UROLOGICAL CARE FOR CHILDREN WITH SPINA BIFIDA

Individual, tailored and without antibiotic prophylaxis

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Individual, tailored and without antibiotic prophylaxis

UROLOGISCHE ZORG VOOR KINDEREN MET SPINA BIFIDA:
individueel afgestemd en zonder antibiotische profylaxe

(met een samenvatting in het Nederlands)

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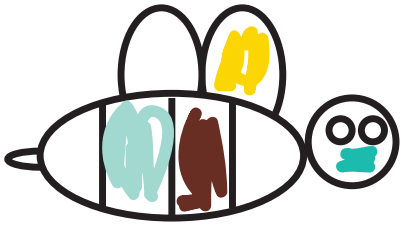
General introduction



GENERAL INTRODUCTION

Spina bifida, pathophysiology

The physiological process of neural tube development, starting at the fifth somite in the end of the third gestational week, resembles an two-way (cranially and caudally) headed zipper. Completion of this process is between day 25 and 28, provided that adequate signaling from the neural plate to the overlying mesoderm and ectoderm occurs *(Figure 1)* (1).

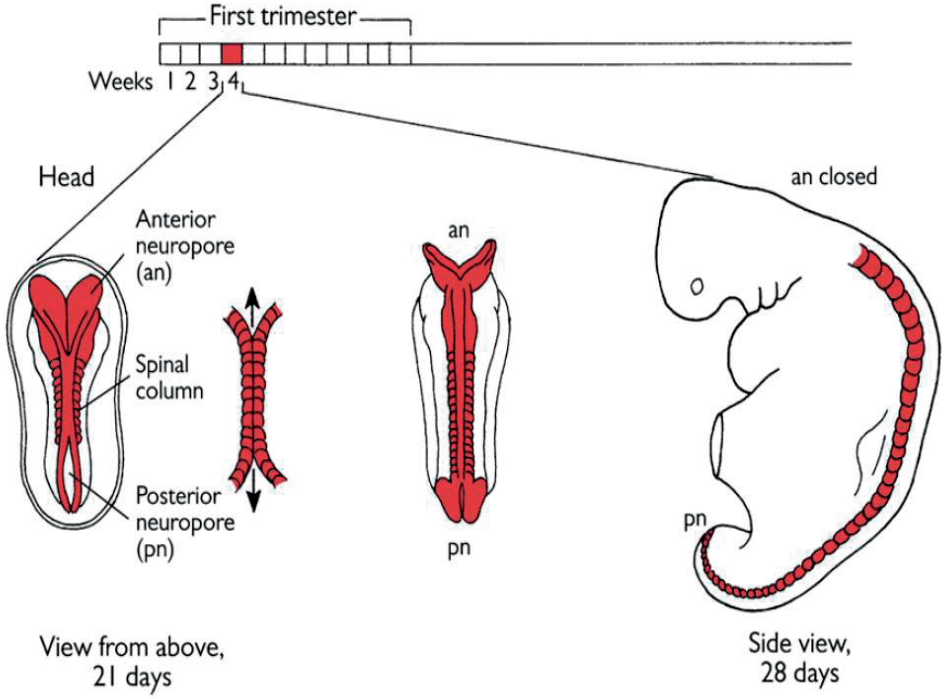


Figure 1: Normal neuro-ectodermal closure in the fourth gestational week, Sandler 1997

Spina bifida (SB), Latin for "split spine", comprises all congenital defects in spine and spinal cord due to an imperfect neural tube development. Although the precise pathogenesis of SB is not yet fully understood, a multifactorial involvement of environment and genetic predisposition is assumed. Primarily, the embryonic neural plate fails to close completely due to lack of ectodermal signaling, resulting in defects in vertebrae formation. Several investigators propose a "two-hit" model, with not only failure of the folding of ectodermal cells in the neural plate but also subsequent damaging and neurodegeneration of the exposed neural cells by the amniotic fluid causing abrasive lesions in utero (1).

In a minority the malformation involves the proximal neural tube, resulting in lethal anencephaly or encephalocele. More often, the distal neural tube fuses incompletely, leaving spinal cord abnormalities such as meningocele (protrusion of spinal cord coverings through the vertebral defect), myelocele (protrusion of only neural structures) and meningomyelocele (protrusion of spinal cord coverings and neural tissue) *(Figure 2)*. Thus, the term spina bifida refers to a variety of neural defects with a broad spectrum in clinical presentation and severity of disability. In all cases the defect has a lifelong extensive impact on every day quality of life and participation in school, work and social life.

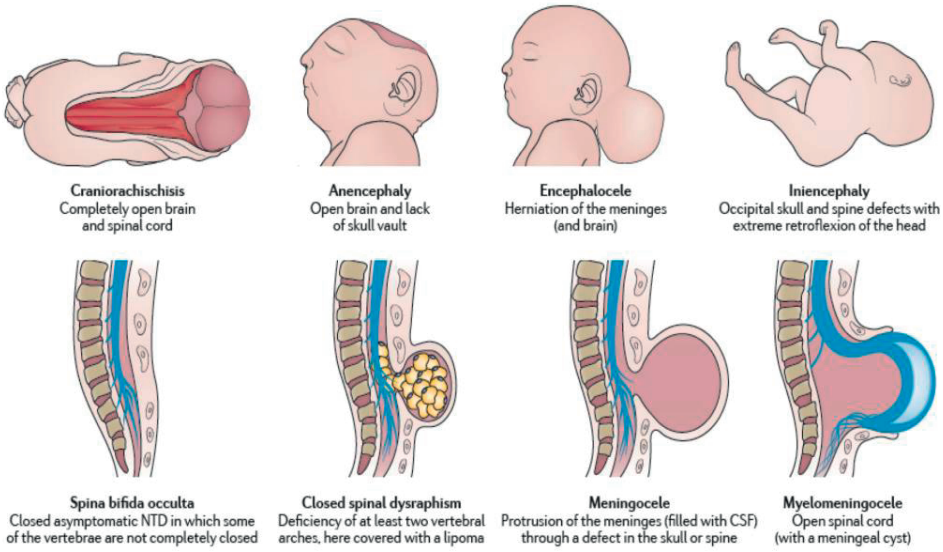


Figure 2: Types of spinal dysraphisms, Copp 2016

Spina bifida, epidemiology

Periconceptional folic acid supplementation, proven to enhance neural tube formation and prevent neural tube defects, and early elective termination of pregnancies have resulted in a decrease of live born neonates with SB (2,3). As a result, incidence of spina bifida has decreased from 1-10 to 0.3-1 per 1,000 live births with variation by region, race and ethnicity (4-8). Still, SB remains the third most common congenital birth defect, after cardiac and uronephrological malformations. In the Netherlands, recent reviews reported an incidence of 0.38 to 0.88 per 1,000 live births, resulting in approximately 90 children with SB born in the Netherlands every year (3).

Spina bifida, outcome

Many organ systems are involved in SB due to the impaired innervation of extremities as well as internal organs like bowel and bladder. Therefore, the impact of SB on physical and psychosomatic Quality of Life is enormous. Until the 1950s the severe neurological complications of SB and inevitable progression of renal insufficiency justified merely palliative care with a survival rate after adolescence of only 10%. After introduction of neurosurgical intervention and the CSF-shunt in the 1950s, the survival and outcome has improved significantly (9-11). Infant mortality is however still 15-35% under two years of age, mainly due to the so-called Chiari II malformation with herniation of the hindbrain (cerebellum and brainstem) into a small posterior fossa. This causes breathing problems with stridor due to vocal cord paralysis, episodes of apnea, food aspiration and spasticity (12).

Most invalidating aspects of SB remain motor impairment and sensory loss in the lower limbs and pelvic region. Studies of determinants of outcome in SB revealed no specific factors, although the presence of hydrocephalus and a higher level of the spinal anomaly are associated with poorer outcomes in behavioral outcome and cognitive functions. Overall, cognitive function is relatively spared, with normal to low-normal intelligence and participation in mainstream education in most SB patients. Still, there are problems in visual perception, motor skills and memory (13), negatively affecting education and occupation, with relatively more patients depending on care takers throughout life.

After introduction of cerebral spinal fluid shunts and intermittent urine catheterization, both neurological and nephrological outcome improved, resulting in better survival rates and Quality of Life (QoL) (14,15). This has enabled specialized centers to start multidisciplinary curative and supportive care, including child neurology, orthopedics, urology, nephrology, general pediatrics, therapeutic rehabilitation, physical therapy and psychology. Measuring effectiveness of multidisciplinary medical and psychosocial care is often difficult and qualitative at best. Considering the current legitimate perception that physical, psychological and social participation is more important than quantitative study outcomes, improvement of QoL is the main stimulant for successful treatment regimens in SB. Recently, the American National Spina Bifida Program has issued proposals for the Spina Bifida Life Course Model, supporting an interdisciplinary transition program for SB patients from childhood into adulthood *(Figure 3)* (16-18).

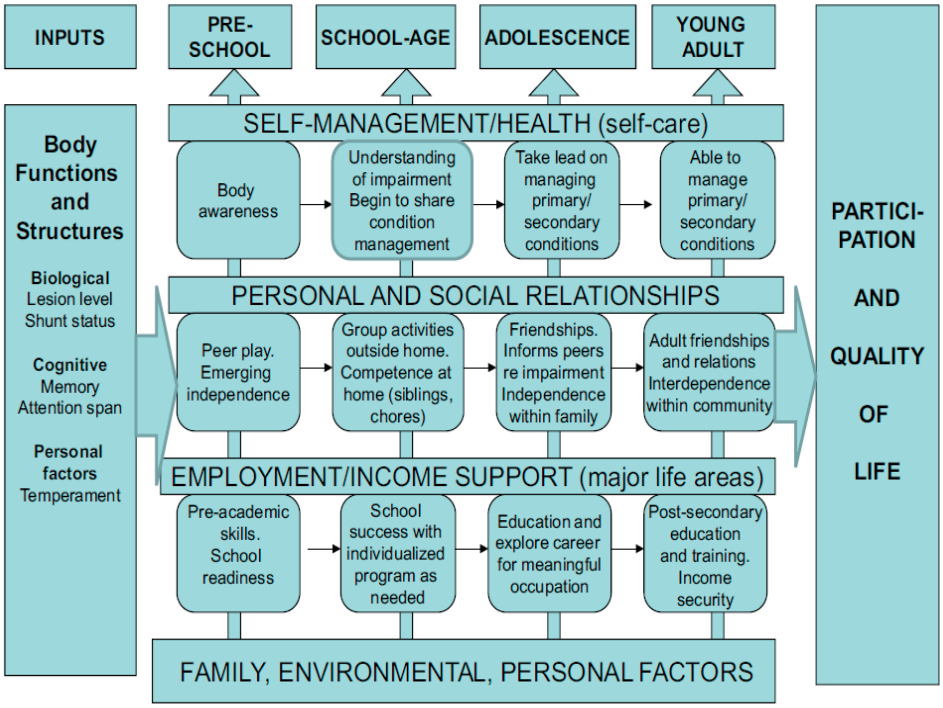
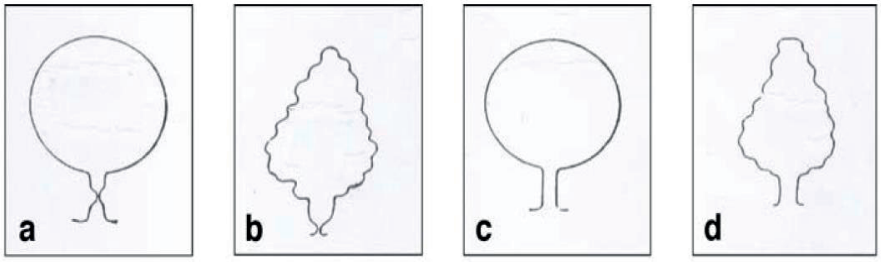


Figure 3: The multidisciplinary Life Course Model for children with spina bifida, Swansson 2010

Spina bifida, urodynamics

Prenatal and postnatal deficient neuromuscular innervation causes several dysfunctional micturation patterns, depending on whether the pelvic floor muscles and bladder wall ("detrusor") are under- or overstimulated. If both systems lack proper innervation, children are incontinent throughout their lives. Overstimulation of both bladder and pelvic floor results in overactive bladders, unable to empty completely due to overactive pelvic floor musculature. An overactive bladder combined with an spastic sphincter as part of detrusor-sphincter dyssynergia (DSD) results in incontinence throughout the day and night, most likely with severe grades of VUR with a high risk of renal deterioration and long term renal failure (19). An underactive detrusor with an overexcited pelvic floor results in bladder extension and VUR with subsequent renal deterioration as well *(Figure 4)*. Independent of DSD type, all children with SB have an increased risk of developing urinary tract infections (UTIs), especially when combined with VUR. These recurring UTIs cause renal scars with progressive deterioration of renal function, with almost imminent end-stage renal failure if the DSD is not corrected in early life.



	dysfunction	*consequences*	*management*
a :	sphincter ++ / detrusor --	unsafe, leaking, infections	safe and dry with CIC
b :	sphincter ++ / detrusor ++	DSD, unsafe from birth (reflux, infections, renal damage)	safe and dry with oxybutynin + CIC
c :	sphincter -- / detrusor --	safe but wet	safe and dry with CIC + outlet surgery *cave* detrusorinstability after outlet surgery
d :	sphincter -- / detrusor ++	wet and unsafe	safe and dry with CIC + oxybutynin + outlet surgery

Figure 4: Types of detrusor sphincter dysynergia, Verpoorten 2008

Spina bifida, urological / renal interventions

In 1972, Lapides showed that regular complete emptying of the bladder in SB by clean intermittent catheterization (CIC) resulted in less UTIs and a reduction in deterioration of renal function (20,21). Adequate emptying of the bladder by CIC has also been proven to be beneficial to minimize high-pressure voiding, alleviate intravesical pressure and achieving urine continence (22,23). With adequate dexterity and motivation, children from around the age of six can perform CIC themselves, improving their autonomy and participation in society, with urine continence achieved in 90% of the children (24). Adequate fluid intake, normal bladder capacity and psychosocial support are required to prevent catheter-related UTIs, urethral strictures and non-compliance to the daily regimen of CIC (24,25). Effective bowel management is also important to prevent impaired bladder filling, urine retention, UTIs and detrusor irritability (26).

Renal insufficiency has been a main risk factor of morbidity and mortality in SB for many decades: in the "pre-catheterization" period, renal insufficiency due to reflux and recurring UTIs accounted for the majority of deaths in SB. Before adequate measures were developed, 58% of patients with SB developed progressive renal failure by the age of three, and half of them needed an renal transplant early or later in life, due to increased intravesical pressure (27). Even after introduction of CIC, 18% of mortality in SB can still be attributed to renal tract complications. Sev-

eral studies have shown that the pivotal pathophysiological factor in renal damage is high bladder pressure, due to low compliance of the bladder wall.

Since the 1950s, many strategies have been developed to prevent renal failure in these children. Prenatal intervention for SB has been controversial: fetal neurosurgery and urological interventions proved not to be superior to postnatal surgical corrections regarding long-term renal outcome (28). Early postnatal urological interventions like anticholinergic medication (24), surgical corrections and botulin injections (29) to alleviate detrusor pressure however have proven to decrease long-term renal damage (24,25,27). These early postnatal interventions have become the main stay in the treatment of DSD, resulting in a dramatic decrease in renal failure and end-stage renal disease to only 1.3%, decimating the need for renal transplants in SB patients (30).

Even when the upper urinary tract is functioning relatively normal at birth, urodynamic and radiologic evaluation has to be performed regularly throughout childhood and adulthood, due to significant urodynamic changes in the fast growth rate in children and adolescents with inevitable elongation and possible traction of the spinal cord with increasing neuronal impairments (22,31-33).

Spina bifida, urinary tract infections

Defining UTI is even more troublesome in SB than in the general population. The definition of UTI varies widely in the studies in SB patients: bacteriuria is mandatory, but leukocyturia, physical symptoms and fever are not always included (34,35). However, mere asymptomatic bacteriuria is seen in 76% of urine samples from SB patients and considered to be non-threatening to the renal function (36). Despite this, many clinicians still prescribe therapeutic antibiotic treatment after randomly obtained positive cultures without any clinical symptoms. This has been proven to be an inadequate medical procedure, with rapidly progressive bacterial resistance for broad spectrum antibiotics, often without eliminating the bacteriuria (36).

A UTI should therefore be defined as bacteriuria accompanied by physical signs such as leukocyturia, fever, foul smelling urine, flank pain and change in continence. These clinical signs and symptoms vary throughout the studies and, to complicate matters even more, UTIs are multifactorial with urodynamic instability (low bladder compliance, high intravesical pressure, detrusor-sphincter dyssynergia), VUR, abnormal bladder urothelium due to decreased immune response and bladder wall ischemia, CIC regimen and used prophylaxis *(Figure 5)* (37-39).

Due to the lack of consensus in defining UTI, the prevalence of UTIs in children with SB varies in the many studies on this subject with an average of approximately 25%. Most of the UTIs are non-febrile, considered not to damage the renal tissue. However, some studies report renal scarring in recurring non-febrile UTIs and even in mere asymptomatic bacteriuria. Therefore there is still a debate on whether the renal damage is caused by perinatal urodynamics, high bladder pressure and VUR or by the subsequent UTIs. Febrile, renal scarring UTIs are less common, and more prevalent in urological tracts with persistent VUR, high bladder pressure and detrusor-sphincter dyssynergia. Recently, adequate guidelines of management of UTIs in children with urinary tract dysfunction with neurological disease has been published by the NICE group, including initial assessment, criteria for referral, treatment of underlying pathology and parental information (40).

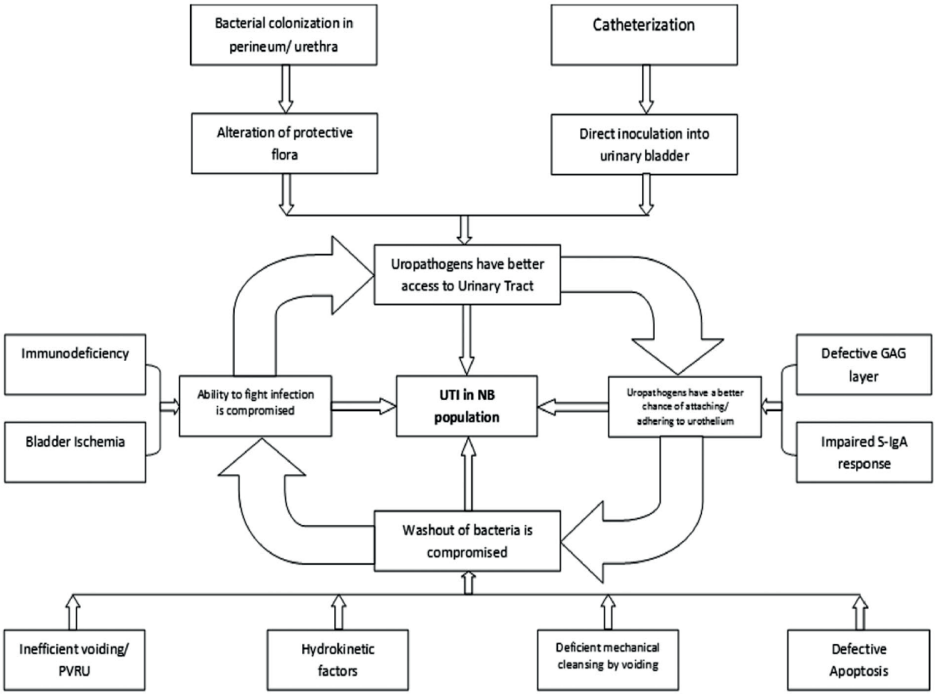


Figure 5: Factors involving UTI in spina bifida, Vasudeva 2014

Spina bifida, antibiotic prophylaxis

The introduction of four to six times daily CIC has resulted in less symptoms of DSD, less urinary tract infections, less incontinence and a decimation in renal transplants in SB patients. On the other hand, it has been suggested that introduction of bacteria into the bladder is inevitable when performing CIC despite proper hygienic

catheterization (36), and therefore low dose antibiotic prophylaxis (AP) should be prescribed to prevent bacteriuria. Depending on local resistance patterns, Trimethoprim and Nitrofurantoin have been the most used AP over the last decades. However, through expert experience and SB patients admitting non-compliance to AP, we know that many SB patients have no or only few UTIs despite stopping or not starting AP.

