were from Mexico, only about one-third of the TB cases came from Mexico, noted the ACET group. The other two-thirds came from other parts of Latin America.

Still, the INS houses lots of detainees at local "contract" facilities, where TB screening may be less scrupulously carried out than at the SPFs and the big detention facilities. New INS regulations enacted in January of this year will change all that within three years; by then, TB screening will be mandatory for all INS detainees, no matter where they are housed, assuming they are kept for at least 24 hours, says Kraushaar. At larger facilities, the INS is moving to teleradiology, or digital chest X-rays.

All told, the tighter screening procedures may net as many as 25% more TB cases, says **Geralyn Johnson**, DDS, MPH, chief of clinical operations at DIHS. "But that's just a guess," she adds; there are many other factors in the screening process to take into account.

Tighter screening on the way

For example, even though 50% of INS beds are rented from local jails at $50 a day, the highest throughput occurs at the DIHS-run SPFs. That suggests most TB cases are already being found. Still, Johnson points out, "we know the more we look for TB, the more we'll find it."

Strictly from a U.S. perspective, the real question is how many deportees with untreated TB are coming back into the country. Here, hard data are elusive. So far, the ACET working group has found that:

• According to the San Francisco TB control program, one in eight deportees with TB were known to have returned.

• According to CURE TB, when 38 cases were examined, 18 patients were lost to follow-up. Of the 20 cases whose whereabouts were known, five (25%) returned.

More reliable data may eventually be available on these "recidivist crossers," says Johnson. Using a system called INS-IDENT, the INS has been collecting fingerprints of people apprehended in border crossings. Recently, the DIHS hired an epidemiologist who plans to begin sifting fingerprint data. Eventually, that will lead to a clearer picture of how much recidivist border-crossing is taking place, she adds.

Also crucial is the question of how many repeat-crossers have drug-resistant disease. If preliminary findings by the ACET working group are on target, the news isn't good:

• The San Francisco program found three of eight cases deported (38%) had isoniazid-resistant disease.

• At CURE TB, five of 22 cases, or 23%, were

drug-resistant — including 4 cases that were INH-resistant and one case that was multidrug-resistant.

Then there are the logistical stumpers. Where would detainees be housed while receiving treatment? Don't look to the INS, warns Kraushaar. "The INS is not in the detention business," she says. "They're in the business of moving people" in or out of the country.

Paroling patients into the community or shipping them to a local program to finish treatment are not options either, despite the fact that most deportees seem not to have committed especially injurious crimes.

The INS gives these statistics about last year's "criminal" deportations:

— 41% of deportees were guilty of drug-related offenses;

— 20% were guilty of "criminal violations of immigration law";

— 8% were guilty of assault;

— 4% were guilty of burglary;

— 4% were guilty of robbery.

Some detainees must be deported

But regardless of the crime's severity, an immigration law enacted in 1996 mandates that detainees who have served a year or more in a correctional facility must be deported. That applies even if the crime was committed years ago. (The 1996 law has resulted in some law-abiding residents being deported many years after they'd "paid their debt" to society; some states have enacted laws to prevent such after-the-fact removals.)

In addition, not even non-criminal detainees bound for deportation can be released or paroled into the U.S. population simply for TB treatment, say Kraushaar and Johnson. This group of non-criminals includes "voluntary returns" — detainees who opt out of the formal deportation hearing and court appearance by pleading "no contest" to their deportation order. Doing so lets them avoid a black mark on their record, which in turn makes it easier to reapply for immigration.

If all that somehow changed, though, and deportees could be held and treated, Johnson says she can think of one way it could be done: Build some sanitarium-style facilities, and use them to house detainees with TB. "That way, they could be held securely, and still get their TB treatment in a humane setting," she says. ■

Entertainment delivers when it comes to TB

Soap operas, prime-time series among vehicles

TB experts in Minnesota are betting that a good story line, like a sugar coating, will help the medicine go down. In Minneapolis, which has a burgeoning population of Somali refugees and immigrants, TB controllers are teaming up with a young Somali film-school graduate to make what may be the world's first soap opera devoted entirely to TB.

