Outcome of human immunodeficiency virus–exposed and –infected children admitted to a pediatric intensive care unit for respiratory failure*

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Objective: **Acute severe pneumonia with respiratory failure in human immunodeficiency virus-infected and -exposed infants carries a high mortality. *Pneumocystis jiroveci* is one cause, but other organisms have been suggested to play a role. Our objective is to describe the coinfections and treatment strategies in a cohort of human immunodeficiency virus-infected and -exposed infants with respiratory failure and acute respiratory distress syndrome, in an attempt to improve survival.**

Design: **Prospective intervention study.**

Setting: **Steve Biko Academic Hospital, Pretoria, South Africa.**

Patients: **Human immunodeficiency virus–exposed infants with respiratory failure and acute respiratory distress syndrome were recruited into the study.**

Interventions: **All infants were treated with routine therapy for *Pneumocystis jiroveci* and bacterial coinfection. However, in addition, all infants received ganciclovir from admission until the cytomegalovirus viral load result was demonstrated to be <log 4.**

Measurements: **Routine investigations included human immunodeficiency virus polymerase chain reaction, cytomegalovirus viral load, blood culture, C-reactive protein, and white cell count. Tracheal aspirates for *Pneumocystis jiroveci* detection, bacterial culture, tuberculosis culture, and viral identification were performed.**

Main Results: **Sixty-three patients met the recruitment criteria. The mortality rate was 30%. *Pneumocystis jiroveci* was positive in 33% of infants, while 38% had cytomegalovirus viral load ≥log 4. Only 7.9% of infants had a positive tuberculosis culture. Nineteen deaths occurred, 13 of which had a cytomegalovirus viral load ≥log 4. Bacterial coinfection and CD4 count were not predictors of mortality.**

Conclusions: **A case fatality rate of 30% is achievable if severe pneumonia with respiratory failure and acute respiratory distress syndrome is managed with a combination of antibiotics and ventilation strategies. Cytomegalovirus infection appears to be associated with an increased risk of death in this syndrome. This may, however, be a marker of as yet undefined pathology. (Pediatr Crit Care Med 2012; 13:516–519)**

Key Words: cytomegalovirus; ganciclovir; human immunodeficiency virus; mortality; pneumocystis syndrome

Within South Africa (as with many other countries) human immunodeficiency virus (HIV) infection is a significant cause of morbidity in women and their infants. In South Africa, 26% of pregnant women are HIV-infected, and in the absence of preventative therapy there is a 15%–30% risk of HIV infection in their infants (1, 2). Even children who are part of the Prevention of Maternal to Child Transmission program have an increased risk of HIV infection relative to those who are not exposed, although that risk is substantially reduced. Mortality in HIV-infected children results primarily from respiratory tract infections (3, 4).

In children (and especially HIV-infected children) with acute severe respiratory disease requiring endotracheal intubation and ventilation, a number of pathogens (including *Pneumocystis jiroveci* and cytomegalovirus [CMV]) have been isolated. Although there has been considerable focus on *P. jiroveci* as a cause of mortality (the term pneumocystis pneumonia [PCP] was retained when *Pneumocystis carinii* was taxonomically renamed jiroveci [5]), it would be important to consider the potential contribution of other pathogens, and in particular, the association of CMV infection, with mortality. CMV infection has been reported to affect nearly 90% of HIV-exposed infants (6) and especially HIV-exposed infants with severe pneumonia.

Admitting HIV-infected infants with severe pneumonia to an intensive care unit in a resource limited setting has created a number of ethical dilemmas for pediatricians, and these dilemmas are created by the historical poor outcome for these patients and the pressure on scarce resources (7).

Study Aim. To report on the pathogens identified in a cohort of HIV-exposed and -infected children admitted to a pediatric intensive care unit (PICU) with respiratory failure and acute respiratory distress syndrome (ARDS), and to explore the relationship between pathogens identified and patient outcomes.

MATERIALS AND METHODS

All HIV-exposed infants admitted to the PICU at the Steve Biko Academic Hospital, Pretoria, South Africa, with respiratory failure were recruited for enrollment into this study. Patients had to fit the diagnosis of ARDS as described by Bernard et al (8), the most important of which was hypoxic acute

*See also p. 597.

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Mr. Omolemo P. Kitchin received scholarships from Discovery Foundation and Nycomed Madaus.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e31824ea143

lower respiratory tract infection with a partial pressure of oxygen in mm Hg over a fraction of inspired oxygen ratio of <200. Each infant was ventilated using a strategy of high positive end-expiratory pressure of 10–15 cm of water, tidal volume of 6–8 mL/kg, and a positive inspiratory pressure not exceeding 30 cm of water. Tidal volume was read from the ventilator display despite limitations of this technique (9, 10). None of the infants were offered high frequency oscillation ventilation due to unavailability of that modality. Total fluid intake was restricted to 60–80 mL/kg/day, and delivered medication was specifically included in the calculation of total fluid volume.

