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INSIDE

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Passport to Montreal—6th Conference of the International Society of Travel Medicine

SPECIAL COVERAGE

Nearly 2000 participants gathered in montreal, québec, for the 6th Conference of the International Society of Travel Medicine. These meetings included plenary sessions on malaria and vaccines, symposia and workshops on all aspects of travel and migration medicine, cases of the day, and the "voices of the host countries"—all amid free communication sessions and posters that were on view for most of the meeting. This rich and varied conference was attended by each of our associate editors who have collaborated to summarize some highlights of those presentations. —**fjb**

Opening Plenary Session—Malaria

Reviewed by Philip R. Fischer, MD, DTM&H

Chairpersons: AEC Rietveld, WHO, Geneva, Switzerland, and Mary Wilson, Mount Auburn Hospital, Cambridge, MA.

New Antimalarial Drugs for Chemoprophylaxis—Dennis Shanks, U.S. Army Medical Research Unit, Nairobi, Kenya.

The opening plenary session of the 6th Conference of the International Society of Travel Medicine focused on malaria. Participants were treated to an entertaining and scholarly review of the latest information about chemoprophylaxis, diagnostic testing, and vaccines. Dennis Shanks, an American working in Kenya, noted that adverse reactions and poor compliance with standard falciparum malaria chemoprophylaxis regimens (including mefloquine, doxycycline, and the combination of chloroquine/proguanil) make it desirable to have better chemoprophylactic options. Newer agents, not yet approved for prophylactic use in many countries, hold promise of improved usefulness.

Azithromycin, a macrolide antibiotic, has been tested during malaria prophylaxis trials in Kenya. It is more than 80% effective when taken daily and about 64% effective with weekly dosing. In Thailand and Indonesia, effectiveness is about 72%. Despite some promise, azithromycin has suboptimal efficacy (especially in nonimmune individuals) and must be taken daily.

The combination of atovaquone and proguanil (with tablets containing 250 mg of atovaquone and 100 mg of proguanil; available commercially largely in

Europe and Australia) is approved in some instances as a curative treatment agent. Studies in several African countries suggest that it is also at least 95% effective in prophylaxis using a single pill daily. There appears to be a "causal" prophylactic effect on liver-phase hypnozoites, so prophylactic treatment can be stopped one week after leaving an endemic area.

Tafenoquine (WR238605) is a primaquine analog that destroys all forms of the malaria parasite. G6PD deficiency should be ruled out in any individual planning to use it, but studies in Kenya, Ghana, and Thailand suggest that twice-weekly dosing is more than 90% effective in preventing malaria. With broad action against the different forms of malaria, it can be discontinued as soon as the treated traveler leaves the malaria-endemic area. Similarly, 15-30 mg of daily primaquine are effective in prophylaxis in G6PD-normal individuals, but the dosing is less convenient than with tafenoquine. Due to its influence on cardiac conduction, halofantrine is not a good choice as a prophylactic agent nor are artemesinin derivatives due to their brief duration of activity. Ciprofloxacin is clinically ineffective against malaria.

New Diagnostics—Kevin Kain, The Toronto Hospital, Toronto, ON, Canada.

Toronto's Kevin Kain then reviewed newer diagnostic tests for malaria. A clinical diagnosis of malaria is accurate in fewer than half of cases. Traditional malaria smear readings in "local" overseas settings were confirmed as accurate in only 25-75% of cases sent to the CDC in one recent study. Thus, there has been considerable interest in developing more accurate diagnostic tests.

One new class of malaria tests uses monoclonal antibodies against proteins released by *P. falciparum* parasites. Parasight F, ICT, and PATH are such examples, and these tests perform better than standard microscopy, with accuracy rates greater than 95%.

Another test strategy, including that used in the Optimal brand, uses antibody binding to test for parasite LDH. These tests are more than 90% sensitive and specific for *P. falciparum* and about 83% sensitive and 95% specific for *P. vivax*. Thus, new tests provide helpful information, but clinicians must realize that inaccurate results are still possible. The Parasight F test, for instance, can produce false-positives in the presence of rheumatoid factor and can also remain positive for up to a month following successful antimalarial treatment.

Malaria Vaccines—Progress and Prospects of Clinical Trials—Blaise Genton, Polyclinique Médicale Universitaire, Lausanne, Switzerland.

