

Total Hits: 1

Search for all ILLs where Status = '3', Authorisation Status = TOACK, Service Level = Rush. Sorted in descending order by illno. (Filters: not supplied messages)

Item 1 of 1

Our Number 9011245

Their Number 9011239

Printed Date 12 Mar 2012

RUSH  
2

Request From Charles Darwin University

	Service 1	Service 2
Service Type	Copy non returnable	Loan
Media Type	Printed	None

Bibliographic Details

Author Pollard, Andrew J.; Finn, Adam, 1959-; British Paediatric Allergy, Immunity, and Infection Group.; European Society for Paediatric Infectious Diseases.; Royal College of Paediatrics and Child Health.

Title Hot topics in infection and immunity in children III

ISBN/ISSN 9780387317830 (cased); 038731783X (cased)

Control Number .b30770245, 2005939184

Publisher Springer

Date of publication 2006.

Call Number held

Verification Libraries Australia/.biball-r20-db07 source

Please return a copy of this request to Interlibrary Loans if it has been:

supplied  not supplied (Please tick)

COPIED BY THE UNIVERSITY OF MELBOURNE LIBRARY FOR SUPPLY UNDER SECTION 50 OF THE COPYRIGHT ACT 1968 DATE 13 MARCH 2012

Article Details

Article Title Antibiotic prophylaxis for the prevention of recurrent urinary tract infections in children

Article Author Long, E. Colquhoun, S. & Carapetis, J.

Pagination 243-248

Service Level Rush

Item Format Conference Proceedings

Request 12 Mar 2012 15:26

Created Date

Expiry Date 15 Mar 2012

Name

Email

Delivery Electronic Mail

Method

Biomed  
618.729 HOT

# Antibiotic Prophylaxis for the Prevention of Recurrent Urinary Tract Infections in Children

Elliot Long, Samantha Colquhoun, and Jonathan R. Carapetis

## 1. Introduction

Urinary tract infections (UTI) in children are common, often recurrent, and sometimes severe. The following discussion explores the reasons for and evidence underlying the use of antibiotic prophylaxis for prevention of recurrent urinary tract infections.

## 2. Why Prevent Urinary Tract Infections in Children?

There are two main reasons for trying to actively prevent UTIs:

- a. *To prevent morbidity/ mortality associated with acute cystitis & pyelonephritis.*

Young children are especially at risk of severe infections, with 6% of UTIs in the first year of life associated with bacteraemia, 2% requiring fluid resuscitation at diagnosis, and 1% requiring ventilatory support (Craig et al., 1998). The incidence of death from urinary sepsis was as high as 11% during the 1960s, but is now rare. Because UTIs often recur – 12% to 30% of children with their first UTI have another infection during the ensuing 12 months (Winberg et al., 1974) – these occasional severe outcomes may justify offering preventive interventions to young children with UTI.

- b. *To prevent long-term sequelae of hypertension and end-stage renal disease.*

The combination of vesicoureteric reflux (VUR) and renal damage from recurrent UTIs has traditionally been thought to lead to end-stage renal

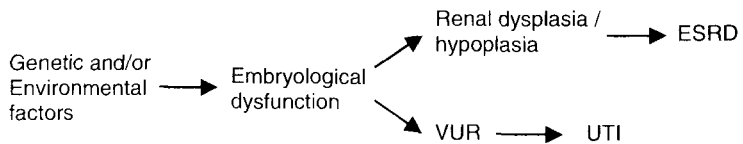
disease (ESRD) (Bailey, 2000). In recent years, however, evidence has emerged that hypertension (HT), renal impairment, and ESRD may not be causally linked with VUR and recurrent UTIs (Figure 20.1) (Wennerstrom et al., 2000b; Yeung et al., 1997; Pope et al., 1999; Marr et al., 2004). Long-term sequelae of HT and renal dysfunction were addressed in a Swedish cohort of children who were examined 16–26 years after their first symptomatic UTI (Wennerstrom et al., 2000a). Sixty-eight participants with renal parenchymal defects on dimerccaptosuccinic acid (DMSA) scan at the time of childhood UTI diagnosis were matched for age and gender with 51 controls (who had UTI with normal DMSA scans). Hypertension was found in 9% of the group with defects and 6% of the group without defects (difference not statistically significant). Glomerular filtration rate (GFR) was well preserved in both study groups, and neither had substantial rates of proteinuria (Wennerstrom et al., 2000a). Although the sample size was small, these data suggest that childhood UTI is not associated with high rates of renal impairment or HT, even if an abnormal DMSA scan is present initially.

