



Impact of HIV infection and exposure on survival in critically ill children who attend a paediatric emergency department in a resource-constrained setting

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ABSTRACT

Objective To assess the impact of HIV infection and exposure on survival in critically ill children requiring resuscitation.

Methods A 6-month descriptive prospective cohort study of all live admissions to the resuscitation room of an urban paediatric emergency department in Blantyre, Malawi.

Results 583 children were resuscitated, of whom 401 (69%) survived to hospital discharge. 26% of all children tested positive for HIV infection (152/576), and this was highest in patients presenting with shock (66%; 162/247), clinically diagnosed septicaemia (57%; 125/218) and malnutrition (40%; 24/60). Of 152 HIV-seropositive children, 30 (20%) died within 24 h, while among 424 seronegative children 36 (8.4%) died within 24 h ($p<0.001$). Later deaths (>24 h) were also more common in HIV-seropositive children compared with HIV-uninfected patients (24.3% vs 12.3%; $p<0.001$). Survival to 24 h was 80% (122/152) and to discharge 56% (85/152) in HIV-seropositive children. In HIV-uninfected children survival to 24 h was 92% (388/424) and to discharge 79% (336/424).

Conclusion Early and late case death rates are greater in HIV-seropositive than in HIV-uninfected children. 80% of HIV-infected children survived the period most influenced by the process of resuscitation, that is, the first 24 h. HIV status alone should not influence the limitation of intervention decisions in the resuscitation room when faced with a critically ill child.

when antiretroviral therapy was not universally available. To our knowledge this is the first study of its kind to address this issue.

BACKGROUND

In Malawi the overall prevalence of HIV infection in the population is 14%, approximately 91 000 being children.⁴ Of children admitted in 2000 to Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, 18.9% were HIV infected; HIV seropositivity being strongly associated with particular diagnoses such as malnutrition (40%) and lung infections (29%) and less so with malaria (11%).⁵ Other studies, also in Malawi have demonstrated poorer outcomes in children with HIV infection who present with bacterial meningitis or severe pneumonia or diarrhoea.^{6–8}

METHODS

Blantyre (population 750 000) is the largest city in southern Malawi. QECH serves as both a tertiary referral centre for the whole of the southern region of the country and as the district hospital for the people of Blantyre. QECH is an 1100-bed hospital, with approximately 180 beds for children. The daily census of inpatient children is 280–350. The Paediatric Emergency Department (PED) manages 80 000 patients a year, of whom 23 000 are admitted. Every year approximately 1000 children are triaged to the resuscitation room of the PED where they are resuscitated and stabilised before transfer to a ward.

From 1 October 2004 to 31 March 2005 we conducted a prospective cohort study of all children presenting with life-threatening critical illness to the resuscitation room in the PED.

A 'critically ill child' was defined as a child who satisfied the entry criteria for resuscitation room care by the triage nurse or clinician at the triage screening desk. These criteria were developed by the World Health Organization (WHO) emergency triage assessment and treatment system for severe illness recognition in children in a resource-constrained settings. This triage system has been in operation since the inception of the emergency department and has shown to be effective for this purpose,^{9 10} table 1.

In the resuscitation room patient demographics were recorded, a thorough clinical history and examination were carried out and appropriate emergency investigations and management were performed. During resuscitation of a child we explained to the mother the problems that we had

The steady decline in child mortality observed in most African countries throughout the 1960s, 1970s and 1980s has stalled in many countries in the 1990s because of the AIDS epidemic.¹ The added burden of HIV/AIDS in children already compromised by easily treatable or preventable diseases, such as acute respiratory, diarrhoeal illness and malaria, is formidable. To these challenges add the problem of resource scarcity when healthcare resources are often allocated to those who may be perceived to derive the most benefit, and one begins to see the scale of the challenge faced by the acutely sick child. We postulate that decisions to limit interventions in the resuscitation room are often made on the basis that perceived HIV seropositivity precludes successful resuscitation, as has been demonstrated in intensive care unit (ICU) settings in similar resource-constrained environments elsewhere.^{2 3} With this in mind, we set out to examine the impact of HIV status on survival in critically ill children who attended a paediatric emergency service in a resource-constrained setting in an era

Table 1 Emergency triage assessment and treatment signs and symptoms assessed to place a patient in the emergency category

