Predictors of Hemolytic Uremic Syndrome in Children During a Large Outbreak of *Escherichia coli* O157:H7 Infections

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ABSTRACT. *Objective.* **To evaluate risk factors for progression of *Escherichia coli* O157:H7 infection to the hemolytic uremic syndrome (HUS).**

Study Design. **We conducted a retrospective cohort study among 278 Washington State children <16 years old who developed symptomatic culture-confirmed *E coli* O157:H7 infection during a large 1993 outbreak. The purpose of the study was to determine the relative risk (RR) of developing HUS according to demographic characteristics, symptoms, laboratory test results, and medication use in the first 3 days of illness.**

Results. **Thirty-seven (14%) children developed HUS. In univariate analysis, no associations were observed between HUS risk and any demographic characteristic, the presence of bloody diarrhea or of fever, or medication use. In multivariate analysis, HUS risk was associated with, in the first 3 days of illness, use of antimotility agents (odds ratio [OR] = 2.9; 95% confidence interval [CI] 1.2–7.5) and, among children <5.5 years old, vomiting (OR = 4.2; 95% CI 1.4–12.7). Among the 128 children tested, those whose white blood cell (WBC) count was 13 000/μL in the first 3 days of illness had a 7-fold increased risk of developing HUS (RR 7.2; 95% CI 2.8–18.5). Thirteen (38%) of the 34 patients with a WBC count 13 000/μL developed HUS, but only 5 (5%) of the 94 children whose initial WBC count was <13 000/μL progressed to HUS. Among children who did not develop HUS, use of antimotility agents in the first 3 days of illness was associated with longer duration of bloody diarrhea.**

Conclusions. **Prospective studies are needed to further evaluate measures to prevent the progression of *E coli* O157:H7 infection to HUS and to assess further clinical and laboratory risk factors. These data argue against the use of antimotility agents in acute childhood diarrhea. Our finding that no intervention decreased HUS risk underscores the importance of preventing *E coli* O157:H7 infections.** *Pediatrics* **1997;100(1). URL: http://www.pediatrics.org/cgi/content/full/100/1/e12;** ***antibiotics, antimotility agents, Escherichia coli O157:H7, kidney failure, leukocytosis.***

ABBREVIATIONS. HUS, hemolytic uremic syndrome; BUN, blood urea nitrogen; RR, relative risk; CI, confidence interval; TMP/SMZ, trimethoprim/sulfamethoxazole; OR, odds ratio; WBC, white blood cell; Stx, Shiga toxin.

Escherichia coli O157:H7 causes bloody and nonbloody diarrhea that progresses to hemolytic uremic syndrome (HUS) in a subset of patients.[1,2] Though the gastrointestinal manifestations of infection with *E coli* O157:H7 can be severe, HUS accounts for the major acute and chronic morbidity and mortality caused by this organism.

Associations between certain host-specific factors and the risk of progression of enteric infection with *E coli* O157:H7 to HUS have been reported. In population-based studies of HUS, age-specific incidence was highest among children <5 years of age, but these studies did not evaluate risk factors for progression of diarrhea or hemorrhagic colitis to HUS.[3–6] In some studies of children with *E coli* O157:H7 infection, girls were more likely than boys to develop HUS.[7,8] Patients who are infected with *E coli* O157:H7 and at the time of presentation to medical care have elevated white blood cell counts, fever, or bloody stools also have been noted to have a higher risk of progression to HUS than patients without these findings.[9–12]

Considerable interest has been focused on the effect of antimicrobial agents on the risk of patients with *E coli* O157:H7 infections developing HUS. In one prospective, randomized controlled trial, antimicrobial agents administered to 47 children late in the course of infection failed to demonstrate any effect.[13]

In 1993, a large outbreak of *E coli* O157:H7 infections resulted from the consumption of inadequately cooked hamburgers in restaurants of Chain A in Washington State, resulting in more than 500 cases.[14] Using interviews and medical-record review, we conducted a study among the cohort of children who sought medical attention during the outbreak to evaluate possible risk factors for progression of *E coli* O157:H7 infection to HUS.

METHODS

Inclusion Criteria

Patients were eligible for inclusion in the study if they had either symptomatic, culture-confirmed *E coli* O157:H7 infection or

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Received for publication Jul 15, 1996; accepted Mar 4, 1997.

