

Prophylactic Antibiotics and Evaluation Scheme Following Febrile Urinary Tract Infection in Children: a Nationwide Israeli Survey

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ABSTRACT: **Background:** Although febrile urinary tract infections are very common in young children, the need for antimicrobial prophylaxis and evaluation following a first event is controversial.

Objectives: To assess the approach of leading pediatric specialists throughout Israel to antimicrobial prophylaxis.

Methods: A questionnaire regarding the approach to antibiotic prophylaxis and diagnostic evaluation following a first event of febrile UTI, according to age and underlying renal abnormality, was sent to all 58 directors of departments of pediatrics, units of pediatric infectious diseases and pediatric nephrology in Israel.

Results: Fifty-six directors (96%) responded. Most prescribed prophylactic antibiotics after UTI. Heads of infectious disease departments prescribed less prophylaxis following UTI at the age of 18 months than heads of pediatrics or heads of pediatric nephrology units (34% vs. 72–75%, $P = 0.018$), but more often in cases of severe vesico-ureteral reflux without UTI. Cephalosporins were used prophylactically more often by directors of pediatrics compared to heads of pediatric nephrology units (71% vs. 38%, $P = 0.048$); the latter used non-beta-lactam prophylaxis (61% vs. 23%, $P = 0.013$) more often. Most pediatricians used renal sonography for evaluation; renal scan was used more commonly by pediatric nephrologists.

Conclusions: The administration of prophylactic antibiotics after UTI is still common practice among pediatric opinion leaders, although the specific approach differs by subspecialty. According to the latest evidence-based data, educational efforts are needed to formulate and implement judicious guidelines.

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KEY WORDS: urinary tract infections, children, prophylaxis, renal anomalies, clinical guidelines

rence is higher during the first year following the infection, peaking in the first 2–6 months [1].

Acute pyelonephritis is associated with a 5%–38% risk of permanent renal damage in the form of parenchymal scarring, as demonstrated by DMSA (dimercaptosuccinic acid) scan performed 6–12 months following an event of pyelonephritis [2–4]. The long-term complications attributed to renal scarring include hypertension, proteinuria and impaired renal function. Its incidence increases with each episode of pyelonephritis, and although previously believed to occur only in infants, it is currently known to occur at any age [1]. Scarring is also related to genetic factors, such as polymorphisms of profibrotic genes, including tumor growth factor-beta and angiotensin-converting enzyme [5,6]. Whether vesico-ureteral reflux is a predisposing factor for acquired renal scarring is uncertain. Several recent studies have demonstrated that VUR acts as a poor predictor of renal damage, and that the incidence of renal damage may be unaffected by the presence of VUR [2,7]. The most significant risk factor appears to be recurrent infection.

The 1999 American Academy of Pediatrics guidelines for infants aged 2 months to 2 years recommends an imaging study in children after a first episode of UTI to evaluate the presence and degree of VUR. If VUR is detected, daily antimicrobial prophylaxis is recommended to prevent recurrent UTIs. Thus, recurrent UTIs with or without VUR are currently a leading cause for long-term prophylactic antibiotics in children. However, these guidelines were not based on solid evidence. Recent data question the efficacy of antibiotic prophylaxis in preventing recurrent infections and subsequent renal scarring, and highlight its disadvantages. A cohort study found that antibiotic prophylaxis was not associated with a decreased rate of recurrent infections but was associated with an increased risk for antibiotic resistance [8]. Garin et al. [2], in a randomized controlled trial, found no difference in the rates of pyelonephritis and cystitis between patients treated with antibiotic prophylaxis, and controls. Similarly, an additional randomized controlled trial found that continuous

Urinary tract infections are among the leading causes of fever in young children. They affect approximately 1% of all boys and 3%–5% of all girls, most of whom will experience a single event and recover promptly. However, 30%–50% will be subject to at least one recurrence. The tendency for recur-

UTI = urinary tract infection
VUR = vesico-ureteral reflux

prophylaxis was ineffective in reducing the rates of recurrent pyelonephritis and renal scarring in children [9].

Several ongoing sizable, well-designed, randomized, double-blind, controlled trials are currently underway, but their results will not be available for several years. Until then, in the absence of an evidence-based accepted approach, post-UTI evaluation and use of antibiotic prophylaxis remain controversial. The aim of this study was to present the approaches of leading pediatric specialists in Israel to a first event of UTI as a major step in establishing uniform guidelines.

