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REVIEW

Urinary tract infection in the newborn and the infant: state of the art

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Abstract

Urinary tract infection is one of the most common cause of infection in newborns. Obtaining a urinary tract infections (UTIs) diagnosis just on the basis of the clinical findings is frequently difficult, however, being the pediatrician's goal to reduce the risk of renal scarring, a prompt diagnosis and treatment is of extreme importance. The key instrument for the diagnosis of UTIs is represented today by urine culture. However, in reality, the caregivers and investigators are increasingly demanding fast and cheap methods for a rapid and effective diagnosis.

Keywords: *Newborn, infant, UTIs, PCT, treatment*

Introduction

The urinary tract infections (UTIs) are so far the leading cause of severe bacterial infections in infants and young children. Population-based studies showed that 3–7% of girls and 1–2% of boys have had at least one UTI by 6 years of age [1].

The UTI location may be strictly limited to the bladder, involving one or both kidneys, or cover both sites. Usually those involving just the bladder (cystitis) are not considered severe bacterial infections despite leading to significant morbidity. On the contrary, urinary infections with kidney involvement by acute pyelonephritis (APN) can cause acute renal morbidity and lead to scarring with consequent hypertension, and chronic renal disease [2]. All newborns and infant who suffered from APN are at higher risk of developing UTI recurrences with cystitis episodes in adult life. In particular, females with renal scarring continued to have a high proportion of pyelonephritic recurrences after 10 years of age, implying that they risk progressive renal disease and should be closely followed into adulthood [3].

Clinical assessment

During the first month of life, the symptoms of infection may be nonspecific with low or no fever in about one-half of the cases. Newborns and infants aged 0–2 months with APN have no symptoms localized to the urinary tract rather nonspecific one as: fever, poor feeding, failure to thrive, prolonged jaundice and severe systemic illness; as a result, the UTI is usually discovered as part of an evaluation for neonatal sepsis. A subnormal or only slightly elevated body temperature or symptoms such as apathy, anorexia, grayish color, and body tenderness can indicate a serious infection. Diagnosis of APN using clinical and laboratory parameters is unreliable in children particularly those less than 2 years. This may lead to the young patients to be at higher risk for renal injury since the lack of localizing signs, associated with intrinsic low immunitary defences, delays the beginning of antimicrobial drugs [2,4].

The 1999 American Academy of Pediatrics (AAP) practice parameter recommended that UTI should be considered in any child younger than 2 years of age with unexplained fever. UTI has accounted for febrile presentations in 7.5% of infants <8 weeks, 5.3% of infants <1 year, and 4.1% of children <2 years [5].

The Pediatric Research in Office Settings (PROS) Network of the AAP study showed UTI in 9% of febrile infants <3 months and 10% of these had bacteraemia.

It must be stressed that a recent study showed urinary candidosis infection without extra-renal infection in term babies with congenital abnormalities and in preterms admitted in Neonatal Intensive Care Units was associated with renal parenchymal disease and extra-renal dissemination. The overall mortality rate occurred in 1/3 of the cases [6].

Risk factors

The UTIs incidence in infants approximately ranges from 0.1% to 2.0% in all newborn infants to 20% in preterm and at risk neonatal population (i.e. low-birth-weight infants) [7,8]. During the first months of life, there were many boys than girls having UTIs, predominantly without high fever; after 6 months of life, girls were prevalent [9].

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Differently by previous reports it has been recently underlined that breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76% [10].

Febrile UTI is considered the most common serious bacterial infection occurring in infancy and early childhood in the developed world. About 10–30% of children with febrile UTIs developed renal scarring. This is actually thought to be a risk factor also for hypertension and renal insufficiency in the longer term [11]. The most important end point, since long-term medical consequences (proteinuria, hypertension, and chronic kidney damage) is generally associated with the presence of renal parenchymal damage.