"We kept hearing the Somali culture is very oral, and that people would pay attention to a good story with a message," says **Marge Higgins**, LSW, the state TB and refugee program coordinator.

Plus, when Higgins was out visiting patients in the field, she'd occasionally glimpse the soaps that are popular on the Minneapolis Somali cable channel. "They were very dramatic — they really grabbed you," she recalls. When the Somali film school graduate told Higgins he'd be willing to work on a tight budget because he was trying to build his resume, things began falling into place.

First, they've got to listen

The idea of using entertainment to get across a message about health isn't unusual. "We've been using the entertainment industry to reach people for 16 years," says **Patrick Coleman**, MA, deputy director of the Center for Communications Program at Johns Hopkins University in Baltimore. The center, funded mainly by the U.S. Agency for International Development, helps health ministries in developing countries get messages to the public. To do so, the center often resorts to media with strong narrative components — street theater, radio shows, TV, or comedy or drama, says Coleman. Offices in the Center produce hundreds of health campaigns every year. About 15 years ago, the center produced a pop song praising sexual abstinence that topped the pop charts in Latin America.

The reason for couching health messages in an entertainment format is simple, says Coleman: "Competition." Those who work in health care or any other social issue arena, he explains, "are competing with the entertainment industry for people's hearts and minds. The first thing you

have to do is get peoples' attention, and using entertainment helps give you that entrée."

Once the decision has been made to go with an entertainment-style format, the same principles that apply to other kinds of communication still hold true, experts say. "You start by talking to your audience," says Coleman. "You have to find out what they do or don't know about a subject. You need to identify any cultural or religious issues. Then you have to get the right message out."

"Knowing your audience" isn't necessarily an easy proposition, communications experts add. For instance, producing Spanish-language materials means more than simply translating an English text into Spanish and then substituting dark-haired, Latino types for blond-haired Anglos, says **Patricia Wren**, PhD, an assistant research scientist at the University of Michigan's School of Public Health in Ann Arbor.

"It's not that simple," Wren says. "Spanish isn't even always Spanish — there are 15 different countries where different kinds of Spanish are spoken."

The team that has put together the story line and script for the Minneapolis soap-opera project includes experts in film, TB, and the Somali culture, says Higgins. From the start, it was clear that the soap opera would have to convey the following key messages:

- **TB is curable.**
- **Infection is different from disease.**
- **Contacts need to be tested.**

"We decided not to go into too much detail about directly observed therapy, since the prospect of a public health representative coming to your house or job might be too threatening," she adds. Instead, the message would be "that someone will help you take your medicine."

The soap opera opens with a revelation: A young man is deeply distressed at the news that he has TB. His roommate and good friend, who knows more about the disease, tries to explain that a TB diagnosis is not a death sentence. The patient's physician — played by an American physician who actually treats many of the Somalis in Minneapolis — calls to provide more encouragement.

The young man's fiancée, sensing something is wrong, also makes an appearance. Gradually, with support from his family, the young man comes to grips with the change in his life.

Coleman's center is grappling with an equally compelling subject: the HIV risk associated with having multiple sex partners. In this case, the format is decidedly more ambitious: Coleman's center is producing a 26-part TV series on the subject. The series will air in prime time on South African TV later this year.

Again, the project began with lots of audience research, followed by decisions about what messages were to be conveyed. "We started with key concepts in HIV," says Coleman. "Then we looked at key situations and at how young people would react. We talked to support groups. We took all that information, and we gave it to a professional scriptwriter."

Despite the heavy message content, the series won't talk down to its audience, Coleman adds. "Audiences are so much more sophisticated now," he notes. "We'll make this as real-life as possible, and at the same time we'll give people something to think about."

With offices in 32 countries, the Hopkins center works mostly abroad. Occasionally, it also does projects commissioned by American public-health agencies. Recent projects for U.S. public-health agencies include an AIDS prevention project in Baltimore, a teen pregnancy prevention project for the state of Maryland, and a project promoting breast-feeding for a WIC program.

The center also maintains a reference library of teaching materials (some entertaining, others straightforward teaching tools). There are eight TB videos listed, for example; 75 English-language printed pamphlets about TB; 93 pamphlets about TB in other languages; and a listing of 24 agencies that produce TB educational materials.

