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INSIDE

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The Expanding Syndrome of Necrotizing Fasciitis

ABSTRACT & COMMENTARY

By Joseph F. John, MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John is a consultant for Cubist, Genzyme, and bioMerieux, and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

Synopsis: *Most clinicians associate the hemolytic streptococci as the major cause of necrotizing fasciitis (NF), an association that is usually the case. There are, however, other emerging causes of the syndrome and, in fact, NF is often a polymicrobial synergistic infection, particularly after surgical procedures. Other risk factors include blunt trauma, cuts, burns, varicella infection, and even muscle strains. With this patient, radiotherapy joins the group of risk factors.*

Source: Kelesidis T, Tsiodras S. Postirradiation *Klebsiella pneumoniae*-associated necrotizing fasciitis in the Western Hemisphere: A rare but life-threatening clinical entity. *Amer J Med Sci*. 2009;338:217-224

A NEW REPORT AND REVIEW OF THE LITERATURE COMES FROM Caritas St. Elizabeth's Medical Center in Boston of a 77-year-old Native American with follicular thyroid cancer post-radiation that spread to his hip, resulting in metastatic disease. He developed septic shock and necrotizing fasciitis of both thighs. Wide debridement was performed on both thighs, which grew only *Klebsiella pneumoniae*; this organism was also present in blood and urine. The patient eventually died.

This patient joins 37 other patients with *K. pneumoniae*-caused NF that the authors gleaned from the literature, together with one case with *K. oxytoca* and one case with *K. aeruginosa*. Several important points differentiate these patients from those with Gram-positive-related NF. Most of the cases occurred in Asian countries: 37% in China, 21% in Taiwan, 13% in Turkey, and four cases in

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Singapore. Only one case, thus far, has been reported in the United States. The authors go on to describe 15 cases of monomicrobial NF caused by *K. pneumoniae*.

These patients had significant comorbidities: diabetes in 80%, cirrhosis in 20%, and one each with chronic renal failure and malignancy, respectively. Many of the previously reported cases had liver abscesses. In 10 cases, at least one other organ was involved. Bacteremia was present in 10 of the 15 patients. In 13 of the patients where mortality was reviewed, 31% of the patients died. There was a suggestion in these NF patients of hematogenous spread from multiple foci, so the concept advanced is that invasive *K. pneumoniae* infection often spreads to multiple organs from where the organism emerges to cause NF.

Therapy with surgical debridement and fasciotomy was the keystone of treatment with the addition of active antimicrobials. In this series only, one isolate was associated with a multiresistant *K. pneumoniae*. Thus, third-generation cephalosporins were the medical treatment of choice.

■ COMMENT

The spectrum of microbial agents capable of causing NF continues to expand. Almost 40 cases have been described related to Klebsiella infection. This genus is notorious over the last half century for causing health-care-related infection, probably due to its propensity to colonize early in the hospitalized patient and to elaborate certain virulence factors, including capsular material and antibiotic resistance, which obfuscate antimicrobial therapy. The presence of exceptionally mucoid *K. pneumoniae* has also recently been associated with severe infection and rapid spread. Klebsiella also have, for years, been notorious for having transmissible plasmids that can carry virulence factors like mucoid along with antimicrobial-resistant determinants.

This present study did not address the possibility that intrinsic or acquired toxins may be part of the infectious arsenal of *K. pneumoniae,* and more work needs to focus on that aspect. Indeed, NF seems to be a response to toxigenic factors in bacteria, classically the streptococcal and staphylococcal toxins. The spectre of Gram-negative toxins hangs over this new review of a classic Gram-negative pathogen, *K. pneumoniae*, as a capable cause, even in monomicrobial settings, of NF. ■

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Pneumocystis Colonization and Pulmonary Infection in Immunocompetent Adults

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for GSK and Cubist.

Synopsis: *The lungs of people who died of trauma and nonviolent sudden death, who underwent autopsy, were examined for Pneumocystis by nested polymerase chain reaction (PCR).* P. jirovecii *was identified in 50 (65%) of 77 individuals overall and in 15 (79%) of 19 individuals who died of nonviolent causes.*

Source: Ponce CA, et al. Pneumocystis colonization is highly prevalent in the autopsied lungs of the general population. *Clin Infect Dis*. 2010;50: 347-53.

Nested PCR using primers to amplify the mitochondrial large subunit of *P. jirovecii* was performed on lungs from patients who underwent autopsy at a large urban medical examiner's office in Chile. Lung-tissue concentration methods were used to analyze approximately 3% of the RUL lung weight, and PCR-negative samples from those in the violent death group were reanalyzed using 6%-7% of RUL lung

weight to confirm the initial results. *P. jirovecii* DNA was detected by nested PCR in 50 (65%) of 77 subjects overall and in 15 (79%) of 19 subjects who died of medical conditions. Immunofluorescent microscopy was used to examine the lungs of all 55 subjects who died of trauma. Pneumocystis forms (which were few in number) were visualized in all 34 subjects who tested positive and in none of those who tested negative by PCR. No sex difference in PCR positivity was noted. *P. jirovecii* did appear to be more common in those < 20 and > 60 years of age.