This prospective study of all consecutive admissions was conducted between January 2008 and December 2009. Children had their initial oxygenation index, Pediatric Risk of Mortality (PRISM), and Revised Pediatric Index of Mortality scores measured at admission to the PICU. Each child had a number of investigations performed at admission, and airway specimens were collected within 2 hrs of endotracheal intubation. Nonbronchoscopic bronchoalveolar lavage specimens were collected for *P. jiroveci* immunofluorescence antibody testing (performed using the Axis Shield diagnostics/UK Code FIPC200 available from Bioweb SA, Randburg, South Africa), bacterial microscopy culture and sensitivity, viral immunofluorescence antibody testing using the Chemicon/Millipore kit (Light Diagnostics, Billerica, MA), and tuberculosis microscopy culture and sensitivity (Wescor aerospray automatic stainer/US for auramine staining available from Nyala Technologies SA, Johannesburg, South Africa). Blood testing was conducted for white cell count (conducted using the automated hematology analyzer Advia 2120 [Siemens Diagnostics, Midrand, South Africa]). C-reactive protein was measured using an immunoturbidometric reaction (Beckman Coulter Synchron LX20 PRO, Beckman Coulter Incorporated, Fullerton, CA). CMV viral load polymerase chain reaction (PCR) was determined using a Toga lab on Cobas Amplicor instrument (Roche Diagnostics, Randburg, Gavleng, South Africa). An HIV deoxyribonucleic acid PCR was determined by means of a Amplicor HIV-1 DNA test, version 1.5 (Roche Diagnostics). A peripheral blood volume of 2 mL was collected for blood culture after careful cleansing of the arm. Blood was immediately injected into relevant blood culture bottles. Blood cultures positive for growth were plated onto agar and sensitivity measured using a Kirby–Bauer technique (Bactec 9240, Becton Dickinson, Sparks, MD).

Each infant was treated, at the time of presentation, with trimethoprim–sulphamethoxazole (20 mg/kg/day of the trimethoprim component and 100 mg/kg/day of the sulphamethoxazole component) and oral steroids (1–2 mg/kg/day). Ampicillin and amikacin were routinely added at the time of admission and administered for 5 days unless a resistant organism was cultured, in which case appropriate antibiotics were administered. This is in accordance with the national guideline, which in turn is based on the common organisms cultured in HIV-infected patients presenting with pneumonia (11). These initial antibacterial antibiotics were changed to meropenem if the patient deteriorated after 48 hrs of admission in order to treat the possibility of more resistant hospital-acquired organisms. Trimethoprim–sulphamethoxazole was continued for 21 days and oral steroids for 14 days.

In addition to these standards of therapy, all children received intravenous ganciclovir (10 mg/kg/day). There are currently no guidelines on what constitutes CMV disease in the setting of CMV viral isolation. For the purposes of this study, CMV infection status was defined as follows: CMV disease—CMV viral load >10,000 copies/mL (log >4); CMV infection—CMV viral load 0.1–10,000 copies/mL (log –1 to log 4); and CMV-uninfected—CMV viral load negative. The value of 10,000 copies/mL is extrapolated from transplant studies (12) and should be used together with clinical, radiological, and laboratory support for CMV disease. PCR holds promise as an alternative diagnostic method (13). Ganciclovir was continued until either CMV viral load was <10,000 copies/mL or for 3 wks after the onset of triple antiretroviral therapy.

Approval to conduct the study was obtained from the Human Ethics Committee of the University of Pretoria, and written informed consent was obtained from each parent with the help of a qualified PICU-trained nursing practitioner who was aware of the study.

In the case of infants who died, permission for postmortem examination was requested of each parent.

Statistical Methodology. The associations of mortality with individual exposure variables, on an ordinal scale, were assessed using Pearson's chi-square test, which was confirmed using Fisher's exact test, and for those exposure variables on a continuous scale, Student's two-sample *t* test was employed and was confirmed using Wilcoxon's rank sum test. Testing was done at the 0.05 level of significance, and those exposure variables significant at the liberal 0.15 level of significance were included into the multivariate logistic regression analysis. Stata 10 (eStataCorp LP, College Station, TX) was used for computations.