Vesico-ureteric reflux (VUR) has been considered for many years as risk factors for APN in young children. Therefore, the prevalence of VUR was similar among children with and without UTI and decreased with increasing age [12]. However, only renal scarring assessed by renal scintigraphy and not VUR (even if high-grade and bilateral) was a predictor of early recurrent UTI [13]. Thus, the occurrence of VUR among children without UTI was found significantly higher than traditional estimates. Finally, the role of VUR in establishing renal scarring has been reappraised and some renal parenchymal abnormalities associated with VUR are noninfectious but congenital or prenatal in origin.

In retrospective studies, circumcision in males was associated with a 10-fold reduction in the incidence of having a UTI during the first year of life. Circumcision prevented recurrent symptomatic UTI in a randomized trial [14]. Therefore, a recent study has, however, showed a higher rate of UTI in male infants during the post-circumcision period, especially in those made in the traditional way than performed in hospital due to lack of sanitary control [15].

Recent advances in genetics have suggested that a deregulation of candidate genes (HSPA1B, CXCR1 & 2, TLR2, TLR4, TGF-β1 genes) in humans may predispose patients to recurrent UTIs [16].

Laboratory diagnosis

Until now, the gold standard for the diagnosis of UTI has always been considered the urine culture collected under sterile conditions (e.g. suprapubic aspiration, or 'in-and-out' catheterization). Therefore, in infants and small children urine is mostly obtained from a bag sampling. A single bag specimen should not be relied on for the diagnosis of UTI, even if there is pure growth of more than 100,000 UFC/ml urine.

Because culture results are not available for at least 24 h, there has been considerable interest in evaluating tests that may predict the results of the urine culture so that appropriate therapy can be initiated at the first encounter with the symptomatic patients. The tests that have received the most attention are urine microscopy for leukocytes and bacteria, and biochemical analyses for leukocyte esterase and nitrite that can be assessed rapidly by dipstick. A dipstick negative for leukocyte esterase and nitrite, or microscopic analysis negative for pyuria and bacteriuria of a clean voided urine, bag, or nappy/pad specimen may reasonably be used to rule out UTI, avoiding the need for further investigations [17]. Therefore, comparing microscopy and urine dipstick testing, using bacterial colony count on urine culture showed no significant difference between the two methods [18].

In the recent years serum procalcitonin, a marker of bacterial disease, has been tested to predict the level of infection in newborns with sepsis and in children with UTI [19–22]. Procalcitonin seems to be a valid biological marker, with an acceptable sensitivity and specificity, which predicts a renal involvement of the infection (pyelonephritis), in comparison with the low specificity of C-reactive protein. Procalcitonin also seems to be correlated with the degree of involvement at the moment of diagnosis of febrile UTIs and with scarring. This measurement could be useful for the treatment of children with febrile UTIs, allowing prediction of patients at risk of permanent parenchymal renal lesions. Although the number of studies published is limited, procalcitonin has, however, demonstrated some specific characteristics that make it more reliable than C-reactive protein in highlighting renal lesions during UTIs. These are, firstly, the velocity with which it is induced by the infectious stimulus, which increases somehow its high negative predictive value; secondly, the grater specificity compared with C-reactive protein in detecting renal involvement during febrile UTIs; and lastly, but maybe the most interesting aspect, even though documented in only two studies, is the progressive increase of its blood concentration correlated with the increase of the renal lesion's entity. In conclusion, for the time being, a value of procalcitonin >0.5 ng/ml can be considered an accurate and sufficiently reliable new biological marker to be used in clinical treatment of febrile UTIs and to predict renal parenchymal involvement, as also evidenced by Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy [23]. Promising results are expected with metabolomic studies on urine of newborn and infants with renal disease compared with controls [24].

Imaging and UTI

Various imaging investigations (including ultrasonography, voiding cystography, and technetium-99m-DMSA scintigraphy) after a first febrile UTI have been widely recommended, with the objective of identifying pathologic malformations and/or risk factors that, if not appropriately diagnosed and managed, might lead to additional infections and ongoing renal parenchymal damage. Evidence of the value of these imaging studies in changing management approaches or affecting subsequent outcomes is limited, especially today, given the questionable role of antibiotic prophylaxis since some authors have reported that long-term antibiotic prophylaxis does not fully prevent UTI or scarring, that antibiotic-related adverse events are known to occur, and that the incidence of APN does not increase in spite of prophylactic antibiotic cessation [25].

