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EDITORIAL COMMENTARY

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# May we go on with antibacterial prophylaxis for urinary tract infections?

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**Abstract** Recurrent urinary tract infections (UTIs), with or without vesicoureteric reflux (VUR), are by far the most frequent reason for long-term antibacterial prophylaxis in infants and children today. However, the strategies of antibacterial prophylaxis for the prevention of recurrent urinary tract infection are no longer universally accepted. In infants and children at risk, the benefits of antibacterial prophylaxis definitively are not yet proven by evident data. To put antibacterial prophylaxis in its place, risk groups for recurrent symptomatic infections, ascending UTI and permanent renal damage have to be defined and the efficacy of prophylaxis in these groups has to be proved by prospective randomised studies. Nevertheless, until the results of these studies are available, antibacterial prophylaxis will remain one of the most frequently practised methods to protect risk patients from pyelonephritic damage and UTI recurrences.

**Keywords** Antibacterial prophylaxis · Pyelonephritis · Renal damage · Urinary tract infections · Vesicoureteric reflux

## Introduction

There are very few commonly accepted indications for long-term antibacterial prophylaxis in paediatric practice. These include asplenic status, severe immunodeficiency and rheumatic fever. In addition, recurrent urinary tract infections (UTIs), with or without vesicoureteric reflux (VUR), are by far the most frequent reason for long-term antibacterial prophylaxis in infants and children today [1]. However, the strategies of antibacterial prophylaxis for the prevention of recurrent urinary tract infection are no longer universally accepted.

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## Historical remarks

In 1941, Helmholtz for the first time recommended the long-term administration of small doses of sulfathiazole for "chronic" urinary infection [2]. Some years later, the advantages of long-term antibacterial therapy, especially nitrofurantoin, in infants and young children were demonstrated by Marshall [3] and Stansfield [4]. Smellie et al. in a study of 200 children with UTI showed that 27% of those with a history of recurrent infection had radiological evidence of chronic pyelonephritic scarring [5]. Based on this observation, they recommended prevention of recurrent UTI by long-term antibacterial prophylaxis. In 1976, the authors demonstrated a reduction of recurrences during medication with trimethoprim-sulfamethoxazole in children with symptomatic UTI [6]. In 1978 Smellie et al. reported on a randomised controlled trial in 45 children with either first or subsequent acute UTI and radiologically normal urinary tracts. They were given either low-dose prophylactic co-trimoxazole or nitrofurantoin or no prophylaxis after each had been treated with a short course of co-trimoxazole. During the 12-month prophylaxis period, none of the 25 children in the intervention group had a further infection, whereas, half of the 22 who received no prophylaxis suffered from at least one symptomatic UTI. Twelve months after stopping prophylactic antibiotics, eight children (32%) in the intervention group compared with 13 (64%) in the control group had had a UTI [7].

Another double-blind crossover trial compared nitrofurantoin with placebo in 18 girls aged 3–13 years without any major urinary tract abnormalities. The authors found two episodes of infection in 1 year in the treatment groups compared with 35 in the control groups ( $p < 0.01$) [8].

Primarily based on these early studies, the concept of antibacterial prophylaxis was adapted by many groups for a growing number of indications. Smellie et al. recommended using antibacterial prophylaxis in children who

have recurrent urinary tract infection, particularly if this condition is causing ill health or absence from school. They also used prophylaxis in children whose kidneys might be adversely affected by any recurrence of infection, especially young children with VUR, whether or not the kidneys were already scarred [9].

However, since the pioneer studies of Smellie et al., only very few well designed studies in children have been performed. A recent meta-analysis identified only five randomised controlled trials among children receiving prophylactic antibiotics [10].

## Current clinical indications for antibacterial prophylaxis

In the first issue of this journal, Jodal and Winberg stated that long-term prophylaxis is indicated primarily at high risk for renal scarring, the most common reasons being VUR with dilatation of the upper urinary tract and recurrent acute pyelonephritis (PN), independent of reflux [11]. A panel convened by the American Urological Association targeting reflux management regarded antibacterial prophylaxis as an appropriate or reasonable initial therapy for all children up to 5 years who have primary reflux grade 1–4 [12]. In UTI with obstructive lesions, prophylaxis is considered until the underlying lesion is successfully operated or has diminished spontaneously [13]. Other indications for long-term prophylaxis include children with frequent symptomatic recurrences (>three per year), particularly when these are associated with underlying bladder instability or abnormal voiding patterns. Antibacterial prophylaxis is also considered in neonates and infants less than 1 year of age who present with a febrile UTI, because approximately one-third of these children are at risk for symptomatic recurrences, more than 90% of which are clinically consistent with pyelonephritis or even urosepsis [14].