Aims of the study

The central hypothesis of this thesis is that antibiotic prophylaxis is not mandatory to prevent urinary tract infections (UTIs) in children with spina bifida. To prove this, we have designed a case-control study in which half of our patient population discontinued prophylaxis for eighteen months, while the other half continued their prophylaxis, and compared the yearly rate of UTIs. We have also evaluated the risk factors for UTIs in spina bifida patients. In addition to the main objective we also evaluated 1. the current care for spina bifida patients in European clinics, 2. the changes in resistance patterns in spina bifida patients on and off prophylaxis, 3. home testing to confirm or exclude a UTI, and 4. Quality of Life in spina bifida patients.

This thesis is the result of a Dutch / Belgian collaboration of pediatric urologists, epidemiologists, neurologists and pediatricians. Data collection started in 2005, with two eligible cohorts of children with spina bifida in the academic medical centers of Utrecht, the Netherlands and Leuven, Belgium.

http://www.controlled-trials.com/ISRCTN56278131/56278131

This thesis addresses the following research questions:

Is there consensus in antibiotic treatment protocols for children with spina bifida in academic European centers?

Is home testing of urine with leukocyte esterase test strips and dip slides accurate to confirm or rule out urinary tract infections in children with spina bifida?

Is antibiotic prophylaxis for urinary tract infections necessary in children with spina bifida on clean intermittent catheterization?

What is the influence of antibiotic prophylaxis on bacterial resistance to antibiotics in children with spina bifida?

What is the influence of antibiotic prophylaxis on the Quality of Life in children with spina bifida?

The research questions are presented in the following five chapters:

Chapter 2 describes the online questionnaire on provided care for spina bifida patients we have sent to European academic hospitals. The respondents were asked whether a protocol for UTIs is present and how suspected UTIs are evaluated and treated.

In *chapter 3* the accuracy of home testing for UTIs with a leukocyte esterase test and dip slide is evaluated and compared to laboratory culture. The results are related with previous studies on home testing for UTIs in healthy children and spina bifida patients.

The main paper is presented in *chapter 4*: a case-control study to evaluate the value of antibiotic prophylaxis in spina bifida patients to prevent UTIs in two groups (discontinuing (cases) versus continuing (controls)) and the risk factors for UTIs in spina bifida.

In *chapter 5* we have evaluated the influence of stopping antibiotic prophylaxis on bacterial resistance for common antibiotics in spina bifida patients.

In *chapter 6* we have studied Health Related Quality of Life in our cohort of spina bifida patients, contributing to previous studies and evaluating the influence of stopping prophylaxis on the perceived Quality of Life.

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Chapter 2

Urinary tract infections in children with spina bifida: an inventory of 41 European centers

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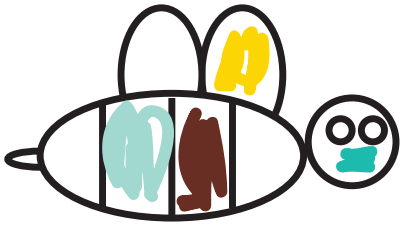

Pediatric Nephrology 2009;24:783-788

ABSTRACT

The introduction of clean intermittent catheterization (CIC) in 1972 and low dose chemoprophylaxis (LDCP, antibiotic prophylaxis), anticholinergic medication and urological surgery in the mid-1980s has improved the long term outcome of renal function in children with neurogenic bladder sphincter dysfunction (NBSD) due to spina bifida (SB). We conducted a European survey of the protocols for diagnosing and treating urinary tract infections (UTIs) in these children, using a web-based questionnaire. The responses from 41 centers in 14 European countries confirm that although most centers have standardized protocols for treating UTIs, there is no consensus among European centers in terms of protocols for preventing, diagnosing and treating UTIs in children with NBSD and for CIC.

INTRODUCTION

Despite periconceptional administration of folic acid and prenatal screening, about 1 in 2000 European children are born with spina bifida occulta or aperta (SB) (1-3). Children born with SB develop impairments due to neurological complications, orthopedic disabilities and nephro-urological problems resulting from the neurologically compromised bladder (4,5). The latter manifest as urinary tract infections (UTIs), neurogenic bladder-sphincter dysfunction (NBSD), vesico-ureteral reflux (VUR), reflux nephropathy and renal insufficiency. The prevalence of renal insufficiency and renal transplantation (<1% of our pediatric patients with NBSD) has decreased significantly over the last two decades with the introduction of clean intermittent catheterization (CIC), anticholinergic medication and the improvement in urological surgery (6-9).

Since the introduction of CIC in 1972, low dose chemoprophylaxis (LDCP) has been administered to reduce the risk of UTIs due to the repeated introduction of a urinary catheter. However, recent studies have revealed that the main risk factor for developing UTIs in children with NBSD is not CIC per se, but rather low-volume, low-compliant bladders and VUR (10-13). In addition, LDCP does not prevent UTIs in children completely (14-17). One study has proven that CIC and oxybutinin started promptly after birth improves the outcome of kidney function (6).

A recent American survey reveals a lack of consensus in terms of protocols for the prevention, evaluation and treatment of UTIs in the American spina bifida clinics (18). No data for the European community are yet available. To evaluate the present European protocols on UTIs in children with NBSD and CIC, we have conducted a web-based inventory aimed at establishing both the presence and the contents of protocols on UTIs in European spina bifida clinics.

MATERIAL AND METHODS

A questionnaire was developed by the spina bifida team of the Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands, and processed into an internet-applicable document by the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands. The questionnaire comprised six fields of evaluation: (1) identification of the center and spina bifida team with which the contact person is affiliated; (2) the number of patients with SB and CIC and the presence (or not) of protocols for treating UTIs in these children;

(3) current standard protocols for prescribing prophylaxis; (4) the diagnostic procedures when a UTI is suspected; (5) the therapeutic antibiotic regimen prescribed for pediatric patients with UTIs; (6) concurrent interventions (anticholinergic medication, urological surgery, indications for urodynamic studies). This questionnaire was sent as a "fill-out" PDF file in a web page link to 253 e-mail addresses of registered specialists, whose name and addresses were supplied by the Society for Research into Hydrocephalus and Spina Bifida (SRHSB) and the European Society for Pediatric Urology (ESPU), as we assumed that these pediatric urologists are involved on a day-to-day basis in the treatment of children with NBSD. We estimated that about 10 min would be required to complete the questionnaire. By including members of the SRHSB, we also obtained answers from colleagues outside of Europe; however, we ultimately decided only to analyze and asses the questionnaires filled out by European clinicians. Data-input and analysis was performed using SPSS 13.0 for Windows (SPSS, Chicago, IL).

RESULTS

Questionnaire response

Of the 253 questionnaires sent, 152 were returned (60% response rate). Ninety-two recipients (60% of 152) replied by e-mail that they were unable to complete the questionnaire (25 forwarded to colleagues, 25 retired/stopped practicing, five treated only adult patients, ten repeatedly returned an out-of-office reply, 13 said that they were unable to open the link to the questionnaire, 14 for various other reasons). The remaining 60 (40%) returned a filled out questionnaire *(Figure1)*: 41 from European centers, and the remaining 19 from American (ten), Canadian (seven), Mexican (one) and Indian (one) centers. The response frequency of the individual European countries is shown in *Figure 2*.

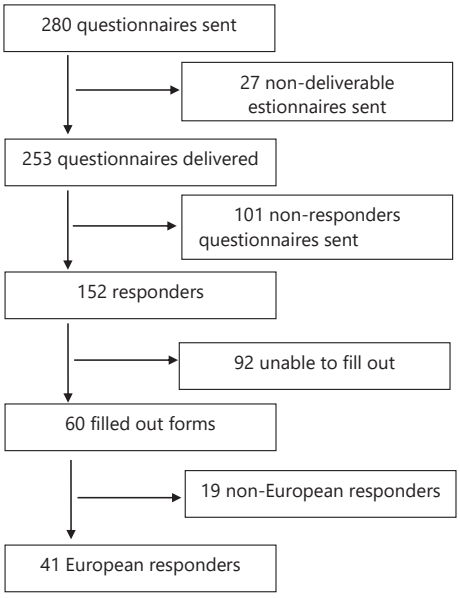

Figure 1: Response-diagram for the questionnaire

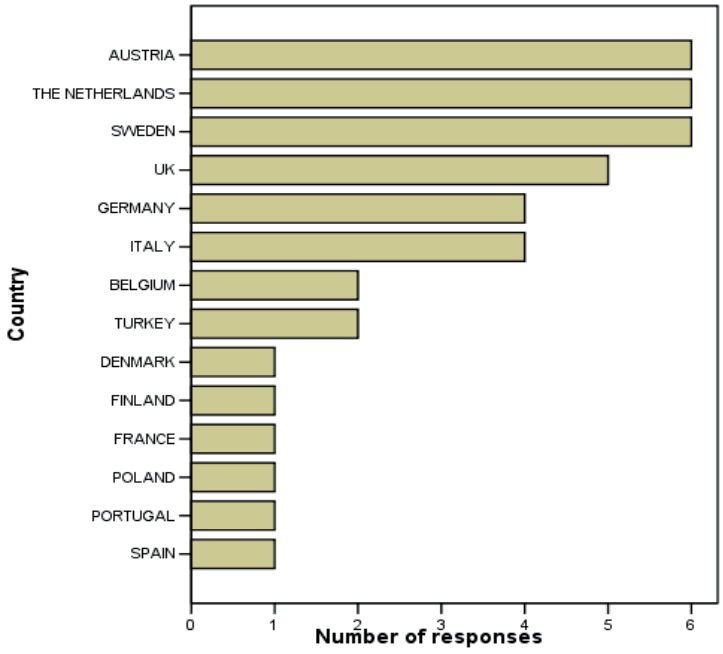

Figure 2: Number of responses per country (total of 41 European responses)

Patient statistics

The 41 participating European centers were treating a total of almost 6000 patients with NBSD. The median percentage of children with NBSD treated with daily CIC in these centers was 85 (range 25 – 100%). A specific protocol for the follow-up of children with NBSD was available in 32 centers. Protocols for the use of prophylactic antibiotics for the prevention of UTIs were used in 27 centers. Diagnostics procedures were standardized in 30 centers, and regimes for treatment of UTIs were standardized in 29.

Current practice in terms of prescribing antibiotic prophylaxis

Thirty-five of the respondents rarely prescribed LDCP to children with NBSD who were not on CIC. Even in children on CIC, more than half of the respondents were reluctant to prescribe LDCP. The main factors taken into account for prescribing LDCP were recurrent UTIs and VUR. Nearly one third of the respondents also considered congenital urological or renal anomalies as a valid argument for prescribing LDCP *(Table 1)*.

Cessation of LDCP in children with NBSD and CIC was considered if UTIs did not occur or did not recur for a prolonged period, on explicit parental request or if VUR had resolved, either spontaneously or by surgery. Bladder pressure did also influence this decision *(Table 2)*.

Table 1: Factors considered by European respondents (n=41) in prescribing low-dose chemoprophylaxis (antibiotic prophylaxis)

Recurrent UTIs	38
VUR	36
Congenital urological or renal anomalies	13
Start of CIC	10
Age of child	9
High intravesical pressure	4
CIC per se	3
Spina bifida per se	1

UTI, urinary tract infection; VUR, vesico-ureteral reflux; CIC, clean intermittent catheterization

Table 2: Factors considered by European responders (n=41) for stopping LDCP

No recurrent UTIs	35
Parental request	12
Normalization of intravesical pressure	9
Resolution of VUR	8

The antibiotics most frequently prescribed as LDCP in children both with and without CIC were trimethoprim (28/41 responders) and nitrofurantoin (29/41). Cotrimoxazol (15/41), cephalosporins (15/41), amoxicillin (7/41), amoxicillin / clavulanate (5/41), ciprofloxacin (3/41), norfloxacin (2/41), nalidixic acid and herbal preparations (2/41) were used as alternatives.

Logistic and diagnostic procedures in case of a suspected UTI

When patients or their parents suspected a UTI, two of the 41 clinics solely relied on the results of a home test strip for leukocyte esterase and nitrite to confirm the UTI and start treatment. In case of a positive home test strip, the majority of the clinicians advised contacting and sending urine cultures to either the general practitioner (18/41), the local pediatrician (12/41) or the spina bifida team itself (13/41). Diagnostic tools, such as test strips (nitrite positive 12/41, leukocytes positive 16/41, both positive 15/41) and leukocyte count on microscopy (10/41), were less important to the respondents in terms of establishing the presence of a UTI than the complaints of the patients (20/41), fever (18/41) and the foul smell of the urine (14/41). The gold standard remained the urine culture from catheterized or midstream urine in children capable of spontaneous voiding: a UTI was diagnosed when either of these was positive for one bacterium. A multi-bacterial specimen was seldom regarded as a UTI when the culture was taken from voided urine (2/41), and more often assessed as a UTI when cultured form urine collected by CIC (10/41). Four responders indicated not to need a urine culture and would treat the patient based on complaints and test strips, rather than cultures. However, most clinics cultured urine before they started the antibiotic treatment (36/41). In this latter group, seven responders indicated that they would wait for the test results and the antibiogram before starting treatment; the others indicated that they would start treatment promptly after the culture was taken, adjusting their choice of antibiotics, if necessary, according to the antibiogram. Clinicians were inclined to disregard the protocol and to start treatment for a suspected UTI earlier in case of known renal or urological abnormalities (12/41), VUR (16/41), and, above all, severe complaints of a UTI (22/41). Remarkably, nine of the 41 responders replied never to deviate from their protocol.

Treatment of UTI in children with NBSD and CIC

The first choice of antibiotics depended on whether or not the child was on LDCP when the UTI was diagnosed: nitrofurantoin, trimethoprim or co-trimoxazol were prescribed more often if no prophylaxis was prescribed, while cephalosporins were more frequently administered in children on LDCP. Amoxicilline/clavulanate was

prescribed equally in both groups. Intravenous antibiotics were seldom used, based on the responses to the questionnaire *(Table 3)*.

Table 3: First choice of antibiotics in urinary tract infections in children

First-choice antibiotics	LDCP	No LDCP
Amoxicillin	3	0
Amoxicillin/clavulanate	11	10
Trimethoprim	4	8
Trimethoprim/sulfamethoxazol	6	9
Nitrofurantoin	3	7
Ciprofloxacillin	3	0
Intravenous antibiotics	1	2
Other, mostly cephalosporins	10	5

Differences between clinics with and without a standardized spina bifida protocol

We performed a separate analysis of centers with and without protocolized care for children with NBSD. No significant differences were observed in the prescription of LDCP, diagnostic procedures and treatment of UTIs between these two groups of centers.

DISCUSSION

Protocols for the prevention, diagnosis and treatment of UTIs in children have recently been reviewed and standardized (NICE, NHS) (19). The prophylactic treatment of the specific group of children with NBSD due to SB has been a major topic for several decades - since the introduction of CIC. A review of publications reporting on UTIs in NBSD reveals a remarkable variation in the prescription of prophylactic and therapeutic antibiotics in these children (11,15,17,20-23), raising the hypothesis that there is no consensus on preventing, diagnosing and treating UTIs in this particular pediatric group. The goal of our web-based survey was to determine whether a definite conclusion can be drawn based on information provided by European specialists.

Antibiotic prophylaxis is one of the many daily medications prescribed for patients with NBSD, although many European centers have already switched to a need-to-treat prophylactic regimen, thereby abandoning the ancient adagium that LDCP should be prescribed to every patient on CIC. The main arguments used for persisting in starting or continuing LDCP are VUR, congenital urinary tract anomalies and

recurrent UTIs (8,10,24,25). When VUR has resolved, either spontaneously, due to anticholinergic medication, or by surgical correction, and UTIs are under control, most clinicians cease the LDCP, in accordance with protocols reported by several studies on VUR and LDCP in the general pediatric population (10,14-18). As the treatment of this specific group of children with NBSD is high in terms of intensity, invasiveness and cost, every effort should be made to minimize the burden of medical intervention. It is yet to be clarified which preventative approach results in the lowest rate of UTIs and, even more importantly, renal insufficiency.

The diagnosis of a UTI is also subject to local preferences: some clinics rely on home testing with a test strip for leukocyte esterase and nitrite, whereas others insist on a laboratory dip slide or culture. Test strips are useful in ruling out UTIs, but in case of a positive test, a probable UTI should be confirmed by culture (26,27). Others have shown that the sensitivity and specificity of home dip slides is low compared to the gold standard of laboratory cultures (28). Our survey reveals widespread variation in the use of diagnostic tests when a UTI is suspected, ranging from only home tests with test strips to awaiting the results of urine cultures.

The treatment of symptomatic UTIs varies substantially but to a similar extent in centers with or without standardized protocols. In general, narrower-spectrum antibiotics are used in children not on LDCP, resulting in a decrease in bacterial resistance as reported by several studies (15,17). Urinary tract infections are treated with oral antibiotics, with only few exceptions, as indicated in our survey.

Analysis of the European data reveals that there is no single procedural protocol by which all centers prevent, diagnose and treat UTIs. This implies that the presence of a designated spina bifida team or protocolized standards for LDCP, diagnostic procedures and treatment of UTIs does not completely prevent patients from being treated differently by different doctors when there is a suspicion of a UTI. This was also concluded by Elliott et al in the survey of American spina bifida centers (18).

To the best of our knowledge, this is the first inventory of the use of LDCP in children with NBSD and CIC in European centers. Our choice for an e-mail questionnaire was supported by several studies, suggesting that percentages of response do not differ between mailed or emailed questionnaires (29,30). The equivalent American survey also used e-mail to assess the 169 national centers, with a response rate of 35%, similar to our 40% (18). A larger sample size probably would not have increased the degree of European consensus, assuming that many of the non-responding clinics do not have a standardized protocol. Consequently, it is likely that the prevalence

of protocols is even overestimated in our analysis of the responders. Our European survey - with 41 respondents – had the result of several nations being represented by only one respondent or even none at all. Therefore, we have analyzed the data for the European continent as a whole - and not for the individual countries. Although our use of the mailing list of the ESPU excludes non-members in spina bifida centers from this survey, most pediatric urologists in European spina bifida centers are member of the ESPU. However, the use of the ESPU mailing list also excludes other caretakers of children with NBSD, such as pediatricians, nephrologists and neurologists. To overcome this drawback, we specifically requested the urologists to either respond themselves or to forward the questionnaire to caretakers that could fill out the questionnaire more accurately. The responses of those clinicians who indicated that their centers do not to have a specific protocol for treating UTIs in children with NBSD and CIC (9 of the 41 responders) are open to question as such a response indicates that their treatment is at the level of personal practice instead of being a clinic-wide method of treatment. We chose to incorporate these answers because they emphasize the lack of consensus even within the specialized centers, let alone in Europe as a whole.

The results of this survey indicate that further studies on the diagnostics, prevention and treatment of UTIs in pediatric patients with NSBD and CIC are warranted. We are currently performing a randomized controlled trial on the use of LDCP to prevent UTIs in patients on CIC. A total of 175 Dutch and Belgian patients are enrolled in this study. We believe that the results will contribute towards establishing evidence-based guidelines on prophylactic antibiotics within the next few years.

CONCLUSIONS

Over 25% of the individual European spina bifida centers do not have standardized protocols for the prevention, diagnosis and treatment of UTIs in CIC, and an overall European consensus on such protocols does not exist. Further studies on UTIs in children with NBSD and CIC are recommended. Antibiotic prophylaxis is the focus of a randomized controlled trial that we are currently running. The results of this trial will contribute towards establishing guidelines for LDCP within a few years.

