VACCINATION USAGE AMONG AN OLD-ORDER AMISH COMMUNITY IN ILLINOIS

Jonathan S. Yoder, MSW, MPH,†*
and Mark S. Dworkin, MD, MPHTM†

Abstract: The Old-Order Amish have low rates of vaccination and are at increased risk for vaccine-preventable diseases. A written survey was mailed to all Amish households in the largest Amish community in Illinois inquiring about their vaccination status and that of their children.

In this survey, the Amish do not universally reject vaccines, adequate vaccination coverage in Amish communities can be achieved, and Amish objections to vaccines might not be for religious reasons.

Key Words: Amish, vaccine, vaccine-preventable diseases

Accepted for publication September 13, 2006.

From the *Centers for Disease Control and Prevention, Atlanta, GA; and the †University of Illinois at Chicago School of Public Health, Chicago, IL.
Address for correspondence: Jonathan Yoder, MSW, MPH, Centers for Disease Control and Prevention, 4770 Buford Highway NE, Mailstop F22, Atlanta, GA 30341 or Mark Dworkin, MD, MPHTM, University of Illinois at Chicago School of Public Health, 1603 West Taylor Street, MC 923, Chicago, IL 60612. E-mail jey9@cdc.gov or mdworkin@uic.edu.

DOI: 10.1097/01.inf.0000246851.19000.3e

Descendants of the Swiss Anabaptists, the Old-Order Amish (hereafter referred to as Amish) are the most distinctive of all Amish sects, relying on traditional beliefs and practices and rejecting as worldly the majority of modern conveniences. Because of a birth rate of approximately 7 children per family and a 90% retention rate for its youth, the Amish population in the United States has increased from 8200 in the early 1900s to approximately 180,000 now.[1]

In Illinois, the largest Amish community is centered around the town of Arthur in the east-central region of the state. Eight additional smaller communities are located throughout central and southern Illinois. Amish genealogic records from the year 2003 list 4538 persons living in these 9 communities; 3431 (76%) of these persons resided in the Arthur community, which consists of 775 households, including 374 households with children aged <15 years.[2]

Amish views on health and health care might contribute to their lack of adoption of vaccination as a means of disease prevention. Health is considered a gift from God and is not solely the result of preventive behaviors or medical intervention.[1] Vaccination is not prohibited by the church; however, it is often not encouraged either. Additionally, Amish consciously avoid dependence on government assistance and might consider acceptance of free vaccinations a form of government welfare.

Multiple studies in the context of outbreaks of vaccine-preventable diseases have made a direct link between the low rate of reported vaccine coverage in Amish communities and their susceptibility to disease outbreaks. Outbreaks of rubella,[3] measles,[4] pertussis,[5] *Haemophilus influenzae*,[6] and polio,[7] as well as increased cases of childhood tetanus,[8] have disproportionately affected Amish communities in the United States. In each of these outbreaks, the vaccination rates were too low to confer herd immunity to the Amish communities, which provided the opportunity for vaccine-preventable diseases to spread largely unchecked among community members and placed vulnerable members of the surrounding community at risk for contracting these diseases. Unvaccinated Amish communities can serve as environments where vaccine-preventable diseases persist, putting unvaccinated persons at risk for illness and slowing progress towards national goals of elimination of vaccine-preventable diseases.

No data exist on vaccination beliefs and practices among the Amish in Illinois. We initiated this study to quantify the proportion of Amish households that reject vaccination and determine how often this rejection is due to religious beliefs.

MATERIALS AND METHODS

In September 2005, questionnaires were mailed to all Amish households in the Arthur community through a community newsletter. To ensure that the questionnaire was culturally sensitive and understandable, Amish community leaders were consulted on appropriate study content and methodology before distribution. The questionnaire asked about the respondent's vaccination status and that of all children aged <15 years residing in the household, where they had received vaccinations, and if applicable, reasons for not receiving vaccinations. Factors that might influence vaccination use (eg, the age of parents and frequency of nonemergency medical care) were also included in the questionnaire. Households without children only answered demographic and personal vaccination history questions. The questionnaires were returned to the Illinois Department of Public Health in prepaid envelopes, with no identifying information provided by the respondents. Univariate analysis was performed by using EpiInfo, version 3.3.2, statistical software (Centers for Disease Control and Prevention, Atlanta, GA) in which odds ratios (ORs) were calculated and hypotheses tested by using the χ^2 test. ORs with 95% confidence intervals (CIs) that excluded 1.0, and P values <.05 were considered statistically significant.

RESULTS

Responses were received by 225 (60%) of the 374 Amish households in the community with children aged <15 years. An additional 120 responses were received by households without children. A total of 189 (84%) households with children reported that all of their children had received vaccinations; 28 (12%) reported that some of their children had received vaccinations; and 8 (4%) reported that none of their children had received vaccinations. Among the 36 respondents who had unvaccinated children, 16 (44%) cited concerns about vaccine safety as the reason their children were unvaccinated; 3 (8%) attributed their children's unvaccinated status to religious objections (Table 1). Not having received vaccinations as a child (OR, 4.2; 95% CI, 1.1–16.3) and seeking nonemergency medical care ≤2 times during the preceding year (OR, 2.6; 95% CI, 1.1–6.0) were statistically associated with having unvaccinated children. Decisions about children's medical care were made by fathers in 6 households (3%), were made by mothers in 29 households (13%), and were made jointly in 188 households (84%). Approximately three quarters (74%) of respondents had gone to the doctor's office to receive vaccinations.

Among all respondents who knew their own vaccination status, 281/313 (90%) reported that they had received vaccinations as children. Stratified analysis revealed that younger respondents were statistically significantly more likely to have been vaccinated as children; 194/202 (96%) respondents aged <45 years had received vaccinations, whereas 87/111 (78%) respondents aged ≥45 years had been vaccinated (OR, 6.7; 95% CI, 2.7–16.9; $P < 0.0001$). The majority of respondents (93%) were uninsured, and the majority of those without insurance (71%) relied on a mutual aid network to assist with medical expenses.

DISCUSSION

This study reveals that Amish households do not universally reject vaccines, and Amish objections to vaccines are not typically for religious reasons. Additionally, the decision to accept vaccinations is based on multiple factors and might be influenced by

TABLE 1. Reasons Given for Lack of Vaccination Among 36 Amish Households with at Least One Unvaccinated Child: Arthur, Illinois*

Reason Given	No. Respondents (%)
Vaccines are not safe for my children	16 (44)
Vaccines are against my personal beliefs	7 (19)
Vaccination is not an effective way to prevent diseases in my children	5 (14)
Vaccination is not as important as other daily activities	4 (11)
Our children are not at risk for becoming ill from any of the diseases prevented by vaccines	4 (11)
I have religious reasons for not getting a vaccine	3 (8)
The clinic hours are inconvenient	2 (6)
I do not want to receive any government handouts	1 (3)
Vaccines are too expensive	1 (3)
Getting a vaccine requires inconvenient travel	1 (3)

*Unknown or undecided responses were excluded from analysis, and respondents may have listed more than 1 reason.

information on vaccine safety provided by trusted medical providers. These data demonstrate that previous reports of Amish vaccination status derived from previous studies should not be generalized to all Amish communities.

The study finding that 90% of respondents had received vaccinations and 84% of families had vaccinated all of their children was surprising, on the basis of our past understanding of Amish vaccination rates. No comprehensive study has examined vaccination coverage among Amish in the United States. Common methods of assessing vaccination status (eg, telephone surveys[9] or college entry surveys) lack the ability to include the Amish as part of the study population because the Amish do not have telephones or attend college. Small community-based surveys of Amish in Pennsylvania[1,6] and Wisconsin[10] demonstrated that the vaccination rates of children in these Amish communities were too low to prevent vaccine-preventable diseases, if introduced, from spreading within the community. This study demonstrates that previous reports of Amish vaccination status should not be generalized to all Amish communities.

The higher rate of vaccination among young adults in our study demonstrates that adoption of vaccination in this community has increased over time. Although the reasons for this increase are not entirely clear, this finding demonstrates that Amish beliefs and practices regarding vaccination are not static and can be influenced by factors in the community.

The objections to vaccinations expressed in this survey indicate that Amish concerns about vaccines are similar to those expressed by other parents of unvaccinated children. Amish parents of unvaccinated children cited objections to vaccines based on concern for their children's well-being rather than objections based on theological, ideological, or philosophic reasons, supporting previous findings that religious objection is not the primary reason for rejecting vaccinations.[1,6] Safety concerns were the most frequently listed reason for not vaccinating, replicating findings from nationwide surveys[9] of non-Amish parents of unvaccinated children. These important concerns, when understood, can be addressed by medical providers.

The Amish rely on trusted health-care providers for information about preventive practices.[1] The study finding that the overwhelming majority of households visit their physicians for vaccinations underscores the importance of the doctor-patient relationship in influencing their decision to vaccinate their children. Additionally, because the majority of Amish families do not have insurance coverage for vaccinations, the fact that the majority qualify for the Vaccines for Children Program makes obtaining vaccinations at their doctor's office economically feasible. These visits provide an important opportunity for the health-care provider to ask about the vaccination status of all eligible children.

Although Amish society is often considered patriarchal, this study revealed that, in the majority of households, the mother is considered to have a joint role in making decisions about their children's medical care. This fact is important to consider when developing educational messages for Amish communities.

Study limitations include a moderate response rate, the lack of ability to correlate survey response with vaccine registry data, and the lack of detailed vaccination information for each child.

