The American Urological Association
Pediatric Vesicoureteral Reflux
Clinical Guidelines Panel

Report on

The Management of Primary Vesicoureteral Reflux in Children

Clinical Practice Guidelines

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The Pediatric Vesicoureteral Reflux Clinical Guidelines Panel consists of board-certified urologists and nephrologists who are experts in vesicoureteral reflux in children. This *Report on the Management of Primary Vesicoureteral Reflux in Children* was extensively reviewed by over 50 urologists throughout the country in the summer of 1996. The Panel finalized its recommendations for the American Urological Association (AUA) Practice Parameters, Guidelines and Standards Committee, chaired by Joseph W. Segura, MD, in November 1996. The AUA Board of Directors approved these practice guidelines in November 1996.

The Summary Report also underwent independent scrutiny by the Editorial Board of the *Journal of Urology*, was accepted for publication in November 1996, and appeared in its May 1997 issue. *A Guide for Parents* and *Evidence Working Papers* have also been developed; both are available from the AUA.

The AUA expresses its gratitude for the dedication and leadership demonstrated by the members of the Pediatric Vesicoureteral Reflux Clinical Guidelines Panel and by the consultants affiliated with Technical Resources International, Inc., in producing this guideline.

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Introduction

Vesicoureteral reflux refers to the retrograde flow of urine from the bladder into the ureter and, usually, into the collecting system of the kidney. In most individuals, reflux results from a congenital anomaly of the ureterovesical junction, whereas in others it results from high-pressure voiding secondary to posterior urethral valves, neuropathic bladder or voiding dysfunction. Between 3–5 percent of girls and 1–2 percent of boys experience a urinary tract infection before puberty (Jodal and Winberg, 1987). Approximately 40 percent of children with a urinary tract infection have reflux (Bourchier, Abbott and Maling, 1984; Drachman, Valevici and Vardy, 1984). Urinary tract infection is the most common bacterial disease during the first 3 months of life (Krober, Bass, Powell, et al., 1985) and accounts for approximately 6 percent of febrile illnesses in infants (Hoberman, Chao, Keller, et al., 1993). Reflux is a predisposing factor for pyelonephritis, which can result in renal injury or scarring, also termed reflux nephropathy. The most serious late consequence of reflux nephropathy is renal insufficiency or end-stage renal disease. Between 3.1–25 percent of children and 10–15 percent of adults with end-stage renal disease have reflux nephropathy (Arant, 1991; Avner, Chavers, Sullivan, et al., 1995; Bailey, Maling and Swainson, 1993). In addition, reflux nephropathy may result in renin-mediated hypertension and cause morbidity in pregnancy (Martinell, Jodal and Lidin-Jason, 1990).

The primary goals in the management of vesicoureteral reflux in children are to prevent pyelonephritis, renal injury and other complications of reflux. Children with reflux may be managed either medically or surgically. The rationale for medical management is prevention of urinary tract infection with daily antimicrobial prophylaxis, regular timed voiding and, in some cases, anticholinergic medication. These children also undergo periodic screening of the urine for infection and radiologic reassessment of the urinary tract for reflux and renal injury. Many children show spontaneous reflux resolution while receiving medical management. Surgical management of reflux consists of repair of the ureterovesical junction abnormality.

Although vesicoureteral reflux is common, there is disagreement regarding the optimal management, even among specialists caring for these children (Elder, Snyder, Peters, et al., 1992; International Reflux Study Committee, 1981). Because of the lack of consensus regarding management of this common condition, the American Urological Association (AUA) convened a panel of experts to develop treatment guidelines for children with vesicoureteral reflux. The panel was charged with the task of producing practice recommendations based primarily on outcomes evidence from the scientific literature. This *Report on the Management of Primary Vesicoureteral Reflux in Children* is the result of the panel's efforts. The panel members represent various geographic areas, ages, professional activities (academic medical centers, private practice, health maintenance organizations) and expertise (pediatric urology, pediatric nephrology), allowing a broad perspective on the management of reflux.

The recommendations in this report are to assist physicians specifically in the treatment of vesicoureteral reflux in children diagnosed following a urinary tract infection. The recommendations apply to children aged 10 years and younger with unilateral or bilateral reflux with or without scarring. The report therefore deals only peripherally with the diagnostic methods of identifying vesicoureteral reflux, renal scarring and management of children with reflux identified incidentally or by screening of asymptomatic siblings. In addition, the report does not pertain to reflux associated with neuropathic bladder, posterior urethral valves, bladder exstrophy or fixed anatomic abnormalities, such as ectopic ureterocele and ectopic ureter.

Because treatment recommendations are made jointly with the parents of the child, *A Guide for Parents,* based on this report, is available to assist the physician in discussing treatment options with the parents. A summary of this report has been published in the *Journal of Urology*, May 1997.

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Executive Summary:

Management of primary vesicoureteral reflux in children

Methodology

In developing recommendations for the management of primary vesicoureteral reflux in children, the AUA Pediatric Vesicoureteral Reflux Guidelines Panel extensively reviewed the available literature on the treatment of pediatric reflux from January 1965 through December 1994 and extracted all relevant data to estimate as accurately as possible desirable and undesirable outcomes of the alternative treatment modalities. The panel followed an explicit approach to the development of practice policies, supplemented by expert opinion. The panel synthesized the evidence using techniques described by Eddy, Hasselblad and Schachter (1992) and Cooper and Hedges (1994). The methodology for these analyses was described by Hasselblad (in press). For a full description of the methodology, see Chapter 2.

Background

Vesicoureteral reflux refers to the retrograde flow of urine from the bladder into the upper urinary tract. Reflux is a birth defect but also may be acquired. Vesicoureteral reflux predisposes an individual to renal infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract. The immunologic and inflammatory reaction caused by a pyelonephritic infection may result in renal injury or scarring. Extensive renal scarring causes reduced renal function and may result in renal insufficiency, end-stage renal disease, renin-mediated hypertension, reduced somatic growth and morbidity during pregnancy.

The primary goals of treatment in children with reflux are to prevent renal injury and symptomatic pyelonephritis. Medical therapy is based on the principle that reflux often resolves with time. The basis for surgical therapy is that, in select situations, ongoing vesicoureteral reflux has caused or has a significant potential for causing renal injury or other reflux-related complications and that elimination of the reflux condition will minimize their likelihood. Chapter 1 documents the various methods of diagnosis, treatment and surveillance and follow-up for children with primary vesicoureteral reflux.

Grading of reflux severity is important because more severe reflux is associated with higher rates of renal injury, and treatment success varies with reflux grade. The International Study Classification is the most common and is the grading system used in this report (International Reflux Study Committee, 1981).

Treatment alternatives and outcomes analysis

The panel considered 7 modalities as treatment alternatives, including:

- No treatment (intermittent antibiotic therapy for UTI);
- Bladder training (including timed voiding and other behavioral techniques);
- Antibiotic prophylaxis (continuous);
- Antibiotic prophylaxis and bladder training;
- Antibiotic prophylaxis, anticholinergics (for bladder instability), and bladder training;
- Open surgical repair; and
- Endoscopic repair.

Outcomes were identified as criteria by which effectiveness of treatment would be analyzed (see evidence matrix on page 21, Chapter 3), and the review of evidence was organized around this framework. The outcomes included intermediate outcomes (those not directly perceived by the patient or family but that are associated with or precede health outcomes), health outcomes (effects directly perceived in some way by patient or family), and harms of various forms of management. The following represents a brief summary of

the statistical analysis that was conducted and that formed the basis of the treatment recommendations.

Intermediate outcomes

Reflux resolution—medical therapy (continuous antibiotic prophylaxis)

The database included 26 reports with data pertaining to reflux resolution after medical therapy, comprising 1,987 patients (1,410 girls and 304 boys273 were not identified) and 2,902 ureters. The individual databases of Skoog, Belman and Majd (1987) and Arant (1992) and the data reported from the International Reflux Study, European Branch (Tamminen-Mobius, Brunier, Ebel, et al., 1992) were used to estimate the probability of reflux resolution with continuous antibiotic prophylaxis (see Figure 3 on page 24, Chapter 3). In general, a lower reflux grade correlated with a better chance of spontaneous resolution. Data for Grades I and II reflux showed no differences in regard to age at presentation or laterality (unilateral vs. bilateral). For Grade III, age and laterality were important prognostic factors, with increasing age at presentation and bilateral reflux decreasing the probability of resolution. Bilateral Grade IV reflux had a particularly low chance of spontaneous resolution. All of these estimates are subject to 2 restrictions: (1) estimates are only valid for up to 5 years after diagnosis; and (2) for Grade IV disease, estimates only apply to the time of diagnosis and are not age specific. No data were available for reflux resolution with intermittent antibiotic therapy.

In children with reflux and voiding dysfunction (frequency, urgency, urge incontinence, incomplete bladder emptying), available results from the series with control groups suggested that the reflux resolution rate increased with anticholinergic therapy and bladder training.

Reflux resolution—surgical therapy

In the articles reviewed by the panel, overall surgical success was reported in 959 of 1,008 patients (95.1 percent) and 7,731 of 8,061 ureters (95.9 percent). Surgical success was achieved in 108 of 109 ureters (99 percent) for Grade I, 874 of 882 (99.1 percent) for Grade II, 993 of 1,010 (98.3 percent) for Grade III, 386 of 392 (98.5 percent) for Grade IV and 155 of 192 (80.7 percent) for Grade V reflux.

For endoscopic therapy, most reports in the literature describe results of the use of polytetrafluoroethylene (Teflon™). Overall reflux was corrected in 77.1 percent of ureters after a single injection. Reflux was resolved after initial treatment in only 6 of 19 ureters (31.6 percent) with Grade V disease. Currently, no injectable substance has been approved for endoscopic antireflux surgery by the U.S. Food and Drug Administration.

Renal scarring

The panel felt that relevant data pertaining to renal scarring should be analyzed primarily from studies with a minimum of 5 years of follow-up. Four prospective trials comparing the outcomes of medical and surgical management included analysis of new renal scarring (Birmingham Reflux Study Group, 1987; Elo et al., 1983; Olbing et al., 1992; Weis et al., 1992). None of these trials showed a statistically significant difference in the rate of new renal scarring. In the European arm of the International Reflux Study, the rate of scarring was similar in patients receiving continuous antibiotic prophylaxis and those treated surgically (Olbing, Claesson, Ebel, et al., 1992). However, 80 percent of the new renal scars in the surgical group appeared by 10 months after randomization, whereas new renal scars appeared throughout the 5 years in the group managed medically (Tamminin-Mobius, Brunier, Ebel, et al., 1992). The Birmingham Reflux Study (1987) identified new scars after 5 years in only 6 percent and 5.2 percent of those treated medically and surgically, respectively, with no additional scars detected after 2 years of follow-up. In the prospective study by the Southwest Pediatric Nephrology Study Group of children younger than 5 years of age with Grades I, II or III reflux, normal kidneys at entry and with continuous antibiotic prophylaxis, 16 percent developed new scars (Arant, 1992). On the other hand, the International Reflux Study found new scars in 15.7 percent (medical) and 17.2 percent (surgical) of refluxing children in Europe and 21.5 percent (medical) and 31.4 percent (surgical) in North America (Olbing, Claesson, Ebel, et al., 1992; Weiss, Duckett and Spitzer, 1992). Few data were available to analyze the relationship between bacteriuria and new renal scarring in children with reflux.

Renal growth and function

On the basis of studies available to date, there is no evidence that renal growth is impaired in unscarred kidneys exposed to sterile reflux of any grade or that surgical correction of reflux facilitates growth of the kidney postoperatively. Surgical

correction of reflux stabilizes the glomerular filtration rate but has not been shown to lead to long-term improvement.

Health outcomes

Urinary tract infection

The panel reviewed 41 articles that described the incidence of urinary tract infection in children with vesicoureteral reflux treated with antibiotic prophylaxis or reimplantation surgery. In children with Grades III to IV reflux, the incidence of pyelonephritis was approximately 2.5 times higher in patients treated with antibiotic prophylaxis than in those treated surgically. The incidence of cystitis in patients with vesicoureteral reflux was not significantly different in patients treated medically or surgically. In children treated medically, recurrent symptomatic urinary tract infections were more common in children with voiding dysfunction than in those with normal bladder function.

Hypertension

In the reports reviewed by the panel, no statistically significant difference was found in the risk of hypertension related to treatment modality. However, these studies indicated that renal scarring increases the relative risk of hypertension to 2.92 (95 percent confidence interval 1.2–7.1), compared to the risk without renal scarring.

Uremia

It was not possible to demonstrate that even optimal treatment of reflux and urinary tract infection can prevent progressive renal failure and ultimately uremia after severe bilateral reflux nephropathy has been diagnosed.

Somatic growth

No evidence substantiated an effect of reflux treatment on somatic growth.

Morbidity during pregnancy

The panel performed a limited search of pertinent literature pertaining to reflux, renal insufficiency and adverse outcomes of pregnancy. Although the available data suggest a greater risk of morbidity from pyelonephritis in women who have persistent reflux during pregnancy, the sample size is small and only limited conclusions can be based on this evidence. The panel reviewed 5 studies that demonstrated that women with renal insufficiency exhibit an increased incidence of toxemia, preterm delivery, fetal growth retardation, fetal loss and deteriorating renal function.

Harms of medical treatment

Adverse drug reactions

Potential adverse reactions to antimicrobial prophylaxis include minor effects, such as skin rash, nausea, vomiting, abdominal pain, a bad taste in the mouth, marrow suppression as well as more serious side effects. Few studies dealing with the medical management of reflux included information on any drug reaction.

Harms of surgery

Obstruction

A total of 33 studies provided rates of obstruction after ureteral reimplantation for reflux. The likelihood of obstruction in the 33 series ranged from 0 to 9.1 percent with a combined rate of 2 percent in studies published after 1986. The reoperation rate ranged from 0.3 to 9.1 percent with an overall prevalence of 2 percent. There was no difference among various surgical techniques.

A total of 15 series provided detailed information about postoperative ureteral obstruction following endoscopic treatment of reflux. The 15 series included refluxing ureters treated using polytetrafluoroethylene or collagen as the injected substance. Seven (0.40 percent) persistent obstructions were reported.

Contralateral reflux

The development of contralateral reflux after unilateral ureteral surgery has been reported in numerous series. Of 1,566 ureters considered at risk there was an overall incidence of 142 reported new cases (9.1 percent) of contralateral reflux. The surgical method of reimplantation did not influence the likelihood of new contralateral reflux. Contralateral reflux generally resolves with time and surgical intervention is not usually recommended for at least 1 year.

Recommendations

The panel generated its practice policy recommendations on the basis of evidence-based outcomes and panel opinion, reflecting its clinical

experience in pediatric urology and pediatric nephrology. In this report, statements based on opinion are explicitly identified, and evidence-based recommendations are accompanied by appropriate references. Only a few recommendations could be derived purely from scientific evidence of a beneficial effect on health outcomes.

As a result, the recommendations were derived from a panel survey of preferred treatment options for 36 clinical categories of children with reflux. The treatment recommendations were classified as guidelines, preferred options and reasonable alternatives. Treatment options selected by 8 or 9 of the 9 panel members are classified as guidelines. Treatment options that received 5 to 7 votes are designated as preferred options, and treatment options that received 3 to 4 votes are designated as reasonable alternatives. Treatments that received no more than 2 votes are designated as having no support.

Assumptions

The recommendations listed on pages 5–7 are intended to assist physicians specifically in the treatment of vesicoureteral reflux in children diagnosed following a urinary tract infection. They apply only to children 10 years and younger with unilateral or bilateral reflux and with or without scarring. The recommendations assume that the patient has uncomplicated reflux (e.g., no voiding dysfunction, neuropathic bladder, posterior urethral valves, bladder exstrophy or fixed anatomical abnormalities).

Rationale for recommendations

Specific treatment recommendations for children with reflux with or without scarring are provided on pages 5–6. The panel's overall recommendations for all children follow. The panel's recommendations to offer continuous antibiotic prophylaxis as initial therapy are based on limited scientific evidence. Controlled studies comparing the efficacy of continuous antibiotic prophylaxis and intermittent therapy on health outcomes in children with reflux have not been performed. However, the opinion of the panel is that maintaining continuous urine sterility is beneficial in reducing the risk of renal scarring and this benefit outweighs the potential adverse effects of antibiotics.

Recommendations to proceed to surgery in children with reflux that has not resolved spontaneously are supported by limited scientific evidence: open antireflux surgery is 95–98 percent effective in correcting reflux, and in children with Grades III–IV reflux the risk of clinical pyelonephritis is 2–2.5 times higher in children treated with continuous prophylaxis than in those treated surgically. Nevertheless, randomized controlled trials of such children have shown that most children treated medically do not develop a urinary tract infection while receiving prophylaxis.

Recommendations for more aggressive treatment of girls than boys (e.g., for persistent Grades III–IV reflux in school-aged children) are based on epidemiological evidence that girls have a higher risk of urinary tract infection than boys. Recommendations for more aggressive treatment of Grade V reflux (e.g., surgical repair as initial therapy) are based on panel opinion that such cases are unlikely to resolve spontaneously over time, surgery is effective in resolving severe reflux and these benefits outweigh the potential harms of surgery. More aggressive recommendations for children who have renal scarring at diagnosis are based on panel opinion that such patients have a higher risk of progressive scarring and decreased renal-functional reserve.