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Chapter 3

Home screening for bacteriuria in children with spina bifida and clean intermittent catheterization

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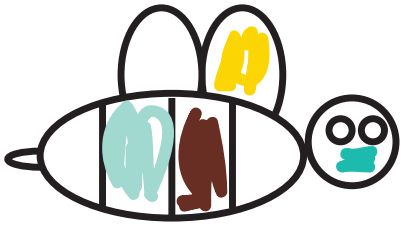

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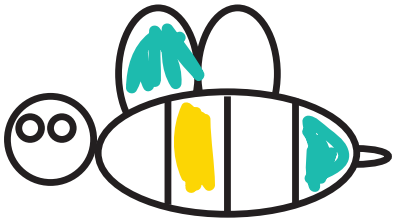

ABSTRACT

Background

Significant bacteriuria (SBU) and urinary tract infections (UTIs) are common in patients with spina bifida and neuropathic detrusor sphincter dysfunction. Laboratory agar plated culture is the gold standard to establish SBU. It has the disadvantage of diagnostic and subsequent therapeutic delay. Leukocyte esterase tests (LETs) and dip slides proved to be useful in the general populations to exclude SBU and UTI. The aim of this study was to evaluate the reliability of LET and dip slide in children with spina bifida without symptoms of UTI. The reliability in children with asymptomatic SBU was not studied before.

Methods

In one hundred and twelve children with spina bifida on clean intermittent catheterization LETs and dip slides were compared with laboratory cultures. Both tests and agar plated cultures were performed on catheterized urine samples. The hypothesis was that the home tests are as accurate as laboratory cultures.

Results

A SBU was found in 45 (40%) of the 112 laboratory cultures. A negative LET excluded SBU (negative predictive value 96%), while a positive LET had a positive predictive value of 72%. The false positive rate was 28%. Dip slide determination of bacterial growth had no added value, other than serving as transport medium.

Conclusions

In spina bifida children, leukocyte esterase testing can be used to exclude significant bacteriuria at home, while dip slide tests have no added value to diagnose or exclude significant bacteriuria.

BACKGROUND

Clean intermittent catheterization (CIC) and antibiotic prophylaxis have reduced the incidence of parenchymal kidney damage in children with spina bifida (1-3). In these patients, the main objective of any urinary diagnostic test is to detect or exclude urinary tract infections (UTIs) to prevent under- and over-treatment. The diagnosis of UTI is made on clinical symptoms, leukocyturia and significant bacteriuria (SBU). Several simple tests to detect a UTI, such as dip slides and leukocyte esterase tests (LET) were studied extensively. Two recent meta-analyses showed that a LET had a negative predictive value (NPV) of 90%, with a positive predictive value (PPV) of 60% (4,5). A UTI therefore has to be confirmed with a urine culture (4), which takes at least three days, and treatment is postponed. Dip slides with two or three culture media were tested to diagnose SBU in primary care (6-9). As PPV was poor, it was concluded that the use of dip slide urine cultures should only be used to exclude SBU.

The aim of the present study was to evaluate the reliability of the LET and dip slide in children with spina bifida. Children with clinical symptoms of UTI participated in a parallel study, and were not included in this study (10). Only children with asymptomatic SBU were included. We also assessed whether general patient characteristics, such as sex, age and use of prophylactic antibiotics can predict asymptomatic SBU. The hypothesis was that LET and Uricult® Duo dip slide are as accurate as laboratory cultures in determining significant bacteriuria.

PATIENTS AND METHODS

One hundred and twelve patients with spina bifida on CIC known at the Gasthuisberg University Hospital Leuven, Belgium participated in the study. Patients catheterized themselves or were catheterized by their parents or primary care takers for a fresh urine sample at the quarterly control visit. Patients who had completed treatment for UTI less than 4 weeks before the visit to the clinic, or who had febrile episodes immediately preceding the visit, or a clinical suspicion for a UTI at the visit were excluded.

A leukocyte esterase test (LET, Combur-2® test strip, Roche, Switzerland) was performed on the urine sample, regarded "positive" in every range of discoloration. The sample was also inoculated onto a dip slide (Uricult® Duo, Orion Diagnostics, Finland), which contains an aselective cystine-lactose-electrolyte deficient (CLED)

agar for Gram-positive bacteria and *enterobacteriaceae*, and MacConkey agar for non-glucose fermenting Gram-negative rods. The dip slide was incubated in a bottle warmer (Philips® SBC 215/00, Philips SA, Belgium) at 36.3 ± 2.5 ºC, as measured over 48 hours with a calibrated Dickson® SK 180 temperature logger (Dickson Corporation, Addison, USA). After 24 hours in the bottle warmer, the dip slide was evaluated for colony forming units by a trained research nurse, and the result was reported as 'no growth' or 'growth' (visible colonies). The same urine sample was also sent for 'gold standard' agar plated culture. SBU was defined as a colony count of $\geq 10^4$ per milliliter of one single species in a catheterized sample. Of patients with multiple samples, only the first was used for analysis.

To establish whether general patient characteristics could discriminate SBU from no SBU, logistic regression was used with gold standard outcome (positive / negative) as dependent variable and age and sex as independent variables. This model was then extended with prophylaxis (model 2), LET testing (model 3), and dip slide testing (model 4). Model results are expressed as odds ratios (95% confidence intervals, and p-values). Discriminative capacity for these four models was evaluated using areas under the Receiver Operator Characteristic (ROC) curves (AUC). This study is approved by the ethics committee from the Leuven University Hospital, and performed after parental or guardian consent.

RESULTS

Of the 112 asymptomatic patients, 45 had a positive agar plated culture, hence the prior probability for SBU was 40%, which is consistent with previous studies. The patients had an age range of 0 to 35 years (median 13.0, long-term spina bifida follow-up patients over 18 years of age are included). Fifty (45%) were boys and 61 (68%) were on antibiotic prophylaxis. *Table 1* shows the results of four consecutive models predicting the gold standard culture outcome. The LET had the strongest discriminative power, while dip slide testing did not add significantly.

In *Figure 1*, the discriminative capacity of the models is shown graphically as ROC curves for age and sex (AUC = 0.64, p = 0.01); age, sex and prophylaxis (AUC = 0.76, p = 0.003); age, sex, prophylaxis and LET (AUC = 0.91, p < 0.0001) and age, sex, prophylaxis, LET and dip slide (AUC = 0.91, p < 0.0001).

Table 1: Determinants of significant bacteriuria

Model		Odds ratio	95% CI	p-value
1	Sex (male vs female)	1.9	0.9 - 4.2	0.10
	Age (yrs)	1.06	1.01 - 1.12	0.03
2	Sex (male vs female)	1.8	0.8 - 4.1	0.13
	Age (yrs)	1.07	1.01 - 1.14	0.02
	Prophylaxis (yes/no)	0.5	0.2 - 1.0	0.06
3	Sex (male vs female)	4.1	1.2 - 14.4	0.03
	Age (yrs)	1.03	0.94 - 1.12	0.54
	Prophylaxis (yes/no)	0.3	0.1 - 1.1	0.07
	LET	101	18 - 583	<0.0001
4	Sex (male vs female)	3.8	1.07 - 13.4	0.04
	Age (yrs)	1.03	0.95 - 1.13	0.46
	Prophylaxis (yes/no)	0.3	0.1 - 1.1	0.07
	LET	75	11 - 495	<0.0001
	Dip slide	1.6	0.5 - 5.4	0.46

LET = leukocyte esterase test

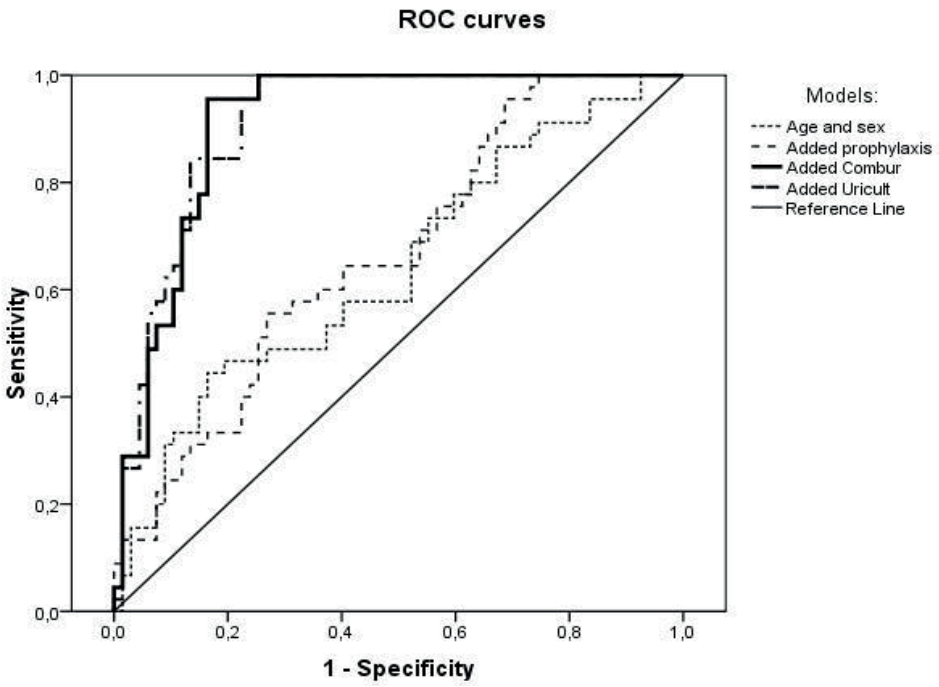

Figure 1: ROC curves of age, sex, Combur LET and Uricult dipslide

As this study addressed the role of LET and dip slide to rule out SBU in spina bifida patients without complaints of UTI, we proceeded with these tests only, as shown in *Table 2*. Given an a-priori chance of SBU of 40%, a positive LET had a PPV of 72%, while a negative LET substantially decreased the chance of a SBU to 4% (NPV = 96%). Dip slide testing had a similar PPV (73% versus 72% for LET) but substantially lower NPV (78% versus 96% for LET). Combining LET with dip slide improved neither PPV (positive LET 72% versus both LET and dip slide positive 74%) nor NPV (negative LET 96% versus both LET and dip slide negative 98%). Pathogens found were *Escherichae coli* (N=26), *Klebsiella pneumonia* (4), *Streptococcus* species (4), *Enterococcus* species (3), *Proteus mirabilis* (3), *Pseudomonas aeruginosa* (2), *Serratia marcescens* (1), *Staphylococcus aureus* (1) and *Providencia rettgeri* (1). In three of the 45 positive cultures (one *Streptococcus*, one *Staphylococcus* and one *Enterococcus* species) the LET was negative, resulting in 93.3% sensitivity. There were 16 false positive LETs in 67 negative cultures, resulting in 76% specificity.

Table 2: Predictive value for significant bacteriuria of (combinations of) the Leukocyte-Esterase Test and dip slide

		Gold standard culture				
		Positive	Negative	Total	PPV in % (95% CI)	NPV in % (95% CI)
LET	Positive	43	17	60	72 (50 – 83)	
	Negative	2	50	52		96 (85 – 99)
Dipslide	Positive	29	11	40	73 (56 – 85)	
	Negative	16	56	72		78 (66 – 87)
Combi	Both positive	28	10	38	74 (57 – 87)	
	Not both positive	17	57	74		77 (66 – 86)
Combi	Not both negative	44	18	62	71 (58 – 82)	
	Both negative	1	49	50		98 (89 – 99)

CI = confidence interval, LET = leukocyte esterase test, NPV = negative predictive value, PPV = positive predictive value

DISCUSSION

In this study of 112 spina bifida patients on clean intermittent catheterization, a negative LET excludes SBU in a home setting with a NPV of 96%. A negative dip slide alone was not effective to rule out SBU, and a negative LET together with a

negative dip slide did not improve NPV. Both a positive LET and dip slide had a false positive rate of more than 20 percent compared to laboratory cultures, and cannot be used to diagnose SBU.

Leukocyte esterase test

Our results are consistent with other studies and meta-analyses, performed in the general pediatric populations (4,5,11-15). Anderson et al. studied the LET in children with neurogenic bladders, combined with nitrite test, with comparable results (16). Adversely, in a similar study population, Liptak et al. found a lower NPV (83%) (17). A significantly lower NPV for the LET (68%) was also seen in adults with spinal cord injury, which could be attributed to their lower threshold to diagnose SBU, with 10^2 colony forming units per milliliter of catheterized urine. In this study, the threshold was 10^4 cfu/ml (18).

In this study, boys had a significantly higher risk of SBU than girls. In a study by Seki et al., girls with myelodysplasia were more likely to get colonized with bacteria (19). Age did not influence the risk for SBU in our population, in accordance with previous studies (20). Prophylactic antibiotics tended to reduce the risk of SBU, as was shown in previous studies both in the general population (21-23) and in patients with spina bifida (22,24,25). Compared to the LET however, age, sex and the use of antibiotic prophylaxis are less reliable to predict SBU in children with spina bifida.

Dip slides

In this study, a negative dip slide with a NPV of 78% and a false negative rate of 22% could not rule out SBU. With a PPV of 73%, and a false positive rate of 27%, SBU cannot be diagnosed with a dip slide. In a recent study in 200 children with UTI symptoms and a positive LET, Uricult® Trio dip slides incubated in a laboratory incubator were compared with colony counts on blood agar plates. The sensitivity of 68%, and a false negative rate of 29% was comparable to this study (26). Two mayor pitfalls were found: the small pin-point colonies of some *Enterococci* and most *Streptococci* on the CLED medium were mistaken for no growth, and transparent *E. coli* colonies are almost invisible. The untrained eye can be aided by the European Urinalysis Guidelines (27). Inspection of the dip slide with a 12× magnifying glass, and comparing the incubated media with those of an unused dip slide. When growth of *E coli*, *Enterococci*, and *Streptococci* on the 14 false negative Uricult® Duo dip slides was identified in this study, the false negatives would have decreased from 27% to 14%.

This study included only asymptomatic patients, and although the bacteriuria is significant, this has no clinical consequences such as therapeutic antibiotic administration. Compared to asymptomatic SBU, in clinical UTI leukocyturia is obligatory, most likely increasing both NPV and PPV of the LET, emphasizing the value of the LET. A further study to evaluate the reliability of the dip slide in children with spina bifida and clinical symptoms of UTI is recommended.

CONCLUSION

In home testing of spina bifida children on clean intermittent catheterization, leukocyte esterase testing can be used to exclude significant bacteriuria. Both leukocyte esterase test and dip slide are not sensitive enough to predict significant bacterial growth, and a agar plated culture should therefore be performed when either test is positive. Other than serving as transport medium, dip slide testing has no added to diagnose or exclude significant bacteriuria.

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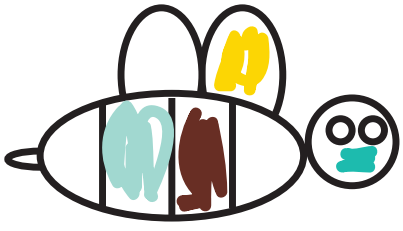
Chapter 4

Antibiotic prophylaxis for urinary tract infections in children with spina bifida on clean intermittent catheterization



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ABSTRACT

Purpose

Antibiotic prophylaxis (low dose chemoprophylaxis) has been prescribed since the introduction of clean intermittent catheterization in children with spina bifida. We hypothesized that stopping low dose chemoprophylaxis does not increase the number of urinary tract infections in these patients.

Patients and methods

A total of 176 patients with spina bifida participated in a randomized controlled trial (ISRCTN trial number 56278131) of either continuation or discontinuation of low dose chemoprophylaxis. During the 18-month study period biweekly urine samples were evaluated for leukocyturia and bacteriuria with dipsticks and cultures. Asymptomatic significant bacteriuria (positive culture results without clinical symptoms) and urinary tract infections (significant bacteriuria with clinical symptoms and leukocyturia) were analyzed.

Results

Discontinuation of low dose chemoprophylaxis resulted in higher rates of asymptomatic significant bacteriuria (incidence rate ratio 1.23, 95% CI 1.08-1.40, p=0.002) and urinary tract infection (IRR 1.44, 95% CI 1.13-1.83, p=0.003). For urinary tract infection the number needed to harm was 2.2, that is if 2 patients discontinued low dose chemoprophylaxis for a year, 1 extra UTI would result. Febrile urinary tract infection occurred once in every 30 patient-years, and slightly more often in the discontinuation group (relative risk 2.0, 95% CI 0.38-10.6, p=0.4). Of 88 patients allocated to discontinuation of low dose chemoprophylaxis 38 (43%) switched back to chemoprophylaxis. The urinary tract infection rate was nonsignificantly higher in presence of vesicoureteral reflux. Male gender and a low pre-study rate of urinary tract infections of UTI rates predicted successful discontinuation.

Conclusion

Patients with spina bifida on clean intermittent catheterization and antibiotic prophylaxis for urinary tract infections can safely discontinue this prophylaxis, in particular males, patients with low urinary tract infection rates and patients without vesicoureteral reflux.

INTRODUCTION

With an incidence of one in every 2,000 live births, spina bifida is still among the most common and serious congenital birth defects (1,2). Most children with spina bifida survive with fairly stable medical and social problems, except for the neuropathic bladder-sphincter dysfunction. About half of all patients suffer from detrusor-sphincter dyssynergia, a functional obstruction of the bladder outlet (3,4). This condition predisposes to incomplete bladder emptying, high bladder pressures due to high sphincter pressure and increased risk of urinary tract infections, which can lead to vesicoureteral reflux, upper urinary tract dilatation, renal scarring and renal failure (5,6).

Clean intermittent catheterization, often combined with anticholinergic medication to decrease detrusor activity, has revolutionized the management of detrusor-sphincter dyssynergia since its introduction in 1972 (7,8). Low dose chemoprophylaxis is commonly used along with CIC and anticholinergics to prevent recurrent UTIs due to the detrusor-sphincter dyssynergia (9,10). Periodic cystometry and urodynamic investigations, along with the aforementioned treatments, have decreased renal scarring, end-stage renal failure and need for kidney replacement therapy or transplantation (11).

Despite these therapeutic adjustments and prophylaxis, children with spina bifida on CIC still manifest bacteriuria and UTIs, necessitating antibiotic treatment(12). These findings are also reported in children without spina bifida, demonstrating a variable benefit of long-term LDCP in recurrent UTI, vesicoureteral reflux, perinatal hydronephrosis and functional anomalies (13,14). As a result, there is ongoing international debate on, and locally variable use of, LDCP.

Differentiation between asymptomatic significant bacteriuria and UTI without fever can be difficult. CIC per se can result in low grade leukocyturia and varying degrees of bacteriuria (15,16), and specific symptoms of UTI, such as pollakiuria, urgency and dysuria, will be absent in most children with spina bifida. However, patients with spina bifida on CIC and their parents often describe specific symptoms during UTI, such as increased incontinence and foul smell of urine. Fever is a strong indicator of pyelonephritis and, as reported in several studies, febrile UTIs specifically cause renal scarring (17,18). UTIs without fever have proved to be less detrimental for renal survival (19).

The long-term use of LDCP induces multi-resistant uropathogens in the fecal flora - a high price to pay for prevention of afebrile UTIs, which are perceived to have little or no renal consequences. We hypothesized that LDCP does not decrease the number of febrile UTIs in spina bifida children on CIC. To our knowledge, there has not been experimental research to prove the effectiveness of LDCP, although its use has become common practice. We present a randomized study aimed at determining whether LDCP in children with spina bifida on CIC can be discontinued safely, as measured by number of febrile urinary tract infections.

PATIENTS AND METHODS

Participants

All patients with known spina bifida seen at the outpatient clinics of Wilhelmina's Children's Hospital, Utrecht and Gasthuisberg University Hospital, Leuven in 2005 were candidates for inclusion in the study, provided they were performing CIC and using LDCP during the preceding 6 months. Combining Utrecht (210 patients) and Leuven (252) populations, 462 patients with spina bifida on CIC and LDCP were identified to be eligible for the study. Eligible patients were invited by personal invitation and written explanation to participate in a randomized trial of discontinuing LDCP. The study ran from February 2005 through March 2009.

