Severe illness in African children with diarrhoea: implications for case management strategies

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To identify clinical disorders associated with severe illness in African children with diarrhoea, we studied a group of under-5-year-olds with diarrhoea who had been brought to a large public hospital in central Côte d'Ivoire. The general condition of children with diarrhoea was assessed and classified according to criteria recommended by WHO, and then used as a nonspecific indicator of severity. Of the 264 children with diarrhoea who were enrolled in the study, 196 had nonsevere illness and 68 severe illness. Children with severe illness were significantly more likely than those with nonsevere illness to be dehydrated (45% versus 11%), moderate-to-severely wasted (47% versus 29%), bacteraemic (26% versus 9%), severely anaemic (haemoglobin level <6 g/dl; 15% versus 6%), have Plasmodium falciparum *parasitaemia (27% versus 14%), and have two or more of these five conditions (60% versus 14%). Nontyphoidal* Salmonella *spp. were present in 68% of the blood isolates but were not associated with seropositivity to human immunodeficiency virus (HIV).*

The study demonstrates the need for a more comprehensive approach to assessment and management of children with diarrhoea that ensures prompt recognition of bacteraemia, anaemia, wasting and malaria, as well as dehydration. Simple nonspecific observational criteria, such as those recommended by WHO for assessing and classifying general condition, are useful for identifying children with diarrhoea who are at high risk of having life-threatening clinical disorders, and can readily be used by health workers whose clinical training and access to diagnostic laboratory facilities are both limited.

Introduction

In sub-Saharan Africa, children suffer an average of four-to-five episodes of diarrhoea each year and diarrhoea is a leading cause of morbidity and mortality among under-5-year-olds (*1*).[a] Although most diarrhoeal illnesses are mild and self-limiting, a small proportion of children develop severe conditions, and consequently are at greater risk of dying. Dehydration has been clearly established as an important cause of severe illness in children with diarrhoea and has been the focus of case management efforts. The role of nondehydrating complications and concurrent illnesses, however, is receiving increased attention but has not been well characterized in Africa, where the epidemiological profile of paediatric diseases differs from that in Asia and Latin America.

Limited data from Africa on severe illness in children with diarrhoea are available from retrospective studies of fatal episodes among hospitalized children. In Lesotho, where there is no endemic malaria, fatal outcomes among children with diarrhoea were associated with young age, diagnosis of a major infection, and long duration of illness (*2*). A similar study of Ethiopian children hospitalized with diarrhoea identified young age, fever, recurrent dehydration after initial improvement, and major infection as risk factors for dying (*3*). In both these studies, laboratory tests were not performed systematically and the investigations were limited by their reliance on clinical diagnoses and incomplete information in medical records. Studies of fatal diarrhoeal episodes may also be less clinically relevant than those of nonfatal severe illnesses if many of the children who die in health facilities are past the point of effective medical intervention when they are admitted.

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[a] *Programme for Control of Diarrhoeal Diseases: ninth programme report 1992–1993.* Unpublished document WHO/CDD/94.46, 1994.

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To identify clinical disorders associated with severe illness in children with diarrhoea, we conducted a study of children with diarrhoea at a public hospital in Côte d'Ivoire.

Methods

The study was conducted at the Centre Hôpitalier Régional (CHR) de Bouaké in central Côte d'Ivoire. This hospital has a paediatric outpatient facility that deals with 30–60 children per day and is the only public paediatric inpatient facility in the region. Children aged <5 years who were brought to the hospital between 10 June and 11 August 1991 with diarrhoea, as reported by a carer, were enrolled prospectively in the study. Because of the intensive nature of the diagnostic work-up of study participants, eligibility was limited to all children with diarrhoea who were hospitalized and up to the first four children with diarrhoea who were treated each day as outpatients. The study period coincided with the end of the dry season and continued up to the beginning of the rainy season. A standard form was used to collect relevant information. The results of a standard physical examination were recorded at the time of enrolment and the children's dates of birth and immunizations were obtained from health cards. Diarrhoea was managed according to WHO guidelines, while other illnesses were treated according to routine clinical practice. Patients were re-evaluated at 7-day intervals until the diarrhoea stopped.

