

REVIEW

Urinary sepsis in children: a systematic review of diagnostic and therapeutic aspects

Infecção urinária em crianças: uma revisão sistemática dos aspectos diagnósticos e terapêuticos

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ABSTRACT

During the last decade, new imaging techniques and biological probes provided further insight into the pathogenesis and natural history of urinary tract infection (UTI) in children. Especially in newborns, UTI is a common cause of fever and probably the most common cause of renal parenchymal loss. In children aged equal or less than 2 years, the symptoms of UTI are vague and non-specific - fever, irritability, poor feeding, vomiting, diarrhea and ill appearance. In neonates, clinical symptoms or laboratory tests could not be used to predict UTI episodes or eliminate the likelihood of a UTI even if other sites of infections are clinically suggested. For this reason, the goal of managing UTI in children is based on identifying and modifying factors that may increase the risk of renal parenchymal and functional loss as from the onset of infection. Moreover, selective antimicrobial pressure is a major concern when treating children with UTI, as renal parenchymal loss may occur within a short period of time, if inadequate antimicrobial agents are utilized. **OBJECTIVES:** This systematic review assessed recent diagnostic and therapeutic aspects of severe UTI in children. We also summarized well-conducted studies and the most important publications regarding diagnosis and treatment of urinary sepsis in the pediatric population. **SEARCH STRATEGY:** Trials and reviews were searched in general and specialized databases (MEDLINE, Cochrane Library) and references were reviewed. **SELECTION CRITERIA:** All published trials and reviews were eligible for inclusion provided they reported results for the pediatric population, included clinically significant events resulting from urinary tract infection, and included specific aspects of diagnosis and therapy. **DATA COLLECTION:** One reviewer extracted information. Diagnostic and therapeutic aspects of urinary sepsis in the pediatric age group were assessed.

Keywords: Urinary tract infections/therapy; Urinary tract infections/diagnosis; Children; Review

RESUMO

INTRODUÇÃO: Nas últimas décadas, novas técnicas de imagem e testes biológicos permitiram maior conhecimento da patogênese e história natural das infecções do trato urinário (ITU) em crianças. Especialmente em recém-nascidos, as ITU são uma causa comum de febre e são, provavelmente, a causa mais freqüente de perda de parênquima renal. Em crianças com idade igual ou inferior a dois

anos, os sintomas de ITU são vagos e inespecíficos – febre, irritabilidade, diminuição do apetite, vômitos, diarreia e mau estado geral. Em recém-nascidos, os sintomas clínicos e testes laboratoriais não podem ser utilizados para prever os episódios de ITU, nem eliminar a possibilidade de uma ITU mesmo quando há suspeita clínica de infecção em outros locais. Portanto, o objetivo do tratamento de ITU em crianças baseia-se na identificação e modificação dos fatores que podem aumentar o risco de perda de parênquima e de função renal, desde a infecção inicial. Além disso, a pressão na escolha de um antimicrobiano seletivo é uma preocupação na conduta de crianças com ITU, pois pode ocorrer perda de parênquima renal em um curto intervalo de tempo, caso não seja utilizado agente antimicrobiano adequado. **OBJETIVOS:** Esta revisão sistemática avaliou alguns aspectos diagnósticos e terapêuticos recentes da ITU grave em crianças. Apresentamos também um resumo dos estudos mais importantes e bem-feitos publicados sobre diagnóstico e tratamento de infecção urinária na população pediátrica. **ESTRATÉGIA DE BUSCA:** Realizou-se uma busca de ensaios e revisões em bancos de dados gerais e especializados (MEDLINE, Cochrane Library) e por meio de revisão das referências bibliográficas. **CRITÉRIOS PARA SELEÇÃO:** Todos os ensaios e revisões publicados atendiam aos critérios de inclusão desde que 1. apresentassem resultados referentes à população pediátrica, 2. incluíssem eventos clinicamente significativos decorrentes de infecção do trato urinário, e 3. incluíssem aspectos específicos de diagnóstico e tratamento. **COLETA DE DADOS:** Um revisor coletou os dados. Avaliaram-se os aspectos diagnósticos e terapêuticos da infecção urinária em pacientes pediátricos.

