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ARTICLE

Should the routine approach to diarrhoea management be modified in an area of high prevalence of paediatric HIV infection?

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Background. Unthinking application of the routine diarrhoea management protocol in patients presenting with diarrhoea could risk possible co-morbidities such as HIV infection being ignored in an environment with a high prevalence of HIV infection. Furthermore, a patterned response to testing for HIV infection only those children in whom it is suspected on clinical grounds will lead to missed opportunities for HIV care.

Aims and methods. This was a retrospective review of patients admitted to Kalafong and Steve Biko referral hospitals to identify the impact of a high prevalence of HIV infection in the community on the routine management of diarrhoea.

Results. A total of 176 patients were included. HIV tests were performed on 99 patients, and HIV infection was therefore not considered as a co-diagnosis in 78 of 176 (44.3%) of patients with diarrhoea.

On admission, the group of children tested for HIV infection were similar to the other groups (not tested for HIV or HIV negative) in age, but showed differences in respect of duration of diarrhoea and preceding events prior to referral. More children tested for HIV infection also had clinical wasting, generalised lymphadenopathy or hepatomegaly compared with untested children ($p<0.005$). However, there were no differences in the proportion of tested children with prior antibiotics before referral, presence of co-morbid pneumonia or urinary infection.

Patients with diarrhoea were more likely to be tested for HIV if they were severely malnourished or clinically wasted, if they had hyponatraemia or hypokalaemia, and if they had hepatomegaly or lymphadenopathy. The presence of shock or severe dehydration on admission, or of co-morbid pneumonia, did not differentiate between those who were tested for HIV and those who were not.

There were statistically significant differences between those tested for HIV and those not tested in respect of outcome. Among the children tested for HIV, 24.2% of survivors had a prolonged hospital stay (more than 10 days), compared with 1.4% among those not tested ($p<0.005$). While more children in the group tested for HIV died in hospital (6.1% v. 2.6%), this did not reach statistical significance ($p=0.466$).

Conclusion. In this study, HIV testing was found to be predominantly based on clinical grounds at the time of admission. Because of considerable clinical overlap between diarrhoea patients with and without HIV infection, HIV co-infection cannot be reliably predicted on clinical features alone and must be actively excluded.

Effective ART is now available. All patients with diarrhoea must therefore be offered HIV testing to provide earlier access to appropriate management.

Acute infective diarrhoea is one of the commonest diseases of infants and young children. Standard case management guidelines have been developed and supported by the World Health Organization (WHO)[1-3] and have contributed to major improvements in case fatality rates. In South Africa, the National Department of Health has published a guideline for primary care and hospital paediatrics levels in the publication *Standard Treatment Guidelines and Essential Drugs List*.[4]

Essentially the guidelines recommend adequate oral rehydration and appropriate feeding during diarrhoeal illness, while advising against the use of antibiotics, anti-diarrhoeal medication or anti-emetics in the treatment of acute infective diarrhoea.

The HIV epidemic has introduced an additional dilemma into the standard case management of diarrhoea in infants. Vertically acquired HIV infection is essentially a gut infection. In neonates and infants, the virus is acquired through the intestinal tract (e.g. by breastfeeding), except for cases in which infection is acquired transplacentally.

In HIV enteropathy, there is altered cytokine regulation and enterocyte differentiation and function, with crypt cell proliferation and an altered crypt/villous ratio and partial villous atrophy. This is accompanied by loss of mucosal surface area, defects of transcellular absorption, loss of brush border enzymes and deranged active transport systems. These features occur against the background of a very high incidence of acute infective

diarrhoea. This means that children with severe diarrhoea who have co-existing HIV infection have worse indicators of mucosal damage than those without.

It is known that patients with diarrhoea and co-existing HIV infection have more serious disease and a higher incidence of complications. Associated oral thrush, generalised lymphadenopathy, hepatosplenomegaly and respiratory symptoms are very suggestive of HIV infection. There may be acute watery diarrhoea, which can lead to persistent dehydrating diarrhoea or persistent diarrhoea with failure to thrive. The stools may contain frank blood. Combinations of malabsorptive features may be found, including lactose or monosaccharide malabsorption and increased stool fat.

