Treatment and Prophylaxis in Pediatric Urinary Tract Infection

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ABSTRACT

Urinary tract infection (UTI) is the most common serious bacterial infection in early life. Appropriate diagnosis and treatment prevent complications such as hypertension, proteinuria and end stage renal disease. A computerized search of MEDLINE, Embase and other databases was done to find the latest results about the treatment and prevention in pediatric UTI. Randomized control trials, systematic reviews and original articles were assessed. Search terms were "UTI, treatment, prophylaxis, prevention, and children". All children with complicated or simple UTI were included in our search study from neonatal period to late childhood and medical aspects of treatment were reviewed. Recently, treatment approaches have been changed by simplification of drug administration. Oral treatment is recommended especially in older infants and children instead of strict intravenous treatment and patient admission. In addition, prophylactic treatment becomes easier and limited to certain cases. In this article, we review the recent information and approaches in this setting.

Keywords: Urinary tract infection; Treatment; Prophylaxis; Prevention; Children.

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Review Article

INTRODUCTION

Urinary tract infection (UTI) is the most common serious bacterial infection in febrile infants and young children, second to otitis media and pharyngitis and more common than bacterial meningitis, pneumonia and occult bacteremia.[1-3] It includes 10% of all febrile children, 13.6% of febrile infants and 7% of febrile newborns.[4-6] UTI occurs in 17 to 20% of pregnancies, resulting in premature rupture of membranes, chorioamnionitis, premature delivery and postpartum maternal and neonatal infection.[7] The majority of patients present during the first year of life. Up to 1% of term neonates and 4-25% of premature ones may be involved.[8] It is more common during neonatal period and early infancy in males, declines afterwards. About 8% of girls (3% prepubertal), and 2% of boys (1% prepubertal) experience at least one episode of UTI up to the age of 7.[5,9] It occurs in 0.1-0.4% of infant girls and increase up to 1.4% during 1-5 years and 0.7-2.3% in school age. Close to 0.2% of circumcised and 0.7% of uncircumcised infant boys are at risk, which reaches to 0.1-0.2 during 1-5 years and 0.04-0.2 in school age.[10] UTI may lead to transient renal failure in 40% and permanent renal damage in 5% of patients.[11] It occurs in 15-33% of kidney transplantations, resulting in acute graft dysfunction and chronic allograft nephropathy, which affects long-term renal survival.[12] It may present as asymptomatic bacteriuria and complicated or uncomplicated infections in upper and lower urinary system.[13] Ideal treatment results in symptomatic relief, prevents progressive renal damage and urosepsis with immediate bacterial eradication.[14] For many years, treatment methods were controversial. Empirical antibiotic must have primary urinary excretion to attain high urinary level.[13] Antibiotic selection depends on identification of dominant uropathogens (age-related), severity of symptoms, patient follow up, antimicrobial sensitivity, community resistance, pharmacokinetics, drug toxicity and cost effectiveness.[15-17]

TREATMENT

Acute pyelonephritis consists of 2/3 of febrile UTIs in early childhood.[1] The following patients must be admitted: neonates less than 1 month for excluding septicemia and meningitis, inadequate drug absorption, immature immune system and increased dissemination of infection,[15]

unfavorable general conditions such as toxicity, septicemia, lethargy, low blood pressure, severe dehydration, low compliance, difficult follow-up, acute illness, immune deficiency and complicated UTI, in drug intolerance or non-compliance, and severe complicated UTI.[15-17]

Oral and outpatient treatment has been safe and effective as intravenous therapy in acute pyelonephritis.[6] Bacteremia occurs in 6.1-22.7% of children less than 2 months and in 9.3% of less than 6 months children. It is not common after 6 months of life.[18] Intravenous (IV) treatment is recommended by many authors in patients less than 1 month (less than 3 months by other authors) for 7-10 days or 3-7 days until clinical improvement followed by oral antibiotics up to 14 days. Oral treatment may be considered in 1-3-month-old infants without bacteremia or meningitis, with close follow up and good general condition.[15] Outpatient IV treatment has been reported safe in another study.[10] There has been no significant difference in the duration of fever, persistence of infection, recurrent UTIs, and renal parenchymal damage between total oral (10-14 days), complete IV (7-14 days) and short IV (2-4 days) treatments, followed by oral treatment (7-11 days) in children older than 2 months without septicemia or meningitis, which compliant to fluid consumption.[19] In children aged 2 months to 2 years, American Academy of Pediatrics (AAP) recommended completion of a 7 to 14-day course of treatment, but it is debatable in older children.[20]