RESULTS

A total of 90 infants with HIV-related pneumonia, respiratory failure, and ARDS were admitted during the study period. Twenty-seven were excluded due to refusal of enrollment into the study. Sixty-three infants qualified for final analysis. The mean age was 3.7 months (range 2–9), median age 3 months. None of the infants in this study had received PCP (trimethoprim–sulphamethoxazole) prophylaxis, and none were on highly active antiretroviral therapy at the time of the study. The mean weight for age of the study population was 4.6 kg (z score = –2.7), which is moderately underweight for age. The median (range) for the oxygenation index, PRISM score, percentage-predicted death rate based on the PRISM score, and percentage-predicted mortality based on the Revised Pediatric Index of Mortality score were 16 (4.3–39.6), 10.0 (4.0–2.0), 6.1 (1.9–9.1), and 18.7 (13.4–52.6), respectively.

All study children were HIV-exposed; 53 (84%) were HIV-infected with a positive HIV DNA-PCR. Ten (16%) of the exposed infants were HIV-uninfected. Nineteen children (30%) died. Thirty-two percent of HIV-infected children died vs. 20% of HIV-uninfected infants ($p = .709$). Twenty-one (33%) of infants had *P. jiroveci* identified from a nonbronchoscopic bronchoalveolar lavage specimen. Thirty-five (55%) children had a positive CMV viral load; while 24 (38% of the total study group) had a CMV viral load in the range determined as CMV-disease.

The most important outcome in this study was deemed to be survival and therefore discharge from PICU. Each parameter or laboratory variable that might have reflected an infection on each patient at admission was analyzed for prediction of mortality. Blood culture was positive for bacterial organisms in five (7.9%) and eight (12.7%) of nonsurvivors and survivors, respectively. Pathogens cultured included coagulase negative *Staphylococcus* (n = 6), and one each of *Streptococcus pneumonia*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Enterococcus faecium*, and *Enterococcus faecalis*. Bacterial culture on nonbronchoscopic bronchoalveolar lavage yielded 19 pathogens, 6 (9.5%) and 13 (20.6%) in nonsurvivors and survivors, respectively. Pathogens included *Klebsiella pneumonia* (n = 4) and two each of extended-spectrum β-lactamase producing *K. pneumonia*, *S. aureus*, *S. maltophilia*, *Escherichia coli*, *and Enterobacter cloacae*. There was one culture of each of *S. pneumonia*, *P. aeruginosa*, *Acenitobacter baumanni*, *Proteus mirabilis*, and coagulase negative *Staphylococcus*. Nine respiratory viruses were isolated, one (1.6%) and eight (12.7%) from nonsurvivors and survivors, respectively. These included respiratory syncytial virus (n = 3), two each of adenovirus, parainfluenza virus 3, and influenza virus B. These bacterial cultures, viral isolates, together with neutropenia (11.1%), and elevated C-reactive protein (15.9%) were not contributors

to mortality (p = .508, p = 1.00, p = .256, p = .685, and p = .162, respectively).

Included into the multivariate logistic regression based on a 0.15 level of significance were CMV status (p = .002), CD4 percentage (p = .142), and tuberculosis (p = .078). From the logistic regression analysis, CMV status emerged as a significant risk factor of mortality (adjusted odds ratio = 6.5; p = .002; 95% confidence interval 1.98–21.23) (Table 2). Positive identification of *P. jiroveci* did not predict mortality *per se*, irrespective of the HIV status (p = .774). The risk of dying was higher in CMV-diseased infants (viral load log ≥4) (58%) (p = .002). Mortality in relation to interaction of *P. jiroveci* and CMV status is documented in Table 1. Mortality in this group of infants with a CMV viral load ≥4 occurs at a mean of 12.9 days. The average length of stay for all surviving infants was 14.1 days (confidence interval 10.4–17.9).

DISCUSSION

Within the context of this study and the methodology used, a number of organisms causing respiratory failure in HIV-infected and -exposed infants have been identified. The limitation of the methodology employed is acknowledged, and PCR testing for most of the organisms is now recognized as a gold standard (14–17). This was not available at the time of the study in our setting.

Within a setting of HIV-disease, mortality from respiratory failure in HIV-infected infants was 12% higher than those exposed but not infected. This was, however, not statistically significant. This may in part be due to the fact that this study is underpowered to detect this effect. What is clear, however, is that HIV-uninfected but exposed children contract PCP. This finding suggests that the immune dysregulation that creates a risk for PCP is present in HIV-exposed but not HIV-infected children. This has been demonstrated in a previous South African study (18). This finding was even more significant as none of the mothers were aware of their children's HIV exposure, and their children were consequently not offered prophylaxis against *P. jiroveci*. Pneumocystis prophylaxis, in HIV-exposed children, has been clearly shown to reduce mortality (19).