With the increased detection rate of asymptomatic urinary malformations by sonographic pre- and postnatal screening programs, an antibacterial prophylaxis was recommended following the detection of even asymptomatic reflux or urinary tract obstruction [15]. Unfortunately, the actual risk for UTI just in these patients is not known, as no prospective, randomised studies ever have been performed to detect the frequency of UTI compared with infants free from urinary malformations.

However, to warrant long-term application of low-dose antibiotics, it would be necessary to define the risks of pyelonephritis and pyelonephritic damage, both being the main goal of antibacterial prophylaxis.

## The risk for (recurrent) pyelonephritis and pyelonephritic damage—is it predictable?

Approximately 1% of boys and 3–5% of girls suffer from at least one UTI during childhood [16]. After their first symptomatic UTI, 30–50% of them are prone to at least one recurrence [17]. Nuutinen and Uhari followed a cohort of 262 children over 3 years who were treated for their first UTI while aged less than 1 year. Thirty-five percent of the boys and 32% of the girls contracted a recurrent UTI during the 3-year follow-up [18]. The recurrence rate is directly correlated with the number of preceding UTIs [19]. In boys, early recurrences are as frequent as in girls. Later, the recurrence rate is much lower in boys than in girls. The susceptibility for recurrences is highest within the first 2–6 months after a UTI [19, 20]. The longer the infection-free interval, the lower the risk for further recurrences [21].

The susceptibility for recurrences is dependent on many individual factors. In girls with recurrent UTI, a defective defence mechanism at the level of uroepithelial cells has been shown to be such a factor [22]. Bladder dysfunction is another important risk factor [23]. This point was frequently mentioned by Smellie et al.: if there is any degree of bladder dysfunction (neurogenic or non-neurogenic), it correlates not only with the susceptibility to UTI and UTI recurrences, but also to breakthrough infections under antibacterial prophylaxis [24].

The role of vesicorenal reflux as a predisposing factor for UTI recurrence is controversial. Nuutinen and Uhari found that recurrence-free survival was significantly shorter and recurrent UTIs occurred more often in the children with grade 3–5 VUR than in those with grade 0–2 VUR and concluded grade 3–5 VUR to be a risk factor for recurrent UTI [18].

In 1.25% to 8% of infants and children with symptomatic UTIs, sonographic imaging revealed a relevant urinary obstruction. This percentage is much higher than in the normal population. It is suggested that urinary tract obstruction may facilitate ascending UTIs, the risk depending on the localisation of the obstruction.

Permanent renal damage in children after acute pyelonephritis has been estimated to occur in 5–20% of cases. These numbers were based on findings seen on intravenous urography. With the use of DMSA scans, the incidence of renal scarring after acute pyelonephritis is much higher, reaching 40% [25, 26].

The incidence of scarring increases with each episode of pyelonephritis [27]. Infants seem to be more susceptible than older children to renal injury and acquired scarring following acute UTI. Ulla Berg et al. showed a reduced glomerular filtration rate (GFR) and p-aminohippuric acid (PAH) clearance being reduced in patients with recurrent UTIs, especially among those in whom the onset of pyelonephritis was in the first 3 years of age. GFR was generally reduced in patients with early onset PN and a history of several PN infections. Thus, the authors believed long-term prophylactic antibacterial therapy was indicated in patients with early onset PN, in order to prevent recurrences [28]. The high vulnerability of infant kidneys may partially be due to the fact that recognition and treatment of pyelonephritis is often delayed within the first years of life. This does not mean that new scars do not also develop in later childhood. In a retrospective study on 74 infants and children with acquired renal damage, Smellie

found that it was less common after the age of 7, but one-third of the kidneys in which new scars developed were normal at the age of 5 [29]. Benador et al. (1997) assessed the frequency of renal lesions in different age groups (>1 year, 1–5 years, and >5 years) with the clinical diagnosis of pyelonephritis by DMSA scintigraphy. The percentage of children with renal lesions partially regressing during the follow-up period, who were assumed to have recent lesions, did not differ in the age groups of 1–5 years and >5 years [30]. Therefore, the authors concluded that their study did not confirm the conventional view that the risk of renal scars after pyelonephritis diminishes with age.