The vaccination rate reported in this study has critical implications for efforts to promote vaccinations among Amish communities. The results of this study indicate that Amish communities might be influenced to accept vaccines if medical providers openly address the topic of vaccination with Amish patients and deal with individual concerns about vaccination. We recommend that federal, state, or local health agencies create culturally sensitive educational materials that specifically address vaccine safety and make these materials available to Amish patients through their health-care providers. These findings provide hope that improved vaccination coverage among Amish communities can be achieved through building relationships and targeted public health efforts.

ACKNOWLEDGMENTS

We appreciate the contributions of Chuck Jennings and Alicia Fry in the conception of this project; of Susan Hays, Angie Hogan, Kae Hunt, and Debbie Rowe in the development of the survey instrument; of Michele McGee for data entry; and of Carol Stutzman and Dorothy Kunz for providing community contacts.

Neither of the authors has a commercial or other association with products or processes that might pose a conflict of interest. No grants or other outside funding sources were used in the collection of these data. The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

REFERENCES

1. Hostetler JA. *Amish Society*. 4th ed. Baltimore: Johns Hopkins University Press; 1993.
2. Schlabach L, Schlabach D. *Illinois Directory: Directory of the Illinois Amish*. 3rd ed. Tuscola, IL: 2003.
3. Briss PA, Fehrs LJ, Hutcheson RH, Schaffner W. Rubella among the Amish: resurgent disease in a highly susceptible community. *Pediatr Infect Dis J*. 1992;11:955–959.
4. Sutter RW, Markowitz LE, Bennetch JM, Morris W, Zell ER, Preblud SR. Measles among the Amish: a comparative study of measles severity in primary and secondary cases in households. *J Infect Dis*. 1991;163:12–16.
5. Etkind P, Lett SM, Macdonald PD, Silva E, Peppe J. Pertussis outbreaks in groups claiming religious exemptions to vaccinations. *Am J Dis Child*. 1992;146:173–176.
6. Fry AM, Lurie P, Gidley M, et al. *Haemophilus influenzae* type B disease among Amish children in Pennsylvania: reasons for persistent disease. *Pediatrics*. 2001;108:60–65.
7. Centers for Disease Control and Prevention. Poliovirus infections in four unvaccinated children: Minnesota, August-October 2005. *JAMA*. 2005; 294:2689–2691.
8. Fair E, Murphy TV, Golaz A, Wharton M. Philosophic objection to vaccination as a risk for tetanus among children younger than 15 years. *Pediatrics*. 2002;109:e2.Available at: http://pediatrics.aappublications.org/cgi/content/full/109/1/e2.
9. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? *Pediatrics*. 2004;114:187–195.
10. Dickinson N, Slesinger DP, Raftery PR. A comparison of the perceived health needs of Amish and non-Amish families in Cashton, Wisconsin. *Wis Med J*. 1996;95:151–156.

COMPARISON OF TRIP CHARACTERISTICS OF CHILDREN AND ADULTS WITH TRAVEL-ACQUIRED HEPATITIS A INFECTION

Cathy Gosselin, MSc, Gaston De Serres, MD,*†*
Isabelle Rouleau, MSc, Bernard Duval, MD,*†*
Ramak Shadmani, MD, Monika Naus, MD,‡*
and Brian J. Ward, MD§

Abstract: We compared the trip characteristics of 84 child and 99 adult cases with travel-acquired hepatitis A (HA). Most pediatric cases had traveled in Asia for more than 30 days and had stayed and eaten most of their meals in the homes of friends and relatives in a country where they had not been born. In contrast, the adults with travel-acquired HA had visited Latin America or the Caribbean for 14 days or less and had stayed primarily in hotels. Specific public health interventions should be undertaken to prevent HA in traveling children.

Key Words: hepatitis A, endemic diseases, travel, health behavior, prevention and control

Accepted for publication September 13, 2006.

From the *Public Health Research Unit, CHUL Research Centre, Laval University, Québec, Canada; †Institut National de Santé Publique du Québec, Québec, Canada; ‡British Columbia Center for Disease Control, Vancouver, British Columbia, Canada; and the §Research Institute of the McGill University Health Center, Center for Tropical Diseases, Faculty of Medicine, McGill University, Montreal, Canada

Address for correspondence: Dr. Gaston De Serres, Institut National de Santé Publique du Québec, 2400 d'Estimauville, Quebec, Quebec, Canada, G1E 7G9. E-mail gaston.deserres@ssss.gouv.qc.ca.

DOI: 10.1097/01.inf.0000246852.21859.92

While adults constitute the majority of travelers to tropical and subtropical countries, the number of children who travel abroad is constantly growing. Young children rarely travel on their own and typically have little to no role in trip planning. The travel conditions of children and of those who travel with children are likely to be quite different from those of adults traveling without children. These differences in travel style may present different risk factors of acquiring disease while abroad. In a study of travel-related hepatitis A (HA) in both children and adults, we compared the characteristics of the trips during which they acquired their disease, to identify particular risk factors for children.

METHODS

As part of study evaluating the risk of HA in travelers,[1] all laboratory-confirmed, travel-related HA cases reported in Quebec and Ontario, Canada, with onset between January 1997 and November 1999, were eligible. Cases were identified from the provincial notifiable disease databases. Telephone interviews were performed between November 1999 and May 2000 to obtain information regarding the trip during which cases acquired their disease.[1]

Trips were categorized into 4 levels of risk as follows: "low risk" included travel for 2 weeks or less, with all nights spent in first-class hotels, "visiting friends and relatives" (VFR) included trips during which more than half of the nights were spent in the homes of friends or relatives, "high-risk" travel was defined as that lasting ≥4 weeks, with ≥50% of the nights spent in low-budget hotels. All other trips were included in the "intermediate-risk" group. Age was divided in 10-year categories, and cases less than 20 years old were considered children.

RESULTS

A total of 315 travel-associated HA cases were reported in Quebec (n = 135) and Ontario (n = 180) during the study period. Interviews were completed for 69% (84/121) of the children and 51% (99/194) of the adult cases. Among the 183 study participants, there were 46% children and 54% adults. Participation rate was 64% in Quebec (67% in children and 62% in adults) and 54% in Ontario (71% in children and 41% in adults). Only a few eligible cases (n = 13) refused to participate in the study. Most of nonrespondents were people who could not be contacted despite 6 to 10 attempts at different times. The proportion of male cases was similar in children and adults: 51% and 49%, respectively. There was a significant increase in household income with the age of cases ($P < 0.001$).

Twenty-two percent of cases were younger than 10 years old, 24% aged 10–19, 20% aged 20–29, 16% aged 30–39, 12% aged 40–49, 3% aged 50–59 and 3% were aged ≥60 (Table 1). Most cases aged <20 years had traveled in Asia (57%), mainly to Pakistan (30%) or India (17%), whereas 68% of adult cases had traveled to Latin America or the Caribbean, mainly Mexico (32%) or the Dominican Republic (10%). Overall, children traveled for longer periods than did adults ($P < 0.0001$) and there was a significant trend of decreasing duration of travel with older age ($P < 0.0001$). The median duration of trips among children was 42 days compared with 14 days in adults. While 60% of children traveled for more than 30 days, only 28% of adults did.

The proportions of cases in each travel risk level varied significantly with age ($P < 0.0001$). Overall, only 6% of cases had taken a trip classified as "high risk," and more than half (55%) had visited friends and relatives. The proportion VFR decreased significantly with age. Only 29% of adults visited friends and relatives while staying abroad, whereas 85% of children did. Children were also more likely to eat ≥50% of their meals in the homes of friends and relatives than adults (85% versus 33%, respectively; $P < 0.0001$). Among children VFR, 63% had traveled to countries in which they had not been born. The self-assessed attitude toward hygiene during trips did not significantly vary with age. Using gastroenteritis as a proxy for unsafe behaviors for enteric diseases, children and adults were affected equally (37% versus 37%). Overall, only 4% of the HA cases reported having visited a travel clinic before departure, a proportion that was similar among children and adults.

Nearly a quarter (23%) of reported cases occurred among individuals born in a HA endemic country (Table 1) (Countries where Hepatitis A is Endemic—listed in Online Only Appendix). The majority of cases among those born in a nonendemic country (including Canada) had visited Latin America or the Caribbean (59%), mainly Mexico (25%) or the Dominican Republic (9%). In contrast, the majority of cases among those born in a HA endemic country had visited Asia (65%), mainly Pakistan (26%) or the Philippines (14%). Travelers born in an endemic country who acquired HA stayed abroad for a longer period than those born in nonendemic countries (35 versus 21 days, $P = 0.004$) and traveled more frequently for >30 days (53% versus 39%). Almost all (93%) of the cases born in HA endemic countries visited friends and relatives (79% in their native country and 14% in other countries) compared with 43% of individuals born in a nonendemic country. Similarly, travelers born in an endemic country were more likely to eat more than half their meals in the homes of friends and relatives than other travelers (91% versus 46%, $P < 0.0001$). Individuals born in HA endemic countries were less aware of the health risks related to travel in a HA endemic country than were other travelers (26% versus 43%, $P = 0.04$).