Simple nonspecific observational criteria are recommended by WHO for assessing and classifying the general condition of children with diarrhoea and are widely used by health workers in developing countries. The general condition of children with diarrhoea was assessed and classified according to criteria recommended by WHO, and then used as a nonspecific indicator of severity.[b] At enrolment children who were considered to be well and alert by the examining health worker were classified as having nonsevere illness; those considered to be abnormally restless or irritable, lethargic, unconscious, or floppy at the time of enrolment were classified as having severe illness. Data were also analysed using hospitalization as the indicator of severity. Hospitalization, however, was likely to have been biased, since a health worker's decision to hospitalize was based, in part, on how far the patient lived from the health facility as well as the perceived severity of the illness.

To assess the independent association between dehydration and severe illness, we used a more specific clinical definition of dehydration than that recommended by WHO, which did not include assessment and classification of mental status changes (*4*). Well-nourished children and those with mild-to-moderate wasting were considered to be dehydrated if they had decreased skin turgor in the abdominal skin pinch test. Severely wasted children were considered to be dehydrated if they had decreased skin turgor in the abdominal skin pinch test and at least one of the following signs: increased thirst, dry mouth and tongue, or no tears when crying (*4*). The number of standard deviations (z) from the reference National Center for Health Statistics median weight-for-height values was calculated for each child using hydrated body weights. Moderate-to-severe wasting was defined as weight-for-height $<-2z$, and severe wasting as weight-for-height $<-3z$. Fever was defined as a rectal temperature >38.5 °C.

At the time of enrolment, and with the informed consent of each child's carer, stool and blood specimens were collected for analysis and an anterior–posterior chest radiograph was taken. Radiographs and the results of on-site laboratory tests were communicated to the treating physician. A positive radiograph was defined as the presence of a parenchymal density consistent with pneumonia, as interpreted by a paediatric radiologist. A fingerprick blood specimen was examined for the presence of *Plasmodium falciparum* parasites in a Giemsa-stained thick blood film. Blood haemoglobin concentrations were determined spectrophotometrically (HemoCue®, Mission Viejo, CA, USA). Sera were tested for electrolyte levels and screened for IgG antibodies to human immunodeficiency virus, type 1 (HIV-1) and human immunodeficiency virus, type 2 (HIV-2). Western blot, immunoblot, and HIV–IgA assays were used to confirm positive sera and to rule out seropositivity resulting only from the passage of maternal antibodies (*5*). An aseptically collected venous blood specimen was cultured using the Septi-Check® system (Roche Diagnostic Systems, Montclair, NJ, USA) and examined daily for 10 days for signs of bacterial growth. Bacteraemia was defined as isolation of *Shigella* spp., *Salmonella* spp., *Streptococcus pneumoniae*, *Pseudomonas* spp. or *Acinetobacter* spp. from blood. Stool specimens were cultured for *Shigella* spp., *Campylobacter jejuni*, *Salmonella* spp., and *Vibrio cholerae*; enzyme-linked immunosorbent assay (ELISA) was used to identify rotavirus. Blood culture isolates and stool specimens were frozen (–70 °C) in transport media and shipped to Emory University, Atlanta, GA, for culture and identification using standard microbiological procedures (*6*). Isolates were tested for antimicrobial resis-

[b] *Management of the patient with diarrhoea.* Unpublished WHO document, 1992.

tance by the disc-diffusion method using standard interpretive guidelines.[c]

The Mantel–Haenszel χ^2 test corrected for continuity was used to compare characteristics of cases and controls in univariate analyses. Logistic regression techniques (*7, 8*) were used to determine the independent association of clinical disorders associated with severe illness in univariate analyses, controlling for the potential confounding effects of age, sex, and rural residence. The interactions among the variables were also examined. A two-sided *P*-value <0.05 was considered to be statistically significant. Using the method described by Bruzzi et al. (*9*), we estimated attributable risks from the multivariate model.

The study protocol was approved by the Côte d'Ivoire Ministry of Health Sub-Committee on Research and Ethics and the Centers for Disease Control and Prevention Institutional Review Board.

Results

Of the 278 children with diarrhoea who were eligible for inclusion in the study, 264 (95%) were enrolled; 11 were not enrolled due to oversight, two carers denied permission, and one child died on arrival. Using the WHO criteria for assessing and classifying the general condition of children with diarrhoea, 196 (74%) of the children were classified as having nonsevere illnesses (well, alert) and 68 (26%) children were classified as having severe illness (abnormally restless or irritable, lethargic, floppy, or unconscious) at the time of enrolment. Dates of birth and immunizations were available for 252 (95%) patients. Of the 245 (93%) patients for whom follow-up was completed, 231 (94%) survived the diarrhoea episode. Children classified as having severe illness were more likely than those with nonsevere illness to be hospitalized on the day they visited the clinic (72% versus 20%; *P* <0.01) and to die before resolution of the diarrhoea episode (14% versus 3%; *P* <0.01).