Baseline measurements

Patient age, gender, type and dose of antibiotic prophylaxis, and type of bladder sphincter dysfunction were recorded. UTIs proved in the year preceding randomization were recorded, and renal ultrasound was performed to determine renal length and presence of pyelum dilatation as a marker for VUR. Urine culture was performed to exclude a current UTI at the start of the study period.

Interventions

Patients were randomly allocated to continue or discontinue LDCP. The Julius Center for Health Sciences and Primary Care, Utrecht performed computer based, random, concealed allocation of patients to either continue or discontinue LDCP. Stratification was performed for age younger and older than 3 years, gender and participating center. Continuation of LDCP meant that the individually prescribed type and dose of antibiotics were continued. The dosages and types were allowed to differ between patients according to antibiotic resistance patterns in pre-study cultures.

Follow-up, outcome measurements and primary outcome definition

During 18-month follow-up biweekly dipstick tests and urine cultures were performed by the patients, their parents or their primary caretakers. The dipstick for urinary leukocytes and nitrite (Combur2LN®) was rated as either negative (no color change), or positive (any color change) by the primary caretakers.

Urine culture was performed using a Uricult® test with MacConkey and cysteine lactose electrolyte deficient media. In Utrecht the culture was sent to the laboratory of clinical microbiology of the University Medical Center for 24-hour incubation at 37°C (98°F). If rated positive, colonies from the culture were plated on sheep-blood agar, incubated for 72 hours and evaluated for significant growth and bacterial resistance patterns. When negative, the culture was not incubated on sheep blood agar. In Leuven the 24-hour incubation period was performed at home by the primary caretakers (parents or nurses), using a feeding bottle warmer (Philips Healthcare, Andover, Massachusetts) at 37°C. If rated positive, the culture was sent to the laboratory of clinical microbiology of the University Hospital, where a sheep blood agar was performed and evaluated after 72 hours of incubation at 37°C for significant growth and bacterial resistance patterns. When rated negative at home, the culture was sent to the trained research nurse for professional review. When the nurse secondarily rated the culture positive after all, it was also sent to the laboratory for incubation.

Significant bacteriuria was defined as more than 10,000 cfu/ml for a single specimen in a catheterized sample, according to previous reviews (13,16). UTI was defined as 1) significant bacteriuria, 2) positive reading of leukocyturia on dipstick and 3) clinical symptoms, such as increasing incontinence and foul smell or cloudiness of the catheterized urine with or without fever greater than 38.5°C (101°F), and treated as such. More than 1 specimen of bacteria with or without clinical symptoms in any culture was considered a contamination, and, therefore, not treated. The primary outcome was the incidence of asymptomatic significant bacteriuria (ABU) and afebrile and febrile UTI per patient year.

Blinding

A priori, we did not use placebo LDCP, aiming to measure both pharmaceutical effects and ceasing induced external effects to mimic the anticipated effects in current clinical practice. Use of placebo would have been difficult since the dosages and types of LDCP differed between participants due to antibiotic resistance patterns in pre-study cultures. We performed blinded outcome evaluation since graders of Uricults and laboratory cultures were unaware of patient treatment allocations.

Statistical methods

Given a 17% annual pre-study UTI rate in our patients with spina bifida on LDCP, randomization of 150 patients was calculated to be sufficient for showing equivalence of continuing or discontinuing LDCP regarding primary outcome, with a power of 80% (alpha = 0.05), accepting a difference of 15% between the groups as bioequivalent. After 6 months the episodes of (a)febrile UTIs were reviewed to determine the need for continuation of the study and the risk of discontinuing LDCP.

Main treatment effect analyses were done according to the intent to treat principle. First, important prognostic characteristics regarding UTIs were tabulated against allocated treatment. Log binomial regression was used with first febrile UTI (yes/no) as dependent variable and a group indicator (LDCP yes/no) as independent variable. Subsequently differences in UTI rates between the 2 treatment groups were analyzed using Poisson regression, with a group indicator (LDCP yes or no) as independent variable. Results are expressed as relative risks (febrile UTI) and incidence rate ratios (UTIs, ABUs) with 95% confidence intervals and p values. As a post hoc analysis, we assessed which baseline characteristics could predict successful compliance with stopping LDCP. We used Poisson regression with offset set at 1 and with successful compliance with discontinuing (yes/no) as dependent variable, and age, gender and history of VUR and UTIs as independent variables. Results are expressed as relative risks with 95% confidence intervals and p values. Data were analyzed using the generalized linear regression module of SPSS®, version 17 for Windows.

RESULTS

Of 462 patients with spina bifida 286 were excluded from the study due to patient and/or parental refusal to participate, disapproval of the treating physician to participate, lack of administration of LDCP 6 months before to the study and language barriers *(Figure 1)*. The remaining 176 eligible patients all agreed to randomization. A total of 88 patients were allocated to discontinue LDCP and 88 patients to continue LDCP. *Figure 1* illustrates the study flowchart for intake and 18 months of followup. The LDCP regimen in participants was diverse, consisting of either trimethoprim, nitrofurantoin, cefuroxim, co-trimoxazole or a combination of prophylactics.

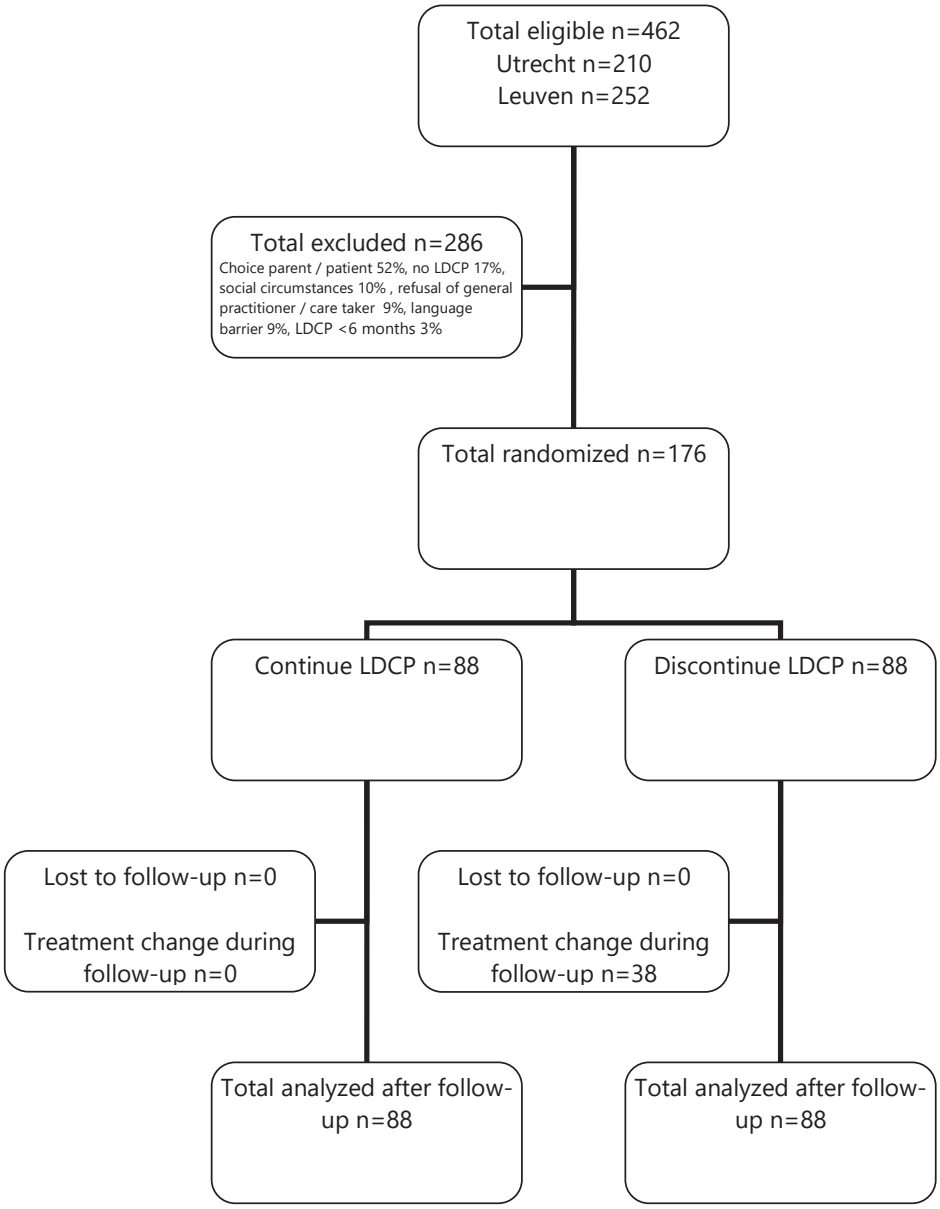

Figure 1: Study enrollment and outcomes flowchart

Table 1 outlines baseline characteristics that were considered prognostic indicators of primary outcome. None of these characteristics differed between the treatment groups. *Table 2* reveals the study results, with febrile UTIs occurring 7 times in 6 patients, 2 in the continuation group and 4 in the discontinuation group. The discontinuation group had a two fold higher risk for a febrile UTI than the continuation group but this difference was not statistically significant. One participant from the stop group suffered 2 febrile UTIs, which occurred *after* switching back to LDCP.

Table 1: Baseline characteristics by treatment group

	Antibiotic prophylaxis discontinued	Antibiotic prophylaxis continued
Mean ± SD age (yrs)	9.4 ± 5.9	8.7 ± 6.7
No. age:		
Younger than 3 yrs	14	16
Older than 3 yrs	74	72
No. males (%)	38 (45%)	38 (42%)
Mean ± SD renal length		
Lt side	75.4 ± 21.3	75.2 ± 19.2
Rt side	74.8 ± 23.7	76.6 ± 16.2
% Overactive detrusor	35.3	31.4
% Overactive sphincter	25.0	22.1
% Reflux		
Rt side	10.3	4.8
Lt side	10.3	9.5
Rt and/or lt side	16.9	17.0
Mean ± SD bladder capacity (ml)	269.8 ± 142.7	280.1 ± 161.3
No. UTI/pt-yr before study	1.88	1.82

Table 2: Effects of antibiotic prophylaxis for urinary tract infections and bacteriuria episodes

	No. ABUs / Pt-Yr#	No. afebrile UTIs / Pt-Yr#	Absolute No. febrile UTIs*
LDCP			
continued	3.64	1.07	2
discontinued	4.58	1.52	4
Relative risk / incidence rate ratio (95% CI)	1.25 (1.08-1.40)	1.44 (1.13-1.83)	2.0 (0.38-10.6)
p-value	0.002	0.003	0.42

ABU = asymptomatic bacteriuria; LDCP = low dose chemoprophylaxis; UTI = urinary tract infection. * log binomial analysis, # Poisson regression analysis

Afebrile UTIs occurred in 84 (47%) of the participants, leaving 92 (53%) without UTIs, with a 44% higher rate in the discontinuation group (1.5 UTIs per year) vs the continuation group (1.1). This finding resulted in a number needed to harm of 2.2, meaning that if 2.2 patients stop LDCP for a year, 1 extra UTI would result. Overall rate of UTIs in patients allocated to discontinue LDCP decreased from 1.8 per year before the study to 1.5 per year during follow-up.

Regarding VUR, the number of UTIs per patient-year was similar in the continuation group (1.2 vs 1.0 UTI per patient-year in those with and without VUR, respectively, p = 0.58), and non-significantly higher in the discontinuing group (2.3 vs 1.3, p 0.22). VUR grade, bladder compliance, bladder capacity, type of LDCP and age did not significantly influence the number of UTIs per patient-year. Finally, ABU occurred at a 23% higher rate in the discontinuation group (incidence rate 4.6 per year) than in the continuation group (3.6).

Of the 88 patients allocated to the discontinuation group, 50 (57%) fully complied with the protocol during the study and 38 (43%) switched back to LDCP. *Table 3* outlines baseline characteristics of children as predictors of compliance with discontinuing LDCP. Age and VUR did not clearly predict compliance. However, males had a 1.4 times increased chance of compliance, and for every extra previous UTI per patient-year there was a 20% decreased chance of compliance.

Table 3: Predictors for compliant discontinuation of low dose chemoprophylaxis.

	Compliance		Univariable analysis		Multivariable analysis	
	Yes	No	Relative risk (95% CI)	p value	Relative risk (95% CI)	p value
Mean age (yrs)	9.0	9.8	0.99 (0.96-1.02)	0.54	0.98 (0.95-1.01)	0.11
No. gender:			1.48 (1.03-2.12)	0.04	1.40 (1.00-1.96)	0.05
M	27	23				
F	12	26				
No. VUR:			0.86 (0.49-1.50)	0.60	0.92 (0.57-1.49)	0.92
present	7	43				
absent	7	31				
Mean UTIs/yr	1.1	2.7	0.80 (0.67-0.96)	0.02	0.79 (0.65-0.96)	0.02

Analysis of 88 children allocated to no LDCP, of whom 38 switched back to LDCP after randomization.
UTI = urinary tract infection, VUR = vesico-ureteral reflux

DISCUSSION

Discontinuation of low dose chemoprophylaxis in patients with spina bifida on CIC resulted in significantly more UTIs overall compared to continuation of chemoprophylaxis. However, this increase was clinically small. If 2.2 patients stopped LDCP for 1 year, only 1 extra, most probably harmless, afebrile UTI would result. The number of febrile UTIs between the discontinuation and continuation groups did not differ significantly.

To our knowledge this is the first randomized trial regarding the necessity of prescribing LDCP in children with spina bifida children on CIC. Previously Clarke et al studied 81 patients with spina bifida on CIC who were randomized to discontinue or continue LDCP with a relatively short follow-up of 4 months (9). However, analysis of the data was performed after excluding 28 patients for noncompliance with randomization and by analysis per protocol instead of the intent to treat principle. Therefore, these results are less applicable in clinical practice. The pragmatic character of our trial design resulted in substantial crossovers in the LDCP discontinuation group, although this result mimics daily practice of many attending physicians.

Importantly the UTIs in our participants were afebrile in all but 7 patients in both groups. These infections are less likely to cause renal damage, according to previous studies (12,19). Our study demonstrated that patients with VUR or younger than 3 years did not suffer from a significantly greater number of UTIs per patient-year, either with or without LDCP. These results are different from regular pediatric cohorts from the past decades (13,20), and may be due to the predominantly low grades of VUR in our patient population.

ABU is a well-known and logical consequence of daily CIC. In earlier studies colonization of the bladder with bacteria is seen in almost 50% of children with spina bifida on CIC (15,21). In our series the number of positive urine cultures without clinical signs was significantly lower, ie 16 and 20% in the continuation and discontinuation group, respectively. These lower percentages can be explained by an evident decrease in positive cultures in the latter months, most likely due to increased hygiene and awareness in participants.

In our study many of the patients who discontinued LDCP had multiple periods of asymptomatic significant bacteriuria and urinary tract infection, causing 43% to restart LDCP during the trial. However, these patients already had a high number of pre-study UTIs per patient-year, and restarting LDCP did not decrease the num-

ber of UTIs per patient-year in the remaining study period. This finding confirms previous results that the minor influence of LDCP on the number of UTIs does not outweigh the disadvantages of daily antibiotic prophylaxis, such as gastrointestinal side effects and, most importantly, increased bacterial resistance patterns (14).

Limitations of our study involve the Uricult method. Analysis of the cultures is prone to interobserver variability, which was overcome by using just 2 research nurses to evaluate the results. We chose greater than 10,000 cfu/ml as cutoff for UTI, according to previous studies and reviews (13,16). If we had chosen more than 100,000 cfu/ml, lower rates of UTI would have been noted in both groups, although without different conclusions regarding LDCP. Transportation was not cooled, which is in accordance with the manufacturer statement of adequate reading of bacterial growth at room temperature after 48 hours. The different approach of culture evaluation in both centers due to logistic circumstances was overcome by a second expert inspection of every sample in the Leuven branch of the study. The objective evaluation of cultures and dipsticks by experts blinded to the prior use of antibiotics strengthens the validity of our conclusions.

Although the difference in UTIs per patient-year was statistically significant, in clinical practice patients with spina bifida have to endure an extensive period of daily antibiotic prophylaxis to prevent a single afebrile non-scarring UTI. VUR, gender, age and bladder compliance and capacity do not influence the risk of UTI. Therefore, antibiotic prophylaxis should be continued only in children with spina bifida with a high rate of febrile UTIs.

CONCLUSION

Discontinuing low dose chemoprophylaxis in patients with spina bifida on clean intermittent catheterization does not significantly increase the number of febrile UTIs. Therefore, prophylaxis may be discontinued once neurogenic bladder-sphincter dyssynergia has been stabilized.

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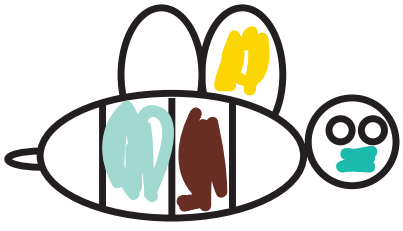
Chapter 5

The influence of antibiotic prophylaxis on bacterial resistance in urinary tract infections in children with spina bifida



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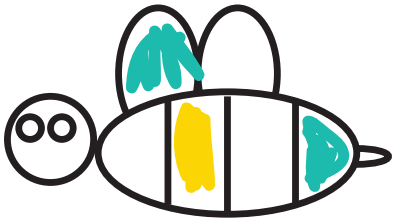

ABSTRACT

Background

Bacterial resistance to antibiotics is an increasingly threatening consequence of antimicrobial exposure for many decades now. In urinary tract infections (UTIs), antibiotic prophylaxis (AP) increases bacterial resistance. We studied the resistance patterns of positive urinary cultures in spina bifida children on clean intermittent catheterization, both continuing and stopping AP.

Methods

In a cohort of 176 spina bifida patients, 88 continued and 88 stopped using AP. During 18 months, a fortnightly catheterized urine sample for bacterial pathogens was cultured. UTIs and significant bacteriuria (SBU) were defined as a positive culture with a single specimen of bacteria, respectively with and without clinical symptoms and leukocyturia. We compared the percentage of resistance to commonly used antibiotics in the isolated bacteria in both groups.

Results

In a total of 4917 cultures, 713 (14.5%) had a positive monoculture, 54.3% of which were *Escherichia coli*. In the group stopping AP, the resistance percentage to antibiotics in UTI / SBU bacteria was lower than in the group remaining on AP, even when excluding the administered prophylaxis.

Conclusion

Stopping antibiotic prophylaxis for urinary tract infections is associated with reduced bacterial resistance to antibiotics in children with spina bifida.

INTRODUCTION

Due to increasing antibiotic use, bacterial resistance has emerged as an significant healthcare problem. The use of broader antibiotics for infections is driven by local antibiotic susceptibility and is influenced by preventive measures, use of antibiotic prophylaxis and previous antibiotic use.

Prior to the recent AAP Guidelines, there has been a trend to prescribe antibiotic prophylaxis (AP) to prevent recurrence of urinary tract infections (UTIs) and possible subsequent renal parenchymal scarring in otherwise healthy children and children with congenital abnormalities of kidney and urological tract (1). The time-delay in culture results leads to the prescription of broad-spectrum antibiotics in suspicion of a UTI. Bacterial resistance for an increasing number of antibiotics is therefore seen in UTIs (2-5).

In children with spina bifida, renal insufficiency due to urological impairments and recurrent UTIs has been the major cause of morbidity and mortality (6). The introduction of clean intermittent bladder catheterization (CIC) in 1972 by Lapides et al. enabled more adequate bladder emptying and a significant decline in UTIs, renal insufficiency and the need for kidney transplantation (7). However, since the introduction of CIC, many clinicians started prescribing AP to prevent CIC-related UTIs (8-10). Due to the lack of general guidelines on the use of AP for children with spina bifida applying CIC (11), caretakers were guided by the clinical course in the individual patient to either continue or stop AP.

