Background

Multidrug-resistant tuberculosis (MDR-TB) is a growing problem worldwide. In some settings, 48% of tuberculosis patients are sick with MDR-TB, or with strains of Mycobacterium tuberculosis resistant to the two most powerful antituberculous agents available today: isoniazid (INH) and rifampin (RIF). Therapy for these patients is more difficult than for patients with pan-susceptible disease. Conventional short-course regimens — which rely on INH and RIF — are less effective. Indeed, in patients for whom an initial regimen failed, the recommended strategy of repeated administration of short-course therapy (usually adding one more drug) results in additional acquired resistance through selective pressure of inadequate regimens. To ensure cure and minimize additional resistance, MDR-TB treatment requires combinations of multiple second-line agents for 18 to 24 months. Yet these regimens reportedly lead to greater toxicity and lower cure rates than short-course regimens for pan-susceptible disease. Advances in comprehensive, community-based management of MDR-TB, however, have changed global policy and offered hope for these once-neglected patients. Successful outcomes require: 1) effective and aggressive antituberculous therapy delivered under direct supervision; 2) careful monitoring of bacteriologic, radiographic, and clinical status, and of adverse events; 3) drug-susceptibility testing (DST) either for individual patients or for accurate, representative surveillance data; 4) nutritional and social support, where necessary.

Designing a regimen

Therapy should be given with a minimum of five drugs to which the patient’s drug-susceptibility pattern is sensitive.

Ask the Expert:

How is Multidrug-Resistant Tuberculosis Managed in Resource-Poor Settings?

Jennifer J. Furin, M.D., Ph.D., Infectious Disease Fellow, Case Western Reserve University, MDR-TB Specialist, Socios En Salud (Partners In Health), Lima, Peru

For 20 years, Dr. Helene Gayle has fought on the front lines of the AIDS pandemic, armed with a pediatrician’s compassion and a policymaker’s broad perspective. In 1984, Gayle joined the U.S. Centers for Disease Control, eventually heading the agency’s HIV, STD, and TB prevention efforts. In 2001, she moved to the Gates Foundation, where her portfolio includes more than $1.2 billion in grants.

Q: The World Health Organization (WHO) recently updated its statistics on the AIDS pandemic: 40 million infected, 5 million new infections in 2003, 3 million deaths. Despite those horrific numbers, are we still at the beginning of the epidemic curve?

A: Yes, definitely. Almost 70 million people have been infected since the epidemic began. Over the next few years, in countries with very large populations — such as China, India, Russia, Nigeria, Ethiopia — many, many millions more people are likely to get infected. By 2010, another 50 million people could become infected with HIV.

Q: Let’s talk about antimicrobial resistance (AMR). The WHO announced a policy of treating 3 million people with antiretroviral drugs by 2005. Yet a few months ago, we learned that 10 percent of newly-diagnosed European patients have strains resistant to at least one antiretroviral. Other reports from China suggest that some patients are stopping therapy for reasons of side effects or cost. How do you recommend an effective strategy to treat MDR-TB patients living in resource-poor settings?

A: Advances in comprehensive, community-based management of MDR-TB, however, have changed global policy and offered hope for these once-neglected patients. Successful outcomes require: 1) effective and aggressive antituberculous therapy delivered under direct supervision; 2) careful monitoring of bacteriologic, radiographic, and clinical status, and of adverse events; 3) drug-susceptibility testing (DST) either for individual patients or for accurate, representative surveillance data; 4) nutritional and social support, where necessary.
Chloroquine-Resistant Malaria: Evolution and Future Prospects

Thomas E. Wellems, M.D., Ph.D.

Head, Malaria Genetics Section & Acting Chief Laboratory of Malaria and Vector Research National Institute of Allergy and Infectious Diseases

The introduction of chloroquine and DDT at the end of World War II brought dramatic new power to malaria control efforts. With post-war economic recovery and a renewed spirit of international cooperation, optimism ran high that these new tools might be used to eliminate malaria, and in 1955 the World Health Organization launched its campaign to eradicate the disease. This goal soon proved overly optimistic, and the centrally-organized DDT-spraying programs at the core of the campaign were discontinued in 1967. The campaign nevertheless brought regional successes that coincided with other factors to dramatically reduce malaria rates in many areas of the world, particularly Africa (Fig. 1a).