TABLE 1. Travel Characteristics and Demographics of Cases by Age and Country of Birth

	Age, yr						Country of Birth	
	Total, N = 183, No. (%)	0–9, N = 40, No. (%)	10–19, N = 44, No. (%)	20–29, N = 36, No. (%)	30–39, N = 30, No. (%)	40+, N = 33, No. (%)	Nonendemic, N = 140 No. (%)	HA Endemic, N = 43 No. (%)
Visited continent								
Latin America	87 (48)	9 (23)*	11 (25)	19 (53)	23 (77)	25 (76)	83 (59)*	4 (9)
Asia	65 (36)	22 (55)	26 (59)*	11 (31)	3 (10)	3 (9)	37 (26)*	28 (65)
Africa	25 (14)	9 (23)	5 (12)	5 (14)	1 (3)	5 (15)	19 (14)	6 (14)
Eastern Europe	6 (3)	0 (0)	2 (5)	1 (3)	3 (10)	0 (0)	1 (1)	5 (12)
Duration of stay (days)								
<8	32 (17)	1 (3)	2 (5)	5 (14)	12 (40)	12 (36)	29 (21)	3 (7)
8–14	33 (18)	5 (13)	3 (7)	7 (19)	7 (23)	11 (33)	32 (23)	1 (2)
15–30	40 (22)	9 (23)	14 (32)	8 (22)	3 (10)	6 (18)	24 (17)	16 (37)*
>30	78 (43)	25 (63)*	25 (57)	16 (44)	8 (27)	4 (12)*	55 (39)	23 (53)
Median	28 (7, 123)	47 (10, 157)	42 (14, 120)	29 (7, 180)	10 (7, 150)	14 (4, 60)*	21 (7, 136)	35 (7, 120)*
Risk levels								
Low-risk	30 (16)	1 (3)	3 (7)	2 (6)	11 (37)	13 (39)	28 (20)	2 (5)
Intermediate-risk	42 (23)	2 (5)	3 (7)	14 (39)	9 (30)	14 (42)	41 (29)	1 (2)
High-risk	11 (6)	0 (0)	4 (9)	5 (14)	2 (7)	0 (0)	11 (8)	0 (0)
VFR in native country	34 (19)	6 (15)	12 (27)	10 (28)	4 (13)	2 (6)	0 (0)	34 (79)*
VFR in a nonnative country	66 (36)	31 (78)*	22 (50)	5 (14)	4 (13)	4 (12)	60 (43)	6 (14)
≥50% Of meals taken								
In low-budget establishments	16 (9)	0 (0)	3 (7)	7 (19)*	4 (13)	2 (6)	16 (11)*	0 (0)
In friends' and relatives' home	104 (57)*	36 (90)	35 (80)	16 (44)	9 (30)	8 (24)	65 (46)	39 (91)*
Aware of health risks	71 (39)	17 (43)	15 (34)	17 (47)	13 (43)	9 (27)	60 (43)	11 (26)*
Attitude towards hygiene								
1–4 (Less careful)	28 (15)	5 (13)	7 (16)	5 (14)	7 (23)	4 (13)	22 (16)	6 (14)
5–7	50 (27)	13 (33)	10 (23)	14 (39)	6 (20)	7 (22)	40 (29)	10 (24)
8–10 (Very careful)	104 (57)	22 (55)	27 (61)	17 (47)	17 (57)	21 (66)	78 (56)	26 (62)
Had gastroenteritis	68 (39)	13 (33)	18 (46)	15 (43)	12 (40)	10 (31)	57 (42)	11 (28)
Household income ($CDN/yr)†								
<20,000	16 (14)	3 (14)	4 (19)	8 (29)	1 (6)	0 (0)	12 (13)	4 (20)
20,000–39,999	31 (27)	8 (36)	7 (33)	10 (36)	3 (17)	3 (12)	25 (26)	6 (30)
40,000–59,999	21 (18)	4 (18)	5 (24)	4 (14)	2 (11)	6 (23)	17 (18)	4 (20)
60,000+	47 (41)	7 (32)	5 (24)	6 (21)	12 (67)	17 (65)	41 (43)	6 (30)

Medians are presented with (5^{th}, 95^{th} percentiles).
*Value(s) most contributing to the difference.
†Sixty-eight (37%) cases did not answer this question.
VFR indicates visiting friends and relatives.

DISCUSSION

Our results indicate that approximately half of the reported travel-associated HA cases occur among children. Most pediatric cases had traveled in Asia for more than 30 days and had stayed and eaten most of their meals in the homes of friends and relatives in a country where they had not been born. Adult cases, on the other hand, had visited Latin America or the Caribbean for 14 days or less and had stayed primarily in low- or moderate-risk establishments. Although the slightly higher participation rate among children than adults may have overrepresented pediatric cases of HA in our series, the greater frequency of asymptomatic HA infection among children would have the opposite effect.[2] Given that HA cases in children were nearly as numerous as in adults, whereas most international travelers are adults, our results suggest that the incidence of HA infection is higher among traveling children than in adults.

Our results also show that individuals who were born in a HA endemic country accounted for nearly a quarter of the reported cases. In contrast to HA-infected travelers born in a nonendemic areas who most frequently took short trips to Latin America or the Caribbean and stayed in first-class hotel (low risk), HA-infected travelers born in endemic countries had typically visited Asia for 30 days or more, where they had visited friends and relatives. Given the rapid increases in immigration from the developing world in the last 2–3 decades and the general decrease in transportation costs, it is reasonable to anticipate steady growth in the total number of foreign-born Canadians who will take trips with the latter characteristics. The scenario of the immigrant family returning to their country of origin with their young children born in the developed world is very common. In our series, 5 families who visited friends and relatives had 2 of their children infected with HA during the same trip, one family had 4, and other had only 1. The majority (68%) of their children were born in developed countries. Although remarkably few such families present to travel clinics before departure, when they do, the parents are invariably most concerned about preventative vaccines for their children.

Our results show that adults returning to their native country are also at elevated risk for endemic diseases, including HA. In our series, adult cases born in endemic countries immigrated to Canada at a median age of 19 years (range, 2–34). Clearly, having lived in an endemic country for many years does not necessarily prevent immigrant travelers from HA.

Our study has limitations. First, all cases were identified through notifiable diseases databases and were eligible if they reported having visited a HA endemic area in the 6 weeks before onset of symptoms. Failure to detect the disease is very likely to have occurred among asymptomatic or mildly symptomatic cases and cases treated abroad. Second, given the retrospective nature of the study, the data collected may have been subject to a certain

degree of recall bias. Because the self-classification of lodging facilities or restaurants was subjective, there is a possibility of misclassification between the types of establishments and food premises. Last, because the countries of origin of immigrants is different between Canada and other countries, this will change the destination of VFR trips.[3] Nevertheless, these limitations are unlikely to change the main observations that trips taken by children are different from those of adults and trips taken by individuals born in HA endemic countries differ from those taken by other travelers in several important respects, including destination, duration and travel style.

In conclusion, travel-acquired HA infection is not limited to adult travelers, and traveling children are at particular risk. Because traveling children rarely arrange their itineraries or housing and eating arrangements and because they are more likely than adults to visit friends and relatives, they may have great difficulty adhering to medical recommendations regarding food and water precautions, even if they are aware of the risks. These particular vulnerabilities of pediatric travelers need to be taken into consideration during pretravel consultation.[4] Similarly, specific recommendations should be given to adult travelers born in HA countries to reduce their risk. Because very few adults and children visit a travel clinic before departure, population-based intervention may need to be implemented to reach the majority of travelers to reduce the burden of travel-related HA.

ACKNOWLEDGMENTS

We are grateful to Gina Pohani, Nicole Boulianne, Monique Douville Fradette and Kevin Kain for their contribution to the initial study.[1]

This study was funded by an unrestricted grant from Glaxo-SmithKline.

REFERENCES

1. De Serres G, Duval B, Shadmani R, et al. Ineffectiveness of the current strategy to prevent hepatitis A in travelers. *J Travel Med*. 2002;9:10–16.
2. Pavia AT, Nielsen L, Armington L, Thurman DJ, Tierney E, Nichols CR. A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. *Am J Epidemiol*. 1990;131:1085–1093.
3. Angell SY, Cetron MS. Health disparities among travellers visiting friends and relatives abroad. *Ann Intern Med*. 2005;142:67–72.
4. Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. *JAMA*. 2004;291:2856–2864.

EFFICACY AND SAFETY OF CASPOFUNGIN THERAPY IN CHILDREN WITH INVASIVE FUNGAL INFECTIONS

Etienne Merlin, MD, Claire Galambrun, MD,† Patricia Ribaud, MD,‡ Thierry Blanc, MD,§ Gérard Michel, MD,‖ Anne Auvrignon, MD,¶ and Jean-Louis Stéphan, MD#*

Abstract: Twenty children with proven (n = 12) or probable (n = 8) invasive fungal infections received caspofungin treatment either as first-line (n = 7) or as salvage (n = 13) therapy and as monotherapy (n = 5) or in combination (n = 15). Eleven had aspergillosis, 7 had candidiasis, and 2 had *Rhodotorula* infections.

Caspofungin was well tolerated. Nine patients experienced 11 drug-related adverse events, none were severe, and none led to drug discontinuation. Caspofungin as a first-line treatment was successful in 5 of the 7 children (these 5 patients survived the infectious episode, with a follow-up of 147 days), and salvage therapy rescued 8 of 13 children, but only 5 of them survived.

Key Words: children, caspofungin, fungal infection

Accepted for publication September 13, 2006.

From the *CHU Clermont-Ferrand, Service de Pédiatrie B et Unité Bioclinique de Thérapie Cellulaire, Hôtel-Dieu, Clermont-Ferrand, France; †Hôpital Debrousse, Service d'Hématologie Pédiatrique, Lyon, France; ‡Service de Transplantation Médullaire, Hôpital St-Louis, Paris; §Réanimation Néonatale, Hôpital Charles Nicolle, Rouen; ‖Pédiatrie et Hématologie Pédiatrique, Hôpital d'Enfants La Timone, Marseille; ¶Hémato-oncologie Pédiatrique, Hôpital d'Enfants Armand Trousseau, Paris; and the #CHU, Hôpital Nord, Unité d'hémato-Oncologie Pédiatrique, St-Etienne, France

Address for correspondence: Jean-Louis Stéphan, MD, Pédiatrie, Hôpital Nord, CHU Saint Etienne, F-42055 St-Etienne, France. E-mail j.louis.stephan@chu-st-etienne.fr.