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HUS beginning in January or February 1993, were <16 years of age, and resided in Washington State. They were considered to have primary cases of infection if illness began within 10 days of eating at a Chain A restaurant. Patients who became ill within 10 days of close contact with a case-patient and who had not eaten at Chain A during that time were considered to have secondary cases.

Data Collection

Data were collected from three sources. First, county health department staff, using a standard questionnaire, interviewed by telephone a parent of each patient within 2 weeks of illness onset and collected demographic data, the dates of illness onset and signs and symptoms of the illness, and the date of eating and food consumed at Chain A. Second, interviewers contacted patients' parents again by telephone 2 to 4 months later. Using a different standard questionnaire, they verified information obtained by the county health department and recorded more detailed information on patients' signs and symptoms, medication use, physician visits and hospitalization. Third, a study coordinator or one of the authors (B.P.B. or P.L.), using a standard data collection form, abstracted recorded signs and symptoms, medications, and test results from medical records.

Case Definition and Variables Examined

We used the onset dates of illness and signs and symptoms first reported by the parent. Diarrhea and vomiting were determined to be present if the family or patient reported these signs. Bloody diarrhea was defined as visible blood in the stool, also by parental report. Fever was defined as any temperature ≥38.5°C at any site. When the parent offered different dates at the time of the second interview, we compared the dates collected from the three sources and used those on which two sources agreed. When considering prescription medication use, we included only those patients where parental report and the medical record agreed on whether the medication was taken. We used the date the medication was started and the number of days taken as reported by the parent for both prescription and nonprescription medication.

Treatment was defined as at least 2 doses of therapy begun within 3 days of first symptoms. Antimotility agents included dicyclomine, diphenoxylate, Donnatal (phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine [A.H. Robins, Richmond, VA]), hyoscyamine sulfate, loperamide, and opioid narcotics. Adsorptive agents were considered to be attapulgite or kaolinpectin. Continuous variables were also considered as categorical variables by dividing at the median or quartile values.

Complete HUS was defined as a platelet count <150 000/μL, hematocrit <30% with evidence of intravascular hemolysis on peripheral blood smear, and blood urea nitrogen (BUN) >20 mg/dL. Incomplete HUS was defined as two of these criteria. Complete and incomplete HUS were combined to form the outcome measure, termed HUS in this study. For children who subsequently developed HUS, only signs and symptoms occurring, and laboratory tests obtained, before HUS developed were included.

Microbiology

Stool samples were submitted to local laboratories, and tested for the presence of *E coli* O157:H7 by inoculation onto sorbitol-MacConkey agar. Serotyping, confirmation, and toxin typing of *E coli* O157:H7 recovered were performed as previously reported.[14]

Statistics

The χ^2 test, Fisher's exact test, Student's t test, and Pearson correlation coefficients were used to examine relationships among independent variables and HUS. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using standard methods or the exact method of Martin and Austin where appropriate.[15,16] Normality was assessed using the Shapiro-Wilk statistic, and for data that were not normally distributed, the Wilcoxon 2-sample and Kruskal-Wallis tests were used. In stratified analyses, possible differences in associations among strata were examined using Cochran-Mantel-Haenzel statistics and the Breslow-Day test. Logistic regression modelling was conducted using SAS (SAS Institute, Inc, Cary, NC) software.[17] Variables associated with the outcome in the univariate analysis at $P \leq .1$ and possible confounding variables were included in the initial model. The most parsimonious model was developed by evaluating the effects of covariates using the −2 Log Likelihood criteria.

RESULTS

Study Population

The study population consisted of 278 (86%) of the 324 children eligible for participation. Of the 46 children who did not participate, the parents of 10 (22%) refused to be interviewed, 25 (54%) refused medical record review, 8 (17%) could not be located, and 3 (7%) had either no medical record or had not visited a physician. The median age of study subjects was 6 years (range 0 to 15); 145 (52%) were female; 245 (88%) were white. Two hundred eighteen (78%) acquired their infection by eating a hamburger at Chain A and 30 (11%) had cases of secondary infection. The source of infection could not be determined in 30 (11%). Ninety-two (33%) patients were hospitalized.

