ISSN 2377-1569

PEDIATRICS AND NEONATAL NURSING
Open Journal

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Systematic Review

Parenteral Diarrhea and Pediatric Urinary Tract Infections: A Systematic Review

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Article information
Received: July 6th, 2022; **Revised:** July 22nd, 2022; **Accepted:** July 29th, 2022; **Published:** July 29th, 2022

Cite this article
Mellick LB, Kalra S, Panacek E. Parenteral diarrhea and pediatric urinary tract infections: A systematic review. *Pediatr Neonatal Nurs Open J*. 2022; 8(2): 38-42. doi: 10.17140/PNNOJ-8-137

ABSTRACT

Background
Parenteral diarrhea is non-infectious diarrhea associated with extraintestinal infections such as urinary tract infection (UTI), but evidence supporting this association is limited. We performed a systematic literature review to determine the reported frequency of UTI in pediatric patients who had diarrhea.

Methods
We searched electronic databases (PubMed, Scopus, Google Scholar, and CINAHL) to identify articles about diarrhea and UTI. We included English-language articles about studies of children (age, ≤5-years) who presented with diarrhea in which the frequency of culture-positive UTI was reported. We excluded studies that examined particular diets or specific pediatric patient populations presenting with diarrhea. Patient and study characteristics were extracted manually.

Results
The database search identified 32 articles. After excluding 25 articles and adding 3 articles identified during manual review of article references, there were 10 articles in the final review including 8 cohort and 2 case control studies. In all 10 studies combined, UTIs were observed in 172 of 1086 children who presented with diarrhea (15.8%), but the frequency of UTI varied between studies (range, 5 to 32%). *Escherichia coli* was the most common bacterial isolate from urine in all 9 studies that reported microbiology results. The stool and urine culture results (*E. coli*) were similar in 4 of the 6 studies that reported stool culture results.

Conclusion
In infants and children up to age 5-years, diarrhea may be associated with an UTI. In patients who have diarrhea of unknown cause, it may be prudent to consider an evaluation for a coexisting UTI.

Keywords
Gastroenterology; Genitourinary system; Diarrhea; Bacteriuria; Urinary tract infection (UTI).

INTRODUCTION

Parenteral diarrhea is noninfectious diarrhea associated with extraintestinal infections such as otitis media, pneumonia, or urinary tract infection (UTI). This condition was first described in the late 19th century and has been discussed in recent reviews.[1-5] However, there is limited understanding of the pathophysiology of non-infectious diarrhea associated with extraintestinal infection, and controversy exists about whether parenteral diarrhea is a distinct clinical condition.

In a retrospective cohort study of children presenting to a pediatric emergency department, non-infectious diarrhea was present in 18.6% of children who had culture-proven UTI.[6] It is important to recognize the association between non-infectious diarrhea and urinary tract infections to avoid delayed diagnosis and treatment of associated urinary tract infections or misdiagnosis of infectious diarrhea.

We hypothesized that an association exists between the presence of diarrhea and culture-proven UTI. The purpose of this systematic review of the literature was to determine the reported frequency of associated UTI in cohort and case control studies of pediatric patients who had diarrhea.

MATERIALS AND METHODS

Literature Search

We searched electronic databases (PubMed, Scopus, Google Scholar, and CINAHL) to identify articles about parenteral diarrhea and UTI using the following terms: "diarrhea" OR "UTI" OR "parenteral diarrhea" OR "extraintestinal diarrhea" OR "extra-intestinal diarrhea". The identified articles were investigated for case series of pediatric diarrhea patients using software (Rayyan Systemic Review, Rayyan Systems, Boston, MA, USA) to identify articles for final review. We secondarily screened the selected articles looking for case series of pediatric diarrhea that reported associated urinary tract infections. Those selected articles were than assessed for eligibility according to our inclusion and exclusion criteria. We also manually reviewed the reference lists in these articles to identify other relevant articles that were not identified in the electronic search. We followed reporting guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[7]