To study the value of AP in children with spina bifida applying CIC, we conducted the SPIN UTI trial in the Netherlands and Belgium (12). In this trial 176 patients were randomized to continue or to stop AP. Stopping AP resulted in significantly more non-febrile UTIs (relative risk 1.44, 95% confidence interval 1.13 – 1.83, p 0.003). However, the absolute risk of UTI was low: on average, AP has to be administered for more than two years to prevent one non-febrile, and therefore non-renal scarring UTI. The recommendation from this study was to start AP upon diagnosing spina bifida, and to stop AP as soon as vesico-ureteral reflux is excluded, overactive bladder symptoms are treated with anticholinergics and CIC is properly implemented. Only spina bifida patients with persisting high grade vesico-ureteral reflux and severe overactive bladder despite anticholinergic medication, which results in significantly more UTIs, may benefit from continuation of AP (12).

During the SPIN UTI study, catheterized urine samples of the 176 patients were investigated fortnightly for a period of 18 months by dip stick and subsequent culture only if the dip stick was positive. This resulted in almost 5000 cultures. In case of a positive culture with one strain of bacteria (monoculture), antimicrobial susceptibility was determined. The main aim of the present analysis was to study the difference in antimicrobial susceptibility in positive urine cultures between patients continuing and stopping AP. Our hypothesis was that children stopping prophylaxis would have better susceptibility of bacteria to commonly used antibiotics.

MATERIALS AND METHODS

Patients

All patients with a meningomyelocele (spina bifida) known at the outpatient clinics of Wilhelmina's Children's Hospital in Utrecht, the Netherlands and Gasthuisberg University Hospital in Leuven, Belgium were eligible for inclusion in the study, provided they had been on CIC and AP during the last 6 months. One hundred and seventy-six patients participated in the study. The study period was from February 2005 until March 2009. This study was approved and registered by the ISRCTN, trial number 56278131 (http://www.controlled-trials.com/ISRCTN56278131/56278131).

Interventions

Patients were randomly allocated to continue or discontinue AP, using a computer based random concealed allocation scheme. Randomization was stratified for ages under and over 3 years, presence of vesico-ureteral reflux, gender and participating center. Patients randomized to continuation of AP continued the individually prescribed type and dosage of antibiotics. The dosages and types were allowed to differ between patients according to antimicrobial susceptibility in pre-study cultures. Patients randomized to stopping of AP were instructed to discontinue the prescribed AP upon study start. The first urine sample was taken two weeks after stopping AP.

Follow-up, outcome measurements, primary outcome definition

During an 18 months follow-up period, fortnightly dip sticks and urine cultures were performed after CIC by the patients themselves, their parents or their primary care takers.

The dip stick for both urinary leukocytes and nitrite (Combur2-LN®, Roche Diagnostics) was rated either as negative (no color change) or as positive (any color change)

by the primary care takers. If the dipstick was positive for leukocytes and / or nitrite, a urine culture was performed using a Uricult™ test (Orion Diagnostica, Finland) with MacConkey and CLED media.

In Utrecht, the Netherlands, the Uricult™ was sent to the laboratory of clinical microbiology of the University Medical Centre Utrecht for a 24 hour incubation period at 37°C (98°F). If rated positive, the Uricult was subcultured on a sheep blood agar for 72 hours followed by identification to the species level by automated bacterial identification and automated antimicrobial susceptibility testing providing MICs (Phoenix, Becton & Dickinson, MD). *Enterococcus* species were identified to the genus level by selective growth on bile esculin agar (BEA) and salt tolerance agar (STA). Enterococcal antimicrobial susceptibility testing was performed with disk diffusion. CLSI breakpoints for MICs and disk diffusion were used for interpretation. When negative, the Uricult™ was not subcultured.

In Leuven, Belgium, the 24 hour incubation period was performed at home by the primary care takers (parents or nurses), using a feeding bottle warmer (Philips®) at 37°C. If rated positive, the Uricult™ was sent to the laboratory of clinical microbiology for the incubation and identification process. When rated negative at home, the Uricult™ was sent to the trained research nurse for professional review. When she rated the Uricult™ positive, it was yet sent to the laboratory for incubation.

Significant bacteriuria (SBU) was defined as more than 10,000 colony forming units of a single specimen per milliliter in the catheterized urine sample. Urinary tract infection (UTI) was defined as an SBU combined with a positive reading of leukocyturia on the dip stick and clinical symptoms, such as increasing incontinence, foul smell or cloudiness of the catheterized urine. Cultures presenting more than one species of bacteria, regardless of clinical symptoms, were considered as a contamination rather than SBU or UTI.

To avoid repeated calculations for bacterial resistance patterns on one period of persistent SBU, we considered multiple consecutive positive cultures (SBU) without clinical signs of UTI, and therefore no antibiotic treatment, as one ongoing colonization.

Primary outcome

The primary outcome in this analysis was bacterial resistance of uropathogens in children with spina bifida on clean intermittent catheterization to commonly used antibiotics.

Statistical methods

Main treatment effect analyses were published previously (12). In brief, differences in rates of UTI between the two treatment groups were analyzed using Poisson regression and pointed at no clinically relevant difference in risk of SBU/UTI after stopping AP.

The present analysis represents a secondary analysis of bacterial resistance patterns observed in incubated cultures of urine samples of children with spina bifida and SBU or UTI and the influence of AP. Bacterial species, type of AP used and antibiotic susceptibility (both AP and non-AP antibiotic) were described according to the randomization group (intention-to-treat) and according to the actual use of antibiotics (per protocol).

Prevalence of AP and non-AP resistance in positive urine cultures was calculated as the number of cultures with resistant pathogens divided by the total number of positive cultures. In this calculation we assumed independence of multiple cultures within patients, which was deemed appropriate given the fact that we only included incident episodes of SBU/UTI. Results were stratified for actual AP use (yes/no) and type of AP used.

Differences in prevalence of pathogenic resistance between cultures with and without AP were statistically tested using the Generalized Linear Mixed Model (GLMM) module of SPSS which takes into account the repeated assessments in patients. We applied the binary logistic link function and a random effect for the individual intercept. As primary predictor of interest we included AP use (yes/no) at the time of SBU/UTI to explore the effect of AP use on the risk of resistance against non-AP antibiotics. In addition we explored the effect of country (the Netherlands vs. Belgium), SBU or UTI and gender as potential confounders by adding these variables to the model with AP. Results from this analysis were expressed as odds ratio (OR) with 95% confidence intervals (95% CI).

All analyses were performed using SPSS, version 19.0 and statistical significance was accepted at a two-sided p-value of 0.05.

RESULTS

Of the 176 participants, 88 were randomized to continue AP and 88 to stop using AP. In the latter group, 38 restarted AP during the 18 month study period, due to recurrent UTIs or specific parental request.

Not all patients complied with the fortnightly cultures in the entire study period of eighteen months. From a possible 6864 cultures if all 176 patients had complied with the protocol during the entire study period, 4917 urine samples were sent to and evaluated by the laboratories. Seven hundred and thirteen (14.5%) of these were positive single-strain cultures, of which 315 (44.2%) were considered a UTI due to clinical symptoms and leukocyturia on the dip stick. The remaining 398 (55.8%) were considered SBU, lacking clinical symptoms or leukocyturia *(Table 1)*. No significant differences were seen between boys and girls.

The most common pathogen seen in about half of both SBU and UTI was *Escherichia coli (E.coli)* (54.3%). The other 45.7% consisted of other well-known uropathogens, like *Klebsiella* species (8.8%), *Enterococcus* species (7.9%), *Pseudomonas aeruginosa* (6.6%), *Proteus mirabilis* (4.8%) and 17.6% of less common pathogens *(Table 1)*. Of the 713 single strain cultures only 82 (11.5%) were Gram-positive bacteria, mostly *Enterococcus* species and *Staphylococcus aureus*. Again, there were no differences between boys and girls in pathogens in either group.

Almost half of the cultures were performed in patients randomized to continue AP (n=343, 48.1%), the remaining 370 cultures (51.9%) were from patients randomized to stopping AP. However, 79 (21%) cultures in the stop group were performed after AP was restarted due to recurrent UTIs or specific parental request. Thus, the majority of SBU and UTI occurred while using AP (N=422, 59.2%), mostly trimethoprim and/or nitrofurantoin *(Table 2)*.

Table 1: Frequency of positive cultures and percentages of uropathogens in 176 children with spina bifida on clean intermittent catheterization on and off antibiotic prophylaxis

	Total		Stop group		Continuing group		
	Number	%	Number	%	Number	%	p-value for stop versus continue
Patients with only negative urine tests	23	13.1	11	12.5	12	13.6	
Patients with one or more positive cultures	153	86.9	77	87.5	76	86.4	Pearson chi-square 0.635
SBU	137	77.8	70	79.5	67	76.1	1.000
UTI	107	60.8	55	62.5	52	59.1	0.643
Number of positive cultures	713	14.5	370		343		
SBU	398	55.8	199	53.8	199	58.0	
UTI	315	44.2	171	46.2	144	42.0	
		CI		CI		CI	
Mean number of positive cultures per patient (95%CI)	4.66	(4.1-5.2)	4.81	(4.1-5.5)	4.51	(3.8-5.2)	negative binominal analysis 0.573
SBU	2.60	(2.3-2.9)	2.58	(2.2-3.0)	2.62	(2.1-3.1)	0.915
UTI	2.06	(1.7-2.4)	2.22	(1.7-2.7)	1.89	(1.4-2.4)	0.364
Uropathogens in positive cultures (% of positive cultures)		%		%		%	
E.coli	387	54.3	200	54.1	187	54.5	Pearson chi-square 0.429
Non E.coli	326	45.7	170	45.9	156	45.5	
Gram negative	631	88.5	326	88.1	305	88.9	0.901
Enterobacteriaceae							
AmpC negative							
E.coli	387	54.3	200	54.1	187	54.5	
Klebsiella pneumoniae	42	5.9	21	5.7	21	6.1	
Proteus mirabilis	34	4.8	15	4.1	19	5.5	
Klebsiella oxytoca	21	2.9	16	4.3	5	1.5	
AmpC positive							
Enterobacter cloacae	18	2.5	10	2.7	8	2.3	
Citrobacter freundii	17	2.4	11	3.0	6	1.7	

Table 1: Frequency of positive cultures and percentages of uropathogens in 176 children with spina bifida on clean intermittent catheterization on and off antibiotic prophylaxis (*continued*)

	Total		Stop group		Continuing group		
	Number	%	Number	%	Number	%	p-value for stop versus continue
Non fermenting bacilli							
Pseudomonas auroginosa	47	6.6	29	7.8	18	5.2	
Other	65	9.1	24	6.5	41	12.0	
Gram positive	82	11.5	44	11.9	38	11.1	0.762
Enterococcal species	56	7.9	30	8.1	26	7.6	
Staphylococcus aureus	18	2.5	10	2.7	8	2.3	
Other gram positive	8	1.1	4	1.1	4	1.2	

SBU = significant bacteriuria, UTI = urinary tract infection

Microbial resistance

Microbial resistance against any antibiotic was present in 65.2% of SBU/UTIs, and significantly more prevalent in urine cultures taken in children with spina bifida on AP (72.2%) than in children without AP (53.3%).

In *Table 3*, determination of resistance patterns to commonly used antibiotics performed on positive urinary cultures with Gram negative bacterial species, tested more than ten times in our patient group, is shown. There were too few Gram positive urinary cultures results to significantly differentiate resistance percentages between the groups on and off AP. The main result shown in this table is that use of AP increases the risk of resistance compared to stopping AP: the percentages of resistance to a specific antibiotic in any bacteria found in the urine cultures were higher when using AP. GLMM analysis estimated the risk of resistance against one or more antibiotics (including the AP) to be 2.3 (95%CI 1.6-3.1) fold higher while using AP relative to not using AP. Adding country, gender or type of culture (SBU or UTI) in the GLMM analysis did not change this estimate. Excluding resistance to the administered AP changed the estimate slightly to OR 1.7 (95%CI 1.2-2.3) for AP use relative to no AP use.

Table 2 depicts the association between type of AP on resistance patterns in 624 Gram negative cultures. Due to statistical insignificance, we left out the few Gram-negative cultures on other AP than trimethoprim, nitrofurantoin, ciprofloxacin or a combination of trimethoprim and nitrofurantoin.

Table 2: Percentages of resistance of Gram-negative uropathogens against commonly used antibiotics per administered antibiotic prophylaxis.

	no prophylaxis	nitrofurantoin prophylaxis	trimetoprim prophylaxis	nitrofurantoin + trimetoprim prophylaxis	ciprofloxacin prophylaxis
number of gram-negative cultures	228	166	131	84	15
antibiotic tested	% resistant				
amoxicillin	**57.0**	**57.3**	**71.3 ***	**79.0 ****	**55.6**
amoxicillin / clavulanic acid	**23.2**	**21.5**	**26.7**	**40.9 ****	**46.2**
piperacillin	**56.6**	**38.6 ***	**62.5**	**70.4**	**41.7**
piperacillin / tazobactam	**5.6**	**4.9**	**3.4**	**23.3 *****	**8.3**
cefazolin	**17.3**	**14.0**	**14.9**	**29.0**	**66.7 ****
cefuroxim	**9.0**	**21.5 ****	**5.2**	**14.3**	**70.0 *****
ceftazidim	**3.4**	**12.9 ***	**1.7**	**5.5**	**9.1**
ceftriaxon	**1.4**	**7.9 ***	**0.0**	**3.1**	**10.0**
meropenem	**0.0**	**2.4**	**1.6**	**1.2**	**8.3**
amikacin	**0.6**	**9.5 ****	**0.8**	**2.5**	**0.0**
gentamicin	**3.2**	**4.4**	**2.6**	**6.3**	**0.0**
tobramycin	**3.1**	**6.0**	**1.6**	**8.6 ***	**0.0**
ciprofloxacin	**3.8**	**7.2**	**12.0**	**2.5**	**58.3 *****
norfloxacin	**5.1**	**8.9**	**11.6**	**3.8**	**63.6 *****
levofloxacin	**5.9**	**10.2**	**11.8**	**2.5**	**53.8 *****
trimetoprim	**38.5**	**38.7**	**90.5 *****	**83.3 *****	**55.6**
co-trimoxazol	**32.1**	**30.9**	**79.1 *****	**71.8 *****	**38.5**
nitrofurantoin	**13.2**	**56.1 *****	**11.6**	**14.3**	**77.8 *****

GLMM used to compare risk of resistance relative to no prophylaxis used, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

ANTIBIOGRAM OF UROPATHOGENS AND THE INFLUENCE OF ANTIBIOTIC PROPHYLAXIS ON RESISTANCE.

Penicillins

In our study cohort, resistance against amoxicillin and piperacillin was common with a overall prevalence of 66.7% and 68.2% in *E.coli* UTIs (*Table 3*). Stopping AP decreased the percentage of resistance in *E.coli* UTIs against amoxicillin and piperacillin from respectively 73.8 and 73.5% to 56.3% and 59.5%. Resistance against amoxicillin / clavulanic acid (29.7%) and piperacillin / tazobactam (7.8%) was less common in *E.coli* UTIs, as well as in other Gram negative UTIs. When discontinuing AP, the prevalence of resistance against amoxicillin / clavulanic acid and piperacillin / tazobactam decreased to respectively 22.7 and 5.5% *(Table 2)*.

Cephalosporins

Gram negative bacteria such as *E.coli* showed moderate resistance for first and second generation cephalosporins (17.9% and 11.4% respectively) in our cohort of spina bifida patients, whereas for third generation cephalosporins *E.coli* had significantly lower resistance of 1.7-1.9% (Table 3). In UTIs with the uropathogen *Klebsiella pneumoniae* however, one in five is resistant to a third generation cephalosporin. Compared to not using AP, trimethoprim (0% and 5%) and nitrofurantoin alternating with trimethoprim (3% and 15%) as AP did not significantly influence resistance to second and third generation cephalosporins. However, the resistance for second generation cephalosporins increased significantly when using nitrofurantoin (21%) or ciprofloxacin (70%) as AP *(Table 2)*.

Fluoroquinolones

In our cohort there was an overall low resistance of around 5% for fluoroquinolones in Gram negative bacteria while not using AP (*Table 2*). This was negatively influenced by prophylaxis: nitrofurantoin and trimethoprim prophylaxis doubled the resistance percentage (7.1 and 13.0% for ciprofloxacin respectively) (*Table 2*). When trimethoprim and nitrofurantoin were taken alternately, the resistance rate remained as low as without AP. The use of ciprofloxacin as AP was associated with a sharp increase in fluoroquinolones resistance (58.3-63.6%) *(Table 2)*.

Trimethoprim / sulfamethoxazole

Even without AP, in our cohort *E.coli* bacteria had high resistance for both trimethoprim (42.9%) and trimethoprim/sulfamethoxazole (35.4%) (*Table 3*). Resistance obviously increased when using AP involved trimethoprim (90.1% and 77.7% respectively) (Table 2). Nitrofurantoin as AP however was not associated with

Table 3: Percentages of resistance of Gram-negative uropathogens against commonly used antibiotics per administered antibiotic prophylaxis

		Gram negative uropathogens		
		AmpC negative		
		E.coli	*Klebsiella pneumoniae*	*Proteus mirabilis*
	number of cultures	387	42	34
antibiogram				
penicillines				
amoxicillin	total	66.7	NC	24.2
	AP+	73.8	NC	11.5
	AP-	56.3	NC	#
amoxicillin / clavulanic acid	total	29.7	9.5	6.1
	AP+	32.8	9.1	7.7
	AP-	25.3	#	#
piperacillin	total	68.2	NC	9.1
	AP+	73.5	NC	9.5
	AP-	59.5	NC	#
piperacillin / tazobactam	total	7.8	17.1	3.0
	AP+	10.3	15.6	3.8
	AP-	4.0	#	#
cephalosporines				
cefazolin (1)	total	17.9	43.8	4.5
	AP+	20.6	54.5	0.0
	AP-	13.5	#	#
cefuroxim (2)	total	11.4	45.2	3.0
	AP+	13.5	51.5	0.0
	AP-	8.2	#	#
ceftazidim (3)	total	1.7	21.7	4.3
	AP+	2.6	29.4	4.5
	AP-	0.0	#	#
ceftriaxon (3)	total	1.9	19.4	0.0
	AP+	2.5	25.0	0.0
	AP-	0.8	#	#
other bactolactam				
meropenem	total	0.0	0.0	0.0
	AP+	0.0	0.0	0.0
	AP-	0.0	#	#
aminoglycosides				
amikacin	total	1.9	19.0	4.2
	AP+	2.6	26.7	4.3
	AP-	0.9	#	#

	AmpC positive			Non-fermenting	
	Klebsiella oxytoca	*Enterobacter cloacae*	*Citrobacter freundii*	*Pseudomonas aeroginosa*	p-value AP+ vs AP-
	21	18	17	47	
	NC	NC	NC	NC	**0.031**
	NC	NC	NC	NC	
	NC	NC	NC	NC	
	9.5	NC	NC	NC	0.172
	#	NC	NC	NC	
	14.3	NC	NC	NC	
	NC	NC	NC	2.6	0.950
	NC	NC	NC	3.1	
	NC	NC	NC	#	
	5.3	#	#	2.2	0.176
	#	#	#	2.7	
	7.7	#	#	#	
	56.3	NC	NC	NC	0.346
	#	NC	NC	NC	
	50.0	NC	NC	NC	
	14.3	NC	NC	NC	**0.016**
	#	NC	NC	NC	
	9.1	NC	NC	NC	
	5.9	NC	NC	4.3	0.161
	#	NC	NC	2.6	
	4.5	NC	NC	#	
	5.9	#	NC	#	0.148
	#	#	NC	#	
	9.1	#	NC	#	
	0.0	0.0	0.0	7.5	0.461
	#	#	#	9.1	
	0.0	#	#	#	
	0.0	0.0	0.0	2.5	0.054
	#	#	#	3.0	
	0.0	#	#	#	

Table 3: Percentages of resistance of Gram-negative uropathogens against commonly used antibiotics per administered antibiotic prophylaxis (*continued*)

		Gram negative uropathogens		
		AmpC negative		
		E.coli	*Klebsiella pneumoniae*	*Proteus mirabilis*
gentamicin	total	4.7	2.4	0.0
	AP+	4.4	3.0	0.0
	AP-	4.8	#	#
tobramicin	total	4.9	4.8	3.0
	AP+	4.8	6.1	3.8
	AP-	4.4	#	#
fluorquinolones				
ciprofloxacin	total	7.8	52.9	0.0
	AP+	10.2	63.6	0.0
	AP-	3.6	#	#
norfloxacin	total	7.7	52.9	0.0
	AP+	9.7	63.6	0.0
	AP-	4.5	#	#
levofloxacin	total	9.4	29.3	0.0
	AP+	10.6	33.3	0.0
	AP-	7.7	#	#
other antibiotics				
trimetoprim	total	66.6	88.2	34.8
	AP+	80.7	63.6	36.4
	AP-	42.9	#	#
cotrimoxazol	total	55.7	52.4	33.3
	AP+	69.7	51.5	30.8
	AP-	35.4	#	#
nitrofurantoin	total	16.4	90.5	NC
	AP+	22.4	93.9	NC
	AP-	7.7	#	NC

= not calculated as less than ten samples tested, NC = not considered due to intrinsic resistance or uncommon clinical drug/bug combination.