SUBJECTS AND METHODS

NATIONWIDE SURVEY

A questionnaire regarding the approach to antimicrobial prophylaxis and to the diagnostic evaluation following a first febrile UTI, according to age and underlying renal abnormality, was sent to all 58 directors of departments of pediatrics, directors of pediatric infectious disease units, and directors of pediatric nephrology units in Israel. The questionnaire contained 12 multiple-choice questions, divided into 5 parts [Appendix]. The first part of the questionnaire relates to the use of prophylactic antibiotics following a first event of febrile UTI, according to age: in children aged 2 weeks (representing the neonatal period), 4 months (representing infancy) and 18 months (representing the second year of life), prior to further investigation (3 questions). The second part concerns the use of prophylactic antibiotics following an event of febrile UTI, when VUR (grade 1–3 or grade 4–5) is detected by cystourethrography, or renal scarring by DMSA scan (3 questions). The third part relates to the use of antimicrobial prophylaxis in a child with mild or severe VUR and no evidence of previous UTI (2 questions).

The physicians were then asked to name their antimicrobial agent of choice for prophylaxis in a 4 month old child (an age at which it is safe to use nitrofurantoin and trimethoprim-sulphamethoxazole) and their imaging modality of choice (renal sonography, VCUG or DMSA scan) by patient age. The survey was conducted between October and December 2007.

STATISTICAL ANALYSIS

The data were entered into an electronic database and analyzed. Rates of use of antibiotic prophylaxis and imaging modalities by the different specialties and in the various settings were compared by chi-square test or Fisher's exact test (when the expected value of any cell was < 5). Significance was defined a priori as $P < 0.05$.

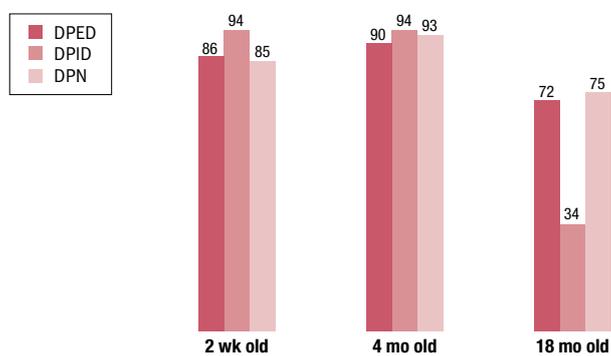
RESULTS

The questionnaire was completed by 56 of the 58 directors (96%) to whom it was sent. The response rates by subspecialty are shown in Table 1.

Table 1. Response rates to the questionnaire by specialty

Directors of	Approached	Responded (%)
Departments of pediatrics	29	28 (96%)
Units of pediatric infectious disease	15	15 (100%)
Units of pediatric nephrology	14	13 (93%)
All	58	56 (96%)

Figure 1. Response of pediatric directors in Israel to questions 1–3 regarding the use of prophylactic antibiotics (%), according to age at the first episode of UTI



USE OF PROPHYLACTIC ANTIBIOTICS BY AGE

Antibiotic prophylaxis was considered necessary after a first febrile UTI by the large majority of responders for both a 14 day old neonate and a 4 month old infant, until further investigation or until the age of one year, with no significant differences among the sub-specialties (range 85%–94%) [Figure 1]. However, for a child aged 18 months, rates were lower and differed significantly among the sub-specialties: prophylaxis would be prescribed by 72% and 75% of pediatrics directors and pediatric nephrologists, respectively, until further investigation, but only by 34% of infectious disease specialists ($P = 0.018$).

USE OF PROPHYLAXIS ACCORDING TO UNDERLYING RENAL ABNORMALITY

Most of the pediatricians chose to prescribe antibiotic prophylaxis to an infant with grade 1 to 3 VUR following febrile UTI (55%, 66% and 66% of the pediatrics, pediatric infectious disease and pediatric nephrology department directors, respectively). The subgroup of responders who did not believe mild VUR warranted prophylaxis were then asked whether they would prescribe prophylaxis to the same child, if a renal scan were positive for parenchymal scars. Positive answers were given by 100% of the pediatric nephrologists compared to only 50% of the pediatrics and 40% of the infectious disease directors, respectively ($P = 0.08$). For children with severe

DMSA = dimercaptosuccinic acid
VCUG = voiding cystourethrography

VUR (grade 4–5), the vast majority of practitioners agreed that antibiotic prophylaxis was necessary (94%, 81% and 75% of the pediatrics, infectious diseases and pediatric nephrology directors, respectively). Again, all the nephrologists who chose not to treat reported that even in the presence of severe VUR they would base their decision on DMSA findings.