These results stand in contrast to previous case-series, in which 18–25% of patients with evidence of renal “scarring” developed hypertension on follow-up 15–30 years after their first UTI (Goonasekera et al., 1996; Smellie et al., 1998). However, those studies selected patients with severe renal parenchymal defects and used conventional and not ambulatory BP measurements, which may account for the discrepancy in results. Jacobson et al. found three of 30 patients followed up 27 years after the detection of non-obstructive pyelonephritic renal scarring had ESRD, and the remainder had significantly lower GFR than matched controls (Jacobson et al., 1989). Martinell et al. followed 54 female patients with renal scarring continuously for 15 years (Martinell et al., 1996). GFR was reduced compared to controls only in those with severe scarring. In summary, there is no clear evidence that renal scarring is a risk factor for the future development of HT, but severe renal scarring may be a risk factor for future reduction in GFR.

#### Traditional hypothesis

VUR → UTI → Renal scars → Renal damage → ESRD

#### Alternative hypothesis



VUR, vesico-ureteric reflux; UTI, urinary tract infection; ESRD, end-stage renal disease

**Figure 20.1.** Traditional and alternative hypotheses of the link between vesico-ureteric reflux, urinary tract infections, and long-term renal damage.

The natural history of renal parenchymal defects as detected by DMSA scans is resolution over time. Forty percent of DMSA scans performed at the time of acute UTI will demonstrate defects. This reduces to 5% three years later (Stokeland et al., 1998). Many of the defects found at the time of a UTI may have been present prior to the infection, possibly due to congenital renal dysplasia (Figure 20.1) (Polito et al., 2000; Wennerstrom et al., 2000b). This may be diagnosed antenatally and may be progressive despite medical and surgical intervention.

### 3. Which Children are at Risk of Recurrent UTI?

Data from a prospective hospital based cohort study in children less than 5 years of age who were identified following their first symptomatic UTI implicates young age and presence of high grade VUR as risk factors for recurrence of UTI (Panaretto et al., 1999). Vesico-ureteric reflux of grade 3 to 5 is an independent risk factor for recurrence (odds ratio: 3.5), as is age less than 6 months (OR: 2.9). Recurrence of UTI is also a predictor of future recurrence. After 2 UTIs, the risk of recurrence within one year is ~60%, and after 3 UTIs the risk of recurrence within one year is ~75% (Hellerstein, 1982).

### 4. Can Recurrent Urinary Tract Infections be Prevented?

A Cochrane meta-analysis of studies comparing antibiotic prophylaxis with antibiotic prophylaxis combined with surgical re-implantation of ureters demonstrated that there may be a small reduction in recurrent UTIs in the surgery plus antibiotic group (Wheeler et al., 2004). However, the effect size was such that nine re-implantations would be needed to prevent one febrile UTI after 5 years. No difference in GFR or abnormalities on DMSA scan was demonstrated between groups. Importantly, none of the studies included a control group that received no treatment.

Williams et al. performed a meta-analysis of 5 existing randomised controlled trials of antibiotic prophylaxis in the prevention of recurrent UTIs (Williams et al., 2001). Three trials (n = 392) examined long-term antibiotic treatment (2–6 months) and subsequent off-treatment development of UTI. These trials included patients with asymptomatic bacteriuria. Two trials (n = 72) examined antibiotic prophylaxis for prevention of recurrent UTI during treatment. Overall, long-term antibiotic treatment reduced the risk of UTI while on treatment (relative risk 0.31, 95% confidence interval 0.10–1.00), but there was no sustained benefit once antibiotic treatment had ceased. The quality of included trials was poor due to lack of blinding and unclear definitions for UTI. The methods of randomization were not described, and allocation concealment was unclear. In addition, the trials included very few boys, infants, and children with abnormal renal tracts. The authors concluded that there remains considerable uncertainty regarding the effectiveness of antibiotic prophylaxis in preventing recurrent UTIs in children.

A systematic review of trials examining antimicrobial prophylaxis for prevention of recurrent UTIs in children with normal urinary tracts was undertaken by Le Saux et al. (Le Saux et al., 2000). They identified two cross-over studies and one randomised controlled trial comparing antibiotic prophylaxis with placebo or no treatment. The quality of the included trials was also poor, with unclear allocation concealment and small sample sizes (mean 28 children). The one randomised trial included was not blinded. There was considerable heterogeneity in rates of recurrence of UTI in each trial, ranging from 0 to 4.0 per 10 patient years in the treatment group and from 4.0 to 16.7 per 10 patient years in the control groups. The authors concluded that the treatment effect observed may have been significantly skewed in favor of antimicrobial prophylaxis by systematic bias.