Any positive finding requires immediate admission to resuscitation room	
A	Airway—blue lips, not breathing, abnormal breathing sounds
B	Breathing—great effort to breathe, tiring
C	Circulation—cold hands and prolonged capillary refill time >3 s
C	Coma—on the AVPU scale—only responding to painful stimulus or unresponsive
C	Convulsion—evidence of convulsion with emphasis on looking for subtle seizures
C	Confusion—the restless, hallucinating child
D	Dehydration—a history of vomiting and/or diarrhoea, and of prolonged skin pinch, sunken eyes and lethargy

AVPU, A (Alert) V (respond to Voice) P (respond to Painful stimuli) U (Unresponsive).

found and the investigations and treatment required. Ethics committee approval was granted to perform anonymous HIV testing.

In obtaining a sample for HIV testing, the study investigators felt more comfortable requesting permission to test for HIV from the guardian when a blood sample was being taken for clinical reasons. The study investigators explained to the guardian that a HIV test would also enable a better understanding of how HIV affects the outcome in seriously ill children. We also asked if she would like to know the results. This was performed in a manner consistent with HIV pre and post-test counselling standards in Malawi. At the time of the study antiretroviral treatment was not universally available through the Malawian National Health Service but cotrimoxazole could be given to prevent opportunistic infections.

We carried out a bedside antibody assay for HIV 1/2 (Determine, Abbott Laboratories, Tokyo, Japan), and saved three drops of blood as dried spots on filter paper for later confirmatory testing for HIV if the first test was positive. The dried spots were kept for PCR testing for HIV RNA. If the mother wished to know the results of the test we told her the test result but explained that any positive test needed confirmation with another test on the ward.

Children were sent from the resuscitation room to the ward when they had received emergency care and had been stabilised. Some children stayed in the resuscitation room for several hours while they received emergency treatment, such as intravenous fluids or blood, waited for vital signs to stabilise, seizures to cease or oxygen saturations to improve to acceptable levels. The

primary outcomes were survival to 24 h and survival to discharge from hospital in those with or without HIV infection.

During admission if a child was confirmed as HIV infected and was over 6 weeks of age prophylactic cotrimoxazole was started and the guardian advised that this would be essential to continue. An appointment was made for the staging clinic for assessment for antiretroviral therapy. Children with malnutrition were either admitted to the nutrition rehabilitation unit or given supplemental ready-to-use therapeutic feeds on the ward and provided with ready-to-use therapeutic feeds on discharge.

DATA COLLECTION

Data were entered on a study proforma and double entered into a Microsoft Excel file. We used Microsoft Excel and Stata version 8 for analysis. The College of Medicine Research and Ethics Committee gave us permission to conduct this audit and gave permission for anonymous HIV tests to be carried out [P.03/04/234].

RESULTS

During the 6-month study period 583 children were admitted to the resuscitation room. In many cases a definitive diagnosis was not made during resuscitation. Many children had more than one problem; for example, a comatose child with malaria, anaemia and hypoglycaemia. Shock was defined using the WHO criteria of cool peripheries with a capillary refill greater than 3 s with or without hypotension.⁹ The presenting symptoms were seldom diagnostic of a particular underlying disease process. When it was possible to do so, a diagnosis was made and recorded.

The resuscitation team was required to manage critically ill children presenting in defined clinical states. These were commonly hypoxia, shock or coma, or a combination of these three problems. Table 2 lists the numbers of children presenting in each of these categories. Coma was the most common presentation of children who required resuscitation (75%, n=423). Hypoxia (46%, n=270) and shock (42%, n=247) were the primary problem in almost half of the children. Hypoglycaemia complicated the illness in 61% (n=355).

Of the 583 children treated in the resuscitation room, 401 (69%) survived to discharge. In 15 cases, the parent or guardian absconded with the child. The HIV infection or exposure rate was 152/576 (26%) (seven children were not tested; two refused, five missed). As a result of technical problems, the PCR tests done on the dried blood spot samples to distinguish HIV

Table 2 Presenting problems, ages, HIV serostatus and outcome of children requiring resuscitation