The overall mortality of patients was significantly higher than predicted using the PRISM score. Use of Revised Pediatric Index of Mortality scores, which specifically include HIV infection as a factor, substantially changes the predicted risk of mortality. In the context of our study and children with respiratory failure only, it appears that the PRISM score underpredicts mortality and the Revised Pediatric Index of Mortality score is a more realistic predictor of mortality, probably because HIV-infection is included as a "high-risk" diagnosis.

A case fatality rate of 30% has been achieved through a meticulous approach to management of the interaction between the host and infection in infants with respiratory failure. This has been demonstrated previously. In 2004, Cooper et al (20) documented that HIV-infected children admitted to a PICU in London had a 38% mortality when every effort is made to treat such children. The actual mortality of these infants beyond the PICU into the first year of life is a subject of an ongoing study. However, all of the patients in this study who were HIV-infected received antiretroviral therapy early in the course of their disease, and survival to 1 yr of age appeared to be better than reported in previous studies (21).

It appears that at least two major infectious diseases coexist in more severely ill patients with this form of pneumonia, namely *P. jiroveci* and CMV. The interaction of these two organisms in HIV-infected individuals has been suggested in previous reports (22, 23). CMV, in fact, appears to be associated with an increased risk of death in our study, with 79% of the deaths occurring in infants coinfected with CMV despite early treatment with ganciclovir. This CMV association with mortality in HIV-infected children has been documented in two recent publications. These report a case fatality rate of 28% (24) and 36% (25), respectively. The second study also reported a PICU mortality of 72% in the patients who were treated with trimethoprim–sulphamethoxazole and ventilated for suspected PCP but who did not respond to treatment. This cohort was not treated with ganciclovir. A possible explanation for the high mortality associated with CMV (and despite ganciclovir use) is the fact that the inflammatory response or pathological state induced by CMV disease may already be well-established at diagnosis and intervention is likely to be unsuccessful (26). Additional explanations may include poor activity of ganciclovir, drug interactions reducing ganciclovir efficacy and the possibility that CMV-infection is but a surrogate marker for another disease process. An explanation for this phenomenon still requires further study.

Despite reasonably small numbers of bacterial, other viral, and tuberculosis coinfections, these offending organisms must be contributing to respiratory failure with ARDS in these infants. Clearly the actual contribution is impossible to determine because the testing methodology of each of the tests employed is imperfect. It is well-known that few children with proven bacterial pneumonia have positive sputa or blood cultures (11). A follow-up study employing PCR for bacterial antigens would be advantageous.

Study Limitations. This study has a number of limitations. The major limitation of our study is the definition of CMV disease. Clearly use of a blood measure of viral load does not imply pulmonary disease. This fact has not escaped our attention, but short of lung biopsy actual proof of CMV infection has proven difficult in previous studies. In addition, the close correlation between CMV viral load and mortality must suggest that this test is identifying some disease process. Exactly what that disease is seems unclear from our study. Some additional limitations include failure to fully identify all potential pathogens through PCR and culture techniques. Such testing would enhance the diagnostic yield in our study but would of course not have changed our therapeutic strategy as all organisms, with the exception of tuberculosis, were

Table 1. Mortality as related to infection status

	Human Immunodeficiency Virus–Infected	Mortality (%)	Human Immunodeficiency Virus–Uninfected	Mortality (%)	Total Mortality (%)
PJP+/CMV+	10	5 (50)	2	2 (100)	7/12 (58.3)
PJP–/CMV+	19	8 (42)	3	0 (0)	8/22 (36.4)
PJP+/CMV–	9	0 (0)	0	0 (0)	0/8 (0)
PJP–/CMV–	15	4 (27)	5	0 (0)	4/21 (19.0)
Total	53	17 (32)	10	2 (20)	19/63 (30)

PJP, *Pneumocystis jiroveci*; CMV, cytomegalovirus.

empirically treated. An attempt was also made to get postmortem biopsies on the 19 deaths, but permission was denied by all the parents. This would have given us the opportunity to observe the histology of the lungs in order to determine whether fibrosis was the end-stage pathology of patients with this form of ARDS.

CONCLUSIONS

Respiratory failure in infants who are HIV-exposed or -infected has more than one etiology, and CMV coinfection appears to be associated with mortality. However, other explanations for this association are possible. Mortality of 30% was achieved through treating coinfection, ventilation in a controlled fashion, and liberal fluid restriction.

Decreasing 30% mortality will require interventions and research in the realm of CMV prevention and possibly better treatment.

It remains pertinent to point out that effective antenatal care with diagnosis and appropriate therapy of infected mothers can virtually eliminate the problems of HIV infection in young children.

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