Blaise Genton, formerly working in Papua, New Guinea, but now based in Switzerland, reviewed the progress and prospects for a malaria vaccine. Currently, no effective vaccine is available, but testing continues using different forms of vaccines and different adjuvants. For the future, DNA vaccines hold the most promise. To produce these vaccines, a fragment of the parasite gene is incorporated into a plasmid vector. When this material is processed within recipient cells, parasite antigen is produced and stimulates an antibody response. Work is in progress at directing these DNA vaccines toward protection against multiple stages of the parasite's life cycle. Nonetheless, it is not clear if vaccines will obviate the need for insect precautions and chemoprophylaxis at any time in the foreseeable future. ❖

Symposium on International Adoption

Reviewed by David R. Hill, MD, DTM&H

Sources: S8.1 Pre-adoption review of medical records. Jenista JA, Adoption/Medical News, St. Joseph Mercy Hospital, Ann Arbor, MI; S8.2 Travel issues for internationally adopting families. Miller L, International Adoption Clinic, Department of Pediatrics, The Floating Hospital for Children at New England Medical Center, Tufts University School of Medicine, Boston, MA; S8.3 Post-arrival evaluation of international adoptees. Johnson DE, International Adoption Clinic, Department of Pediatrics, University of Minnesota, Minneapolis, MN.

Travel for international adoption is increasing. There were nearly 16,000 children adopted from foreign countries in 1998. A symposium that addressed this topic was led by three speakers who are recognized as leaders in the field. Dr. Jenista from the St. Joseph Mercy Hospital in Ann Arbor, MI, spoke on preadoption review of medical records, Dr. Miller from New England Medical Center, Boston, MA, spoke on travel issues for the adopting family, and Dr. Johnson from the University of Minnesota concluded with information on evaluation of adopted children after return to the United States. The subject of international adoption was recently reviewed by *Travel Medicine Advisor Update*.

Jenista discussed the country of origin of adopted children, which has changed over the last decade; now, more than 50% originate from China or the states of the former Soviet Union. Many children up for adoption are living in orphanages rather than foster care and they may be older (mean age, 22 months), leading to a higher frequency of developmental and medical problems. Medical records are sometimes provided and parents may request a review of them by health care providers in order to make informed decisions about their potential children. These records can include medical information, photographs, and video

clips. Jenista presented information on more than 2800 records, primarily from countries in eastern Europe, the former Soviet Union, and China. Records from the former Soviet Union described children with a high risk of maternal drug or alcohol use, neglect, prematurity, low birth weight, developmental delays, and frequent neurologic diagnoses. However, many data were lacking or inaccurate, such as the immunization history, and many of the diagnoses were unsubstantiated after arrival in the United States. Similar problems were seen with records from China, and up to 50% of the time they did not even represent the adoptive child. In the final analysis, records frequently had misinformation and the absence of important information; thus, the child could not be accurately assessed from them. If a video was included, it often raised concern about previously unrecorded diagnoses. This leaves prospective parents with a high degree of uncertainty about their potential child, and caused up to 50% of parents not to adopt the child. Jenista stressed that the records she reviewed probably represented only 10% of all adoptive children. Nevertheless, there should be a process to provide more accurate information.

Miller focused on the actual adoption and the preparations that should be undertaken by parents and family members. The goal is to have families informed, realistic, and medically prepared. Those persons who are traveling to adopt the child should receive the appropriate pretravel advice, immunizations, and medications. Parents, siblings, and other caregivers should consider initiating hepatitis B vaccine if their child originates from an endemic country. Parents need to be aware of the conditions in which they may find their child, and they need to be realistic about the health of the child. In addition to infectious diseases, growth, developmental, and emotional delays are most prominent, particularly among institutionalized children. About 50% of children will be delayed in height, 30% in weight, and 37% in head circumference. Developmental delays may be seen in 90-100%, and 60% of children aged 2 years may lack any language skills.

Johnson concluded the symposium by describing the health of children after they have been adopted and returned to the United States. Physical examination and laboratory testing are critical to proper evaluation of children. The prevalence of infectious disease depends upon the child's country of origin. As examples, 28% of children from Romania were hepatitis B carriers in 1998, children from eastern Europe had a high prevalence of intestinal parasites, primarily giardiasis and ascariasisis, and 25% of children from Russia in 1998 were PPD positive, compared with 5% positivity in children from China. Congenital syphilis seems to be uncommon. Elevation of blood-lead levels and iodine deficiency were seen in children from China. In terms of growth, catchup usually occurred, particularly if children were adopted at younger than 20 months of age, but there were long-term emotional, developmental, and intellectual effects of institutionalization. Many of these were not apparent for years after adoption, so ongoing testing is important. Johnson summarized by stating that after a few years in the United States, 35% of children have made great progress, 35% are left with few serious problems, and about 30% may have serious issues. Adoptive families will need ongoing support and should enter the process with realistic expectations about the future capabilities of their children. ❖

Suggested Readings

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6. Hill DR. The health of internationally adopted children. *Trav Med Advisor Update* 1998;8:17-20.

