

Is it Possible to Predict which Diarrhoea Episodes Will Lead to Life-Threatening Dehydration?

CESAR G VICTORA*, BETTY R KIRKWOOD†, SANDRA C FUCHS*, CINTIA LOMBARDI* AND FERNANDO C BARROS*

Victora CG (Departamento de Medicina Social, Universidade Federal de Pelotas, CP 464, 96001 Pelotas, RS, Brazil), Kirkwood BR, Fuchs SC, Lombardi C and Barros FC. Is it possible to predict which diarrhoea episodes will lead to life-threatening dehydration? *International Journal of Epidemiology* 1990, **19**: 736–742.

Early detection of children who are likely to develop life-threatening dehydration as a consequence of diarrhoea would be of great value for health care workers in developing countries. We carried out a case-control study to compare the symptoms and signs observed on the first day of diarrhoea in two groups of 192 children aged under two years, in the Brazilian city of Porto Alegre. The cases were children admitted to a hospital with moderate or severe dehydration, and controls were children from the same neighbourhoods as the cases, who had diarrhoea which did not lead to hospital admission. The sensitivity and specificity of different clinical indicators were calculated. Alterations in thirst (82%), followed by six or more stools (71%), fever (60%), vomiting (58%) and loss of appetite (57%) had the highest sensitivities, whereas the specificities were largest for blood in the stools (97%), fever (78%) and vomiting (78%). Assuming that dehydration occurs in 5% of all episodes of diarrhoea, the use of fever as a screening criterion, or the use of vomiting, would select 24% of all children with diarrhoea, and capture about 60% of all episodes of dehydration. The combination of fever or vomiting would increase the proportion selected to 36%, and capture 75% of episodes of dehydration.

Diarrhoeal diseases are one of the leading causes of childhood morbidity and mortality in developing countries.¹⁻³ They are responsible for approximately one-third of the 15 million deaths that occur each year among children aged less than five years. An average child is estimated to experience 3.3 episodes of diarrhoea a year, although in some areas the rate may be as high as ten.⁴ Although the majority of episodes are self-limited, a small proportion quickly lead to dehydration and death.^{2,3,5} Many such deaths could be averted with appropriate oral rehydration therapy (ORT).

In many developing countries scarce resources make it neither feasible to treat all episodes of diarrhoea at health facilities nor to administer oral rehydration solution (ORS) in all cases. The World Health Organization therefore recommends that use of ORS should be restricted to the treatment of children who have already developed dehydration. The recommended procedure for mild episodes of diarrhoea is an increase

of appropriate home-based fluids, such as teas and rice water, together with continued feeding.⁶

The ability to identify, early on, episodes at highest risk of leading to dehydration is therefore important for several reasons. Knowledge of early warning signs would be useful to target health education messages to mothers of at-risk children, encouraging them to seek early treatment. In addition it would enable health workers to recognize potentially severe cases, treat them appropriately and keep them under closer surveillance, for example, by requesting that the child should return to the clinic the next day.

One approach to studying this issue would be to identify a large number of children at the onset of a diarrhoea episode and to follow them closely throughout their illness. Those episodes in which severe dehydration occurred would then be compared with those episodes where severe dehydration did not develop, with respect to the signs and symptoms present at the onset of the illness. This approach has at least two serious drawbacks. Firstly, the outcome of interest, severe dehydration, cannot ethically be measured, since it would be necessary both to give general advice to the

* Departamento de Medicina Social, Universidade Federal de Pelotas, CP 464, 96001 Pelotas, RS, Brazil.

† Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK.

mother about the management of the episode and to intervene at the first sign of dehydration. Secondly, the study size would have to be exceedingly large, since severe dehydration only occurs in a small proportion of episodes. For example, Black *et al*⁷ observed severe dehydration in only 2.2% of an average of 9.8 episodes of diarrhoea experienced during the first year of life by infants in an underprivileged peri-urban community of Lima, Peru.