DOI: 10.1097/01.inf.0000246844.42159.a0

Invasive fungal infections are an important cause of morbidity and mortality, especially in patients with hematologic malignancy. Despite the availability of new drugs and more aggressive therapeutic strategies, mortality rates in immunocompromised patients remain extremely high.[1]

Caspofungin is the first of a new class of antifungals (echinocandins) that inhibit the synthesis of the 1,3-beta-D-glycan, an essential cellswall polysaccharide.[2]

Caspofungin is fungicidal against *Candida* species, even those resistant to fluconazole including *C. kruzei* and *C. glabrata* and efficacious against a broad spectrum of fungi, including all *Aspergillus* species. Moreover, its original mechanism of action warrants the association of caspofungin in patients who are refractory to the other antifungal therapies. It does not require special precaution in adults, nor dosage adjustment according to renal or liver function. Together with its good safety profile in adults, the product characteristics provide good arguments for salvage therapy in the pediatric population with invasive fungal infections.

Few reports have addressed the use of caspofungin in children with documented invasive fungal infections. In the Franklin et al[3] study, only 13 patients had documented infections; the others were treated empirically; and Odio et al[4] reported salvage treatment in a series of 10 neonates. We report on 20 children with proven or probable invasive fungal infection who received caspofungin, either alone or as an add-on therapy during the Compassionate Use French Program before the product was approved. Their records were reviewed and analyzed for efficacy and safety of the drug.

PATIENTS AND METHODS

Patient's records were reviewed to identify patients diagnosed with a probable or proven invasive fungal infection and who had received at least 7 days of caspofungin treatment as part of the French Compassionate Use program between July 2001 and June 2003. Critically ill patients who received caspofungin during less than 7 days were not evaluable and, therefore, were excluded from the study. Informed consent was obtained from all patients' parents before caspofungin administration.

A retrospective chart review was performed from those 20 patients being managed in 1 intensive care and 6 transplantation units in France. Patients' demographics (age, sex, weight) and history of the underlying disease were collected. Most attention was given to the description of the fungal infection, by its localizations, identification of the fungus, and classification as proven or probable infection, according to the consensus committee definition of the European Organization for Research and Treatment of Cancer/Mycoses Study Group of the National Institute of Allergy and Infectious Diseases.[5] All adverse events emerging during caspofungin treatment were collected. Complete and partial responses were classified as successful outcomes. Survival was assessed at day 7,

15, 30, 60, 90, and 180 of treatment and at the end of the treatment. Mean treatment-free follow-up was 102 days (median, 60; range, 0–450 days).

Patients' Characteristics. Twenty children (12 boys and 8 girls) were evaluated. Their mean age was 10.2 years (median, 12; range, 0.1–16), and their mean weight was 39.6 kg (median, 47; range, 2.5–70). Seventeen had underlying hematologic malignancy, predominantly acute leukemia (n = 16), 1 had a severe aplastic anemia, 1 had Fanconi disease, and 1 neonate had a complex malformation (esophageal atresia with pulmonary sequestration).

Sixteen patients had neutropenia (less than 500/μL) in the 2 months before the diagnosis of fungal infection, with a mean duration of the aplastic phase of 27 days (median, 12; range, 0–180 days). Five patients had undergone allogenic bone marrow transplantation, and 17 had received different courses of conventional chemotherapy. Eleven children had *Aspergillus* infections, proven in 4 cases, and probable for 7. Six of those 11 patients had localized pulmonary infection and the others, disseminated infections. Seven patients had documented candidiasis, 6 proven (6 disseminated infections by *C. albicans* [n = 3], *C. parapsilosis* [n = 1], *C. glabrata* [n = 1], *C. krusei* [n = 1]) and 1 probable (1 pulmonary [*C. albicans*]). Two patients had infection with *Rhodotorula*, 1 proven and 1 probable (1 disseminated and 1 pulmonary, respectively). The 2 patients with probable pulmonary yeast infections had both clinical infectious symptoms (fever and cough), radiologic abnormalities compatible with a fungal infection, and a yeast (*C. albicans* and *Rhodotorula* sp., respectively) on bronchoalveolar lavage fluid samples. Four patients had renal insufficiency resulting from amphotericin B or cyclosporine A therapy; 1 had a major dyslipemia and 1, a chronic liver graft-versus-host disease associated with a cholestasis and 3- to 5-fold increased liver enzymes.

Drug Administration. Before caspofungin initiation, 13 patients had been treated with 1 or 2 antifungals: 9 with amphotericin B, 3 with fluconazole, 1 with voriconazole and 1 with flucytosine. Nine of these 13 patients received caspofungin because they were not responding (one as monotherapy, the other as combination) and 4 of 13 because they were intolerant to liposomal amphotericin B (one in monotherapy, others as combination). Seven patients received caspofungin as first-line therapy (5 as monotherapy, 2 as combined to other antifungal therapy[ies]).

Other concurrent antifungals were administered concomitantly to caspofungin to 14 of the patients: amphotericin B (n = 8) and/or voriconazole (n = 7) and/or fluconazole (n = 2) and/or flucytosine (n = 1).

Caspofungin was administered through a central venous infusion in all patients (1-hour infusion) except temporarily via peripheral access in 3 patients whose central venous catheter had been removed for a few days.

Out of the 12 patients weighing more than 45 kg, 10 received 70 mg on day 1, followed by 50 mg per day, and 2 received 50 mg per day from day 1 on. The other 8 patients received between 1 and 4 mg/kg/d, the daily average being 1.88 mg/kg (median, 1.40; range, 0.95–3.85 mg/kg). The mean duration of caspofungin administration was 54 days (median, 35; range, 7–280 days). The mean cumulative dose was 65 mg/kg (median, 34; range, 13–270 mg/kg).

Patients were also receiving other therapies for their malignancies, and 5 patients were receiving cyclosporine A.

RESULTS

Safety. Forty-five treatment emergent adverse events (TEAEs) were observed in 15 patients and 11 adverse events considered as possibly drug related (DRAEs) were experienced by 9 patients, of WHO grades 1 to 3. None of the TEAEs led to caspofungin discontinuation.

One patient exhibited a livedo considered as possibly drug related, 2 patients complained of nausea and vomiting during the drug infusion. Six patients had elevated liver enzymes, 5 were mild and considered possibly drug related (one of them concomitantly receiving cyclosporine A); the sixth patient suffered from a hepatic graft-versus-host disease, with serum aminotransferases values more than 3 times the normal upper limit. Two patients had moderate hypokalemia; both were concomitantly receiving fluconazole. One patient had a peripheral venous thrombosis at the injection site; he was simultaneously treated with quinupristine/dalfopristine. Renal function of patients with renal insufficiency did not deteriorate.

Efficacy. Overall survival is shown in Table 1 There were 6 deaths observed while patients were receiving caspofungin therapy; none of them was related to drug intolerance but either to the lack of treatment efficacy (uncontrolled invasive fungal infection in 5 patients) or to the underlying condition (1 patient).

For the 11 patients with aspergillosis, 8 patients exhibit a successful response: 3 were treated with monotherapy and 5 with an antifungal combination (caspofungin + voriconazole). The final survival rate was 5 of 11 patients. Four patients died of their invasive fungal infections: 1 refractory patient who died at day 7 of adding on caspofungin to liposomal amphotericin B, 2 despite the concurrent administration of liposomal amphotericin B or voriconazole (both were in relapse of an AML), and 1 who had an initial partial response but died of the invasive fungal infections associated with a Gram-negative sepsis. Two patients died of other causes after caspofungin discontinuation once the invasive fungal infection was cured (one from a bilateral pneumothorax and the other from the leukemia relapse).

All the 7 patients but 1 in the candidiasis cohort received antifungal therapy in combination. The 3 patients who did not respond to treatment (caspofungin + fluconazole in 2 patients, caspofungin + amphotericin B in 1) were all infected by *C. albicans*, and 2 of them actually died of their invasive fungal infection. Two other patients did survive the candidiasis but died later of other events with no fungal infection, one from chronic GVH disease and the other from multiorgan failure after bone marrow transplantation.

TABLE 1. Reponses and Survival After Caspofungin Initiation

	Response		Survival	
	Complete	Partial	Day 90	Overall
Aspergillus	8/11	2/11	7/11	5/11
First-line therapy	4/5	1/5	4/5	3/5
Refractory	4/5	0/5	2/5	2/5
Intolerant	0/1	1/1	1/1	0/1
Candida	4/7	1/7	4/7	3/7
First-line therapy	1/2	—	2/2	2/2
Refractory	2/3	—	1/3	0/3
Intolerant	1/2	1/2	1/2	1/2
Rhodotorula	1/2	1/2	2/2	2/2
Refractory	0/1	1/1	1/1	1/1
Intolerant	1/1		1/1	1/1
Total	13/20	4/20	13/20	10/20
Monotherapy	5/5	—	4/5	3/5
Combination	8/15	4/15	9/15	7/15
First-line therapy	5/7	1/7	6/7	5/7
Refractory	6/9	1/9	4/9	3/9
Intolerant	2/4	2/4	3/4	2/4

Median follow-up was 161 days (range, 7–502 days).

Of the 2 patients with *Rhodotorula* infections, one had a complete response; the other was stable when treated with caspofungin alone and exhibited a complete response after the adjunction of voriconazole. Both survived.

DISCUSSION

This study is the second largest report of the use of caspofungin in children as salvage therapy or first line treatment.[3] The overall 50% survival rate and 65% of complete response rate constitute an encouraging evidence of caspofungin efficacy in this pediatric population with invasive fungal infections. This study's main limitations are its small size (n = 20) and retrospective nature which precludes the assessment of specific safety events.

