

## Review

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# The Prevalence of Shiga toxin-producing Escherichia coli in Patients with Gastroenteritis and Sources of Infections in Iran: A Systematic Review Study Protocol

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Hemolytic Uremic Syndrome (HUS) is a leading cause of acute kidney injury in infants and children. The majority of HUS in children is secondary to Shiga toxin induced Escherichia Coli (STEC). Many countries have a strategy to identify the source of infection and annually estimate the rate of this infection but there is no prevention strategy to identify this infection in Iran.

The aim of this study is to find the percentage of STEC identified in various samples, in addition to find the outcome of STEC infected patients in Iran.

We will search PubMed, EMBASE, Google Scholar, Google, OVID, SCOPUS, Web of Sciences, IranMedex, MagIran, and SID, dociran, PDFiran, ganj.irandoc, and all online university database for thesis, and abstract books of regional or international congresses between January 1985 and January 2016.

One author will do the search screen for potentially eligible studies and two authors independently assess whether the studies meet the inclusion criteria. Discrepancies between the two authors will be resolved through discussion and arbitration by a third author. Data from the selected studies shall be extracted using a data collection form. The methodological quality of studies will be assessed using the STORBE checklist and risk of bias assessment tool developed by Hoy et al for assessing risk of bias for epidemiological studies. We will use random effects models to assess inter-study heterogeneity. Dichotomous data will be analyzed using relative risk and continuous will be assessed with data mean differences, both with 95% CIs.

**Keywords:** Gastroenteritis; Humans; Iran; Prevalence; shiga Yoxin 2; shiga-Toxigenic Escherichia coli.

**Running Title:** The Prevalence of Shiga toxin-producing E- coli in Patients with AGE

## Introduction

Hemolytic Uremic Syndrome (HUS) is a leading cause of acute kidney injury in infants and children [1]. By the prevalence of 18%, HUS consists the second most common cause of AKI in Iranian children [2-3]. It is associated with high morbidity and mortality especially in underdeveloped countries. The worldwide annual estimation of acute infection with STEC was 2,801,000; 3890 of them lead to HUS, 270 suffered of ESRD, and 230

died [4]. The mortality rate in two retrospective studies in tertiary centers of Iran, regardless of etiology, was between 19.5% and 35% [5-6]. There are few reports of morbidity in Iran including acute abdomen need surgical exploration [7] or common bile duct stone due to severe hemolysis has been reported in an HUS child [8]. STEC is the most common cause of post-infectious HUS. The prevalence of E.coli 0157 in USA is 0.95 per 100000

population that shows a decline by 30% in 2015 [9]. In Australia, an 11-year survey showed a steady state by annual rate of 0.4 cases per 100000 per year [10]. It is a food borne disease or acquired from person-to-person transmission. After the outbreak of atypical STEC on 2011, the laboratories in 32 countries tried to increase the capabilities to identify the infected cases [11]. However, there has been some improvement in diagnosis of thrombotic thrombocytopenic purpura and atypical HUS secondary to complement dysregulation in Iran [12]; There is no laboratory to check routinely the hemorrhagic colitis or bloody diarrhea for STEC. Therefore, we do not have a rough figure of the prevalence of this microorganism in Iran. There are some retrospective reports of Iranian children with HUS but none of them had any data that what portion was secondary to STEC. A meta-analysis placed Iran among infected region with pooled prevalence of 3.08% - 6.25% in cattle [13].

The presentation ranges from mild diarrhea and hemorrhagic colitis that can progress to bowel gangrene, to acute kidney injury and death, or HUS with central nervous system (CNS) or other extrarenal organ injury. A retrospective study on 104 children with HUS, 7% required abdominal exploration for gastrointestinal intussusceptions, gangrene or necrosis [7]. It can lead to chronic or even end stage kidney disease, or result in permanent brain or other organ injury. A survey of biopsy studied in atypical HUS, 41% lead to CKD and the pathology was correlated with higher vascular score [14]. Besides that, a registry of CAPD in Iranian children revealed that 10% of them suffered of HUS [15].

### Objectives

- 1- To find the prevalence and incidence of Shiga toxin-producing E. coli (STEC) in stool culture of gastroenteritis patients in Iran.
- 2- To find the major sources of STEC infections in Iran.

### Types of studies

The following designs will be considered for the study: Cross-sectional, case-control, longitudinal and cohort studies, epidemiological studies, systematic review or metanalysis, Conference proceedings, thesis or unpublished data will be used

### Types of Participants

All patients presented with gastroenteritis, diarrhea, hemorrhagic colitis, dysentery, or

hemolytic uremic syndrome. Moreover, all studies performed on cattle, farms, contaminated drinking water, dairy products and other produce will be included. There is no limitation of age and language. Only studies performed on different provinces of Iran are considered.

### Study settings

The laboratories, hospitals, outpatient facilities, day-care centers, and military institutions, groceries, restaurants, prepared food, dairy product factories, farms, and preserved foods.

### Intervention(s), exposure(s)

Inclusion criteria: samples: type of specimens as feces or rectal swab and any specimens obtained from cattle intestines, feces, dairy products, farms, foods, vegetables or waters.