Outcomes Identified

There were 33 children (12%) with complete HUS and 4 (2%) with incomplete HUS. These 4 patients had anemia (median hematocrit 27%; range 23–29) and thrombocytopenia (median 42 000/μL; range 29 000 to 122 000), but no azotemia; 3 had proteinuria or hematuria. The median interval between onset of the first symptom to hospitalization for HUS was 6 days (range 1 to 12).

Demographic Risk Factors Analyzed

We found no association between the risk of HUS and age, sex, or annual household income (Table 1). Although 2 of the 3 fatalities (all from complications of HUS) occurred in children who had secondary cases of infection, patients with secondary cases were no more likely to develop HUS (3/30; 10%) than were patients with primary cases (30/218; 14%). A similar proportion of patients with mental retardation or developmental delay developed HUS (1/8; 13%) as patients without these conditions (36/169; 21%).

TABLE 1. Risk of HUS by Selected Demographic Characteristics

Factor	Proportion of Patients With Factor Who Developed HUS	Rate Ratio (95% CI)	*P* Value
	Number/Total (%)		
Age (y)			
<3	12/76 (16)	2.1 (0.8–5.7)	.13
3–4	9/63 (14)	1.9 (0.7–5.4)	.21
5–8	11/72 (15)	2.1 (0.8–5.6)	.15
>8	5/67 (7)	Referent	
Sex			
Female	23/145 (16)	1.5 (0.8–2.8)	.19
Male	14/133 (11)	Referent	
Annual family income			
<$30 000	12/93 (13)	Referent	
$30 000–$50 000	11/81 (14)	1.0 (0.5–2.3)	.91
>$50 000	10/81 (12)	1.0 (0.4–2.1)	.90

Clinical Risk Factors Analyzed

We initially examined clinical characteristics present at any time before HUS developed. Children whose parents reported vomiting had 3 times the risk of developing HUS (29/153 [19%]) compared with children who did not (8/125 [6%]; RR = 3.0; 95% CI 1.4–6.2). HUS developed in a larger proportion of children with bloody diarrhea compared with children who had diarrhea without blood, and in a larger proportion of children with fever, but the differences were not statistically significant: 34/243 (14%) with bloody diarrhea developed HUS vs 2/28 (7%) without bloody diarrhea (RR = 2.0; 95% CI .5–7.7); 11/56 (20%) with fever developed HUS vs. 20/169 (12%) without fever (RR = 1.8; 95% CI .8–4.1).

To investigate early predictors of HUS, we evaluated the risk of HUS by clinical characteristics measured within the first 3 days of illness (Table 2). Vomiting during this interval was again significantly associated with HUS, conferring nearly twice the risk. This association was modified by age. Among children <5.5 years old, vomiting in the first 3 days of illness was strongly associated with HUS risk (RR = 3.5; 95% CI 1.4–9.4). In contrast, no association was observed between vomiting in the first 3 days of illness and HUS risk among children ≥5.5 years old (RR = 1.0; 95% CI .4–2.4).

Medication Risk Factors Analyzed

Fifty (18.0%) children received an antimicrobial agent, and 34 (12.5%) received an antimotility agent during the first 3 days of illness. No association was observed between treatment with any of these agents and age, sex, or hospitalization. Children treated with antimicrobial agents were more likely to live in households that had annual household incomes of more than $29 000 per year (RR = 1.7; 95% CI 1.0–2.8).

Thirty-one (62%) of the 50 children who received antimicrobial agents were treated with trimethoprim/sulfamethoxazole (TMP/SMZ), 13 (26%) received ampicillin or amoxicillin, 6 (12%) received a cephalosporin, and 4 (8%) received metronidazole. Tetracycline, erythromycin, ciprofloxacin, and gentamicin each were given to 1 child. Eleven children received more than 1 antimicrobial agent. There was no association between treatment with any antimicrobial agent or with TMP/SMZ, and HUS risk (Table 3).

In univariate analysis, children treated with antimotility agents had twice the risk of developing HUS, but this finding failed to reach statistical significance (Table 3). There was no association between receiving antimotility agents and the risk of developing HUS when these analyses were restricted to children <5.5 years old. No patients treated with adsorbents alone developed HUS.