In the past, most studies concentrated on the prevalence of urologic abnormalities and not the effect that early detection and management of anomalies might have on preventing subsequent renal parenchymal damage. Renal ultrasonography and renal scanning at the time of the acute illness are of limited value, because they do not provide information that modifies management. Up to now there is no firm evidence of using routine imaging for children under 2 years old and for the one of 2 or more with an initial UTI it is still not recommended, in fact the exact role of routine imaging studies after the diagnosis of a first febrile UTI in 309 children 1–24 months of age it is still to be established. However, children 2–5 old with an initial UTI should be monitored and investigated further if they experienced a second UTI [26].

A test for the localization of UTI as an initial step in the investigation of these patients would allow the exclusion of all children with a lower UTI from further investigation. A non-invasive test would be desirable. Acute Tc-99m-DMSA scintigraphy remains the reference standard for the localization of UTI. Therefore, these scans are expensive, invasive, and incur a radiation load. However, there is insufficient evidence to recommend any further investigation routinely: in the absence of any effect on patient outcome, universal imaging (for example, VCUG for reflux or DMSA scintigraphy for renal scarring) cannot be justified. The decision on whether or not to perform these examinations should be made on individual patient basis. Actually, many authors suggest that VCUG should be reserved for those children who have been deemed to require further investigation, after the demonstration of an abnormal DMSA scan and abnormal urinary tract by US.

Treatment

Pharmacotherapy is the cornerstone of the treatment of UTI in newborns and children. Any recommendation about (initial) antibiotic treatment should be regularly updated and adapted to local resistance profiles and to economical factors in different health systems [27].

In sick newborns and young infants, antibiotics are generally used empirically prior to availability of urine or blood culture results. Based on local bacterial ecology and the known causative organisms for septicemia and urinary tract infection, ampicillin and an aminoglycoside (e.g. gentamicin) are used parenterally. Gentamicin is extensively used and increasingly given once a day in newborn infants. This dosing regime increases peak concentrations of the drug without increasing plasma trough levels and nephrotoxicity. However, there is a trend to use third and fourth generation cephalosporins such as, cefotaxime, ceftazidime, cefepime. These drugs are excreted mainly via renal elimination, and like most drugs, the plasma elimination of these agents in newborns is prolonged compared to that of the adults and older children. Therefore, dosing regimens are adjusted for newborns of various fetal and postnatal maturities. It is strictly forbidden the use of cefriaxone in newborns [27–30].

The benefits demonstrated after the beginning of antibiotic treatment were the eradication of infection in all cases and the time to resolution of fever.

In older infants and children, Doganis et al. reported that delayed treatment over 24 h did not seem to increase the risk of renal scars. In fact frequency of scarring: 11 out of 24 infants treated in the first 24 h *versus* 28 out 52 treated later [31].

Moreover, no significant difference in the incidence of scarring was observed in relation to the selection and route of administration of antibiotics [32]. Despite some limitations, the first concerning exact time of the onset of infection, this study reflects accurately the clinical situation in which a child presents as febrile and unwell, with symptoms suggesting APN. At such a time, with the inflammatory process well established, it seems that antibiotics do little to reduce scarring. They though it is possible to advise a less-urgent approach for children with fever who appear otherwise well, even if there is a risk of recurrent UTI.

This topic is controversial and there is still a debate in the literature: some authors suggest in their title that early antibiotic treatment of pyelonephritis in children is still mandatory [33].

Coulthard et al. report that being febrile or unwell during a UTI does not predict the development of scars, but prompt treatment appears to prevent scarring in children with VUR [34].

Numerous studies have addressed the treatment of APN in children, comparing different antibiotics and different modes and durations of administration [35,36]. In quite all of those studies, the outcomes (kidney damage) are similar in the various arms, leading to the assumption that all treatments are equally effective in reducing scarring secondary to APN.