An important variable in the scope of treatment is the presence of voiding dysfunction, a common occurrence among children with reflux. Such children may require more aggressive treatment with anticholinergics and bladder training in addition to antibiotic prophylaxis. Surgical repair of reflux is slightly less successful in children with voiding dysfunction and, thus, a higher threshold is necessary before surgery is recommended in such patients. Consequently, children with reflux should be assessed for voiding dysfunction as part of the initial evaluation.

Literature limitations and research priorities

Limitations of the literature

The panel attempted to rely on published evidence whenever possible. Many studies that addressed a particular issue could not be used quantitatively in the various syntheses because of inconsistent reporting of data, limited follow-up, incomplete description of treatments or poorly defined patient populations. Analyses were also complicated by the existence of at least 5 methods

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Treatment recommendations for children without scarring at diagnosis

Age at diagnosis: Infants (<1 year)

Initial treatment. Infants with Grades I–IV reflux should be treated initially with continuous antibiotic prophylaxis. In infants with Grade V reflux, continuous antibiotic prophylaxis is the preferred option for initial treatment.

Follow-up treatment. In infants who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. For patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic therapy, periodic cystography or surgery. Surgical repair is the preferred option, however, for patients with persistent unilateral Grades III–IV reflux. Patients with persistent bilateral Grades III–IV reflux or Grade V reflux should undergo surgical repair.

Age at diagnosis: Preschool children (ages 1–5 years)

Initial treatment. Preschool children with Grades I–II reflux or unilateral Grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis. Continuous antibiotic prophylaxis is the preferred option in preschool children with bilateral Grades III–IV reflux. In patients with unilateral Grade V reflux, continuous antibiotic prophylaxis is the preferred option for initial treatment, although surgical repair is a reasonable alternative. In patients with bilateral Grade V reflux, surgical repair is the preferred option and continuous antibiotic prophylaxis is a reasonable alternative.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. In children with persistent Grades I–II reflux, there is no consensus regarding the role of continued antibiotic therapy, periodic cystography or surgery. Surgery is the preferred option for children with persistent Grades III–IV reflux. Patients with persistent Grade V reflux should undergo surgical repair.

Age at diagnosis: School children (ages 6–10 years)

Initial treatment. School children with Grades I–II reflux should be treated initially with continuous antibiotic prophylaxis. Continuous antibiotic prophylaxis is the preferred option for initial treatment of patients with unilateral Grades III–IV reflux. In patients with bilateral Grades III–IV reflux, surgical repair is the preferred option, although continuous antibiotic prophylaxis is a reasonable alternative. Patients with Grade V reflux should undergo surgical repair.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography or surgery. Surgery is the preferred option for persistent reflux in children with Grades III–IV reflux.

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Treatment recommendations for children with scarring at diagnosis

Age at diagnosis: Infants (<1 year)

Initial treatment. Infants with scarring at diagnosis and Grades I–IV reflux should be treated initially with continuous antibiotic prophylaxis. In infants with Grade V reflux and scarring, continuous antibiotic prophylaxis is the preferred option for initial treatment, and surgical repair is a reasonable alternative.

Follow-up treatment. In infants who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography or surgery. In boys with persistent unilateral Grades III–IV reflux, surgical repair is the preferred option. Boys with persistent bilateral Grades III–IV reflux, girls with persistent Grades III–IV reflux, and boys and girls with persistent Grade V reflux should undergo surgical repair.

Age at diagnosis: Preschool children (ages 1–5 years)

Initial treatment. Preschool children with scarring at diagnosis and either Grades I–II reflux or unilateral Grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis. Antibiotic therapy is the preferred option in children with bilateral Grades III–IV reflux and scarring, and surgical repair is a reasonable alternative. Surgery is the preferred option for patients with unilateral Grade V reflux. Patients with bilateral Grade V disease and scarring should undergo surgical repair as initial treatment.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography or surgery. Girls with persistent Grades III–IV reflux and boys with persistent bilateral Grades III–IV reflux should undergo surgical repair. Surgery is the preferred option for boys with persistent unilateral Grades III–IV reflux. For patients with persistent Grade V reflux who have not undergone surgery as initial treatment, surgical repair is the preferred option.

Age at diagnosis: School children (ages 6–10 years)

Initial treatment. School children with scarring at diagnosis and Grades I–II reflux should be treated initially with continuous antibiotic prophylaxis. In children with unilateral Grades III–IV reflux and scarring, antibiotic therapy is the preferred option. Patients with bilateral Grades III–IV reflux or Grade V reflux should undergo surgical repair as initial treatment.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued. In patients who have persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography or surgery. Patients with persistent unilateral Grades III–IV reflux who have not undergone surgery as initial treatment should undergo surgical repair.

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Other recommendations for children with reflux

In children with vesicoureteral reflux, urethral dilation and internal urethrotomy are not beneficial. In addition, cystoscopic examination of the ureteral orifices does not appear to aid in predicting whether reflux will resolve. In children with symptoms of voiding dysfunction, urodynamic evaluation may be helpful, but evocative cystometry is unnecessary in children with reflux and a normal voiding pattern.

In children with reflux who are toilet trained, regular, volitional low-pressure voiding with complete bladder emptying should be encouraged. If it is suspected that the child is experiencing uninhibited bladder contractions, anticholinergic therapy may be beneficial.

The clinician should provide parents with information about the known benefits and harms of available options, including continuous antibiotic prophylaxis, surgery and intermittent antibiotic therapy. The clinician should indicate to what extent the estimates of benefits and harms are based on scientific evidence or on opinion and clinical experience. Given the general lack of direct evidence that any one treatment option is superior to another (especially when total benefits, harms, costs and inconvenience are considered), parent and patient preferences regarding treatment options should generally be honored.

In children for whom antireflux surgery is chosen, the panel does not recommend the endoscopic form of therapy because of the lack of proven long-term safety and efficacy of the materials used for injection and the lack of approval of such materials by the U.S. Food and Drug Administration.

Follow-up evaluation should be performed at least annually, at which time the patient's height and weight should be recorded and a urinalysis should be performed. If the child has renal scarring, the blood pressure should be measured. In deciding how often to obtain follow-up cystography in children managed medically, the clinician should take into consideration the likelihood of spontaneous resolution (see Figure 3 on page 24, Chapter 3), the risk of continued antibiotic prophylaxis and the risks of radiologic study. In general, cystography does not need to be performed more than once per year.

used for grading reflux, nonuniformity in characterizing reflux grade and patient population, and lack of a standard method for reporting outcomes. Only 3 prospective randomized controlled trials compared medical to surgical therapy—the Birmingham Reflux Study (1987), the International Reflux Study in Children (Olbing, Claesson, Ebel, et al., 1992; Weiss, Duckett and Spitzer, 1992), and a study from Erasmus University, Rotterdam, The Netherlands (Scholtmeijer, 1991). The literature on certain issues, such as complication rates of surgery and adverse drug reactions, was limited and in some cases so sparse that judgments were made on the basis of expert opinion.

Research priorities

The panel identified many research areas as needing further investigation. Presently, there is little information regarding health outcomes pertaining to reflux, and a significant priority should be to continue to acquire this information.

Basic research into the pathogenesis as well as the genetics of vesicoureteral reflux is needed. Further randomized controlled trials studying the role of medical and surgical therapy using dimercaptosuccinic acid scan for evaluation of renal scarring are indicated. Future studies should stratify results by patient gender, age and reflux grade, reporting reflux resolution both by rate of ureteral and patient resolution. Also worthwhile would be studies to confirm the panel's finding that resolution of Grade III reflux depends on patient age or laterality (unilateral vs. bilateral) and the finding that resolution of Grades I and II reflux does not depend on age or laterality.

The extent to which reflux increases the risk of renal scarring associated with urinary tract infection and the mechanism of this effect deserves investigation. Comparison of the efficacy of intermittent and continuous antibiotic therapy would be beneficial. The role of voiding dysfunction in the pathogenesis of reflux and its risk on reflux complications, such as renal scarring and the complications of surgery, also deserve further investigation. Matched controlled studies of anticholinergic therapy and bladder training on reflux-related outcomes in children with voiding dysfunction are necessary.

Less traumatic methods of determining whether reflux is present should be developed as well as techniques of voiding cystourethrography that result in less radiation exposure. Analysis of the costs of reflux treatment and surveillance is important, particularly comparing those associated with medical and surgical therapy. The impact of screening at-risk populations and early medical or surgical intervention on reflux-related outcomes in such patients should be analyzed.

Development of minimally invasive techniques of antireflux surgery is indicated. Newer materials that can be used for endoscopic subureteral injection and that are safe in children should be studied.

The natural history of vesicoureteral reflux in adult women with persistent reflux deserves investigation, including an analysis of the morbidity of persistent reflux, and need for and efficacy of prophylaxis in pregnant and nonpregnant women.

Chapter 1:
Pediatric vesicoureteral reflux and its management

Background

Vesicoureteral reflux (VUR or "reflux") refers to the retrograde flow of urine from the bladder into the upper urinary tract. Normally, the ureter is attached to the bladder in an oblique direction, perforating the bladder muscle (detrusor) laterally and proceeding between the bladder mucosa and detrusor muscle (the "intramural" or submucosal tunnel) before entering the bladder lumen. As the bladder fills, the ureteral lumen is flattened between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents VUR. Reflux occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent and/or there is weak detrusor backing (Figure 1, page 10). In general, the severity of reflux correlates with the degree of deformity of the ureterovesical junction. Reflux is usually a birth defect. In some cases, reflux will disappear as the child grows. Reflux was described in the writings of Galen (Polk, 1965) and da Vinci (Lines, 1982). It was not until the observations of Hutch in 1952, however, that the relationship between reflux and acute pyelonephritis was appreciated (Hutch, 1952).

VUR predisposes an individual to renal infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract. The inflammatory reaction caused by a pyelonephritic infection may result in renal injury or scarring. Extensive renal scarring impairs renal function and may result in renin-mediated hypertension, renal insufficiency, end-stage renal disease (ESRD), reduced somatic growth, and morbidity during pregnancy.

VUR may be primary or secondary. Primary VUR refers to reflux resulting from an anatomic deformity of the ureterovesical junction without a causative urinary tract abnormality that may cause reflux. Secondary VUR can result from increased bladder pressure (e.g., detrusor-sphincter discoordination, neuropathic bladder, posterior urethral valves), which destabilizes the ureterovesical junction; abnormal attachment of the ureter (ectopic ureter); or associated lower urinary tract abnormalities (e.g., ectopic ureterocele, prune belly syndrome, bladder exstrophy) that affect ureteral insertion.

The prevalence of reflux in healthy children is unknown but is estimated to be 1 percent (Arant, 1991). In 1993, in the United States approximately 15,000 individuals under 15 years of age were admitted to the hospital for a total of 62,000 days for treatment of pyelonephritis, and reflux was present in approximately 40–50 percent of these patients (U.S. Department of Health and Human Services, 1993).

Approximately 44,000 children are treated (inpatient and outpatient) for urinary tract infection (UTI) associated with VUR each year in the United States (Woodwell, 1993). Woodwell (1993) observed that of the 9.8 million outpatient visits made to urologists annually, 492,000 (5 percent of urologic practice) involve the health of children under age 15. Of these children seen for a variety of urinary complaints, 369,000 were boys and 123,000 were girls under 15 years. Other data (based on the 9.8 million reported visits) suggested that voiding symptoms, urine abnormalities, painful urination, enuresis, bladder symptoms, and UTI (all symptoms not initially related to a diagnosis of VUR) account for 3 million visits to urologists and represented 25.6 percent of symptoms requiring evaluation. Assuming uniform distribution of these complaints within urologic practice, 125,952 visits ($492{,}000 \times 0.256 = 125{,}952$) to urologists caring for children would encompass the symptoms listed above. Data from Lindberg, et al. (1975) estimate that 20 percent of symptomatic individuals will have reflux; therefore, 25,190 visits a year to urologists would include encounters for care and assessment of reflux ($125{,}952 \times 0.2 = 25{,}190$). Health Care Financing Administration data indicate that VUR is diagnosed in 7,000–14,000 hospitalized patients, and that 2 to 3 times as many children are seen as outpatients for evaluation and treatment of reflux.

The typical patient with VUR is a child younger than 10 years old who develops a UTI, either clinical pyelonephritis with fever, abdominal/flank pain, malaise and/or nausea, vomiting, or cystitis

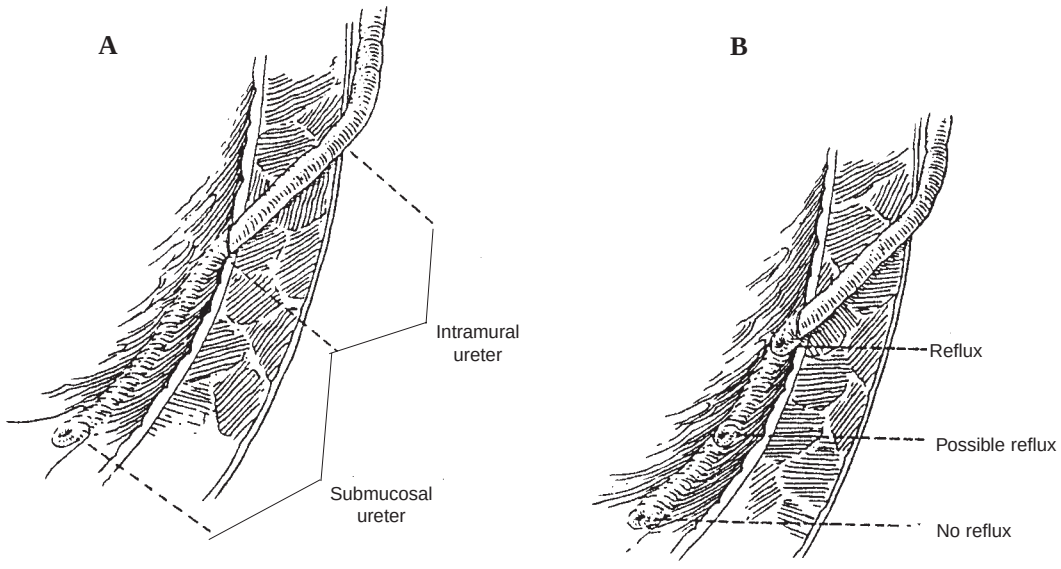

Figure 1. (A) Normal ureterovesical junction. Demonstration of length of intravesical submucosal ureteral segment. (B) Refluxing ureterovesical junction. Same anatomic features as nonrefluxing orifice, except for inadequate length of intravesical submucosal ureter, are shown. Some orifices reflux intermittently with borderline submucosal tunnels (Politano, 1975).

with dysuria, frequency, urgency, and often urge incontinence. Neonates and infants with VUR and pyelonephritis may have nonspecific symptoms.

The average age for diagnosis of reflux in children is 2–3 years. Approximately 75–80 percent of children with primary reflux diagnosed following a UTI are girls, presumably because the incidence of UTI in girls is greater than in boys after 6 months of age. The mean age for the onset of UTI in children is 2–3 years, corresponding to the average age when toilet training occurs. It is thought, by some, that during the process of toilet training, bladder-sphincter dyssynergia occurs, which predisposes to UTI, allowing children who also have VUR to be diagnosed.

A substantial proportion of children with VUR have incomplete maturation of bladder function, with symptoms of bladder instability characterized by urgency, frequency, and diurnal incontinence (van Gool, Hjalmas, Tamminen-Mobius, et al., 1992; Koff, 1992). Because the associated high intravesical pressures can contribute to reflux, assessment of voiding habits is important in evaluating children with VUR.

In recent years, reflux has been discovered prenatally by detection of fetal hydronephrosis, although the diagnosis of VUR is not made until postnatal studies are performed. Approximately 80 percent of these neonates are boys (Elder, 1992), and most have more severe reflux than do females with VUR discovered after UTI. This phenomenon may result from higher voiding pressures in male infants (and presumably fetuses) than in females (Hjalmas, 1976; Sillen, Bachelard, Hermanson, et al., 1996).

Reflux appears to be an inherited trait. For example, in 1 study of 354 siblings of 275 known patients with prior diagnosis of reflux, 34 percent had reflux, and 75 percent of these children were asymptomatic (Noe, 1992). In that study, 13 percent of siblings with reflux already had evidence of renal scarring, and 66 percent of these children had not had a documented UTI. In addition, as many as 67 percent of offspring of women with reflux also have reflux (Noe, Wyatt, Peeden, et al., 1992). Reflux is less common in African-American than in caucasian children (Skoog and Belman, 1991).

Reflux severity can be graded (Figure 2). Reflux grade is important because more severe reflux is associated with higher rates of renal injury, and treatment success varies with reflux grade. In addition, the reflux grade is an indirect indication of the degree of abnormality of the ureterovesical junction. Numerous grading systems have been used.