The above is, however, mainly a retrospective view. Patients with severe diarrhoea and malnutrition without HIV infection may also suffer from co-morbidities, and on presentation it may not be clinically apparent which patients with diarrhoea are actually infected with HIV.

A standard 'treatment guideline' patterned response to diarrhoea in an unthinking application of the routine treatment guideline could risk co-morbidities such as HIV infection being ignored. Also, a patterned response to testing only those children for HIV infection in whom it may be suspected on clinical grounds will lead to missed opportunities for HIV care.

Now that access to counselling and treatment for HIV-infected children is improving in South Africa, an intercurrent disease such as gastro-enteritis may be an important opportunity to diagnose HIV. An early diagnosis of previously unsuspected HIV infection is of benefit by allowing early and adequate management.

Aims and methods

A retrospective audit was performed on patients with diarrhoea admitted to the referral hospitals in Pretoria to determine whether there are differences in clinical presentation on admission, associated features, drug treatment, need for hydration therapy, duration of hospital stay and outcome between diarrhoea patients with and without HIV exposure or infection.

A retrospective descriptive folder review of patients with the admission diagnosis 'gastro-enteritis', 'diarrhoea', 'diarrhoeal dehydration' and 'dehydration' over a 1-year period was carried out, with permission from the Institutional Ethics Review Board (protocol 138/2009) and the hospital CEO. We analysed all files of patients with diarrhoea, but recorded only the clinical admission findings, except for the data regarding HIV test results, management and outcome.

HIV infection was confirmed with a positive polymerase chain reaction (PCR) in children under 18 months, or with a positive enzyme-linked immunosorbent assay (ELISA) in those older than 18 months.

The patients were allocated to groups according to the categories: 'HIV tested' and 'HIV not tested'. Further analysis was performed in categories 'HIV diagnosis confirmed', 'HIV not infected' and 'HIV not considered/ HIV unknown'. The data were tabulated and compared statistically with appropriate parametric and non-parametric tests.

Results

A total of 176 patients were included. HIV tests were performed on 99 patients. In 33 patients the infection was confirmed. In 4 patients HIV infection was considered to be likely on the basis of a positive ELISA without PCR confirmation, and 5 patients had a positive ELISA and a negative PCR. Accordingly, 37 patients were considered to be HIV positive (37.4% of those tested, 21% of the study sample), and 62 were considered not to be infected. In 78 patients the HIV status was unknown, including 2 patients with confirmed HIV exposure but who had not been tested. HIV infection was therefore not considered as a co-diagnosis in 78 of 176 (44.3%) of patients with diarrhoea.

The possible incidence of HIV infection among patients admitted to our referral hospitals with diarrhoea therefore ranges from 21.0% to 37.4%.

HIV exposure as a history of maternal positive HIV status during pregnancy or access to the prevention of mother-to-child transmission (PMTCT) programme was recorded in 20% of HIV uninfected patients, but also in 8% of those patients with diarrhoea in whom HIV infection was not considered as a diagnosis.

At presentation, the history did not enable differentiation between HIV-infected and uninfected children. HIV- infected children were similar to the other groups in age (Fig. 1). They had had more prior treatment before referral and had a sickness duration marginally longer than the uninfected children, but the significance of this is uncertain in a referral hospital. Similar numbers of infected and uninfected children had bloodstained stools.

Tables 1 and 2 show the comparison of clinical features in groups tested or not tested for HIV, and according to their HIV status. On admission, children tested for HIV infection were similar to the other groups in age, but showed differences in respect of duration of disease prior to referral ($p<0.05$) and preceding events, and were more malnourished (83% had weight-for-age (WFA) z-scores <-2 v. 49% of untested children, $p<0.005$). Also, more children tested for HIV infection had clinical wasting, generalised lymphadenopathy or hepatomegaly compared with the untested children ($p<0.005$), but there were no differences in the proportions of tested children with prior antibiotics before referral, presence of co-morbid pneumonia or urinary infection. More HIV-infected children had additional co-morbid conditions.

