Enteroaggregative *Escherichia coli* Is a Cause of Acute Diarrheal Illness: A Meta-Analysis

David B. Huang, 1 James P. Nataro, 6 Herbert L. DuPont, 1,2,4 Paresh P. Kamat, 3 Ashwini D. Mhatre, 3 Pablo C. Okhuysen, 1,2,3 and Tom Chiang 5

1Division of Infectious Diseases, Baylor College of Medicine, 2Health Science Center, Division of Infectious Diseases, and 3School of Public Health, University of Texas at Houston, and 4St. Luke’s Episcopal Hospital, Houston, Texas; 5Department of Medicine, New Jersey Veterans Affairs Medical Center, East Orange, New Jersey; and 6University of Maryland School of Medicine, Baltimore, Maryland

**Background.** Conflicting studies exist regarding the role of enteroaggregative *Escherichia coli* (EAEC) as a cause of acute diarrheal illness. The objective of this meta-analysis was to determine whether identification of EAEC in stool samples is associated with acute diarrheal illness among different subpopulations, by geographic area.

**Methods.** A comprehensive search of electronic bibliographic databases (Medline and PubMed) from August 1985 to January 2006, as well as a search of conference proceedings, references of articles, and contacts with investigators of EAEC, yielded 354 studies.

**Results.** Forty-one studies (12%) that met the selection criteria (i.e., that examined the association between acute diarrheal illness and the excretion of EAEC among different subpopulations) were included. In this meta-analysis, presence of EAEC identified with the HEp-2 cell adherence assay was found to be significantly associated with acute diarrheal illness among children residing in developing regions (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.36–1.83) and industrialized regions (OR, 1.23; 95% CI, 1.03–1.48), adults with human immunodeficiency virus infection residing in developing regions (OR, 6.43; 95% CI, 2.91–14.16), adults residing in developing regions (OR, 7.15; 95% CI, 1.96–26.04), and international travelers to developing regions (OR, 6.72; 95% CI, 2.62–17.20). A limited number of studies were available that examined the role of EAEC identified by its virulence genes by a DNA probe.

**Conclusions.** On the basis of this meta-analysis, we conclude that EAEC is a cause of acute diarrheal illness among many different subpopulations in both developing and industrialized regions, that EAEC strains are very heterogeneous and that additional studies that examine the role of EAEC in acute diarrheal illness are needed.

Enteroaggregative *Escherichia coli* (EAEC) was first described in 1987 as *E. coli* that adhered to HEp-2 cells in culture in a characteristic, stacked-brick aggregative phenotype. Within the first few years after its description, this pathotype became associated with diarrheal illness in Chile, India, and Mexico. However, several subsequent epidemiologic studies did not find an association between EAEC and diarrheal illness, and at present, some authors continue to question the identity of EAEC as a true diarrheal pathogen [1]. Various studies over the years have addressed several possible clinical roles for EAEC. EAEC has been implicated as a cause of acute diarrhea illness among children, adults, and persons with HIV infection in both developing and industrialized countries [2–4]. The pathogenicity of at least some EAEC strains has been proven definitively in both outbreaks [5, 6] and volunteer studies [7]; nevertheless, it remains unclear whether virulent strains can be identified epidemiologically. A large number of laboratory studies have sought to implicate specific virulence factors in EAEC pathogenesis. Such studies could provide a molecular signature for truly virulent EAEC isolates [8]. We conducted a meta-analysis of all available and qualifying studies that have been conducted from the first description of EAEC in the literature, in 1985, to January 2006 to provide a systematic review of EAEC as a potential human pathogen and the clinical settings in which this pathogen plays a role.
METHODS

Study identification. Studies evaluating the clinical outcome of EAEC infection were identified with a literature search using PubMed and Medline between 1985 (the year of the first publication concerning EAEC) and January 2006. The key words employed were “enteroaggregative Escherichia coli,” “enteroadherent Escherichia coli,” “enteric pathogens,” and “diarrhea.” Reference lists of relevant publications were reviewed to identify additional studies. Abstracts from international meetings (e.g., the Interscience Conference on Antimicrobial Agents and Chemotherapy and Infectious Diseases Society of America Annual Meeting) were searched to identify relevant studies that were unpublished.