In order to overcome these difficulties, we opted for a case-control design. The cases were children admitted to a hospital with moderate or severe dehydration as a consequence of diarrhoea. Controls were children from the same neighbourhood as the cases. They had also had diarrhoea in the previous week but this was not severe enough to require admission to a hospital. By comparing these two groups of children with respect to the frequencies of symptoms and signs reported as present on the first day of their episodes, it is possible to identify indicators associated with a higher risk of dehydration.

The design used is an extension of the standard case-control methodology since both cases and controls have diarrhoea, the case-control status being defined according to the severity rather than the presence or absence of disease.⁸ Data were also collected regarding a wide range of other prognostic factors: these results will be presented at a later stage. This is the first report from three similar studies supported by the World Health Organization in Brazil, Bangladesh and Egypt.

SUBJECTS AND METHODS

The study was carried out in the metropolitan area of Porto Alegre in Southern Brazil during the main diarrhoea season (December 1987 to April 1988). Cases were recruited from the two largest paediatric hospitals in the city, which serve the low-income sector of the population. They were children admitted with diarrhoea of less than eight days duration, accompanied by moderate or severe dehydration, defined as a persistent skinfold plus at least one of the following signs: sunken fontanelle, dry mouth and tongue, sunken eyes, reduced urinary output, weak pulse, sleepy or irritable condition.⁸ Selection was restricted to those aged 0–23 months, the most vulnerable age-group both for morbidity and mortality.¹ All 184 children satisfying these conditions were included. Sixteen other children were included who had not been examined for skin turgor, either because they were too ill or because they arrived during the weekends or at night, but who experienced a weight gain greater than 5% after rehydration.

One neighbourhood control was selected for each

case. This was the child living nearest to the case's home, within the same broad age range (0–11 or 12–23 months) as the case, who had had a diarrhoea episode starting in the seven days preceding the interview.

Data were collected from the children's mothers or caretakers regarding the symptoms and signs presented by the children in the first 24 hours of the diarrhoea episode, as well as in the preceding 24 hours. These included the number and appearance of the stools, vomiting, thirst, fever and loss of appetite.

Cases and controls were compared using logistic regression for matched studies.⁹ Odds ratios for the occurrence of dehydration associated with the presence of each sign (and with combinations of signs) were calculated. The significance of the associations were assessed by the likelihood ratio test.

The sensitivity and specificity of each sign (and of combinations of signs) in predicting episodes of diarrhoea likely to lead to dehydration are presented. The sensitivity measures the proportion of dehydrating episodes that would be correctly predicted, while the specificity measures the proportion of mild episodes that would be correctly identified as such. One minus the specificity therefore indicates the proportion of mild episodes that would be unnecessarily identified as at risk. The best cut-off points for the number of stools and of vomiting episodes were selected using receiver operator characteristic (ROC) curves which show the sensitivity and specificity achieved with different cut-off values.¹⁰ Also presented are the proportions of all episodes that would be identified as at risk, calculated by the following formula:

$$\text{Proportion Selected} = \text{Incidence} \times \text{Sensitivity} + (1 - \text{Incidence}) \times (1 - \text{Specificity})$$

In this calculation, the incidence of moderate or severe dehydration among all children with diarrhoea was assumed to equal 5%. The results were very similar for other choices of incidence between 0% and 15%.

RESULTS

A total of 200 cases were selected, of whom eight (4%) could not be studied because their parents were not available for interview. One neighbourhood control was selected for each of the remaining 192 cases. On seven occasions (4%), it was not possible to interview the first control identified: these were replaced by the next nearest neighbour satisfying the criteria.

Comparison of Cases and Controls

Table 1 shows the distribution of cases and controls according to signs and symptoms observed in the first 24 hours of the episode, together with the corresponding odds ratios. Cases differed significantly from con-

TABLE 1 Reported signs and symptoms in the first 24 hours of a diarrhoea episode, and their relationship to the occurrence of dehydration. Comparison of cases with neighbourhood controls.