SELECTED ANTIBIOTICS

Initial treatment is often empiric. It must have good parenchymal penetration, low toxicity and well tolerated. Some of the well known ones are ampicillin and gentamycin for enterococcus, group B streptococcus and gram negative bactetia,[15] and third (ceftazidime or ceftriaxone beyond 1 month) or fourth (cefepime) generations of cephalosporin are used especially in resistant uropathogens with less nephrotoxicity.[17] Several studies have demonstrated that once-daily parenteral administration of gentamycin or ceftriaxone in a day treatment center is safe, efficient and cost effective in UTI.[15] A single daily dose of gentamycin is safe with similar or more therapeutic effects, similar or less nephrotoxicity and ototoxicity compared to 3 times a day.[3,19] Broad spectrum antibiotics such as amoxicillin/clavulanic acid, second (cefuroxime, cefprozil) and third (cefixime, cefpodoxime, ceftibuten, cefdinir) generations of cephalosporins and trimethoprim-sulfamethoxazole are recommended for oral treatment.[2,21] Nitrofurantoin has high urinary and low serum level concentration and not recommended in acute pyelonephritis.[10] One study showed that 14 days oral ceftibuten has similar effect to ceftriaxone/ceftibuten in generation of renal scarring.[18] A systematic review did not show any significant difference between short course and standard treatment in the development of resistant organisms.[21]

ACUTE CYSTITIS

Oral short term (3-5 days) treatment is effective and acceptable in stable children more than 2 years of age with normal urinary tract condition.[14,22] It is as effective as 7-14 days regimen in the treatment of lower UTIs.[23] In acute cystitis, single dose regimen has less efficiency and high recurrence rate (20%).[15] Empiric treatment is the main treatment in uncomplicated cystitis. Options include broad spectrum antibiotics such as sulfonamides, trimethoprim-sulfamethoxazole, nitrofurantoin, amoxicillin clavulanate, cephalosporins and trimethoprim.[14] According to microbial resistance, amoxycillin and first generation of cephalosporins are not considered in the empiric therapy.[2] Short term fluoroquinolones has been reported safe and well tolerated, as the second line treatment in complicated UTI. Conservative treatment with anti-inflammatory medications and adequate hydration is recommended in healthy children with self-limited hemorrhagic cystitis. Ribavirin is indicated in immune deficient patients with hemorrhagic adenovirus infection. Cidofovir is suggested in polyoma and severe adenovirus infection with limited indications.[10,14] WHO guideline recommends oral cotrimoxazole or appropriate alternatives such as ampicillin, amoxicillin and cephalexin in patients with UTI for 5 days. IV treatment with ampicillin and gentamycin or cephalosporins is recommended in resistant patients suspicious to acute pyelonephritis and infants less than 2 months, followed by outpatient treatment in stable patients.[4]

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria (ABU) is more considered as a separate entity than a precursor of symptomatic infection.[20] Urine culture becomes negative in 40-50% of children during 2-5 years.[2] It will not progress to symptomatic infection, renal scarring and impairment of renal

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growth or function. Antimicrobial treatment results in eradication of normal flora, tissue invasion and pyelonephritis with different bacterial species, and usually is not recommended.[16,20] Periodic follow-up without antimicrobial treatment is recommended in patients without urologic abnormalities,[17] decreased renal growth or function, renal scarring and symptomatic UTI.[16] Treatment is indicated in immune deficiency, before urologic surgery, in mucosal damage, mucosal biopsy during cystoscopy,[22] pregnancy, and symptomatic patients.