Definition of EAEC. The gold standard for the identification of EAEC is the HEp-2 cell adherence assay [9]. EAEC strains are defined as E. coli strains that do not secrete heat-labile or heat-stable toxins and that adhere to HEp-2 cells in an aggregative, adherent pattern characterized as stacked brick [9]. Historically, these bacteria have also been called enteroadherent E. coli.

Study selection and quality. Studies evaluating the clinical outcomes of EAEC infection were reviewed for the following criteria: (1) inclusion of human subjects, (2) report on a series of patients with documented EAEC infection (both symptomatic patients [case patients] and asymptomatic patients [control subjects]), (3) bacteriological confirmation of EAEC by the HEp-2 cell adherence assay or by the EAEC DNA probe, (4) the provision of clear definitions of acute diarrhea, (5) exclusion of subjects who received an antibacterial drug with activity against EAEC (e.g., fluoroquinolones, macrolides, azalides, or trimethoprim-sulfamethoxazole) or who received antimicrobial medication (e.g., loperamide, bismuth subsalicylate, or kapectate) within the week before stool examination, and (6) an adequate assessment of the relationship between clinical outcomes and EAEC infection.

Data extraction and definition of terms. The primary outcome of interest was acute diarrheal illness, defined as ≥2 unformed stools in a 24-h period. This definition was used to define diarrheal illness in an effort to include all relevant EAEC studies in this meta-analysis. The secondary outcome of interest was the distribution of virulence genes of EAEC isolates among persons excreting EAEC. EAEC infections were stratified by subpopulation, geographic area of study, diagnostic method (HEp-2 cell adherence assay and the EAEC DNA probe), and the presence of putative virulence genes. The population of each study was defined as one of the following: children residing in developing regions, children residing in industrialized regions (defined as the United States, Australia, and European countries), adults with HIV infection residing in developing regions, adults with HIV infection residing in industrialized regions, adults residing in industrialized regions, adults residing in developing regions, and international visitors (or travelers) to developing regions. The primary and secondary outcomes from each study were abstracted using a standardized data extraction spreadsheet.

Statistical analysis. The meta-analysis was processed using Microsoft Excel, version 2002 (Microsoft) and Stata statistical software, version 8.2 (Stata). The number of patients with diarrhea from whom EAEC was isolated and who were symptomatic (case patients) was compared with the number of patients from whom EAEC was isolated and who were asymptomatic (control subjects). This relationship was expressed as an OR with a 95% CI. Data on the presence of acute diarrhea, virulence genes, and EAEC in stool samples of persons were abstracted as dichotomous variables. An OR >1 indicated an association of acute diarrheal illness with EAEC infection. ORs were calculated both for individual studies and as a pooled OR by subpopulation and geographic area of study using the Mantel-Haenszel fixed-effects model [10]. Testing for heterogeneity was performed with the Breslow-Day method [11].

RESULTS

Figure 1 shows the selection process for study inclusion in the meta-analysis. From a total of 354 published articles concerning EAEC, 42 case-control studies (12%) met the inclusion criteria. Twenty-nine (69%) of the 42 EAEC studies were conducted in developing countries. The articles that were excluded from this meta-analysis consisted of reviews, commentaries, studies on pathogenesis or treatment, and studies that lacked a control group. Appendix 1 and 2 (included in the online version of this article in the electronic edition of Clinical Infectious Diseases) provide a descriptive summary of each included study, by method of EAEC identification (HEp-2 cell adherence assay and DNA probe), subpopulation, clinical setting, study site, study period, number of subjects, and health status. Figures 2.
Figure 2. Acute diarrheal illness among different subpopulations excreting fecal enteroaggregative *Escherichia coli* identified by the HEp-2 cell adherence assay.

and 3 provide the pooled ORs and 95% CIs, by method of EAEC identification and subpopulation.

A total of 22 studies examined the role of EAEC identified by the HEp-2 cell adherence assay in acute diarrheal illness among children residing in developing regions [2, 5, 12–31]. The pooled OR reflecting the association between diarrhea and EAEC was statistically significant (OR, 1.58; 95% CI, 1.36–1.83). Eleven studies examined the role of EAEC identified by DNA probe in acute diarrheal illness among children residing in developing regions [17, 32–41]. The pooled OR reflecting the association between diarrhea and EAEC was statistically significant in children (OR, 1.21; 95% CI, 1.07–1.38).