The demographic and historical characteristics of patients enrolled in the study are shown in Table 1. In all, 45% of the patients were infants and 59% were male. The median duration of diarrhoea at presentation was 3 days, and 90% of patients had three or more loose or watery stools per day. Two-thirds of the patients had a history of fever; and half had a history of vomiting and cough. A total of 8% of patients had persistent diarrhoea (≥14 days' duration) on enrolment and 15% reportedly had blood in their stools.

Most of the patients came from urban or periurban areas of Bouaké and all but three were breastfed. Of the 177 patients who were aged ≥9 months and who had health cards, 70% had a record of measles immunization. A traditional medicine, usually an infusion of guava leaves, had been given to 31% of the children before arrival at the hospital. A total of 7% of the carers reported having treated the current episode of diarrhoea with a recommended home fluid before coming to the hospital; only 24% of the carers reported ever having used an oral rehydration salt solution. None of these demographic and historical characteristics differed significantly between children with severe and nonsevere illness.

Children with diarrhoea and severe illness were more likely than those with diarrhoea and nonsevere illness to have signs of dehydration (45% versus 11%; *P* <0.01), severe wasting (22% versus 7%; *P* <0.01), anaemia (29% versus 13%; *P* = 0.01) and laboratory evidence of bacteraemia (26% versus 9%, *P* <0.01), and malarial parasitaemia (27% versus 14%; *P* = 0.02) (Table 2). Comparison of blood sodium, potassium and haemoglobin levels confirmed the association between severe illness and dehydration and anaemia. Nontyphoidal *Salmonella* spp. accounted for 23 (68%) of the 34 bacterial pathogens

Table 1: **Distribution of the presenting demographic and historical characteristics of the study children aged <5 years with diarrhoea, by severity of illness** (univariate analysis)

	Severe illness	Nonsevere illness	Odds ratio	*P*-value
No. of patients	68	196	—	—
% <12 months old	39	46	0.8 (0.4–1.3)[a]	0.40
% male	67	57	1.5 (0.9–2.7)	0.20
% with rural residence	15	7	2.5 (1.0–6.0)	0.06
% with diarrhoea for >3 days	50	47	1.1 (0.7–2.0)	0.74
% with fever	66	66	1.0 (0.5–1.8)	0.92
% vomiting	58	57	1.1 (0.6–1.9)	0.91
% with cough	46	43	1.1 (0.6–1.9)	0.86
% breast-fed	100	98	0.6 (0.3–1.1)	0.79
% with measles immunization	61	73	0.6 (0.3–1.2)	0.21
% treated with a home fluid	10	6	1.8 (0.7–4.7)	0.38
% of carers who ever used ORS	20	25	0.8 (0.4–1.5)	0.53

[a] Figures in parentheses are the 95% confidence interval.

[c] *Performance standards for antimicrobial disk susceptibility tests, 4th edit: Approved Standard.* Villanova, National Committee for Clinical Laboratory Standards, document M2-A4, 1990.

isolated from blood and were sensitive to chloramphenicol, sulfamethoxazole + trimethoprim, and quinolone agents. Of the 23 children with nontyphoidal *Salmonella* bacteraemia, 19 (83%) were at least 6 months of age and none were HIV-seropositive. The commonest *Salmonella* serotypes isolated from blood were *S. enteritidis* and *S. typhimurium*. The following pathogens were also isolated from blood: *S. pneumoniae* ($n = 3$), *P. aeruginosa* ($n = 2$), *P. stutzeri* ($n = 1$), *A. lwoffi* ($n = 3$), and *Shigella* spp. ($n = 2$).

A total of 16 (6%) of the children were seropositive for HIV-1 or HIV-2; 13 were seropositive for HIV-1, two for HIV-2, and one child was seropositive for HIV-1 and HIV-2. A total of 14% of the patients had chest radiographs that had appearances consistent with pneumonia. Rotavirus ($n = 41$) was the commonest pathogen identified in stool specimens, followed by *C. jejeuni* ($n = 22$), *Shigella* spp. ($n = 21$) and *Salmonella* spp ($n = 10$). *S. typhi*, *V. cholerae* and *S. dysenteriae* type 1 were not isolated from blood or stool specimens of any of the patients. In all, 18% of the patients had a measured fever (>38.5 °C) at enrolment. There were no significant differences between children with severe and nonsevere illness in terms of the frequency of fever, HIV seropositivity, pneumonia, or identification of any or of a specific enteric pathogen.