The relationship between VUR, UTI and renal scarring has been reported earlier [31]. However, genetic congenital renal abnormalities and secondary scarring were not separated in most of the early studies. The role of VUR as a predisposition for acquired renal scarring with pyelonephritic episodes has been questioned in recent years. In several studies, scarring occurred more often in the absence of reflux [32]. Garin et al. have recently re-emphasised the finding that the incidence of scarring is unaffected by the presence of reflux [33]. Wennerström et al. showed that girls with normal findings on a urogram after a symptomatic UTI might subsequently develop segmental renal scarring typical of pyelonephritis. Some of these children had VUR as a risk factor for subsequent scarring. However, of particular interest was the finding that the acquired renal scars correlated best with recurrent UTI and not with VUR, a risk factor that until recently was thought to be the most important for scar formation [34]. Rushton et al. emphasised that new renal scars form less often in kidneys with VUR (25%) than in those without (37%) [35]. After a meta-analysis of randomised controlled trials concerning antibiotics and surgery for vesicoureteric reflux, D. Wheeler et al. came to the conclusion that, "It is uncertain whether the identification and treatment of children with VUR confers clinically important benefit" [36]. Why vesicoureteric reflux is progressively losing its image as a main factor for susceptibility to ascending UTI and pyelonephritis is due to the results from many studies in recent years using a DMSA scan to detect early pyelonephritic changes and subsequent renal scars. The majority of these studies showed a comparable risk for pyelonephritic scars between refluxing renal units and non-refluxing ones. The common clinical practice to base antibacterial prophylaxis mainly on the detection of vesicoureteric reflux has consequently been questioned [36].

## Is the concept of antibacterial prophylaxis still valid?

The efficacy of antibacterial prophylaxis per se has been questioned in several reviews [9, 32, 37, 38]. Garin HE et al. came to the conclusion that "the current available data do not support a role for continuous urinary antibiotic prophylaxis in the prevention of renal scars in patients with vesicoureteric reflux" [33]. Likewise, Larcombe stated that the long-term benefits of prophylaxis have not been adequately evaluated, even for children with VUR [37]. In an actual Cochrane Review, Williams et al. concluded that there is considerable uncertainty about the effectiveness of long-term, low-dose antibiotic administration for the prevention of UTI in children [10]. Finally, Le Saux et al. criticized that the available evidence for using antibacterial prophylaxis to prevent UTI in children with normal urinary tracts or neurogenic bladder was of low quality [38]. In addition, they found a surprising lack of evidence for children with reflux.

Most of the authors of these articles criticize the lack of evidence for using antibacterial prophylaxis, due to the low quality of clinical trials and the small number of patients. Indeed, several authors of reviews came to the conclusion that it is not clear whether any intervention for children with primary VUR—a domain for antibiotic prophylaxis—does more good than harm [32, 36]. Therefore, several authors demand new, well-designed randomised trials focusing on groups with different risk stratifications [36, 38, 39].

Which consequence should we draw for our daily paediatric practice from these provocative statements? Should we change our concepts of antibacterial prophylaxis, which are mainly based on expert opinion and clinical experience? Our patients and we ourselves will have to wait years for the results of prospective, randomised, controlled studies required to prove the usefulness of antibacterial prophylaxis. Which strategy should we follow until such studies become available? In addition, studies in infants and children today are difficult, and it might be nearly impossible, from an ethical point of view, to repeat the basic studies of the seventies in this population using the current quality standards.

## Rationales for current concepts

For the time being, we have to justify our clinical practice of antibacterial prophylaxis referring to personnel experience and available studies, mainly focussed on the following three questions:

1. How effective is long-term antibacterial prophylaxis in preventing urinary tract infections?

There is some evidence from a number of studies that antibiotics may prevent recurrent UTI in children, particularly during the period of prophylaxis. Previous trials in children have demonstrated the combination of trimethoprim-sulfamethoxazole, trimethoprim and nitrofurantoin to be effective prophylactic drugs [7, 8, 10, 24].