Overall, the therapy was well tolerated and no major safety issues were seen, similar to reports of others.[6–10] The most frequent DRAEs were fever, nausea and vomiting, hepatic enzyme elevation and hypokalemia, as observed in the current study, phlebitis (as reported in one patient simultaneously treated with another venotoxic product), and renal insufficiency not reported here. Out of the 5 patients receiving cyclosporine A, only 1 experienced elevated aminotransferases. The association is usually avoided because concomitant use has been associated with transient elevated aminotransferases; however, 2 recent retrospective studies seem to indicate that this adverse event does not occur in most cases.[11,12]

In terms of efficacy, we recognize that the sampled population is small and that many patients had received combination therapy with other antifungals. Results were excellent in patients receiving caspofungin as first-line therapy (75% CR and 75% survival) or as monotherapy (100% CR, 75% survival). This latter result could be explained by the fact that patients who received caspofungin as monotherapy had a less aggressive infection. Conversely, when employed as first-line therapy, caspofungin was most frequently associated with 1 or 2 other antifungals. Interestingly, the association of voriconazole + caspofungin in aspergillosis gave an 80% response rate (60% survival), despite the lack of evidence of a potential in vitro synergy, but in accordance with animal data[13] and clinical case reports.[14] Whether this combination might have better chances of success than a combination of caspofungin + liposomal amphotericin B, as observed for the salvage treatment of aspergillosis in patients with hematologic malignancies,[9] remains to be established by prospective randomized studies.

We found no relationship between the response and the localization of the invasive fungal infections (pulmonary or disseminated), its character (proven or probable), the age of the patients, the underlying condition or the administrated dosage. Recently, Walsh et al[15] emphasized that the dosage of 1 mg/kg/d led to a suboptimal product exposure in children. The comparable exposure to that of adult patients treated with 50 mg/d is reached by the administration of 50 mg/m^2/d. Hence, 4 of 7 patients receiving less than 45 kg were at a suboptimal dose. Three had a complete response and survived, and 1 died of his aspergillosis.

ACKNOWLEDGMENTS

The authors thank Dr Laure Ory-Lavollée and Mr Vinz Michard for their editorial assistance.

REFERENCES

1. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32:358–366.
2. Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. *Expert Opin Investig Drugs*. 2003;12:1313–1333.
3. Franklin JA, McCormick J, Flynn PM. Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J*. 2003;22:747–749.
4. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy in neonates with invasive candidiasis. *Pediatr Infect Dis J*. 2004;23:1093–1097.
5. Ascioglu S, Rex JH, de Pauw B, et al, Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, Mycoses Study Group of the National Institute of Allergy and Infectious Diseases, Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002;34:7–14.
6. Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics of Caspofungin in pediatric patients. In: *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, M-896, 2002*. Washington, DC: American Society of Microbiology. Abstract 395.
7. Mora-Duarte J, Betts R, Rotstein C, et al, Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;19:2020–2029.
8. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med*. 2002;113:294–299.
9. Villanueva A, Arathoon EG, Gotuzzo E, Berman RS, DiNubile MJ, Sable CA. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis*. 2001;33:1529–1535.
10. Kontoyiannis DP, Hachem R, Lewis RE, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary and salvage treatment of invasive aspergillosis in patients with hematologic malignancies. *Cancer*. 2003;98:292–293.
11. Marr KA, Hachem R, Papanicolaou G, et al. Retrospective study of the hepatic safety profile of patients concomitantly treated with caspofungin and cyclosporin A. *Transpl Infect Dis*. 2004;6:110–116.
12. Sanz-Rodriguez C, Lopez-Duarte M, Jurado M, et al. Safety of the concomitant use of caspofungin and cyclosporin A in patients with invasive fungal infections. *Bone Marrow Transplant*. 2004;34:13–20.
13. Kirkpatrick WR, Perea S, Coco BJ, Patterson TF. Efficacy of caspofungin alone and in combination with voriconazole in a guinea pig model of invasive aspergillosis. *Antimicrob Agents Chemother*. 2002;46:2564–2568.
14. Damaj G, Ivanov V, Le Brigand B, et al. Rapid improvement of disseminated aspergillosis with caspofungin/voriconazole combination in an adult leukemic patient. *Ann Hematol*. 2004;83:390–393.
15. Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother*. 2005;49:4536–4545.

THE RISK OF RESPIRATORY SYNCYTIAL VIRUS–RELATED HOSPITALIZATIONS IN PRETERM INFANTS OF 29 TO 35 WEEKS' GESTATIONAL AGE

Gunther Doering, MD, MPH, Walter Gusenleitner, MD,‡ Bernd H. Belohradsky, MD,† Stefan Burdach, MD,* Bernhard Resch, MD,‡ and Johannes G. Liese, MD, MSc†*

Abstract: Among 1158 preterm infants of 29–35 weeks' gestational age, respiratory syncytial virus (RSV) –related hospitalizations (RSV-H) occurred in 4.2% during the first year of life. Four independent factors influenced the risk for RSV-H: neurologic problems (odds ratio [OR], 3.6), male gender (OR, 2.8), presence of an older sibling (OR, 1.7) and discharge from October to December (OR, 1.7). The estimated risk of RSV-H varied between 1% (no risk factor present) and 30% (4 risk factors present).

Key Words: palivizumab, risk factors, multivariate logistic regression

Accepted for publication September 13, 2006.

From the *University Children's Hospital Munich, Technische Universität, Munich, Germany; †University Children's Hospital Munich, Dr. von Haunersches Kinderspital, Ludwig Maximilians-Universität, Munich, Germany; and ‡Medical University Graz, Department of Pediatrics, Graz, Austria

Address for correspondence: Gunther Doering, MD, MPH, University Children's Hospital Munich, Technische Universität, Kölner Platz 1, D-80804 Munich Germany. E-mail gunther.doering@lrz.tu-muenchen.de.

DOI: 10.1097/01.inf.0000246978.58565.b5

Respiratory syncytial virus (RSV) occurs in annual epidemics and is the leading cause of lower respiratory tract infections (LRTI) in infants and young children. Severe LRTI with considerable morbidity requiring hospitalization is found especially in young children with underlying clinical conditions. In addition, further predisposing environmental and demographic risk factors for severe RSV infection have been described: male sex, young age (<6 months), birth in the first half of the RSV season, crowding/siblings and daycare exposure.[1]

Prophylaxis with palivizumab (Synagis) significantly reduces hospitalizations due to RSV (RSV-H) in preterm children. Due to the high cost of this prophylaxis, however, there is an ongoing discussion concerning which preterm children have the greatest benefit from palivizumab. We therefore evaluated risk factors for RSV-H in a large German-Austrian cohort of preterm children with a GA of 29 to 35 weeks.

METHODS

A cohort of 1236 preterm children with a GA of 29 to 35 weeks (ie, 29 + 0 to 35 + 6) was formed by pooling the Munich RSV-study cohort and the Austrian 29–32 RSV-study cohort. Results from both studies have been previously published.[2,3]

The Munich RSV-study cohort consisted of 620 preterm children with a GA of 29 (29 + 0) to 35 (35 + 6) weeks who had been admitted to 9 neonatal intensive care units in Bavaria between November 1, 1998, and October 31, 1999.

The Austrian 29–32 RSV-study cohort consisted of 616 preterm children with a GA of 29 (29 + 0) to 32 (32 + 6) weeks, born between June 1, 2001, and December 31, 2002, who had been admitted to 20 neonatal units in Austria.

Written informed consent was obtained from all parents or guardians of children included in these studies. One thousand one hundred fifty-eight children remained in the pooled cohort as 78 (6.3%) children were excluded because they had received palivizumab during the surveillance period. Medical discharge letters of all ARI-H during follow-up were analyzed for RSV-H. Only the child's first RSV-H was regarded. Definite RSV-H was assumed for all patients with ARI-H who had a positive RSV antigen test. Because RSV tests were not regularly performed in all hospitals, an additional clinical case definition for RSV-H was used: Children hospitalized between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classified as suffering from a probable RSV infection. All analyses refer to the sum of laboratory-proven and probable clinical RSV-H during the first year of life. Children with suspected nosocomial RSV infection, who developed clinical respiratory symptoms or a positive RSV test after day 3 of hospitalization were excluded. Neurologic disorder was defined as the presence of 1 or more of the following diagnoses: intracranial hemorrhage (ICH) grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia (cPVL), cerebral infarction, hydrocephalus or other symptomatic neurologic conditions.

Statistical Analyses. The cumulative incidence (or risk) of RSV-H/ARI-H was calculated as the percentage of children admitted for RSV-H/ARI-H during the first year of life. Nonparametric comparisons between groups were conducted with the χ^2 test or Fisher exact test, and continuous variables were compared using Student *t*-test. Univariate and multivariate logistic regression analyses were used to assess independent risk factors for RSV-H. We included variables with a level of statistical significance below 0.15 in the multivariate logistic regression model using the backward selection procedure. Based on a multivariate logistic regression model, the estimated risk of RSV-H was calculated by:

$$p = \frac{1}{1 + e^{-(\alpha + \beta\,\text{neurological} + \beta\,\text{male} + \beta\,\text{older sibling} + \beta\,\text{discharge})}}$$

Differences between groups were considered to be significant if the *P* value of the statistical test was below 0.05. Statistical analyses were conducted with SAS, Release 8.02 (Cary, NC).

