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Urinary tract infection in spina bifida

Yazan F. Rawashdeh[1]
Gitte M. Hvistendahl[2]
[1]Paediatric Urology Section, Department of Urology, Aarhus University Hospital, -, Denmark
[2]Aarhus University Hospital, Aarhus, Denmark

Abstract

The urological consequences of spina bifida in children remain challenging for the paediatric urologist and nephrologist. And as the majority of these patients are born with normal urinary tracts and renal function the mainstay of modern management has been to preserve renal function by countering the effects of high bladder pressures, detrusor sphincter dyssynergia and urinary tract infection (UTI) by clean intermittent catheterization (CIC), combined with administering anticholinergics and at times prophylactic antibiotics. Solid evidence derived from well-designed clinical trials for such management protocols are sparse and patently in need of revision and empirical confirmation. Reviewing MEDLINE and The Cochrane Library for English language studies dealing with UTI in paediatric spina bifida over the last decade resulted in 47 hits which were subsequently reviewed shortlisting 22 publications of sufficient relevance and quality for final analysis. Despite the heterogeneous nature of results data indicate that CIC remains a cardinal aspect of management and that regardless of catheter type (single use vs. reusable) no increase in UTI rates were detectable. Furthermore, studies confirm that use of prophylactic antibiotics in paediatric spina bifida patients is superfluous and can safely be discontinued at minimal risk.

Summary of recommendations

1. Rates of UTI in children with spina bifida is unaffected by the type of catheter used (single use versus reusable or coated hydrophilic versus polyvinylchloride) (GoR A).
2. Leucocyte esterase tests and dipsticks used for UTI screening purposes can only be used to exclude infection, not to confirm it or confirm significant bacteriuria (GoR B).
3. In children with spina bifida on CIC, prophylactic antibiotics can safely be discontinued, particularly in male patients with a history of low UTI rates and those without vesico-ureteral reflux (GoR A).
4. Antibiotic prophylaxis decreases the rate of bacterial colonization, but may change the colonizing flora to more pathogenic bacterial species (GoR B).

1 Introduction

Despite concerted efforts to decrease the incidence of neural tube defects by folic acid fortification, improvement of periconceptional care and prenatal screening about 1 in 2,000 European children are born with spina bifida [1], [2]. Although seemingly low compared to other congenital anomalies such as malformations of the urinary tract for example, spina bifida, which comes in two main forms; spina bifida occulta and the less common but more severe spina bifida aperta (both of which henceforth will be referred to collectively as spina bifida), is a condition which is severe and a subsuming anomaly not only involving the spinal column and CNS, but may also lead to hydrocephalus, paraplegia, mental retardation and neuropathic bowel and bladder. Such a multi-systemic effect renders spina bifida patients severely afflicted and in need of multidisciplinary management and care, posing immense challenges to involved health professionals, care givers and society as a whole not to mention the economic burdens amassed with increasing life expectancy and management options [3].

At birth patients with spina bifida have normal urinary tracts and renal function, so any progressive deterioration of renal function over time occurs due to the effects of neuropathic bladder dysfunction with its attendant detrusor overactivity, detrusor sphincter dyssynergia, and low bladder compliance which results in incomplete bladder emptying, urinary tract infection (UTI) and vesicoureteric reflux [4]. Untreated most of these children will develop end stage renal disease and therefore the mainstay of

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therapy through the last many decades has been aimed at countering high bladder pressures through clean intermittent catheterization (CIC) combined with the administration of anticholinergics in addition to low dose antibiotic chemoprophylaxis to prevent UTIs.

Other than being a main contributing factor for progressive renal deterioration in patients with spina bifida, recurrent UTIs account for much morbidity and hospitalization in this patient group [3]. A recent analysis of data collected on spina bifida patients over a twenty year observation period showed that 50% of patients developed at least one UTI by 15 months of age increasing to over 80% by the age of 15 years and approximately half the patients developed recurrent UTIs with a high prevalence of *Pseudomonas* infections and other atypical bacteria [5]. And whereas standardized guidelines for the diagnosis, prevention and management of UTIs in children are under constant review and updating [6] no such consensus exists for children with spina bifida [7]. Lack of consensus on guidelines for managing UTI in this patient subset is undoubtedly multifactorial and most likely stems, at least in part, from the difficulty in designing prospective randomized controlled studies in a patient population often marginalized and with an, at times, unclear chain of command and responsibility with regards to the many specialties assigned to their management. Recognizing the difficulties associated with conducting meaningful randomized controlled studies the Center for Disease Control in association with the Spina Bifida Association recently launched a prospective standardized protocol in the United States in order to optimize urological care by recruiting several large centers treating spina bifida patients, in an effort focused on preventing UTI and renal scarring with the ultimate goal being the preservation of renal function. Prospective data collected will help guide future management protocols and this ambitious study is scheduled to run over a five year period and is a welcome step in the right direction [8].