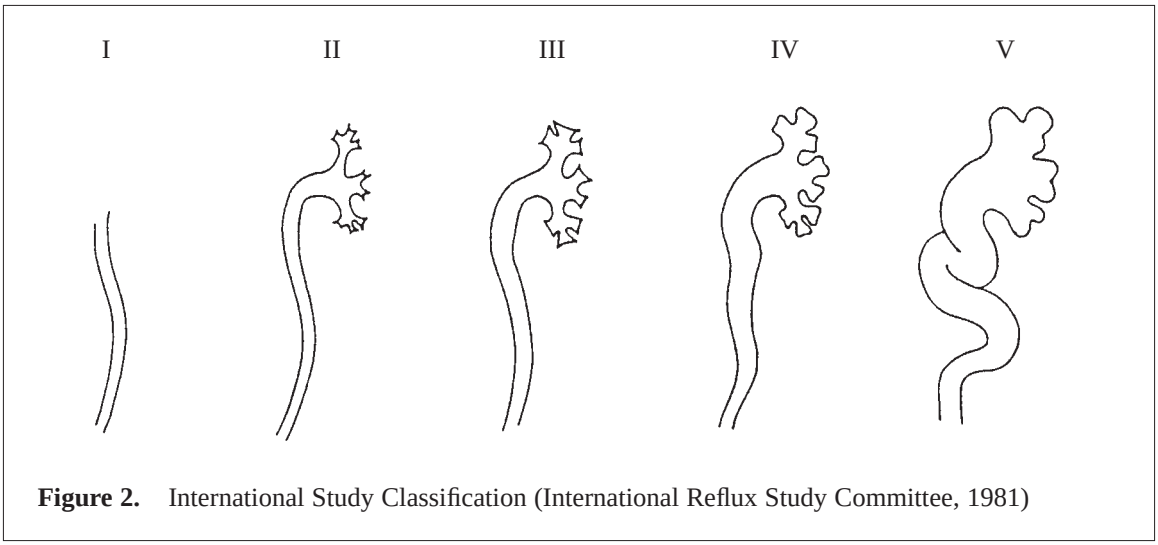

Figure 2. International Study Classification (International Reflux Study Committee, 1981)

The most common classifications are shown in Table 1. These classifications are based on a standard contrast voiding cystourethrogram. The International Study Classification, which was adopted by the International Reflux Study Committee in 1981, is the most common and is the grading system used in this report.

Pathophysiology of renal injury

The likelihood of renal injury after a UTI depends on bacterial virulence factors, the presence or absence of reflux, adherence characteristics of the uroepithelium, anatomic characteristics of the infected kidney, and host inflammatory response. During infection, certain bacteria, particularly those with P-fimbria, may ascend the ureter and enter the renal pelvis and calyces. Bacterial ascent is promoted by the presence of reflux. Intrarenal reflux (reflux from the minor calyx into the collecting duct) of infected urine results in renal parenchymal infection (pyelonephritis). In previously normal kidneys, this initial infection often occurs in the upper or lower poles, because these typically contain compound papillae that favor intrarenal reflux (Ransley and Risdon, 1979). Bacteria often produce an endotoxin, which causes a cellular and humoral immune response as well as an inflammatory response (Roberts, 1992). The sequel of the host reaction is renal parenchymal fibrosis, a renal injury termed reflux nephropathy.

Table 1. Common classifications of vesicoureteral reflux

Description	Grade/classification					
International Study Classification[1]	0	I	II	III	IV	V
Dwoskin-Perlmutter	0	1	2a	2b	3	4
Birmingham	0	1	2	←	3 →	
Australia/NZ		← Mild →		Moderate	← Severe →	
Great Britain		I	II (Voiding)	III (Filling and voiding)		IV (Dilatation)

[1] Classification used in this Report.

Reflux is an important risk factor for developing pyelonephritis. Pyelonephritis occurs in children with and without VUR, as well as in children in whom reflux has resolved spontaneously and in children whose reflux is undetected on a voiding cystourethrogram. In children who develop pyelonephritis, renal scarring results in as many as 40 percent (Rushton and Majd, 1992). Children younger than 5 years old appear to be at greatest risk of renal injury from pyelonephritis, but older children also may develop renal scarring. In 1 report of 34 children older than age 5 who had normal kidneys and who later developed renal scarring, nearly all had both UTI and reflux (Smellie, Ransley, Normand, et al., 1985).

In the neonate with prenatally diagnosed hydronephrosis, medium- or high-grade reflux often is diagnosed. In some of these neonates, typical patterns of renal scarring are found even though no bacteriuria is present. The cause of the renal abnormality is uncertain but may be secondary to abnormal induction of the metanephric blastema by the ureteral bud (Mackie and Stephens, 1975) and/or possibly high voiding pressures during renal development.

Although reflux associated with bacteriuria may cause renal scarring, sterile VUR is not thought to result in renal injury unless abnormally elevated bladder pressures exist (i.e., with posterior urethral valves, neuropathic bladder, bladder outlet obstruction, or detrusor-sphincter dyssynergia) (Ransley and Risdon, 1979).

Diagnosis

In most cases, reflux is diagnosed during evaluation of a UTI. In some cases reflux is diagnosed "incidentally" during screening of patients at risk, for example, those who have a sibling with reflux (Noe, 1992; Wan, Greenfield, Ng, et al., 1996), a mother with reflux (Noe, Wyatt, Peeden, et al., 1992), a multicystic kidney (Selzman and Elder, 1995) or hydronephrosis (Elder, 1992).

The panel did not undertake a formal evaluation of the radiologic literature regarding the accuracy of various methods of diagnosing reflux or detecting upper urinary tract changes secondary to or associated with reflux, because these considerations were deemed outside the scope of treatment guidelines in a child with VUR.

Diagnosis of VUR requires catheterization of the bladder, instillation of a solution containing iodinated contrast or a radiopharmaceutical and radiologic imaging of the lower and upper urinary tract, termed a voiding cystourethrogram (VCUG) or radionuclide cystogram, respectively. The bladder and upper urinary tracts are imaged during bladder filling and voiding. Reflux occurring during bladder filling is termed low-pressure or passive reflux, and reflux occurring during voiding is termed high-pressure or active reflux. Children with passive reflux are less likely to show spontaneous reflux resolution than children who exhibit only active reflux (Mozley, Heyman, Duckett, et al., 1994). Radiation exposure during radionuclide cystography is less than with standard contrast cystography. In the past, many children underwent cystography under general anesthesia. However, this method is flawed because normal micturition does not occur under anesthesia. Other methods for detecting reflux, such as indirect cystography and renal ultrasound, are thought to be less accurate (Blane, DiPietro, Zerin, et al., 1993; de Sadeleer, de Boe, Keuppens, et al., 1994).

Assessment of upper urinary tract

The goal of upper tract imaging is to assess whether renal scarring and associated urinary tract anomalies are present. In a child with VUR, the upper urinary tract can be evaluated by one of several techniques, including renal cortical scintigraphy (renal scan), excretory urography (intravenous pyelography, or IVP), and renal ultrasound. Radiopharmaceuticals used for renal scanning include dimercaptosuccinic acid (DMSA), glucoheptonate, and mercaptoacetyltriglycine (MAG-3). On an IVP, renal scarring is evident from reduction in the thickness of the renal cortex. Several specific patterns of renal scarring have been described (Smellie, Edwards, Hunter, et al., 1975). Renal sonography, a noninvasive method of evaluating the kidney, can show hydronephrosis, renal duplication with an obstructed upper pole and gross renal scars. The surface areas of the kidney on renal sonography roughly correlate with differential renal function (Sargent and Gupta, 1993).

Following an episode of pyelonephritis, renal scarring usually is apparent on scintigraphy within 3 months, but may not be apparent on an IVP or sonography until 1–2 years later.

Assessment of lower urinary tract

The goal of lower urinary tract assessment is to determine whether the bladder empties satisfactorily, whether a bladder abnormality such as a paraureteral diverticulum is present, and in males, to assure that no bladder outlet obstruction such as posterior urethral valves is present. This information is often obtained from the voiding cystourethrogram. At times, bladder trabeculation may be present and suggest that voiding dysfunction is present. Cystoscopic examination of the ureteral orifices has not been helpful in predicting whether spontaneous resolution of a child's reflux is likely (Bellinger and Duckett, 1984; Mulcahy and Kelalis, 1978). Evocative cystometry also does not appear to provide useful information in children with normal voiding function. However, urodynamics may be beneficial in children with voiding dysfunction.

Treatment methods

The primary goals of treatment in children with reflux are to prevent pyelonephritis, renal injury and other complications of reflux. Medical therapy is based on the principle that VUR often resolves over time, and that the morbidity or complications of reflux may be prevented nonsurgically. The basis for surgical therapy is that in selected situations, ongoing VUR has caused or has a significant potential for causing renal injury or other reflux-related complications and that elimination of reflux will minimize the likelihood of these problems. The 7 treatment modalities for VUR considered by the panel follow:

- No treatment (intermittent antibiotic therapy for UTI);
- Bladder training (including timed voiding and other behavioral techniques);
- Antibiotic prophylaxis (continuous);
- Antibiotic prophylaxis and bladder training;
- Antibiotic prophylaxis, anticholinergics (for bladder instability), and bladder training;
- Open surgical repair; and
- Endoscopic repair.

Neither urethral dilation nor urethrotomy have been found to be beneficial in the treatment of children with reflux (Forbes, Drummond, and Nogrady, 1969; Hendrey, Stanton, and Williams, 1973; Kaplan, Sammons, and King, 1973).

No treatment

This management modality involves treating patients with UTI with antibiotics at each occurrence. The philosophy of this therapy is that prompt diagnosis and treatment of UTI will eliminate or minimize the risk of reflux-associated renal infection. Because the continuous antibiotic prophylaxis approach has been used in recent years, few data are available on the intermittent treatment approach.

Bladder training

Bladder training refers to regular, volitional, complete emptying of the bladder through behavioral conditioning to achieve balanced, low-pressure voiding with coordinated relaxation of the external sphincter and pelvic floor during voiding. Measures include a voiding schedule (e.g., every 2–3 hours), complete emptying of the bladder during micturition, re-education in proper voiding dynamics if voiding dysfunction is present, and elimination of constipation. The practice also includes genital and perineal hygiene. The goal of bladder training is to reduce the likelihood of developing UTI and reduce voiding pressure. Infrequent voiding, detrusor-sphincter dyssynergia, and constipation can increase the likelihood of bacteriuria (Smith and Elder, 1994).

Antibiotic prophylaxis

Continuous antibiotic prophylaxis has become the cornerstone in the initial management of patients with reflux. This form of therapy is based on the observations of Lenaghan, Whitaker, Jensen, et al. (1976), who reported that 21 percent of previously normal refluxing kidneys showed scarring on follow-up with intermittent antibiotic therapy, and Smellie, Edwards, Hunter, et al. (1975), who found that children on continuous antibiotic prophylaxis who were kept free of infection did not develop new renal scarring.

Drugs commonly used for prophylaxis include sulfamethoxazole-trimethoprim, trimethoprim alone, and nitrofurantoin, generally administered once daily at a dose calculated to be one-fourth to one-third of the dose necessary to treat an acute infection (Birmingham Reflux Study Group, 1987; Cardiff-Oxford Bacteriuria Study Group, 1978;

Goldraich and Goldraich, 1992; Hannerz, Wikstad, Celsi, et al., 1989; Hanson, Hansson, and Jodal, 1989; Pinter, Jaszai, and Dober, 1988; Smellie, Gruneberg, Bantock, et al., 1988). Prophylaxis usually is continued until reflux resolves or until the risk of reflux to the individual is considered to be low. Many clinicians treating children with reflux obtain urine specimens periodically for urinalysis and/or culture, although the frequency of urine sampling varies widely (Elder, Snyder, Peters, et al., 1992).

Medical management with antibiotic prophylaxis is considered to be successful if the child remains free of infection, develops no new renal scarring, and the reflux resolves spontaneously. On the other hand, breakthrough UTI, the development of new renal scars, or failure of reflux to resolve would be considered failure of medical management. Noncompliance (Smyth and Judd, 1993), allergic reaction, or side effects to the prescribed medication may preclude medical management or lead to its failure.

Antibiotic prophylaxis and bladder training

Many clinicians emphasize the principles of bladder training when placing children with VUR on antimicrobial prophylaxis. Most studies in the literature do not specify whether attention to bladder training was emphasized in the treatment plan, and assessment of the contribution of bladder training to outcome has not been studied in any controlled trials.

Antibiotic prophylaxis, anticholinergics and bladder training

Before toilet training, voiding is an automatic process. During toilet training, however, children may demonstrate a discoordinated pattern, with incomplete relaxation of the external sphincter during voiding, resulting in high intravesical pressure and incomplete bladder emptying. The terms bladder instability, uninhibited bladder contractions, and pediatric unstable bladder refer to reflex detrusor contractions at low bladder volumes. Children with bladder instability typically experience frequency, urgency, and urge incontinence, and girls with this condition may cross their legs or squat down to try to avoid incontinence. Anticholinergic medication, in conjunction with timed voiding, is thought to improve the symptoms of dysfunctional voiding. Typical anticholinergic medications (also often classified as antimuscarinic/antispasmodic agents) include oxybutynin chloride, propantheline bromide, and hyoscyamine.

Open surgical repair

Open surgical management involves modifying the abnormal ureterovesical attachment to create a 4:1 to 5:1 ratio of length of intramural ureter to ureteral diameter. Numerous techniques have been described, and each has undergone minor modifications. The primary techniques evaluated by the panel include intravesical operations, including the Politano-Leadbetter (Politano and Leadbetter, 1958), Glenn-Anderson (Glenn and Anderson, 1967), Cohen transtrigonal (Cohen, 1975) and Paquin and Gil-Vernet procedures, and extravesical operations, including the Lich-Gregoir procedure (Gregoir, 1974) and detrusorrhaphy (Zaontz, Maizels, Sugar, et al., 1987). Surgical techniques for management of children with refluxing megaureter and reflux associated with ureteral duplication were evaluated separately. Studies dealing with laparoscopic correction of reflux, bladder neck plasty/Y-V plasty, and nephrectomy or partial nephrectomy as management for reflux were not reviewed.

Endoscopic repair

The technique of endoscopic injection of polytetrafluoroethylene paste (polytef, Teflon™), for the correction of VUR was reported in 1986 by O'Donnell and Puri (1986). The technique involves injecting 0.1–1 ml of polytef paste into the submucosa deep to the affected ureter. The injected bolus provides a firm buttress against which the ureteric roof may be compressed with rising intravesical pressure. This operative procedure, termed the "STING" (subtrigonal injection) has become very popular, particularly in Europe, because it is less invasive than open surgical techniques and can be performed as an outpatient procedure under general anesthesia. If the initial injection fails to correct reflux, the procedure can be repeated. Polytef is an inert material, yet the long-term safety of this foreign material in the bladder has not been documented (Aaronson, 1995; Puri, 1995). Furthermore, polytef has not been approved by the U.S. Food and Drug Administration for use in the treatment of reflux.

Another substance that has been used for endoscopic therapy is cross-linked bovine collagen (Leonard, Canning, Peters, et al., 1991). Other materials for injection currently under investigation

include autologous collagen, a mixture of cross-linked dextran and hyaluronadan, polyvinyl alcohol foam (Ivalon), polydimethylsiloxane, blood, fat, chondrocytes embedded in biodegradable polymer, bioactive glass, and detachable balloons. The panel did not review studies focusing on the use of these materials. Until an injectable substance is developed with acceptable known risks, open surgical correction of reflux remains the surgical treatment of choice. Nevertheless, the appeal of a safe and effective outpatient procedure for the correction of reflux will undoubtedly continue to stimulate investigation of this technique.

Surveillance and follow-up

In a child with VUR, periodic surveillance is generally recommended to monitor for UTI, because the complications of reflux often occur when infection is present. No guidelines exist for frequency of monitoring (e.g., monthly, every 3 months) or type of surveillance (urine dipstick, dipstick with microscopy, urine culture, or a combination) (Elder, Snyder, Peters, et al., 1992). If the child has symptoms of a UTI, a urine culture should be performed, even if the urinalysis is normal.

Follow-up radiologic testing is performed to monitor the status of reflux, that is, whether it is present (worse, improved, no change) or absent. In addition, studies to determine whether renal injury has occurred may also be performed. In children undergoing medical or surgical therapy, no guidelines exist for frequency or type of follow-up (Elder, Snyder, Peters, et al., 1992).

In a child receiving medical therapy, follow-up cystography is generally performed every 12–18 months. The radionuclide cystogram is preferred by many, because the radiation dose to the gonads is significantly lower than that with a standard contrast cystogram (Conway, King, Belman, et al., 1972). The 2 techniques are sufficiently dissimilar, therefore, the assessment of reflux severity may not be comparable. With digital fluoroscopy equipment and a “tailored” or individualized contrast cystogram performed by a pediatric radiologist, the radiation dose also is significantly lower than that with a standard VCUG (Kleinman, Diamond, Karellas, et al., 1994). In a child with reflux that appears to have resolved spontaneously by cystography, as many as 20 percent might show reflux if the study were repeated in 1 year (Arant, 1992). Most clinicians do not obtain a second cystogram, unless recurrent urinary tract infections have occurred. In addition, periodic upper tract imaging studies (ultrasound, IVP, renal scintigraphy) are often performed, although the ability of these tests to detect renal scarring and growth is variable. In a child treated surgically, follow-up lower and upper tract studies are generally performed at least one time to assess the success of the surgical procedure and to determine whether any complications have occurred.

The panel did not perform an assessment of the accuracy of these tests, nor is there any agreement on the effect these tests have on outcomes. Such studies do, however, document the status of the reflux problem.

Chapter 2: Methodology

The AUA Pediatric Vesicoureteral Reflux Panel developed the recommendations in this *Report on the Management of Primary Vesicoureteral Reflux in Children* following an explicit approach to the development of practice policies (Eddy, 1992) supplemented by expert opinion. The explicit approach provides mechanisms that take into account the relevant factors for making selections from alternative interventions. The use of scientific evidence in estimating the outcomes of intervention is emphasized.