RESULTS

One hundred ten of 1158 children had an ARI-H (9.5%) and 57 (4.9%) children had a RSV-H during the follow-up period. Thirty-one of 57 children had a laboratory-proven RSV-H. Among the 26 of 57 children classified as probable RSV-H, 21 were not tested for RSV infection. Five children with only 1 test were tested negative but had a documented clinical diagnosis of RSV infection. Forty-eight children (4.2%) were hospitalized for RSV infection during the first year of life. Children from the Munich RSV-study were significantly more likely to be twins or triplets ($P = 0.02$) than children from the Austrian study. In a stratified analysis that controlled for gestational age, no significant differences between the 2 study populations were found for birth weight, gender, visit to child care, presence of older siblings, neurologic disorders, cardiac abnormalities or CLD. There was also no significant difference concerning the risk of RSV-H and ARI-H between children with a GA of 29 to 32 weeks and children with a GA of 33 to 35 weeks.

Neurologic problems (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.3–9.9; $P = 0.01$), male gender (OR, 2.8; 95% CI = 1.6–5.5; $P < 0.01$), presence of an older sibling (OR, 1.7; 95% CI = 1.0–3.2; $P = 0.07$) and discharge from October to December (ie, time from Oct. 1 to Dec. 31) (OR, 1.7; 95% CI = 0.9–3.1; $P = 0.09$) were independent risk factors for RSV-H in a multivariate analysis. Based on this multivariate logistic regression model (Table 1), the risk of RSV-H according to combinations of these risk factors was calculated and ranged from 1% (no risk factor present) to 30% (4 risk factors present); different combinations of either 2 or 3 of the risk factors yielded a risk of 4%–12% and 10%–20% RSV-H, respectively.

DISCUSSION

We assessed the risk of RSV-H in a large German-Austrian cohort of preterm children from 29–35 weeks GA. The incidence of RSV-H found in our study is comparable to similar studies from Canada[4] (RSV-H 3.6% during the first RSV-season; GA 33–35 weeks) and Austria[5] (RSV-H 4.4%; GA 29–35 weeks). The incidence of RSV-H in children without any of the identified risk factors in our study (1%) is almost equal to the yearly incidence of RSV-H in children <1 year, regardless of prematurity, as found in a population based study from northern Germany (1.2%).[6] Aside from that, no significant difference concerning the risk of RSV-H and ARI-H was found between children with a GA of 29 to 32 weeks and children with a GA of 33 to 35 weeks. This shows that, in preterm infants of more than 28 weeks of GA, the risk of RSV-H is more dependent on other risk factors than gestational age per se.

We assume that the sum of definite and probable cases in our study approximated the real number of RSV-H. Considering the

TABLE 1. Risk of Hospitalizations Due to RSV (RSV-H) During the First Year of Life According to Combinations of Risk Factors

Neurol. Problem	Male Gender	Older Sibling	Discharge Oct-Dec	Estimated Risk	Actual Risk in Cohort (n/n)
x	x	x	x	30%	20% (1/5)
x	x	x	0	20%	17% (1/6)
x	x	0	x	19%	— (0/1)
x	0	x	x	13%	50% (1/2)
0	x	x	x	10%	8% (5/66)
x	x	0	0	12%	17% (1/6)
x	0	x	0	8%	— (0/16)
x	0	0	x	8%	— (0/1)
0	x	x	0	6%	9% (13/141)
0	x	0	x	6%	5% (5/106)
0	0	x	x	4%	5% (2/42)
x	0	0	0	5%	7% (1/14)
0	x	0	0	4%	4% (10/279)
0	0	x	0	2%	1% (1/139)
0	0	0	x	2%	5% (5/106)
0	0	0	0	1%	1% (2/235)

The "Estimated risk" was calculated on the basis of a multivariate logistic regression model; the "Actual risk in cohort" is the risk of RSV-H as found in the subgroups of the pooled study population The estimated risk was calculated by:

$$p = \frac{1}{1 + e^{-(\alpha + \beta\,\text{neurological} + \beta\,\text{male} + \beta\,\text{older sibling} + \beta\,\text{discharge})}}$$

sensitivity of commonly used RSV-antigen tests (44%–91%), negative RSV-tests might have been falsely negative in spite of typical RSV symptoms and a high proportion of RSV in young infants with ARI during the RSV season.[7] The proportion of probable and definite RSV-H in all ARI-H was 52%, which conforms very closely with the reported proportions (50%–63%) in the medical literature. If all children with a negative RSV antigen test were excluded, the overall incidence for RSV-H would have changed only from 4.9% to 4.5%.

Four independent risk factors for RSV-H were identified. The presence of a cerebral event during the neonatal period and a subsequent neurodevelopmental handicap during the first 2 years of life were significant risk factors for RSV-H in another cohort study of preterm infants from Austria.[5] Children with a neurologic handicap have an increased risk of developing pulmonary infections caused by repeated aspiration and gastroesophageal reflux,[9] and chronic aspirations are associated with reactive airway disease.[10]

Male gender and the presence of 1 or more older siblings were identified as significant independent risk factors for RSV-H in accordance with the medical literature.[1]

Young age at the beginning of the RSV season is a consistent risk factor for RSV-H in most studies concerning preterm children,[1] as was also seen in our study (discharge during the time from October to December). Several reasons may account for this: The most severe RSV disease occurs during the first 6 months of life, and children born or discharged during the beginning of the season, rather than during the rest of the year, experience a relatively longer exposure to RSV at a relatively younger chronologic age.

We found 4 independent risk factors that significantly influence the individual risk for severe RSV-disease. Our data show that the risk of RSV-H in preterm children with a GA of 29–35 weeks and with 3 or more of the risk factors ranges between 10% and 30%. Prophylaxis with palivizumab should be considered in these children because they have a high risk for severe RSV infection, comparable to extremely preterm children (GA ≤28 weeks) and children with CLD, for whom prophylaxis is currently recommended by most guidelines/advisory boards. In addition, established risk factors derived from literature may be included in a risk score concerning the risk of severe RSV infection in children of comparable preterm populations.

ACKNOWLEDGMENTS

The authors thank all participants of the Munich RSV and Austrian RSV 29–32 Study Groups for their cooperation.

The study was supported by an unrestricted grant from Abbott Laboratories, Germany. G. Doering, J. G. Liese, and B. Resch participate in advisory board meetings concerning the "RSV Risk Assessment," sponsored by Abbott Int.

REFERENCES

1. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143(5 suppl):118–126.
2. Liese JG, Grill E, Fischer B, et al. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. *Eur J Pediatr*. 2003;162:230–236.
3. Resch B, Gusenleitner W, Müller WD, Haas J. Observational study on respiratory syncytial virus associated hospitalisations and the use of palivizumab in premature infants of 29 to 32 weeks gestational age. *Eur J Clin Microbiol Infect Dis*. 2006;25:120–122.
4. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004;23:806–814.
5. Resch B, Pasnocht A, Gusenleitner W, Muller W. Rehospitalisations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29–36 weeks gestational age. *J Infect*. 2005;50:397–403.
6. Weigl JA, Puppe W, Schmitt HJ. Incidence of respiratory syncytial virus-positive hospitalizations in Germany. *Eur J Clin Microbiol Infect Dis*. 2001;20:452–459.
7. Weigl JA, Puppe W, Schmitt HJ. Can respiratory syncytial virus etiology be diagnosed clinically? A hospital-based case-control study in children under two years of age. *Eur J Epidemiol*. 2003;18:431–439.
8. (Deleted in proof).
9. Fonkalsrud EW, Ament ME. Gastroesophageal reflux in childhood. *Curr Probl Surg*. 1996;33:1–70.
10. Meer S, Groothuis JR, Harbeck R, et al. The potential role of gastroesophageal reflux in the pathogenesis of food-induced wheezing. *Pediatr Allergy Immunol*. 1996;7:167–170.

LOBAR PNEUMONIA CAUSED BY NONTYPHOIDAL *SALMONELLA* IN A MALAWIAN CHILD

Limangeni A. Mankhambo, MB BS, Kwame W. Chiwaya, MB BS, Agib Phiri, MD, and Stephen M. Graham, FRACP

Abstract: Nontyphoidal *Salmonella* (NTS) is recognized as a common cause of bacteremia in malaria-endemic Africa but its importance as a cause of pneumonia is uncertain. We report a case of pneumonia caused by NTS confirmed by culture of lung aspirate from a consolidated left lung in a 16 month-old HIV-uninfected girl who had been admitted to the hospital 1 month previously with severe malaria. She did not respond to first-line antibiotic therapy for benzylpenicillin and gentamicin but improved with ceftriaxone therapy.

Key Words: nontyphoidal *Salmonella*, pneumonia, lung aspirate, child

Accepted for publication August 31, 2006.

From the Malawi-Liverpool-Wellcome Trust Programme of Clinical Tropical Research and Department of Paediatrics, College of Medicine, Blantyre, Malawi

Address correspondence to: Stephen M. Graham, FRACP, MLW Research Programme, P.O. Box 30096, Blantyre 3, Malawi. E-mail sgraham@mlw.medcol.mw.

DOI: 10.1097/01.inf.0000245098.82276.d6

Nontyphoidal *Salmonella* strains (NTS) are the most common cause of bacteremia in malaria-endemic Africa and a common cause of meningitis and septic arthritis.[1–5] Previous studies reported NTS bacteremia in African children with a clinical diagnosis of pneumonia,[6,7] but there is no report from the region that confirms NTS as a cause of pneumonia. We report the novel finding of lobar pneumonia caused by *Salmonella typhimurium*.

CASE REPORT

A 16 month-old Malawian girl with a 5-day history of fever, cough and dyspnea was admitted to the pediatric research ward at Queen Elizabeth Central Hospital (QECH), Blantyre on February 11, 2006. Two days before admission, she developed poor feeding and irritability. There was no history of diarrhea, vomiting or abdominal pain or of tuberculosis contact.