Table 3 shows that patients with diarrhoea were more likely to be tested for HIV if they were severely malnourished with WFA z-scores <-2 (odds ratio (OR) 3.34, 95% confidence interval (CI) 1.78 - 6.3) or clinical marasmus (OR 8.6, 95% CI 2.89 - 25.6), if they had hyponatraemia (OR 5.88, 95% CI 2.15 - 16.07) or hypokalaemia (OR 2.85, 95% CI 1.47 - 5.42), and if they had hepatomegaly (OR 5.06, 95% CI 1.84 - 13.9) or lymphadenopathy (OR 2.82, 95 CI 1.13 - 7). The presence of shock or severe dehydration on admission, or of co-morbid pneumonia, did not differentiate between those who were tested for HIV and those who were not.

There were statistically significant differences in outcome between patients tested for HIV and those not tested. Children tested for HIV had a median hospital stay of 5.5 days (interquartile range (IQR) 3 - 10 days, range 1 - 45) compared with 2 days (IQR 1 - 4 days, range 1 - 11) for those not tested ($p<0.005$). Among the children tested for HIV, 24.2% of survivors had a prolonged hospital stay of more than 10 days, compared with 1.4% of those not tested ($p<0.005$).

While more children in the group tested for HIV died in hospital (6.1% v. 2.6%), this did not reach statistical significance ($p=0.466$).

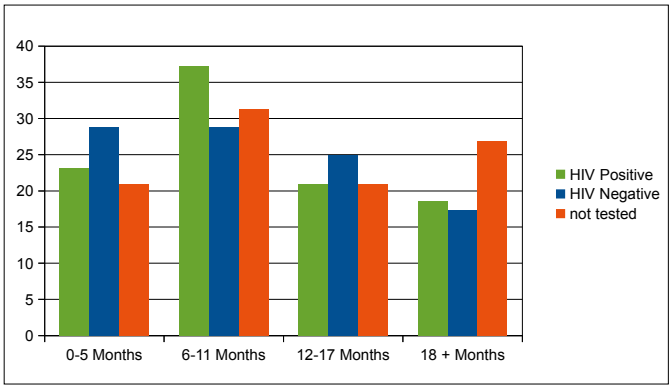

Fig. 1. Age distribution.

TABLE 1. PATIENT CHARACTERISTICS AND OUTCOME

	HIV tested	HIV not tested	*p*-value
Patients	99	76	
Age (mo.), median	9.5	9.5	
Age (mo.), range	1 - 35	1 - 40	0.380***
% aged <6 mo.	26.5	23.7	0.668*
Nutritional state			
WFA z-score <-2 (%)	62.1	32.9	<0.005*
Clinical wasting (%)	20.2	3.9	0.001**
Prior disease			
Duration of disease before admission			
Median (d)	4	3	
25 - 75%	2 - 7	2 - 5	
Range (d)	1 - 30	1 - 7	
Bloodstained stools (%)	28.3	36.8	0.229*
Prior antibiotics before referral (%)	22.2	11.8	0.075*
Status on admission			
Shock (%)	27.8	16.7	0.035*
Moderate dehydration (%)	27.8	47.2	0.035*
Anaemia (%)	28.3	10.5	0.004*
Pneumonia (%)	19.2	13.2	0.287*
Oral thrush (%)	21.2	5.3	0.004**
Lymphadenopathy (%)	77.8	9.2	0.022**
Hepatomegaly (%)	26.3	6.6	<0.005**
Outcome			
Hospital stay (survivors)			
Median (d)	5.5	2	
25 - 75%	3 - 10	1 - 4	
Range (d)	1 - 45	1 - 11	<0.005****
Hospital stay >10 d (survivors) (%)	24.2	1.4	<0.005***
Deaths (%)	6.1	2.6	0.466***

*Pearson's chi-square test.
**Fischer's exact test.
***Mann-Whitney test.

These findings suggest that the admitting doctors' decision to perform HIV testing in children referred for treatment of diarrhoea was based primarily on the clinical features at presentation.

On clinical presentation the HIV-infected children had a greater frequency of anaemia, oral thrush, lymphadenopathy, hepatomegaly and associated pneumonia than the uninfected children, but there was considerable clinical overlap. Even though patients with circulatory or metabolic disturbances such as shock, hyponatraemia or hypokalaemia were more likely to have been tested for HIV, there was no significant difference between HIV-infected and uninfected children in respect of these metabolic parameters on admission.