A stark exception to this general progress is sub-Saharan Africa, where malaria remains deeply entrenched. Even the most committed spraying and eradication programs in endemic areas of this region could not defeat malaria's efficient transmission by the African mosquito, Anopheles gambiae. The wide availability and use of chloroquine did, however, boost the health of young African children who suffer most from Plasmodium falciparum, the species responsible for the most deadly form of malaria. As chloroquine became increasingly available, death rates from malaria in Africa began to drop and in

Malaria death rates in the 20th century. Dramatic reductions in mortality have been achieved outside sub-Saharan Africa. Mortality rates declined after the introduction of chloroquine, but rose again after the spread of chloroquine resistance across the continent. (Adapted from Carter and Mendis, 2002 [ref. 1]).
the 1970s, approached half the level of the pre-chloroquine years. 1

Unfortunately, the massive use of chloroquine (hundreds of tons sufficient for hundreds of millions of treatments annually in the 1980s) 3 selected for chloroquine-resistant *P. falciparum* strains when they finally entered and spread across Africa. In the 1980s and 1990s, malaria resurfaced and death rates increased. The impact of chloroquine resistance was especially evident in young children, who do not have the partially protective antimalarial immunity that usually develops after repeated episodes of the illness 4 (Fig. 1b).

Chloroquine treatment works by killing malaria parasites in the human bloodstream, where they trigger the pathogenic events responsible for the disease. As each parasite in this stage of the life cycle grows and consumes the contents of its red blood cell, it breaks down hemoglobin within a large digestive vacuole and releases heme molecules that are poisonous if not detoxified. Malaria parasites normally allow these heme molecules to polymerize into inert crystals called hemozoin. Chloroquine acts by forming toxic complexes with heme molecules and interfering with their crystallization 5 (Fig. 2). This mechanism of chloroquine action explains why the drug is effective against growing parasites in red blood cells, but ineffective against other parasite stages that do not actively consume hemoglobin.

Chloroquine-resistant *P. falciparum* parasites reduce the amount of drug that accumulates in their digestive vacuoles. 6 The mechanism involves mutations in a highly conserved transport molecule of the digestive vacuole membrane termed PfCRT (*P. falciparum* chloroquine resistance transporter). 7-9 The mutations always include a key change from lysine to threonine in the 76th predicted amino acid (K76T), plus additional mutations that depend on their geographic origin. These additional mutations have helped to identify at least five foci of chloroquine resistance: two in South America; one in Southeast Asia that spread to Africa; one or more in Papua and Papua New Guinea; and one in the Philippines 7, 10, 11 (Fig. 3, next page). The sweeps of chloroquine-resistant *P. falciparum* from these foci into most malaria regions demonstrate the power of evolutionary selection exerted by drug pressure. This selection activity is evident in the association of the K76T marker with age-related plasma chloroquine levels 12 and with outcome failures in children after directly-observed administration of the drug 13.

While PfCRT is the central determinant of chloroquine resistance, other host and parasite factors also influence treatment outcomes. For example, infections of chloroquine-resistant parasites have been observed to clear after chloroquine administration in some individuals with the immunity that develops from repeated episodes of malaria 10, 13. The ability of particular individuals to achieve these clearances may be associated with human genetic variations that, individually or in combination, affect malaria pathogenesis and host responses to infection. Parasite transport molecules in addition to PfCRT...
have also been proposed to modulate or contribute to the ability of chloroquine-resistant parasites to cope with the drug.\textsuperscript{14}

Chloroquine-sensitive strains may repopulate regions where the drug has been removed from use because of overwhelming chloroquine resistance. Significant drops in treatment failure rates have been reported from China (Hainan Island) and Gabon within 5-10 years after treatment policy was changed away from chloroquine.\textsuperscript{15} In Malawi, the switch from chloroquine to sulfadoxine-pyrimethamine was followed by decreasing prevalence of the PfCRT K76T marker, from 85% in 1993 to 13% in 2000; chloroquine in 2001 was shown to clear 100% of 63 asymptomatic malaria infections, and no infections with chloroquine-resistant parasites were detected.\textsuperscript{16} These results suggest a slight advantage of the native PfCRT molecule over its mutant forms in the absence of drug pressure and point to the possible value of drug-rotation strategies in antimalarial policies.