Descritores: Infecções urinárias/terapia; Infecções urinárias/diagnóstico; Criança; Revisão

INTRODUCTION

Urinary tract infection (UTI) in children is one of the most common bacterial infections seen by clinicians in the care of young patients. Its true incidence is difficult to estimate and rates vary according to gender, method of urine collection and definition of infection. The estimated rate for newborns is 2.9% for premature and 0.7% for full-term babies⁽¹⁾. Boys are 5 to 8 times more likely than girls to be infected, and male predominance persists for the first 3 months of life. After that,

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girls are more prone to infection⁽²⁾, with a prevalence of 1-3% in girls, aged 1-5 years, whereas boys at the same age have few infections. This age group is most likely to experience the first symptomatic infection. Taking into account preschool children, symptomatic infections occur 10 to 20 times more in girls than in boys.

Considering all episodes of infections, UTI accounted for 7.5% of febrile episodes in infants aged under 8 weeks⁽³⁾, 5.3% in children younger than 1 year⁽⁴⁾, 4.1% in those younger than 2 years⁽⁵⁾ and 1.7% in children under 5 years⁽⁶⁾. Recurrences are more common in girls than in boys, regardless of urinary tract abnormalities. The greatest risk of re-infection is during the first few months following the first episode. Recurrences are less likely to occur the longer the children remain free of infection.

Except for the first 8 to 12 weeks of life, when UTI may be secondary to a hematogenous source, this infection is believed to arise by the ascending route following entry of bacteria via the urethra⁽⁷⁾. The sequence of events leading to an ascending infection of the urinary tract is thought to begin when bacteria residing in the gastrointestinal tract colonize the periurethral mucosa. Periurethral bacteria may then ascend into the bladder and from there to the kidneys via the ureters, establishing a risk of subsequent bladder mucosal or renal parenchymal infection. Thus, in order to acquire infection it is thought that at least small numbers of *Escherichia coli* or other uropathogens must colonize the urethra and gain entry into the bladder. To explain these observations, Stamey et al. proposed the 'host susceptibility theory', which hypothesizes that enteric bacteria tend to colonize the vaginal vestibule and urethra of females with recurrent UTI more frequently and in higher numbers than in otherwise healthy females⁽⁸⁾. In contrast, Cattell et al.⁽⁹⁾ proposed the 'chance colonization theory', in which all females with normal urinary tracts are at the same risk of developing a first episode of UTI. Once established, each infection sets the stage for the next infection. The theory by Stamey et al.⁽⁸⁾ is supported by data on blood group antigens (ABO, P, Lewis and secretor)⁽¹⁰⁻¹¹⁾ and risk of infection. The theory by Cattell et al.⁽⁹⁾ could be supported by work on virulence factors expressed by *E. coli* that may increase the risk of UTI in healthy females⁽¹²⁾.

Perhaps the most important goal for clinicians dealing with a suspected UTI is to establish a correct and prompt diagnosis, thus allowing for the identification of urinary tract abnormalities and the preservation of kidney function in the growing organ. The diagnosis of UTI in children burdens a urologic work-up for boys in the first episode of infection, and the second documented episode has the same impact for girls. The evaluation must exclude any urinary tract malformation that allows the pathogen to ascend and adhere to the urothelium in young children. Non-functioning kidneys and kidney segments serve as a nidus for bacterial infection and cause bacterial persistence, since antimicrobial concentrations adequate to treat UTI are unlikely to occur in a poorly concentrating renal segment.

The radiological evaluation of children with UTI may be performed according to several protocols, but is usually carried out after treatment of an acute infection with sonography, intravenous pyelography and voiding cystourethrography, aiming at identification of the most common anatomical and functional

abnormalities. Several special conditions of genitourinary obstruction (partial or total) and urinary functional impairment may increase the risk of renal damage during a UTI episode. Common urologic conditions, such as vesicoureteral reflux, neurogenic bladder and iatrogenic catheter-induced urinary infections play an important role in the incidence of UTI and are also related to bacteremia and sepsis in children.