2 Methods

A systematic literature search was performed for the last 10 years in MEDLINE and the Cochrane library with the following key words: spina bifida, child, urinary tract infection, and antibiotic prophylaxis with the following limitations: English publications and human studies.

A total of 47 publications were identified, which were screened by title and abstract and subsequently supplemented by publications mentioned in selected publications or known by the authors. Studies were analyzed and rated according to the level of evidence (LoE) and the strength of recommendations graded (GoR) according to a system used in the EUA guidelines (2015) modified from the Oxford Centre for Evidence-based Medicine [9].

3 Results and discussion

In all, searches produced 47 hits which after screening by title and abstract and supplementation as previously mentioned resulted in 22 studies incorporated into this overview. Over all there was a rarity of randomized controlled trials or prospective studies on this specific topic. Out of the 22 studies mentioned only two randomized trials, and three nonrandomized comparative trials, were present. The remainder comprised mainly of retrospectives studies in addition to cross sectional reports, surveys, guidelines and expert opinion. It can hence be said that the level of evidence present in the body of literature concerning UTI in paediatric spina bifida patients is poor and patently in need of review based on well-designed prospective randomized control trials which although difficult to attain, constitute the only viable way forward and therefore must be strived for.

4 Definition of UTI

A major point of contention and a prerequisite for any meaningful strategy on preventing UTI in spina bifida patients is the agreement on what constitutes infection. As opposed to normal children where a clear definition exists [6], a lack of consensus on this very basic aspect is noticed when reviewing the relevant spina bifida literature. In a systematic review of spina bifida studies reporting on UTI by Madden-Fuentes et al. only 39.3% of studies published in paediatric journals provided an explicit definition of UTI and the overall definitions were heterogeneous and have not improved in peer reviewed publications over the last five decades as might be expected with the adoption of more rigorous publication criteria. This of course limits any collective conclusions that can be drawn on incidences, management and prevention of UTI from meta-analyzing the literature [10]. Definitions are further complicated by the fact that a majority of spina bifida patients performs CIC and therefore may have colonized urine without actually being infected [11]. Based on their systematic review Madden-Fuentes and colleagues recommend future studies to a priori define UTI as; more than two signs/symptoms (fever >38°C, abdominal pain, new back pain, new or worsening incontinence, pain with CIC or urination in addition to

cloudy malodourous urine) AND >100,000 colony forming units per mL urine of a single organism AND >10 white blood cells per high power field on urine microscopy. Although strict this definition can serve as a uniform starting point amenable to refinement and reconsideration based on study outcomes [10]. In a prospective observational study comparing leucocyte esterase tests (LET) and dipsticks with laboratory cultures in spina bifida children on CIC it was found that home screening with LET could be used to exclude significant bacteriuria but had no role in diagnosing infection or significant bacterial growth [12].

5 CIC

Since its introduction in the early seventies CIC has become a cardinal aspect of bladder management in spina bifida patients [13]. Its proactive use in these children is also advocated as studies have shown that early CIC onset decreases the risk of renal function deterioration and bladder augmentation [14], [15], [16], [17]. However CIC is not without complications; such as hematuria, pain, creation of false passages and UTI with some studies even suggesting that proactive CIC may be without long-term benefit and should therefore be reserved to patients where catheterization cannot be avoided [18] [19]. In their retrospective review of 107 patients, from the newborn period to three years of age, Kaye et al. compared incidences of UTI in patients managed by CIC versus patients able to void spontaneously. They found a statistically significant higher incidence of UTI in the CIC group on final follow up leading them to conclude that proactive early onset CIC may not be warranted in infants with spina bifida and should be deferred till a time when it cannot be avoided [19]. Other than its retrospective nature and relatively small cohort, it must be assumed that the study is biased by the fact that patients at the authors' institute were managed by CIC on "a need basis" and not proactively since they had the two subsets to compare in the same cohort. This weakens any conclusions reached on the effectiveness or lack hereof of proactive CIC protocols. It can further be argued that deviance from the accepted paradigm of early CIC rendered patients more susceptible to UTI when they transitioned from being spontaneous voiders to reliant on CIC as late onset CIC may have been detrimental to bladder function and dynamics. Results and conclusions have therefore to be taken with some reservation pending prospective randomized studies on this topic.