A Cochrane review of three trials ( $n = 151$ ) comparing antibiotics with placebo demonstrated a reduction in risk of recurrent UTI with antibiotic prophylaxis (RR 0.36, CI 0.25–0.92) (Williams et al., 2001). The rate of recurrent UTI in the placebo group was 63% overall. Improper allocation concealment, lack of blinding, and lack of intention-to-treat analysis were thought to bias these trials in favor of overestimating any treatment effect. Additionally, the criteria for diagnosis of UTI differed between studies and two studies did not state their method of randomization. The authors concluded that the evidence for effectiveness of antibiotic prophylaxis in preventing recurrent UTIs is unreliable, and the small number of studies performed to date are of poor quality. One trial ( $n = 120$ ) found nitrofurantoin to be more effective than trimethoprim at preventing recurrent UTI (RR 0.48; CI 0.25–0.92), although nitrofurantoin was poorly tolerated due to gastrointestinal side-effects. Patients who received nitrofurantoin were three times more likely to stop their antibiotic than those receiving trimethoprim because of nausea, vomiting, and abdominal pain.

There is considerable evidence that chemoprophylaxis has a significant failure rate. One quarter of children with moderate to severe VUR in the Birmingham Reflux Study and one third of children in the International Reflux Study developed breakthrough UTI regardless of treatment with antibiotics alone or antibiotics and surgery (Birmingham Reflux Study Group, 1987; Hjalmas et al., 1982). Neither study was placebo controlled.

## **5. Is There Any Harm Associated with the Long-Term Use of Antibiotic Prophylaxis?**

Antibiotic prophylaxis is not always a benign intervention. The presence of *E. coli* resistant to trimethoprim has been demonstrated in up to 66% of children on antibiotic prophylaxis following breakthrough infection, suggesting that prophylaxis may play a role in inducing the emergence of antibiotic-resistant organisms (Braendstrup et al., 1990). Moreover, there is an 8–10% risk of adverse reactions with antimicrobial prophylaxis (Uhari et al., 1996). Trimethoprim-sulfamethoxazole has been associated with nausea and vomiting (5%), skin reactions (2%), diarrhea (1%), and blood dyscrasias (<0.5%). Nitrofurantoin has been associated with abdominal pain limiting adherence.

## 6. Do Non-antibiotic Interventions Have a Role in Preventing Recurrent Urinary Tract Infections?

Cranberry juice has been examined as a UTI prophylactic in a Cochrane meta-analysis. No difference in incidence of bacteriuria between treatment and control groups was found, although small numbers may have underestimated any treatment effect (Jepson et al., 2004). The authors concluded that this safe intervention requires larger trials to evaluate its efficacy.

Addressing voiding dysfunction with bladder training programs with or without the additional use of anticholinergic agents may be an alternative to prophylactic chemotherapy. The anticholinergic oxyphenonium bromide was found to be effective at decreasing detrusor contractility and the degree of reflux in children with these conditions (Scholtmeijer and Van Mastrigt, 1991), although it has not been proven to decrease the incidence of UTI.

Circumcision has been demonstrated to reduce the incidence of UTI in boys 10-fold in a retrospective cohort study (Schoen et al., 2000). This intervention may not be appealing as a first-line preventive strategy, but may benefit boys with multiple recurrent UTIs.

## 7. Recommendations for the Use of Antibiotic Prophylaxis

Current clinical guidelines regarding the use of antimicrobial prophylaxis for recurrent UTIs in children highlight the uncertainty that surrounds their efficacy. For example, the American Academy of Pediatrics currently recommends the use of prophylactic antibiotics for all children with UTIs in whom documented VUR exists (American Academy of Pediatrics, 1999), whereas Swedish guidelines limit prophylaxis to high grades of reflux (4–5) only (Jodal and Lindburg, 1999).