Mulitivariate Modeling

In multivariate modeling, children who were treated with antimotility agents were more likely to develop HUS than were children who did not receive them (odds ratio [OR] = 2.9; 95% CI 1.2–7.5). The relationship between vomiting during the first 3 days of illness and HUS risk identified in the univariate analysis was also observed in the multivariate model, but the adjusted OR for the risk of HUS among children younger than 5.5 years with vomiting was larger (OR = 4.2; 95% CI 1.4–12.7). There was no association between vomiting and HUS risk among children at least 5.5 years old (OR = 1.0; 95% CI .4–3.0).

Laboratory Risk Factors Analyzed

Among the 128 children who had a laboratory test in the first 3 days of illness, patients with a total white blood (WBC) cell count >10 500/μL were at a 5-fold increased risk of HUS (Table 2); this association was not modified by age. The risk increased to 7-fold among children with a WBC count ≥13 000/μL, the upper quartile in this population. No other laboratory test result on specimens obtained during the first 3 days of illness was associated with the subsequent development of HUS.

TABLE 2. Risk of HUS by Selected Clinical Characteristics Beginning ≤3 Days After Diarrheal Illness Onset and by Laboratory Values Among Children Tested Within 3 Days of Diarrheal Illness Onset

Factor	Proportion of Patients With Factor Who Developed HUS	Proportion of Patients Without Factor Who Developed HUS	Rate Ratio (95% CI)	*P* Value
	Number/Total (%)	Number/Total (%)		
Vomiting	22/127 (17)	13/140 (9)	1.9 (1.0–3.5)	.05
Bloody diarrhea	29/213 (14)	7/59 (12)	1.1 (0.5–2.5)	.73
Fever	11/56 (20)	20/169 (12)	1.8 (0.8–4.1)	.14
Hematocrit				
>39%	10/70 (14)	8/58 (14)	1.0 (0.4–2.5)	.94
Platelets				
>310 000/μL	10/59 (17)	8/67 (12)	1.4 (0.6–3.6)	.42
BUN				
>9 mg/dL	7/64 (11)	8/49 (16)	0.7 (0.3–1.7)	.40
WBC count				
>10 500/μL	15/63 (24)	3/65 (5)	5.2 (1.6–17.0)	<.01
≥13 000/μL	13/34 (38)	5/94 (5)	7.2 (2.8–18.5)	<.01
Segmented neutrophils				
>69%	9/56 (16)	7/53 (13)	1.2 (0.5–3.0)	.67
Any band forms	11/57 (19)	5/52 (10)	2.0 (0.7–5.4)	.15

TABLE 3. Risk of HUS by Medications Begun Within 3 Days of Diarrheal Illness Onset

Factor	Proportion of Patients With Factor Who Developed HUS	Proportion of Patients Without Factor Who Developed HUS	Rate Ratio (95% CI)	*P* Value
	Number/Total (%)	Number/Total (%)		
Any antimicrobial agent	8/50 (16)	28/218 (13)	1.3 (0.6–2.6)	.56
TMP/SMZ*	6/31 (19)	30/234 (13)	1.5 (0.7–3.3)	.32
Antimotility agent†	8/34 (24)	28/238 (12)	2.0 (1.0–4.0)	.10
Adsorbent and/or antimotility agent‡	8/43 (19)	28/229 (12)	1.5 (0.7–3.1)	.26

* Trimethoprim/sulfamethoxazole.
† Includes dicyclomine, diphenoxylate, Donnatal, hyoscyamine sulfate, loperamide, or narcotic.
‡ Attapulgite, kaolin-pectin.

Less Severe Outcomes

Among children who did not develop HUS, we examined possible relationships between more common, but less severe, outcomes and treatment with antimicrobial or antimotility agents in the first 3 days of illness. We found no statistically significant associations between the number of days of diarrhea or of bloody diarrhea and antimicrobial agent use (Table 4). There was no difference in the median duration of diarrhea among children treated with antimotility agents compared with those who did not receive them, but the median duration of bloody diarrhea was longer (4 vs 3 days, respectively, $P < .05$) (Table 4).