To develop recommendations for this report, the panel undertook an extensive review of the literature on vesicoureteral reflux and extracted data.

The panel reviewed the evidence tabulated in the database and focused attention on randomized, controlled studies wherever possible. The level of availability and quality of the data from which outcomes could be estimated are displayed on the evidence matrix on page 21.

Expert opinion was polled by questionnaire or survey in a blinded fashion when scientific evidence was lacking. The panel generated its practice policy recommendations on the basis of evidence-based outcomes and on expert opinion. In this report, statements based on opinion are explicitly identified, and evidence-based recommendations are accompanied by appropriate references. The recommendations were derived from a survey of preferred treatment options for 36 clinical categories of children with reflux. The treatment recommendations were classified as follows:

- **Guidelines:** Treatment recommendations selected by 8 or 9 of the 9 panel members are classified as guidelines and are strongly worded using "should"; e.g., "Children with Grade V reflux should undergo surgical repair."
- **Preferred options:** Treatment recommendations that received 5 to 7 votes are worded with this classification.
- **Reasonable alternatives:** Treatment recommendations that received 3 to 4 votes are worded with this classification.
- **No consensus:** Treatment recommendations that received no more than 2 votes are worded with this classification and are not to be considered recommendations.

Literature search

The reference database was developed from MEDLINE literature searches encompassing the period January 1965 through December 1994. The search strategy was all-inclusive, using vesico-ureteral-reflux as the major or minor medical subject heading (MeSH keyword). It was important to use this specific form of vesico-ureteral-reflux because similar alternatives (e.g., vesicoureteric reflux) do not capture all reflux articles. All of the citations were imported into a Papyrus Bibliography System (Research Software Design, Portland, OR) and assigned a Papyrus Reference Number. Articles were accepted on the basis of specific criteria (outlined on page 17), as well as the interpretability of the data and inclusion of new data (relative to older published reports updating ongoing studies). A total of 3,207 references were retrieved and reviewed. Of these, 413 (13 percent) were selected for initial panel review. From this group, 168 were accepted for analysis (5.2 percent of initially retrieved articles). Bibliographies of reflux literature from 1960–1965 were reviewed manually to identify any relevant articles that would not have been retrieved electronically; however, no articles from which data could be extracted were identified in this manner. The articles from which outcomes data were extracted are listed in Table A-1 (Appendix A) and are the basis for the panel's analysis of vesicoureteral reflux.

Evidence on some outcomes was reviewed from selected articles that were not analyzed systematically, due to the nature of the material or the lack of a significant number of adequate articles. These areas included the impact of reflux on pregnancy, hospitalization due to antireflux surgery and due to pyelonephritis, adverse drug reactions, adverse effects of surveillance testing, and other surgical harms.

Article selection and data extraction

After identifying articles from the literature search, the panel reviewed the abstracts and selected relevant citations for data extraction. Criteria for admissible evidence included (1) English language and (2) peer-reviewed studies of primary VUR in children younger than 10 years old. The initial exclusions were based on article title, keywords (other than vesicoureteral reflux) or review of the abstract, if present. Specific exclusion criteria included review articles, non–English language studies, non–peer-reviewed studies, older duplicate studies, animal studies, adult studies, case reports with fewer than 5 patients, laboratory studies, studies without treatment outcomes, studies of secondary reflux, letters, editorials, and data from unpublished material.

Each article was accepted for inclusion or rejected on the basis of the treatment outcome data it contained. Inclusion or exclusion of each article was verified by 2 panel members in consultation with the panel chair. Articles were rejected by consensus of the 2 reviewers and the panel chair. Two individual panel members extracted data from each accepted article, and the data were tabulated on the data retrieval form developed by the panel (Appendix B). Each data retrieval sheet was reviewed by the panel chair, providing triple review for each article. Figures A-1–A-4 (Appendix A) list the articles reviewed and accepted by year, the source of the articles, the type of study for the accepted articles, and the reason for article rejection. From this review, reports were accepted for inclusion in the working bibliographic database.

The data were entered into a FoxPro™ (Microsoft Corp.) database. All computer entries were reviewed to ensure accuracy. The tabulated data were categorized according to the pediatric vesicoureteral reflux evidence matrix to facilitate review and to identify areas where limited or no data exist.

Limitations of the literature

The panel attempted to rely on published evidence whenever possible. Many studies that addressed a particular issue could not be used quantitatively in the various syntheses because of inconsistent reporting of data, limited time of follow-up, incomplete description of treatments utilized, or poorly defined patient populations. In addition, many of the datasets that were extracted still contained some deficiencies. Practical problems were encountered in analysis of the scientific literature as follows:

- Only 3 prospective randomized controlled trials (RCTs) compared medical with surgical therapy: the Birmingham Reflux Study, the International Reflux Study in Children, and a study from Erasmus University, Rotterdam, The Netherlands. The strongest evidence for the comparison of efficacy of treatments comes from these RCTs. Because even RCTs can have methodological problems, additional analyses were conducted on cohort studies for selected issues. In general, the results from these analyses were consistent with those of the RCTs.
- At least 5 different methods are used for grading reflux (see Table 1, page 11). The International Study Classification is currently the most common method for reporting data on reflux, and the Dwoskin-Perlmutter System corresponds closely to this grading system. The other systems tend to combine higher reflux grades, frequently making it difficult to extract outcomes data for specific grades of reflux.
- Many studies did not report outcomes by separate reflux grade, and instead combined various grades. Often, the results were not broken down by initial grade of reflux. In some cases, an attempt was made to adjust for this statistically; in other cases, the results were excluded from the analyses. (See Appendix C.)
- Although reflux is diagnosed more frequently in girls than in boys and the sequelae of reflux may be different in girls and boys, most outcomes were not reported separately by patient gender. The literature and data available suggested no difference in resolution by gender.
- No standard method was used for reporting outcomes in children with reflux. Some studies reported selected outcomes on reflux by patient grade, and other studies reported outcomes by ureteral grade. Some studies reported demographic data by patient data and outcome by ureteral data, or vice versa. Consequently, the panel had to assess which information was more important. For example, are patients with unilateral Grade II or III reflux more likely to show

reflux resolution than those with bilateral Grade II or bilateral Grade III reflux? Are patients with bilateral reflux, Grade IV on one side and Grade III on the other, as likely to show reflux resolution as patients with Grade IV reflux on one side and Grade I or II reflux on the other side?

- In series reporting outcomes of surgical correction of reflux, the duration of follow-up tended to be shorter than that in series of medical therapy. Thus, determining the long-term incidence of outcomes such as renal scarring and UTI after surgical therapy was difficult.
- In most series of reflux resolution on medical therapy, the resolution rate by year of follow-up was not provided, and patients were included with varying lengths of follow-up. This factor made combining the data in these series difficult.
- Few studies reported side effects of medical therapy or provided the reasons for changing the prophylactic medication. In addition, most studies of medical therapy did not stratify outcomes by specific antibiotic prophylaxis, making it impossible to analyze whether a particular form of prophylaxis is better than another.

  Issues such as adverse drug reactions or complication rates from surgery are most accurately estimated from large cohort samples taken from the same populations about which inferences are to be made. The literature on issues such as complication rates and adverse reactions was usually based on a convenience sample. In some cases, the information was so sparse that judgments had to be made on the basis of expert opinion.
- Most studies of reflux resolution on medical therapy did not stratify results by patient age, making it difficult to determine whether, for a specific grade of reflux, younger children are more likely than older children to experience reflux resolution. In addition, some studies reported the number of children who had reflux resolution at specific ages, but the initial reflux grade and the age at diagnosis in these patients were not provided.

Combining the evidence

To generate an evidence matrix (see page 21), estimates of the probabilities and/or magnitudes of the outcomes are required for each alternative intervention. Ideally, these come from a synthesis of the evi]dence, either from all available studies or a subset of high-quality data. Some cells in the evidence matrix were derived from a single dataset. If several studies had some degree of relevance to a particular cell or cells of the evidence matrix, the panel used more complicated methods of data synthesis—the Confidence Profile Method (Eddy, Hasselblad, and Shachter, 1992)—as a general framework, and the FAST*PRO software computer package (Eddy and Hasselblad, 1992) for calculations. The more complicated analyses were conducted using logistic models with random effects (Hasselblad, in press), and these calculations were performed using EGRET software (Statistics and Epidemiology Research Corp., 1993). The use of these logistic models for estimating parameters with dichotomous outcomes is described in Appendix C.

Panel members used expert opinion to address outcomes in the evidence matrix for which direct evidence was lacking, recognizing the limitations of opinion as a basis for reaching conclusions about effectiveness. They completed a mailed questionnaire in which they were asked to contrast, on the basis of their opinions and clinical experience, the relative effectiveness of several treatment options (e.g., anticholinergic therapy, bladder training, continuous antibiotic prophylaxis, surgery) in relation to various intermediate and health outcomes. The questionnaire also explored their opinions regarding the natural history and pathogenesis of VUR and the risk of adverse effects from continuous antibiotic prophylaxis and surgical repair. These pooled estimates, which were later presented at a panel meeting to help the group fill in the evidence matrix, are cited in this report along with an explicit statement that they originate from a panel survey and are gross estimates based on expert opinion and not on scientific data.

Dataset analysis

In addition, the panel was able to obtain the datasets of the large studies of Skoog and Belman (1991)[1] and Arant (1992). Analysis of these datasets provided a unique chance to answer some specific questions about resolution of reflux. In particular, the studies were used to determine whether

[1] Provided by Regina O'Donnell of Washington, D.C.

age of presentation affected resolution rates. Standard survival analyses were completed, and parametric analysis was used so that results could be combined across the 2 studies where appropriate. In general, a Weibull hazard model was used, and in many cases the exponential model (a special case of the Weibull model) was appropriate because it involved fewer parameters. Goodness of fit statistics were used to determine the adequacy of each model.

Analytic process

The recommendations in this report were developed on the basis of the scientific evidence and expert opinion, summarized according to the above methodology. A structured approach was used to translate the information into recommendations: confidential voting on standardized questions was conducted to give each panel member an equal voice in the recommendations, and explicit language was used to clarify the rationale for the recommendations and to document whether the assumptions were based on scientific evidence or expert opinion. After systematically reviewing the strengths and limitations of the evidence for each of the principal outcomes in the evidence matrix, panel members completed a confidential survey in which they designated preferred treatments for children presenting initially with reflux and for those with persistent reflux following initial treatment. Separate survey forms (see example in Appendix D) were completed for 36 clinical scenarios that incorporated all possible combinations of patient age (infancy, ages 1–5, ages 6–10), reflux severity (Grades I–II, Grades III–IV, Grade V), laterality (unilateral, bilateral) and the presence or absence of renal scarring at diagnosis. Voting was conducted in September 1995 and again in May 1996 after new data on spontaneous resolution rates became available. Recommended treatments were classified as guidelines, preferred options, reasonable alternatives, or no consensus, as defined on page 16.[2]

The text that resulted from this protocol was presented to the panel for review. Although the panel edited the text to improve consistency and readability, the panel did not deviate from the above protocol, either in determining what to recommend or in the wording of the recommendations. For example, even if some panel members believed that surgical repair is a reasonable alternative for specific clinical situations, the group did not recommend surgery if it received fewer than 3 votes on the survey. Finally, working with a facilitator, the panel listed individually the explicit arguments that formed the rationale for each of its recommendations. These arguments are summarized in Rationale for Recommendations (page 53), which also specifies whether the assumptions are based on scientific evidence or expert opinion. Special caveats about the limited scope of the recommendations (e.g., applying only to patients with uncomplicated reflux) also were made explicit. The final text that resulted from this process appears on pages 49–53.

[2] An exception occurred in evaluating treatments for patients with persistent reflux, because the denominator (the number of panel members voting) was less than 9 if any panel members recommended surgery as initial treatment (i.e., they would not participate in voting for additional treatments). Accordingly, votes for persistent reflux were classified as guidelines if a treatment received 85–100 percent of the total votes or as preferred option if it received 50–84 percent of total votes. No treatments for persistent reflux were classified as reasonable alternatives; if a treatment received no more than 50 percent of the votes, the text stated that there was no consensus. Because of the small sample size in this voting process, a change in the vote of a single panel member could affect the strength of the recommendations (e.g., making a “preferred option” a “guideline”). When differences due to rounding error resulted in illogical discrepancies in the recommendations (e.g., recommending more aggressive treatment for unilateral than for bilateral reflux), the response rate for the overall class of patients was used to calculate the strength of the recommendations.

Chapter 3:
Outcomes analysis for treatment alternatives

Intermediate outcomes and health benefits and harms

Health outcomes are the effects of a medical condition or intervention on patients that are directly perceived in some way by the patient or family. Harms are health outcomes that have a negative impact on the well-being of the patient, ranging from the impact of an acute illness or diagnostic testing (such as a VCUG), to the need for surgery or hospitalization, to death. Health benefits are generally expressed as a reduction in the severity or frequency of a harm.

It is important to distinguish between outcomes directly experienced and appreciated by a patient or parent (health outcomes) and those that patients cannot feel or experience but that are either associated with or precede health outcomes (intermediate outcomes). A patient or parent is only concerned about reflux if it causes symptoms that negatively affect them or if it has the potential to cause such problems. For example, although a direct relationship may be evident between reflux and pyelonephritis, it is the clinical condition of pyelonephritis with fever, pain, and hospitalization that is experienced by the patient. Similarly, renal scarring itself may not affect a patient's well-being, but possible sequelae of hypertension, renal insufficiency, clinical renal failure, symptoms of azotemia, or the need for dialysis, have direct impact. Consequently, reflux and reflux grade are intermediate outcomes, as are renal scarring, serum creatinine, or asymptomatic bacteriuria. In contrast, symptomatic UTI, azotemia, growth failure, as well as the need for x-ray studies, medications, surgery, or dialysis are health outcomes.

Many studies reported in the literature record only intermediate outcomes because the causal connection between intermediate outcomes and health outcomes is assumed or inferred. Analyses of intermediate outcomes are important in developing practice guidelines, but a firm causal connection with health outcomes is essential for validity and relevance.

Analysis of data quality

The evidence matrix on page 21 presents the outcomes of interest, indicating health outcomes, intermediate outcomes and harms for various forms of management, including no treatment, medical therapy and surgical therapies. Areas in which good (defined as 2 or more datasets available), fair (1 well-done dataset), and poor (very little) data are available are indicated. In some areas, a significant amount of interpretable information is available to integrate into a clinical decision, while in others a surprising lack of evidence was found. The areas lacking useful outcomes data highlight the deficiencies in the literature on VUR and emphasize the need for well-developed studies to address areas of uncertainty. The text following the evidence matrix notes areas in which relative benefits and harms may differ by patient population (e.g., different patient ages and grades of reflux).

Analysis of outcomes

The following sections detail the analysis of the variables included on the evidence matrix. The information is organized in relation to outcomes listed on the left side of the evidence matrix, beginning with intermediate outcomes.

Intermediate outcomes

Resolution and diminution of reflux

Over time a considerable proportion of children with reflux will experience resolution or diminution in reflux grade. Because the significance of diminution in reflux grade was difficult to assess, the panel used reflux resolution as an indication of success.

Medical therapy. The database included 26 reports with data pertaining to reflux resolution after medical therapy, encompassing 1,987 patients

(continued on page 22)

Evidence matrix: quality of data–studies of primary vesicoureteral reflux

Key: Good | Fair | Poor | NA Not applicable | No data

Good = 2 or more datasets, Fair = one well-done dataset, Poor = very little data

	No treatment[1]	Bladder training[2]	Antibiotic prophylaxis	Antibiotic prophylaxis & bladder training	Antibiotic prophylaxis, anti-cholinergics & bladder training	Open surgical repair[3]	Endo-scopic repair[4]
Intermediate outcomes (not considered admissible evidence of effectiveness)							
Decrease grade of reflux							
Duration of reflux							
Renal scarring							
Renal growth							
Renal function							
Health outcomes							
UTI							
Pyelonephritis							
Cystitis							
Hypertension							
Uremia							
Growth							
Morbidity during pregnancy[5]							
Death							
Harms (medical treatment)							
Adverse drug reactions						NA	
Hospitalization							
Adverse effects of surveillance testing							
Harms (surgery)							
Obstruction	NA						
Bleeding/transfusion							
Infection							
Contralateral reflux							
Bladder injury							
Pain							
Hospitalization							
Adverse effects of surveillance testing							

Health benefits are positive outcomes that patients can feel or experience directly.
Intermediate outcomes are pathophysiological outcomes that lead to, or are associated with, the development of health outcomes.

1. Includes intermittent antibiotic therapy for episodic UTI.
2. Includes timed voiding and other behavioral techniques.
3. Politano-Leadbetter, Glenn-Anderson, transtrigonal (Cohen), Lich-Gregoir, Paquin, Gil-Vernet, detrusorrhaphy, etc. Also includes repair of duplication anomalies (e.g., common sheath reimplant, ureteroureterostomy, partial nephrectomy).
4. Teflon™, collagen, Ivalon, blood, fat, etc.
5. Women with reflux/reflux nephropathy appear to have a higher risk of UTIs and/or pyelonephritis during pregnancy. UTIs during pregnancy can result in eclampsia, premature delivery, reduced fetal growth and possible fetal loss. Pyelonephritis would require maternal hospitalization. If there is pre-existing renal functional impairment secondary to reflux nephropathy, deterioration of renal function may occur during pregnancy.