Children with malarial parasitaemia and bacteraemia present with similar relatively nonspecific clinical symptoms and signs. To determine whether there were any simple characteristics that could be used to discriminate between patients with these disorders, we compared the frequency of historical and clinical characteristics for the 40 patients with malarial parasitaemia with those of the 29 patients with bacteraemia; the five patients with malarial parasitaemia and bacteraemia were excluded from this analysis. The only characteristic that differed significantly was dehydration. Children with diarrhoea and bacteraemia were three times more likely to be dehydrated than those with diarrhoea and malaria parasitaemia (39% versus 13%; $P = 0.02$).

The distribution of the total number of clinical disorders (dehydration, moderate–severe wasting, bacteraemia, malarial parasitaemia, and severe anaemia) identified in each child is shown in Fig. 1. The majority of children with diarrhoea and severe illness had at least two different clinical disorders. Children with diarrhoea and severe illness were four times more likely than those with diarrhoea and nonsevere illness to have two or more concurrent disorders (60% versus 14%; $P < 0.01$).

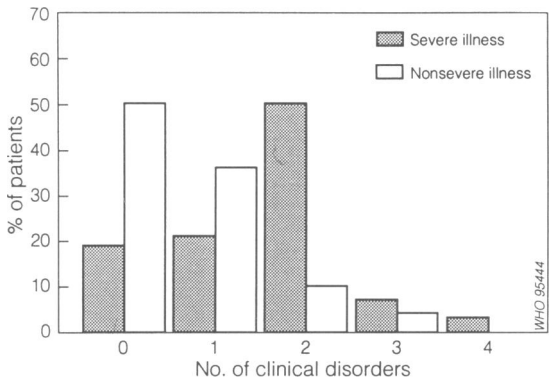
To estimate the independent association of the five clinical disorders associated with severe illness in the univariate analyses, while controlling for the potentially confounding effects of age, sex and rural residence, we used multivariate techniques. In a multivariate model with severe illness as the dependent variable, dehydration, low weight-for-height, malarial parasitaemia and bacteraemia were independently and significantly associated with severe illness; severe anaemia was not (Table 3). Interaction terms, including all two-way interactions of the explanatory variables with age, sex and residence, were not statistically significant and did not improve the fit of the model. The findings were similar when hospitalization was used as the criterion for severe illness. Children hospitalized on the day of enrolment were significantly more likely to have signs of de-

Table 2: **Distribution of presenting clinical and laboratory characteristics of the study children aged <5 years with diarrhoea, by severity of illness** (univariate analysis)

	Severe illness	Nonsevere illness	Odds ratio	*P*-value
No. of patients	68	196	—	—
% dehydrated	45	11	6.4 (3.3–12.3)[a]	<0.01
% with weight-for-height <–2 *z*	47	29	2.2 (1.2–3.9)	0.01
% with weight-for-height <–3 *z*	22	7	3.6 (1.6–8.0)	<0.01
% with conjunctival pallor	29	13	2.8 (1.4–5.5)	0.01
% with haemoglobin level <6 g/dl	15	6	2.7 (1.1–6.5)	0.05
% with serum sodium level <135 mmol/l	49	18	4.4 (2.4–8.1)	<0.01
% with serum potassium level <3.6 mmol/l	31	20	1.8 (1.0–3.4)	0.09
% with bacteraemia	26	9	3.6 (1.7–7.6)	<0.01
% with *Salmonella* bacteraemia	17	6	3.1 (1.3–7.3)	0.02
% with malarial parasitaemia	27	14	2.3 (1.2–4.5)	0.02
% HIV-seropositive	6	6	1.0 (0.3–3.2)	0.79

[a] Figures in parentheses are the 95% confidence interval.

Fig. 1. **Frequency distributions of the number of different clinical disorders per patient, by severity of illness among under-5-year-olds with diarrhoea, Bouaké, Côte d'Ivoire.**



hydration, low weight-for-height, and laboratory evidence of bacteraemia and anaemia.