Symposium on Drug Resistance

Reviewed by Frank J. Bia, MD, MPH

Organizers of the 6th cistm planned an extensive four-speaker symposium intended to cover new developments in the field of drug-resistant pathogens. These included enteric infections due to *Salmonella* species by Eduardo Gotuzzo from Lima, Peru; malaria standby therapy by Blaise Genton of Lausanne, Switzerland; sexually transmitted diseases by George Schmid, Atlanta, GA; and tuberculosis by E. Jane Carter, Providence, R.I.

Salmonellosis and Typhoid Fever

Gotuzzo began this symposium by noting that salmonellosis represents a typical zoonotic infection associated with acute diarrhea and, occasionally, systemic manifestations of infection. However, typhoid fever does not involve ani-

mals and is a systemic illness transmitted from human to human. This distinction is important, particularly when observing the beneficial effects of antibiotic therapy upon fecal excretion and transmission of *S. typhi*. Gotuzzo emphasized a now-predominant role for the fluoroquinolones in the therapy of both salmonellosis and typhoid fever based upon several important attributes of the quinolones. These include their convenience and efficacy—specifically, high fecal concentrations of orally administered quinolones (frequently reaching 1000-2000 mcg/g of feces), secretion of quinolones by bowel mucosa, low minimum inhibitory concentrations against *Salmonella* sp. including resistant strains, elimination of plasmid-carrying resistance genes, and excellent reduction in fecal excretion times and carrier rates along with prevention of relapses when these agents are used appropriately. The quinolones alleviate diarrhea and rapidly eliminate *Salmonella* sp. from stool, both reducing excretion and transmission while preventing complications of bacteremia such as osteomyelitis and splenic abscess formation.

In Latin America, chloramphenicol remains the standard for treatment of *Salmonella* infections due to both its low cost and efficacy. Gotuzzo warned that alternatives to chloramphenicol other than the quinolones, including as beta-lactams and folic acid antagonists, may not perform as well. Nor were all quinolones created equal with respect to the treatment of serious *Salmonella* infections. As the spectrum of quinolone coverage has increased to include more respiratory pathogens, their coverage for Gram-negative pathogens has not been enhanced, and in some cases it has decreased. Quinolones are not used to treat meningitis, especially in newborns. For treatment of *Salmonella* infections of the central nervous system, third-generation cephalosporins are best used.

In treating typhoid fever (*S. typhi*), there are important goals to keep in mind. One attempts to abort the complications occurring after the initial period of fever and prevent relapse rates that can reach 10%. The standard of therapy in Latin America has been two weeks of chloramphenicol therapy, which produces nearly 100% response rates, as do the alternatives, ampicillin and trimethoprim/sulfamethoxazole. However, these agents do not reduce either relapse rates or transient carrier state, and only produce 20% cure rates when used to treat resistant strains of *S. typhi*. When standard oral quinolone therapy with an agent such as ciprofloxacin is used, Gotuzzo recommends a full 10 days of therapy; this is required to prevent relapses occurring after treatment of *S. typhi* infections.

Those practicing in developed countries face an unusual situation in which more than 60% of typhoid fever represents imported cases—often resistant to antimicrobial agents other than the quinolones. Cases that do originate in developed countries and are not imported are more likely to be missed since they are not clinically suspected at first. Mortality is greater in this group, as it is for the elderly with typhoid fever.

When oral quinolones were used twice daily for 10 days, cure rates approached 100% in adults studied in Peru, and there were essentially no relapses as compared to a rate of 5-10% for chloramphenicol. Quinolones rapidly clear *S. typhi* from stool, reduce both fecal excretion and community exposure, possibly also decreasing the incidence of subsequent gall bladder cancers associated with chronic carriage. If quinolones are only used for 5-7 days, relapse rates approach 10% and Gotuzzo was firm in his recommendations for a full 10 days of therapy. Alternative agents include third-generation cephalosporins, but the monobactam, aztreonam, has been disappointing in the treatment of adults with typhoid fever, representing a third-line drug with only 70% cure rates.