PREVENTION

Antibiotic prophylaxis (daily treatment for at least 2 months) has been introduced by Helmholtz in 1941 for the prevention of recurrent UTI (2 or more infections during 6 months) and renal damage. Recurrent UTI may occur in 30-50% of patients[25] especially in the first 2-6 months. Currently, early diagnosis and treatment of anaphylactic purpura nephritis (APN) has been considered as the only effective approach to reduce renal scarring. Peak effect is during the first 6 months of treatment,[25] in which the risk of UTI recurrence is highest. Predisposing factors include vesicoureteral reflux (especially high grades), genetics (urothelial receptors), genitourinary abnormalities, female gender, fecal and perineal colonization, immune compromised states, secretor status, IL8 deficiency, neutrophil mediated and chemokine receptor (CXCR1), bladder instability, previous UTI, infrequent voiding, voiding dysfunction, hypercalciuria, poor fluid intake, inadequate genital hygiene, diabetic patients, constipation, encopresis, abnormal kidneys, young age (less than 6 months at first UTI) and white race. Surgical cause of bacterial persistence include Infection stone, infected nonfunctional renal segments, infected ureteral stumps after nephrectomy, vesicointestinal or urethrorectal fistula, vesicovaginal fistula, infected necrotic papillae in papillary necrosis, unilateral medullary sponge kidney, infected urachal cyst, infected urethral diverticulum or periurethral glands.[9,26]

Prophylaxis must continue until the decline in the incidence of risk factors, such as males more than 1 year with monitored vesicoureteral reflux (VUR), males with low grade VUR, children more than 7-8 years with low grade VUR) or the omission of renal scarring risk (older age).[16,25] Prophylaxis is indicated in high risk conditions for development of renal scarring or urosepsis (dilated VUR, severe obstruction, recurrent symptomatic UTI, especially with bladder instability or voiding dysfunction and girls with frequent UTIs for symptomatic relief, infective stones, up to reconstruction of renal abnormality predisposed to UTI, symptomatic VUR, at risk patients for recurrent pyelonephritis (more than one episode of pyelonephritis), symptomatic reflux,[24] high risk of recurrent UTI and renal scarring, children less than 8 years with VUR and recurrent symptomatic UTIs, VUR in neurogenic bladder, children less than 18 months with non-reflux acute pyelonephritis,[16] up to completion of imaging procedures and institution of treatment strategy,[6] susceptible patients to recurrent UTI without any documented source,[5] immune deficiency,[17] and up to resolution of obstruction.[26] Recurrent cystitis is a questionable indication.[27] Bubble bathing, cleaning pattern (back to front) and swimming are not considered with convincing evidence.[2,28]

IDEAL PROPHYLACTIC DRUGS

Ideal treatment depends on local antimicrobial susceptibility.[17] It must have low serum and high urine level, wide spectrum activity, as well as the least effect on fecal flora, minimal side effects and minimal bacterial resistance.[24,26] Ampicillin, amoxicillin and cephalexin are appropriate prophylactic drugs in children less than 3 months. Nitrofurantoin, trimethoprim, cotrimoxazole and cephalexin are appropriate drugs in children older than 4 months.[16] Prophylactic effect of cefixime is more than that of NFT, and the latter's effect more than that of TMP with more adverse effects. Discontinuation of NFT is more probable than cotrimoxazole for its gastrointestinal complications.[11] Increasing antimicrobial resistance to ampicillin and amoxicillin made them less effective and are not recommended beyond the first 2 months.[29] Beneficial effects of prophylaxis seems to be small[25] and is no longer universally accepted.[24] Prophylactic antibiotic is not very effective in the prevention of recurrent UTI, recurrent APN or new renal scar and may result in the emergence of resistant organisms in recurrent UTI.[30] The effect of prophylaxis is questionable in VUR.[31] Mild or moderate grades of VUR do not increase the incidence of APN or renal scar.[30,32] Complications of prophylaxis are greater in low grade reflux than its benefits[23] and prophylaxis has not been recommended in low grade reflux in a Swedish guideline and some other refer-