(1,410 girls and 304 boys or a ratio of girl to boy, 4.3:1) and 2,902 ureters. In those studies in which the reflux could be classified as unilateral or bilateral, the distribution of ureters was almost equal (767 and 763, respectively). To accommodate a clinically relevant management strategy, children were divided into groups by age at diagnosis as follows: younger than age 1 year; preschool (1–5 years); and school age (6–10 years). The panel excluded from its consideration teenage youths and adults.

The data in these reports were difficult to collate because: (1) the minimum length of follow-up was often 6 months or less; (2) some studies did not report reflux resolution specifically but rather combined resolution and reduction in reflux grade; (3) some studies reported reflux resolution by ureter, and others reported reflux resolution by patient; (4) data showing reflux resolution often combined multiple grades of reflux, particularly in the older literature that did not use either the International or the Dwoskin-Perlmutter System of grading reflux; (5) reflux was not usually assessed annually for all patients, making it difficult to evaluate reflux by year in the majority of studies; and (6) some studies only reported the age at resolution of reflux, making it impossible to determine the actual range of time to reflux resolution.

For these reasons, 3 datasets were used to estimate the probability of reflux resolution as a function of initial grade, age at presentation and initial grade of reflux and laterality (unilateral/bilateral). The individual databases from the studies of Skoog, Belman, and Majd (1987) and Arant (1992) allowed analysis of these specific parameters, whereas the study of Tamminen-Mobius, Brunier, Ebel, et al. (1992) only provided summary resolution curves and sample sizes. The Arant dataset provided information on children with initial grades of I, II and III for ages 0–60 months. The Skoog dataset provided information primarily on Grades II and III for all ages. The Tamminen-Mobius study provided information primarily on Grade IV for all ages, but the results were not available by age. The study of McLorie, McKenna, Jumper, et al. (1990) was also analyzed for Grades III and IV reflux in a manner similar to Tamminen-Mobius, but was not included because the study data were not adequately described for analysis using the Weibull model determined to be the most appropriate for the analysis of the other studies.

The survival curves of these studies were fitted to the data. The results were pooled using an empirical Bayes model (Hedges and Olkin, 1985) when 2 or more studies provided information for a single risk category. The data for Grades I and II did not show any differences by age or laterality. For Grade III reflux, however, age and laterality were important.

Table 2 (page 23) shows the estimated chance of resolution for a child with reflux of a given grade, age and laterality (unilateral/bilateral). For example, assume that a child aged 30 months (2½ years) is diagnosed with unilateral Grade III reflux. Table 2 indicates that the chance of that child's reflux resolving in the next year is 13.4 percent. The chance of that same child experiencing reflux resolution in 3 years is 35.1 percent. The chance of resolution does not depend on how long the child has had reflux before diagnosis or treatment. If reflux does not resolve in the child described previously in the first year, the chance of resolution for the next year is still 13.4 percent. However, the table indicates 25 percent due to patients dropping out once their reflux resolved. For example, 100 patients, age 25–60 months, are diagnosed with Grade III, unilateral reflux. The first year, 13.4 percent will resolve. Therefore, approximately 87 patients remain. During the second year, another 13.4 percent of the 87 patients will resolve, leaving 75 patients with reflux, which means 25 percent of the original 100 patients resolved. A graphic presentation of the data is provided in Figure 3 on page 24.

All of these estimates are subject to 2 restrictions: (1) the estimates are only valid for up to 5 years after diagnosis; and (2) for Grade IV, the estimates only apply to the time of diagnosis, and they are not age specific. Children younger than 1 year with Grade IV reflux may have a higher chance of resolution, and children older than age 5 may have a lower probability.

The mean age at reflux resolution is 4.6–6.8 years (Skoog, Belman, and Majd, 1987; Bellinger and Duckett, 1984). The age beyond which reflux is unlikely to undergo spontaneous resolution is not well documented, however. Goldraich and Goldraich (1992) reported that almost all 10-year-old girls with persistent Grade I or II reflux underwent reflux resolution by age 13. In contrast, only 50 percent of 10-year-old boys with Grade I or II reflux showed resolution by age 13. Few 10-year-old girls or boys with Grade III or IV showed reflux resolution between 10 and 13 years of age. Lenaghan, Whitaker, Jensen, et al. (1976) reported that of 83 refluxing ureters that resolved, reflux resolution occurred after age 14 in 22 (27 percent).

Table 2. Medical therapy–Percent chance of reflux resolution after specified number of years[1]

Risk category (age in months) (number of patients on which estimates are based)	Percent chance (95% confidence interval)				
	1 year	2 years	3 years	4 years	5 years
Grade I[2] (N=15)	39.3 (24.6–51.1)	63.1 (43.2–76.1)	77.6 (57.2–88.3)	86.4 (67.7–94.3)	91.8 (75.7–97.2)
Grade II[2] (N=250)	28 (24.1–31.7)	48.1 (42.3–53.4)	62.7 (56.2–68.1)	73.1 (66.8–78.2)	80.6 (74.8–85.1)
Grade III, unilateral, age 0–24 (N=27)	21.4 (10.8–30.8)	38.2 (20.4–52.1)	51.5 (29–66.8)	61.9 (36.6–77.1)	70 (43.5–84.1)
Grade III, unilateral, age 25–60 (N=27)	13.4 (4.6–21.4)	25 (8.9–38.3)	35.1 (13.1–51.5)	43.8 (17.1–61.9)	51.3 (20.9–70.1)
Grade III, unilateral, age 61–120 (N=15)	10.8 (3.5–17.5)	20.5 (6.9–32)	29.1 (10.2–43.9)	36.7 (13.4–53.8)	43.6 (16.5–61.9)
Grade III, bilateral, age 0–24 (N=62)	12.7 (7–18.1)	23.8 (13.5–32.9)	33.5 (19.5–45)	41.9 (25.1–55)	49.3 (30.3–63.1)
Grade III, bilateral, age 25–60 (N=53)	7 (3.1–10.8)	13.5 (6.1–20.4)	19.6 (9–28.9)	25.2 (11.8–36.6)	30.5 (14.6–43.4)
Grade III, bilateral, age 61–120 (N=14)	2.6 (0.7–4.5)	5.2 (1.4–8.8)	7.7 (2.1–13)	10.1 (2.8–16.9)	12.5 (3.5–20.7)
Grade IV, unilateral[3] (N=28)	16.1 (8.5–23.1)	29.7 (16.4–40.8)	41 (23.5–54.5)	50.5 (30–65)	58.5 (36–73.1)
Grade IV, bilateral[3] (N=96)	4.5 (1–7.9)	6.4 (2–15.1)	7.8 (3–21.8)	8.9 (4–28)	9.9 (4.9–33.7)

[1] The yearly rate of reflux resolution remains constant for each group.
[2] No difference shown by age or laterality (unilateral/bilateral); therefore, these categories were combined.
[3] Estimates only apply to the time of diagnosis and are not age specific.

Medical resolution of reflux in patients with voiding dysfunction. Many children have voiding disorders exhibited by bladder and external sphincter discoordination along with bladder instability that contribute to VUR (Hinman and Baumann, 1973; Hinman, 1986; Allen, 1977, 1978). Clinically, these children in addition to having reflux and UTIs also have a combination of day and night-time enuresis, holding maneuvers, constipation, encopresis, and abdominal pain. The voiding disturbances are primarily a learned phenomenon that significantly increase voiding pressures resulting in decompensation of the ureterovesical junction and reflux. Inappropriate contraction of the voluntary external sphincter during detrusor contraction causes a functional obstruction to urinary flow with the development of elevated intravesical pressure. Many children perform this maneuver to delay bladder emptying while playing games, watching television, or being involved in other activities.

The cornerstone of treatment of patients with voiding dysfunction includes bladder retraining (timed voiding, relaxed voiding, biofeedback) with or without pharmacologic intervention directed at decreasing bladder or sphincter hyperactivity. Children with concomitant constipation or encopresis are often placed on a bowel program. Three prospective studies have found that neither urethral dilatation nor urethrotomy benefited children with VUR (Forbes, Drummond, and Nogrady, 1969; Kaplan, Sammons, and King, 1973; Hendry, Stanton, and Williams, 1973).

The panel selected 2 series that specifically examined the impact of voiding dysfunction on the course of reflux resolution without any intervention

(continued on page 26)

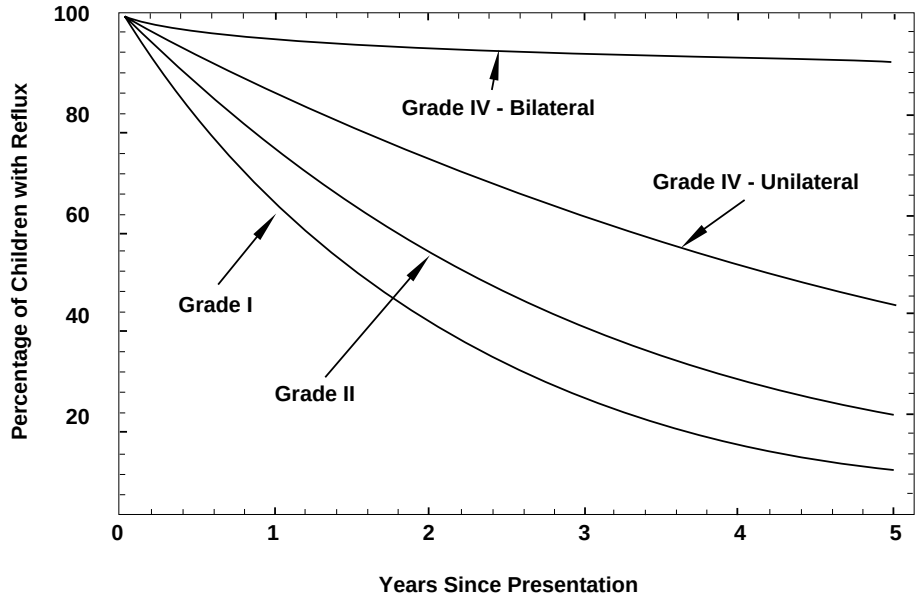

Figure 3-a. Percent chance of reflux persistence, grades I, II and IV, for 1 to 5 years following presentation

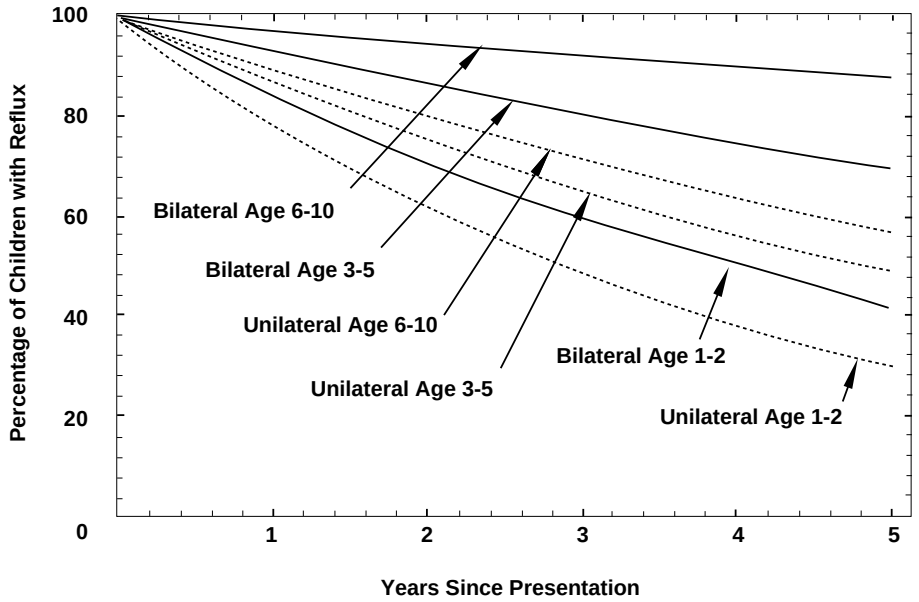

Figure 3-b. Percent chance of reflux persistence by age at presentation, grade III, for 1 to 5 years following presentation

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Source: Based on the databases from the studies of: Arant, 1992; Skoog, Belman, and Majd, 1987; and Tamminen-Mobius, Brunier, Ebel, et al., 1992.

Table 3. Medical resolution of reflux in patients with voiding dysfunction (untreated)

	Inclusion criteria	# Patients and/or # ureters	Resolution (patients)	Resolution (ureters)	Resolution by grade					Treatment regimen	Follow-up period
					I	II	III	IV	V		
Van Gool, Hjalmas, Tamminen-Mobius, et al., 1992	Patients in IRSC with questionnaire suggestive of voiding dysfunction	37/-	4/37 (11%)*		Patients predominantly with Grade III and IV reflux					Daily antibiotic prophylaxis	5 years
Van Gool, Hjalmas, Tamminen-Mobius, et al., 1992	Patients in IRSC with questionnaire not suggestive of voiding dysfunction (control group for above)	147/-	36/147 (25%)*		Patients predominantly with Grade III and IV reflux					Daily antibiotic prophylaxis	5 years
Koff and Murtagh, 1983	Patients with voiding dysfunction with uninhibited contractions on urodynamic evaluation (noncompliant with treatment of voiding dysfunction)	8/12		4/12 (33%)	0/3	1/4	2/3	1/2	0/0	Daily antibiotic prophylaxis Patients were noncompliant with • Anticholinegic medication • Bowel/bladder retraining program	Range 1.5–7 years (mean, 3.9 years)

* $p < 0.05$

directed at abnormal bladder function (van Gool, Hjalmas, Tamminen-Mobius, et al., 1992; Koff and Murtagh, 1983) (Table 3, page 25). In the International Reflux Study in Children, the rate of spontaneous reflux resolution in 37 patients with mild voiding dysfunction was 11 percent (4/37) compared with 25 percent (36/147) in a similar group without voiding dysfunction ($p < 0.05$) at 5 years of follow-up (van Gool, Hjalmas, Tamminen-Mobius, et al., 1992). In addition, recurrent symptomatic UTIs were more common in the group with voiding dysfunction (44 percent) compared with those with normal bladder function (25 percent) during 5 years of follow-up. Despite the increased propensity for symptomatic infections, the International Reflux Study in Children could not demonstrate a correlation between new renal scarring and the presence or absence of voiding dysfunction. Koff and Murtagh (1983) demonstrated a low reflux resolution rate in a small group of 8 children with voiding dysfunction who were noncompliant with treatment of their bladder dysfunction. The reflux resolution rate was 33 percent (4/12 ureters: Grade I, 0/3; Grade II, 1/4; Grade III, 2/3; Grade IV, 1/2) at a mean follow-up of 3.9 years. The rate of symptomatic and asymptomatic infections was 63 percent in this group over the same follow-up. These studies suggest that non-treatment of voiding dysfunction is associated with a lower spontaneous reflux resolution rate and an increased risk of UTI.

Resolution in patients receiving antibiotic prophylaxis, anticholinergics and bladder retraining. Improving voiding dynamics with bladder retraining and pharmacologic intervention can bring about diminution of both voiding and storage pressures. Five clinical series (not randomized controlled trials) specifically examined the role of bladder training and/or pharmacologic intervention in addition to antibiotic prophylaxis in the treatment of children with VUR (Table 4 on pages 27-28). In each study, different inclusion criteria were used to define each treatment group. In addition, each used a variety of techniques to improve bladder training (timed voiding, relaxed voiding, or biofeedback) with single or multiple pharmacologic agents (oxybutynin, imipramine, baclofen, flavoxate, dicyclomine, and diazepam) directed at decreasing bladder or sphincteric hyperactivity. The rate of UTIs for each group over the same period was 16, 63 and 71 percent, respectively. This study concluded that treatment of voiding dysfunction, as demonstrated by uninhibited contractions on urodynamic evaluation, increased the reflux resolution rate and decreased the rate of UTI. Seruca (1989) compared a group of patients prospectively studied and treated for voiding dysfunction with a retrospective control group of patients who were not treated. The overall reflux resolution rate (by ureter) was 92 percent for the former group and 54 percent for the latter. The follow-up period was not specified. Reflux resolution rates in the other 3 studies, which did not include any controls, are also summarized in Table 4. The wide variation in results (37–83 percent) is likely due to differences in inclusion criteria, treatment regimens, and follow-up period.

Available results from the series with control groups suggest that the reflux resolution rate increases with active treatment of those patients with a clinical history suggestive of voiding dysfunction. Given the variability of treatment regimens and the disparity of results, there is a need for controlled, matched studies in this area.

Medical resolution of reflux in patients with duplicated systems. Among the 168 articles reviewed by the panel, 14 included data on patients with duplicated collecting systems. Five studies included data on spontaneous resolution of reflux in patients receiving medical prophylaxis. The 14 studies reporting data on ureteral duplication included 498 patients or at least 546 affected renal units. Three studies, representing a total of 45 patients, did not report data on renal units. Assuming that each of the 45 patients had at least 1 affected renal unit, the total units would approximate 591 renal units or more. Duplication was identified predominantly in girls, with a ratio of 1 male (57) to 5.6 female (322) individuals.