These studies were performed in children with radiologically normal urinary tracts. However, the domain of antibacterial prophylaxis today is symptomatic vesicoureteric reflux. Unfortunately, there exist no representative controlled, prospective studies that compare recurrence rate with prophylaxis in non-operated children with reflux with the rate in a control group without prophylaxis. In a single study, published only as an abstract in

the Proceedings of AAP 1997, children with VUR were randomised to receive either no treatment, daily antibiotic prophylaxis, or prophylaxis given on 3 days each week. There was no significant difference in risk for UTI or renal parenchymal injury between children given no therapy and children given daily antibiotics [40].

In connatal dilatations of the upper urinary tract, as in those caused by ureteropelvic junction obstruction or megaureter, early detection by ultrasound screening led to different concepts regarding the prevention of UTIs. Some recommended putting the newborn on antibacterial prophylaxis until a furosemide renogram excludes significant obstruction or until a surgical reconstruction has been performed. Others give an antibacterial prophylaxis in cases with significantly dilated upper urinary tracts, at least during the first year of life [41]. It is an open question, however, whether the incidence of UTIs and pyelonephritic damage would be higher without prophylaxis. There is some indication that prophylaxis may have less effect than previously believed. Madden et al. observed 53 infants with prenatally diagnosed ureteropelvic junction obstruction during at least 1 year [42]. In 19 children, a surgical correction was performed within the first months of life. Thirty-four infants were observed without operation. Thirty-seven children received antibacterial prophylaxis, and 14% of them suffered from at least one UTI. Of 16 patients who did not receive antibacterial prophylaxis, 19% also had UTIs. The difference was not significant (chi quadrate test $p > 0.1$). The authors concluded that antibacterial prophylaxis in children with ureteropelvic junction obstruction was not useful [42].

In neurogenic bladder dysfunction, the question of efficacy of antibacterial prophylaxis is also not yet sufficiently answered [43]. Whereas, several studies showed a positive effect of antibacterial prophylaxis [44, 45], many authors did not find any superiority to placebo [46, 47]. A recently published meta-analysis of 15 studies comes to the conclusion that there is no significant reduction of symptomatic UTIs under antibiotic prophylaxis in neurogenic bladder [48].

Taken together, one has to agree with the statement of Le Saux et al. that, "The available evidence for using antibacterial prophylaxis to prevent UTI in children with normal urinary tracts or neurogenic bladder is of low quality" [38]. However, as in many other fields of pharmacological therapy, data which prove the benefit of a medication have to be transferred from study results in adults into paediatric practice, due to lack of data for children. Therefore, it seems more than questionable to exclusively evaluate data from paediatric series coming to the conclusion that the magnitude of any benefit of antibacterial prophylaxis for UTI in children "should at best be questioned" [38]. Although the authors of the meta-analysis focused their statement on children with normal urinary tracts, the same problems may be asserted for the use of antibacterial substances for long-term prophylaxis in children with urinary tract abnormalities.

If the data from studies in children are insufficient, what can we learn from prospective, randomised studies in adults? They might even be more meaningful, due to greater study groups and longer periods of observation before commencing medication.

**Table 1** Randomised, placebo-controlled studies reporting long-term low-dose antibacterial prophylaxis in recurrent urinary infections in adults (adapted from Nicolle 1998) (*TMP-SMX* trimethoprim-sulfamethoxazole)

| Reference | Regimen | Infections/ patient-year |
|---|---|---|
| Bailey et al., 1971 | (a) Nitrofurantoin 50 mg daily or 100 mg daily | 0.09 |
| | (b) Nitrofurantoin 50 mg daily | 0.19 |
| | (c) Placebo | 2.1 |
| Harding and Ronald, 1974 | (a) Sulfamethoxazole 500 mg daily | 2.5 |
| | (b) TMP-SMX 40/200 mg daily | 0.1 |
| | (c) Methenamine mandelate 2 g / ascorbic acid 2 g daily | 1.6 |
| | (d) No drug | 3.4 |
| Stamm et al., 1980 | (a) TMP-SMX 40/200 mg daily | 0.15 |
| | (b) Trimethoprim 100 mg daily | 0 |
| | (c) Nitrofurantoin macrocrystals 100 mg daily | 0.14 |
| | (d) Placebo | 2.8 |
| Rugendorff and Haralambie, 1988 | (a) Norfloxacin 200 mg daily | 0.38 |
| | (b) Placebo | 1.6 |
| Nicolle at al.,1991 | (a) Norfloxacin 200 mg daily | 0 |
| | (b) Placebo | 1.6 |

In adults, long-term, low-dose antibacterial prophylaxis is preferably used in women with frequently recurring UTIs. Whereas, short courses of a single dose or 3 days of antibacterial therapy are generally successful, many patients suffer from frequent disruptive and distressing episodes of UTI and seek long-term resolution from symptoms such as alguria and urge. Long-term low-dose prophylactic therapy is recommended for women who experience two or more symptomatic episodes of UTI within a 6-month period. It is generally initially given for 6 or 12 months [49, 50].