We know that UTIs may be severe, particularly in infants, and that frequent recurrent UTIs are associated with, but not necessarily the cause of, permanent renal damage in a small percentage of cases. There is a limited amount of poor-quality evidence that recurrent UTIs may be prevented by long-term prophylactic antibiotics, although it is not known if the benefits of this approach (if any) outweigh the risks. It is very difficult to determine if antibiotic prophylaxis can prevent the development of long-term renal damage. In Australia, where reflux nephropathy accounts for approximately 4% of all ESRD cases, there has been no apparent reduction in reflux-nephropathy associated ESRD over the past 20 years, during which time antibiotic prophylaxis for children with UTI and VUR has been a common practice (Craig et al., 2000). Therefore, until we have better data as to whether UTI is linked with long-term renal damage, and whether antibiotic prophylaxis can prevent recurrent UTI, it will be difficult to provide clinicians with clear evidence-based recommendations. It is our practice to consider a voiding cystourethrogram in infants, particularly those aged less than six months, presenting with their first UTI and to offer antibiotic prophylaxis to those with grade 3 or more reflux. We also consider antibiotic prophylaxis in other children at increased risk of severe or recurrent UTI (Figure 20.2). We prescribe a daily dose of trimethoprim-sulphamethoxazole (2 mg

- Infants, particularly age <6 months
- Grade 3 or higher vesico-ureteric reflux
- A history of a previous UTI
- A family history of recurrent UTI or vesico-ureteric reflux

**Figure 20.2.** Risk factors for recurrent urinary tract infection or vesico-ureteric reflux in children with urinary tract infection.

trimethoprim – 10 mg sulphamethoxazole per kg) for six to twelve months or until the child is no longer wearing nappies, before a trial off prophylaxis. Given the uncertainties in this area, other clinicians will have different indications for the use of prophylaxis, and many will not use it at all. Hopefully the next few years will see better evidence emerge so that recommendations can be revised with confidence.

## Acknowledgements

The authors would like to thank Dr. Jonathan Craig for his assistance with the preparation of this manuscript.

## References

- American Academy of Pediatrics (1999) *Practice Parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children.*, *Pediatr. Inf. Dis. J.*, **103**, 843–853.
- Bailey, R. (2000) *The relationship of vesicoureteral reflux to urinary tract infection and chronic pyelonephritis nephropathy.*, *Clin. Nephrol.*, **1**, 132–141.
- Birmingham Reflux Study Group (1987) *Prospective trial of operative versus non-operative treatment of vesicoureteric reflux in children: five year's observation.*, *Br. Med. J.*, **295**, 237–241.
- Braendstrup, L., Hjelt, K., Petersen, K., Petersen, S., Andersen, E.A., Daugbjerg, P., Stagegaard, B.R., Nielsen, O.H., Vejlsgaard, R. and Schon, G. (1990) *Nitrofurantoin versus trimethoprim prophylaxis in recurrent urinarytract infection in children.*, *Acta Paediatr. Scand.*, **79**, 1225–1234.
- Craig, J., Irwig, L., Knight, J., Sureshkumar, P. and Roy, L.P. (1998) *Symptomatic urinary tract infection in Australian preschool children: clinical features, microbiology, renal tract abnormalities, and short-term outcomes.*, *J. Paediatr. Child Health.*, **34**, 154–159.
- Craig, J.C., Irwig, L.M., Knight, J.F. and Roy, L.P. (2000) *Does treatment of vesicoureteric reflux in childhood prevent end-stage renal disease attributable to reflux nephropathy?*, *Pediatr. Inf. Dis. J.*, **105**, 1236–1241.
- Goonasekera, C., Shah, V., Wade, A.M., Barratt, T.M. and Dillon, M.J. (1996) *15-year follow-up of renin and blood pressure in reflux nephropathy.*, *Lancet.*, **347**, 640–643.
- Hellerstein, S. (1982) *Recurrent urinary tract infections in children.*, *Paediatr. Inf. Dis.*, **1**, 271–281.
- Hjalmas, K., Lohr, G., Tamminen-Mobius, T., Seppanen, J., Olbing, H. and Wikstrom, S. (1982) *Surgical Results in the International Reflux Study in Children (Europe).*, *J. Urol.*, **148**, 1657–1661.
- Jacobson, S.H., Eklof, O., Erikson, C.G., Linsl, E., Tidgren, B. and Winberg, J. (1989) *Development of hypertension and uremia after pyelonephritis in childhood: 27 years of follow-up.*, *Br. Med. J.*, **299**, 703–706.