There were 9 studies that used the HEp-2 cell adherence assay to examine the role of EAEC in acute diarrheal illness among children residing in industrialized regions [42–50]. The pooled OR reflecting the association between diarrhea and EAEC was statistically significant (OR, 1.23; 95% CI, 1.03–1.48). Nine studies examined the role of EAEC identified by DNA probe in acute diarrheal illness among children residing in industrialized regions [42, 44, 46, 48, 51–55]. The pooled OR of these 9 studies was statistically significant (OR, 1.80; 95% CI, 1.39–2.33), reflecting an association between diarrhea and EAEC.

A total of 3 studies that used the HEp-2 cell adherence assay examined the role of EAEC in acute diarrheal illness among HIV-infected persons residing in developing regions [56–58]. The OR reflecting the association between diarrhea and EAEC was statistically significant (OR, 6.43; 95% CI, 2.91–14.16). One study examined the role of EAEC that was identified by DNA probe in acute diarrheal illness among HIV-infected adults living in developing regions [56]. The OR reflecting the association between diarrhea and EAEC was statistically significant (OR, 14.12; 95% CI, 4.59–43.40).

Two studies examined the role of EAEC identified using the HEp-2 cell adherence assay in acute diarrheal illness among HIV-infected persons residing in industrialized regions [59, 60]. The pooled OR reflecting the association between diarrheal illness and EAEC isolated from stool samples was not statistically significant (OR, 1.04; 95% CI, 0.64–1.69).

Two studies examined the role of EAEC in acute diarrheal illness among adults residing in industrialized regions using the HEp-2 cell adherence assay [61, 62]. The overall OR reflecting the association between diarrhea and EAEC isolated from stool samples was not statistically significant (OR, 1.70; 95% CI, 0.77–3.73). Two different studies examined the role of EAEC identified by DNA probe in acute diarrheal illness among adults residing in industrialized regions [43, 63]. The pooled OR reflecting the association between diarrhea and EAEC was statistically significant (OR, 2.77; 95% CI, 2.00–3.84).

Two studies examined the role of EAEC in acute diarrheal illness among adults residing in developing regions using the HEp-2 cell adherence assay [64, 65]. The overall OR reflecting the association between diarrhea and EAEC isolated from stool samples was statistically significant (OR, 7.15; 95% CI, 1.96–26.04).

One study examined the role of EAEC in acute diarrheal illness among adult international travelers to developing regions using the HEp-2 cell adherence assay [66]. The overall OR reflecting the association between diarrhea and EAEC isolated
Enteroaggregative E. coli: A Meta-Analysis

• CID 2006:43 (1 September)

559

Figure 3. Acute diarrheal illness among different subpopulations excreting fecal enteroaggregative Escherichia coli identified by DNA probe from stool samples was statistically significant (OR, 6.72; 95% CI, 2.62–17.20).

Role of EAEC putative virulence factors. Table 1 shows the distributions of putative virulence genes of EAEC isolates among persons excreting EAEC. A total of 4 studies examined the putative role of EAEC virulence genes in acute diarrheal illness among children residing in developing regions [12–15]. These 4 studies found that aafa (OR, 3.10; 95% CI, 1.54–6.25), astA (OR, 2.90; 95% CI, 1.21–3.62), and 4A18 (OR, 2.49; 95% CI, 1.19–5.20) were associated with acute diarrheal illness.

DISCUSSION

In this meta-analysis, EAEC identified by the HEp-2 cell adherence assay was associated with acute diarrheal illness among children residing in developing and industrialized regions, HIV-infected persons residing in developing regions, adults residing in developing regions, and adult travelers to developing regions. EAEC identified by the DNA probe was associated with acute diarrheal illness among children residing in developing and developed regions, HIV-infected persons residing in developing regions, and adults residing in industrialized regions. We were not able to identify any seasonal variation associated with the development of diarrhea due to EAEC, and we were unable to identify any outbreaks of diarrhea due to EAEC among the included studies, which suggests that this enteric pathogen is endemic in the many countries.

Many, but not all, of the case-control studies of children—especially those <2 years of age and those residing in areas where EAEC is endemic—had a statistically significant association between acute diarrheal illness and EAEC. Children have a less well-developed immune system, compared with adults who reside in the same area and who may have had multiple exposures to EAEC and subsequently developed mucosal antibodies to these bacteria. The geographic areas where EAEC was most frequently identified in children with acute diarrhea were Belgrade, Yugoslavia (12 [75%] of 16 persons) [5] and Fortaleza, Brazil (24 [46%] of 52) [16] (among developing countries) and New Orleans, Louisiana (5 [24%] of 21) (among industrialized countries).