Reported sign/symptom	Cases (No. = 192)	Controls (No. = 192)	Odds ratio (95% CI)
Number of stools**			
3-4	38	59	1.0
5-7	51	61	1.5 (0.8-2.6)
8-10	47	40	1.9 (1.0-3.5)
>10	52	30	2.7 (1.4-5.0)
Colour of stools NS			
Yellow	92	104	1.0
Green	84	66	1.4 (0.9-2.1)
Other	12	20	0.6 (0.3-1.4)
Consistency of stools*			
Loose	77	99	1.0
Formed	11	12	1.2 (0.4-3.1)
Liquid	100	77	1.7 (1.1-2.6)
Blood in the stools (NS)			
No	176	184	1.0
Yes	11	5	2.8 (0.9-8.6)
Mucus in the stools (NS)			
No	127	133	1.0
Yes	60	56	1.2 (0.7-1.8)
Number of vomiting episodes**			
None	77	148	1.0
1 to 7 times	33	20	3.2 (1.5-6.8)
8 to 14 times	39	19	3.3 (1.7-6.5)
15 or + times	34	3	21.8 (5.1-93.6)
Vomiting duration (hours)**			
No vomiting	77	148	1.0
<1 hr	17	10	2.7 (1.1-6.6)
1 to 7 hr	29	11	3.5 (1.7-7.4)
8 to 14 hr	21	12	2.7 (1.2-6.1)
15 or + hr	28	8	5.1 (2.2-12.2)
Fever**			
No	75	148	1.0
Yes	112	41	5.7 (3.3-9.8)
Thirst**			
Normal	34	90	1.0
Reduced	21	14	4.1 (1.7-9.8)
Increased	132	86	4.7 (2.7-8.3)
Appetite**			
Normal	80	122	1.0
Reduced	107	68	2.5 (1.6-4.0)

NS Non-significant

* $P < 0.05$

** $P < 0.001$

Note: Mothers were occasionally unable to report whether or not a sign/symptom was present in the first 24 hours; the numbers in the Table do not therefore always sum to 192.

controls regarding most signs and symptoms. The number of stools and their consistency were both associated with the prognosis of the diarrhoea episode. The presence of blood indicated a three-fold increase in the risk of dehydration, although this was not quite significant

($P = 0.07$). On the other hand, the associations with the colour of stools and with the presence of mucus were not significant.

The number of vomiting episodes was considerably greater among cases than controls. Overall, cases were almost five times as likely to have vomited as controls, and almost 22 times as likely to have vomited eight times or more during the first 24 hours. A mother's perception of either an increase or a decrease in the child's thirst was associated with a four- to five-fold increase in the risk of dehydration, and the reported presence of fever with almost a six-fold increase. The loss of appetite was associated with a less marked, but still significant, increased risk, being 2.5 times more common among cases than controls. These analyses were repeated after excluding the 16 cases who had not been assessed for skin turgor and their matched controls, but the odds ratios remained virtually unchanged.

Sensitivity and Specificity

The sensitivity and specificity of each sign and symptom are shown in Table 2. The appropriate cut-off points for the two continuous variables, the number of stools and the number of vomiting episodes, were chosen using the ROC curves shown in Figure 1. Vomiting is clearly a better indicator of dehydration than the frequency of stools, being superior in terms of both sensitivity and specificity. Figure 1 also shows that the cut-off point for vomiting episodes that best discriminates cases from controls is 0-1. The choice is not so clear for the frequency of stools. Two cut-off values were used for analyses, 5-6 favouring sensitivity at the

TABLE 2 Sensitivity and specificity of reported signs and symptoms during the first 24 hours of a diarrhoea episode as prognostic factors for the development of dehydration.