Evidence of renal scarring per DMSA scan, following an event of UTI, regardless of the presence of VUR, was also considered as an indication for prophylaxis by most, but not all of the practitioners: 71% of the pediatricians, 75% of the infectious disease specialists and 75% of the nephrologists. Several physicians did not answer this question, stating that they would not base their decision on DMSA scan findings but on the presence of VUR alone.

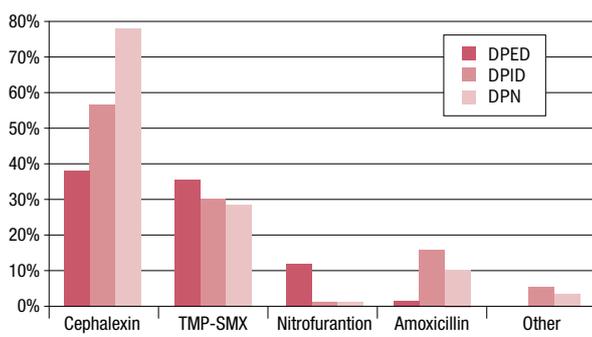
Most of the responders would administer prophylaxis to children with VUR grade 4 to 5, even in the absence of a documented event of UTI. However, the rates differed significantly between the infectious disease specialists (100%) and both pediatricians and nephrologists (72% and 70%, respectively, $P = 0.016$). Even for children with mild VUR (grade 1 to 3) but no documented event of febrile UTI, a considerable number of pediatricians would prescribe prophylactic antibiotics: 23% of pediatricians, 46% of infectious disease specialists and 38% of nephrologists. Regarding the cessation of prophylaxis, the majority would do so on improvement of the reflux, as indicated by repeated VCUG.

ANTIMICROBIAL AGENT OF CHOICE FOR PROPHYLAXIS

For a 4 month old infant, a first-generation cephalosporin (cephalexin) was selected for prophylaxis at significantly higher rates by pediatricians than by nephrologists (71% vs. 38%, $P = 0.048$). In contrast, non-beta-lactam prophylaxis was used significantly more often by nephrologists than by the other specialists (61% vs. 23%, $P = 0.013$), including TMP-SMX (46% vs. 23%, $P = 0.107$) and nitrofurantoin (15% vs. 0%, $P = 0.051$). More details are shown in Figure 2.

TMP-SMX = trimethoprim-sulphamethoxazole

Figure 2. Response of pediatric directors in Israel to question 8 regarding the preferred antimicrobial agent for prophylaxis, according to sub-specialty (%)



EVALUATION SCHEME

Most of the practitioners of all sub-specialties stated that they would recommend renal sonography in every child younger than 5 years with febrile UTI [Figure 3]. Furthermore, 14% of pediatricians and 23% of nephrologists added in free text that they would perform renal sonography in every child following a first event of UTI, regardless of age. Pediatric nephrologists used DMSA scan in the routine workup of infants under 2 years of age more often than pediatricians (46% vs. 17%, $P = 0.065$) and infectious disease specialists (28%). Pediatric nephrologists also used routine VCUG less often than the other specialists: 41% as compared with 59% of pediatricians and 73% of infectious disease specialists, although this difference did not reach statistical significance ($P = 0.25$).

DISCUSSION

To our knowledge, this is the first survey designed to evaluate current approaches to the management of UTI in children among experts in the field. A considerable disagreement among leading pediatric specialists in Israel was noted, with some regimens lacking evidence in the medical literature. We found that it is common practice among all three groups of leading pediatricians to prescribe prophylactic antibiotics following a single episode of UTI in most clinical settings. Unfortunately, there are few evidence-based data supporting the benefits of this approach. Indeed, the AAP guidelines, to which most Israeli doctors adhere, are based on a few poorly designed controlled studies dating back to the 1970s. More recent studies indicate that the efficacy of prophylactic antibiotics may be lower than estimated in the past, and that the extensive use of antibiotics is probably one of the major reasons for the increasing antibiotic resistance of the bacteria causing urinary tract infections. A randomized controlled trial published in 2008 reported no reduction in the rate of recurrent pyelonephritis or renal scarring in children who received continuous prophylaxis compared to those who did not over a follow-up of 4 years [9]. Although a large-scale randomized, double-blind trial on the efficacy of the prophylactic antibiotics is currently underway, it will be several years before unequivocal conclusions can be drawn. We believe that until more information becomes available prophylactic treatment should be reserved for children at high risk for recurrent pyelonephritis and consequent renal scarring.