To estimate the practical importance of the statistical findings, we calculated the attributable risk for each clinical disorder associated with severe illness from the multivariate model (Table 3). The attributable risk (etiological fraction) is the proportion of severe illness attributable to each clinical disorder and takes into account the strength of the association and the prevalence of the disorder; for example, the estimated attributable risk of 37% found for dehydration in the study indicates that if dehydration could have been eliminated in the study population without affecting the other clinical disorders, 37% of the severe illnesses could have been prevented. This estimate is only approximate since the association between the individual clinical disorders and severe illness may be complicated by the presence of unmeasured confounding factors, and most interventions will affect more than one clinical disorder; none the less, it is a reasonable summary of the relative clinical importance of the various disorders.

Table 3: **Multivariate analysis of clinical disorders associated with severe illness among the study children aged <5 years with diarrhoea**

Clinical disorder	Odds ratio	*P*-value	% attributable risk
Dehydration	5.4	<0.01	37
Low weight-for-height *z*-score	1.5	0.02	32
Malarial parasitaemia	3.2	<0.01	19
Bacteraemia	2.9	0.02	17

Conclusions

Among our patient population, dehydration was the clinical disorder most strongly associated with severe illness and also had the largest attributable risk; in addition, however, several other common life-threatening disorders were associated with severe illness including bacteraemia, malarial parasitaemia, wasting, and anaemia. The majority of children with severe illness had two or more concurrent disorders and were much more likely to have multiple disorders than were children with nonsevere illness. These findings suggest that children at risk of becoming severely ill with diarrhoea may, to a large extent, be the same children who are at risk of becoming severely ill with any of the diseases that are common causes of childhood mortality in Africa. The study demonstrates the need for a more comprehensive approach to the assessment and management of children with diarrhoea in Africa and provides support for the recent initiative by WHO and UNICEF[d] to develop an integrated approach to management of sick children that combines case-management algorithms for the commonest causes of severe illness in childhood.

A surprisingly high proportion of children with severe illness in the study were bacteraemic, with nontyphoidal *Salmonella* spp. accounting for two-thirds of the blood isolates. The high proportion of children with nontyphoidal *Salmonella* bacteraemia did not arise because a large percentage of the study patients were very young infants or were infected with HIV, both of which are risk factors for acquiring extra-intestinal nontyphoidal *Salmonella* infections (*10, 11*).

Nontyphoidal *Salmonella* spp. may be a common and underrecognized invasive complication of paediatric gastroenteritis of particular importance in sub-Saharan Africa that merits further attention. For example, in Rwanda, nontyphoidal *Salmonella* spp. were isolated from 4% of blood cultures from febrile children seen at an outpatient clinic (*12*). In comparison, nontyphoidal *Salmonella* spp. were only isolated from 0.4% of blood cultures from children hospitalized for diarrhoea and suspected sepsis in Bangladesh (*13*). A review of 915 blood-culture isolates at a hospital laboratory in Ibadan, Nigeria, found that 50% were *Salmonella* spp.; of these, over 70% were reportedly nontyphoidal *Salmonella* spp. (*14*).

Children with severe illness in our study were as likely to have bacteraemia as malarial parasitaemia.

[d] *The WHO/UNICEF approach to integrated management of the sick child: update—November 1994.* Unpublished WHO document, 1994.

Clinical signs of dehydration were commoner among patients with bacteraemia than among those with malarial parasitaemia. The results of the present study are consistent with those of Lepage et al., who observed that febrile children with bacteraemia were significantly more likely than febrile children with malarial parasitaemia to have diarrhoea and signs of dehydration (*12*). Clinical signs of dehydration may be useful for differentiating between patients with these illnesses in settings when confirmatory laboratory tests are unavailable.

The protective effect of breast-feeding against severe diarrhoeal morbidity and mortality has been well documented (*15*). We did not observe an association between breast-feeding and severe illness, but were limited in our ability to do so by the almost universal prevalence of breast-feeding in our study population. The association between persistent diarrhoea and diarrhoea-associated mortality has been most convincingly demonstrated in community-based studies (*16*). In contrast, we did not find an association between persistent diarrhoea and severe illness among our study population. Either persistent diarrhoea may not be an important problem in the catchment area of the study hospital or our findings may reflect differences in health-care-seeking behaviours by the carers of children with diarrhoea during different phases of the disease episode. Children who develop persistent diarrhoea and severe illnesses may be brought to a health facility during the acute stages and not when the episode becomes persistent. *S. dysenteriae* type 1 and *V. cholerae* were not isolated from any of the patients in the study. In areas where infections with these organisms are highly endemic or epidemic, dysentery and dehydration may be more important causes of severe illness than among our study population.