Several lines of evidence now indicate that chloroquine resistance involves a specific interaction between the structure of the drug and the modified form of PfCRT\textsuperscript{8} in an energy-dependent efflux mechanism.\textsuperscript{17} The structural specificity of the mechanism may explain why compounds related to chloroquine (i.e. piperazine, pyronaridine) are active against chloroquine-resistant \textit{P. falciparum}.\textsuperscript{18} Certain side-chain derivatives and isomers of chloroquine and of amodiaquine, a related 4-aminoquinoline, have been found to have similar efficacy against chloroquine-resistant and chloroquine-sensitive \textit{P. falciparum}.\textsuperscript{19} An important potential for new antimalarial drugs therefore lies in these compounds.

Antimalarial agents that act on heme or take advantage of its potential for free radical activation remain the drugs of choice for severe malaria because of their rapid action and consequent ability to quickly clear parasites from the bloodstream. In addition to chloroquine, examples include the quinine alkaloids and endoperoxide-containing artemisinin derivatives from the medicinal plant \textit{Qing hao}. Malaria parasites appear to have difficulty resisting these classes of drugs. The amino acid substitutions in PfCRT responsible for chloroquine resistance were slow to evolve because of their complexity, and the artemisinins and quinine alkaloids remain effective after long histories of use (although the quinine responses of \textit{P. falciparum} have become less sensitive). Among old and new targets for antimalarial agents, heme, a nonmutable host molecule, thus remains attractive for drug development because it can be repeatedly attacked as long as mechanisms of resistance to specific drugs can be avoided or defeated. The favorable pharmaceutical properties and low cost of certain endoperoxides and 4-aminoquinoline derivatives have established them as promising leads for drug discovery; some are being pursued in private-public partnering arrangements sponsored by organizations such as the Malaria Medicines Venture (http://www.mmv.org).

Learn more about APUA’s partnership with CDC’s “Get Smart” campaign on page 11.
Prevalence of Methicillin-Resistant Staphylococcus aureus Nasal Carriage in a Young Lebanese Population

Ziad Daoud, Ph.D.
Assistant Professor, University of Balamand, Head of Clinical Microbiology, Saint George University Hospital, Lebanon APUA-Lebanon Chapter Coordinator

Background

Staphylococcus aureus is a well-recognized cause of serious community-acquired infections, and a leading cause of nosocomial infections. At any given time, the bacterium colonizes the anterior nares of 20% to 30% of individuals. A substantial body of evidence suggests that individuals who are asymptomatic nasal carriers of S. aureus are at increased risk of developing serious staphylococcal infections. In a variety of populations, nasal carriage is therefore considered a risk factor for infection. Reports from various geographic regions indicate that the prevalence of community-acquired methicillin-resistant Staphylococcus aureus (MRSA) infection is increasing. The primary reservoir is the anterior nares. Little is known about MRSA nasal carriage rates among the Lebanese population and the associated likelihood of community MRSA transmission.

Methods

Nasal swabs were collected from 300 young university students at both the Balamand University and the Lebanese University. Cultures were plated onto selective and non-selective staphylococcal media, with or without oxacillin. S. aureus isolates were confirmed by coagulate tube test, DNase production and mannitol fermentation. Antibiotic susceptibilities were determined by standard disc diffusion method and E-tests (National Committee for Clinical Laboratory Standards).

Results

From 300 students, 12 strains of S. aureus were isolated (Table 1). Of these, six were oxacillin-resistant (i.e., MRSA: 2 isolates had an MIC of 2 µg/ml and 4 isolates had an MIC of 4 µg/ml) (Table 2).

Conclusion

MRSA nasal colonization is present within a healthy young Lebanese population.

Both methicillin-resistant and susceptible strains of S. aureus continue to pose problems for patients, clinicians, and infection control personnel. More attention must be devoted to improving the adherence of the general population to hand hygiene measures and to establishing barrier precautions.

Table 1: Antibiotic susceptibilities of all S. aureus (n=12)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>n</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>2</td>
<td>16.7</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>6</td>
<td>50.0</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>6</td>
<td>50.0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>9</td>
<td>75.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>7</td>
<td>58.3</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>10</td>
<td>66.7</td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>11</td>
<td>83.3</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>12</td>
<td>91.7</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>12</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2: Antibiotic susceptibilities of MRSA (n=6)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>n</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>3</td>
<td>50.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>5</td>
<td>83.3</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>5</td>
<td>83.3</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6</td>
<td>100.0</td>
</tr>
</tbody>
</table>
TB and HIV need to be seen almost together. What do you think?

more cost-effective to treat TB and HIV

A: Yes, we should be concerned about resistance. But we also know that resistance can be avoided by working with many people to adhere to their medications. Already we’re seeing in countries like Botswana — which for more than a year has had large numbers of people on antiretroviral therapy — that adherence rates are 80-plus percent: equal to, or even better than, what we see in rich nations.