Antibacterial prophylaxis has been shown to be safe and has been repeatedly documented to decrease symptomatic recurrences of uncomplicated recurrent UTI in women [51, 52, 53, 54). Brumfitt and Hamilton-Miller demonstrated that the mean incidence of symptomatic episodes decreased 5.4-fold during prophylaxis in 219 female patients who were given long-term prophylaxis with nitrofurantoin for the prevention of recurrent UTIs [55]. Many other studies, reported from several different countries, show a remarkably consistent re-infection rate of 2.0–3.0 per patient year, reduced to 0.1–0.2 per patient year with prophylaxis (Table 1).

However, the evidence that antibacterial prophylaxis works in uncomplicated UTI in young women does not mean that it is also effective in the prevention of recurrent UTIs in children. Additionally, prophylaxis in adults is preferably carried out to reduce the rate of cystitis in women; whereas, in children efforts are made to avoid pyelonephritic episodes, which might lead to renal scars. The question as to whether antibacterial prophylaxis is

effective in children, therefore, presumably has to be focussed on the development of renal scars with and without medication.

### 2. How effective is long-term prophylaxis in preventing renal scars?

In 1999, Bollgren stated that, "No results are available for an unselected population of children with reflux on development of new renal scarring, which compare children on prophylaxis with children managed without prophylaxis" [70]. This is also true today. Therefore, our daily practice is mainly based on indirect indices for the benefit of prophylaxis. The hypothesis that lowering the rate of recurrences of UTI would diminish the rate of renal scars seems to be a poor argument in this respect. For the first line, it is therapeutic delay that has been associated with an increased frequency of renal scarring in experimental [56] and clinical reports [16, 29]. If therapy starts within the first 3 or 4 days of fever, there seems to be no difference in the frequency of renal scarring. Jakobsson et al. found no difference between their patient groups with or without scars with respect to the duration of fever and the levels of C-reactive protein or with white cell count at the time of infection [25].

Unfortunately, there exists no prospective, randomised study that would prove the hypothesis that acute therapy of recurrent pyelonephritic episodes is superior to continuous prophylaxis in preventing renal damage. It is not known at which time point after parenchymal bacterial invasion and onset of clinical viewable signs like fever and/or flank pain the risk for permanent renal damage begins and how it increases with the duration of non-treatment.

In spite of these uncertainties, Linshaw stated that, "Currently, the only effective approach to reduce renal scarring appears to be early diagnosis and treatment of symptomatic UTIs with effective antibiotics" [32]. For risk patients with recurrent UTI, Winberg formulated a similar statement: "Efficient and robust routines for a thorough follow-up and measures to guarantee immediate diagnosis and treatment of recurrent infections in children known to be at risk may be more important for the preservation of the kidneys than a stereotyped policy of 'endless' antibiotic prophylaxis" [57].

Nevertheless, there is quite a difference between side effects of long-term antibacterial prophylaxis and the discomfort with febrile UTIs, the latter sometimes making hospital admission inevitable. Additionally, from an economic point of view, it may be much more expensive to treat recurrent pyelonephritic episodes than to prevent them with prophylactic antibiotics.

### 3. Can we identify risk groups as targets for long-term antibacterial prophylaxis?

The available evidence does not justify a widespread use of antibacterial prophylaxis in children. In order to put antibacterial prophylaxis on a rational basis, one has to define the risk patient who will probably profit from long-term prophylaxis.

Today, most clinicians believe that in children with UTI and VUR, the refluxing kidney is most at risk of both congenital and acquired renal damage, and that this risk increases with severity of reflux [14, 58, 59]. The combination of recurrent UTI, severe VUR, and the presence of renal scarring at first presentation are associated with the worst prognosis. Merrick et al. found that the combination of both scarring and reflux at presentation, or either one of these components accompanied by subsequent documented UTI, was associated with a 17-fold increase in the relative risk of progressive renal damage compared with children with UTI but without these features [60]. The child at risk for pyelonephritic damage undoubtedly exists and needs protection from recurrent pyelonephritis episodes.