Main presenting problem* (all causes included)	Total	HIV seropositive (%)	Death <24 h (%)	Death >24 h (%)	Median age (range in months)
Hypoxia	270	66 (24)	42 (15)	48 (18)	14 (0–192)
Shock	247	162 (66)	67 (27)	52 (21)	9 (0–192)
Coma	423	106 (25)	57 (13)	67 (16)	9 (0–192)
Hypoglycaemia	355	102 (29)	56 (16)	64 (18)	12 (0–168)
Septicaemia	218	125 (57)	42 (19)	50 (23)	9 (0–168)
Acidosis + dehydration	109	26 (25)	22 (20)	23 (21)	8 (0–168)
Underlying diagnoses—made at resuscitation*					
Meningitis	67	24 (36)	7 (10)	14 (21)	12 (0–156)
Malaria	206	33 (16)	9 (4)	18 (9)	23 (3–156)
Severe anaemia	149	30 (20)	11 (7)	15 (10)	19 (0–168)
Malnutrition	60	24 (40)	11 (18)	12 (20)	14.5 (0–168)
Trauma	19	1 (5)	1 (5)	3 (16)	84 (19–120)
Total children tested	576	26%	66 (11%)	89 (15%)	14 (0–168)
Nine cholera, seven bronchospasm, one rabies, one neonatal tetanus					

*Many children presented with more than one problem or diagnosis.

infection from HIV exposure in the infants aged 18 months or less ($n=94$) were unreliable. The survival rate to discharge in children who were HIV infected or exposed was 56%, whereas the rate in HIV-seronegative children was 79%.

The HIV seropositivity rate in each of the clinical syndromes and diagnostic categories is shown in table 2. The highest rates were in shock (66%), a clinical diagnosis of septicaemia (57%), malnutrition (40%) and meningitis (36%). Clinical groups often overlapped, and many children were critically ill with evidence of combined shock, coma and/or hypoxia.

In 542 (93%) children a blood sample was taken for culture; in 41(7%) cases it was thought unnecessary. A pathogen was grown from blood culture in 93 (17%) of the children from whom a sample was taken. Blood culture yielded a pathogen in 42 of 152 HIV-seropositive cases (28%) and in 50 of 424 seronegative children (12%; $p<0.001$), table 3.

Of 152 HIV-seropositive children, 30 (20%) died within 24 h, whereas among 424 seronegative admissions, 36 (8.4%) died within 24 h ($p<0.001$). The death rate after 24 h among seropositive patients was 37 (24.3%) of 152 admissions, compared with 52 (12.3%) of 424 seronegative admissions ($p<0.001$). Table 4 shows the number and interval times of deaths from arrival at the emergency department in HIV-seropositive and HIV-seronegative children.

The case death rate in HIV-seropositive children was approximately double the rate in seronegative children, both before and after 24 h (table 3). HIV seropositivity was associated with a relative risk (RR) of death within 24 h of 2.32 (95% CI 1.49 to 3.6) and after 24 h of 1.98 (95% CI 1.36 to 2.9). Approximately 44% of deaths occurred within the first 24 h, irrespective of serostatus.

One hundred and forty-six children over 18 months of age were tested and 58 (39.7%) were HIV infected. Of these, 38 (65.5%) survived to discharge, 10 (17.2%) died within 24 h and 13 died (22.4%) after 24 h of admission. Of the 60.2% (88 of 146) of HIV-uninfected children aged 18 months or more, 63 (71.6%) survived to discharge, nine (10.2%) died within 24 h and 16 (18.2%) after 24 h.

Forty (26%; 40/155) of the total number of children who died had a positive blood culture. The rate of blood culture positivity was 28/67 (41.7%) in the HIV-seropositive group and 12/88 (13.6%) in the HIV-uninfected group (RR 3.06; 95% CI 1.69 to 10.7, $p<0.001$).

Table 2 shows that coma alone has a relatively good prognosis (case death rate 13%), but the risk of a fatal outcome increases with the addition of hypoxia (15%) or shock (27%) in the first 24 h. The presence of all three clinical problems, such as in patients with septicaemia, is associated with a case death rate of 58%.