■ **COMMENTARY**

Pneumocystosis is a fascinating disease, and our understanding of it, while still evolving, has changed tremendously over the 38 years that I have been in medicine. While *Pneumocystis carinii* pneumonia (PCP) was first described in malnourished orphaned infants, it first came to be recognized as an important clinical entity in iatrogenically immunocompromised patients in the late 1960s. I saw a handful of PCP cases each year in this group and, in the 1980s, as HIV infection spread in the United States, I often saw several new cases of PCP each week. It has been appreciated for many years that pneumocystis infection was almost universal in young children and generally subclinical in healthy children. It was initially assumed that symptomatic pneumocystosis usually occurred as a result of reactivation of "latent" infection (analogous to toxoplasma encephalitis) in immunocompromised patients. However, different Pneumocystis genotypes were later demonstrated in HIV-infected patients who experienced two episodes of pneumonia occurring > 6 months apart, thereby casting doubt on the reactivation hypothesis.[1] In addition, clusters of PCP have been described in wards of immunocompromised patients, and the lack of PCP reactivation in CD4 T-cell-deficient mice makes latency unlikely. Lastly, the presence of cyst and trophozoite forms seen on immunofluorescent microscopy in the present study, and the presence of viable, actively replicating Pneumocystis organisms in immunocompetent animal models, all point to the common occurrence of recurrent Pneumocystis infections throughout life in healthy individuals, and suggests PCP in immunocompromised patients is due to reinfection.

In the same issue of *Clinical Infectious Diseases*, the same group report on the results of their study of 110 older adults who had oropharyngeal wash and nasal swab specimens examined by the same nested PCR technique used in the autopsy study.[2] *P. jirovecii* DNA was detected in 21.5% of paired specimens, demonstrating that upper respiratory tract colonization by *P. jirovecii* is common in older healthy adults. ■

References:

1. Keely SP, et al. Genetic variation among Pneumocystis carinii hominis isolates in recurrent pneumocystis. *J Infect Dis*. 1995;172:595-598.
2. Vargas SL, et al. Pneumocystis colonization in older adults and diagnostic yield of single versus paired noninvasive respiratory sampling. *Clin Infect Dis*. 2010;50:e19-21.

Acyclovir for Prevention of HIV Transmission

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In a randomized, placebo-controlled trial of suppressive therapy for HSV-2 (acyclovir 400 mg BID) in HIV-1 serodiscordant couples, acyclovir did not reduce the risk of transmission of HIV-1 despite a reduction in the levels of HIV-1 RNA.*

Source: Celum C, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362:427-439.

In a study of HIV transmission, 3,408 HIV-1 serodiscordant couples were enrolled at 14 sites in Africa. All patients had CD4+ lymphocyte counts ≥ 250/uL, were also infected with HSV-2, and were not receiving antiretroviral therapy (ARVs). Sixty-eight percent of the HIV-1 infected partners were women. There were 132 HIV-1 seroconversions; 84 were linked within couples by sequencing. Of these, 41 occurred in the acyclovir (ACV) group and 43 in the placebo group. ACV treatment reduced the mean plasma concentration of HIV-1 by 0.25 $\log_{10}$ copies/mL and the occurrence of HSV-2 + genital ulcers by 73%. Ninety-two percent of the partners infected with HIV-1, and 84% of the partners not infected with HIV-1, remained in the study for 24 months. ACV adherence was 96%.

■ **COMMENTARY**

The correlation between genital ulcer disease and HIV-1 infection, especially in heterosexual couples, has been appreciated since the mid-1980s. The logical postulation is that by disrupting normal cutaneous and mucosal barriers, genital ulcer disease directly facili-

tates the transmission of HIV-1. In addition, a large body of research over the last 25 years has demonstrated that many HSV-encoded proteins can directly promote the transcription of HIV-1, as well as nonspecifically enhancing host cytokine levels, which generally facilitate NFkB-mediated up-regulation of HIV-1 transcription. In fact, earlier clinical studies have demonstrated that daily therapy with ACV for 8-12 weeks reduced plasma HIV-1 RNA levels by 0.25-0.50 $\log_{10}$ copies/mL.

This large, randomized, placebo-controlled trial represented a logical hypothesis that anti-HSV nucleoside analogs, such as ACV, could reduce the transmission of HIV-1 in serodiscordant couples by both reducing genital ulcer disease and by modestly lowering plasma (and genital fluid) levels of HIV-1. This approach is attractive for a number of reasons, since the majority of HIV-1 transmission in Africa is heterosexual and the prevalence of ulcerative genital disease (mostly due to HSV-2) is high. Additionally, the cost of ACV has come down considerably since it is now available as a generic drug, and is certainly less expensive than antiretroviral therapy.

Unfortunately, despite high levels of adherence to daily ACV therapy (and demonstrated reduction in genital ulcer disease and modest reduction in HIV-1 RNA levels), this intervention is just not good enough to reduce HIV transmission. Interestingly, the authors point out that the rate of HIV transmission in both the ACV and placebo groups were relatively low compared to historical data. The authors attribute this low transmission rate to the effect of intervention on promoting condom use and safer sex practices within the study.