Q: What interventions assured that kind of adherence?

A: First of all, explaining to patients why it’s so important that they take their medications at the correct time. Secondly, involving families and communities, so every patient is asked to identify a medication buddy — a family member or friend — who can encourage them, work with them, chide them, keep them aware of the importance of adhering to their medication. In Haiti, they have community workers who help patients taking the medications — they are actually putting in place a system analogous to directly-observed therapy for tuberculosis. There are a lot of systems that encourage that sort of adherence, and that involve the community and family members in maintaining that adherence. That has another motivational aspect as well — it’s not just the individual who is involved.

Q: Sandra Thurman, of the International AIDS Trust, contends that it’s more cost-effective to treat TB and HIV together. What do you think?

A: TB and HIV need to be seen almost as one disease. TB is the leading cause of death for people with HIV. It is the disease most frequently associated with HIV in developing countries, and treating TB improves the natural history of HIV. Treating HIV-infected people with antiretroviral therapy helps their tuberculosis, because the immune system doesn’t erode as quickly. That makes it either less likely for active tuberculosis to develop or easier to treat the tuberculosis if it has already developed into active disease.

Q: Will resistance to HIV/AIDS drugs play out differently in rich and poor countries?

A: We don’t have enough experience yet with developing nations, because very few countries have had wide scale access to antiretroviral therapy. It’s something that we can learn from the rich nations, where antiretroviral therapy has been available for longer. We can learn from the patterns of resistance and the development of resistance, and try to put systems in place that would help minimize that.

Q: Do you think the new generic antiretroviral recently approved by the WHO will mitigate resistance, since it’s just one pill taken twice a day?

A: The simpler the regimen, the easier time people will have adhering. Back five or six years ago, people had to take in the neighborhood of 15 to 20 pills a day. Now the average person in a rich nation takes perhaps four to six pills a day. But there is no magic bullet. Some people can’t tolerate the new combinations in one pill.

Q: Will the new rapid finger-prick test — the dry blood test that can help assess drug effectiveness and resistance — affect treatment in developing nations?

A: There’s a lot of focus now on trying to make the monitoring test simpler and less expensive. The diagnostic test is very simple — there are rapid tests that can be done very simply. But what is still not as simple and still fairly expensive are the monitoring tools for viral load, CD4 cell count, and other things that you have to monitor while somebody is on antiretroviral therapy.

Q: Hasn’t such a test just been marketed?

A: There are a variety of tests that are coming out, with simpler technology. There isn’t one yet that has had wide enough use that it’s become standard care.

Q: Are you worried about drug resistance in opportunistic bacterial infections, such as enterococcus or staph?

A: That’s not a major problem for the moment. In these infections, the course of treatment is generally short enough that most people complete it and adhere to it and there isn’t as much resistance. Now, tuberculosis is a major concern, because the more complicated the regimen and the longer you have to take it, the more likely that there will be adherence problems.

Q: Hasn’t there been resistance seen in gonorrhea, which predisposes people to HIV?

A: There has been resistance in gonorrhoea. But there are good antibiotic regimens for the bacterial sexually-transmitted diseases. Some of them can be treated with a single dose of an antibiotic, which decreases the chance of resistance, because adherence is not an issue. So bacterial sexually-transmitted diseases can be easily treated, completely treated, and cured.

Q: You’ve said that the current financial commitment to preventing and treating HIV/AIDS is just a fraction of what’s needed. Ideally, how much should we be investing?

A: Estimates suggest that somewhere in the range of $10 billion a year is what’s necessary. In 2002, we spent in the range of $4 billion.

Q: As you know, APUA has 25 chapters in the developing world. In the AIDS pandemic, what is the role of these local, grassroots, “on-the-ground” groups?