OBJECTIVES

This systematic review had two main purposes. First, we summarized the most important concepts of diagnosis and treatment of urinary sepsis in the pediatric population. Second, the review selected well-conducted studies and the most important publications regarding diagnosis and treatment of urinary sepsis in the pediatric population and summarized new diagnostic and therapeutic tools for this condition.

METHODOLOGY

Criteria for considering studies for this review:

Types of studies

For background data regarding diagnosis and treatment of urinary sepsis in children we reviewed textbook chapters and classic studies conducted in the past and summarized the most important concepts for severe UTI in children. For the review on new diagnostic and therapeutic tools, only studies published in the medical literature were included (MEDLINE and The Cochrane Library).

Search strategy for identification of studies

A comprehensive literature search was performed to identify all relevant publications. The search process used MEDLINE and The Cochrane Library. The MEDLINE search focused on studies published as of 1966 that included any one of the following terms in the title, abstract or in their keyword list: urinary, sepsis, child and bacteremia. The literature search and selection were initially performed with the terms urinary and sepsis, yielding 2,875 studies. We added the term child and the search furnished 542 studies. The term bacteremia was also added, and enabled retrieval of 151 studies. With the objective of filtering search results, we restricted it only to reviews and meta-analysis studies (according to MEDLINE MeSH terms), and thus recovered 15 reviews and no meta-analysis. All abstracts were assessed and we selected the 5 best studies according to date of publication (preference was given to more recent studies) and methodology.

The Cochrane Library was also searched for studies with the terms urinary and sepsis. It provided 245 titles, and the most important were 47 systematic reviews, 11 protocols, 9 abstracts of quality, 6 collaborative studies, 13 abstracts of economic evaluations of health care interventions, 6 collaborative review groups and 1 field of knowledge. The titles were all reviewed and none referred to diagnosis and treatment of severe UTI in children.

RESULTS

Unchanged background knowledge:

Diagnosis – As in any pathological condition, physical examination is mandatory for evaluation of a septic child. However, there are no specific signs for UTI in infants. In rare cases, such as children with xantogranulomatous pyelonephritis or infected severe hydronephrosis, a mass in the flank is palpated. Perineal examination in girls may reveal an ectopic ureteral opening, ureterocele or urethral discharge. The septic child with UTI usually presents with generalized abdominal or upper quadrant pain.

The gold-standard test for diagnosis of UTI in children is quantitative urine culture. However, good urinary specimens without perineal, rectal or preputial contamination are difficult to obtain and may represent a delay in the correct diagnosis of the site of infection. The most reliable urine specimen for culture is obtained by suprapubic bladder aspiration. It can be obtained safely in infants and children, and organisms present in the aspirate are pathognomonic of bacteriuria. A major drawback in suprapubic aspiration is inconvenience for children, parents and physicians. Since urine culture may take 24 h or longer before bacterial colony counting units grow, indirect urinary tests could be performed to help physicians decide therapeutic aspects in the septic child. Urinary leukocyte esterase, microscopic urine examination for white blood cells and bacteria and urinary nitrite may be combined and help anticipating which patients will have a positive culture with a positive predictive value of up to 88%⁽⁴⁾ and a negative predictive value of up to 100%⁽¹³⁾.

To detect and confirm the presence of bacteria in the bloodstream secondary to a UTI, quantitative blood culture remains the gold-standard test, with a high positive predictive value, especially when the bacteria found in blood culture are the same in urine cultures.

TREATMENT

The most important aspect in treatment of a severely ill infant or child is the prompt and correct method for adequate diagnosis of the source of infection. After performing all tests and collecting samples, the therapeutic strategy is first to minimize renal damage during the acutely diagnosed UTI and second to minimize the risk of future renal sequela from subsequent infections⁽¹⁴⁾. Clinical and experimental data show that early antimicrobial treatment is the most effective means of preventing morbidity and mortality in severely ill children.

The treatment of sepsis of urinary origin in children is based on the use of parenteral broad-spectrum antimicrobial agents, such as a third-generation cephalosporin or the combination of an aminoglycoside with cephalosporin. Hospitalization, parenteral fluid administration, treatment of symptoms and close monitoring for clinical changes are mandatory and part of the treatment for children with severe UTI.