The take-home message, from my perspective, is that the only way we are going to significantly reduce HIV transmission is by making universal antiretroviral therapy available throughout the world. While the cost of nucleoside and nucleotide analogue reverse transcriptase inhibitors and non-nucleoside RT inhibitors has come down, HIV protease inhibitors will likely remain unaffordable in much of the developing world. This is actually not due to greedy pharmaceutical companies, but rather the hard fact that PIs require multiple synthetic steps and use generally costly precursor chemicals in their synthesis. Unfortunately, with the rising prevalence of NRTI and nnRTI resistance in transmitted virus, I remain skeptical about our chances of successfully eradicating HIV infection in the developing world using NRTI/nnRTI combinations alone, even if the goal of universal antiretroviral therapy is achieved. ■

Building Laboratory Capacity in Resource-poor Settings: Part 1

SPECIAL FEATURE

By Ellen Jo Baron, MD, PhD

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Dr. Baron reports no financial relationships relevant to this field of study.

PHYSICIANS IN THE DEVELOPED PARTS OF THE WORLD have an unrealistic expectation that when they order a patient's specimen to be sent to the microbiology laboratory for culture that the results they receive in the laboratory's report are always reliable and can be used to initiate or modify the patient's therapeutic regimen. For the most part, physicians have placed their trust in a number of important events occurring in the appropriate order and in the appropriate manner. In reality, numerous roadblocks exist between clinicians' high expectations and the outcome. Many types of mistakes, or oversights, can happen, starting from the time the initial order was placed.

Common events, from my experience, serve as examples. The type of order required may not be the order placed into the system and acted on by the laboratory. For example, a respiratory secretion sample from a patient with cystic fibrosis (CF) must be inoculated onto at least two special, selective agars to have any chance of detecting two major pathogens in this population: *Burkholderia cepacia* selective agar and *Staphylococcus aureus* selective agar. If the laboratory is not aware that the patient has CF, the special media will not be used and the mucoid *Pseudomonas aeruginosa*, which is the hallmark of this disease, will overgrow the Petri plates and negate any possibility of recovering the other pathogens. Failure to detect one of these key pathogens can lead to severe negative consequences for the patient. If a physician obtains an endocervical swab but the swab doesn't reach the laboratory until the next day, small quantities of *Neisseria gonorrhoeae* may not survive. Molecular tests for *N. gonorrhoeae* may be more robust because viable organisms are not necessary, but if the endocervical pus was not removed before sample collection, the amplification process may be inhibited and the test will be indeterminate. Tissues are inadvertently

placed in formalin when cultures are needed, tiny needle biopsies can dry out before they reach the laboratory, containers with precious samples can be diverted and then lost in a blind tunnel of the pneumatic tube (in one case for months) and, once, a group of inoculated blood culture bottles were found days after collection in a small refrigerator under a counter in the chemistry laboratory. Seth Haber, a clever pathologist who wrote a column in *CAP Today* for many years, created a set of laws that tried to inject a bit of humor into a devastating situation (Haber's Laws) (www.CAPToday.com), one of which I will paraphrase as "if a technologist drops a precious patient sample, it will fall on the most delicate piece of equipment in the laboratory, destroying both items."

These comments do not even begin to represent examples of problems that occur after the sample reaches the laboratory. Several years ago, in a laboratory in Southern California, a tired second-shift laboratory assistant plated an entire night's worth of urine cultures onto a selective agar plate that looked like standard blood agar but contained antibiotics and other inhibitors that killed every organism except group A streptococci, the one organism unlikely to be present in urine in the first place. These events are far from rare. In the future, we could present an entire article on common laboratory errors that result in frustrations for the physician and delays or worse for the patient. The more we realize the sorts of unwelcome incidents that can happen, the more defensive actions we can take to try to prevent these mistakes. Sadly, bad events happen too often, even in the best of laboratories staffed by professionals who have the worthiest of intentions.

Now, consider the nascent microbiology laboratories in the developing world. Although similar situations can be found in scores of countries, this report focuses on Cambodia because that is where support from World Health Organization (WHO) and the Global Health and Security Initiative of the Nuclear Threat Initiative allows our non-profit organization Diagnostic Microbiology Development Program (DMDP) to provide assistance in the form of supplies, infrastructure development, and volunteers who bring diagnostic microbiology expertise to a few primitive sites in this impoverished and devastated country.

The earthquake in Haiti, a disaster of monumental proportions, has shed a spotlight on the world's poorest countries. In one list of 194 countries ranked by gross domestic product, Haiti was 168 but Cambodia was nearby at 154. A number of African countries are at the bottom and the U.S. was #8 in this listing (www.who.int). Problems in Cambodia began with the legacy left by the despot Pol Pot. Within the lifetime of many Cambodians age 32 and older, one of the world's worst genocides occurred. Most adults today remember a time when all they had to eat were a few brown rice kernels that fell off the wagons of rice that they were forced to grow for export. As many Cambodians died from starvation and diarrheal disease, many were killed outright. Pol Pot's troops, no more than children themselves, tortured and killed anyone with an education, anyone who spoke French, anyone who could read, and even anyone who wore glasses. Most of the generation of Cambodians administering the country today have grown up without cultural, spiritual, or educational role models. They are still living in the mindset of "get whatever you can for yourself to survive." Unfortunately, that does not leave much emotional space to care for other citizens of the country beyond their circle of friends and family. Right now, the primary sources of revenue are tourism (Angkor Wat and the surrounding ancient temples) and the country's land, including some lovely seacoast, which the leaders are fast selling off to foreign developers, to the detrimental, sometimes fatal, outcomes of the locals who had lived there for generations and are now moved inland to locations with no possible means of making a living. Cambodia, even without a gigantic natural disaster, is in desperate straits. Fifty percent of the population is less than 25 years old.[1] This is the only country in the world where the mortality rate among children < 5 years old is increasing. Medical care is virtually nonexistent. Almost without exception, if you become seriously ill in Cambodia, your only chance of survival is to fly to Bangkok quickly enough to get decent medicine.