Although 2 reports presented controlled studies comparing single ureteral reflux to duplicated systems (Husmann and Allen, 1991; Ben-Ami, Gayer, Hertz, et al., 1989), limited data are available on medical treatment of reflux in the patients with duplicated systems. The data show that within the population of patients with duplicated systems, Grades I–II may be treated medically whereas Grades III, IV, and V have been treated surgically in most cases. Data on resolution by grade in patients receiving medical treatment are minimal compared with those in patients with duplicated systems treated surgically. Table 5 on page 29 provides data from the 5 studies, including data on resolution in patients with duplicated systems receiving medical therapy.

(continued on page 29)

Table 4. Medical resolution of reflux in patients with voiding dysfunction (treated)

	Inclusion criteria	# Patients and/or # ureters	Resolution (patients)	Resolution (ureters)	Resolution by grade					Treatment regimen	Follow-up period
					I	II	III	IV	V		
Koff and Murtagh, 1983	Patients with voiding dysfunction with uninhibited contractions on urodynamic evaluation (compliant with treatment of voiding dysfunction)	26/43		19/43 (44%)	5/9	3/10	7/11	2/10	2/3	Daily antibiotic prophylaxis treatment for voiding dysfunction: • anticholinergic medication (oxybutynin) • Bowel and bladder retraining program.	Range 1.5-7 years (mean, 3.9 years)
Koff and Murtagh, 1983	Normal urodynamic evaluation (control group for above 2 groups)	28/47		8/47 (17%)	1/3	3/11	4/17	0/9	0/7	Antibiotic prophylaxis	Range 1.5 - 7 years (mean, 3.9 years)
Seruca, 1989	Elevated bladder pressures during bladder filling and/or voiding, with or without abnormal perineal muscle activity	53/74	46/53	68/74 (92%)	8/8	33/33	26/27	1/4	0/2	Daily antibiotic prophylaxis for 6 months, then stopped. Baclofen, flavoxate, dicyclomine, or diazepam given individually or in combination for each type of bladder dysfunction seen on urodynamic evaluation for 12-30 months. 2 patients treated for constipation.	Unknown
Seruca, 1989	Retrospective “control” group from 1980-85 (for the above group)	48/67		36/67 (54%)	12/12	22/35	2/18	0/2	—	Daily antibiotic prophylaxis	Unknown

Table 4. Medical resolution of reflux in patients with voiding dysfunction (treated) (continued)

	Inclusion criteria	# Patients and/or # ureters	Resolution (patients)	Resolution (ureters)	Resolution by grade					Treatment regimen	Follow-up period
					I	II	III	IV	V		
Homsy, Nsouli, Hamburger, et al., 1985	Urodynamic demonstration of detrusor hyperreflexia (15) or detrusor hyperreflexia or dyssynergia (25)	40/53		27/53 (51%)	4/5	18/32	5/8	0/8	—	Daily antibiotic prophylaxis. Oxybutinin for 3-18 months Constipation treated with diet and softeners.	Unknown
Nasrallah and Simon, 1984	History consistent with voiding dysfunction	15/18		15/18 (83%)	4/4	6/7	3/4	2/3	—	Daily antibiotic prophylaxis. Detrusor hyperreflexia: oxybutynin Sphincter spasm: counseling and bladder retraining Nocturnal enuresis: imipramine Small bladder syndrome: imipramine & bladder retraining Detrusor areflexia: Bethanecol and timed voiding.	2 years minimum
Scholtmeijer and Griffiths, 1990	Detrusor instability on video-urodynamic	20/27		10/27 (37%)	1/1	6/13	3/8	0/5	—	Daily antibiotic prophylaxis. Anticholinergic medication	1 year

Table 5. Reflux resolution in patients with duplicated systems treated medically

Study	Grade	Patients in whom reflux resolved	Patients treated medically	Follow-up
Husmann and Allen, 1991	II	7 (10%)	71	0.5–5 years
Peppas, Skoog, Canning, et al., 1991	I–V	10 (14%)	70	Not stated
Kaplan, Nasrallah, and King, 1978	Not stated	5 (22%)	23	Not stated
Lee, Diamond, Duffy, et al., 1991	I–V	19 (50%)	38	1–11 years
Ben–Ami, Gayer, Hertz, et al., 1989	I–IV	14 (44%)	32	Min. 1 year
Total		**55 (24%)**	**234**	

The 5 studies, representing 234 patients, included data on follow-up of patients considered medically stable for variable periods from 1–5 years. Reflux resolution occurred in 24 percent of patients (55/234). The range of time to resolution varied from 24 months (Husmann and Allen, 1991) to 39–68 months (Lee, Diamond, Duffy, et al., 1991). The studies including matched control populations showed that the chance of resolution in patients with duplicated systems is lower or equal to that in patients with single systems (Husmann and Allen, 1991; Ben-Ami, Gayer, Hertz, et al., 1989).

Resolution—Open surgery. The panel reviewed 86 reports outlining open surgical success, encompassing 6,472 patients and 8,563 ureters (see Table E-1, Appendix E). Because results were reported in 1 of these 2 categories, the data represent different populations. Surgical success is defined as an open operation performed through an abdominal incision that corrected VUR without postoperative ureteral obstruction and that was confirmed by postoperative cystography. Surgical success was obtained both with "standard" techniques such as the Politano-Leadbetter procedure (16 reports), Cohen transtrigonal procedure (12 reports), Lich-Gregoir with modifications (13 reports) and Gil-Vernet (4 reports), and with mixtures of the above procedures (that could not be separated) or unique operations that could not be classified within the above procedures (44 reports).

Overall, surgical success was reported by patients in 959 of 1,008 patients (95.1 percent), or reported by ureter in 7,731 of 8,061 ureters (95.9 percent). When surgical success was reported by reflux grade, a smaller database was available for analysis. Surgical success was achieved in 108 of 109 ureters (99 percent) for Grade I reflux, 874 of 882 ureters (99.1 percent) for Grade II, 993 of 1,010 (98.3 percent) for Grade III, 386 of 392 (98.5 percent) for Grade IV, and 155 of 192 (80.7 percent) for Grade V. Surgical success in Grade V reflux, which was treated using a wide variety of procedures, is shown in Table E-2, Appendix E. Surgical success was also analyzed by surgical technique when that information was available (Table E-3, Appendix E).

Overall, the data on surgical success by any technique suggest a narrow range of success rates centering around 95 percent. Surgical success is most likely in Grades I–III, with at least median success in Grade IV reflux. For Grade V, the success rate ranges from 34 to 100 percent.

Resolution—Endoscopic therapy. Endoscopic therapy is a newer form of surgical treatment for reflux and refers to the subureteric injection of some material under the refluxing ureteral orifice. The technique and its limitations are described in Chapter 1. Most reports in the literature describe results of the use of polytetrafluoroethylene (Teflon™) (Table 6 on page 30). If the procedure is unsuccessful, as assessed by postoperative VCUG, it may be repeated. The results of this type of therapy are difficult to interpret because success is often described as resolution or reduced grade of reflux after 1, 2, 3, or even 4 injection procedures. Most reports focus on reflux resolution by ureter

Table 6. Results of endoscopic correction (Teflon™) for vesicoureteral reflux

Study	Grade	Procedures[1]				Patient cure (1 injection)
		1st	2nd	3rd	Obstruction	
Puri and O'Donnell, 1987	IV-V	28/42	6/12	3/6	0/42	
Sweeney and Thomas, 1987	All	99/153			1/153[2]	
King and Gollow, 1988	III-IV	31/36	4/5		0/36	
Farkas, Moriel, and Lupa, 1990	All	79/88				44/52
	II-IV	79/84	4/5	0/1	0/84	44/49
	V	0/4				0/3
Lacombe, 1990	All	132/174	6/8			67/100
Sauvage, Saussine, Laustriat, et al., 1990	All	159/210			0/210	
	I-II	25/33			0/33	
	III	76/93			0/93	
	IV	52/70			0/70	
	V	6/14			0/14	
Dodat and Takvorian, 1990	All	181/213			2/213	
	I-II	84/94				
	III	80/93				
	IV	23/29				
	V	0/1				
Puri, 1990	II-V	113/143	19/23	3/4	1/143	
Schulman, Pamart, Hall, et al., 1990	All	139/173			2/173	
Davies and Atwell, 1991	All	26/40	6/7		1/40	
Bhatti, Khattak, and Boston, 1993	All	152/206	28/41	1/1	0/206	65/88
Total		**1139/1478 (77.1%)**	**73/101 (72.3%)**	**7/12 (58.3%)**	**7/1300 (0.5%)**	

[1] Results by ureter; lst, 2nd, and 3rd refer to specific treatment.
[2] Eight other ureters reported to be obstructed, but did not need surgical correction.

rather than by patient. Overall, reflux was corrected in 77.1 percent of ureters after a single injection. However, reflux was resolved after the initial treatment in only 6 of 19 ureters (32 percent) with Grade V reflux. In patients with a completely duplicated system, reflux was corrected in 58.1 percent of ureters after 1 injection (Table 7 on page 31).

Success with collagen injections is even more difficult to interpret because reflux correction may not be durable. For example, in 1 report of 60

Table 7. Reflux resolution following endoscopic correction (Teflon™) for vesicoureteral reflux, duplicated systems

		Procedures1			
Study	**Grade**	**1st**	**2nd**	**3rd**	**Obst**
Farkas, Moriel, and Lupa, 1990	III-IV	13/16			0/16
Sauvage, Saussine, Laustriat, et al., 1990	All	9/13			0/13
Dodat and Takvorian, 1990	All	8/10			
Schulman, Pamart, Hall, et al. 1990	All	11/19			
Dewan and O'Donnell, 1991	All	13/35	6/19	6/19	1/35
Total		**54/93 (58.1%)**			**1/64 (1.6%)**

[1] Results by ureter; lst, 2nd, and 3rd refer to specific treatment.

ureters with primary reflux, 47 (78 percent) showed resolution 1 month after treatment, but only 29 of 47 (61 percent) still showed resolution at 1 year (Leonard, Canning, Peters, et al., 1991). In another series, all 97 treated ureters showed resolution immediately after injection, but reflux recurred in 40 ureters (41.2 percent) at 1 month and in 5 more ureters (5.2 percent) at 1 year following therapy (Frey, Berger, Jenny, et al., 1992). Whether more systems would begin to reflux with time because of implant degradation or migration is uncertain.

At present, endoscopic treatment remains an investigational procedure in the United States, awaiting testing of a material that has proven benefit and safety.

Renal scarring

Renal scarring is an important outcome in the long-term assessment of results of medical or surgical therapy. Renal scarring may predispose to hypertension requiring medical therapy. Extensive renal scarring may cause renal insufficiency and end-stage renal disease, with its attendant morbidity and mortality.

The presence of renal scarring is documented on imaging studies, including renal scan (DMSA, MAG-3), excretory urography (IVP) and renal sonography. These techniques have certain limitations. For example, there is variable sensitivity among these studies in their ability to detect renal scars. Furthermore, timing of the imaging study is important; a renal scar may be evident on DMSA scan within 6 months of an episode of pyelonephritis, whereas it may not be apparent on IVP or sonography for 1–2 years. Early identification of renal inflammation by DMSA during an episode of pyelonephritis does not necessarily indicate that these areas will later develop scarring, however. Interpretation of the studies is variable among radiologists (Patel, Charron, Hoberman, et al., 1993). In an individual with renal scarring, it may be difficult to distinguish between a new scar adjacent to the existing one and progression of an old scar. Finally, in an individual who is found to have a renal scar on the first imaging study of the kidney, it is impossible to determine whether the scar resulted from infection or was congenital, since 20–40 percent of neonates with prenatally diagnosed hydronephrosis secondary to VUR have renal parenchymal abnormalities at birth (Elder, 1992).

Renal scarring may be new or progressive. The finding of new renal scarring suggests that a new renal injury has occurred since the previous imaging study. Progressive renal scarring, on the other hand, may represent either extension of the original renal injury or may result from a newer renal insult.

Prevention of new renal scarring is one of the primary goals of treatment of VUR. Most studies of reflux have not assessed this specific outcome. When interpreting the results of various studies pertaining to reflux, it is important to understand the limitations of each type of imaging study used in the evaluation of renal scarring (see page 12). Unless otherwise indicated, studies that combined patients with both new and progressive renal scarring have not been included in the panel's analysis.

Table 8. Scarring after treatment in prospective trials of surgery compared with antibiotic treatment for vesicoureteral reflux

Study	Population	Method of evaluation	Treatment	Follow-up	New scarring
Elo, Tallgren, Alfthan, et al., 1983	Matched uncontrolled follow-up study with 40 girls in each arm. Mean age of 5.2 years	IVP	Medical—antibiotic, primarily sulfisoxazole	4.3 years (average)	7.5% (3/40)
			Surgery—Politano-Leadbetter procedure	4.3 years (average)	17.5% (7/40)
Birmingham Reflux Study Group, 1987	161 children younger than age 15 years, allocated randomly to either surgery or antibiotic treatment	IVP	Medical treatment	5 years	6% (5/84)
			Surgical treatment	5 years	5.2% (4/77)
Olbing, Claesson, Ebel, et al., 1992	306 children younger than age 11 years, with nonobstructive Grades III or IV VUR and with previous UTI	IVP	Medical treatment	5 years	15.7% (19/121)
			Surgical treatment	5 years	17.2% (20/116)
Weiss, Duckett, and Spitzer, 1992	Infants and children with Grades III and IV primary VUR	IVP	Medical treatment	4½ years	21.5% (14/65)
			Surgical treatment	4½ years	31.4% (16/51)

Four prospective trials comparing the outcomes of medical and surgical management included analysis of new renal scarring (Table 8 on page 32). None of these trials showed a statistically significant difference in the rate of new renal scarring. The combined relative risk slightly favored medical management but was not statistically significant (see Figure 4 on page 33). In the European arm of the International Reflux Study (Olbing, Claesson, Ebel, et al., 1992), the rate of scarring was similar among those managed medically and those treated surgically; however, 80 percent of the new renal scars in the surgical group appeared by 10 months after randomization, whereas new renal scars appeared throughout the 5 years in the group managed medically.

Several single-arm studies also reported rates of new scarring after medical or surgical treatment. The combined risk for new scarring for 14 such medical reports was 4.1 percent (range, 0–24.7 percent) (Aggarwal, Verrier-Jones, Asscher, et al., 1991; Arant, 1992; Bellinger and Duckett, 1984; Ben-Ami, Sinai, Hertz, et al., 1989; Birmingham Reflux Study Group, 1987; Burge, Griffiths, Malone, et al., 1992; Cardiff-Oxford Bacteriuria Study Group, 1978; Edwards, Normand, Prescod, et al., 1977; Homsy, Nsouli, Hamburger, et al., 1985; Husmann and Allen, 1991; Jakobsen, Genster, Olesen, et al., 1977; Koff and Murtagh, 1983; Scholtmeijer and Griffiths, 1988; Shah, Robins, and White 1978), and for 7 such surgical reports was 4.6 percent (range, 0–16.7 percent) (Beetz, Schulte-Wisserman, Tröger, et al., 1989; Birmingham Reflux Study Group, 1987; Burge, Griffiths, Malone, et al., 1992; Carpentier, Bettink, Hop, et al., 1982; Hjalmas, Lohr, Tamminen-Mobius, et al., 1992; Scholtmeijer and Griffiths, 1988; Scott, Blackford, Joyce, et al., 1986). These reports are difficult to compare directly, however, because the length of follow-up and distribution of reflux grades varied among the studies. In the majority of these studies, the minimum follow-up

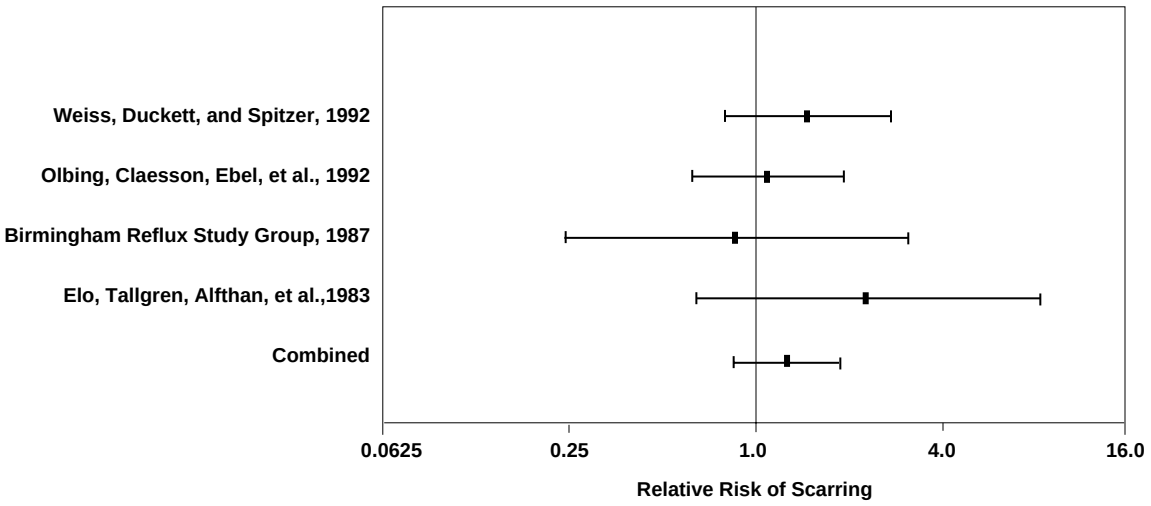

Figure 4. Relative risk of new scarring for surgery compared with antibiotic treatment

Analysis from 4 prospective trials of the risk of new scarring after surgery compared to that after medical treatment showed that the combined relative risk slightly favored medical management but was not statistically significant.

was 3 months. Furthermore, identification of renal scarring in most studies has depended on intravenous urography, but the quality of films and expertise of radiologists were probably inconsistent. The Birmingham Reflux Study (1987) identified new scars after 5 years in only 6 percent and 5.2 percent of children treated medically and surgically, respectively, with no additional scars detected after 2 years of follow-up. On the other hand, the International Reflux Study found new scars in 15.7 percent (medical) and 17.2 percent (surgical) of refluxing children in Europe and 21.5 percent (medical) and 31.4 percent (surgical) in North America (Table 8). When patients with VUR discovered before 5 years of age whose kidneys were of normal size by planimetry and had no evidence of renal scarring on initial intravenous urography were treated medically and followed for 5 years, renal scarring was detected in 10 percent of patients with Grades I or II reflux and 28 percent of those with Grade III VUR. Of the scars, 42 percent were detected after 1 year of follow-up, 25 percent after 3 years and 33 percent after 5 years (Arant, 1992). More recently, renal scarring has been confirmed on DMSA scan within 6 months after acute pyelonephritis in children (Rushton and Majd, 1992).