A: Being able to give guidance on the prudent use of antibiotics, looking for resistance, making sure that communities and individuals are aware and have appropriate information. I think that’s a huge role.
Q: What are the priorities at the community level for scaling up treatment and prevention?
A: For treatment, it’s important that we develop the health infrastructures necessary for providing high-quality care to people with HIV — having systems in place that can allow for wide access to appropriate treatment, whether that’s antiretroviral therapy or treatment for tuberculosis or other opportunistic infections. We also need systems for getting people tested, since over 90 percent of people in developing countries are unaware of their HIV status, and so can continue to pass on HIV without knowing it. These individuals also aren’t able to avail themselves of treatment as it becomes available. Then, increasingly, we need to continue prevention programs that provide information to the general population, so people are aware of the risk of HIV. We need to make sure that high-quality treatment for sexually-transmitted diseases exists. We need to make sure that drugs for mothers who are HIV-infected and pregnant are available. We need to improve access to voluntary counseling and testing, as needed. We also have an opportunity to integrate prevention in the context of care, because once people are coming in regularly for treatment, that’s also a wonderful opportunity to reinforce information and skills and services to reduce the risk of somebody who is infected passing that infection on.

Q: Are all the funders moving in the same direction? There had been dissension on some policies.
A: For the most part, people recognize that we need to have a vigorous response for prevention as well as treatment. There are differences of opinion about the balance of services and information and how to do it. But this issue is big enough that all perspectives add something to this battle. We’re talking about a whole spectrum of people. We have to have options for different people, different lives, different life circumstances.

Q: How do you stay optimistic, knowing the projected death toll?
A: I’m optimistic every time I am in the field and see what people at the grassroots level are doing. It’s hard for me to believe that with the motivation and passion that people have for their work, and the care that they have for their fellow human beings, that we’re not going to make a difference. I am convinced that already we have saved millions of lives. By scaling up access to antiretroviral treatments, we will save millions more. If we continue to increase resources and support, ultimately we will be able to turn HIV infection around.

Q: What is at stake if the world doesn’t act?
A: At stake are tens of millions of lives, as well as societies, economies, and stability. The World Bank reported that some of the most hard-hit countries, like South Africa, could face economic collapse over the next generation. There’s already 14 million children orphaned by AIDS, and it’s estimated that that number could go as high as 20 to 25 million children over the next decade. We think about losses to the health care system, to the educational system, shortages in food. The human tragedy and death are totally intolerable. But when we think beyond that, to the economic and social aspects, we have even more to lose.

“[At stake are tens of millions of lives, as well as societies, economies, and stability.]”

Dr. Helene Gayle

Q: You’ve spoken about the need for evidence-based interventions. How far along are we in collecting that information?
A: We’ve learned an incredible amount over the last 20-plus years, but we still need to continue to evaluate what we’re doing. Most of what we’ve done in the past has been small-scale interventions that have not been national in scale, which is part of the reason why we haven’t had as much of an impact as we could have. But increasingly, we’re seeing successes in countries starting to bring down the rates of HIV infections. We’re seeing more positive examples of getting treatments to people in resource-poor settings. I think the more we look at those with rigor, and synthesize and analyze lessons learned, we’ll be more effective.

Q: At the CDC and now at the Gates Foundation, you’ve been setting policy. How is your perspective different from that of people in the field?
A: When you’re at the field level, you’re very focused on making your program as excellent as possible. When you’re at the policy level, you think about what is it going to take to enable people at the field level to make their programs as excellent as possible.

Dr. Helene Gayle, M.D., M.P.H., Director of the HIV, TB & Reproductive Health Program for the Bill & Melinda Gates Foundation, was recently interviewed by associate editor Madeline Drexler.
Whenever possible, therapeutic regimens should be designed using DST. Not all regions of the world, however, have access to DST. In these settings, samples should be sent to one of the World Health Organization’s Supranational Reference Laboratories for analysis. If DST is not possible, regimens should be designed using knowledge of local epidemiology and based on the principle of avoiding drugs which the patient, or his/her contact, has received in the past.

**Monitoring and follow-up**
During two years of therapy, close patient monitoring is paramount. In the first reported community-based, individualized treatment program for MDR-TB infecting strain is likely to be susceptible. We recommend the following algorithm to guide regimen development: 1) Use of all first-line oral agents to which an isolate is sensitive. 2) Use of injectable (aminoglycosides or capreomycin) to which an isolate is sensitive; administered for at least six months after culture conversion, as it is often one of only two bactericidal components of the regimen. 3) Use of fluoroquinolone: if the isolate is sensitive to ciprofloxacin, the lowest priced, available fluoroquinolone is used. 4) At least five drugs to which the isolate is sensitive will be used, including other second-line agents (Table). Among second-line agents, ethionamide and cycloserine will be used if the isolate is sensitive; PAS will be used in patients with higher-grade resistance (See Table).