Malaria and Stand-by Therapy

Swiss and German investigators have considerable published experience offering stand-by malaria therapy to travelers. Stand-by therapy is used in place of prophylaxis for treatment of fevers that might represent malaria in travelers who have resided in an endemic area for more than one week, but without ready access to medical care within. Patients are instructed to follow-up stand-by therapy with an appropriate medical evaluation. Blaise Genton summarized several issues regarding stand-by therapy for malaria and when to use such a strategy, rather than a prophylaxis regimen. Situations include travel to areas of low or moderate malaria endemicity, short-term travel, brief and repeated malaria exposure, or travel to areas where multiresistant malaria is present and stand-by therapy must be provided.

However, there are problems associated with the use of stand-by therapy for malaria that might not have been fully anticipated. Studies have shown approximately 8-10% of travelers in Swiss and German studies experienced episodes of fever. The prediction had been that stand-by therapy would be overused by such travelers, but the reverse actually occurred. Stand-by therapy appears to be underused since patients do not follow these recommendations, often waiting for symptoms to resolve on their own, and not seeking appropriate medical advice awaiting fever resolution. Often, travelers do not think their fever represents malaria, since it has not been made clear that fevers while residing in endemic regions are likely, rather than unlikely, to be caused by malaria. The inability to rapidly self-diagnose malaria with convenient diagnostic kits hinders many who might benefit. These kits are not easy to use and, even with diagnostic certainty, travelers may fear adverse drug effects while lacking better tolerated agents to choose from.

Two new agents that offer considerable promise for the future of stand-by therapy include Malarone (ato-

vaquone/proguanil) and Riamet (artemether/benflumitol). Riamet will be discussed in our next issue by our Associate Editor, Maria Mileno, MD, and *TMA Update* for Jan/Feb 1997 (Vol. 7, no. 1) contains a summary of a recent Malarone symposium. Riamet provides rapid parasite clearance but, like halofantrine, it may also prolong the QTc interval. Two important advantages for Malarone stand-by therapy include its effects upon the liver stage (hypnozoite) of malaria parasites, making it a potential tissue schizonticide, or causal prophylactic agent—one that can be discontinued a week after leaving a malaria-endemic region. Its relative safety and lack of contraindications to use, other than resistance, make it an attractive possibility for stand-by therapy.

Sexually Transmitted Diseases

George Schmid from the CDC gave participants an extensive view of the status of antimicrobial resistance among organisms responsible for sexually transmitted diseases. The ideal goal is cure of infection with prevention of sequelae. This is readily achievable for bacterial and parasitic agents, but not for viral pathogens. He notes that for most viral agents in this group our goals are to alleviate and possibly cure symptoms while preventing sequelae of infection. As for antiviral resistance, there is currently no worldwide laboratory system for monitoring antiviral resistance.

Fortunately, antibiotic resistance is not yet a problem with regard to *Treponema pallidum*. For *Neisseria gonorrhoeae*, extended spectrum cephalosporins are effective worldwide. However, low-dose azithromycin is becoming an issue. The appropriate dosing for that agent is two grams, not one gram, for the treatment of gonorrhea, or treatment failures may occur. Resistance to agents other than the beta-lactams is appearing in the form of widespread quinolone resistance in Asia. The best studied agents are ciprofloxacin and ofloxacin. Resistance to quinolones is inducible, meaning that exposure to increasing levels of these agents in the laboratory will induce resistance by one of three mechanisms: decreased drug penetration due to porin channel alterations, active transport out of cells, and alterations in the target DNA gyrase. Quinolone resistance has become common in Asia since 1993. Resistance rates are so high that gonorrhea acquired in Asia cannot be assumed to be sensitive to the quinolones. In any case, when ciprofloxacin is used for the treatment of gonorrhea, the dose should be 500 mg, not 250 mg—similar to the situation for azithromycin.

Many in the audience learned from this presentation about the current situation with the genitourinary pathogen, *C. trachomatis*, an organism that is generally treated with tetracycline but for which cases of tetracycline resistance are being reported. There have been at least two clinical reports of resistance to the tetracyclines and, when treated, a small residuum (< 1%) of tetracycline-resistant *C. trachomatis* isolates are found. They only represent a fraction of the total population of organisms (so-called "heterotypic resistance"). Schmid addressed the issues of both clinical significance and whether this phenomenon is increasing over time. He shared unpublished data from currently available information in the treatment of adolescents showing that cure rates are lower when associated with isolation-resistant organisms, but could identify no real temporal trends toward increasing resistance or failure to cure. Hence, tetracycline resistance is a real phenomenon with clinical significance although the temporal trends do not yet indicate this is increasing.