	AmpC positive		Non-fermenting	
Klebsiella oxytoca	*Enterobacter cloacae*	*Citrobacter freundii*	*Pseudomonas aeroginosa*	p-value AP+ vs AP-
0.0	0.0	0.0	0.0	0.500
#	#	#	0.0	
0.0	#	0.0	#	
0.0	0.0	0.0	2.1	0.194
#	#	#	2.6	
0.0	#	0.0	#	
0.0	0.0	0.0	5.0	**0.021**
#	#	#	6.1	
0.0	#	0.0	#	
0.0	0.0	0.0	9.4	**0.047**
#	#	#	11.1	
0.0	#	0.0	#	
0.0	0.0	0.0	9.4	0.057
#	#	#	11.1	
0.0	#	0.0	#	
23.5	16.7	66.7	NC	**<0.001**
#	#	#	NC	
18.2	#	90.9	NC	
19.0	11.8	47.1	NC	**<0.001**
#	#	#	NC	
14.3	#	10.1	NC	
28.6	64.7	0.0	NC	**<0.001**
#	#	#	NC	
21.4	#	0.0	NC	

increased resistance for trimethoprim (38.1%) or trimethoprim/sulfamethoxazole (30.7%) in Gram negative bacteria, whereas ciprofloxacin as AP only mildly increased resistance to trimethoprim (45.5%) and trimethoprim/sulfamethoxazole (33.3%) *(Table 2)*.

Aminoglycosides

There was a low resistance rate for intravenous aminoglycosides in our cohort (3%), not influenced by AP nitrofurantoin (4%) or trimethoprim (3%). When using ciprofloxacin as AP, the Gram negative bacteria also remained sensitive to gentamicin, amikacin or tobramycin *(Table 3)*.

Nitrofurantoin

Without AP, 13.2% of UTIs were resistant for nitrofurantoin treatment (*Table 2*). This resistance for nitrofurantoin treatment remained stable when using trimethoprim as AP (11.6%), while resistance significantly increased when using ciprofloxacin (77.8%) or nitrofurantoin itself (56.1%) as AP *(Table 2)*.

The presence of resistance was not associated with age or gender. Microbial resistance against the prophylactic AP was not 100%: bacterial pathogens were still sensitive for treatment with the used AP in 43.9% of nitrofurantoin, 41.7% of ciprofloxacin and 9.5% of trimethoprim prescribed patients *(Table 2)*.

DISCUSSION

Bacterial resistance is an emerging and hazardous phenomenon occurring with ever-increasing use of antibiotics. Antibiotic prophylaxis (AP) administered to prevent recurrent urinary tract infections (UTIs) contributes to this resistance (13), although it has been proven that AP does not decrease the risk of renal scarring (1).

We compared bacterial susceptibility patterns in positive urine cultures in children with spina bifida and CIC continuing or stopping AP. Overall, our study showed a decrease in resistance to commonly used antibiotics when AP is stopped, confirming our hypothesis. Even when the administered AP is excluded from these calculations, the number of antibiotics to which the cultured pathogen is resistant remains higher in the continuing group. These findings in spina bifida patients on CIC is in accordance with previous studies for resistance patterns comparing AP to no AP in patients with community-acquired UTIs (14-18). The fact that a particular class of antibiotics is associated with resistance towards other classes of antibiotics

might be explained by the observation that bacterial resistance traits can be linked (19,20).

E.coli accounts for 75-90% of community-acquired UTIs (21,22), whereas *E.coli* is responsible for only 54.3% of the SBUs and UTIs in our specific population of children with spina bifida, with higher percentages of other uropathogens causing SBU/UTI. This difference is a common feature in non community-acquired UTIs, as described in previous studies in non-spina bifida patients, from Landhani et al (40% *E.coli* in children with underlying pathology), Lutter et al (58% *E.coli* in non-spina bifida children on AP) and Wagenlehner et al (35-60% *E.coli* in adult hospital-acquired UTIs due to catheterization with introduction of alternative pathogens) (15,16,23).

Choice of antibiotic prophylaxis in children with spina bifida

Our SPIN UTI study has shown that, whenever safe according to urological care, AP to prevent UTIs should be stopped in children with spina bifida. In a previous article we have shown that every child has to take two years of daily AP to prevent one extra non-febrile, non-scarring UTI (12), and this current study reveals a significant improvement in susceptibility to any necessary antibiotic treatment for a UTI when stopping AP. This article therefore emphasizes the necessity to stop the use of AP in children whenever possible to prevent bacterial resistance, especially since AP has proven not to prevent renal scarring (1).

When however, for reasons of recurrent UTIs, a persistent overactive bladder or high grade vesico-ureteral reflux, AP is a necessity, the choice of prophylaxis has impact on the bacterial resistance to commonly used therapeutic antibiotics. Trimethoprim as AP has the least negative influence on bacterial resistance: in our study cohort, the susceptibility of most therapeutic antibiotics remains relatively stable, except for fluoroquinolones, trimethoprim itself and trimethoprim / sulfamethoxazole. In our study, the use of nitrofurantoin as AP is associated with an increased resistance to cephalosporines, aminoglycosides and fluoroquinolones, with an increased risk of treatment failure, compared to non-AP patients. Particularly AP with fluoroquinolones is associated with a high percentage of resistance, especially to therapeutic oral antibiotic possibilities when necessary, and should therefore be discouraged.

Choice of therapeutic antibiotics in children with spina bifida

First consideration in choosing an appropriate antibiotic when a UTI is suspected or confirmed is the manner of administration: when clinically not ill, oral antibiotic treatment is adequate, whilst in sick children with spina bifida due to a UTI intravenous administration of antibiotics is often necessary. This determines the choice

of antibiotic treatment, along with previous culture results and resistance patterns, presence or absence of fever and recently prescribed AP. In our study cohort, nitrofurantoin is first choice medication for a UTI without fever or recent AP. Without fever but with prophylaxis, in children with trimethoprim as AP nitrofurantoin is still first choice. In other AP and in children with fever on or off AP, oral treatment for UTI depends on local susceptibility, with ciprofloxacin and cefuroxim as antibiotics with high a priori chance of treatment success in our study cohort. When intravenous treatment is warranted, a third generation cephalosporin, fluoroquinolon or carbapenem is possible. However, we emphasize that the choice of therapeutic antibiotics depends on local susceptibility and individual resistance patterns in previous urinary cultures.

The strength of this study is the large number of adequate catheterized urinary cultures in a cohort of susceptible children with spina bifida. Remarkable is the relatively high percentage of susceptibility of bacteria for the already administered AP.

CONCLUSION

Discontinuation of antibiotic prophylaxis decreases bacterial resistance for commonly used antibiotics in children with spina bifida on clean intermittent catheterization should be pursued to prevent bacterial resistance, long term side effects of prophylactic antibiotics and the need for hospital admissions for broad spectrum intravenous antibiotics.

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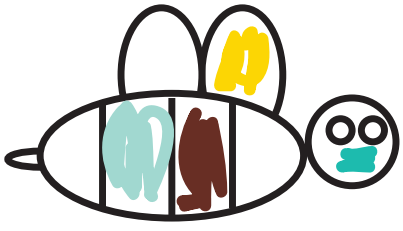
Chapter 6

Quality of Life in children with spina bifida: a cross-sectional evaluation of 102 patients and their parents



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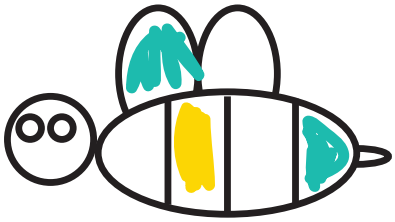

ABSTRACT

Background

In the so-called SPIN UTI study on 176 patients with spina bifida and clean intermittent catheterization (CIC) we have studied the influence of antibiotic prophylaxis (AP) on the number of yearly urinary tract infections (UTIs) and bacterial resistance to commonly used antibiotics. We have proven that stopping AP increased the number of yearly UTIs only slightly and clinically irrelevant: patients would have to take AP for two years to prevent one extra non-febrile, non-scarring UTI. We have also shown that bacterial resistance improved over time when AP was stopped. In this article we study the influence of the recommended discontinuation of AP on Health Related Quality of Life (HRQL) in spina bifida.

Methods and findings

Participating children aged between 4 and 16 years and their parents were asked to fill out the validated KINDL-R questionnaire, combined with specific spina bifida questions. Scores in study participants were compared with healthy controls. Also, the impact of AP, gender, level of spinal lesion, hydrocephalus, methods of catheterization and defecation, mobility and level of schooling on HRQL was evaluated.

Results

One hundred and two of the 133 eligible children (77%) filled out the KINDL-R. Patients and their parents had significantly lower HRQL scores than healthy controls ($p<0.001$). Parents rated significantly lower scores than their children, especially in the psychological domains. Severity of co-morbidity was not associated with differences in HRQL. There were no differences between children who continued and stopped AP.

Conclusions

HRQL scores are lower in spina bifida patients compared to healthy children. Parents rated even lower scores, especially in the psychological domains. Stopping antibiotic prophylaxis does not adversely affect HRQL, and should therefore be pursued to improve bacterial resistance patterns in spina bifida patients.

INTRODUCTION

Despite periconceptional administration of folic acid and prenatal ultrasound screening, spina bifida is the second most common congenital birth defect (1). Due to genetic and environmental factors, prevalence varies throughout the world, with approximately one in every two thousand live births in the Western World (2). After the innate postnatal surgical morbidity, there is a life long burden of neurological, urological and orthopedic consequences and severely disabling emotional and behavioral problems (3-6).

In many studies the Health Related Quality of Life (HRQL) was assessed in children with spina bifida (3,6-12). A wide variety of HRQL questionnaires has been developed, addressing the psychological and physiological aspects of various domains of everyday life activities, either with or without specific spina bifida related questions. Most studies show that parental expectancy, patient mobility and urinary continence are the most important factors to predict HRQL in patients with spina bifida (6,9,11).

We recently conducted the so-called SPIN UTI randomized controlled trial to assess whether stopping antibiotic prophylaxis (AP) in 176 patients with spina bifida on clean intermittent catheterization (CIC) influenced the number of urinary tract infections (UTIs) (13). Stopping prophylaxis increased the number of yearly UTIs only slightly. Patients would have to take prophylaxis for two years to prevent one extra non-febrile, non-scarring UTI. Therefore it was concluded that most spina bifida patients on CIC can safely discontinue AP.

Bacterial resistance is common in everyday AP use. In our study on bacterial resistance patterns in continuing and stopping AP, bacterial susceptibility for commonly used antibiotics improved when AP was stopped. Discontinuation of AP should therefore be pursued to improve bacterial susceptibility for antibiotics as long as this has no negative effect on the number of UTIs and perceived HRQL in spina bifida patients on CIC.

Our aim in this study is to investigate the HRQL in our cohort of 133 eligible children, and whether stopping AP either increased HRQL due to less daily medication or decreased HRQL due to loss of perceived antibiotic protection.

METHOD

Study population

From 2005 through 2008, 176 patients with spina bifida on CIC were included in the SPIN UTI study and randomized to either continue or stop daily AP; primary outcome was the number of urinary tract infections over an 18 month study period. Details and results of the study are described elsewhere (13). Out of the 176 participants, 133 were between age 4 and 16 years old and therefore eligible for the HRQL sub-study.

Procedure

At the end of the study period, the 133 eligible patients and their parents were asked to fill out the validated KINDL-R questionnaire (12). KINDL-R consists of two separate lists: one list with general questions on six domains (physical well-being, emotional well-being, self-esteem, family, friends and school), each domain containing four specific questions, and one chronic disease module with extra questions for the parents. We also added the KINDL-R list of 37 specific spina bifida related questions for parents (12). The first two lists were validated for both chronic disease and children with spina bifida, with 1501 healthy German primary school children as historical controls (12,14). The added specific spina bifida questionnaire has not been validated yet. The answers to the questions were compared with the results of previous studies of HRQL observations in both healthy controls and spina bifida children and their parents (5,11,14,15). The answers to the questions were alculated into a combined total HRQL score and scores per domain.

Demographic data and current functional status

To determine the influence of gender and severity of disability in the participating patients, gender, level of spina bifida lesion, manner of micturation and defecation, mobility and level of schooling were also evaluated, using regression analysis.

Statistical analysis

First, general characteristics of the patients were tabulated by intervention (stop or continue antibiotic prophylaxis). Only a subgroup of children in the trial was age-eligible for KINDL-R (133 of 176) of whom 77% did participate in this quality of life study. Therefore, the randomization principle was violated and we tested for group differences in general characteristics using Chi-square tests or Fisher's exact tests where appropriate. Subsequently, differences in HRQL scores between the intervention groups were tested for both patients and parents with independent samples T-tests. Univariable linear regression analyses were used to correct for the

effect of differences in general characteristics that might confound the association between intervention and HRQL. Additionally, we intended to test for differences between patients' and parents' perceived quality of life. This was done in the total patient group, and we intended to use paired t-tests in case of no treatment effect or general linear models in case of a treatment effect on HRQL. As all analyses of sub domains of HRQL are part of one overriding hypothesis, we did not account for multiple testing. All statistical analyses were performed using SPSS, version 19.0 (IBM Company).

RESULTS

Subject responses and baseline characteristics

One hundred and two (77%) of the 133 eligible children and their parents filled out the KINDL-R questionnaire at the end of the trial period between 2006 and 2010. Patient characteristics are described in *Table 1*. There were no significant differences in the relevant variables between the stopping and continuing group, with the exception of the division of children over 8 years of age in the stop and continuing group ($p=0.03$).

Quality of Life scores

Compared to healthy controls, both spina bifida children and their parent proxy have significantly lower HRQL scores on every domain except disease, as well as in the total score (*Table 2*). Patients generally had higher HRQL scores than their parent proxy (62.0 vs. 56.8, $p<0.001$), specifically in the domains of disease ($p<0.001$), emotional well-being ($p=0.005$), self-esteem ($p<0.001$), friends ($p=0.002$) and school ($p=0.02$). Regression analyses revealed no significant influence of gender, level of spinal lesion, presence of hydrocephalus, route of catheterization, manner of defecation or level of mobility and schooling on HRQL.

Table 1: Patient characteristics of evaluated children with spina bifida on clean intermittent catheterization.

		Total group		Continue AP		Stop AP		
		N=102		N=54		N=48		p-value
		N	**%**	N	**%**	N	**%**	
Gender	male	45	**44**	25	**46**	20	**42**	0.64
	female	57	**56**	29	**54**	28	**58**	
Age	4-7 years	49	**48**	26	**48**	23	**48**	0.03
	8-12 years	23	**23**	17	**32**	6	**13**	
	12-16 years	30	**29**	11	**20**	19	**40**	
School	regular	65	**64**	37	**69**	28	**58**	0.98
	special	28	**27**	16	**30**	12	**25**	
	missing	9	**9**	1	**2**	8	**17**	
Level of lesion	thoracal	11	**11**	7	**13**	4	**8**	0.16
	lumbal	60	**59**	27	**50**	33	**69**	
	sacral	31	**30**	20	**57**	11	**23**	
Hydrocephalus	no	32	**31**	21	**39**	11	**23**	0.08
	yes	70	**69**	33	**61**	37	**77**	
Mobility	ambulatory	65	**64**	35	**65**	30	**63**	0.81
	wheelchair	37	**36**	19	**35**	18	**38**	
CIC	vesicostoma	13	**13**	7	**13**	6	**13**	0.94
	transurethral	89	**87**	47	**87**	42	**88**	
Defecation	spontaneous	23	**22**	14	**26**	9	**19**	0.41
	colon cleansing	69	**68**	36	**67**	33	**69**	
	manual evacuation	1	**1**	1	**2**	0	**0**	
	stoma	9	**9**	3	**6**	6	**13**	

AP = antibiotic prophylaxis, CIC = clean intermittent catheterization

Table 2.: HRQL scores in spina bifida children, their parents and healthy controls.

	parents		**children**			**reference**	
	mean	SD	mean	SD	p-value[1]	mean	SD
physical well-being	57.86	14.6	60.61	14.2	0.34	73.78	3.53
emotional well-being	60.38	12.3	67.88	11.5	0.005	81.64	1.76
self-esteem	45.85	8.65	59.15	13.5	< 0.001	63.91	3.75
family	60.00	11.6	63.21	13.8	0.22	81.18	3.81
friends	48.90	16.3	58.70	14.5	0.002	78.16	0.11
school	56.46	12.5	62.44	8.52	0.021	70.28	4.17
disease	41.88	15.9	63.04	9.15	<0.001	62.54	1.94
total score	56.76	6.13	61.97	8.52	<0.001	75.94	1.98

[1] *Estimated with paired t-test*

There was no difference between the sub-domain HRQL scores of the group stopping daily AP and the group that continued AP in any specific domain (*Table 3*). Also, the total HRQL score, both in patients (62.0 in stop group vs. 62.3 in continuing group, p=0.92) and parents (57.2 vs. 54.8, p=0.16) did not differ significantly between stopping or continuing prophylaxis (*Table 3*).

Table 3: Differences in HRQL scores in continuing and stopping antibiotic prophylaxis in spina bifida patients and their parents.

Children	**continue**		**stop**		
	mean	SD	mean	SD	p-value[1]
physical well-being	60.20	14.89	61.80	14.06	0.70
emotional well-being	66.07	13.43	69.80	8.35	0.24
self-esteem	57.68	14.17	60.80	12.88	0.41
family	60.71	16.26	66.00	9.90	0.16
friends	56.61	16.67	61.74	10.72	0.21
school	63.26	9.72	63.10	8.44	0.95
disease	61.81	10.90	65.19	7.52	0.27
total score	62.25	8.89	62.03	7.53	0.92

Parents	**continue**		**stop**		
	mean	SD	mean	SD	p-value[1]
physical well-being	56.94	15.00	59.24	12.15	0.41
emotional well-being	59.26	13.58	63.37	10.33	0.10
self-esteem	46.04	8.79	47.34	8.07	0.44
family	63.11	11.82	60.94	11.47	0.35
friends	49.53	14.94	52.20	14.36	0.39
school	55.33	12.49	58.60	9.72	0.17
kiddy parents	51.04	9.28	50.07	6.57	0.75
disease	41.15	15.75	37.54	13.42	0.39
spina	62.98	9.05	62.51	7.57	0.84
total score	54.83	7.88	57.24	7.16	0.16

[1] estimated with paired t-test

DISCUSSION

Spina bifida patients and their parents have lower HRQL scores than healthy controls, and parents have lower HRQL scores than their children. Severity of the spinal lesion and stopping daily AP for urinary tract infections in children with spina bifida on CIC has no significant effect on HRQL.