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ences.[27,31] According to uncertainty about the beneficial effect of long term prophylaxis and low efficacy in some studies,[26,27] more investigations with control group are recommended in the evaluation of this treatment.[1,33] Complications of prolonged antibiotic prophylaxis occur in 8-10% of patients, especially during the first 6 months including nausea, vomiting, skin reactions, hepatotoxicity and hematologic complications, with negative effect in producing enteric and oropharyngeal resistant organisms[25,30] and increased risk of symptomatic urinary tract infection by resistant organisms,[27] even in patients with clean intermittent catheterization[31] and increased resistance to the 3rd generation of cephalosporines.[26] Conway reported 7 times increase in recurrent UTI with resistant organisms by antimicrobial prophylaxis.[1]

Complications are less frequent in children than in adults, due to lower dosage, and usually lack of drug interaction in children.[26] Angocin Anti-Infekt N, a herbal medicinal product, has efficacy and safety in the prophylactic treatment of chronically recurrent UTIs.[34] Urinary catheterization is an important factor in nosocomial infections. Duration of catheterization is important in iatrogenic infection. Catheterization increased the chance of UTI by 5-10% in each day after the first 48 hours. Therefore, hand hygiene, sterile catheterization, closed sterile catheter and reduced time of catheterization is recommended to prevent nosocomial UTI. Catheterization is recommended in necessary conditions.[35,36]

ADDITIONAL TREATMENTS

There are many non pharmaceutical recommendations in the prevention of recurrent UTI. Some of them are as follows:

- Improving voiding dysfunction by timed voiding, biofeedback procedures and anticholinergic drugs in patients with unstable and small bladder.[16]
- Improving voiding dysfunction by timed voiding with bowel regimens in patients with infrequent voiding.[16]
- Increased fluid intake.
- Pelvic floor therapy, especially in recurrent UTI with detrusor sphincter dyssynergia or dysfunctional voiding.[37] Improvement of intestinal emptying habits (constipation, fecal incontinence).[16]
- Circumcision to reduce the risk to 0.18%,[9] up to 10 times in the first 6 months.[5] Recommendation for routine circumcision is controversial not supported by the existing evidence.[17,26] It is specifically effective in susceptible patients to recurrent UTI without any documented source, newborns with prenatal hydronephrosis and VUR, neonates with high grade reflux or genitourinary abnormalities,[5] VUR in males with unilateral agenesis or multicystic dysplastic kidney, children with high risk to HIV infection[2,5] and children susceptible to recurrent UTI.[26]
- Cranberries have been advocated for the prevention and treatment of UTI. Cranberry has a low transient effect in reducing urinary PH[7] and may be beneficial in patients older than 60 years. It seems to be ineffective in the prevention or reduction of UTI.[6] But, there is no meta-analysis to support the beneficial effect of cranberry in children and it needs more investigation in children.[25]

Vitamin C is considered to acidify urine pH, with insufficient evidence. Increased formation of calcium oxalate stones has reduced its clinical usage.[7] Vitamin A, horseradish (armoracia rusticana radix), probiotics, cranberry, and nasturtium (tropaeoli majoris herba) have favourable, but inconclusive results in adults. Recurrent infections are still possible.[25] There is not sufficient data about the preventive effect of probiotics in recurrent UTI especially in children[7,16] suggesting to have limited significance. A randomized trial in 2007 demonstrated a non-significant difference between probiotics and cotrimoxazole in prevention of UTI.[25] It has been reported that vaccination with inactivated uropathogens, urovaxom, for 3 consecutive weeks and a booster dose at 6 months is an effective modality and reduced the possibility of infection and increased the urinary secretory IgA level.[26] Breast milk contains protective factors like secretory IgA, lactoferrin, anti-adhesive oligosaccharides, glycoproteins and cytokines which are protective against UTI in the first 7 months of life.[14] There is no clinical trial of methenamine hippurate in children. It might be beneficial in normal renal tract without major disturbances.[25]

CONCLUSION

Treatment of UTI has been a therapeutical challenge in pediatric nephrology. According to drug resistance and change in mind, newer drugs and treatment protocols have been suggested. Severity and duration of treatment declined and easier methods with fewer limitations are introduced.

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