DISCUSSION

We demonstrate that an elevated total WBC count early in the course of *E coli* O157:H7 infection is strongly associated with the development of HUS. Vomiting, the only sign associated with HUS risk, was not previously noted to be a factor for progression of *E coli* O157:H7 infection to HUS[8,9,11,18,19]. Vomiting may indicate severe gastrointestinal injury, higher intestinal concentrations of Shiga toxin (Stx), host susceptibility, or systemic toxemia with central nervous system effects.[20] We were unable to demonstrate an association between developmental delay and risk of progression to HUS, as has been previously noted.[21]

Reduced power may have contributed to our failure to associate bloody diarrhea or fever with HUS risk, because almost all children studied had bloody diarrhea, and parental recall might have caused imprecise reporting of fever. Also, we found no relationship between age, female sex, or higher socioeconomic status and HUS risk among infected patients. However, these risk factors for HUS might reflect differential exposure to *E coli* O157:H7 or ascertainment of HUS patients rather than increased risk of HUS among clinically infected patients. Because there were few nonwhite children in this study population, the relationship of race/ethnicity and HUS risk could not be assessed.

Our study had limited power to associate antimotility agents and HUS risk because few patients received these agents. Nonetheless, on multivariate analysis, there was a statistically significantly increased risk of progression of *E coli* O157:H7 infection to HUS among children who took agents that slowed peristalsis. Among children who did not develop HUS, antimotility agent use was associated with longer duration of bloody diarrhea. On the basis of these data, and in consideration of similar data from British Columbia,[8,19] we advise against administering agents that slow peristalsis to children with bloody diarrhea or *E coli* O157:H7 infection. In addition, because nonbloody diarrhea precedes bloody diarrhea in most *E coli* O157:H7 infections,[22] the absence of visible blood in stools does not indicate that a patient is not infected with *E coli* O157:H7 or another Stx-producing organism. In view of the lack of any demonstrated therapeutic benefit from these agents, we advise against administering agents that slow peristalsis to any child with acute diarrhea.

Antibiotics might injure or lyse intracolonic *E coli* O157:H7, liberating more Stx for systemic absorption,[23,24] or eliminate competitive colonic flora. Conversely, antibiotic-induced clearance of *E coli* O157:H7 might decrease the risk of progression to HUS. However, we demonstrate no benefit of antibiotics in *E coli* O157:H7 infection. In two *E coli* O157:H7 outbreaks, antimicrobials, particularly TMP/SMZ, increased the risk of HUS or of death,[9,11] a trend, albeit not statistically significant, also noted in Washington State in 1987.[22] Prolonged antimicrobial therapy was associated with reduced risk of HUS among patients in a case series from British Columbia, Canada, but the timing of administration with respect to illness onset was not reported,[8] and this outcome may reflect a bias toward continuation of antibiotics in children who were not destined to

TABLE 4. Duration of Diarrhea and Bloody Diarrhea by Medications Begun Within the First 3 Days of Illness Among Patients Who Did Not Develop HUS

Factor	Diarrhea		Bloody Diarrhea	
	No. of Days of Symptom, Median (Mean)	*P* Value	No. of Days of Symptom, Median (Mean)	*P* Value
Antimicrobial Agent				
Yes	6.0 (6.9)		4.5 (4.5)	
No	6.5 (7.7)	.2	4.0 (4.6)	.6
Antimotility Agent*				
Yes	7.0 (8.3)		5.0 (5.2)	
No	6.0 (7.5)	.3	4.0 (4.5)	.04
Adsorbent† and/or Antimotility Agent				
Yes	7.0 (8.3)		5.0 (4.8)	
No	6.0 (7.5)	.2	4.0 (4.6)	.3

* Dicyclomine, diphenoxylate, Donnatal, hyoscyamine sulfate, loperamide, or narcotic.
† Attapulgite, kaolin-pectin.

develop HUS. In an expanded case series, antimicrobial use and HUS risk were not associated.[20] In two prospective randomized, controlled studies, antimicrobial agents had no effect on the risk of HUS, but the sample sizes were small,[9] and therapy was commenced late.[13]

Our study has several strengths. By interviewing parents and reviewing medical records, we verified that prescribed antimicrobial agents were actually given, and, like Akashi et al,[12] we focused on the early stage of illness. By assessing the effect of early antimicrobial therapy, we may have reduced the possible confounding inherent in retrospective studies: antimicrobial agents may appear to have a deleterious effect because physicians prescribed them for sicker children (ie, those "destined" to develop HUS) as their illnesses became more severe. Furthermore, medication administered or continued[8] late in the course, once the pathophysiologic processes resulting in HUS have either begun or been avoided, might not affect illness outcome.