Renal scarring: Relationship to bacteriuria. Because VUR is most frequently diagnosed after an infant or child presents with UTI and animal models of ascending pyelonephritis (via surgically created VUR) reliably produce renal scarring, the 2 events, when they occur clinically, are often thought to be causally related. Renal scarring is often detectable on the initial renal imaging study obtained following the diagnosis of UTI, and is proportional to the severity of VUR and the sensitivity of the technique. This observation suggests that previous undiagnosed UTIs may have occurred, which resulted in pyelonephritic injury. However, new or progressive renal scarring during follow-up is less common, despite additional episodes of bacteriuria.

The panel attempted to analyze the relationship between bacteriuria and new renal scarring in children with reflux. However, few data are available that would permit such an analysis. Only 14 reports described the frequency of UTI in children with and without new or progressive renal scarring (Aggarwal, Verrier-Jones, Asscher, et al., 1991; Anderson and Rickwood, 1991; Arant, 1992; Beetz, Schulte-Wissermann, Tröger, et al., 1989; Birmingham Reflux Study Group, 1983; Birmingham Reflux Study Group, 1987; Cardiff-Oxford Bacteriuria Study Group, 1978; Edwards, Normand, Prescod, et al., 1977; Goldraich and Goldraich, 1992; McLorie, McKenna, Jumper, et al., 1990; Shah, Robins, and White, 1978; Skoog, Belman,

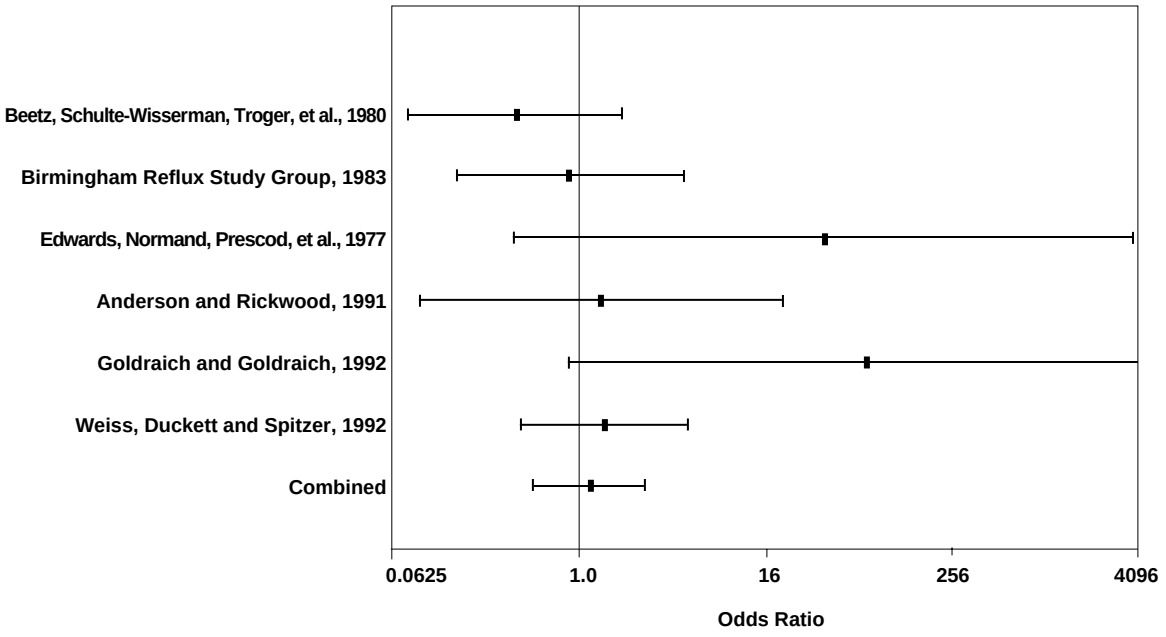

Figure 5. New or progressive scarring and bacteriuria

Analysis of the relationship of bacteriuria and renal scarring in children with reflux showed that the risk of developing new or progressive scarring was 1.18 times as great for an individual with UTI as that for an individual without infection (i.e., the risk is only slightly increased).

and Majd, 1987; Smellie, Gruneberg, Leakey, et al., 1976; Weiss, Duckett, and Spitzer, 1992). Most of these studies provided information only for the presence or absence of bacteriuria in those with new or progressive scarring, and not for those who did not develop such scarring. Using the empirical Bayes method of Hedges and Olkin (1985), an estimated odds ratio of 1.18 (95% CI 0.52–2.68) is derived (see Figure 5 on page 34). In other words, the risk of developing new or progressive scarring for an individual with UTI is 1.18 times as great as that for an individual without infection, that is, the risk of developing new or progressive scarring is only slightly increased.

Several factors may contribute to this surprising lack of association between scarring and infection in children with reflux. First, few of the reports characterized the types of infections (febrile, nonfebrile, asymptomatic) in these children. Febrile UTIs are more likely to represent renal parenchymal inflammation, and thus place the patient at greater risk for scarring than does nonfebrile UTI. In the study by Goldraich and Goldraich (1992), all 7 of the children with new renal scars by DMSA scan had a febrile UTI in the previous year. The remainder of the reports were not as precise. In addition, the progressive scarring recorded may have been the result of a UTI that occurred before treatment (medical or surgical) was initiated. The radiologic technique used to detect new or progressive scarring may not have been sufficiently sensitive to evaluate this parameter properly. Furthermore, once the initial diagnosis of UTI and VUR has been made, most parents/patients are more likely to be attuned to the symptoms of UTI (particularly fever), and patients are more likely to receive prompt diagnosis and treatment. In addition, it is possible that UTIs were under-reported to the investigator by referring physicians, or that suspected UTIs (or episodes of unexplained fever) may have been treated with an antibiotic without urine culture. For example, in a study of 50 febrile infants, all of whom underwent protocol urine culture, 15 ultimately found to have bacteriuria initially had received diagnoses other than UTI (Hoberman, Chao, Keller, et al., 1993).

Renal growth

A clinical impression, supported by many reports, is that renal growth is impaired when VUR

is present (Scott and Stansfield, 1968; Lyon, 1973; Redman, Scriber, and Bissada, 1974), especially with Grades IV and V reflux (Pinter, Jaszai, and Dober, 1988; McRae, Shannon, and Utley, 1974), or recurrent infection (Peratoner, Messi, and Fonda, 1984; Scott and Stansfield, 1968; Kelalis, 1971). Moreover, accelerated renal growth has been recorded after reflux was corrected (Carson, Kelalis, and Hoffman, 1982; Atwell and Vijay, 1978; Willscher, Bauer, Zammuto, et al., 1976; Scott and Stansfield, 1968) or during adolescence (Claesson, Jacobsson, Jodal, et al., 1981). Most studies with useful data on renal growth have been conducted retrospectively without an appropriate control group and for durations of follow-up in which some patients may have been followed no more than 1 year (Atwell and Cox, 1981; Atwell and Vijay, 1978; Willscher, Bauer, Zammuto, et al., 1976). Standardized methods for assessing renal growth have seldom been used, making comparisons among studies difficult. Furthermore, many patients have renal scarring when reflux is recognized or develop new or progressive scarring during follow-up (Birmingham Reflux Study Group, 1987; Bellinger and Duckett, 1984; Weiss, Duckett, and Spitzer, 1992; Olbing, Claesson, Ebel, et al., 1992; Smellie, Edwards, Normand, et al., 1981).

Renal growth is most often assessed as renal length measured from intravenous urography or, more commonly in recent years, by renal ultrasonography. Before interpreting data obtained using these techniques, it must be recognized that the distance between the table top and tray alters the renal image projected onto the film (Riggs, 1977). Renal dimensions are distorted when the distance between the x-ray source and film is altered and magnified when urographic films are taken when the patient is in the prone position. Poor technique or inadequate bowel preparation may obscure the exact margins of the renal outline. With renal ultrasonography, the angle of the transducer to the longitudinal aspect of the kidney may distort renal dimensions.

Of the various estimates of renal size from renal length, standards exist only for normal—not scarred—kidneys (Hodson, Drewe, Karn, et al., 1962; Hodson, Davies, and Prescod, 1975; Eklof and Ringertz, 1976; Rosenbaum, Korngold, and Teele, 1984). Moreover, some kidneys are "short and fat" while others are "long and thin." Renal scarring is noted most often in upper or lower poles (Hannerz, Wikstad, Johansson, et al., 1987). Renal size can be assessed more reproducibly by estimating planimetric surface area (Claesson, Jacobsson, Olsson, et al., 1981). This two-dimensional measurement of renal parenchyma surface area from a standardized urographic film is not compromised by differences in renal width or hydronephrosis. In addition, identification of parenchymal thinning may be a more sensitive indicator of renal scarring in the small but growing kidney (Olbing, Claesson, Ebel, et al., 1992). Even when a parenchymal scar is not obvious, discrepancies in renal size between kidneys suggest unilateral disease in the smaller kidney, especially when compensatory hypertrophy in the contralateral kidney results in its being larger than expected for age, body length, or vertebral height (Claesson, Jacobsson, and Jodal, 1981). Renal size cannot be estimated from any radionuclear study currently in use. Even when a kidney contributes more than 50 percent of total renal function on a radionuclide scan, normal renal size cannot be presumed.

Two reported studies provide data on renal growth in patients with reflux treated either medically or surgically; each was conducted prospectively and had a minimum of 5 years of follow-up in every patient. The Birmingham Reflux Study (1987) used renal length whereas the International Reflux Study (Weiss, Duckett, and Spitzer, 1992) employed planimetric surface area—both taken from intravenous urography. At the outset of both studies, each treatment group included many patients with previous renal scarring. No differences in renal growth were detected between groups in either study. Another study that was not conducted prospectively reported similar findings—no difference in renal growth during medical management or after surgical correction of reflux (Peratoner, Messi, and Fonda, 1984). However, patients in both treatment groups had kidneys that were smaller than normal or that grew suboptimally during the follow-up period. The number of kidneys that were small because of renal scarring or parenchymal thinning was not reported. On the basis of clinical studies available to date, there is no evidence to support the notion that in the absence of voiding dysfunction, renal growth is impaired in unscarred kidneys exposed to sterile reflux of any grade (Arant, 1992; Smellie, Edwards, Normand, et al., 1981) or that surgical correction of reflux facilitates growth of the kidney postoperatively (Birmingham Reflux Study Group, 1987; Peratoner, Messi, and Fonda, 1984; Beetz, Hohenfellner, Schofer, et al., 1991; Weiss, Duckett, and Spitzer, 1992).

Renal function

The rationale for identifying reflux early is to introduce treatment that best prevents scarring and preserves renal function. Scott, Blackford, Joyce, et al. (1986) reported marked improvement in glomerular filtration rate (GFR) for most patients in whom reflux was corrected surgically. Using the same technique for measuring GFR, however, Poulsen, Johannesen, Nielsen, et al. (1989) found that GFR was preserved during nonsurgical management of children with reflux. During long-term observations, others have found no adverse effect of continued sterile reflux on kidney function (Birmingham Reflux Study Group, 1987; Weiss, Duckett, and Spitzer, 1992). In prospective, controlled treatment trials, surgical correction of even severe reflux has had no benefit on GFR 5 years later (Birmingham Reflux Study Group, 1987; Weiss, Duckett, and Spitzer, 1992).

When renal scarring is severe but unilateral, renal function would be expected to be normal. Even when both kidneys are scarred, overall renal function may be preserved by compensatory changes in structure and function of remaining nephrons (Berg, 1992). In fact, the degree of renal functional impairment in patients with reflux nephropathy has been related directly to parenchymal size of both kidneys (Claesson, Jacobsson, Jodal, et al., 1981). Serum creatinine concentration will remain within the range of normal values for age until scarring reduces functional nephron mass sufficiently to lower GFR. When renal function is decreased below normal for age, one must conclude that maximal functional compensation has taken place already in kidneys that are small or scarred.

A radionuclide study that reports an allocation of the percent of isotope excreted by right and left kidneys cannot be used to interpret overall renal function. Total GFR should be corrected to 1.73 m^2 body surface area and calculated by timed urine collection and clearance methodology, from serum creatinine and height (Schwartz formula) or from another radionuclide study that measures and reports actual GFR as well as split functions. No decision to remove a kidney or surgically correct VUR can be made on the basis of split functions alone. When a patient has bilateral renal scarring, every functioning nephron should be conserved because each contributes to overall renal function.

Health outcomes

Urinary tract infection

Most infants and children with VUR present with UTI, usually acute pyelonephritis with the attendant risk of renal parenchymal injury (Weiss, Tamminen-Mobius, Koskimies, et al., 1992). The relationship between renal injury (presumably pyelonephritic scarring) and UTI complicated by acute pyelonephritis has been examined (Martinell, Claesson, Lidin-Janson, et al., 1995). UTIs were characterized retrospectively by conventional criteria (e.g., fever) as either acute pyelonephritis, cystitis or unspecified. Of the 45 patients with renal scarring, 33 (73 percent) had acute pyelonephritis as their first UTI, compared with 18/42 (43 percent) who did not have renal scarring ($p < .001$).

Pyelonephritis can result in destruction of one or more lobes of the kidney with replacement of normal kidney by fibrotic tissue (renal scarring). In addition to short-term morbidity, the long-term consequences of renal scarring include hypertension and functional impairment, both most frequently seen after loss of critical mass of kidney tissue. Thus, prevention of UTI, and particularly acute pyelonephritis, is an important goal in the management of infants and children with VUR.

UTI may occur following diagnosis of reflux and initiation of therapy. If it occurs in a child receiving antibiotic prophylaxis, the infection may occur because of antibiotic resistance to the prophylactic antibiotic (in which case the organism is resistant to the antimicrobial) or because of non-compliance with therapy (in which case the organism is usually sensitive to the antimicrobial). Children who have undergone successful surgical therapy often do not continue to receive antibiotic prophylaxis after the imaging studies demonstrating reflux resolution have been performed. In these children, development of UTI is independent of the previous structural abnormality and secondary to host uroepithelial adherence characteristics and bacterial virulence factors.

The panel reviewed 41 articles that reported the incidence of UTI (as defined by bacteriuria, regardless of clinical symptoms) in children with VUR treated either with antibiotic prophylaxis or reimplantation surgery. The International Reflux Study in Children randomized infants and children with Grades III and IV VUR to either medical or surgical management. In the European branch of the study (Jodal, Koskimies, Hanson, et al., 1992), 59

of 151 surgical patients (39.1 percent) had at least 1 UTI during the 5-year follow-up (0.65 per 100 patient-months), compared with 59 of 155 medical patients (38.1 percent) (0.63 per 100 patient-months). In the U.S. branch (Weiss, Duckett, and Spitzer, 1992), 21 of 64 surgical patients (32.8 percent) (1.8 per 100 patient-months) compared with 20 of 68 medical patients (29.4 percent) (2.3 per 100 patient-months) had at least 1 UTI during the 5-year follow-up. There was no significant difference in UTI rate between medical and surgical treatment either in the European or the U.S. data. The incidence of UTI in a third uncontrolled, but matched (n = 40 each) study was 2.81 per 100 patient-months following surgery and 3.34 per 100 patient-months with medical management with a comparable duration of follow-up (Elo, Tallgren, Alfthan, et al., 1983). Combining data from all 3 studies yields a relative risk of 0.97 (95% CI 0.79–1.19), indicating almost no difference between the 2 treatments with respect to the risk of bacteriuria. In support of this observation, another study (Beetz, Schulte-Wissermann, Tröger, et al., 1989) reported an incidence of UTI after surgery alone that was comparable to the surgical arms of the 2 randomized controlled trials, and a study of UTI with antibiotic prophylaxis alone (Hanson, Hansson, and Jodal, 1989) reported rates comparable to those in the medical arms of the 2 randomized controlled trials.