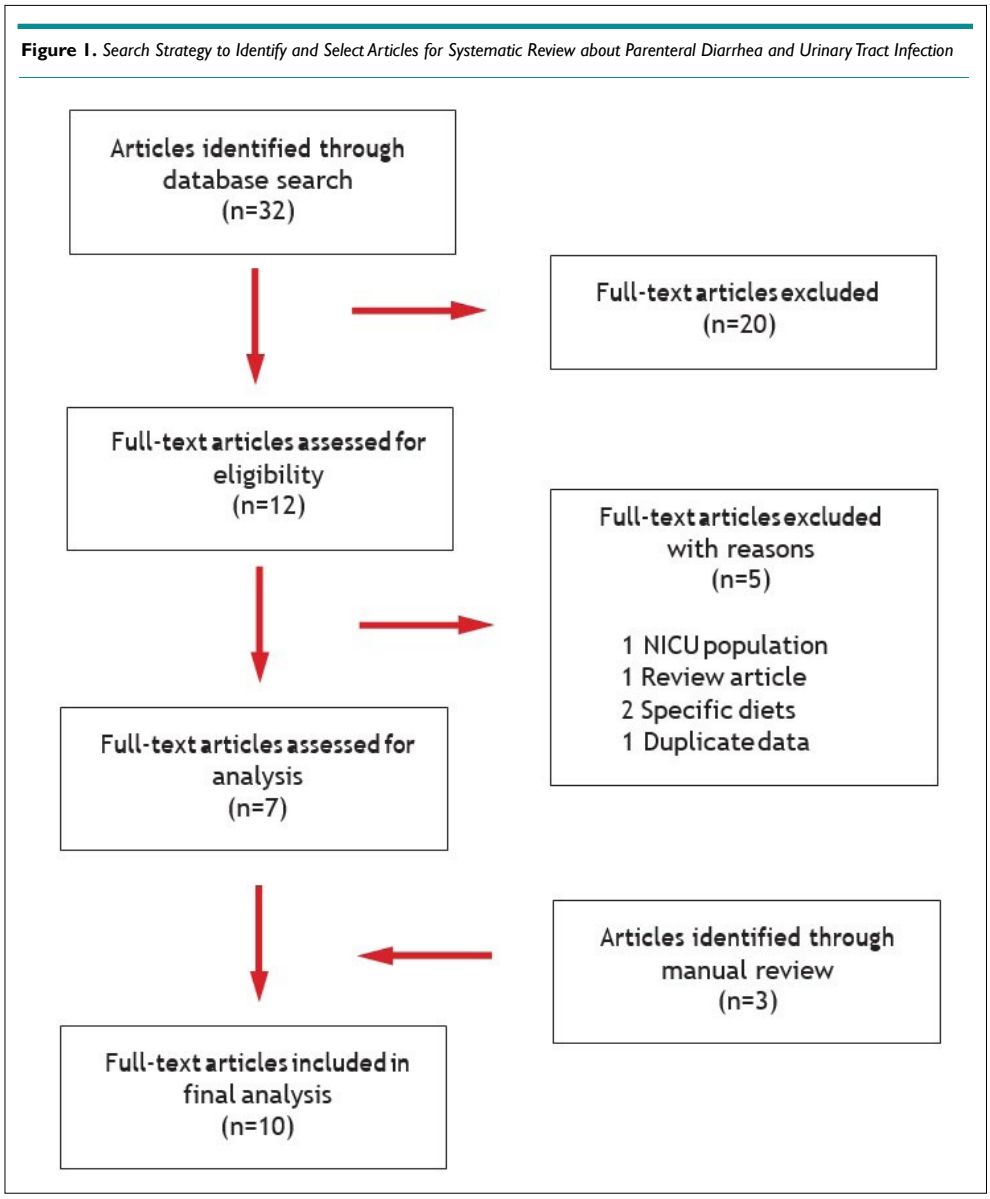
Inclusion and Exclusion Criteria

We included English-language articles about case series studies of children aged less than or equal to 5-years who presented with diarrhea in which the frequency of culture-positive UTIs was reported. We excluded studies that examined particular diets such as breastfed or low-lactose or specific pediatric patient populations presenting with diarrhea (NICU patients). The articles were reviewed independently by 2 authors (LM, SK). Interrater reliability was not evaluated because of the small number of articles resulting from the search.

Data Extraction

Characteristics of studies and study patients were extracted manually including country, study type, patient age range, clinical history, presence of fever, urine sample method, number of patients in the study, number of patients who had UTI, microbiology results, and study level of evidence,[8] quality,[9] and limitations.

Figure 1. *Search Strategy to Identify and Select Articles for Systematic Review about Parenteral Diarrhea and Urinary Tract Infection*



RESULTS

The database search identified 32 articles that were screened as full-text articles, and 20 of these articles were excluded for multiple reasons including age ranges (e.g., under 2-months) duplicates, populations studied (e.g., malnourished, chronic), article types (e.g., review), and lack of UTI reporting. In the 12 remaining articles, 5 articles were excluded because of article type (1 review article), neonatal intensive care unit population (1 article), specific diets (breastfeeding, 1 article; low-lactose diet, 1 article), and duplicate data publication (1 article). During manual review of article references, we identified 3 additional articles for inclusion, resulting in 10 articles in the final review (Figure 1).[10-19]