Identification: Detection of STEC infection by stool culture using Sorbitol-MacConkey (SMAC) agar which contains sorbitol as a carbon source instead of lactose, followed by serotyping by any of the recognized techniques such as latex agglutination test, slide agglutination test, tube agglutination, and/or PCR for rfbO157 or other STEC-specific genes.

### Type of Outcome measures

#### Primary outcomes

The percentage of STEC identified in total samples. The percentage of studies of various sources and of STEC carriers

#### Secondary outcomes

The final outcome of STEC infected patients (death, HUS, resolution, not specified)

### Search methods for identification of studies

PubMed, EMBASE, Google Scholar, Google, OVID, SCOPUS, Web of Sciences, IranMedex, MagIran, and SID, dociran, PDFiran, and ganj.irandoc will be searched. Moreover, the database of thesis in each medical university in Iran. The references in each study will be review to find missed studies. Hand search among thesis in Iranian Medical Universities that are not included in online database, and the abstract books of congresses (International, regional, local), and even unpublished studies collected from the Iranian investigators. Studies published between January 1985 and January 2016 will be considered. The search will be re-run just before the final analyses and if relevant studies are found they will be included in the study.

### Provisional Search strategy for Pubmed

"shiga-toxigenic escherichia coli"[MeSH Terms] OR ("shiga-toxigenic"[All Fields] AND "escherichia"[All Fields] AND "coli"[All Fields]) OR "shiga-toxigenic escherichia coli"[All Fields] OR "stec"[All Fields] "iran"[MeSH Terms] OR "iran"[All Fields] "gastroenteritis"[MeSH Terms] OR "gastroenteritis"[All Fields] ("shiga-toxigenic escherichia coli"[MeSH Terms] OR ("shiga-toxigenic"[All Fields] AND "escherichia"[All Fields] AND "coli"[All Fields]) OR "shiga-toxigenic escherichia coli"[All Fields] OR "stec"[All Fields]) AND ("iran"[MeSH Terms] OR "iran"[All Fields])

(("Shiga-Toxigenic Escherichia coli"[Mesh] AND "Diarrhea"[Mesh]) OR "Diarrhea prodrome Hemolytic-Uremic Syndrome"[Supplementary Concept]) OR "Hemolytic-Uremic Syndrome"[Mesh]) AND "Iran"[Mesh]

We use equivalent Persian term for the above mentioned words to find among the articles in Iranian database.

Review Registration number: PROSPERO, CRD42016033019.

### Data Collection and analysis

Three independent reviewers (NH, RMG, SN) will review the abstracts to select the relevant studies, in the case of discrepancy NH will be arbiter. STROBE statement will be used to assess the quality of studies and their eligibility. A quality assessment scores out of 22 will be determined for each study by assigning a point per STROBE item addressed. Good/fair quality papers will be categorized as having a score of =14/22 and poor quality papers will be classified as having a score of less than 14/22.

"MY" is qualified to do statistical and meta-analyses.

Data to be extracted: The following items and data would be collected from the articles:

Authors name, title of study, journal, year, volume, number, page ; Language of study, center of study, type of study, period of study, sample size, patient information( age, disease, gender), specimen (stool, food, meat, vegetables, dairy products,etc), technique of culture, technique of serology study, type of E.Coli, other bacteria mentioned in study as comparison, technique of STEC detection, type of STEC (1,2, both), the region of study, antibiogram, method of bacterial genum extraction, primer and probe design, length of follow up, outcome-recovery, HUS, death, unreported, funding sources

### Risk of bias (quality) assessment

We use the risk of bias assessment tool developed by Hoy et al (2012) in order to report the risk of bias of included studies. LOW RISK OF BIAS: 8 or more "yes" answers. Further research is very unlikely to change our confidence in the estimate. MODERATE RISK OF BIAS: 6 to 7 "yes" answers. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. HIGH RISK OF BIAS: 5 or fewer "yes" answers. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

### Strategy for data synthesis

First of all, we will give a narrative synthesis of the data extracted from the included studies will be provided. Then we will calculate risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). If studies can be clustered: we will pool results for studies that have used the same technique and the same outcome. We will use a random-effects meta-analysis and risk ratios for binary outcomes. And we will calculate 95% confidence intervals. If the studies cannot be clustered: we use both the Chi-squared test and the I-squared statistic to assess heterogeneity between the studies in effect measures (I-squared value> 50% indicate substantial heterogeneity).

### Analysis of subgroups or subsets

Subgroup analysis will be done for different ages (children- adults), various regions and different source of infection.

### Dissemination plans

We will produce a report for the funder of this review. In addition, we will submit the results to a leading journal in this field. If the findings of the review warrant a change in practice (recommend that central laboratories test for STEC and develop screening protocols for meat and/or agricultural produce and drinking water). The more important, a one-page summary report will be prepared and sent to the Iranian Ministry of Health. Besides that, we would disseminate the result by presenting summaries at relevant local conferences or seminars

### Ethics and disseminations

The planned systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42016033019 [16].

This type of study does not need formal ethical review and approval. The findings of this systematic review will be published in peer-reviewed journal and conference presentations. The frequency of STEC in Iran would help in clinical and health care decision-making, and the future research design and direction on this topic.

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### Conflict of interest

The authors declare that they have no conflicts of interest.

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