There are possibly as many as 20 hospitals in this country of 14,250,000 people, most run by non-governmental aid organizations (NGOs) from around the world.[1] A few small hospitals in Phnom Penh, notably the Pasteur Institute facility, have the capability of performing a microbiological culture and delivering relatively accurate results. But, such services come at a pretty high cost — only the wealthy (here you may substitute "foreigners" or "corrupt officials") can afford them. In another model, exemplified by the hospitals built with foreign donations by Dr. Beat Richter, facilities are staffed mostly by foreign volunteers or missionaries, and Cambodians work primarily in unskilled jobs. In these NGO hospitals, some locals learn skills through on-the-job training, as there

are very few schools of higher learning, and none with adequate general laboratory or microbiology training programs. In the bulk of the country, government-run hospitals get by with minimal support, but laboratory services are virtually non-existent. Patients are expected to pay for whatever care or medicines they receive when they visit the clinic or enter the hospital. In a country where the average annual income is $2,000, this is not easy, and laboratory tests are not high on their list of necessities.

With regard to microbiology laboratory training, there is one governmental laboratory technical school but the microbiology portion of the curriculum is rudimentary or nonexistent. And practical laboratory skills are not taught at all. The Merieux Foundation supports a pharmacy school with at least one microbiology class; this school (still taught in French, which is not spoken anywhere else in the country) turns out almost all of the laboratory directors in Cambodia, and the graduates know more microbiology than anyone else (which is not much and certainly not enough to perform a simple urine culture). These people are paid $30 a month by the Ministry of Health to work in and manage the government hospital laboratories, but the pharmacists actually make their living by owning and running a private pharmacy (which also performs microbiology culture studies) on the side. This causes conflict of interest, as the work in the hospital laboratory is hurriedly finished each day to allow time to go to the private pharmacy/laboratory and make money. Supplies are "transferred" off site, and worst of all, the most promising young technicians are hired to work in the private laboratory for wages that cannot be turned down. Samples from patients who have the ability to pay for laboratory tests are diverted to the private laboratory. Motivation to work hard for the hospital patients, who usually have barely enough money to pay for minimal services, is lacking. It is this environment in which we try to motivate technicians to upgrade their knowledge and abilities and perform quality diagnostic work. How do you convince such workers to perform daily quality control activities? How do you cajole them to come in on a weekend to read susceptibility results on an important culture? The environment of caring for the patient's well being is not there.

Equally as daunting as the challenges posed by the economic and educational environment are challenges involved in obtaining the resources needed to perform reliable microbiology. In the United States, we take for granted that we will have sufficient components for the media used in agar plates. Sheep and horses are plentiful in the developed world, and it is not technically difficult to bleed the animals and collect their blood aseptically, defibrinate it to remove clots, and use that blood to pour the plates. We depend on the growth characteristics on blood agar of the organisms we recover in cultures to begin the identification steps needed to determine the genus and species. For more than a century, microbiologists have used key colony morphology and the nature of red cell hemolytic activity on sheep and horse blood to name the pathogens. There are no sheep in Cambodia. It is too hot, there are too many parasites, and the local population would not know how to care for or manage sheep. Horses are out of the question, being too expensive, requiring too much land and support, and being also rare in Cambodia and many developing countries.

So Cambodian technicians as well as microbiologists everywhere else in the developing regions of the tropics with insufficient resources to purchase blood from out of country use outdated human blood bank blood to make their media. This poses two problems: human blood is unsafe, often carrying hepatitis or HIV; and human blood does not grow pathogens or other human microbes either very well or with recognizable colony morphologies, negative characteristics that degrade even more after storage. In other words, human blood doesn't work. We have purchased a few scrawny sheep and found another NGO willing to husband and to bleed them, but it is not the most satisfactory arrangement, and the sheep are not thriving. There will be more on a potential solution for the problem of obtaining the blood component of media in a future column.