While the vast majority of responders to our survey would prescribe prophylaxis to a neonate and a 4 month old infant following a first UTI, fewer would do so in the case of an 18 month old child with the same presentation. However, neonatal UTI is commonly a result of hematogenous spread and does not necessarily indicate increased susceptibility to recurrent UTI in the future; whether prophylaxis is required

AAP = American Academy of Pediatrics

at this age is unclear. At the same time, the tendency not to prescribe prophylaxis to an 18 month old infant could be explained by the assumption that the risk of renal scarring decreases with age. However, studies have shown that scarring may occur at any age [10], therefore relying on age as a guide to the use of antibiotic prophylaxis is questionable.

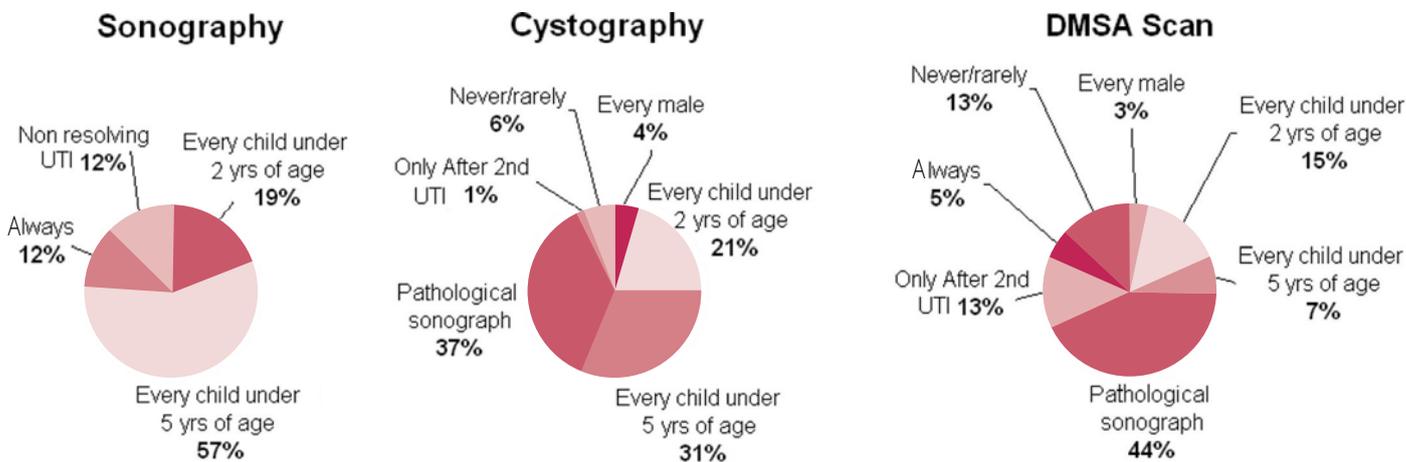
Most of our responders regarded VUR, particularly grades 4 and 5, as a significant consideration in their decision to prescribe antibiotic prophylaxis. The majority would prescribe prophylaxis in the presence of severe VUR, even in the absence of a prior episode of UTI. However, while VUR by itself was previously believed to be a major risk factor for renal scarring, it is probably rather the recurrence of renal infection that correlates with consequent parenchymal scarring [11]. In numerous studies, most patients with abnormal DMSA scans following acute pyelonephritis (60–68%) do not have demonstrable VUR at the time of investigation [11]. Garin and co-authors [2] reported no significant difference in the incidence of renal scarring following acute pyelonephritis between children with grade 1 to 3 reflux and children with normal urinary tracts. A meta-analysis of 11 studies (1148 children) on treatment strategies in children with VUR concluded that even children who were given combined treatment – correction of the reflux and prophylactic antibiotics – did not show a reduced rate of progressive renal damage in 10 years of follow-up [12]. Two small studies included in this review failed to show any advantage of prophylaxis over conservative follow-up, prompt diagnosis and antibiotic treatment upon diagnosis of febrile UTI.