Antituberculosis Drugs

Jane Carter brought her extensive experience in the area of tuberculosis control to conference participants with a thorough review of resistance of *M. tuberculosis* to currently available agents beginning with a discussion of known levels of spontaneously appearing resistance in virtually any population of *M. tuberculosis*. Unlike other bacteria, there is no evidence for horizontal gene transfer of antimicrobial resistance for *M. tuberculosis*. Hence, multidrug resistant tuberculosis (MDR-TB) is a manmade amplification of a natural phenomenon (i.e., spontaneous resistance with a defined frequency in a population of mycobacteria). It has been known since 1949 that we can select such organisms out with monotherapy.

No single gene is responsible for MDR-TB. If the spontaneous rate of resistance to any single agent is one in 10^8 mycobacteria (rifampin) and an average patient with cavitary tuberculosis harbors 10^{12} organisms, the potential for the emergence of resistance exists in such cases depending upon how they are treated with antituberculous agents, particularly if monotherapy is used. Why, then, is resistance becoming such a problem throughout the world? There are many contributing factors and to the extent that they can be eliminated, the problem can be lessened.

With regard to decisions made on the part of patients, the cost of available agents and their side effects hinder compliance, particularly when patient education is not included in a tuberculosis treatment program. Human nature being what it is, when patients feel better they often discontinue the very drugs that are producing the cure because of cost, inconvenience, or side effects. Physicians contribute to the problem by not understanding either the nature of spontaneous resistance or the prevalence of resistant tuberculosis in various populations—then adding a single drug to an already failing regimen. This is an all too common scenario that only ensures additional resistance will occur. In fact, monotherapy also effectively occurs when such a diagnosis is missed, or when monitoring is inadequate to detect a failing regimen.

The system for treatment of tuberculosis has several inherent problems. Drug supplies are not well controlled in some countries and can either be erratic or used indiscriminately. All antituberculous agents are not manufactured equally, and lack of quality control in drug production can place patients on a regimen that approaches monotherapy and predisposes to the emergence of an already present resistant subpopulation—a population that should have been eliminated by using a true multiple-drug regimen. Unforeseen events include variable drug absorption, drug-drug interactions, and the influence of underlying disease such as AIDS, diabetes, and malnutrition, which also influence host response to therapy and can predispose to the emergence of resistance. Carter noted that the current cure rates for multidrug-resistant tuberculosis are around 60%, which are only 10% above rates for the preantibiotic era. Fifty years of what has effectively been episodic monotherapy mean we cannot simply use two drugs but must initiate therapy with four drug regimens. Often, the course that must be continued is over two years for MDR-TB therapy to be curative and may have to include surgical resection. ❖

Reference

1. Symposium S5—Drug resistance. Gotuzzo E, et al. 6th Conference of the International Society of Travel Medicine. Montreal, Québec, Canada, June 6-10, 1999.

Infants at Altitude

ABSTRACT & COMMENTARY

Synopsis: *When presented with concentrations of oxygen similar to what would be found at high altitude, a small proportion of infants develop prolonged hypoxemia. The relationships between sudden infantile death and pulmonary hypertension due to altitude, however, have not been fully elucidated.*

Source: Parkins KJ, et al. Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: Interventional study. *BMJ* 1998;316:887-894.

Stimulated by two reports of sudden infant death following intercontinental flights, Parkins and colleagues became interested in the effects of airway hypoxia on respiratory control. Thirty-four seemingly healthy infants (mean age, 3 months), some of whom (13 of 34) were siblings of a sudden infant death victim were exposed to 15% oxygen. Respiratory patterns and oxygenation were noted during overnight recordings with the child in room air and in a reduced oxygen environment. Oxygen saturation was variable (85-100%) but had a lower mean (93%) in 15% oxygen (vs 98% in room air). Initial room air oxygen saturation, however, did not predict the extent of the subsequent fall in oxygen saturation. The amount of time spent with a regular breathing pattern was reduced with exposure to 15% oxygen, and episodes of "periodic apnea" were increased. (None of these pauses was greater than 20 seconds in duration, so they did not constitute true "apnea.") No baseline variables were identified that could predict which infants would develop prolonged oxygen desaturation. Parkins et al conclude that "airline travel and holidays at high altitude may result in hypoxemia in a small proportion of infants."