To visit the Johns Hopkins Center for Communication Program's library on-line, go to www.jhuccp.org/mmc. ■

TB Alliance surprises with pick of new head

Popular Roscigno to stay on in 'senior' role

The Global Alliance for TB Drug Development handed a surprise to the international TB community last month. **Giorgio Roscigno**, MD, the popular and widely respected acting chief executive officer of the alliance, will be replaced by Maria C. Freire, PhD, veteran of the National Institutes of Health (NIH) in Bethesda, MD.

Despite the word "acting" before his title, Roscigno had widely been presumed to be permanently in his position. Higher-ups in the organization spent some time smoothing feathers ruffled by the announcement of his departure from the top post, giving assurances that Roscigno would stay on in "a senior position." Specifics of that arrangement are reportedly still being worked out.

Freire, who is to assume her duties on the 15th of this month, is said to have turned up on "a short list "of prospects recruited by a headhunter firm engaged by the alliance. A native of Peru, Freire is notably well-versed in the intricacies of intellectual property rights, a skill sure to come in handy at her new job. That's because along with trying to pick potential "hit" drugs and nurture them into development, the alliance needs to acquire and retain intellectual property rights. Doing so is the only way it can make sure new drugs become available at prices resource-poor countries can afford.

Roscigno has a different strength: his long career in and ties to the pharmaceutical industry, where he oversaw the development of drugs with important public-health applications, including rifapentine.

Assuming Roscigno stays on, the pairing of his skills with those of Freire will make for a formidable combination, says **Jim Kim**, MD, PhD, executive director of Boston-based Partners in Health. "Freire is one of a handful of people in the world who really understand the issues around the movement of intellectual property between the private and public sectors," says Kim. "That complements very well Roscigno's knowledge of the pharmaceutical industry."

Well-known on the Hill

At the NIH, Freire (whose name is pronounced to rhyme with "fair") headed the Office of Technology Transfer (OTT). She took the OTT, which had been suffering from poor management as well as laboring under the threat of governmental sanctions, and reshaped it into a respected economic powerhouse, with strong visibility on Capitol Hill. During the stem-cell research debate, Freire was frequently called upon to testify.

The OTT's mission is to make sure NIH scientists and academics who develop intellectual property are reimbursed for their work, if and when it bears fruit as a commercially viable pharmaceutical product.

According to Kim, Freire's real challenge at the TB alliance will be to develop what Kim calls "creative agreements" around intellectual property, ensuring that companies which develop drugs with public-health applications agree to give poor countries a break. ■

Behind scenes with a deadly epidemic

Time Bomb *due out next month*

To TB experts, much of the ground covered by the book *Time Bomb: The Global Epidemic of Multi-Drug Resistant Tuberculosis* will be familiar territory. There's the advent of HIV, the growth of antibiotic resistance, the chilling revelations about the Russian prison system, and the unresponsiveness of the pharmaceutical industry.

Familiar, too, will be many of the book's personalities and much of its politics. There are Gates and Soros, Kochi and Khomenko — plus the ongoing struggle to wrest attention and resources from players by turns indifferent and hostile.

Right place at the right time

But it's a safe bet that relatively few readers will have the author's insider, eyewitness perspective. **Lee Reichman**, MD, MPH, director of the National Tuberculosis Center at the New Jersey Medical School in Newark (as well as an editorial adviser to this newsletter), has a canny knack for being in the right place at the right time when seismic events in the TB world happen — and, as often as not, for helping make them happen.

In 1986, for example, Reichman and colleagues published a seminal account of an unusual kind of TB that seemed to be turning up in patients with an as-yet-unexplained immune deficiency.

In the 1990s, as TB cases began mounting and deaths from multidrug-resistant tuberculosis (MDR-TB) grabbed headlines, Reichman was elected head of the American Lung Association, a post he used as a bully pulpit to raise public awareness about TB and to get the funding spigots flowing.