In an interesting paper entitled 'Urinary tract infections revisited' Godaly and Svanborg suggest a potential tailored management of pediatric UTI in the next future, considering bacterial virulence and host immune response: standard antibiotic treatment should be reserved only to patients with high bacterial virulence and high immune response [37].

The use of prophylactic antibiotic following UTI, particularly in young children with VUR, has been a common practice for decades. However, at such a time, with the inflammatory process well established, it seems that antibiotics do very little to reduce scarring [38].

Additional research is needed to explore other avenues of therapy, such as the use of steroids or other anti-inflammatory agents, and to evaluate the role of genetic factors that may predispose patients to scar formation [38].

Conclusion

Early treatment of UTI, namely febrile, is considered strictly mandatory in newborns. In infants and young children early treatment of APN seems to have no significant effect on the incidence of subsequent renal scarring; antimicrobial prophylaxis seems to have little effect in preventing UTI recurrences and the exact role of the imaging after a first UTI is still debated.

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References

1. Mahant S, Friedman J, MacArthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. Arch Dis Child 2002;86:419–420.
2. Cataldi L, Mussap M, Fanos V. Urinary tract infections in infants and children. J Chemother 2006;18:5–8.
3. Martinell J, Claesson I, Lidin-Janson G, Jodal U. Urinary infection, reflux and renal scarring in females continuously followed for 13–38 years. Pediatr Nephrol 1995; 9:131–136.
4. Wald E. Urinary tract infections in infants and children: a comprehensive overview. Curr Opin Pediatr 2004;16:85–88.
5. Schlager TA. Urinary tract infections in children younger than 5 years of age: epidemiology, diagnosis, treatment, outcomes and prevention. Paediatr Drugs 2001;3:219–227.
6. Robinson JL, Davies HD, Barton M, O'Brien K, Simpson K, Asztalos E, Synnes A, Rubin E, Le Saux N, Hui C, et al. Characteristics and outcome of infants with candiduria in neonatal intensive care – a Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study. BMC Infect Dis 2009;9:183.
7. Cataldi L, Fanos V. Urinary tract infections in the newborn: diagnosis and therapy. In: Cataldi L, Fanos V,