The basic microbiology procedures advocated by our program result in identifying a pathogenic isolate only enough to allow the clinician to make an informed decision and then performing simple disk--diffusion antimicrobial susceptibilities. No automated methods, no multi-well biochemical panels, no expensive additional tests. The identification of isolates depends on colony and Gram stain morphology, rapid spot tests (catalase, coagulase, indole, oxidase, and pyrrolidonyl aminopeptidase), and a few typing sera. If an important organism from a patient requires a definitive identification beyond the local laboratory's capability or resources, it is sent to the U.S. Naval Army Medical Research Unit Laboratory in Phnom Penh, which does an excellent job for free, albeit with delayed results. But the reagents and supplies needed even for the very minimal rapid spot tests are difficult to obtain. One can order them from a supplier from another country, but the price

becomes exorbitant. In fact, one spot reagent kit used in the Stanford laboratory that costs us $18 to purchase, ended up costing the Cambodian laboratory $200 (paid for by WHO, of course). What contributes to this enormous price inflation? The only factor is the amount of taxes, fees, and gratuities extracted from stakeholders along the way as the product moves through official importation channels. We would like to purchase our supplies in the U.S. and carry or mail them directly into Cambodia, but the head of WHO in country does not want to flout the official government process. Unfortunately a lot of the official process is unofficial. So having enough supplies on hand is challenging, and many times the laboratory has to improvise. Also regrettably, improvisation is not a skill either inherent in most technicians in the developing world, nor is it taught in the schools. The Cambodians are a wonderful, generally cheerful, group of people, but with major traits of fatalism and inertia in the face of decades of obstacles. They deserve a better future.

Given this scenario, there doesn't seem to be a lot of cause for optimism on the laboratory scene. The objective of the DMDP is to have four laboratories in Cambodia capable of performing basic microbiology, starting with a Gram stain, then moving to tasks such as a urine culture, CSF culture, blood culture, sputum or wound culture, and finally performing antimicrobial susceptibility tests on the appropriate organisms recovered in culture. One year into the work, we have a pretty good laboratory in Kampong Cham, approximately two hours up the Mekong River from Phnom Penh. Our success there is largely due to Madame Somary, a very motivated and enthusiastic pharmacist who wants to learn as much as possible and perform high-quality microbiology. We have to live with the fact that the best work is done in her private pharmacy laboratory; nevertheless, her leadership in the hospital laboratory has been superb. They identified a *Streptococcus pneumoniae* from a CSF last week, and they have recovered and identified Shigella, Salmonella, Acinetobacter, *Haemophilus influenzae*, and *Staphylococcus aureus*, among others. The susceptibility QC is being done weekly, and physicians are beginning to send samples as they develop more trust in the laboratory. The WHO liaison for the program project has proudly taken visitors up to Kampong Cham Hospital to showcase this laboratory. Recently an Australian volunteer arrived in Kampong Cham to live and work in the laboratory for more than a year, and she is continuing to enforce our program. This is the kind of support these laboratories need, and we hope other agencies will also come into the system.

A space has been identified for a microbiology laboratory in Battambang, the second largest city in Cambodia, located about five hours by bus northwest of Phnom Penh, and our group has contracted for renovation and building of the laboratory space. This summer we will move our next volunteer there to spend a more extended time (up to 6 months) to try to get that laboratory up and running. Our great good luck was to find a current Stanford Clinical Laboratory Science student willing to go there when she graduates this summer, but the best part is that she is ethnic Cambodian, speaks Khmer, and has an uncle living in Battambang. This extraordinarily fortunate situation must be celebrated. A third laboratory is slated for Takeo (in southern Cambodia), but the plan is not complete yet. The fourth laboratory, the National Pediatric Hospital in Phnom Penh, has major problems with laboratory staff motivation and interest. The director of the hospital laboratory also has his private laboratory, where all of the promising technicians' work is done, so there is no authority from above advocating dedication to the hospital patients' cultures. Even after four months of constant volunteer support, the laboratory won't do its quality control, cultures are left for days without examination, workbenches are dirty and supplies are disorganized, but worst of all results are unreliable. Without better leadership, volunteers cannot be effective, so we will not spend our precious resources placing them there. There is hope that the most promising technician, who won a scholarship to study microbiology in Thailand for six months, will return to the laboratory and provide the skills and leadership needed to motivate the others. Since she also has her private business nearby in downtown Phnom Penh, there is hope that she will stay in the laboratory.

This article covered some of the aspects and obstacles encountered in trying to enhance microbiology diagnostic capability in a developing world venue. If nothing else, it should cause you to appreciate the laboratory you use now. Despite a few failures and shortcomings, realize that results are generally reasonable and helpful and that the information delivered to you is timely and relevant to your patients. Some day we hope that at least a few laboratories in Cambodia can deliver the same results. ■

Reference

1. http://www.cia.gov/library/publications/the-world-factbook/geos/cb.html

Land-to-sea Transmission of Toxoplasmosis ... And Back Again

ASTM CONFERENCE COVERAGE

By Mary-Louise Scully, MD

Dr. Scully is Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA.

Dr. Scully reports no financial relationships relevant to this field of study.

This study originally appeared in the February issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, and peer reviewed by Mary-Louise Scully, MD. Dr. Bia is Professor (Emeritus) of Internal Medicine (Infectious Disease and Clinical Microbiology), Yale University School of Medicine, and Dr. Scully is Director, Travel and Tropical Medicine Center, SansumClinic, Santa Barbara, CA.; they both report no financial relationships relevant to this field of study.*