When Alex Goldfarb, a former Russian dissi-

dent, persuaded wealthy financier George Soros to give millions to fight multidrug-resistant TB in Russia, Reichman was part of a team that brought back the first detailed reports of the country's crumbling public health infrastructure. Later, he would go back to report on the shocking conditions inside the Russian gulag.

Never one to sit out a good fight, Reichman allied himself with a small band of feisty Harvard idealists who pricked the conscience of the World Health Organization, forcing it to agree to start treating MDR-TB victims in poor countries (who had previously been considered untreatable).

Next, when Russian chest physicians offered fierce resistance to new Western-style treatment strategies, Reichman befriended and supported one of the most powerful pro-Western TB researchers in the country.

Now that World Bank negotiations for a crucial public-health loan to Russia hang by a mere thread, Reichman is back again, taking the reader behind the scenes to the hot-tempered, high-level meetings.

The story of the rise of multidrug-resistant TB is one that needs urgently to be told, and it is hard to think of someone better equipped to tell it than Reichman.

[Editor's note: Time Bomb *by Lee Reichman (with Janice Hopkins Tanne), from McGraw-Hill publishers, will be in bookstores next month.]* ■

Video trains camera on pediatric TB expert

Up close with gastric aspiration and chest X-rays

A new video that takes a broad look at pediatric tuberculosis started its life as a short film with appeal to what can only be described as a very, very limited audience. "Pediatric Tuberculosis: A Video Guide to Diagnosis and Treatment" (now available from the Francis J. Curry National Tuberculosis Center in San Francisco) was originally conceived as a short film about how to collect gastric aspirate from young patients.

The video's featured physician — **Ann Loeffler**, MD, the one-woman pediatric faculty at the Curry center — has a special talent for that particular task, she cheerfully confesses. "One day," she recalls, "someone said, 'Ann, you do a very good gastric aspirate. Why don't we make a video of you showing how?'"

For a time, that was the plan. Then Loeffler says she found herself reconsidering. "You know, guys, that's really a niche market," she remembers saying. At that point, the concept expanded to a project that would cover not just gastric aspirates, but all the basics of handling pediatric TB. It's probably a good thing, since passing a tube down the throat of an unwilling six-month-old is just one of several challenges pediatric TB specialists must be ready to surmount.

For example, the video spends lots of time addressing pediatric diagnostics, with Loeffler taking viewers through the various pitfalls of reading youngsters' chest radiographs. "They don't always look the way specialists in adult radiography expect them to," she notes. Often, for example, the disease isn't cavitary, and often not in an apical location, but rather in any lobe. (Indeed, it's multi-lobar 25% of the time, Loeffler notes.) "Frequently, it's associated with hilar lymph node enlargement, which some adult radiologists misinterpret as pulmonary vessels," she adds.

As age rises, gastric yield falls

As for collecting those gastric aspirates, Loeffler says the first thing to know is that as a diagnostic tool, "they're very imperfect." Overall, the yield is about 40%, she says, for the simple reason that children have very few organisms.

The younger the child, the better the yield, she notes. "In children under six months, the yield is almost 100%," she adds. For that reason and others, Loeffler hardly ever does aspirates on children older than two or three years. "Can you imagine strapping down a four-year-old, especially when you know the yield will be only about 30%? That child would never speak to you again, much less take the medications you prescribe!"

For situations when an aspirate is indicated, Loeffler says the best yields can be found in early-morning, first-day collections (following a night when the child is NPO). The reason why that's the case may have something to do with fear, she speculates. "My theory is that by the second day, they see me coming, and they have that fight-or-flight response, and it empties their stomachs," she says.

On the subject of drugs, Loeffler says it's time to put to rest any reservations about kids and ethambutol. "Two recent papers on this subject conclude there's maybe been one case in the world where using ethambutol has resulted in optic toxicity," she says. Even so, guidelines from the Centers for Disease Control and Prevention continue to counsel physicians to "weigh risks and benefits" before giving the drug to children who aren't old enough to report changes in vision.

Another argument for four drugs is the fact that obtaining a specimen from a child is difficult, with the result that data on resistance are hard to come by, "so you're essentially working in the dark with a lot of kids," Loeffler points out. Besides, the guidelines also say four drugs should be used whenever the county of residence has more than 4% background resistance rate, or when the source case acquired the disease in such an area.