We found that simple loosely defined criteria for assessing and classifying the severity of a diarrhoeal illness identified children at high risk of having potentially life-threatening clinical disorders. When inexperienced health workers in Kenya were asked to classify sick infants as having severe or mild illness based on the presence or absence of several simple clinical signs and symptoms, the health workers' impression that the infant "appeared ill" had the highest sensitivity (90%) and specificity (89%) compared with an independent classification by an experienced paediatrician (*17*). Simple nonspecific observational criteria, such as those recommended by WHO for assessing and classifying the general condition of children with diarrhoea, are useful indicators of severity that can be readily used by health workers whose clinical training and access to diagnostic laboratory facilities are both limited.

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Résumé

Maladie grave chez les enfants africains atteints de diarrhée: répercussions sur les études de prise en charge des cas

La diarrhée est une cause majeure de morbidité et de mortalité chez les enfants de moins de 5 ans en Afrique subsaharienne. La plupart des cas sont bénins et guérissent spontanément, mais une petite proportion d'enfants font une maladie grave qui augmente le risque de décès. Afin d'identifier les manifestations cliniques qui accompagnent les cas graves de diarrhée chez l'enfant en Afrique, nous avons réalisé une étude sur des enfants admis pour diarrhée dans un hôpital public de Côte d'Ivoire centrale.

Les enfants de moins de 5 ans conduits à l'hôpital entre le 10 juin et le 11 août 1991 pour diarrhée ont été inclus prospectivement dans l'étude. Les critères recommandés par l'OMS pour l'évaluation et la classification de l'état général des enfants atteints de diarrhée ont été utilisés comme indicateurs non spécifiques de gravité.

Sur les 278 enfants inclus dans l'étude, 68 (26%) ont été classés comme ayant une maladie grave et 196 (74%) comme ayant une maladie sans gravité. Sur les 245 malades (93%) suivis jusqu'à la fin de l'étude, 231 (94%) ont survécu à l'épisode diarrhéique. Les enfants gravement malades avaient une probabilité significativement plus grande que les autres d'être hospitalisés le jour même de leur visite au dispensaire (72% contre 20%) et de mourir avant la fin de l'épisode diarrhéique (14% contre 3%). Les deux tiers des cas avaient des antécédents de fièvre et la moitié, des antécédents de vomissements et de toux.

Chez les enfants gravements malades, le risque de présenter des signes de déshydratation était plus élevé que chez les enfants non gravement atteints (45% contre 11%; p <0,01) de même que l'amaigrissement sévère (22% contre 7%; p <0,01), l'anémie (29% contre 13%; p=0,01), une bactériémie mise en évidence au laboratoire (26% contre 9%; p <0,01), et une parasitémie à *Plasmodium* (27% contre 14%; p=0,02). On n'a en revanche observé aucune différence significative en ce qui concerne la fréquence de la fièvre, de la séropositivité vis-à-vis du virus de l'immunodéficience humaine (VIH), de la pneumonie ou de l'identification d'un agent entérique pathogène à l'examen coprologique. Chez les enfants gravement malades, la probabilité d'avoir deux ou plusieurs maladies concomitantes était 4 fois plus élevée que chez les enfants ayant une maladie classée comme sans gravité (60% contre 14%; p <0,01).

Outre la déshydratation, la maladie grave était associée à plusieurs autres affections potentiellement graves, dues dans la plupart des cas à une maladie concomitante non diarrhéique. Nos observations démontrent la nécessité d'une approche plus globale de l'évaluation et de la prise en charge des enfants diarrhéiques, assurant une reconnaissance rapide de la bactériémie, de l'anémie, de l'amaigrissement sévère et du paludisme, ainsi que de la déshydratation. Des critères d'observation simples et non spécifiques sont utiles pour identifier, parmi les enfants diarrhéiques, ceux chez qui le risque d'affections cliniques engageant le pronostic vital est le plus élevé, et peuvent être facilement appliqués par des agents de santé ayant une formation clinique rudimentaire et un accès limité à des moyens de diagnostic de laboratoire.

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