At the recent 58th annual meeting of American Society of Tropical Medicine and Hygiene held in Washington D.C., Dr. Patricia Conrad of the University of California, Davis School of Veterinary Medicine, provided an excellent presentation during the Scientific Session on Protozoa entitled "Tracking *Toxoplasma* gondii from Land to Sea." Conrad and her colleagues have been exploring the complex relationship between marine and terrestrial environments in toxoplasmosis transmission to California sea otters. Their research shows that the increasing prevalence of toxoplasmosis in California sea otters is linked to coastal fresh water runoff of infective *Toxoplasma gondii* (*T. gondii*) oocysts from cat feces, both domestic and feral. These findings are especially noteworthy in that a recent study found ingestion of raw or undercooked clams, oysters, and mussels to be an emerging risk factor for human toxoplasmosis acquisition as well.[1]

Sea otters were once abundant along the Pacific Rim, but these animals were hunted to near extinction for their soft, dense, highly valued fur, often referred to as "soft gold" among hunters. In 1911, sea otter hunting was finally banned under an international treaty signed by Russia, Japan, Great Britain, and the United States. Under legal protection, some sea otter populations in Alaska and the Pacific Northwest have rebounded. However, the California southern sea otter (*Enhydra lutris nereis*) has struggled, and remains listed as a threatened species, numbering only about 2,800. The causes for their decline are likely multi-factorial, but a partial explanation is parasitic infections such as *T. gondii* and *Sarcocystis neurona*.

T. gondii can infect a wide variety of animals, but domestic and wild felids (felines) are the only definitive hosts where sexual multiplication of the parasite results in formation of oocysts that are passed in the feces, sporulate in the environment, and are infective to susceptible hosts. Cats are infected by eating tissue cysts of infected birds or rodents or by eating sporulated cysts from other cats. Under laboratory conditions, cats can shed as many as 500 million oocysts, and they may shed oocysts for up to 20 days. The natural instinct of cats to bury their feces and defecate in shaded areas can allow the cysts to remain infective for as long as 18 months.[2] These infective oocysts in soil may then be transported into freshwater and marine waters via sewage, storm, and freshwater runoff.

It is known that *T. gondii* can cause fatal encephalitis in California sea otters. Conrad and colleagues studied 223 live and dead sea otters between 1997 and 2001 and found a seroprevalence rate of 42% (49/116) for live otters and 62% (66/107) for dead otters. Importantly, they found that otters sampled near coastal areas of freshwater runoff were approximately three times more likely to be seropositive for *T. gondii* compared to otters living in areas of low-flow runoff.[3] Therefore, land-based surface runoff appears to be the mechanism by which infective *T. gondii* oocysts enter the marine environment.

The exact means by which sea otters and other marine mammals acquire *T. gondii* in the marine environment is unknown. Previous laboratory studies demonstrated that *T. gondii* oocysts may be concentrated by filter feeding marine bivalves such as mussels, but more recent research has shown that specific feeding preferences of sea otters also may affect toxoplasmosis prevalence. Sea otters with diets composed of $\geq$ 10% marine snails were 12 times more likely to be infected with *T. gondii* than sea otters that ate fewer marine snails. In contrast, sea otters with diets consisting mainly of abalone had a much lower risk of infection.[4] In another study, the specific physical properties of *T. gondii* oocysts (i.e., the loss of electrical charge in saline waters) was shown to promote flocculation and sedimentation of *T. gondii* oocysts in areas where marine and fresh waters meet, such as estuaries and near-coast habitats. These are areas where marine snails and sea otters frequently feed, but also where humans may be more exposed by water-related activities to infective oocysts as well.[5]

Several human toxoplasmosis outbreaks have been epidemiologically linked to contaminated water sources, including one outbreak in a municipal water reservoir in British Columbia, Canada.[6] It is also

known that wastewater treatment practices and chlorination are not effective at destroying the oocysts of *T. gondii,* and they can remain viable in seawater for up to six months. The Palo Alto Medical Foundation Toxoplasma Serology Laboratory in conjunction with the CDC recently published a case control study of 148 adults infected with *T. gondii*. In this study, eating raw oysters, clams, or mussels was a risk factor for acquisition of toxoplasmosis in the subset of patients asked this question. Other risk factors were eating raw ground beef or rare lamb, working with meat, eating locally produced cured, dried, or smoked meat, drinking unpasteurized goat's milk, and having three or more kittens.[1]

It is estimated that 32% of households in the United States own cats (an estimated 78 million cats); an additional 73 million cats are feral.[7] With these large numbers, the potential land-to-sea transport of infectious *T. gondii* oocysts is impressive. Cat owners can help by not flushing cat litter down the toilet. Instead, cat litter should be bagged and disposed of in approved landfills where runoff is well controlled. This includes cat litter products that are advertised as "flushable litter." Some cat litter products may even be advertised as "eco-friendly" to be added to compost piles, but this should be avoided as well. In 2006 California Governor Arnold Schwarzenegger signed a bill into law requiring that all cat litter sold in California carry a warning label not to dispose of the litter in toilets or storm drains. However, many people remain unaware or perhaps unconvinced of the importance of this law.

What is in our backyards, be it cat feces or the chemicals used in our homes or lawns, invariably will end up in our oceans. The connection between the health of marine mammals and human health is more evident each day. Scientists in both realms now realize that the environment we share together means we share the same risks and, eventually, the same fates. As Jean-Michel Cousteau, the renowned explorer and passionate advocate of protection of the marine environment, tells us, "Protect the oceans, and we protect ourselves."