## Suggested indications for long-term antibacterial prophylaxis

Increased vigilance of parents and paediatricians for signs of pyelonephritis in risk patients as well as avoidance of delayed diagnosis and therapy may prove to be the most important prophylactic measures. This is especially true in connatal anomalies of the kidneys and urinary tract (CAKUT) in young infants detected by pre- or postnatal sonographic screening.

However, in selected cases, continuous long-term antibacterial prophylaxis should be considered, at least until evidence exists that they are not endangered by avoiding it:

- Infants and young children at high risk for pyelonephritic recurrences (more than one previous pyelonephritic episode)
- Children at high risk for pyelonephritic scars and/or urosepsis (infant with dilating reflux, especially if renal scars have been detected and pyelonephritis has happened earlier, infant with severe obstructive uropathy)
- Children with infection stones
- Children with voiding disturbances and recurrent cystitis/pyelonephritis, supplementary to bladder training
- Girls who suffer from frequent disruptive and distressing episodes of UTI and seek long-term resolution from symptoms such as alguria and urge

## Which substances for antibacterial prophylaxis?

Antimicrobials selected for prophylaxis should fulfil the following requirements [70]:

- Effectiveness against the majority of uropathogens
- Causing a minimum of serious side effects
- Causing minimal bacterial resistance

– Making little ecological impact on indigenous bacterial flora

For many years, trimethoprim or co-trimoxazole and nitrofurantoin have been the substances most used for antibacterial prophylaxis of UTI in children. Due to restrictions, in many countries, on using these substances in early infancy, oral cephalosporins are preferred in this age group. The latter also are widely used as alternative substances in countries where nitrofurantoin is not available, as in Japan [71]. Whereas, cephalosporins and trimethoprim/co-trimoxazole work by eradicating the aerobic gram-negative flora of the gut and vagina continuously, nitrofurantoin eliminates occasionally ascended bacteria immediately after oral intake [41, 49, 51].

In comparative studies, nitrofurantoin produced significantly more side effects than trimethoprim. The differences were due to higher rates of complaints of gastrointestinal symptoms, such as nausea or vomiting, as well as the mixture's unpleasant taste [61]. In adults, the use of nitrofurantoin is limited because of the relatively high frequency of severe adverse reactions, especially including pulmonary fibrosis and polyneuropathy [62]. The situation in childhood appears to be markedly different. Coraggio et al. in 1989 reviewed the serious adverse reaction reports submitted to the US Food and Drug Administration since 1953. There were only 26 cases of serious reactions to nitrofurantoin in American children and adolescents who were younger than 20 years of age. Neurologic and hepatic reactions occurred in seven and nine patients, respectively, which equated to 0.8 and 1.0 cases/million uses, respectively [63]. On the basis of these data and of clinical experience, it may be concluded that nitrofurantoin is a safe and effective antibiotic for prophylaxis in children with recurrent UTI [19]. In spite of its potential side effects, the value of nitrofurantoin as an alternative to trimethoprim in children for antibacterial prophylaxis will probably undergo a renaissance, since bacterial resistance to trimethoprim has in recent years been shown to increase rapidly in many regions of the world.

## Long-term prophylaxis: how long?

The optimal duration of long-term antibacterial prophylaxis is as unclear as its indication. According to the rationales for antibacterial prophylaxis mentioned above, it should be continued until the risk of pyelonephritic recurrences is diminished and/or the risk of renal scars is outgrown.

Interestingly, there may be a long-lasting effect of antibacterial prophylaxis, even after discontinuation. In a randomised, prospective, placebo-controlled study in children, 32% of the intervention group compared with 64% of the control group had had a UTI 12 months after stopping prophylactic antibiotics [7]. Some authors found in adults that a course of antibacterial prophylaxis did not alter the frequency of symptomatic episodes after therapy is discontinued [49, 51]. Other authors demonstrated that recurrent infections occurred less often after prophylactic treatment for 1 year. In adult women with recurrent UTIs, prophylaxis given for 1 year gave better results than when given for 6 months [64].

The decision to discontinue antibacterial prophylaxis is quite easy in boys with vesicoureteric reflux. Long-term prophylaxis in boys over 1 year of age with conservatively monitored vesicoureteric reflux has long been questioned, because at this age the risk of recurrence is extremely low in boys [65]. In girls with vesicorenal reflux and an above-average susceptibility for UTIs, the decision for stopping antibacterial prophylaxis is comparatively more difficult. As restraint in surgical correction has increased, the situation has become even more complicated during the last 10 years.