Simeoni U, editors. Neonatal nephrology in progress. Lecce: Agorà Ed; 1996. pp 183–198.
8. Cataldi L, Salvaggio E, Prota M. L'infection urinaire du prématuré: existe-t-elle? Progrès en Néonatologie 1990:271–273.
9. Jakobsson B, Esbjörner E, Hansson S. Minimum incidence and diagnostic rate of first urinary tract infection. Pediatrics 1999;104(2 Part 1):222–226.
10. Katikaneni R, Ponnapakkam T, Ponnapakkam A, Gensure R. Breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76%. Clin Pediatr (Phila) 2009;48: 750–755.
11. Bell LE, Mattoo TK. Update on childhood urinary tract infection and vesicoureteral reflux. Semin Nephrol 2009; 29:349–359.
12. Hannula A, Venhola M, Renko M, Pokka T, Huttunen NP, Uhari M. Vesicoureteral reflux in children with suspected and proven urinary tract infection. Pediatr Nephrol 2010;25: 1463–1469.
13. Yamazaki Y, Shiroyanagi Y, Matsuno D, Nishi M. Predicting early recurrent urinary tract infection in pretoilet trained children with vesicoureteral reflux. J Urol 2009;182(4 Suppl): 1699–1702.
14. Nayir A. Circumcision for the prevention of significant bacteriuria in boys. Pediatr Nephrol 2001;16:1129–1134.
15. Prais D, Shoov-Furman R, Amir J. Is ritual circumcision a risk factor for neonatal urinary tract infection. Arch Dis Child 2009;94(3):191–194.
16. Zaffanello M, Malerba G, Cataldi L, Antoniazzi F, Franchini M, Monti E, Fanos V. Genetic risk for recurrent urinary tract infections in humans: a systematic review. J Biomed Biotechnol 2010;2010:321082.
17. Whiting P, Westwood M, Watt I, Cooper J, Kleijnen J. Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr 2005;5:4.
18. Mori R, Yonemoto N, Fitzgerald A, Tullus K, Verrier-Jones K, Lakhanpaul M. Diagnostic performance of urine dipstick testing in children with suspected UTI: a systematic review of relationship with age and comparison with microscopy. Acta Paediatr 2010;99:581–584.
19. Mussap M, Degrandi R, Cataldi L, Fanos V, Plebani M. Biochemical markers for the early assessment of neonatal sepsis: the role of procalcitonin. J Chemother 2007;19:35–38.
20. Spada S, Cuccu A, Mussap M, Testa M, Puddu M, Pisu C, Burrai P, Fanos V. Reliability of procalcitonin in neonatology. Experience in 59 preterm newborns. J Matern Fetal Neonatal Med 2009;22 (Suppl 3):96–101.
21. Zaffanello M, Brugnara M, Franchini M, Fanos V. Is serum procalcitonin able to predict long-term kidney morbidity from urinary tract infections in children? Clin Chem Lab Med 2008;46:1358–1363.
22. Pecile P, Romanello C. Procalcitonin and pyelonephritis in children. Curr Opin Infect Dis 2007;20:83–87.
23. Mantaddakis E, Plessa E, Vouloumanou EK, Karageorgopoulos DE, Chatzimichael A, Falagas ME. Serum procalcitonin prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. J Paediatr 2009;155:875–881.
24. Atzori L, Antonucci R, Barberini L, Locci E, Cesare Marincola F, Scano P, Cortesi P, Agostiniani R, Weljie A, Lai A, et al. ^{1}H NMR-based metabolic profiling of urine from children with nephrouropathies. Front Biosci (Elite Ed) 2010; 2:725–732.
25. Hayashi Y, Kojima Y. Is antibiotic prophylaxis effective in preventing urinary tract infections in patients with vesicoureteral reflux? Expert Rev Anti Infect Ther 2010;8:51–58.
26. Montini G, Zucchetta P, Tomasi L, Talenti E, Rigamonti W, Picco G, Ballan A, Zucchini A, Serra L, Canella V, et al. Value of imaging studies after a first febrile urinary tract infection in young children: data from Italian renal infection study 1. Pediatrics 2009;123:e239–e246.
27. Bensman A, Ulinski T. Pharmacotherapy of lower urinary tract infections and pyelonephritis in children. Expert Opin Pharmacother 2009;10:2075–2080.
28. Aranda JV, Cataldi L, Fanos V. Clinical pharmacology of antimicrobials for urinary tract infections in newborns and young infants. J Chemother 2006;18 (Suppl 3):14–15.
29. Fanos V, Antonucci R, Mussap M, Zaffanello M. Drug-induced nephrotoxicity in the newborn: the state of the art. Pediatr Drugs, in press.
30. Fanos V, Cuzzolin L, Atzei A, Testa M. Antibiotics and antifungals in neonatal intensive care units: a review. J Chemother 2007;19:5–20.
31. Doganis D, Siafas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G, Kostanto Poulosa A, Sinaniotis K. Does early treatment of urinary tract infection prevent renal damage? Pediatrics 2007;120.
32. Hewitt IK, Zucchetta P, Rigon L, Maschio F, Molinari PP, Tomasi L, Toffolo A, Pavanello L, Crivellaro C, Bellato S, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. Pediatrics 2008;122:486–490.
33. Doganis D, Sinaniotis K. Early antibiotic treatment of pyelonephritis in children is still mandatory. Pediatrics 2009; 123:e173–e174.
34. Coulthard MG, Verber I, Jani JC, Lawson GR, Stuart CA, Sharma V, Lamb WH, Keir MJ. Can prompt treatment of childhood UTI prevent kidney scarring? Pediatr Nephrol 2009;24:2059–2063.
35. Hodson EM, Willis NS, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev 2007;(4):CD003772.
36. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. Cochrane Database Syst Rev 2007;(4):CD003237.
37. Godaly G, Svanborg C. Urinary tract infections revisited. Kidney Int 2007;71:721–723.
38. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, Cecchin D, Pavanello L, Molinari PP, Maschio F, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, non-inferiority trial. Pediatrics 2008;122:1064–1071.