All articles described prospective cohort studies except for 2 case control studies (1 prospective and 1 retrospective), and

Table 1. *Cohort and Case Control Studies Found During Systematic and Manual Review Describing the Prevalence of Urinary Tract Infections in Pediatric Patients Diagnosed with Diarrhea*

Study	Type	Location	Sample Size	UTI	Age	Urine Collection Methods	Limitations/Quality	Level of	Stool Studies
Uppal et al[10]	Prospective cohort	India	80	6 (7.5%)	<2-years	Urine specimens were collected by midstream and suprapubic aspiration.	Study included only admitted patients which may introduce selection bias. Low quality	2b	7.5% of cases with acute gastroenteritis had culture positive UTI.
Sardjito et al[11]	Prospective cohort	Indonesia	25	8 (32%)	9-days to 18-month	Suprapubic aspiration was used to collect urine specimens.	Study only looked at prevalence for sicker patient population. Low quality	2b	32% of patients with acute gastroenteritis had culture positive UTI.
Santhanakrishnan et al[12]	Prospective cohort	India	130	20 (15.3%)	<2-years	Urine obtained by clean catch or by suprapubic aspiration.	Included children with recurrent diarrhea which may predispose them to UTI due to higher risk of contamination. Low quality	2b	15.3% of children with diarrhea had a culture positive UTI. 75% patients were females.
Thakar et al[13]	Prospective cohort	India	100	8 (8%)	<2-years	Suprapubic aspiration was used to obtain urine samples for culture and analysis.	No comparative group in the study. Mod quality	2b	8% children presenting with diarrhea had a urinary tract infection.
Fallahzadeh et al[14]	Prospective cohort	Iran	120	8 (6.7%)	4-weeks to 5-years	Urine samples collected by either bag or mid-stream for toilet trained children.	Wide range of age intervals. Low quality	2b	6.7% of patients with diarrhea had a urinary tract infection. 88% patients were females.
Narayanappa et al[15]	Prospective cohort	India	239	12 (5%)	1-month to 5-years	Urine specimens were collected by suprapubic aspiration.	Study considered admitted patients only which could be sicker than outpatient population. Wide age range. Mod quality	2b	5% of patients admitted for acute diarrhea had a culture positive UTI.
Soleimani et al[16]	Prospective case control	Iran	100	27 (27%)	2-month to 5-years	Urine obtained by catheterization<2-years and midstream clean catch for older children. Two positive urines required.	Case control design with lack of baseline characteristics comparison between two groups. Wide age intervals. Low-mod quality	3b	27% of patients presenting with acute gastroenteritis had a culture positive UTI.
Das et al[17]	Retrospective case control	Bangladesh	104	26 (25%)	<5-years	Urine samples were obtained by clean catch.	Wide age range could potentially be adding confounding for which adjusted analyses could have been an important addition. Low quality	3b	25% of children under 5 presenting with diarrhea had a UTI.
Bashir et al[18]	Prospective Cohort	Pakistan	100	30 (30%)	<5-years	Urine samples were obtained by catheterization.	Lack of control group and wide age range intervals. Low quality	2b	30% of patients with diarrhea had a culture positive UTI.
Afridi et al[19]	Prospective cohort	Pakistan	88	27 (31%)	<5-years	Urine samples were obtained by catheterization.	While it was a prospective design, study lacked robust statistical analyses. Low quality	2b	31% of patients with diarrhea had a culture positive UTI. 59% patients were females.
Total			1086	172 (15.8%)					

all articles reported the frequency of documented UTIs in case series of children presenting with acute diarrhea (Table 1).[10-19] In all 10 studies combined, UTIs were observed in 172 of all 1086 children who presented with diarrhea (15.8%), but the frequency of UTIs varied substantially between studies (range, 5 to 32%) (Table 1). Eight of 10 studies reported patient genders and 84 of 136 (61.8%) patients with UTIs were females. The microorganisms cultured from urine were typical for UTIs, and *Escherichia coli* (*E. coli*) was the most common bacterial isolate from urine in all 9 studies that reported microbiology results (Table 2). The stool and urine culture results were mostly similar in 4 of the 6 studies that reported stool culture results,[10,12,13,15] with *E. coli* being the most frequently cultured organism, but *E. coli* subtyping was not performed in any of the studies (Table 2). In addition, 2 studies reported organisms cultured from stool that were not observed in urine culture results (*Streptococcus faecalis* and *Shigella*, 1 study each).[10,14]

Table 2. *Urine and Stool Culture Results Reported in 10 Cohort and Case Control Studies Discovered During Our Systematic and Manual Review*