This is the largest study of its kind to date, and has additional strengths that improve the ability to generalize our findings. Because of the publicity surrounding this community-wide outbreak, a diverse group of children with a broad spectrum of disease severity may have been brought to medical attention. Only culture-confirmed cases of *E coli* O157:H7 infection were included and in almost all cases infection was caused by the same strain,[25] reducing bias from the inclusion of infections caused by *E coli* O157:H7 strains with varying virulence traits.[26]

This study has several limitations. Parental recall of the child's symptoms and of medications used, and completeness and accuracy of medical records, may have varied with the severity of the child's illness. Such differential reporting would bias toward an association between the factor and the risk of HUS. Second, the data in this retrospective study may have been imprecise. The information contained in the medical record was not collected in a standardized manner, and recall was requested for an event several weeks or months before the interview. Such nondifferential inaccuracies would reduce power and decrease the likelihood of finding an association. Third, power to detect an effect of antimicrobial agents on HUS risk would have been greater if a larger proportion of children had been treated; however, the study had sufficient power to detect a difference in risk of approximately 2.5-fold or greater. Finally, the results may not apply to disease caused by *E coli* O157:H7 that produces Stx 2 but not Stx 1. However, most *E coli* O157:H7 strains, like the outbreak strain, produce both Stx 1 and Stx 2.[26]

Our results may help clinicians. Only 5 of the 94 children with *E coli* O157:H7 infection tested in the first 3 days of illness who had a WBC count $<13\,000/\mu$L subsequently developed HUS (negative predictive value of 95%). This finding should be confirmed in other populations, but a low WBC count early in the course of *E coli* O157:H7 infection in children may indicate low HUS risk. Obtaining a WBC count early in the course of illness is possible; 49 (86%) of the 57 children who sought medical attention before the outbreak was publicized presented within 3 days of illness onset. A high WBC count was a moderately sensitive predictor of the likelihood to progression to HUS in our study; 13 (38%) of 34 children with a WBC count $\geq 13\,000/\mu$L in the first 3 days of illness subsequently developed HUS compared with 18 (14%) of the total of 128 children tested. However, because a normal WBC count does not absolutely indicate a benign course, all patients should be followed closely until diarrhea is resolved for several days to confirm that urine output remains adequate and mental status is normal.

These data may help plan trials to evaluate interventions to prevent HUS following *E coli* O157:H7 infection. Most infected patients recover spontaneously within approximately 1 week. If patients with a higher likelihood of developing HUS could be identified at presentation, this group could be studied in prospective, randomized, controlled trials to assess the role of antimicrobial agents, toxin binders, antitoxins, or other modalities to prevent HUS. Using the criteria of a WBC count $\geq 13\,000/\mu$L in the first 3 days of illness, we would have identified 13 (72%) of the 18 patients who developed HUS among the 128 patients in whom the laboratory test was obtained. Twenty-one (16%) patients meeting this criterion failed to develop HUS.

No intervention decreased the risk of developing HUS. Factors that reflect the host's early response to infection (vomiting and leukocytosis in the first three days of illness) predicted the subsequent development of HUS. These findings suggest that the pathophysiologic processes resulting in HUS often are initiated by the time medical attention is initially sought. These findings underscore the importance of preventing *E coli* O157:H7 infection as the most effective way to prevent HUS.

ACKNOWLEDGMENTS

This research was supported by grants from the Children's Hospital Foundation (Seattle) and the American College of Gastroenterology.

We wish to thank Charla deBolt, RN, Marcia Goldoft, MD, MPH, Gail Hansen, DVM, Steven Hooker, MD, MPH, Kathy Carroll, RN, Carole Winegar, RN, Cynthia Miron, RN, Annette Fitzpatrick for assistance in the collection of the data, and the medical record staffs, attending physicians, and family members of patients for supplying clinical information used in this investigation.

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DOI: 10.1542/peds.100.1.e12

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