COMMENT BY PHILIP R. FISCHER, MD, DTM&H

It has been 14 months since Southall's group published their paper, but it continues to stimulate discussion. Initially, it was accompanied by one editorial suggesting infants were safe in commercial aircraft[1] and another questioning the wisdom of taking infants higher than 2000 meters.[2] The *BMJ* pursued the issues in published correspondence, and both travel medicine practitioners and wilderness medicine participants have continued to discuss children at altitude through newsletters and electronic groups. Meanwhile, the lay literature includes reasonable but scientifically unsupported recommendations to avoid air travel under certain ages. What do the data actually say about infants at altitude?

Adaptation to Altitude

The paper by Parkins et al clearly showed that some, but not all, children drop their oxygen saturation during short-term exposure to hypoxic environments. Similarly, children living at high altitude have lower oxygen saturations than children dwelling at low altitude. At 4018 meters elevation, preschool-aged children had mean oxygen saturations of 87%; the fact that saturations were not as low in older children suggested that some adaptation was taking place.[3] Acutely, it is not clear that the adaptive responses, such as the changed breathing pattern noted by Southall's group, have clinical significance. Over time, however, children permanently exposed to high-altitude hypoxia show enhanced oxygen uptake associated with increases in ventilation, lung compliance, and pulmonary diffusion. Chest volumes and hemoglobin concentrations are also increased. In addition, the decreased partial pressure of oxygen in the lungs is associated with elevated pulmonary artery pressures.[4] Thus, children living at altitude adapt during infancy to compensate for the hypoxia to which they are exposed. The risks of pulmonary hypertension, however, might negate some of the beneficial adaptations.

Pulmonary Hypertension at Altitude

There is evidence that chronic, altitude-associated

pulmonary hypertension can be devastating for children. An autopsy study of 15 infants in Lhasa, Tibet (3600 meters above sea level), showed extreme medial hypertrophy of muscular pulmonary arteries and muscularization of pulmonary arterioles along with massive hypertrophy and dilation of the right ventricle.[5] Interestingly, 14 of the 15 were of Han rather than indigenous Tibetan origin, and 13 of the 15 had been born at low altitude and then moved to Lhasa (mean duration of residence at altitude was two months among those who had immigrated). The pathologic findings suggested that the etiology was pulmonary vascular disease rather than parenchymal disease or primary cardiac disease. Affected individuals were not polycythemic (as are adults with "chronic mountain sickness"). Sui and colleagues claimed that such death is "not uncommon" in Tibet, but they didn't actually present any population or historic data to support frequency or causality conclusions.

In the 1960s, 32 "healthy" children aged 1-14 years were subjected to right heart catheterization in Peru (approximately 4500 meters elevation).[6] Pulmonary hypertension was common but became less significant with advancing age. In Colorado, 11 children became severely symptomatic with two deaths due to pulmonary hypertension.[7] With treatment and relocation to lower altitude, the nine survivors were reported to be "enjoying a normal life."

What can we conclude from all this? Clearly, significant pulmonary hypertension has been reported in children born in and/or living at high altitude. It is reasonable to think that the low oxygen content at these altitudes was a significant etiologic factor. What is not clear is whether this maladaptation to high altitude is common, predictable, or a risk for travelers.

Might genetics play a role in predisposing some infants to pulmonary hypertension at altitude? It has been noted that Tibetans had higher arterial oxygen saturation at birth and during the first four months of life than Han newborns in the same setting.[8] It was suggested that genetic factors might be protective for the Tibetan children. Indeed, genetic analysis has recently suggested that an allele dominant for higher oxygen saturation might be present in some Tibetans and might be providing them with a selective advantage in their high-altitude hypoxic environment.[9] Interestingly, genetic factors even seem to affect the presentation of high-altitude pulmonary edema.[10]

Sudden Infant Death

The impetus for the study by Parkins et al was two anecdotal reports of "crib death" shortly after intercontinental travel (with a night-length duration of exposure to air pressure and oxygen content similar to that of approximately 2000 meters).[11] Might altitude be related to sudden infant death (SID)?