There were more deaths among HIV-infected than uninfected children (4/37, 10.8% compared with 2/62, 3.2%) or children in whom HIV had not been considered (2/76, 2.6%). HIV-infected survivors had a hospital stay double that of uninfected children, with 46.9% of infected children remaining in hospital for longer than 10 days compared with 11.9% of uninfected children. Of children in whom HIV had not been considered, only 1.4% had a hospital stay longer than 10 days.

TABLE 2. PRIOR ANTIBIOTICS AND STATUS ON ADMISSION OF THOSE TESTED FOR HIV

	HIV +ve	HIV –ve	*p*-value*
No.	37	62	
Prior antibiotics before admission (%)	32.4	16.1	0.059
Clinical status on admission			
Shock (%)	38.9	21.3	0.1753
Moderate dehydration (%)	44.4	57.4	0.1753
Oral thrush (%)	29.7	16.1	0.109
Lymphadenopathy (%)	40.5	11.3	0.00007
Hepatomegaly (%)	45.9	14.5	0.0005
Pneumonia (%)	27	14.5	0.126
Investigations			
Hyponatraemia (Na <130 mmol/l) (%)	32.4	27.4	0.596
Hypernatraemia (Na >145 mmol/l) (%)	16.2	19.7	0.6684
Hypokalaemia (K <3.5 mmol/l) (%)	51.4	46.8	0.653
Acidosis (CO_2 <10 mmol/l) (%)	27	32.3	0.5837
Anion gap >20 mmol/l	30.3	37	0.512
Anaemia (Hb <10 g/dl) (%)	59.5	9.7	<0.005

*Pearson's chi-square test.

Discussion

HIV infection was found as an underlying co-morbidity in 21.0 - 37.4% of patients admitted to our referral hospitals with diarrhoea.

Despite this high prevalence, HIV infection was not considered as a diagnosis in more than 40% of patients admitted with diarrhoea. This tends to confirm that health professionals in our hospitals approach the management of patients with diarrhoea in a patterned response according to the diarrhoea guideline, even when HIV exposure had been documented.

The HIV treatment guideline recommends 'consider HIV in every patient', yet the likelihood of offering an HIV test to children admitted with diarrhoea was predominantly determined by the clinical state. Patients were likely to be tested for HIV if they 'looked like HIV'.

Our findings corroborate the published literature. Diarrhoea is a more severe disease and has a worse outcome in HIV-infected children than uninfected children. This is demonstrated by the fact that they are more malnourished, have more dehydration and shock, and have more co-morbid conditions. Protocol management of HIV-

Patients were likely to be tested for HIV if they 'looked like HIV'.

TABLE 3. DETERMINANTS OF HIV TESTING IN DIARRHOEA CASES

	Of those tested for HIV (%)	Of those not tested for HIV (%)	OR	95% CI	*p*-value
Nutritional state					
WFA z-score <-2	62.1	32.9	3.34	1.78 - 6.3	<0.001
Kwashiorkor /marasmus	32.1	5.3	8.6	2.89 - 25.6	<0.001
Circulation and electrolyte status					
Shock/severe dehydration	27.8	16.7	1.93	0.9 - 4.13	0.091
Hyponatraemia	29.3	6.6	5.88	2.15 - 16.07	<0.001
Hypernatraemia	18.4	6.6	0.78	0.37 - 1.64	0.514
Hypokalaemia	48.5	25	2.85	1.47 - 5.42	0.001
Some physical findings					
Hepatomegaly	26.3	6.6	5.06	1.84 - 13.9	0.002
Lymphadenopathy	22.2	9.2	2.82	1.13 - 7	0.018
Co-morbid conditions					
Pneumonia	19.2	13.2	1.57	0.68 - 3.6	0.283
Urinary tract infection	13.1	10.5	1.28	0.5 - 1.64	0.514

associated diarrhoea must be adapted for this increased risk of severity and complications.

Conclusions

HIV infection cannot be reliably predicted on clinical features alone and must be actively excluded. With effective ART now available, all patients with diarrhoea must be offered HIV diagnosis in order to offer earlier access to appropriate management.

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