Limited numbers of studies regarding the role of EAEC in acute diarrheal illness in adults were available. In industrialized regions of the world, Svenungsson et al. [61] identified EAEC as a cause of acute diarrhea in 2% of 760 Swiss patients, compared with 1% of 203 asymptomatic persons (OR, 2.17; 95% CI, 0.49–9.54), whereas Schultz et al. [62] identified EAEC as a cause of acute diarrhea in 10% of 169 European patients, compared with 7% of 108 asymptomatic persons (OR, 1.51; 95% CI, 0.60–3.81). In developing regions of the world, Pai et al. [64] identified EAEC as a cause of acute diarrhea in 55% of 20 patients with diarrhea and in 9% of 11 persons without diarrhea (OR, 12.22; 95% CI, 0.96–156.08), and Okeke et al. [65] identified diarrhea due to EAEC infection in 16% of 113 Nigerian patients, compared with 3% of 63 asymptomatic persons (OR, 5.78; 95% CI, 1.25–26.7) [65]. HIV infection status of the subjects in these studies was not reported. It is likely that many of the subjects who had diarrhea, especially those persons living in Nigeria, were HIV seropositive, making the interpretation of whether EAEC is a cause of diarrhea among adult HIV-negative nontravelers difficult.

Several studies have suggested that EAEC has a role in causing...
Among children residing in developing regions.

The clinical manifestations of EAEC infection involve a complex host-pathogen interaction. The heterogeneity of EAEC strains, inoculum of EAEC ingested, host immune response, and the host susceptibility to EAEC infection likely explain the differing clinical presentations of persons with EAEC infection [71]. Studies on EAEC have been conducted in different countries, both in developing and developed regions of the world, and this study confirms that EAEC strains exhibit heterogeneity between and within geographical areas [71].

Because of the small number of studies available, it was difficult to adequately assess the role of specific EAEC genes in travelers’ diarrhea [67–69]. Mathewson and colleagues [66] identified EAEC as a cause of acute diarrhea in 29% of 89 travelers and as a cause of asymptomatic infection in 6% of 121 travelers to Guadalajara, Mexico. International travelers are at high risk for acute diarrheal illness, because they are immunologically naive and are less frequently exposed to EAEC.

Two studies examined the role of EAEC in acute diarrhea among HIV-infected persons from industrialized regions. Durrrer et al. [59] identified EAEC in 22% of 111 adults with HIV infection who had diarrhea, compared with 31% of 68 adults with HIV infection who did not have diarrhea, and Wanke et al. [60] identified EAEC in 44% of 68 adults with HIV infection who had diarrhea, compared with 30% of 60 adults with HIV infection who did not have diarrhea. Neither study identified EAEC as a significant cause of acute diarrheal illness in HIV-infected persons, which suggests that these geographic areas (Zurich, Switzerland, and Boston, Massachusetts) are areas of endemicity for these bacteria. In contrast to studies of EAEC and acute diarrhea among persons with HIV infection who live in industrialized regions, a statistically significant OR was found for diarrhea and EAEC among HIV-infected persons residing in developing regions (OR, 6.43; 95% CI, 2.91–14.16).

Four studies examined the distribution of EAEC genes in children who were excreting EAEC [12–15]. A total of 13 EAEC genes were studied among these 4 studies. EAEC strains from all 4 studies exhibited heterogeneity. This meta-analysis found aafA, astA, and 4A18 to be associated with acute diarrheal illness among children residing in developing regions. aafA encodes for the aggregative adherence fimbria (AAF/II). The AAF/II serves as a structural subunit of the aggregative adherence fimbria of EAEC and is responsible for intestinal mucosal adherence. astA encodes for heat-stable enterotoxin 1. Heat-stable enterotoxin 1 is similar to enterotoxigenic E. coli heat-stable toxin, because both toxins share physical and mechanistic similarities. 4A18 is a pAA2 replicon with an unknown function [15]. It is likely that other EAEC genes are important in virulence; however, because of the limited number of studies available, additional studies powered to examine the relationship between virulence genes and diarrheal illness are needed. It has been suggested that heat-stable enterotoxin 1 is a virulence factor in EAEC, though it is also found among other diarrheagenic E. coli pathotypes and in commensal E. coli [70]. Our data suggest that heat-stable enterotoxin 1 may, indeed, be a virulence factor in EAEC, and further studies should address this possibility.