In the United States, the incidence of SIDS was noted to correlate directly with altitude of residence.[12] Two other factors, however, must be considered before becoming alarmed by this report. First, studies of SIDS are plagued by diagnostic variability in different reports and studies. Not all sudden infant deaths are truly idiopathic and due to SIDS. This is clearly noted by Southall's group. One of their subjects studied as a sibling of two SIDS victims later died; it was eventually learned that all three children in that family were actually victims of infanticide. Second, the association of altitude with SIDS should be re-evaluated again now that sleep position and passive smoke exposure have been clearly linked to SIDS and interventions focused on these factors are drastically reducing the incidence of SIDS in the United States. If altitude is an important factor in the etiology of SIDS, it is likely not the most important factor. Caution is needed before restricting all infants from exposure to commercial aircraft or to high altitudes.

Acute Mountain Sickness

What of acute mountain sickness in children? In 1993, it was reported that 28% of children aged 9-14 years developed signs of acute mountain sickness when vacationing at 2835 meters elevation.[13] Interestingly, however, 21% of similar children vacationing at sea level developed similar symptoms, and it wasn't clear how much of the "mountain sickness" was due to elevation as opposed to other factors such as travel, anxiety, and disruption of daily routine. More recently, younger, preverbal children were studied.[14] Twenty-two percent of children aged 3-36 months were symptomatic for acute mountain sickness, a frequency similar to that reported in adults. There is also some evidence that the inflammation of a viral upper respiratory tract infection might predispose some children to high-altitude pulmonary edema.[15] Studies on the efficacy of acetazolamide in preventing mountain sickness in children have not been reported.

A Personal Plea

In the wake of World War II, it was considered "unethical" to do research in children. Now, the dearth of data on which to base good pediatric care has prompted a swing in what is considered "ethical." The National Institutes of Health are now encouraging that most research projects include children. Clearly, the effects of high-altitude exposure are different in children than in adults. More investigation is needed to help advise parents and to care for children who might be born in or travel to high-altitude areas.

The first commentary I wrote for *Travel Medicine Advisor Update* was in 1995 and dealt with earache in children traveling by air. I noted that there were no data on which to base a decision about the prophylactic use of pseudoephedrine in traveling children and suggested that

research was needed. That commentary prompted a project that was published in May in *Archives of Pediatrics and Adolescent Medicine*. Perhaps this commentary will prompt someone else to further investigate the acute, subacute, and chronic problems of altitude exposure in children. Such work is sorely needed.

In the Meantime...

While awaiting more definitive data, we can summarize the current understanding about children at altitude. First, children do undergo physiologic adaptations trying to respond to low-oxygen, high-altitude environments. Second, pulmonary hypertension is not an unusual part of a child's adaptation at altitude and can present as life-threatening right heart failure. Sudden infant death has not been causally linked to airplane travel or high-altitude travel. Third, occasionally children develop so much pulmonary hypertension at altitude that their survival is placed in jeopardy. Fourth, there are some genetic factors linked to a child's adaptation to altitude, but it is not currently possible to predict which children risk adverse health effects at altitude. Fifth, acute mountain sickness occurs in children as in adults, but preventive therapy has not been tested.

So, should infants be prohibited from traveling in commercial aircraft or from visiting high-altitude locations? There are no clear data to support such a prohibition. Nonetheless, infants traveling at high altitude, like all other children, should be taken promptly to competent medical care if they act sick and have tachypnea. ❖

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CME Questions

10. Infants spending time at high altitude:

a. risk sudden myocardial infarction and death.
b. might have low oxygen saturations while sleeping.
c. usually develop severe pulmonary hypertension.
d. only rarely show signs of acute mountain sickness.

11. Which of the following holds the best promise as a potential antimalarial chemoprophylactic agent?

a. Artemesinin derivatives
b. Tafenoquine
c. Halofantrine
d. Ciprofloxacin
e. Azithromycin

12. The fluoroquinolones are increasingly indicated in the treatment of salmonellosis and sexually transmitted diseases for all of the following reasons or situations *except*:

a. Orally administered quinolones can achieve high fecal concentrations and rapidly eliminate fecal carriage.
b. The quinolones are the drugs of choice for the empiric treatment of gonorrhea acquired in Asia.
c. Quinolones are likely to prevent relapses of *Salmonella* infections when used for at least 10 days.
d. Quinolones are not indicated for the treatment of meningitis in children.
e. In Latin America, quinolones are useful in the treatment of drug-resistant salmonellosis.