Study	Urine Cultures	Stool Studies
Uppal et al[10]	*E. coli* (5) Klebsiella (1)	Strep Faecalis (2) *E. coli* (2)
Sardjito et al[11]	*E. coli* (6) *Aerobacter Aerogenes* (2)	Not reported
Santhanakrishnan et al[12]	*E. coli* (6) *Aerobacter Aerogenes* (2)	*E. coli* (5) Klebsiella (1) *Strep Faecalis* (1)
Thakar et al[13]	*E. coli* (5) Klebsiella (2) Candida (1)	"Same organism" cultured from urine and stool (3)
Fallahzadeh et al[14]	*E. coli* (7) Pseudomonas (1)	Shigella (1)
Narayanappa et al[15]	*E. coli* (10) Klebsiella (1) Citrobacter (1)	"Same organism" cultured from urine and stool (9)
Soleimani et al[16]	Not reported	Not reported
Das et al[17]	*E. coli* (18) Klebsiella (4) Acinetobacter (1) Enterococcus (1) Group B streptococcus (1)	No stool pathogens were cultured.
Bashir et al[18]	*E. coli* (20) Citrobacter (5) Pseudomonas (5)	Not reported
Afridi et al[19]	*E. coli* (15) Citrobacter (8) Pseudomonas (4)	Not reported

DISCUSSION

The present systematic review showed that a substantial proportion of children who presented with diarrhea had an associated urinary tract infection (UTI). Although there was wide variation in the prevalence of UTI between studies, the findings provide evidence in favor of the proposed association between noninfectious diarrhea and UTI, as observed in a recent retrospective cohort study.[6]

Although 8 studies in the systematic review did not include comparison groups of children not presenting with diarrhea, the 2 case control studies that included comparison groups reported UTI in 7% of their combined control patients,[14,16] which is consistent with the reported prevalence of UTI in febrile and afebrile pediatric patients (3.1% to 5.3%).[20-23]

Although UTIs are caused by bacteria ascending from the perineum and gastrointestinal tract according to the fecal-perineal-urethral hypothesis, a study of parenteral or extraintestinal diarrhea requires documentation of the absence of any pathogens in diarrheal stool samples. Furthermore, when stool and urine cultures are performed, there should ideally be no correlation between the pathogenic bacteria cultured from the urine and stool. A UTI caused by the same agent responsible for infectious diarrhea may suggest that the UTI resulted from the diarrhea. In the 10 studies included in the systematic review, *E. coli*, which is a normal aerobic colonic microflora and the most common cause of UTI, was the most common microorganism cultured from stool that correlated with the urine culture results.

Perineal soiling that may occur with diarrheal stools may contribute to the development of an ascending UTI. Although *E. coli* was observed as the common bacterial agent most frequently in the studies that included stool and urine cultures, pathogenic *E. coli* subspecies with acquired specialized virulence factors may cause diarrhea, and specific testing is required to identify these subspecies. As subspecies data were not reported in the included studies, it was not feasible to determine whether the concurrent UTIs were caused by diarrheal disease and associated perineal soiling. Consequently, the conundrum of whether the diagnosed urinary tract infection is caused by perineal soiling of an infectious diarrhea *versus* a urinary tract infection causing a non-infectious diarrhea cannot be answered in this study.

As might be expected because of anatomical differences there was a slight predominance of females in eight of 10 studies that reported patient genders with urinary tract infections (61.8%).

Limitations of the present study included the low quality of most studies in the systematic review, which mostly were observational studies, even though reliable urine collection techniques such as suprapubic aspiration and catheterization were used in 8 of the 10 studies. All ten studies were performed in either Asian or Middle Eastern countries, and consequently, these results may not be applicable in other parts of the world. Furthermore, it is unknown whether the *E. coli* cultured in both urine and stool were pathogenic subspecies because of the absence of subtyping data. As the review provides evidence about the association between diarrhea and culture-proven UTI, future studies are justified that include *E. coli* subtyping in patients presenting with UTI and diarrhea.

CONCLUSION

The present systematic review confirmed an association between diarrhea and UTIs in 15.8% of infants and children up to age 5-years presenting with diarrhea, which is decidedly greater than the prevalence of UTI in febrile and afebrile young children.[20-23] In pediatric patients who present with diarrhea of unknown cause, it may be prudent for practitioners to consider an evaluation for possible coexisting UTI.

ACKNOWLEDGMENTS

The authors thank Clista Clanton MSLS, Charles M. Baugh Biomedical Library, University of South Alabama College of Medicine, for assistance with the systematic review and literature search and Emily Wilson and Elly Trepman for editorial support.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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