This is in accordance with prior studies (11,15), and may be explained by the fact that children appreciate life as they know it: their answers reflect current and short term social functioning, while they disregard potential future threats. Parents however tend to incorporate possible future outcome in their responses, and therefore have a less optimistic view of social status, relationships and employment possibilities of their offspring. Another explanation could be that children want to protect their parents by concealing their true feelings. Janse et al showed that pediatricians tend to misunderstand perception of HRQL in patients' parents (17). Therefore, systematic assessment of HRQL is needed in all patients with spina bifida as well as their parents, as this may differ from the assumed HRQL by the health care professional. Proper assessment of HRQL thus contributes to a tailored psychosocial and somatic counseling by health care professionals treating spina bifida patients.

The level of the spinal lesion, presence of hydrocephalus, manner of both micturation and defecation, gender and level of mobility and schooling does not influence the HRQL scores in either patients or their parents. This is in accordance with previous studies (5,16). Padua et al. found that patients with high disability have lower scores in physical domains, whilst patients with milder lesions have more emotional problems, due to their incontinence problems. Spina bifida itself is therefore the main factor contributing to perception of HRQL, and not so much the severity of the morbidity.

In our study, stopping AP neither improved nor worsened HRQL scores at the end of the study period. Although there is a slight increase in the incidence of UTIs in the stopping group, this increase was clinically irrelevant because every patient would have to use daily antibiotics for more than two years to prevent one extra non-febrile UTI (13). Also, bacterial resistance for commonly used antibiotics improved in the months after stopping AP. Thus, stopping daily AP does not only result in a decrease in medication consumption and an improvement of bacterial susceptibility to antibiotics: it can be done without decreasing the experienced HRQL in children with spina bifida.

CONCLUSION

Spina bifida patients have lower HRQL scores than their healthy peers. Parents have even lower scores, especially in the psychological domains. Stopping daily antibiotic prophylaxis in children with spina bifida on clean intermittent catheterization can be done safely to improve bacterial resistance for antibiotics without influencing their quality of life.

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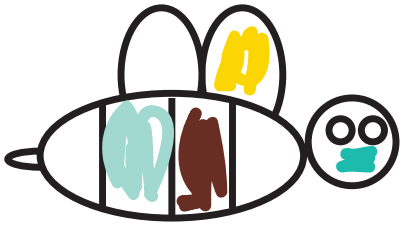
Chapter 7

General discussion

Developments in spina bifida: the rapid progression from poor prognosis to multidisciplinary challenges



SPINA BIFIDA

Despite many efforts to minimize the occurrence of neural tube defects (NTDs), it is still the second most common birth defect in newborns after congenital heart anomalies, with an incidence of 1 in every 2,000 newborns, or 300,000 to 400,000 new-born children worldwide every year (1). NTDs result from a malformation in the primary neurulation in the fourth gestational week, with failure of folding and fusion of the elevated lateral edges of the ectodermal neural plate. The precise etiology is unknown, and probably multifactorial with genetic, environmental and nutritional influences, like insulin-dependent gestational diabetes, obesity, medication and inadequate dietary folate (2). The so-called two-hit model has given the insight that not only primary failure of closure is responsible for the neurological deficits, but also secondary damage due to the negative influence of the amniotic fluid on neurological development (3, 4).

Severity of NTDs varies from anencephaly and encephalocele to spina bifida, or: meningocele (MC) and myelomeningocele (MMC), characterized by a bone defect in the spinal column with protrusion of a fluid filled sac with (MMC) or without (MC) spinal cord tissue. Spina bifida can be overt or occult, with dermal closure over the defect. An important factor determining the severity of NTD is the presence or absence of cerebellar herniation in a so-called Chiari II malformation. When herniation is present, a shunt of the cerebral spinal fluid (CSFS) is necessary to prevent obstructive hydrocephalus and abnormal development of the brain.

Clinical symptoms depend on the level of neurological involvement, but always include lower extremity motor deficit and bladder / bowel dysfunction due to disrupted neural innervations. Ambulatory abilities vary form wheelchair bound to ambulation without aid.

RENAL INVOLVEMENT

Until the mid-1980s, life expectancy in children with MMC was short, due to the many detrimental co-morbidities, like early end-stage renal insufficiency and hydrocephalus. Most neurological clinicians were therefore reluctant to perform curative interventions and provided important but merely supportive care. Hence, live-born children with MMC did not survive past their third decade of life, mainly due to urinary complications and renal insufficiency.

In urological care of patients with MMC, clinicians have always recognized the dyssynergia between pelvic floor muscle status and detrusor muscle activity (DSD) (5, 6): both can be either over- or underactive (7, 8). In 85% of children with MMC, this results in irregular micturation with a high prevalence of urinary tract infections (UTIs) due to residual urine, vesico-ureteral reflux and increased bladder pressure, with subsequent volume pressure in the renal calices and nephrological units (9-11), and smaller kidney size (12). These two phenomena resulted in progressive renal insufficiency in early life, with the need for dialysis and renal transplantation in childhood or early adulthood.

Also, multiple other factors increase the risk for UTIs like genetic variations that affect innate immunity (13, 14), a defective glycosaminoglycan layer, abnormal bladder epithelium and chronic inflammation (15), alteration of protective intestinal flora, impaired secretory immunoglobulin(Ig)-A response, defective apoptosis and bladder ischemia (16).

LIFE-PROLONGING UROLOGICAL INTERVENTIONS

In the past five decades, many pre- and postnatal interventions have tried, and some have proven to be beneficial to renal outcome in MMC. In 1972, Lapides has proven that clean intermittent transurethral catheterization (CIC) was an excellent manner of alleviating the high bladder pressure, with less or no residual urine after bladder emptying(17). In long-term studies, children on CIC achieved not only urinary continence with tremendous improvement of social life, but also a demise in renal deterioration due to high bladder pressure and UTIs (6, 18). Anticholinergic medication, administered orally or intravesically, has also contributed to alleviation of bladder pressure and subsequent renal deterioration, as well as botulinum-toxin injections in the bladder wall. In case of non-compliant bladders, enterocystoplasty has proven to be the gold standard for bladder augmentation (18). Sacral neuromodulation and transurethral electrical bladder stimulation are recent promising interventions, improving micturation and incontinence (19-21).

Due to all these recent improvements, DSD with high pressure bladders has decreased, overcoming the rapid progression of renal deterioration. This has prolonged the life span of children with MMC with decades. However, close urological observation is necessary through the entire life-span: several reviews have described long-term urological outcome in MMC, concluding that life-long follow-up is necessary as DSD can deteriorate beyond adolescence (22-24).

FURTHER IMPROVEMENTS IN THE CARE OF SPINA BIFIDA

Combining the improved urological care with the introduction of cerebral spinal fluid shunt to either the peritoneum or the cardiac atrium, both neurological and uronephrological outcome has improved significantly over the last few decades, and therefore life-expectancy. This implied that the overall care for children with MMC had to improve: after the life-prolonging renal en neurological improvements, the long-term orthopedic and psychological co-morbidities became more prominent and have replaced renal insufficiency as bottleneck for a good life (25).

With the prolonged survival rates, many clinicians have studied preventive and supportive measures to improve clinical outcome and quality of life of children with MMC even further:

1. Prevention of NTDs with periconceptionally administered **folic acid** since 1998 has been proven in both ovine and human studies. Since mandatory folic acid fortification, the prevalence of serum folate deficiency has dropped from 30% to <1%, and a 28-70% decline in the prevalence of MMC has been observed (1, 26).
2. Since 1984, **fetal neurosurgery** for MMC has been performed to prevent the second hit of the damaging influence of amniotic fluid(3). In the MOMS study in the mid-1990s, endoscopic intervention did not improve postnatal outcome, but open surgery resulted in both less cerebellar herniation and need for CSFS (from 84 to 44%) as well as better motor skills compared to postnatal correction of MMC (66% independent ambulatory) and cognitive function in the average to high range in 83% of patients with MMC, albeit with more behavioral abnormalities and deficits in executive functions (27). Unfortunately, until now urological outcome has not improved despite prenatal neurosurgery (28-30); up to 94% still has lower urinary tract dysfunction (31).
3. Tissue engineering, focusing on repair, replacement or regeneration of cells, tissues and organs, combines cell biology, bioengineering, gene therapy and pharmacology. It comprises cells, scaffolds and nutrients, with exogenous and/or endogenous cellular components. With the hypothesis that prenatal local administration of neural crest **stem cells** could improve neurological connections and function, studies in both ovine and human subjects have been performed since the early 2000s (32-34). Despite the promising increase of neural tissue in the MMC in offspring and children after stem cell infusion and scaffolds with natural or synthetic materials (35-37), until now no significant improvements in neurologic functional outcome has been observed, besides less herniation through Chiari II malformation (36).

4. **Fetal urological surgery** to alleviate the detrimental bladder pressure prenatally has been studied in the 1990's. Unfortunately, all studied revealed that many shunts between bladder and amniotic fluid were either displaced or blocked, resulting in no better urological outcome compared with postnatal intervention (1). It has also been postulated that renal damage occurs already in the very early antenatal stage of MMC, not to be prevented by shunts in later pregnancy.

WHAT HAS THIS THESIS CHANGED IN THE CARE FOR CHILDREN WITH SPINA BIFIDA?

Our thesis on urological aspects of MMC has provided new insights.

1. Due to the unknown and unpredictable long-term effects of prenatal and postnatal interventions, no consensus exists on the frequency and intensity of urological evaluations to prevent urological deterioration of DSD. Also, the diagnostics and treatment of occurring UTIs and the use of antibiotic prophylaxis (AP) in MMC and CIC is subject to local preferences and protocols (38).
2. Home screening for UTIs enables ruling out infection by using leukocyte esterase test (LET) only. This prevents unnecessary hospital visits to diagnose or treat UTIs. However, when LET is positive, a laboratory culture should always be performed, for both confirming the UTI as well as determining the resistance pattern for appropriate antibiotic treatment. Test characteristics of Uricult® does not support its use for UTI in children with spina bifida (39).
3. In this thesis, we have proven that antibiotic prophylaxis (AP) decreases the number of symptomatic UTIs in children with MMC. Its general may be questioned as AP is administered daily for two years to prevent one non-febrile UTI. We advise to stop AP once urological care has provided lower bladder pressure and a decrease of vesico-ureteral reflux (40).
4. This thesis shows a demise in bacterial resistance against commonly used antibiotics once AP has been stopped in children with MMC. This is both a substantial contribution to the present believe that bacterial resistance is caused by abundant administration of antibiotics as well as a an convincing argument to stop AP to prevent an increase in UTIs that can only be treated by intravenous broad-spectrum antibiotics (41).
5. Quality of life in children with MMC depends on many factors but cannot be estimated by any caregiver by looking at level of lesion: both children and their parents have unsuspected and unexpected feelings about psychical and psychosocial aspects of MMC. In everyday care for children with MMC, regular inventory of experienced quality of life is mandatory to provide proper adjust-

ments in care, not just for medical aspects but, at least as important, for maximal mental and social health.

SO CLOSE, YET SO FAR AWAY....

The prognosis of MMC has improved significantly over the last five decades. Several measures have justified the change from the initial supportive and palliative care to aggressive early neurosurgical and urological care. This has resulted in significant improvements in the quantitative and qualitative outcome of children born with MMC.

When looking at the life of children with spina bifida, however, there is still need to improve prevention, early intervention and long-term care. In our opinion, the following questions are food-for-thought for upcoming researchers:

1. Whole exome sequencing (WES) in patients with spina bifida has already resulted in many candidate genes, like polar cell polarity genes (Celsl1, Ptk7, Vangl2) and genetic mutations causing Meckel syndrome with occipital encephalocele (MKS1, TMEM 216, CEP290) (2). As in many conditions, the currently widespread application of WES will most certainly result in an etiological gene-pool for MMC. Will specific genetic screening and proper parental genetic counseling therefore be possible in the near future?
2. Intrauterine surgery and application of neural crest stem cells has been applied for two decades. Until now, results have been ambivalent and overall unsatisfactory. Can new techniques in prenatal neurosurgery prevent neural damage by amniotic fluid? Is further research into selection of administered neural stem cells in utero still valid? Is the combination of prenatal neurosurgery with intralesional application of neural crest stem cell therapy superior to one of those on itself?
3. In this thesis, we have focused on DSD, CIC and prophylaxis as determining factors for UTIs. Also increasing the risk of UTIs in MMC are many other known factors that cause an aberrant protective function of urothelium (15). Presumably, the abnormal neural innervation and autonomic dysregulation play an important role in this malformation of the bladder wall. Is there a role for implantation of progenitor bladder wall cells to normalize bladder wall development to minimize DSD and the risk of UTIs?

In my personal experience, I have witnessed a significant change in the care for children with spina bifida. I will never forget my first premature newborn with spina

bifida in the early 1990s, and the comforting words from the consulting neurologist for the inconsolable parents, explaining the palliative trajectory because of the poor prognosis. Only one decade later, in many cases the same neurologist can announce a much more optimistic message, although still paved with multiple obstacles in the many different aspects of spina bifida. During inclusion and follow-up of our study, most of the participants told me they have an adequate to good quality of life, despite wheelchair or walking aid dependency, and despite the need for intermittent catheterization and bowel therapy. Expectancy management, maximal support of overall normal schooling, integrated rehabilitation programs and adequate neurological, urological and orthopedic care have resulted in satisfactory social lives in the majority of these children. I can only hope that new techniques and therapies will be developed to improve physical and social outcome in this vulnerable group of patients even further. Future research should, in my opinion, be focused at preconceptional genetic counseling, urological alteration of the aberrant bladder wall urothelium and more individually tailored psychological support in patients with MMC.

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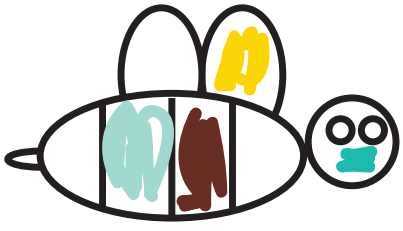
Chapter 8

Summary

Nederlandse samenvatting



SUMMARY

Although major improvements in neurosurgical repair and urological care have been accomplished, children with spina bifida still suffer from disabling urological, neurological, orthopedic, behavioral and cognitive impairments. In our so-called SPIN UTI study, we have focused on the urological problems, urinary tract infections and Quality of Life in spina bifida children. We have assembled a cohort of 176 pediatric patients from the Wilhelmina Children's Hospital at the University Medical Center in Utrecht, the Netherlands and the Gasthuisberg University Hospital in Leuven, Belgium. For eighteen months, we have analyzed the diagnosing, treatment and prevention of urinary tract infections in children with spina bifida and their Quality of Life.

Chapter 2: lack of consensus on urological care in spina bifida

We have evaluated the European protocols for prevention, evaluation and treatment of urinary tract infections and urological care for children with spina bifida. Forty-one European centers providing care for children with spina bifida filled out a questionnaire on six domains: 1. identification of the center and team, 2. number of patients and presence of written protocols, 3. current standard protocols, 4. diagnostic testing when suspecting a urinary tract infection, 5. therapeutic antibiotic regimen and 6. concurrent interventions like urodynamic studies, medication or surgery.

Data-analysis of the 41 centers revealed that there is no common single procedural protocol to prevent, diagnose and treat urinary tract infections. Antibiotic prophylaxis is rarely prescribed to children not on clean intermittent catheterization, and even when on catheterization, most replying centers are reluctant to prescribe antibiotic prophylaxis. Cessation of prophylaxis is considered in the absence of urinary tract infections, on parental request and stabilization of urological dynamics. When an infection is suspected, testing urine samples with test strips and microscopy was considered equally important as clinical complaints, fever and foul smelling urine. To prove or exclude a urinary tract infections, cultures are mandatory in almost all centers. Treatment of an established urinary tract infection is usually orally.

We have concluded from this survey that there is no consensus in urological care in spina bifida patients. With this conclusion in mind, we decided to address several items in the care for urinary tract infections in spina bifida patients: 1. an easy but accurate home test when suspecting a urinary tract infection, 2. to prove that use of antibiotic prophylaxis is unnecessary in patients with spina bifida on clean

intermittent catheterization, 3. to minimize use of antibiotics to decrease bacterial resistance and 4. to evaluate Quality of Life in patients with spina bifida.

Chapter 3: home testing for suspected urinary tract infections in spina bifida

We have evaluated the accuracy of home testing with a leukocyte esterase test and a dip slide urine culture. The leukocyte esterase test is a small stick with a sponge containing the enzyme leukocyte esterase. Discoloration means presence of leukocytes, proving a urinary tract infection when combined with culture-confirmed significant bacteriuria. The other test, the dip slide, contains two agars for Gram-positive bacteria and Gram-negative rods. A urine sample was also sent to our laboratories for a 'gold standard' agar plated culture.

Of the 112 included patients, 45 had a positive agar plated culture, resulting in a-priori probability for bacteriuria of 40%. A positive leukocyte esterase test had a positive predictive value of merely 72%. The negative predictive value of 96% in our study is consistent with previous studies. The esterase test was negative in 3 of the 45 positive cultures, resulting in 93% sensitivity, and positive in 16 of the 67 negative cultures, resulting in 76% specificity. The dip slide test had a similar moderate positive predictive value (73%) as the esterase test, but a substantially lower negative positive predictive value (78%). Combining the dip slide with a esterase test did not improve positive or negative predictive value..

This study reveals that a negative esterase test in home setting excludes bacteriuria and urinary tract infection in 96% of the cases: when the esterase test is negative, there is no indication for culture or antibiotic treatment. A dip slide is not accurate enough to exclude bacteriuria. Both the esterase test and the dip slide have a high false positive rate and cannot be used to diagnose bacteriuria or confirm a urinary tract infection.

Chapter 4: the (mis)sense of antibiotic prophylaxis in children with spina bifida

We evaluated the value of antibiotic prophylaxis for prevention of urinary tract infections in children with spina bifida on clean intermittent catheterization. During an eighteen-month period, biweekly urine samples were evaluated using a leukocyte esterase test and agar plated urine culture. Presence or absence of fever ≥ 38.5°C was used to discriminate between respectively pyelonephritis and cystitis. After computer based allocation and randomization, one half of the patients were asked to stop their prophylaxis and the other half to continue their prophylaxis. Analyses

were performed according the intention to treat principle. Baseline demographics did not differ between the two groups.

Non-febrile urinary tract infections (significant bacteriuria with leukocyturia and clinical symptoms) occurred at least once in 84 (47%) of the patients, with a higher rate in the discontinuation group: 1.5 urinary tract infections per patient year versus 1.1 in the continuation group. This relative risk of 1.44 (95% confidence interval 1.13 – 1.83) when stopping antibiotic prophylaxis is statistically significant, but clinically not relevant: antibiotic prophylaxis has to be administered daily for 2.2 years to prevent one non-febrile urinary tract infection. A pyelonephritis occurred only seven times in six patients: two patients in the continuing group, four in the stopping group. A significant number of patients in the stop group (38 of 88 in total, 43%) switched back to prophylaxis because of recurrent urinary tract infections: 2.7 per patient year versus 1.1 in the compliant group. These were however high-risk patients with more severe vesico-ureteral reflux and an high number of pre-study urinary tract infections. More important, the number of infections per patient year did not decrease after restarting prophylaxis. In our study, low grades of reflux, gender, age and bladder compliance and capacity did not influence the risk of urinary tract infection.

We recommend that antibiotic prophylaxis is discontinued once neurogenic bladder sphincter dyssynergia has been stabilized, and should only be continued in spina bifida children with a high rate of febrile and therefore kidney-damaging urinary tract infections.

Chapter 5: the influence of antibiotic prophylaxis on bacterial resistance

Bacterial resistance to commonly used antibiotics is an worldwide emerging and hazardous phenomenon occurring with ever-increasing use of antibiotics worldwide. The nearly 5,000 bacterial cultures we have collected in our study enabled us to evaluate the influence of stopping antibiotic prophylaxis on the bacterial resistance pattern. Overall, our study showed a decrease in bacterial resistance to commonly used antibiotics once prophylaxis is stopped.