The following risk factors have been strongly associated with acquired renal scarring: recurrent episodes of pyelonephritis, previously demonstrated renal scarring following pyelonephritis, settings in which diagnosis of febrile UTI is likely to be delayed, and voiding disturbances [1].

Regarding the antimicrobial agent of choice for prophylaxis, we found that pediatric nephrologists were more aware of current recommendations than the other specialists. Whereas the majority of pediatricians and infectious disease specialists reported common use of first-generation cephalosporins, more pediatric nephrologists preferred TMP-SMX and nitrofurantoin [Figure 2]. A cohort study published in 2007 by Conway et al. [8] observed that prophylactic antibiotics increased the risk of bacterial resistance in the event of recurrence. This finding supports the results of an earlier, prospective study published in 2005 by Marcus et al. [13], designed to define antibiotic susceptibilities of *Escherichia coli* and non-*E. coli* UTIs and to determine predictors of non-*E. coli* UTIs [13]. The study found that non-*E. coli* UTI was associated with higher antimicrobial resistance and a higher rate of inappropriate empiric antibiotic therapy. Non-*E. coli* UTI was noted in all children who had received a prophylactic beta-lactam, but only in 40% of those treated with TMP-SMX. This may be explained by the relatively poor absorption of beta-lactams in the small bowel, thus exposing colonic flora to the antimicrobial agents and leading to their increased resistance [14]. Resistance to TMP-SMX has also been reported in increasing numbers. Nitrofurantoin, however, although well absorbed in the upper gastrointestinal tract and approved for children from the age of one month, was not often prescribed by the pediatricians in our survey, despite the rarity of its adverse effects in pediatric patients.

Regarding the evaluation scheme for children after UTI, the use of VCUG to detect anomalies of the urinary tract, mainly VUR, was common among the physicians of all subspecialties, despite recent reports of its redundancy in the era of DMSA scans. A meta-analysis was performed in 2003 to determine the effectiveness of VCUG in predicting renal damage as demonstrated on DMSA scan in hospitalized children with UTI [7].

Figure 3. The use of investigational modalities by all pediatric directors (regardless of subspecialty) following a febrile UTI



The results showed that the presence of primary VUR is a poor predictor of renal damage in this patient population. However, the absence of VUR by no means rules out renal damage, and VCUG therefore should not be used as a screening tool to exclude renal defects. Two more recent studies also claimed that performing VCUG in a child with a normal DMSA scan following first UTI is unnecessary [15,16]. Considering that most practitioners in our survey would base their decision on the use of prophylaxis on the presence of VUR rather than renal scars, children with abnormal cystography may sometimes receive prophylaxis unnecessarily, while others with undetected renal scars may remain untreated and at consequent risk of recurrent UTI and long-term sequelae.

CONCLUSIONS

The administration of prophylactic antibiotics after a single event of febrile UTI in children remains common practice among leading pediatricians in Israel, despite the lack of evidence supporting its efficacy and the continuous increase in antibiotic resistance in recent years. Pediatric infectious disease specialists prescribe significantly less prophylaxis for infants aged 18 months with a first UTI. On the other hand, they base their decision on whom to treat in the presence of VUR and use significantly more prophylaxis in children with VUR grade 4 to 5 with no prior urinary infection. Directors of pediatric nephrology units administer non-beta-lactams as prophylaxis significantly more than other pediatric specialists and more often routinely recommend DMSA scans until the age of 2 years.

Since there is no proof that the efficacy of antibiotic prophylaxis outweighs its role in increasing bacterial resistance, we suggest that physicians carefully consider its use. We suggest that the presence of VUR should not serve as a sole criterion for administration of prophylactic antibiotics. Until additional evidence-based data become available, we recommend that prophylactic antibiotics be given to children who meet the following criteria, indicating a high risk for renal scarring:

- Following a second event of acute pyelonephritis
- Evidence of renal scars or renal dysplasia on DMSA scan
- Children with dysfunctional voiding
- Cases in whom we cannot guarantee prompt diagnosis and treatment of a recurrent UTI.

We recommend nitrofurantoin as the agent of choice for prophylaxis, owing to its low risk of adverse effects in children and the increase in bacterial resistance to other effective agents.