Generally parenteral antimicrobial treatment is continued for 3 to 5 days or until fever is gone and bacterial sensitivity tests are available to allow treatment with a narrower spectrum drug. The child clinical status is improved, meaning afebrile with sterile urine and able to take fluids.

An important aspect of treatment is early urinary tract imaging. Circumstances such as a poor response to appropriate antimicrobial treatment after 2 to 4 days of administration, a history of diabetes, calculi, papillary necrosis or neurogenic bladder, a newly diagnosed azotemia, an unusual infecting organism or a known partial urinary obstruction may warrant early urinary tract imaging. The urologic work-up is usually carried out with some form of renal and upper collecting system examination and a voiding cystourethrography. Obstruction and other forms of urologic abnormalities demand further diagnostic evaluation before adequate and definitive treatment is initiated and must be individually performed.

RECENT GENERATED CONCEPTS

In the review by Rehm⁽¹⁵⁾, diagnosis and management of UTI are debated. A very common problem in pediatric emergency services is to rule out urinary infection in febrile children. With the purpose of reducing unnecessary urine cultures, Gorelick and Shaw⁽¹⁶⁾ verified that the presence of two or more out of five variables would predict UTI with a sensitivity of up to 95% and a specificity of 31%. The following variables were assessed: age under 12 years, Caucasian, temperature of 39° C or higher, fever for more than 2 days and absence of a source of fever in the physical examination. They verified that by using these screening parameters one would identify 95% of children with UTI and eliminate 30% of unnecessary urine cultures. This study, however, has some limitations. It has to be validated in a larger study, and is likely to guide pediatricians determine a high-risk population for UTI, and reduce the need to collect urine in girls who do not meet high-risk criteria.

A recent review by Baraff⁽¹⁷⁾ points out some important aspects of diagnosis and treatment of UTI in children. First, approximately 60 to 65% of febrile children will have evidence of pyelonephritis on 99m-Tc dimercapto succinic acid renal scanning; second, microscopic urinalysis could be used as the basis for initiating antimicrobial treatment of febrile children with suspected UTI; third, and perhaps the most important aspect of the treatment, the choice of antibiotics must be guided by local sensitivity testing. Third-generation cephalosporin is usually the drug of choice, because most areas already present a significant uropathogen resistance to sulfas, amoxicillin and ampicillin. These aspects were also validated by Schlager⁽¹⁸⁾, who also considers broad coverage for group B streptococci and Enterobacteriaceae during the first 8 weeks of life. Their review also points out that a single dose to three-day therapy is not as effective as treating for 7 to 14 days, according to current studies. In regard to prophylaxis for patients with suspected urinary tract abnormalities and for children with prenatal diagnosed hydronephrosis, Schlager et al. recommend the use of nitrofurantoin or cotrimoxazole in a single daily dose for the first and amoxicillin for the latter.

In a retrospective cohort study, Pitetti and Choi⁽¹⁹⁾ verified that bacteremia in children with UTI is more common in early infancy (less than 2 months), whereas children with UTI between the ages of 2 months and 12 years appear to have a low risk of developing bacteremia. Moreover, bacteremic children are likely to have identical organisms with identical antimicrobial sensitivity in both urine and blood cultures.

DISCUSSION/CONCLUSION

Recent studies on diagnosis and management of febrile children with UTI continue to explore the clinician's ability to predict serious bacterial infection, determine the most cost-effective treatment and all complications related to the course of disease and therapy. The evolving knowledge of UTI in children focuses on the pathogenesis of renal scarring, which ultimately may lead to hypertension and end-stage renal disease. Efforts have been made to determine better diagnostic tools and therapeutic approaches to initiate early treatment and avoid these complications in children, especially when bacteremia and sepsis are suspected. The aforementioned establish the same goals for the management of UTI: prompt diagnosis, prevention of progressive renal damage and resolution of acute symptoms. Even more important, they summarize important concepts and depict new approaches for management of the condition. Although many questions still remain unanswered, investigators and physicians continue to improve the ability to diagnose and manage the common febrile UTI in children.

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