Avoiding 'a messy situation with resistance'

"I get a lot of calls from people who started with three drugs and got into trouble," she says. "That means adding two more drugs — drugs that have a lot more toxicity, cost a lot more, and sometimes have to be given more than just once a day." True, children typically have small bacillary loads and manage to muster their way to a cure, even with suboptimal regimens, she concedes. "But you really don't want to get into a messy situation with resistance," she concludes. "So why go there?" All the same, she warns parents to watch their children closely for any signs of optic toxicity, such as rubbing of the eyes, sitting closer to the TV set, or a diminished ability to manipulate small objects.

The video is the successor to an earlier audio tape Loeffler made, focusing mostly on the how-to's of treating latent infection in children. That tape comes with free CME credits and is still available at no cost. The new video comes with a 27-page booklet filled with what Loeffler calls "meaty, practical information," including dosing charts for once- and twice-weekly schedules suitable for hanging in a clinical workspace. CME credits accompany the video. The video, booklet, and CME credits are free of charge.

To obtain a copy of the video and booklet or of the audio tape, contact the Curry TB Center at (415) 502-4600 or via e-mail at tbcenter@nationaltbcenter.edu. ■

CONFERENCE COVERAGE

By **Lin H. Chen**, MD
Clinical Instructor, Harvard Medical School
Boston

A number of epidemiology and outbreak reports were presented at the 7th Conference of the International Society of Travel Medicine, held in Innsbruck, Austria, in May. A plenary session titled "Under-Appreciated Infectious Risks in Travel Medicine" included discussions on TB.

Here is a summary of the proceedings:

• Cobelens F, Van Deutekom H. **Tuberculosis.**

The epidemiology of TB was reviewed by Frank Cobelens, MD. One-third of the world's population has been infected with TB. Approximately 8.4 million infections occur per year, and 2 million deaths occur each year. World Health Organization studies of TB in 54 settings showed that up to 37% of infected people are resistant to at least one drug, and up to 14% have multidrug-resistant tuberculosis (MDR-TB).

In some of the settings studied in Russia, Iran, China, and Estonia, 75% of cases were shown to be MDR-TB. The risk of TB in long-term travelers to areas of high incidence has been estimated to be three in 1,000 per month. Therefore, the risk of latent TB infection (LTBI) in travelers is greater than the risk of hepatitis B, typhoid fever, or meningococcal disease.

The two approaches to prevention of TB in travelers are vaccination with Bacille Calmette-Guerin (BCG) and identification of LTBI using a tuberculin skin test (TST) followed by prophylactic treatment. The protective efficacy of BCG against TB has been difficult to predict for the individual traveler. The duration of BCG protection is unclear (10-15 years), and there are limited data on the efficacy of repeated BCG vaccinations. TST, on the other hand, is dependent upon good technique, proper interpretation, and the tuberculin used.

The sensitivity of TST is decreased in individuals with cellular immune suppression. The specificity of TST may be complicated by the booster effect, which may result from LTBI in individuals with waning immunity as well as atypical mycobacterial infections and past BCG vaccinations. In order to reconcile the effect of BCG on TST, two-step testing at a one-week interval is recommended in travelers who have had BCG vaccination in the remote past, looking for a booster response.

For physicians who treat patients diagnosed with LTBI, there is an increasing choice of regimens. Isoniazid for six to nine months is currently the most common therapy but is associated with hepatotoxicity in 1% of patients. If resistance were suspected, the combination of rifampin and pyrazinamide for two months becomes the regimen of choice. If intolerance to pyrazinamide were to develop, rifampin alone would be used for four months. Patients need to be monitored clinically for hepatotoxicity, and baseline liver function tests should be considered in patients with increased risk for hepatotoxicity. ▼