**Advances in comprehensive, community-based management of MDR-TB have changed global policy and offered hope for these once-neglected patients.**

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**Second-line antituberculous agents, dosing, and common adverse events**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1gm IM QD</td>
<td>Renal failure, ototoxicity, peripheral neuropathy</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1gm IM QD</td>
<td>Renal failure, electrolyte abnormalities, ototoxicity</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>1gm IM QD</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td>Well tolerated in general; GI side effects, Achilles tendon rupture</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500mg PO QD</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>400mg PO QD</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400mg PO QD</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>500-1000mg PO QD</td>
<td>Nausea, vomiting, hypothyroidism</td>
</tr>
<tr>
<td>Prothionamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>500-1000mg PO QD</td>
<td>Psychiatric disturbances</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS)</td>
<td>4gm PO BID-TID</td>
<td>Nausea, vomiting, hypothyroidism</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>200-300mg PO QD</td>
<td>GI disturbances, skin discoloration</td>
</tr>
<tr>
<td>Amoxicillin-Clavulanic acid</td>
<td>1500-2000mg PO QD</td>
<td>GI disturbances</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1000mg PO QD</td>
<td>GI disturbances</td>
</tr>
</tbody>
</table>

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**MDR-TB in special populations**
MDR-TB therapy has been delivered successfully in pediatric populations as well as in pregnant women. Adjuvant surgical therapy may be warranted in patients who have resectable disease, and in whom sputum conversion is not induced through antituberculous therapy alone. Patients co-infected with MDR-TB and HIV have been shown to experience worse clinical outcomes — suggesting that prompt diagnosis of both diseases and initiation of highly active antiretroviral therapy are crucial.

**Conclusion**
MDR-TB should be treated using a comprehensive management approach. Such a strategy enhances the ability of the global community to confront the MDR-TB epidemic, as well as other chronic infectious diseases. By implementing community-based programs grounded in the therapeutic principles that prevail in the world’s wealthiest nations, thousands of patients in resource-poor settings can hope for a cure. In addition to saving the lives of individuals who are already sick, effective treatment of MDR-TB is the best way to curb additional resistance among circulating strains of mycobacteria, and to arrest the global spread of this historic scourge.
campaigns have targeted consumers. The Bureau of National Health Insurance, Department of Health, now regulates payments for antibiotics. Hospitals have launched model interventions, particularly in intensive care units, to alleviate the prevalence of resistant nosocomial pathogens.

After joining APUA, and with its support, Taiwan is far better positioned to address antibiotic resistance challenges.

References

The artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin, are now widely marketed and will be available at progressively lower prices in the future. Yearly evaluation and widespread application in Asia and Africa provide reassurance that therapeutic doses of these compounds are safe and at least as effective as quinine for the treatment of malaria. Continued efforts, however, are needed to ensure the proper use, quality, and availability of these and other antimarial drugs; guarding against counterfeiters who sell sophisticated packages of fake preparations on international markets is also important. These efforts, in conjunction with wider use of effective drug combinations and presumptive intermittent therapy (PIT) treatment programs for children and pregnant women, will enhance and extend the public health benefits of antimalarial chemotherapy.

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References

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References
News from the APUA International Chapter Program

PAHO Technical Advisory Group (TAG) Meeting in Asunción, Paraguay

The PAHO Washington Office of Communicable Diseases convened AMR experts in Asunción, Paraguay on October 26-31, 2003. The meeting was lead by Dr. Gabriel Schmunis and Mrs. Roxanne S. Gonzalez.

Participants reviewed and updated AMR activities in Latin American and the Caribbean region for 2004-2008, and worked intensively on a regional AMR action plan that PAHO will implement. Dr. Anibal Sosa, representing APUA, attended the TAG meeting.

APUA-Philippines Hosted Inaugural Scientific Meeting

At the Philippine Society for Microbiology and Infectious Diseases (PSMID) December 3 and 4, 2003, APUA-Philippines held its first official scientific meeting. Dr. Anibal Sosa gave the plenary presentation, “Antibiotic Policies in Developing Countries.”