It is widely accepted that the risk for pyelonephritic renal scars decreases with increasing age. This has led to a recommendation to cease antibacterial prophylaxis in later childhood, despite continuing reflux. In a retrospective study of 196 patients with known VUR treated initially with and subsequently without antibiotic prophylaxis, new renal scarring occurred in only five and seven patients (7–10%), respectively, of those who had UTIs during follow-up [65].

However, the question as to whether kidneys really outgrow the risk of acquired reflux nephropathy is as yet unanswered. Coulthard et al. proposed that the risk of scarring starts high and falls to virtually nil by 4 years not due to maturation leading to an increased resistance to scarring, but because the most vulnerable subjects have already scarred their kidneys in infancy. "If a girl is born with VUR and IRR, but is kept free of urine infections with prophylactic antibiotics up to 4 years, she will have been prevented from scarring if she also outgrows her reflux by 4 years. If, however, she still has VUR when she stops her prophylaxis, she will become as vulnerable to scarring at 4 years as she was as a newborn with VUR. The risk period will merely have been postponed" [66]. In an experimental study, Coulthard et al. showed severe inflammatory changes and early scar formation when exposing adult pigs to urine infections after surgery to produce unilateral VUR. The risk of reflux nephropathy was not eliminated by maturation of the kidney in pigs [67].

## Essential future research

As pointed out, a small but sufficient number of studies in children and many larger studies in adults clearly have proven the efficacy of antibacterial prophylaxis in recurrent UTIs. From an ethical point of view, it seems irresponsible to repeat prospective, randomised, placebo-controlled studies in infants and children at high risk for recurrent complicated pyelonephritis and/or renal scars. As stated by J. Craig, "We do not simply need more studies. We need the right studies done right" [68].

One problem of previous clinical studies was the poor definition of the risk of recurrence. It is highly dependent

on the number of previous UTIs. This means that the randomisation should include a stratifying for the number of recurrences before the start of the study. Factors such as underlying anomalies of the urinary tract, bladder dysfunction, or other predisposing factors influence the outcome of prophylactic treatment and make the evaluation of the drug per se difficult [69].

Another problem is poor information on patient compliance [70]. Daschner and Marget (1975) tested compliance with long-term antibiotic therapy by urine check in 93 children with recurrent UTIs. Only 32.2% of the children took the prescribed drugs at regular intervals, and 19% did not take the antibiotics at all [72]. Similar results have been shown in children with vesicoureteric reflux [73]. Treatment studies should take particular care in evaluation compliance.

Fortunately, prospective studies are in progress. For instance, the Italian Renal Infection Study (IRIS) group currently has initiated a controlled, randomised clinical trial to evaluate the effectiveness of antibacterial prophylaxis in children with a previous clinically diagnosed upper UTI. Primary endpoints are UTI-recurrence rate and the development of renal damage (parenchymal scar) after 12 months [74].

In addition, full advantage must be taken of the new and additional research opportunities emanating particularly from pre- and postnatal sonographic screening. The following questions should be answered:

- How long should we continue antibacterial prophylaxis in children with a history of pyelonephritic episodes and persisting vesicoureteric reflux?
- Do we need to screen risk groups (newborns with dilatation of the upper urinary tract, siblings of reflux patients) for vesicorenal reflux and treat them with antibacterial prophylaxis?
- Should we treat asymptomatic newborns and infants with incidentally detected obstructions of the urinary tract by antibacterial prophylaxis?
- How efficient are alternative measures, i.e., vaccines (or bio-therapeutic agents [75])?

Indeed, it is quite difficult to perform a prospective study in children with the question of efficacy and harmlessness of antibacterial prophylaxis [76]. Many factors involved in clinical course and prognosis must be taken into consideration, including age, sex, malformations, bladder emptying, bacterial characteristics, localization of infection and treatment. This only can be done by dividing the children into different study groups and—simultaneously—by stratification according to the most important factors [39]. To make antibacterial prophylaxis work, excludable predisposing factors for recurrent UTI have to be removed or taken into consideration by careful stratification. This is not only true for daily practice but also for each prospective study, which aims to test the benefit of antibacterial prophylaxis on UTI recurrence rates and renal scars. Otherwise, the study results may be influenced by more or less meaningful susceptibility factors.

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