More information about marine conservation and sea otter research can be found at www.oceanfutures.org and www.seaottersresearch.org. ■

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CME Question

25. What Gram-negative bacterium has recently emerged as a cause of necrotizing fasciitis?

a. *Pseudomonas aeruginosa*
b. *Morganella morganii*
c. *Salmonella enteritidis*
d. *Klebsiella pneumoniae*

26. Which of the following is correct?

a. Healthy people may be colonized by *Pneumocystis jiroveci*.
b. The detection of *Pneumocystis jiroveci* is invariably an indication for treatment.
c. *Pneumocystis jiroveci* is only found in the lower respiratory tract.
d. Clusters of disease due to *Pneumocystis jiroveci* have never been reported.

27. Which of the following is correct with regard to acyclovir administration to HIV-1 serodiscordant couples?

a. Acyclovir administration reduces transmission of HIV-1 in couples serodiscordant for HIV infection.
b. Acyclovir administration was associated with a 0.25 $\log_{10}$ decrease in HIV-1 viral load.
c. Acyclovir was ineffective in reducing the frequency of genital ulcers due to HSV-2.
d. Adherence to acyclovir treatment in the study was poor.

Answers: 25. (d); 26. (a); 27. (b)

CME Objectives

Upon completion of this educational activity, participants should be able to:

• discuss the diagnosis and treatment of infectious diseases;

• explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• discuss the latest information regarding risks, benefits and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies. ■

In Future Issues:

Human Metapneumovirus Infection

UPDATES

By Carol A. Kemper, MD, FACP

Schistosomiasis as IRES in HIV

Source: Psevdos G Jr. *Schistosoma mansoni* colitis in an AIDS patient. *The AIDS Reader.* December 16, 2009.

An increasing number of HIV-positive immigrants and refugees, many from Africa, are cared for in the United States. The standard battery of HIV-related blood studies does not include screening studies for strongyloides and schistosomiasis. HIV co-infection with these two parasites is common in certain countries. At least 20% of HIV+ patients with bloody diarrhea in Zimbabwe had schistosomiasis. In a 10-year post-mortem survey in Puerto Rico, histologic evidence of *S. mansoni* was found in 10% of AIDS patients who died.

This author describes a patient with newly diagnosed AIDS, who had just started antiretroviral therapy four weeks earlier, who developed non-bloody diarrhea, fever, and peripheral eosinophilia (13%). Stool studies for bacteria, *C. difficile*, and ova and parasites were negative, and he failed to respond to an empiric course of metronidazole. Colonoscopy showed diffuse hyperemia, and biopsy showed an intense granulomatous response to schistosoma ova. Within days of starting praziquantel, his diarrhea resolved. A second similar case, described elsewhere, also presented with diarrhea within weeks of initiation of HAART therapy. Colonoscopy revealed patchy colitis with a granulomatous response to schistosoma ova.

Schistosoma infection may result in acute symptomatic enteritis in patients with HIV as a manifestation of immune reactivation.

Tick-borne *B. henselae*

Source: Angelakis E, et al. Scalp eschar and neck lymphadenopathy caused by *Bartonella henselae* after tick bite. *Clin Infect Dis*. 2010;50:549-551.

Tick-borne lymphadenopathy (also referred to as TIBOLA) is usually a mild illness characterized by the presence of an eschar, usually on the scalp, with surrounding erythema and painful cervical lymphadenopathy. In Spain, the disease has also been referred to as Debonel, or Dermacentor-borne necrosis-erythema-lymphadenopathy. The disease tends to occur in the cooler months of the year (in late fall or early spring) on the Eurasian continent, where the dermacentor ticks are prevalent in wooded areas and fields. The median time of incubation is 4 to 7 days. Most bites occur on the scalp, and are associated with an eschar, or tache noire, and painful, regional lymphadenopathy in the head and neck area. Fever occurs in some cases, but skin rash is uncommon. Persistent local alopecia at the site of the tick bite may occur, and some infections appear to respond to doxycycline.

Molecular-based studies suggest that about one-fourth of these infections are due to *Rickettsia slovaca*, a rickettsial species first isolated in Czechoslovakia from its tick vector, *Dermacentor marginatus*. Further research has identified a second rickettsial species, *R. raoultii*, in a small number of cases. Another case of TIBOLA has been described with co-infection due to *R. slovaca* and *Coxiella burnetii*.

For a number of these cases, researchers have not been able to identify a causative agent. On a hunt to investigate other possible bacteriologic causes of TIBOLA, the authors performed extensive serological, microbiological, and molecular studies on blood and tissue specimens from 28 patients (ages 3 to 68 years) with the syndrome. Specimens were routinely tested for Rickettsial and Bartonella spp, *C. burnetii*, *B. burgdorferi*, and Francisella spp. About half (53%) of the cases were infected with *R. slovaca* and another 10.7% with *R. raoultii*; three (10.7%) cases had serological evidence of *B. henselae.* Tissue specimens from the site of the eschar were positive for *R. henselae* DNA in two of these patients, both of whom had animal contact. Tissue biopsy in the third patient, performed about 1.5 months following the infection was negative using real-time PCR, but the Dermacentor tick provided by the patient tested positive for *B. henselae* DNA.