Indicator	Sensitivity	Specificity
Single sign/symptom:		
Abnormal thirst	82%	47%
6+ stools	71%	45%
Fever	60%	78%
Vomiting	58%	78%
Reduced appetite	57%	64%
Watery stools	53%	59%
9+ stools	48%	71%
Green stools	45%	65%
Mucus in stools	32%	70%
Blood in stools	6%	97%
Combination of signs/symptoms:		
Thirst or fever or vomiting	90%	38%
Thirst or fever	89%	44%
Thirst or vomiting	89%	40%
3+ signs	85%	57%
Fever or vomiting	75%	66%

* Either increased or reduced thirst.

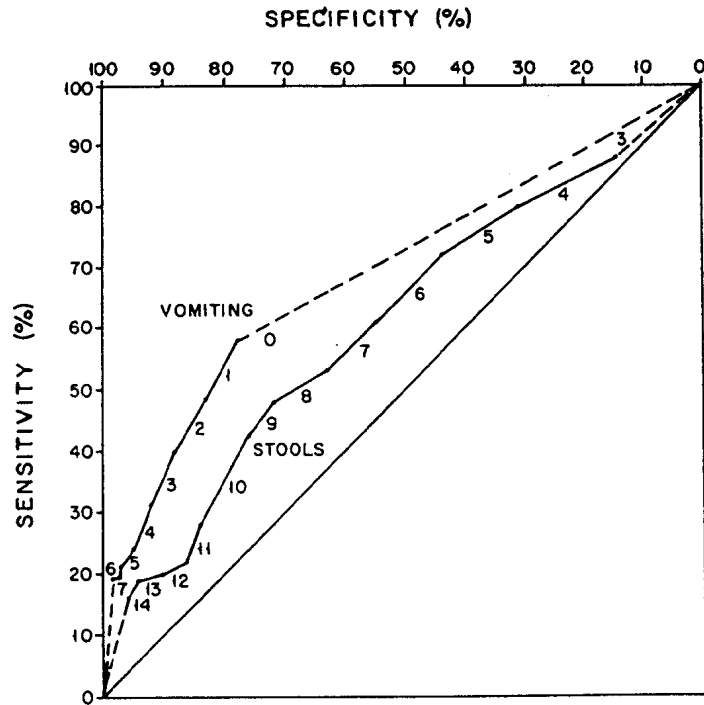


FIGURE 1 Receiver operator characteristic (ROC) curves showing the sensitivity and specificity of different cut-off values for the number of vomiting episodes and the frequency of stools in the first 24 hours of a diarrhoea episode, as predictors for the occurrence of severe dehydration.

expense of specificity, and 8–9 favouring specificity at the expense of sensitivity.

Table 2 shows that alterations in thirst (either a reported increase or decrease, compared to normal thirst) had the highest sensitivity at 82%, followed by six or more stools at 71%. However, both these signs have relatively low specificities, 47% and 45% respectively. Thus although abnormal thirst alone would be capable of predicting 82% of episodes truly at risk of developing dehydration, it would also incorrectly identify 53% of mild episodes as at risk. The next best indicators in terms of sensitivity were fever, vomiting, lack of appetite and the presence of watery stools, with values ranging between 60% and 53%. These indicators had specificities of 59% or more.

Overall, the best indicator in terms of specificity was blood in the stools with a value of 97%, but its sensitivity was extremely poor (6%). Furthermore, although the high specificity means that only a small proportion of mild episodes would be wrongly identified as at risk, this is not accompanied by a high predictive value, as the incidence of severe dehydration is low. For example, if the incidence were 5%, the positive predictive value would be 10%, meaning that only one-tenth of children with bloody diarrhoea would be at

risk of dehydration. Blood in stools, therefore, offers no advantage as an indicator for prediction. The next best indicators in terms of specificity were fever, vomiting and nine or more stools, with values ranging from 78% to 71%. Of these, fever and vomiting were more sensitive than nine or more stools, 60% and 58% respectively compared to 48%.