DISCUSSION

There are few reports of the outcomes of children resuscitated in emergency departments in resource-constrained parts of the

Table 3 Blood culture results (%) in HIV-seropositive and seronegative children taken during resuscitation

Culture results	HIV seropositive	HIV seronegative	HIV status unknown	Total
Pathogens	42 (27.6)	50 (11.8)	1 (14.2)	93 (16)
Contaminants	35 (23)	84 (19.8)	3 (42.9)	122 (20.9)
No growth on culture	69 (45.4)	255 (60.1)	3 (42.9)	327 (56.1)
Culture not done	6 (4)	35 (8.3)	0	41 (7)
Total	152	424	7	583

Table 4 Number and interval time of deaths in children requiring resuscitation in relation to HIV serostatus

HIV serostatus*	No of deaths (%)		
	All deaths	Within 24 h	After 24 h
HIV seronegative N=424	88 (21)	36 (9)	55 (12.3)
HIV seropositive N=152	67 (44)	30 (20)	37 (24)
Total N=576*	155† (27)	66 (11)	89 (15)

*Seven (1.2%) children not tested—two refused, five missed.

†Excluded—one serostatus unknown.

world, and none that we could find of the impact of HIV infection or exposure on the outcomes of attempted resuscitation in children. It is known that HIV infection affects inpatient mortality, but it has not been reported whether this is in response to resuscitation efforts or later. Clinicians have had to make difficult decisions especially in ICU where beds are scarce and priority has to be given to those in whom a good outcome is most likely. In some cases, at the time of this study, HIV-infected patients were not admitted to an ICU, as it was felt that scarce critical care resources should be targeted elsewhere.

When a critically ill child is brought into the resuscitation room of our department it is usually not known whether the child is HIV infected, nor does it seem appropriate to be counselling for HIV status when the child is acutely ill and in need of emergency care. It is departmental policy to attempt resuscitation for all children who need it and to desist only when all efforts have failed.

Overall, the hospital death rate was nearly twice as high in HIV-seropositive as in seronegative children, but the proportion of these deaths occurring in the first 24 h—approximately 44%—was almost identical in the two groups.

Survival to 24 h was 80% (122/152) and to discharge 56% (85/152) in HIV-seropositive children. In HIV-uninfected children survival to 24 h was 92% (388/424) and to discharge 79% (336/424). We consider the relatively high rate of successful resuscitation in HIV-seropositive children in our setting as an opportunity to place more children on antiretroviral therapy, thus allowing them to resolve infections clinically as their immune status improves preventing the likelihood of severe relapses.

We acknowledge that this study has some limitations. Unfortunately, our attempts to identify HIV infection in seropositive children under 18 months of age were unsuccessful because of technical failures. Facilities were not available for measuring CD4 cell or %CD4/lymphocyte counts in the context of this study. In this audit we have therefore analysed the findings by seropositivity. We will have inevitably included some HIV-uninfected but exposed children in our 'seropositive' group. It is unlikely that this has had a substantial effect on the conclusions.

HIV seropositivity in children over 18 months of age indicates HIV infection, and the results from this group of children do not differ greatly from those of the whole group of children. The HIV antibody test used (Determine HIV1/HIV2; Abbott Laboratories, Tokyo, Japan) is reported to have an almost 100% specificity and sensitivity. It is a near patient test, results becoming available in real time and is in wide use in resource-constrained settings. Both false positives and negatives are very rare.¹¹ There is a higher number of positive cases among the older children, probably because our admissions are skewed towards younger children, with more admissions in children under 2 years of age who present with more straightforward infections (ie, without underlying comorbidities) than in the

older group of children. The clinicians knew the HIV test results during the resuscitation of a child and this may have influenced their management. It could be argued that it may have influenced them positively or negatively and gives the doubt some equipoise.

CONCLUSIONS

Our results show that 80% of seropositive children admitted to the resuscitation room survived at least 24 h, the period most influenced by the process of resuscitation. Although the death rate is approximately double that in HIV-seronegative children, this reflects the overall greater mortality in the seropositive group and does not appear to be attributable to a lower efficacy of resuscitative procedures.

RECOMMENDATIONS

In the chain of survival of the critically ill child, our findings support a policy of aggressive resuscitation, when applicable, for all children with emergency presentations regardless of HIV status.

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Competing interests None.

Ethics approval This study was conducted with the approval of the College of Medicine Research and Ethics Committee.

Contributors SA conceived the study, wrote the ethics committee proposal, provided clinical care of the patients, collected clinical information and wrote the paper. HK provided clinical care of the patients and collected clinical information. JCE provided clinical care of the patients, collected clinical information and followed up all patients who were admitted to discharge or death and contributed to the paper. EMM reviewed the ethics committee proposal, provided clinical care of the patients, collected clinical information and wrote the paper. EMM acts as guarantor.

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