- Jepson, R., Mihalejvic, L. and Craig, J. (2004) *Cranberries for preventing urinary tract infections. Cochrane Database Syst. Rev.*, **1**:CD001321.
- Jodal, U. and Lindburg, U. (1999) *Guidelines for management of children with urinary tract infection and vesico-ureteral reflux. Recommendations from a Swedish state-of-the-art conference.*, *Acta Paediatr. Suppl.*, **431**, 87–89.
- Le Saux, N., Pham, B. and Moher, D. (2000) *Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review.*, *Can. Med. Assoc. J.*, **163**, 523–529.
- Marr, G., Oppezzo, C., Ardissino, G., Dacco, V., Testa, S., Avolia, L., Taioli, E. and Sereni, F. (2004) *Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ITALKID project.*, *J. Pediatr.*, **144**, 677–681.
- Martinell, J., Linden-Jansen, O., Jagenburg, G., Sivertsson, R., Claesson, I. and Jodal, U. (1996) *Girls prone to urinary tract infections followed into adulthood: indices of renal disease.*, *Pediatr. Nephrol.*, **10**, 139–142.
- Panaretto, K., Craig, J., Knight, J., Giles, R., Sureshkumar, P. and Roy, L. (1999) *Risk factors for recurrent urinary tract infection in preschool children.*, *J. Paediatr. Child Health.*, **35**, 454–459.
- Polito, C., La Manna, A., Rambaldi, P.F., Nappi, B., Mansi, L. and Di Toro, R. (2000) *High incidence of a generally small kidney and primary vesicoureteral reflux.*, *J. Urol.*, **164**, 479–482.
- Pope, J.C., Brock, J.W., Adams, M.C., Stephens, F.D. and Ichikawa, I. (1999) *How they begin and how they end: classic and new theories for the development and deterioration of Congenital Anomalies of the Kidney and Urinary Tract, CAKUT.*, *J. Am. Soc. Nephrol.*, **10**, 2018–2028.
- Schoen, E., Colby, C. and Ray, G. (2000) *Newborn circumcision decreases incidence and costs of urinary tract infection in the first year of life.*, *Pediatr. Inf. Dis. J.*, **105**, 7789–7793.
- Scholtmeijer, R. and Van Mastrigt, R. (1991) *The effect of Oxyphenonium Bromide and Oxybutynin Hydrochloride on Detrusor Contractility and Reflux in Children with Vesicoureteral Reflux and Voiding Dysfunction.*, *J. Urol.*, **146**, 660–662.
- Smellie, J., Prescod, N.P., Shaw, P.J., Risdon, R.A. and Bryant, T.N. (1998) *Childhood reflux and urinary tract infection: a follow-up of 10–41 years in 226 adults.*, *Pediatr. Nephrol.*, **12**, 727–736.
- Stokeland, E., Hellstrom, M., Jacobsson, S., Jodal, U. and Sixt, R. (1998) *Evaluation of DMSA scintigraphy and urography in assessing both acute and permanent renal damage in children.*, *Acta Radiol.*, **39**, 447–452.
- Uhari, M., Nuutinen, M. and Turtinen, J. (1996) *Adverse reactions in children during long-term antimicrobial therapy.*, *Pediatr. Inf. Dis. J.*, **15**, 404–408.
- Wennerstrom, M., Hansson, M., Jodal, U., Sixt, R. and Stokland, E. (2000a) *Renal function 16 to 26 years after the first urinary tract infection in childhood.*, *Arch. Pediatr. Adol. Med.*, **154**, 339–345.
- Wennerstrom, M., Hansson, S., Jodal, U. and Stokland, U. (2000b) *Primary and acquired renal scarring in boys and girls with urinary tract infection.*, *J. Pediatr.*, **136**, 30–34.
- Wheeler, D.M., Vimalachandra, D., Hodson, E.M., Smith, G.H. and Craig, J.C. (2004) *Interventions for primary vesicoureteric reflux.*, *Cochrane Database Syst. Rev.*, **3**:CD001532.
- Williams, G., Lee, A. and Craig, J. (2001) *Long-term antibiotics for preventing recurrent urinary tract infection in children.*, *Cochrane Database Syst. Rev.*, **4**:CD001534.
- Winberg, J., Andersén, H.J., Bergstrom, T., Jacobsson, B., Larson, H. and Lincoln, K. (1974) *Epidemiology of symptomatic urinary tract infections in childhood.*, *Acta Paediatr. Scand.*, **Suppl.** **252**, 1–20.
- Yeung, C.K., Godley, M.L., Dhillon, H.K., Gordon, I., Duffy, P.G. and Ransley, P.G. (1997) *The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis.*, *Br. J. Urol.*, **80**, 319–327.