• Metteeli A, et al. **Tuberculosis in travelers and long-term immigrants.**

GeoSentinel, a global surveillance network of travel and tropical medicine clinics established to track disease trends in travelers, has been collecting data on confirmed TB cases in travelers, long-term immigrants, and short-term immigrants. Long-term immigrants are those who immigrated five or more years prior to the diagnosis. The network has registered 10,785 travelers and long-term immigrants and 2,786 short-term immigrants from January 1997 through November 2000. There were 95 TB cases among the short-term immigrants (rate = 3.41%) and 44 TB cases among travelers and long-term immigrants (rate = 0.45%). Seven of these cases occurred in travelers / expatriates. This information should lead to some clarification of TB risk in travelers. ■

WHO boosts multidrug-resistant TB therapy

People suffering from multidrug-resistant tuberculosis (MDR-TB) will in the future have access to top-quality "second-line" drugs at prices reduced by as much as 94% and to better treatment regimes as a result of international efforts by the World Health Organization (WHO), Doctors Without Borders, and the Harvard Medical School, say fans of recent developments.

Doctors Without Borders, based in Paris, France, has been instrumental in negotiations with the pharmaceutical industry for the second-line drugs, which presently cost up to $19,000 to treat one person. WHO is working via a multi-agency committee called the Green Light Committee, which helps countries benefiting from these reduced prices to plan effective administration of the drugs and to contribute to the rapid development of a global policy on the treatment of MDR-TB.

"WHO and our partners will provide teams of experts to help countries use these expensive but vital anti-TB drugs supplied through this effort properly and safely, in order not to develop further drug resistance," says **J.W. Lee**, MD, director of Stop TB at WHO. In recent years, outbreaks of

TB Monitor™ (ISSN# 1082-8664), including **Common Sense about TB™** and **TB Guide for Health Care Workers™**, is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **TB Monitor™**, P.O. Box 740059, Atlanta, GA 30374.

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Editor: **Alice Alexander**, (404) 371-8067, (alicealex@mindspring.com).
Vice President/Group Publisher: **Donald R. Johnston**, (404) 262-5439, (don.johnston@ahcpub.com).
Editorial Group Head: **Glen Harris**, (404) 262-5461, (glen.harris@ahcpub.com).
Managing Editor: **Robin Mason**, (404) 262-5517, (robin.mason@ahcpub.com).
Production Editor: **Brent Winter**.

Editorial Questions
For questions or comments, call **Alice Alexander** at (404) 371-8067.

MDR-TB in public institutions (hospitals, prisons, and homeless shelters) in the United States, Europe, and Latin America have caused many deaths and raised concerns about epidemic transmission of MDR-TB. ■

CE objectives

After reading each issue of *TB Monitor,* health care professionals will be able to:

• Identify clinical, ethical, legal, and social issues related to the care of TB patients.

• Summarize new information about TB prevention, control, and treatment.

• Explain developments in the regulatory arena and how they apply to TB control measures.

• Share acquired knowledge of new clinical and technological developments and advances with staff. ■

TB Monitor 2001 CME Survey

In each January and July issue of *TB Monitor*, CME tests are mailed to participants. For readers who participate in the CME program, please complete the following brief questionnaire and fax to **(404) 262-5447, Attn: Glen Harris.** The results of the survey will be used to improve the program.

1. Did the *TB Monitor* CME program meet its objectives as defined in the promotional literature? Those objectives are to enable the participant to: "discuss up-to-date information on all aspects of TB care, including new drugs and drug combinations, techniques for administering drugs and gaining patient compliance, studies, trials, books, federal regulations and guidelines, teaching aids, and other information pertinent to TB treatment." (circle one)

Yes
No

2. Were the test questions well written? (circle one)

Always
Most of the time
Some of the time

If you answered "Most of the time" or "Some of the time," how should the way the test questions are written be improved?

_____

_____

3. Was the test a fair assessment of the learning activity? (circle one)

Yes
No

4. Were the tests graded and returned promptly? (circle one)

Yes
No

5. Has the CME program improved your professional effectiveness? (circle one)

Yes
No

Comment: _____

6. *TB Monitor* offers: (circle one)

Too many credit hours for my needs
Too few credit hours for my needs
The right amount of credit hours for my needs

7. What suggestions do you have for improving the CME program? Please be specific.

_____

Please fax to: (404) 262-5447, ATTN: Glen Harris.