Dr. Sosa visited the Philippines General Hospital in Manila and talked to residents and fellows of the Metro Manila Hospitals on “Strategies to Control AMR.” He also visited the facilities of the Philippines Research Institute for Tropical Medicine (RITM) at the FILINVEST Corporate City, Alabang, Muntinlupa City, where he met Remigio M. Olveda, MD, Director of RITM.

APUA-Zambia

Sponsored by the USAID/Rational Pharmaceutical Management Plus Program, Anibal Sosa, MD., APUA International Program Director and John Stelling, MD., MPH, Senior Advisor for APUA, traveled to Lusaka, Zambia to participate in the launching ceremony of the APUA-Zambia chapter.

The event was held at the Lusaka University Teaching Hospital amphitheater. Among the 150 in attendance were the WHO representative in Zambia and keynote speaker, Dr. Stella Anyangwe, and Dr. B.U. Chirwa, Director General, Central Board of Health, who officially launched the chapter. APUA-Zambia will be led by co-coordinators Oliver Hazemba and Dr. James Mwansa.

APUA welcomes new chapters to the global network of 50

APUA-Paraguay

The Infectious Disease Society of Paraguay met at the Hotel Excelsior on October 29, 2003 to create the APUA-Paraguay chapter. Dr. Anibal Sosa discussed APUA’s impact on rational antibiotic use. The president of the Infectious Disease Society of Paraguay, Dr. Adolfo Galeano, led the election of the APUA-Paraguay board of directors: Dr. Ana Campuzano de Rolón, APUA Chapter Coordinator, Lic. Mercedes Zarracho, Dr. Antonio Arbo Sosa, Dr. Adolfo Galeano, Dr. Dulio Nunez, Dr. Ivan Allende and Dr. Dolores Lovera.

APUA-Bolivia

Dr. Christian Trigoso, Director of Laboratorio Nacional de Referencia en Bacteriologia Clinica (INLASA), La Paz, Bolivia, has directed the establishment of an APUA-Bolivia chapter. Other founding members include Esther Damiani, Dr. Eduardo Aranda, Patricia Rosales Rojas and Jorge Remo Estevez.

APUA-Kenya

Dr Sam Kariuki of the Centre for Microbiology Research, KEMRI, has directed the establishment of an APUA chapter in Kenya, under the umbrella of the Kenya Association of Microbiology. Other founding members include Joseph Oundo, Rose Kakai, Faith Mulai, Kiyukia Ciira and Paul Okemo.

APUA-Serbia and Montenegro Advances AMR Surveillance

With funding from the Serbian government, APUA-Serbia and Montenegro is carrying out routine surveillance in human and veterinary populations, and is creating a surveillance network in the Vojvodina region.

Grassroots Global Research to Improve Antimicrobial Policy and Practice (GRIP)

APUA-Moldova Conducts Analysis of Antimicrobial Consumption

With support from a small grant from the GRIP program, APUA-Moldova conducted a detailed analysis of antimicrobial consumption trends in five hospitals and three children’s emergency rooms in Moldova. The analysis compared results from 1991 and 2001. Among the study’s major findings:

1. Decreasing consumption in all hospitals of penicillin, chloramphenicol, kanamycin, carbenicillin, and streptomycin.
2. Increasing consumption of cephalosporins (all generations), gentamicin, and cotrimoxazole.
3. Use of new antibiotics such as clarithromycin and ciprofloxacin.
4. Increasing use of antibiotics that had not been prescribed before in a hospital system, including erythromycin, doxycycline, and rifampicin.

APUA-Ukraine Presents Findings from GRIP Project

APUA-Ukraine presented findings from the APUA-supported study, “Estimation of the Economic Impact of Inappropriate Microbiological Sample Culturing in a Nigerian City Hospital,” at the 5th annual Clinical Antibioticotherapy conference in Kyiv, Ukraine.
ROAR Awards First Subgrant

APUA has awarded its first ROAR subgrant under The Reservoir of Antibiotic Resistance (ROAR) Project, a five-year effort funded by the National Institute of Allergy and Infectious Diseases and coordinated by APUA. The ROAR Project’s goal is to define the role of commensal organisms as reservoirs of antibiotic resistance that may be transferred to pathogenic organisms.