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Because of the small number of studies available, it was difficult to adequately assess the role of specific EAEC genes in

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<td>1.15 (0.57–2.31)</td>
<td>2.12 (0.91–4.95)</td>
<td>2.90 (1.21–3.62)</td>
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NOTE. NA, not available.

* For aafA, \( \chi^2 = 3.17 \) and \( P = .08 \). For set1A, \( \chi^2 = 1.14 \) and \( P = .29 \). For astA, \( \chi^2 = 0.90 \) and \( P = .34 \). For daaC, \( \chi^2 = 0.23 \) and \( P = .63 \).
diarrheal illness. No study included in this meta-analysis examined the susceptibility of the host to EAEC infection. Jiang et al. [72] found a single nucleotide polymorphism in the promoter region at the −251 site of IL-8 to be associated with an increased risk of developing symptomatic EAEC infection and increased concentration of fecal IL-8 [72]. Studies examining the importance of host susceptibility and EAEC virulence are currently ongoing. Other possible reasons for the differing clinical presentation of persons with EAEC infection include differing levels of acquired immunity to EAEC, especially in persons residing in regions where EAEC is endemic [72].

Limited numbers of studies were available that examined the role of EAEC in acute diarrheal illness using both the HEp-2 cell adherence assay and the DNA probe. However, identification of EAEC by both methods, especially the HEp-2 cell adherence assay, likely encompasses both pathogenic and non-pathogenic strains, which share a factor or factors conferring a common phenotype. The DNA probe for EAEC is based on a 1-kilobase DNA fragment labeled pCVD432 from the 60-MDa plasmid of the EAEC strain 17–2. Using this probe to detect EAEC strains has produced variable results. The sensitivity of the DNA probe for identifying EAEC ranges from 15% to 89% [73, 74]. The varying sensitivity of the DNA probe is caused by the heterogeneity of EAEC and the observation that many EAEC strains lack definable virulence properties [72]. The results of Dutta et al. [17] suggest that the HEp-2 cell adherence assay is a better method for identifying pathogenic EAEC, compared with nonpathogenic EAEC. In contrast, the results of Cohen et al. [42] suggest that the DNA probe is a better diagnostic method for identifying pathogenic EAEC strains. These conflicting results are likely explained by the differences in laboratory techniques, the DNA probes used, and the presence of heterogeneous EAEC strains in developing and industrialized regions.

Potential limitations to this study include the limitations inherent in a meta-analysis. Among the studies reviewed, there was tremendous diversity in the EAEC strains isolated, subpopulations, sample size, geographical area, and time period during which the studies were performed. We addressed this by examining these confounding variables by EAEC virulence genes present and geographic area and by stratifying by different subpopulations. Many of the included studies that showed no association between acute diarrheal illness and EAEC were underpowered, which made interpretation and conclusions regarding the importance of EAEC to acute diarrheal illness difficult. Thus, conclusions based on underpowered studies at a strict statistical significance $P$ value, typically $P < .05$, do not mean that no association exists.

We note that our study addressed only the role of EAEC in acute diarrheal illness. In several studies, EAEC has been suggested to be a cause of characteristically persistent illness. Unfortunately, we found such studies to be prone to methodologic diversity, and they were, therefore, not considered in this analysis.

In summary, this meta-analysis showed that strains of EAEC were associated with acute diarrheal illness among children residing in developing and developed regions, persons with HIV infection residing in developing regions, adults residing in developing regions, and adult travelers to developing regions. Limited numbers of studies were available that examined the
independent roles of the many putative EAEC virulence genes in acute diarrheal illness. The HEp-2 cell adherence assay remains the gold standard for identifying EAEC; however, the role of the DNA probe for identifying EAEC is uncertain. Additional studies that are powered to determine the role of EAEC and its putative virulence genes in acute diarrheal illness in adults and HIV-infected persons in both the developing and developed world are needed. Future studies are also needed to examine the importance of EAEC from a host-pathogen perspective.

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