Choice of antibiotic prophylaxis in children with spina bifida

In chapter 4, we have shown that every child has to take daily antibiotic prophylaxis for more than two years to prevent one extra non-febrile, non-scarring urinary tract infection. Combined with the significant improvement in bacterial susceptibility when stopping prophylaxis, this emphasizes the necessity to stop using prophylaxis in children whenever possible to prevent bacterial resistance. When recurrent uri-

nary tract infections, persistent overactive bladder or high grade reflux necessitate the use of antibiotic prophylaxis, trimethoprim has the least negative influence on bacterial resistance. The use of nitrofurantoin as prophylaxis is associated with an increased resistance to cephalosporines, aminoglycosides and fluoroquinolones. Prophylactic fluoroquinolones should be discouraged considering the high percentage of resistance, especially to orally administered antibiotics.

Choice of therapeutic antibiotics in children with spina bifida
Oral antibiotic treatment is adequate for urinary tract infections in clinically not-ill children. Previous culture results and resistance patterns, fever and administered prophylaxis should determine the choice of antibiotic treatment. In our study cohort, nitrofurantoin is first choice medication for a non-febrile urinary tract infection without prophylaxis. When using prophylaxis and in febrile urinary tract infections, oral treatment depends on local susceptibility, with ciprofloxacin and cefuroxim as antibiotics with high a priori chance of treatment success. When intravenous treatment is warranted, a third generation cephalosporin, fluoroquinolone or carbapenem is preferred.

Chapter 6: Quality of Life in children with spina bifida

Despite major improvements and early surgical interventions in children with spina bifida, a lifelong burden of disabling physical consequences and emotional problems remain. The 1970s' switch to aggressive supportive care has resulted in higher survival rates and the necessity to improve long-term health care, in respect to psychical and mental health, functional independence and Quality of Life. In our cohort, we asked 133 eligible patients to fill out the KINDL-R questionnaire to evaluate their Quality of Life. This questionnaire consists of general questions on six domains (physical en emotional well-being, self-esteem, family, friends and school) and a chronic disease module. We also added the KINDL-R list of specific spina bifida related questions.

One hundred and two (77%) children and their parents filled out the questionnaire. Compared to 1500 healthy controls, both the children and their parents have significantly lower Quality of Life scores. Patients have higher scores than their parents, without significant influence of gender, level of spinal lesion, presence of hydrocephalus, manner of defecation and micturation, level of mobility, schooling or use of antibiotic prophylaxis on their scores.

Overall, severity of the morbidity is poorly correlated with perceived Quality of Life, and should not be used by health care professionals to estimate a patients well-

being: the perception of Quality of Life in children with spina bifida may differ from the perception of parents and health care professionals. Our recommendation is to systematically assess Quality of Life in patients with spina bifida throughout life, as this contributes to tailored psychosocial and somatic counseling.

CONCLUSION

In our study we have shown that there is no current consensus on nephro-urological care in patients with spina bifida. Proper urological care can be improved by implementing our findings from the SPIN UTI study: 1. antibiotic prophylaxis is only warranted in children with frequently recurring urinary tract infections, 2. bacterial susceptibility to commonly used therapeutic antibiotics is higher when refraining from every day antibiotic prophylaxis, 3. exclusion of a suspected urinary tract infection can be done at home, performing a simple leukocyte esterase test, and 4. individual repetitive assessment of Quality of Life ensures tailored counseling and psychosocial care in patients with spina bifida. Investigations in genetic screening, improvements of pre- and postnatal neurosurgery and further development of intrauterine stem cell application should be studied in the near future to lower the incidence and severity of spina bifida in the next generations.

NEDERLANDSE SAMENVATTING

Ondanks grote vooruitgang in neurochirurgische ingrepen en urologische zorg, worden kinderen met spina bifida nog altijd beperkt door urologische, neurologische, orthopedische en verstandelijke aandoeningen. In onze SPIN-UTI studie hebben we ons gericht op de urologische problematiek, urineweginfecties en Kwaliteit van Leven bij kinderen met spina bifida. Vanuit het Wilhelmina KinderZiekenhuis in Utrecht en het Gasthuisberg UniversiteitsZiekenhuis in Leuven is een onderzoeksgroep van 176 kinderen gevormd, die we 18 maanden hebben vervolgd op de diagnostiek, behandeling en preventie van urineweginfecties en op Kwaliteit van Leven.

Hoofdstuk 2: gebrek aan uniformiteit in urologische spina bifida zorg

De Europese centra voor kinderen met spina bifida zijn gevraagd naar de aanwezigheid van protocollen voor de preventie, evaluatie en behandeling van urineweginfecties en urologische zorg. Eenenveertig centra vulden een vragenlijst in op zes domeinen: 1. identificatie van het centrum en het team, 2. aantal patiënten en aanwezigheid van protocollen, 3. huidige standaard protocollen, 4. diagnostiek bij verdenking urineweginfectie, 5. behandeling van urineweginfectie en 6. protocollen voor urodynamische studies, medicatie en chirurgische interventies.

Bij analyse blijkt er geen gemeenschappelijk protocol te bestaan voor preventie, diagnostiek en behandeling van urineweginfecties. Onderhoudsantibiotica worden zelden voorgeschreven, onafhankelijk of het kind wel of niet dagelijks katheteriseert. Het stoppen van onderhoudsantibiotica wordt overwogen als er weinig tot geen urineweginfecties zijn, als de urodynamica van de blaas en urinewegen veilig zijn of als de ouders er dringend om vragen. Bij verdenking op een urineweginfectie worden teststrips en beoordeling van de urine met de microscoop minstens zo belangrijk geacht als de klachten van het kind, zoals koorts, riekende urine en buikpijn. Om een urineweginfectie daadwerkelijk aan te tonen of uit te sluiten wordt vrijwel altijd een urinekweek ingezet. Behandeling van een bewezen urineweginfectie gebeurt vrijwel altijd oraal.

Wij concludeerden uit deze inventarisatie dat er geen uniform urologisch beleid is voor kinderen met spina bifida. Met dit in gedachten hebben we besloten de volgende punten te onderzoeken: 1. een eenvoudige en accurate thuistest voor urineweginfecties, 2. aantonen dat onderhoudsantibiotica niet nodig zijn bij kinderen met spina bifida die dagelijks moeten katheteriseren, 3. aantonen dat stoppen van onderhoudsantibiotica de gevoeligheid van urinewegbacteriën voor

antibiotica verbetert en 4. hoe ziet de Kwaliteit van Leven van kinderen met spina bifida er uit.

Hoofdstuk 3: thuistesten bij verdenking op een urineweginfectie

Om te onderzoeken of thuistesten voor een urineweginfectie mogelijk is, hebben we zowel de leukocyten-esterasetest als de dipslide vergeleken met de gouden-standaard laboratoriumkweek. De leukocyten-esterasetest is een klein stickje met een spons met het enzym leukocyten-esterase die verkleurt als de urine witte bloedcellen bevat. Witte bloedcellen gecombineerd met een positieve urinekweek is bewijzend voor een urineweginfectie. De dipslide is een stick met twee agar-kweekplaatjes voor Gram-positieve en Gram-negatieve bacteriën.

Van de 112 laboratoriumkweken bleken er 45 positief, wat een vooraf-kans van 40% op aanwezigheid van bacteriën in de urine geeft, wat overeenkomt met eerdere studies. Een positieve uitslag van de esterasetest had een voorspellende waarde van slechts 72%, maar een negatieve esterasetest bleek in 96% correct: geen bacteriegroei in de kweek. Bij de 45 positieve kweken, was de esterasetest in 3 gevallen negatief, wat een 93% gevoeligheid oplevert. Bij de 67 negatieve kweken bleek de esterasetest in een kwart van de gevallen fout-positief. De dipslide had een slechtere negatief-voorspellende waarde van 78% en een vergelijkbaar slechte positief-voorspellende waarde als de esterasetest. Ook de gevoeligheid van de dipslide bleek slecht en het combineren van de esterasetest met de dipslide gaf hierin geen verbetering.

We hebben aangetoond dat een urineweginfectie prima thuis kan worden uitgesloten door een negatieve esterasetest en dat nader onderzoek of starten van antibiotica dan ook niet meer nodig is. Dit in tegenstelling tot een dipslide die minder betrouwbaar is. Beide media zijn onbetrouwbaar om een urineweginfectie aan te tonen, ook als ze worden gecombineerd met elkaar.

Hoofdstuk 4: de zin en onzin van onderhoudsantibiotica bij kinderen met spina bifida

Om de waarde van onderhoudsantibiotica bij urineweginfecties te beoordelen, hebben we bij de 176 kinderen tweewekelijkse urinemonsters beoordeeld gedurende 18 maanden door middel van een leukocyten-esterasetest en een urinekweek. Bij positieve kweken en urineklachten zonder koorts spraken we van een blaasontsteking, mét koorts van een nierbekkenontsteking. We hebben de kinderen met een computer eerlijk verdeeld naar leeftijd, geslacht en deelnemend land en de helft

gevraagd om te stoppen met de onderhoudsantibiotica, terwijl de andere helft doorging met de antibiotica.

Bijna de helft van de kinderen maakten minimaal één blaasontsteking door. In de groep die stopte met de onderhoudsantibiotica, kwamen meer infecties voor: 1,5 per jaar tegenover 1,1 per jaar in de groep die doorging met de antibiotica. Statistisch gezien is het verhoogde risico (1,44 keer meer kans) weliswaar significant maar in de dagelijkse praktijk niet van belang: het zou betekenen dat je elk kind gedurende meer dan 2 jaar elke dag antibiotica moet geven om één extra blaasontsteking te voorkómen. Nierbekkenontstekingen kwamen in totaal 7 keer voor bij 6 patiënten: 4 in de stopgroep, 2 in de antibioticagroep. Een groot deel (38 van de 88) van de stopgroep herstartte de onderhoudsantibiotica tijdens het onderzoek vanwege urineweginfecties en op verzoek van ouders. Deze groep had dan ook meer infecties: 2,7 per jaar tegenover 1,1 per jaar in de groep die blijvend stopten. De herstarters bleken echter vóór de studie ook al meer urineweginfecties te hebben, onder andere door ernstige reflux en bleven ook ná het herstarten van de onderhoudsantibiotica meer infecties houden. Een lage graad van reflux, geslacht, leeftijd en overactiviteit van de blaas bleken geen invloed op het aantal urineweginfecties te hebben.

Het is onze aanbeveling om de onderhoudsantibiotica te stoppen op het moment dat urodynamisch onderzoek van de blaas en urinewegen geen hoge druk of reflux meer laat zien en er vrijwel geen urineweginfecties zijn. Alleen bij terugkerende urineweginfecties en een hoge graad reflux is doorgaan met onderhoudsantibiotica nodig.

Hoofdstuk 5: de invloed van onderhoudsantibiotica op resistentie van bacteriën

Ongevoeligheid van bacteriën voor antibiotica door het toenemend gebruik van antibiotica is een wereldwijd toenemend gevaar. We gebruikten de bijna 5.000 kweken van onze studie om de invloed van het stoppen van de onderhoudsantibiotica op de gevoeligheid van bacteriën te beoordelen. Al met al zagen we, na stoppen van de onderhoudsantibiotica, een forse verbetering van de gevoeligheid van bacteriën voor de meest gebruikte antibiotica.

Keuze van onderhoudsantibiotica bij kinderen met spina bifida

In het voorgaande hoofdstuk hebben we laten zien dat elk kind meer dan 2 jaar onderhoudsantibiotica moet nemen om één extra blaasontsteking te voorkómen. Dat, gecombineerd met de verbetering in bacteriële gevoeligheid na het stoppen van

de onderhoudsantibiotica, benadrukt het belang van het zo mogelijk stoppen van de antibiotica. Als onderhoudsantibiotica toch nodig zijn door hoge graad reflux of terugkerende urineweginfecties, heeft Trimethoprim de minste invloed op de gevoeligheid van bacteriën. Als Nitrofurantoïne als onderhoud wordt gebruikt, zien we namelijk meer ongevoeligheid voor specifieke groepen antibiotica, zoals cephalosporines, aminoglycosides en fluoroquinolonen. Onderhoudsbehandeling met fluoroquinolonen, zoals Ciprofloxacine moet worden ontraden aangezien er dan een hoog percentage ongevoeligheid ontstaat, met name voor orale antibiotica.

Keuze voor therapeutische antibiotica bij een urineweginfectie
Bij niet-zieke kinderen met spina bifida is orale antibiotica voor een urineweginfectie meestal voldoende. De keuze van antibioticum wordt bepaald door (eerdere) kweekresultaten met gevoeligheidsbepalingen, al dan niet koorts en onderhoudsantibiotica. In onze studie is Nitrofurantoïne de eerste keuze bij blaasontsteking als er geen onderhoudsantibiotica worden genomen. Bij nierbekkenontsteking of als er onderhoudsantibiotica genomen worden, hangt de keuze af van de regionale gevoeligheid, waarbij Ciprofloxacine en Cefuroxim oraal de meeste kans van slagen hebben. Wanneer het kind te ziek is en de antibiotica via een infuus moet worden gegeven, heeft een derde-generatie cephalosporine, fluoroquinolone of carbapenem de voorkeur.

Hoofstuk 6: Kwaliteit van Leven bij kinderen met spina bifida

Ondanks alle verbeteringen en vooruitgang in de prenatale zorg en vroege postnatale ingrepen bij kinderen met spina bifida, blijven er levenslange consequenties en beperkingen op lichamelijk en psychisch vlak. Nadat er gestart werd met katheteriseren en er shunts voor hydrocefalus uitgevonden zijn, werd de overleving sterk verbeterd en verlengd. Dit betekende echter ook dat de langetermijnszorg op zowel lichamelijk en psychisch vlak, als ook op het gebied van onafhankelijkheid en Kwaliteit van Leven verbeterd moet worden. Binnen onze studie vroegen we de 133 kinderen tussen 4 en 16 jaar en hun ouders om de KINDL-R vragenlijst in te vullen. Deze vragenlijst bevat vragen over de domeinen lichamelijk en geestelijk welbevinden, zelfbeeld, familie, vrienden en school, alsook een module over chronisch ziekzijn. We voegden ook nog de spina bifida-specifieke KINDL-R vragenlijst toe. De lijst, door 102 kinderen en hun ouders ingevuld, liet duidelijk lagere scores zien in vergelijking met de 1500 gezonde controlekinderen. Ouders hebben daarbij nog lagere scores dan hun kinderen zelf. De scores worden aanwezigheid van hydrocefalus, manier van ontlasten en plassen, mate van mobiliteit, schoolniveau of onderhoudsantibiotica.

Al met al is de beleefde Kwaliteit van Leven van patiënten maar matig afhankelijk van de ernst van de spina bifida en is het van belang te beseffen dat hulpverleners niet kunnen vertrouwen op hun eigen inschatting van de Kwaliteit van Leven van hun patiënten. Onze aanbeveling is dan ook dat de Kwaliteit van Leven met regelmaat wordt beoordeeld door middel van valide vragenlijsten gedurende het gehele leven van een patiënt, zodat de resultaten een individueel passend psychosociaal en somatisch beleid mogelijk maken.

CONCLUSIE

In onze studie hebben we laten zien dat er nog geen uniformiteit is in de urologische zorg voor kinderen met spina bifida. Deze zorg kan worden verbeterd door de bevindingen van de SPIN UTI studie toe te passen: 1. onderhoudsantibiotica zijn niet nodig bij kinderen met spina bifida, en moeten alleen overwogen worden bij terugkerende urineweginfecties, 2. het stoppen van onderhoudsantibiotica verbetert de bacteriële gevoeligheid voor antibiotica, 3. het uitsluiten van een urineweginfectie kan thuis gebeuren door middel van een leukocyten-esterasetest, en 4. het herhaald meten van Kwaliteit van Leven gedurende het gehele leven bevordert individueel toegespitste psychosociale en somatische zorg.

Om het vóórkomen van spina bifida en de ernst hiervan in de toekomst te verminderen moet naar onze mening nader onderzoek verricht worden naar genetische screening, verbeteringen in de perinatale neurochirurgie en verdere ontwikkeling van stamceltherapie tijdens de zwangerschap.

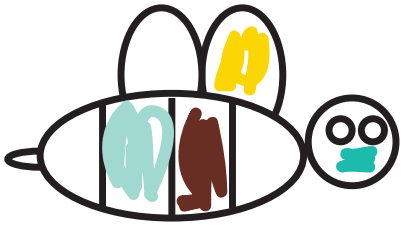
Chapter 9

Dankwoord

Curriculum vitae

Publications

Abbreviations



DANKWOORD

De afgelopen jaren hebben ontelbaar veel mensen mij direct of indirect gesteund in het SPIN UTI onderzoek. Dankzij jullie is dit resultaat bereikt en ik hoop dan ook dat ik niemand vergeet te bedanken. Mensen die zichzelf niet terugzien hieronder: weet dat ik dit niet met opzet heb gedaan.

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CURRICULUM VITAE

De auteur van dit proefschrift wordt op 30 augustus 1972 in Nijmegen geboren als Sebastiaan Hermanus Johannes Zegers. Hij behaalt in 1990 zijn gymnasium-diploma aan het RK Dominicus-college in Nijmegen. Van 1990 tot 1998 studeert hij Geneeskunde aan de Radboud Universiteit in Nijmegen, waarna hij als ANIOS Kindergeneeskunde werkt op de Neonatale Intensive Care Unit van het Radboud.

Onder professor Sengers start hij in 1999 de opleiding tot kinderarts aan diezelfde Radboud Universiteit, met het externe gedeelte van de opleiding in het toenmalige Sint Joseph Ziekenhuis in Veldhoven, nu Máxima Medisch Centrum.

Na afronding van de opleiding begint hij in 2004 als algemeen kinderarts in het Máxima Medisch Centrum, met een verdiepingsstage nefrologie en urologie van zes maanden in het Wilhelmina Kinderziekenhuis in Utrecht, waar hij in overleg met Teau de Jong-de Vos van Steenwijk start met het SPIN UTI onderzoek waarvan dit boekje het resultaat is.

In 2013 start hij met de specialisatie tot kinderarts – sociale pediatrie onder leiding van Thea van Zeben-van der Aa en Hans Jansen in het Maastricht Universitair Medisch Centrum, de Mutsaersstichting in Venlo en Libragroep revalidatie, locatie Blixembosch in Eindhoven. De specialisatie wordt in 2016 afgerond.

The author is born on August 30th, 1972 as Sebastiaan Hermanus Johannes Zegers in Nijmegen, the Netherlands. After finishing Gymnasium at the Dominicus College in Nijmegen in 1990, he starts his study in Medicine at the Radboud University in Nijmegen.

After graduation in 1998, he becomes an intern in Pediatrics at the Neonatal Intensive Care Unit at the Radboud University Medical Center in Nijmegen. His following residency for pediatrician in Nijmegen, under the late professor Sengers, includes an internship at the Sint Joseph Hospital (now Máxima Medical Center) in Veldhoven.

He is included in the pediatric staff at that same hospital in 2004. He starts with six months of nephrology and urology internship at the Wilhelmina Children's Hospital at the University Medical Center in Utrecht, where he also gets involved in the SPIN UTI study. Besides general pediatrics, his areas of interest are in nephrology, urotherapy and congenital renal and urological abnormalities. In 2013, he starts a fellowship in social pediatrics under Thea van Zeben-van der Aa and Hans Jansen, which is finished in 2016.

PUBLICATIONS

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ABBREVIATIONS / AFKORTINGEN

ABU	asymptomatic bacteriuria
AP	antibiotic prophylaxis
CI	confidence interval
CIC	clean intermittent catheterization
CSF	cerebral spinal fluid
DSD	detrusor sphincter dyssynergy
GLMM	generalized linear mixed model
IRR	incidence rate ratio
LDCP	low-dose chemo prophylaxis
LET	leukocyte esterase test
MMC	meningomyelocele
NBSD	neurogenic bladder sphincter dysfunction
OR	odds ratio
SB	spina bifida
SBU	significant bacteriuria
UTI	urinary tract infection
VUR	vesico-ureteral reflux