Drs. Ruth M. Hall and Jon Iredell, of the University of Sydney’s Centre for Infectious Diseases and Microbiology, will conduct research concerning “Antibiotic Resistance Genes and their Context in Commensal and Disease-Associated Clinical Isolates of Gram Negative Bacteria.” This study was chosen by an APUA-organized expert review committee, which considered over 40 applications. The research is based on analysis of integrons and plasmids within three complementary strain collections. The researchers will address the hypotheses that commensal organisms serve as reservoirs for the emergence and proliferation of antibiotic resistance genes in disease-associated bacteria.

The APUA ROAR Project will issue another request for proposals in 2004, and will be funding two studies from the 2004 pool of proposals. Awards of up to $60,000 for one year, with possible renewal for the second year, are considered pilot grants to obtain data useful in testing hypotheses and developing more comprehensive studies.

The ROAR Workgroup is also preparing the new ROAR website, expected to go online in March 2004. The improved website will feature a comprehensive literature library focused on resistance in commensal bacteria, as well as an up-to-date archive of the ROAR Network’s email list. The site will also include the isolate database compiled from ROAR studies.

In May 2004, the annual ROAR ‘04 Steering Committee meeting will take place in New Orleans, to coincide with the General Meeting for the American Society for Microbiology.

To get involved in the ROAR Project or the ROAR email list, please visit our website at www.ROARProject.org, or contact Allison Hodges Myerson at allison.hodges@tufts.edu.

International Consultation on Agriculture and Veterinary Usage of Antimicrobials

The Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organization for Animal Health (OIE) organized the Joint First FAO/OIE/WHO Expert Workshop on Non-human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment. The meeting took place at WHO Headquarters in Geneva, Switzerland, December 1-5, 2003. Stephen DeVincent, DVM, MA, Director of APUA’s Ecology Program, was invited to participate, along with other specialists from the fields of animal feeding practice, epidemiology, microbiology, public health, risk assessment and veterinary medicine.

Because antimicrobial usage and antimicrobial resistance are multifactorial problems, the Executive Committee of the Codex Alimentarius Commission had recommended that FAO, WHO and OIE convene a multidisciplinary expert consultation. The purpose of the Workshop was to present and discuss scientific findings to develop consensus on health aspects of antimicrobial usage and antimicrobial resistance in animal and agriculture production. The scientific consultation assessed non-human use of antimicrobials, and considered antimicrobials for agriculture and veterinary purposes (including aquaculture). The roles played by antimicrobials as essential human and veterinary medicines, as well as findings of previous expert consultations and reports — including APUA’s FAAIR Report (accessible at www.apua.org, click on Ecology) — were taken into account.

Documents from the Expert Workshop in Geneva, including the final report, can be accessed at http://www.who.int/foodsafety/publications/micro/nov2003/en/. The findings of this scientific analysis on risk assessment are intended to serve as the foundation for a second joint meeting in March 2004, the goal of which is to support development of risk management options to contain antimicrobial resistance.

Upcoming APUA Chapter Events on Website

APUA is launching a new feature on the APUA website (http://www.tufts.edu/med/duapui Intl/events.html) that will highlight upcoming activities and events among the 50 APUA chapters. This feature will inform APUA members about chapter initiatives, help members plan for international meetings, and facilitate the exchange of resources and knowledge.

To post an activity or event, email Flora Traub, International Program Coordinator, at flora.traub@tufts.edu.

APUA Partners with CDC’s “Get Smart” Campaign

In September 2003, the U.S. Centers for Disease Control launched their “Get Smart, Know When Antibiotics Work” educational campaign (see PSA on page 4). Among the campaign partners are APUA, the World Health Organization, The American Academy of Family Physicians, American Academy of Pediatrics and the American Medical Association. To get involved visit http://www.cdc.gov/getsmart.
If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax-deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

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*Membership is complimentary in the developing world.
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Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

★ Headquarters
- Chapters: Argentina, Australia, Bangladesh, Belarus, Bolivia, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Croatia, Cuba, Dominican Republic, Ecuador, El Salvador, Fiji Islands, Georgia, Greece, Guatemala, India, Italy, Kazakhstan, Kenya, Lebanon, Mexico, Moldova, Nepal, Nicaragua, Nigeria, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Russia, Senegal, Serbia and Montenegro, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, Uruguay, Venezuela, Vietnam, Zambia

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