Since its inception, and despite improvements and modifications in catheter design, introduction of single use catheters and pre-lubricated hydrophilic portable catheters, CIC outcomes remain unaltered. This has been documented in a large Cochrane review, where the authors found no convincing evidence that the incidence of UTI is affected by use of aseptic or clean technique, coated or uncoated catheters, single (sterile) or multiple-use catheters, self-catheterization or catheterization by others, or by any other strategy [20]. Similar results have been confirmed in a recent paediatric randomized crossover trial comparing single use hydrophilic coated catheters with multiple use polyvinylchloride catheters with regards to incidences of UTI. The results actually showed a significantly higher incidence of self-reported UTI measured in (person-weeks of UTI) in the hydrophilic single use catheter group but no significant difference in weeks of febrile UTI or antibiotic use between the groups. A plausible explanation put forward for the higher rate of self-reported UTI in the hydrophilic catheter cohort was the issue of slipperiness of the coated hydrophilic catheters leading to difficult catheterization. Overall, the study however simply reiterates the findings of the Cochrane review in paediatric spina bifida patients and underscores that when CIC is done properly catheter type and for that matter technique, have no implications on outcome [21].

6 Antibiotic prophylaxis

The general use of prophylactic antibiotics to prevent infection in patients presumed to be at a higher risk for developing UTI is commonplace albeit controversial. The same goes for patients with spina bifida especially those on CIC. Conventional wisdom has it that periurethral flora originating from the gastrointestinal tract can be introduced into the bladder and ultimately the upper tracts by the passing of a catheter particularly when done multiple times during the day and hence be the cause for bacteriuria and UTI. This has led to an intuitive adoption of antibiotic prophylaxis in an effort to prevent colonization and infection even though it may be that the natural history of colonized urine in spina bifida patients on CIC is completely benign and not a forerunner to UTI as shown in a small observational study by Schlager et al. [22]. In pediatric spina bifida patients there are only a few studies, of proper design and even less with proper strength to have taken on such a claim. In a double blinded placebo controlled cross-over trial of 15 children on CIC receiving either nitrofurantoin or placebo over a period of 11 months it was shown that although symptomatic UTIs dropped significantly to half in the nitrofurantoin group, bacterial colonization in this group, which decreased slightly by about 10%, remained as high as 65% with the flora responsible for colonization changing from the normal *Escherichia coli* to the more resistant Klebsiella spp. and Pseudomonas spp. that however were not the cause of any infections during the study's observational period [23]. In a more recent and larger study of 176 patients by Zegers and

collaborates, spina bifida paediatric patients on CIC were randomized to either continue or discontinue antibiotic prophylaxis. The main outcomes were in line with those of Schlager et al. [23] in that discontinuation of prophylaxis lead to a significant increase in the rates of asymptomatic significant bacteriuria and afebrile simple UTIs but did not alter the rates of febrile UTIs between the groups. For simple UTI the relative harm of stopping prophylaxis was calculated to be 2.2; that is if two patients discontinued antibiotic prophylaxis for one year, one extra simple nonfebrile UTI would occur. Based on these results the study concluded that spina bifida patients on CIC and low dose antibiotic prophylaxis could safely discontinue chemoprophylaxis in particular males, patients with a history of low UTI rates and those without VUR [24].

7 Further research

Much of the current knowledge on UTI, prevention and management in paediatric spina bifida patients is anecdotal, based on experience, trial and error or grounded in the adult literature. Very little emanates from solid factual and empirical evidence harnessed from clinical trials. Therefore future well-designed studies need to tackle even the most basic principles of management preferably in the setting of randomized controlled trials. Issues that have to be revisited in studies of large paediatric cohorts include those of antibiotic prophylaxis, proactive CIC protocols as there remain a lot of unsettled disputes. Furthermore, ancillary though significant matters of relevance on UTI incidences in these patients have also to be addressed such as bowel management, issues of continence both urinary and fecal in addition to the indications of surgical and neurosurgical intervention and their timing on the long-term outcome and quality of life of this patient category. For such studies to succeed multi-center collaboration, standardization of definitions and treatment protocols are essential prerequisites.

8 Conclusions

Spina bifida patients are born with normal urinary tracts, which places great responsibility on the managing paediatric urologists and nephrologists to preserve renal function in this very vulnerable population. And hence preventing and managing UTI assumes special relevance for meeting these ends. Current evidence supports the need for early onset “preemptive” CIC in order to improve bladder emptying and counter the effects of high detrusor pressures especially when combined with anticholinergics. There is no convincing evidence that suggests that CIC induces UTI with or without concomitant continuous low dose antibiotic prophylaxis with most of the evidence tipping the balance in favor of not needing prophylaxis in these patients and even suggesting that their use might have untoward effects on the natural commensal flora in the urinary tract.

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Corresponding authors: Yazan F. Rawashdeh, Aarhus University Hospital, Paediatric Urology Section, Department of Urology, - -, Denmark, Phone: -, E-mail: yazan@clin.au.dk

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