The sensitivity and specificity of combinations of signs and symptoms were also tested. Serial combinations, such as vomiting *and* fever, tended to increase specificity at the cost of sensitivity, while the reverse was true for parallel combinations, such as vomiting *or* fever. No serial combination achieved a sensitivity greater than 50%. Attention was therefore focused on parallel combinations. The five which yielded the highest sensitivities, and were improvements over the separate constituent indicators, are listed in the bottom half of Table 2. The best combinations of two signs were thirst or fever and thirst or vomiting, both with specificities of 89%, but both with specificities below 50%. Combining all three, thirst or fever or vomiting, gave a negligible increase in sensitivity, and an even lower specificity. On the other hand, the presence of *any* three signs achieved an equally high sensitivity (85%), and a much improved specificity (57%). The

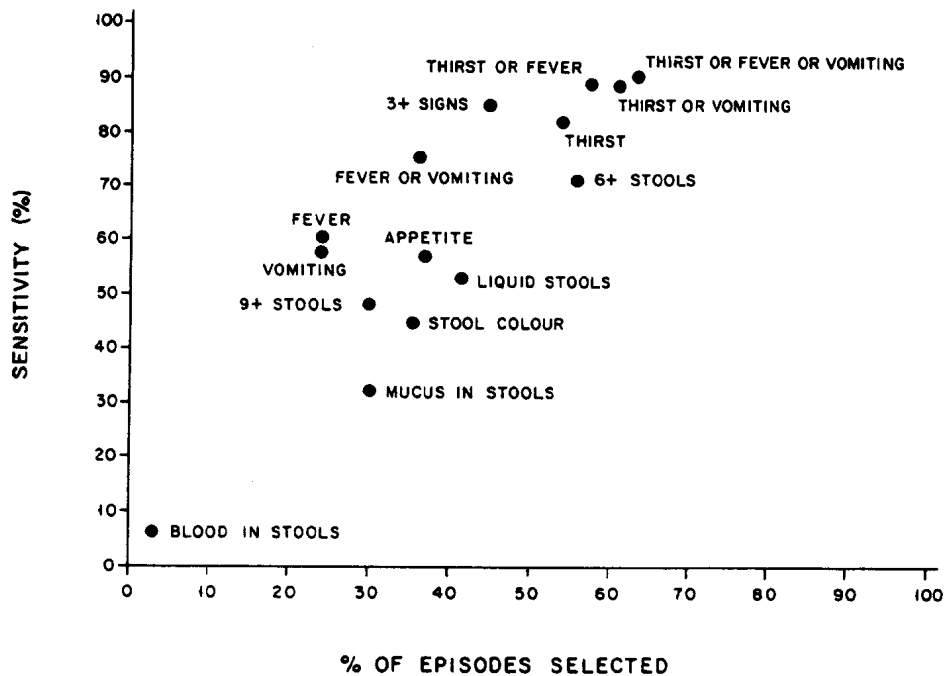


FIGURE 2. Sensitivity of different indicators of dehydration plotted against the percentage of all episodes of diarrhoea that would have to receive special care if the indicator were used for screening (assuming a 5% incidence of dehydration).

highest specificity (66%) was achieved by the fifth combination, fever or vomiting, but this had a somewhat lower sensitivity (75%).

Proportion of Episodes Selected as At Risk

In order to be useful, a prognostic factor for dehydration needs to be present in a large proportion of episodes which ultimately lead to dehydration, and yet identify only a relatively small subgroup of all episodes of diarrhoea as potentially at risk, and therefore requiring close surveillance. The ability of the various indicators to do this is assessed in Figure 2, where the sensitivity of each indicator is plotted against the proportion of episodes that it would select as at risk, assuming that the incidence of dehydration is 5%. It shows that although thirst alone or in combination would identify over 80% of the dehydrating episodes, more than half of all children with diarrhoea would have to receive special care to achieve this effect. The same is true for the combination of any three signs. On the other hand, the combination of fever or vomiting has a sensitivity of 75%, but would require special care in only about one-third of all episodes of childhood diarrhoea. The corresponding sensitivity and proportion selected for the presence of fever (with or without vomiting) are 60% and 24%, and for vomiting (with or without fever) 58% and 24%.