Although this is not conclusive evidence that Dermacentor is a competent vector for *B. henselae*, it seems likely that tick-transmitted *B. henselae* may result in TIBOLA.

Update on ACIP Adult Immunization Guidelines

Sources: ACIP. Recommended Adult Immunization Schedule: United States, 2010. *Ann Intern Med*. 2010;152:36-39; Hopkins RH, Jr, and Vyas KS. Adult Immunization Guidelines: Challenges and Opportunities. *Ann Intern Med*. 2010;152:59-60.

The revised ACIP adult vaccination Schedule, published January 5, 2010, includes the following changes (documented in full at www.cdc.gov/vaccines/recs/ACIP/default.htm):

HPV

• A second HPV vaccine is now approved for use in young adults with-

in the United States. In contrast to the earlier HPV quadrivalent vaccine, which provided protection against four strains of HPV, including two strains associated with genital warts, the newer bivalent vaccine includes only two HPV strains associated with 70% of cases of genital dysplasia and cervical cancer.

• Vaccination of young men at risk for HPV is now also recommended.

MMR

• Two doses of MMR vaccine, administered four weeks apart, are now additionally recommended for certain groups, including health care workers, students in post-secondary educational institutions, international travelers, and adults with exposure to measles or mumps.

• All other adults born after 1957 do not require a booster dose of MMR if they have documentation of an initial primary dose.

• Heath care facilities should consider pre-emptively providing MMR for non-immune employees born before 1957.

Hepatitis A Vaccine:

• HAV is now recommended for all parents and caregivers of international adoptees.

Meningococcal Vaccine:

• A one-time booster dose of meningococcal conjugate vaccine is recommended after five years for anyone with ongoing risk factors for meningococcus, except those in campus housing.

***Haemophilus Influenzae* Type B (Hib) Vaccine;**

• A footnote in the guidelines suggests that Hib is not "contraindicated" in adults with leukemia, sickle cell disease, HIV, or splenectomy, for those clinicians wondering what to do for patients at increased risk for encapsulated organisms.

The accompanying editorial discusses the likelihood of an increased focus on adult immunization as a quality measure. Newer electronic medical records will have embedded prompts for routine adult vaccination. Providers should anticipate that audits of electronic medical records may more readily provide feedback to clinicians regarding rates of adult vaccination, and remuneration may eventually be tied to this in some areas. I recommend posting the updated ACIP document (and the ACIP document from 2009) somewhere near your desk for quick reference, as some of the recommendations for adult vaccination are not always as straightforward as the authorities make them out to be, and questions are likely to arise.

Strategies for Pandemic Flu

Source: Perlroth D, et al. Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States. *Clin Infect Dis*. 2010;50:165-174.

Numerous strategies for managing outbreaks of Influenza within the community were variously employed during the 2009 Influenza A/H1N1 pandemic, with little coordination on a broader scale and no real good sense of which strategy — or strategies — was most important or most necessary. These included antiviral therapy and prophylaxis, recommendations for social distancing (whereby you voluntarily limit your non-household, non-work social contact by approximately 50%) for either children or adults, network modeling for controlling behaviors, school closures, and household quarantine. But which strategy is most cost-effective?

A community-based simulation model was developed based on influenza disease severity and mortality, transmissibility (Ro, meaning the average number of secondary cases caused by one case patient in a susceptible population), and cost of the interventions and medical care. The baseline model estimated a 1% influenza mortality rate, an Ro of 2.1, a 60% compliance rate with the interventions, and no circulating resistance to antiviral therapy.

The "do nothing" approach was compared to various interventions, used singly or in combination. Using the above estimates, the single, most cost-effective intervention was the use of antiviral therapy and prophylaxis. Social distancing for both adults and children was the least costly intervention, and did result in modest improvement in health outcomes. In contrast, school closure alone was the most expensive intervention.

Based on the above model, the most cost-effective approach proved to be a multilayered one, using a combination of antiviral therapy, school closure, and social distancing, resulting in a reduction in cases from 35% to 10% of the population, with a price tag of approximately $1,250 per community member. This combined approach resulted in a quality-adjusted life expectancy of 20.2 years per community member, for a cost of $2,700 per case averted, and an overall gain of $31,300 per quality-adjusted life year (QALY).

However, as soon as antiretroviral drugs are no longer available — or effective — this same multilayer strategy reduces the percentage of cases in the community to only 22%, and is no longer as cost-effective. And if the influenza mortality rate falls below 1%, then the success of the model depends on the infectivity rate and compliance with interventions. For low-severity epidemics with a case-fatality rate < 0.5 and Ro < 1.6, the most cost-effective strategy shifts away from more costly interventions, such as school closure. Interestingly, while the case-fatality rate for the Influenza A/H1N1 epidemic is not clear, the higher estimates from Mexico suggest a CFR of 0.4%, with an Ro of 1.4-1.6. Based on these figures, the most cost-effective policy choice would be the combined use of antiviral therapy and voluntary social distancing; in this scenario, school closure would up the cost by almost $300,000 per QALY. ■

INFECTIOUS DISEASE ALERT®

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CUMULATIVE INDEX

Volume 28, Numbers 1-12, Pages 1-134

October 2008—September 2009

I

K

L

M

N

O

P

R

S

T

U

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Hospital Medicine Alert, Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■