Our findings highlight the need for large-scale, prospective, randomized controlled studies that will provide the evidence for updated guidelines. Meanwhile, our findings, together with recent evidence-based data, dictate that educational efforts are needed to implement a judicious approach to UTIs in children in Israel and to formulate nationwide guidelines.

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Appendix. The Questionnaire

In the following questionnaire, please choose the most appropriate answer reflecting your approach to a child with a single event of febrile UTI

1. Your approach to antimicrobial prophylaxis following a first febrile UTI in a 2 week old neonate:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until performing voiding cystography
 - c. I would prescribe antimicrobial prophylaxis until the age of one year
 - d. I would prescribe antimicrobial prophylaxis until performing DMSA scintigraphy
 - e. None of the above, details: _____
2. Your approach to antimicrobial prophylaxis following a first febrile UTI in a 4 month old infant:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until performing voiding cystography
 - c. I would prescribe antimicrobial prophylaxis until the age of one year
 - d. I would prescribe antimicrobial prophylaxis until performing DMSA scintigraphy
 - e. None of the above, details: _____
3. Your approach to antimicrobial prophylaxis following a first febrile UTI in an 18 month old infant:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until performing voiding cystography
 - c. I would prescribe antimicrobial prophylaxis until the age of one year
 - d. I would prescribe antimicrobial prophylaxis until performing DMSA scintigraphy
 - e. None of the above, details: _____
4. Your approach to antimicrobial prophylaxis following a first febrile UTI in an infant with grade 1–3 VUR:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until complete resolution of the reflux
 - c. I would prescribe antimicrobial prophylaxis until the age of one year
 - d. I would prescribe antimicrobial prophylaxis only if pathological findings are present on DMSA scan
 - e. None of the above, details: _____
5. Your approach to antimicrobial prophylaxis following a first febrile UTI in an infant with grade 4–5 VUR:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until complete resolution of the reflux
 - c. I would prescribe antimicrobial prophylaxis until reflux diminishes to grade 3 or less
 - d. I would prescribe antimicrobial prophylaxis until the age of one year
 - e. Antimicrobial prophylaxis only if pathological findings are present on DMSA scan
 - f. None of the above, details: _____
6. Your approach to antimicrobial prophylaxis in an infant with grade 1–3 VUR, with no history of UTI in the past:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until complete resolution of the reflux
 - c. I would prescribe antimicrobial prophylaxis until the age of one year
7. Your approach to antimicrobial prophylaxis in an infant with grade 4–5 VUR, with no history of UTI in the past:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until complete resolution of the reflux
 - c. I would prescribe antimicrobial prophylaxis until reflux diminishes to grade 3 or less
 - d. I would prescribe antimicrobial prophylaxis until one year of age
 - e. None of the above, details: _____
8. Which is your agent of choice for antimicrobial prophylaxis in a 3 month old infant?
 - a. amoxicillin
 - b. amoxicillin + clavulanate
 - c. cephalixin
 - d. trimethoprim-sulfamethoxazole
 - e. nitrofurantoin
 - f. nalidixic acid
 - g. none of the above, details: _____
9. In which of the following cases would you recommend a renal ultrasound following a first febrile UTI?
 - a. Every male
 - b. Every child (male/female) until the age of 2 years
 - c. Every child until the age of 5 years
 - d. Lack of clinical response to antibiotic treatment within 48–72 hours
 - e. Only after a second event of UTI
 - f. None of the above, details: _____
10. In which of the following cases would you recommend a voiding cystography following a first febrile UTI?
 - a. Every male
 - b. Every child (male/female) until the age of 2 years
 - c. Every child until the age of 5 years
 - d. Every child with a pathological renal ultrasound
 - e. Only after a second event of UTI
 - f. None of the above, details: _____
11. In which of the following cases would you recommend a DMSA scan following a first febrile UTI?
 - a. Every male
 - b. Every child (male/female) until the age of 2 years
 - c. Every child until the age of 5 years
 - d. Every child with a pathological renal ultrasound
 - e. Only after a second event of UTI
 - f. None of the above, details: _____
12. Your approach to antimicrobial prophylaxis following a first febrile UTI in an infant with a pathological DMSA scan:
 - a. I would not give antimicrobial prophylaxis
 - b. I would prescribe antimicrobial prophylaxis until the age of one year
 - c. None of the above, details: _____