DISCUSSION

We have used the case-control approach to investigate whether it is possible to discriminate early in a diarrhoea episode between episodes which are self-limited and those which are likely to lead to moderate or severe dehydration. In a recent case-control study of infant mortality,¹¹ it was found that approximately 90% of the children who died from diarrhoea had been admitted to a hospital (Victoria C., unpublished findings). It is therefore likely that the cases in the present study account for a large proportion of the children with dehydration from the catchment areas of the two hospitals. Also, as community-based studies have shown that the incidence of moderate to severe dehydration among children with diarrhoea is very low, well under 5%⁷ (World Health Organization, Diarrhoeal Diseases Control Programme, unpublished data), it is unlikely that many of the neighbourhood controls were either dehydrated at interview or developed dehydration at a later stage in the episode.

The results may have been affected by misclassification, since the data collected on signs and symptoms during the first day of the episode depended on information provided by the mothers. For example, although 153 mothers reported that the child had fever, only 84 actually measured the child's temperature. Relative to children without fever, the odds ratio for

children with measured fever was 6.8, whereas it was 4.2 for those with reported fever which was not measured. This suggests that misclassification was present but it resulted in lower estimates of the relative risk and thus underestimation of sensitivity and specificity.¹² It must also be stressed that our results are intended for use in practical situations in which misclassification is also likely to be present.

A more important source of concern is the possibility of differential misclassification, or recall bias. The median recall times were similar for cases and controls, being five and four days respectively. However, mothers of cases may have exaggerated their child's early symptoms as they were obviously aware, at the time of the interview, that their child had severe diarrhoea. Although this possibility cannot be ruled out, much emphasis was placed during the interviews on collecting data on signs and symptoms in the first 24 hours of the illness, and that these should not be confused with the following days. In addition, comparison between cases and a second control group of children taken to the hospital with diarrhoea, but who were not admitted, showed similar results. Finally, the wide range of sensitivities and specificities associated with the different indicators also lessens the likelihood of recall bias.

Cases were on average younger than controls, but this should not affect the present findings, as one is concerned with markers of severe disease. Even if age is a confounding variable—being associated with certain symptoms and also with severity—this should not affect the predictive value of these symptoms.

Our results have shown that it is possible to identify, on the first day of a diarrhoea episode, signs and symptoms which indicate an increased likelihood of dehydration developing. Just 1% of the cases were admitted during the first 24 hours of the episode, and 66% were admitted on the third day or later. The single indicator with the greatest sensitivity was an alteration in thirst (either an increase or a reduction). This finding may be explained in terms of increased thirst being a sign of moderate dehydration, and reduced thirst a sign or consequence of severe dehydration. The next indicators in terms of sensitivity, which also make clinical sense, were six or more stools, presence of fever (judged by the mother), vomiting and a reduction in appetite. It is interesting to note that variables relating to other characteristics of the stools (consistency, colour and presence of mucus or blood) all had lower sensitivities than the indicators mentioned above.

Oral rehydration therapy is the best choice for the prevention of dehydration as a consequence of diarrhoea, and for the treatment of mild and moderate

forms of dehydration.^{2,3,6} Since ORT is safe, inexpensive and effective, the risk of having false negatives is greater than the risk of false positives. In other words, one should be more concerned with sensitivity than with specificity. On the other hand, diarrhoea is very common, and the selection of too large a proportion of episodes as at risk would place intolerable demands on the scarce resources of many developing countries. We have used an index based on the sensitivity and specificity which shows the proportion of children with diarrhoea that an indicator would select as at high risk. This analysis showed that if selection was based on the presence of fever, vomiting, or both, approximately one-third of episodes of childhood diarrhoea would be identified as at high risk; these episodes would include 75% of those which would lead to dehydration. Other indicators with greater sensitivity, such as thirst, could be used, but the penalty would be the identification of the majority of episodes as being of high risk. Further studies are needed to verify whether the same prognostic factors apply to other parts of the world, where the aetiology and clinical presentation of diarrhoea may vary considerably.

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