Relevant history included an admission to the research ward 1 month previously with a diagnosis of cerebral malaria and anemia on the basis of acute fever and convulsions, coma, a positive thick film for *Plasmodium falciparum* trophozoites and packed cell volume (PCV) of 21%. Cerebrospinal fluid was normal. She was treated with intravenous quinine and oral sulfadoxine–pyrimethamine, regaining full consciousness within 48 hours. PCV fell to 15% on day 3 after admission and was 20% at discharge on day 5. She did not receive a blood transfusion and did not receive antibiotics or iron therapy. Blood culture was negative after 5 days and she was discharged well.

On examination, she was fully alert with weight 8.1 kg, height 70 cm and weight for height of >85%. She was febrile (axillary temperature 38.6°C) and tachycardic (pulse rate 161 beats/minute) with normal capillary refill and blood pressure. She had marked respiratory distress with a respiratory rate of 80 breaths per minute, nasal flaring, grunting and subcostal indrawing but was not cyanotic. Clinical signs on chest examination were bronchial breathing and coarse inspiratory crackles on auscultation of the left lung consistent with consolidation. The remaining examination was unremarkable. A clinical diagnosis of pneumonia was made and she was treated with 6 mg/kg gentamicin daily and 50,000 IU/kg benzyl penicillin 4 times a day.

Chest radiograph revealed diffuse opacification of the left lung. Blood culture and aspirate of the left lung were taken before starting antibiotics. Thick blood film was negative for malaria parasites and PCV was 23%. Lung aspirate showed a white cell count of 6/mm^3 and 1500/mm^3 red blood cells and no organisms on Gram stain. Repeat chest radiograph postaspiration on day 2 showed complete opacification of the left lung and shift of trachea to the right. Chest ultrasound on day 3 found diffuse homogeneity of the left lung but no visible pleural fluid.

On day 3, she remained unwell, febrile and required oxygen. The antibiotic regimen was changed to 100 mg/kg ceftriaxone per day. Culture of lung aspirate grew *S. typhimurium* susceptible in vitro to gentamicin, ceftriaxone and ciprofloxacin and resistant to ampicillin, chloramphenicol and trimethoprim–sulfamethoxazole. A tuberculin skin test was nonreactive and 2 rapid HIV tests were negative. Blood culture was negative. By day 2 of ceftriaxone therapy, she had improved, was afebrile and oxygen therapy was discontinued. Ceftriaxone was continued for 7 days followed by 5 mg/kg oral ciprofloxacin twice daily for a further 7 days. At follow up 1 month after discharge, she was well and had a normal chest radiograph.

DISCUSSION

Invasive extraintestinal infections resulting from NTS, usually *S. typhimurium* and *Salmonella enteritidis*, are common in tropical Africa and associated with high mortality.[1–3] At QECH in Blantyre, Malawi, NTS are the most common cause of pediatric bacteremia and septic arthritis and a common cause of meningitis.[3–5] Although NTS have occasionally been reported elsewhere as a cause of pleuropulmonary disease, especially of empyema in immunocompromised adults,[8,9] the importance of NTS as a cause of acute bacterial pneumonia in African children is unclear. Studies from the region have shown that NTS is a common isolate, second only to *Streptococcus pneumoniae*, from the blood of children who have a diagnosis of pneumonia based on clinical findings,[6,7] yet studies using lung aspiration in children with acute severe pneumonia have not isolated NTS from the lungs.[10,11] This case report confirms NTS as a cause of acute community-acquired lobar pneumonia.

This child did not respond to first-line antibiotic therapy. In Malawi and the region of subsaharan Africa, recommended empiric therapy is penicillin for severe pneumonia and chloramphenicol for very severe pneumonia because it is assumed that *S. pneumoniae* and *Haemophilus influenzae* are the most common causes.[10,12] Since the introduction in Malawi of the Hib conjugate vaccine in 2001 and a marked fall in disease resulting from *H. influenzae*, first-line antibiotics at QECH for invasive bacterial disease in children are aimed primarily at *S. pneumoniae* and NTS. This includes pneumonia because it is recognized that many children with NTS bacteremia present with clinical features that are consistent with a diagnosis of pneumonia.[1,2] The in vitro susceptibility profile reported in this case for the *S. typhimurium* isolate is the same as for approximately 90% of more than 500 NTS isolates from children admitted to QECH since 2001 (S.M. Graham, unpublished data). Penicillin is not active against NTS and failure of chloramphenicol in vivo to treat NTS is now so common at QECH that gentamicin is routinely added to penicillin or chloramphenicol as first-line therapy for pneumonia or suspected septicemia, respectively. Gentamicin was not effective in this case despite in vitro susceptibility possibly because of poor tissue penetration outside the intravascular compartment. Third-generation cephalosporins are not widely available in Malawi but would be preferable as first-line therapy for severe pneumonia as is the case in resource-rich countries.

We included the recent history of an episode of severe malaria with anemia because it is relevant to the presentation of NTS disease.[1,2] At our hospital, NTS bacteremia and meningitis have been reported to have a strong association with hospitalization for severe malarial anemia in the previous few months compared with other common bacterial pathogens.[13] Most African children with invasive NTS disease are not HIV-infected in contrast to the very strong association with HIV infection in African adults.[1,2]

ACKNOWLEDGMENTS

The parents of the child gave written informed consent for this case to be published. The authors thank the nursing staff of the Malawi-Liverpool-Wellcome Trust and Blantyre Malaria Project Pediatric Research Ward for their contribution to the management of this child.

REFERENCES

1. Graham SM, Molyneux EM, Walsh AL, Cheesbrough JS, Molyneux ME, Hart CA. Nontyphoidal *Salmonella* infections of children in tropical Africa. *Pediatr Infect Dis J*. 2000;19:1189–1196.
2. Brent A, Oundo J. O, Mwangi I, et al. Salmonella bacteremia in Kenyan children. *Pediatr Infect Dis J*. 2006;25:230–236.

3. Walsh AL, Phiri AJ, Graham SM, Molyneux EM, Molyneux ME. Bacteremia in febrile Malawian children: Clinical and microbiological features. *Pediatr Infect Dis J*. 2000;19:32–38.
4. Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: A randomised controlled trial. *Lancet*. 2002;360:211–218.
5. Lavy CB, Thyoka M, Pitani AD. Clinical features and microbiology in 204 cases of septic arthritis in Malawian children. *J Bone Joint Surg* [*Br*]. 2005;87:1545–1548.
6. O'Dempsey TJ, Mcardle TF, Lloyd-Evans N, et al. Importance of enteric bacteria as a cause of pneumonia, meningitis and septicemia among children in a rural community in the Gambia, West Africa. *Pediatr Infect Dis J*. 1994;13:122–128.
7. Berkley JA, Maitland K, Mwangi I, et al. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: Observational study. *BMJ*. 2005;330:995. Epub 2005 Mar 29.
8. Aguado JM, Obeso G, Cabanillas JJ, Fernandez-Guerrero M, Ales J. Pleuropulmonary infections due to nontyphoidal strains of *Salmonella*. *Arch Intern Med*. 1990;150:54–56.
9. Crum N. Non-typhi *Salmonella* empyema: Case report and review of the literature. *Scan J Infect Dis*. 2005;37:852–857.
10. Shann F. The management of pneumonia in children in developing countries. *Clin Infect Dis*. 1995;21(suppl 3):S218–225.
11. Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. *Ann Trop Paediatr*. 1997;17:315–319.
12. *Acute Respiratory Infections in Children: Case Management in Small Hospitals in Developing Countries: A Manual for Doctors and Other Senior Health Workers*. Geneva: World Health Organization; 1990.
13. Walsh AL, Molyneux EM, Kabudula M, Phiri A, Molyneux ME, Graham SM. Bacteraemia following blood transfusion in Malawian children: Predominance of *Salmonella*. *Trans R Soc Trop Med Hyg*. 2002;96:276–277.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND AMEBIASIS

*Douglas M. Bowley, FRCS (Gen Surg),**
Jerome Loveland, FCS (SA), Tanvier Omar, MBBCh,†*
*and Graeme J. Pitcher, FCS (SA)**

Abstract: Pediatric human immunodeficiency virus (HIV) infection is a major and increasing burden worldwide, but particularly in sub-Saharan Africa. Coinfection with other pathogens increases the likelihood of progression of HIV/acquired immunodeficiency syndrome (AIDS), and the immunosuppressive consequences of the disease predispose to opportunistic infections that can run a fulminant course. Despite high prevalence, amebiasis has not appeared as a major source of morbidity during the HIV/AIDS pandemic. Information from recent sources, however, appears to suggest that amebiasis may indeed be a risk for individuals living with HIV/AIDS.

Key Words: amebiasis, pediatric, HIV/AIDS, South Africa
Accepted for publication September 13, 2006.
From the *Division of Paediatric Surgery and †Department of Anatomical Pathology, University of Witwatersrand, Johannesburg, South Africa
Address for correspondence: Douglas M. Bowley, FRCS, University of Witwatersrand, Johannesburg, South Africa. E-mail dougbowley@aol.com.
DOI: 10.1097/01.inf.0000246805.41422.77

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) is now South Africa's leading cause of death,[3] and pediatric HIV infection is a major contributor to childhood mortality. Gastrointestinal infections are more common and more severe in immunocompromised individuals, and gastroenteritis is the second most common cause for admission to the hospital for South African children with HIV infection.[4,5]

Amebiasis is the second leading cause of death from parasitic disease worldwide.[6] Despite the high prevalence of amebiasis, the HIV pandemic has not led to a huge increase in instances of invasive amebiasis. Indeed, in the early phases of the HIV/AIDS crisis, *Entamoeba histolytica* was labeled as a "missing infection."[7] More recently, the possible link between amebiasis and HIV infection has received increasing attention.[1,2,8] We report the case of an infant with amebic colitis, the outcome of which was strongly associated with the immunosuppression of the child.

CASE REPORT

In June 2005, a 10-month-old male, HIV-exposed infant presented to a peripheral hospital with a 7-day history of bloody diarrhea and a 24-hour history of abdominal distension and vomiting. The child had not previously come to the attention of health care providers, and no specific treatment had been given to the child in the week leading up to his hospital attendance. Radiologic examination revealed free intraperitoneal air, and the child was transferred to our hospital. The child had an acutely tender abdomen and was acidotic. Intravenous fluids and broad-spectrum antibiotics were given. HIV positivity was confirmed by polymerase chain reaction of whole blood; however, neither CD4 counts nor viral load was obtained.

At operation, multiple colonic perforations were discovered, there was minimal omental tissue, and colonic wrapping of the areas of perforation was not seen, and there was no intussusception. A subtotal colectomy and ileostomy were undertaken and the infant was transferred to a neonatal ICU. Despite maximal supportive therapy, sepsis progressed rapidly, organ failure developed, and death occurred 72 hours postoperatively.

Macroscopic examination of the resected specimen revealed bowel with a friable, dusky serosa. The opened colon demonstrated disseminated, irregular ulcers up to 30 mm in diameter, with a greenish exudate lining the base. The ileum was uninvolved. Microscopic examination confirmed widespread mucosal ulceration associated with characteristic basophilic granular exudates in which numerous *Entamoeba* trophozoites were identified. In many areas, transmural necrosis with perforation resulted in an amoebic peritonitis. The inflammatory response was sparse. (Photographs of microscopy specimens are in the On-Line version of this article).

DISCUSSION

Gastrointestinal illness is a common reason for hospital admission in pediatric patients with HIV infection, and diarrhea, poor nutritional status, and failure to thrive are extremely common.[5,9,10] Children with HIV-1 infection are likely to have more frequent episodes of diarrhea and are more likely to present with fever and moderate or severe dehydration and to have persistent or fatal infection.[11] Several pathogens may be implicated, including *Cryptosporidium parvum*, enteroadherence factor–positive *Escherichia coli* and nontyphoid *Salmonella*.[11,12] Other opportunistic infections can be major enteric pathogen in pediatric AIDS patients. Cytomegalovirus can cause mucosal ulceration, enterocolitis, severe hemorrhage, obstruction or perforation.[13,14] Infection with *Mycobacterium tuberculosis* or *M. avium intracellulare* can present with obstruction or abdominal pain, fever, weight loss, and diarrhea,[15,16] and invasive candidiasis can lead to intestinal perforation and obstruction.[17]

E. histolytica is estimated to cause 10,000 to 40,000 deaths annually and is the second leading cause of death from parasitic disease.[6] Although manifestations of *E. histolytica* infection are predominantly gastrointestinal, extraintestinal dissemination can lead to liver abscess and pleuropulmonary, pericardial, cerebral,

urinary or cutaneous amebiasis.[6] Although complicated amebic colitis has been reported in the first few weeks of life,[18,19] it is rare in infants. In a multicenter study conducted in developing countries involving 3640 children aged less than 3 years of age with acute diarrhea, amebiasis was the cause in only 0.3% of all diarrhea episodes.[20]

Despite the relative paucity of identified cases, interest has focused on a possible link between HIV/AIDS and amebiasis. Moran et al[8] compared 203 Mexican HIV/AIDS patients receiving a triple antiviral medication scheme with 140 HIV-negative contacts and found no difference in the rate of intestinal colonization with *E. histolytica.* Further, no patient infected with *E. histolytica* had developed diarrhea or invasive amebiasis in the 12 months before the study, and no association was found between rate of colonization and stage of HIV disease. They concluded that HIV-1 virus infection was not a risk factor for amebiasis. However, in 1999, Hung and coworkers[1] published a retrospective study of 18 HIV-positive patients with invasive amebiasis where the amebic infection was the HIV-presenting illness in 9 cases. In a prospective, controlled study, Hung et al[2] compared HIV-positive patients with uninfected individuals with or without gastrointestinal symptoms. A high indirect hemagglutination antibody titer was detected in 39 (6.2%) of 634 HIV-infected persons compared with 10 (2.3%) of 429 uninfected controls with gastrointestinal symptoms and 0 of 178 uninfected healthy controls ($P < 0.001$). More than 5% of the HIV-positive patients had episodes of invasive amebiasis. Their conclusion was that individuals infected with HIV can exhibit a relatively high frequency of elevated antibody titers and intestinal colonization with *E. histolytica* and are at increased risk for invasive disease.[2]

In South African children with vertically acquired HIV-1 infection, the onset of illness is early and deterioration to AIDS and death may be rapid. Bobat et al[9] studied 48 children with vertically transmitted HIV-1 infection. Seventy percent of infected infants were symptomatic by 6 months, and the most frequent findings were diarrhea (78%), pneumonia (76%) and lymphadenopathy (70%). Mortality in infected infants was 35.4%, and 76% of deaths occurred within the first year. Nevertheless, two thirds of HIV-infected infants survived into early childhood. Rapidly progressive HIV-1 and early death may occur in HIV-1-infected babies that clinically manifest in the neonatal period with perinatal coinfections. In a cohort of HIV-1 exposed neonates from Durban, South Africa, the predominant clinical presentation was growth retardation and prematurity. More than 80% of the group had died by 9 months, with a mean age at death of 3.5 months, and perinatal infections that had been detected included tuberculosis, syphilis and cytomegalovirus.[21]

REFERENCES

1. Hung CC, Chen PJ, Hsieh SM, et al. Invasive amoebiasis: an emerging parasitic disease in patients infected with HIV in an area endemic for amoebic infection. *AIDS.* 1999;13:2421–2428.
2. Hung CC, Deng HY, Hsiao WH, et al. Invasive amebiasis as an emerging parasitic disease in patients with human immunodeficiency virus type 1 infection in Taiwan. *Arch Intern Med*. 2005;165:409–415.
3. South African National Burden of Disease Study 2000: estimates of provincial mortality. Available at: http://www.mrc.ac.za/bod/estimates.htm. 2005.
4. Lewthwaite P, Gill GV, Hart CA, Beeching NJ. Gastrointestinal parasites in the immunocompromised. *Curr Opin Infect Dis*. 2005;18:427–435.
5. Meyers TM, Pettifor JM, Gray GE, Crewe-Brown H, Galpin JS. Pediatric admissions with human immunodeficiency virus infection at a regional hospital in Soweto, South Africa. *J Trop Pediatr*. 2000;46:224–230.
6. Stanley SL Jr. Amoebiasis. *Lancet*. 2003;361:1034.
7. Lucas SB. Missing infections in AIDS. *Trans R Soc Trop Med Hyg*. 1990;84(suppl 1):34–38.
8. Moran P, Ramos F, Ramiro M, et al. Infection by human immunodeficiency virus-1 is not a risk factor for amebiasis. *Am J Trop Med Hyg*. 2005;73:296–300.
9. Bobat R, Moodley D, Coutsoudis A, Coovadia H, Gouws E. The early natural history of vertically transmitted HIV-1 infection in African children from Durban, South Africa. *Ann Trop Paediatr*. 1998;18:187–196.
10. Bobat R, Coovadia H, Moodley D, Coutsoudis A. Mortality in a cohort of children born to HIV-1 infected women from Durban, South Africa. *S Afr Med J*. 1999;89:646–648.
11. Pavia AT, Long EG, Ryder RW, et al. Diarrhea among African children born to human immunodeficiency virus 1-infected mothers: clinical, microbiologic and epidemiologic features. *Pediatr Infect Dis J*. 1992;11:996–1003.
12. Amadi B, Kelly P, Mwiya M, et al. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhea and malnutrition. *J Pediatr Gastroenterol Nutr*. 2001;32:550–554.
13. Dolgin SE, Larsen JG, Shah KD, David E. CMV enteritis causing hemorrhage and obstruction in an infant with AIDS. *J Pediatr Surg*. 1990;25:696–698.
14. Kram HB, Shoemaker WC. Intestinal perforation due to cytomegalovirus infection in patients with AIDS. *Dis Colon Rectum*. 1990;33:1037–1040.
15. Aston NO. Abdominal tuberculosis. *World J Surg*. 1997;21:492–499.
16. Cappell MS, Hassan T, Rosenthal S, Mascarenhas M. Gastrointestinal obstruction due to *Mycobacterium avium intracellulare* associated with the acquired immunodeficiency syndrome. *Am J Gastroenterol*. 1992;87:1823–1827.
17. Loveland J, Bowley DM, Beavon IR, Pitcher GJ. Bowel obstruction in an infant with AIDS. *Arch Dis Child*. 2003;88:825–826.
18. Vargas M, Pena A. Toxic amoebic colitis and amoebic colon perforation in children: an improved prognosis. *J Pediatr Surg*. 1976;11:223–225.
19. Rennert W, Ray C. Fulminant amebic colitis in a ten-day-old infant. *Pediatr Infect Dis J*. 2000;19:1111–1112.
20. Huilan S, Zhen LG, Mathan MM, et al. Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries. *Bull World Health Organ*. 1991;69:549–555.
21. Pillay T, Adhikari M, Mokili J, et al. Severe, rapidly progressive human immunodeficiency virus type 1 disease in newborns with coinfections. *Pediatr Infect Dis J*. 2001;20:404–410.