Because the risk of renal injury is related to acute pyelonephritis rather than to UTI in general, incidence rates of acute pyelonephritis were compared in both the European and U.S. branches of the International Reflux Study in Children. In the European branch (Jodal, Koskimies, Hanson, et al., 1992), acute pyelonephritis was observed in 15 of 151 surgical patients (9.3 percent) (0.17 per 100 patient-months) compared with 33 of 155 medical patients (21.3 percent) (0.35 per 100 patient-months) (p = 0.03). In the U.S. branch (Weiss, Duckett, and Spitzer, 1992), 5 of 64 surgical patients (7.8 percent) (0.3 per 100 patient-months) compared with 15 of 68 medical patients (22.1 percent) (0.7 per 100 patient-months) had at least 1 episode of acute pyelonephritis (p = 0.085). In the nonrandomized and uncontrolled, but matched study (Elo, Tallgren, Alfthan, et al., 1983), 72.5 percent medical patients compared with 22.5 percent surgical patients (1.41 per 100 patient-months medical and 0.44 per 100 patient-months surgical) had acute pyelonephritis. Combining the data from the 3 studies, the relative risk of acute pyelonephritis with surgical treatment is 0.39 (95% CI 0.26–0.58) compared with medical treatment (Figure 6). An additional uncontrolled and unmatched study examined the incidence of acute pyelonephritis with either surgery or medical therapy (Amar, Singer, and Chabra, 1976). Follow-up varied from 1–14 years. Acute pyelonephritis was reported in

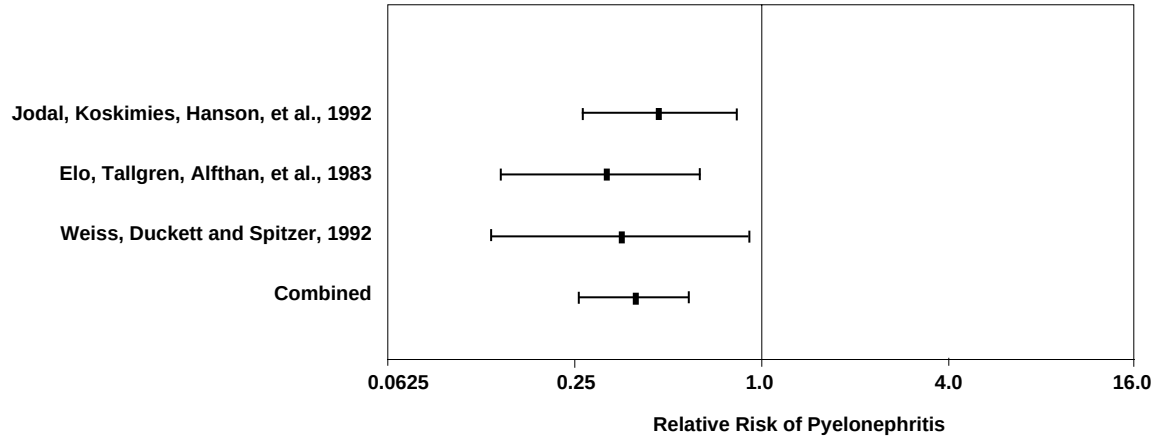

Figure 6. Relative risk of pyelonephritis for surgery compared with antibiotic treatment

Analysis of the risk of acute pyelonephritis after surgery compared to that after medical treatment showed the combined relative risk significantly favored surgical treatment. The combined relative risk of acute pyelonephritis with surgical treatment is 0.39 (95% CI 0.26–0.58) compared with medical treatment.

none of 111 surgical patients compared with 5 of 99 medical patients. In a study of surgical patients only (Willscher, Bauer, Zammuto, et al., 1976), 223 children were followed postoperatively for 0.5–7 years. Three of 175 girls (1.7 percent) had acute pyelonephritis. In a study of medical patients only (Hanson, Hansson, and Jodal, 1989), 12 of 44 (27.3 percent) girls who were treated for 860 months developed acute pyelonephritis (1.44 per 100 patient-months).

In summary, of the few studies that were adequate for analysis, the overall incidence of UTI in patients with VUR was not significantly different in patients treated with antibiotic prophylaxis (medical management) or ureteral reimplantation (surgical management). The incidence of acute pyelonephritis was significantly greater with medical management. Despite the risk of renal parenchymal injury from acute pyelonephritis and its potential for healing with scarring, the incidence of scarring was no greater in medical than in surgical patients (Jodal, Koskimies, Hanson, et al., 1992; Weiss, Duckett, and Spitzer, 1992). The factors that may account for the surprising lack of an association between new or progressive renal scarring and pyelonephritis in the literature are discussed on pages 33–34.

Hypertension

Reflux nephropathy is considered one of the most common causes of severe hypertension in children, when it is examined in a retrospective fashion (i.e., of those who present with severe hypertension, reflux nephropathy is a frequent diagnosis). The panel reviewed 10 studies that reported blood pressure (BP) measurements after reimplantation surgery. Only 2 characterized the patient population sufficiently to provide meaningful analysis. Wallace, Rothwell, and Williams (1978) reported longer than 10-year follow-up of 166 children with VUR treated surgically. Of 158 preoperative BP measurements that were compared with the American Academy of Pediatrics 1977 BP norms, 24 (15.2 percent) had BP higher than the 95th percentile for age and sex (either systolic, diastolic, or both.) Hypertension was defined as a BP of ≥140/90 in their follow-up, because all 141 subjects were older than 14 years of age. Eighteen (12.8 percent) were hypertensive. Of these, 7 had preoperative bilateral renal scarring (of 38 with this finding on IVU) and 7 had preoperative unilateral renal scarring (of 62 with this finding on IVU). In Beetz' series (Beetz, Schulte-Wissermann, Tröger, et al., 1989), 189 children were evaluated at least 5 years after successful VUR surgery. Ten patients (5.3 percent), all of whom were older than age 14, were found to be hypertensive (BP > 140/90). Of 61 patients with renal scarring (all preoperative), 7 (11.5 percent) were hypertensive at the time of follow-up compared with 3 of 128 patients (2 percent) of those without scarring. Preoperative BP levels were not reported.

Lenaghan, Whitaker, Jensen, et al. (1976) reported hypertension (defined as >140/90) in 10 of 102 children (9.8 percent) treated nonsurgically, who were followed-up for 5–18 years. Patients with scarred kidneys were not distinguished from those without scarring.

Thus, no statistically significant difference was found in the risk of hypertension related to treatment modality (medical or surgical). These studies indicated that renal scarring increases the relative risk of hypertension to 2.92 (95% CI 1.2–7.1), compared with the risk in patients without renal scarring.

Numerous medications are used to treat hypertension in children and adults with renal scarring. Angiotensin-converting enzyme inhibitors, which may be used for treatment of those with renin-mediated hypertension, may be associated with some side effects (Kim and Swartz, 1993). In addition, use of these drugs during pregnancy may cause oligohydramnios and irreversible neonatal renal failure (Rosa, Bosco, Graham, et al., 1989).

Uremia

Since 1987, the North American Pediatric Renal Transplant Cooperative Study has registered virtually all children with end-stage renal disease (ESRD), defined as a GFR so low that only kidney dialysis or transplantation will sustain life. Although overlap of diagnostic categories (e.g., hypoplasia, dysplasia, obstructive uropathy) is likely, VUR was the primary diagnosis in 3.1 percent of this population (Avner, Chavers, Sullivan, et al., 1995). Those with VUR who develop ESRD typically have been those who present with reduced GFR and bilaterally small, scarred kidneys. It is thought that independent of further pyelonephritic injury, these patients have sustained the loss of a critical mass of renal tissue, such that progressive loss of function due to glomerulosclerosis is mediated by maladaptive hemodynamic events (Neuringer and Brenner, 1993).

Although UTI is the most frequent presentation of VUR, it is less commonly the presentation of those patients with impaired GFR, virtually all of

whom have bilateral extensive renal scarring on the initial kidney imaging study. Also, antenatal detection of bilateral hydronephrosis has identified a population of neonates with severe bilateral VUR and impaired GFR before any UTI has occurred. How many patients develop uremia from congenital reflux nephropathy (or dysplasia associated with VUR), rather than after acquired reflux nephropathy from 1 or more pyelonephritic events, remains unknown. Thus, it would not be possible to demonstrate that even optimal treatment of VUR and UTI can prevent progressive renal failure and, ultimately, uremia, once bilateral reflux nephropathy has been diagnosed.

Somatic growth

Two studies mentioned somatic growth associated with nonsurgical VUR treatment and follow-up (Pinter, Jaszai, and Dober, 1988; Smellie, Preece, and Paton, 1983). Neither study substantiated an effect of VUR treatment on somatic growth.

Morbidity during pregnancy

Because of the known association between bacteriuria and adverse outcomes in pregnancy, there is a common perception that the increased risks of pyelonephritis and renal scarring in patients with vesicoureteral reflux may potentially result in increased morbidity during pregnancy in women who have persistent reflux. The panel did not undertake an extensive literature search of references pertaining to the association between reflux and adverse outcomes of pregnancy. However, based on a more selective review, what follows is the panel's current understanding of this association.

One of the potential late complications of VUR and/or pyelonephritic scarring in females is maternal and fetal morbidity. Maternal problems include pyelonephritis, septicemia, renal scarring, hypertension, toxemia, and reduction in renal function, which in some women progresses to ESRD. Fetal complications include preterm delivery, low birth weight, and fetal loss.

On the basis of a retrospective review of 26 studies that included a total of 82,364 pregnancies, approximately 4–7 percent of pregnant women have asymptomatic bacteriuria (Sweet, 1977). If asymptomatic bacteriuria is not treated, pyelonephritis is common. From a combination of 18 studies of pregnant bacteriuric women who were not treated with antibiotics, 28 percent of 1,699 women developed pyelonephritis (Sweet, 1977). Kass (1960) observed a 42-percent incidence of pyelonephritis in 48 patients when asymptomatic bacteriuria in pregnancy was not treated. When bacteriuria was eliminated, pyelonephritis did not occur (Kass, 1960). Women with a history of UTI in childhood appear to have a higher risk of asymptomatic bacteriuria. Martinell, Jodal, and Lidin-Janson (1990) and Sacks, Roberts, Verrier Jones, et al. (1987) found an incidence of 37 percent (24/65 pregnancies) and 50 percent (24/48 pregnancies), respectively. If renal scarring was present, the risk increased to 47 percent (9/19) (Martinell, Jodal, and Lidin-Janson, 1990) and 60 percent (9/15) (Sacks, Roberts, Verrier-Jones, et al., 1987).

Pregnant women with pyelonephritic renal scarring appear to be at higher risk for pyelonephritis than those without renal scarring. In a study of 41 pregnant women with a history of childhood UTI, Martinell, Jodal, and Lidin-Janson (1990) reported an incidence of 21 percent (4/19) in those with scarring compared with 5 percent (1/22) in those without renal scarring. Jacobson (1991) reported that 3 of 30 pregnant women with renal scarring developed pyelonephritis.

The relationship between asymptomatic bacteriuria and maternal/fetal complications is controversial. A meta-analysis of 17 cohort studies including 23,298 patients showed that in women with asymptomatic bacteriuria, the risk of preterm delivery was 2 times higher and the risk of having a low-birthweight baby was 1.5 times higher compared with women without bacteriuria (Romero, Oyarzun, Mazor, et al., 1989). Kincaid-Smith and Bullen (1965) demonstrated that women with bacteriuria at their first prenatal visit had a 2.9 times higher risk of fetal loss during the second and third trimesters, the risk of preterm delivery was 2.7 times higher and the risk of pre-eclampsia was 1.8 times higher than that in women without bacteriuria. Many of these women also had underlying renal scarring. Schieve, Handler, Hershow, et al. (1994) reported on the effects of pyelonephritis during pregnancy on maternal and fetal outcome. Of the 25,476 mother/infant pairs studied, 7.7 percent had a documented UTI. In those with pyelonephritis, the risk of perinatal death was 2.6 times higher and the risk of preterm delivery or low birth weight was 2.5 times higher than in those without UTI.

In women with reflux nephropathy and reduced renal function, the risk of complications is considerable. In addition to pyelonephritis, potential problems include further reduction in GFR, toxemia, preterm delivery, and fetal loss (see Table 9 on page 40). Women with renal scarring and chronic

Table 9. Maternal and fetal complications in patients with moderate or severe renal insufficiency

Study	Further decrease in renal function	Toxemia	Preterm delivery	Fetal growth retardation	Fetal loss
Kincaid-Smith and Fairley, 1987					
95 women - 227 pregnancies, normal renal function	2%	13%	—	—	9%
42 women - 118 pregnancies, SCr > 1.25 mg%	8%	36%	—	—	24%
Becker, Ihle, Fairley, et al., 1986					
20 women, SCr 2.3–4.5 mg%, including:					
6 women preg. duration >12 wk.	100%1	—	—	—	—
14 women preg. duration <12 wk	29%2	—	—	—	—
Cunningham, Cox, Harstad, et al., 1990					
37 women, SCr 1.4–9.4 mg%	16%3, 4	60%	40%	—	—
+ chronic htn	24%	80%	57%	38%	54%
+ toxemia, including:	—	—	53%	—	—
26 women, SCr 1.4–2.5 mg% (ave. 1.7)	19%	—	30%	35%	8%
+ chronic htn	29%	79%	43%	36%	—
11 women, SCr >2.6 mg% (ave. 4.8)	9%		86%	43%	18%
+ chronic htn	14%	86%	86%	43%	—
Jungers, Houillier, Forget, et al., 1991					
104 women with reflux nephropathy- 254 pregnancies	—	—	—	—	13%
14 women, 19 pregnancies, SCr >1.5 mg% at conception	—	—	—	—	63%
+ htn	—	—	—	—	75%
14 women, SCr 2–5.5 mg% at conception	36%5	—	—	—	—
Jones and Hayslett, 1996					
67 women - 82 pregnancies, SCr≥1.4 mg%	43%6	—	59%	37%	7%
67 pregnancies, SCr 1.4–2.4 mg%	—	—	55%	31%	9%
15 pregnancies, SCr ≥2.5 mg%	—	—	73%	57%	0%

[1] Rapid deterioration in renal function in all 6 women; 4 progressed to ESRD within 2 years post delivery.
[2] Four with uncontrolled hypertension had rapid deterioration in renal function with progression to ESRD; 10 had slow deterioration in renal function over 7 years but not to ESRD.
[3] Renal deterioration defined by an increase in SCr of 50% during pregnancy.
[4] Of 7 patients without deterioration of renal function during pregnancy, 6 later had deterioration of renal function and 4 required dialysis within a mean interval of 39 months.
[5] Five of 14 patients had accelerated deterioration of renal function with progression to ESRD in 6 months to 4 years.
[6] During pregnancy and up to 6 weeks postpartum; 31% after 6 months postpartum.

hypertension who are receiving angio-tensin-converting enzyme inhibitor therapy (captopril, enalapril) are at particular risk for oligohydramnios and neonatal renal failure, which may be irreversible (Rosa, Bosco, Graham, et al., 1989). This class of drugs, which often is extremely effective, should not be used during pregnancy (Cunningham and Lindheimer, 1992).

The morbidity of persistent reflux during pregnancy has not been studied extensively. Williams, Davies, Evans, et al. (1968) found that 21 percent of women with asymptomatic bacteriuria during pregnancy had reflux on VCUG performed 6 months postpartum, compared with 1.7 percent in a randomly selected group of women examined immediately postpartum (Heidrick, Mattingly, and Amberg, 1967). Martinell, Jodal, and Lidin-Janson (1990) reported that pyelonephritis occurred during pregnancy in 3 of 8 women with reflux, but only 2 of 33 in those without reflux. In the 8 patients with reflux, pyelonephritis occurred in 3 of 9 of pregnancies managed with continuous antibiotic prophylaxis and 2 of 4 managed without prophylaxis.

In this series, reflux generally was Grade I or II. Heidrick, Mattingly, and Amberg (1967) reported that 3 of 9 women with reflux developed pyelonephritis during pregnancy compared with 15 of 312 women without reflux. Although the data suggest a greater risk of morbidity from pyelonephritis in women who have persistent reflux during pregnancy, the sample size is small and only limited conclusions can be made on the basis of this evidence.

Few studies have focused on the outcomes of pregnancies of women with surgically treated reflux. Fryczkowski, Maruszewska, Paradysz, et al. (1991) reported that in 59 pregnancies in 34 women who had undergone antireflux surgery in childhood, 65 percent (22/34) had a UTI during pregnancy, but the incidence of pyelonephritis was not reported. Mansfield, Snow, Cartwright, et al. (1995) studied 62 women who underwent antireflux surgery as children and compared them with 21 women with uncorrected childhood reflux who had not had radiologic follow-up and whose reflux status was unknown. In the surgically treated group, 40 percent (57/141) of pregnancies were complicated by a UTI (18 percent pyelonephritis; 22 percent cystitis). In the uncorrected group, 1.3 percent (1/75) had pyelonephritis and 13.3 percent (10/75) had cystitis. The 2.5 times higher incidence of UTIs demonstrated in the surgically treated group has not yet been explained adequately but may be related to host factors that subject them to a higher inherent risk of UTI. In this retrospective study, no data were presented concerning the initial presentations, voiding dysfunction, indications for patient selection for surgery, or extent of renal scarring. Antibiotic prophylaxis during pregnancy was inconsistently prescribed. There was no significant difference in the rate of fetal loss in the 2 groups. Although these studies indicate that UTIs are common during pregnancy in patients who have undergone antireflux surgery, data are not presented on the effect of antireflux surgery on subsequent pyelonephritis.

Death

Death can be attributed to VUR only indirectly. Unrecognized or inadequately treated UTI may result in urosepsis and death, which occurred frequently in the pre-antibiotic era. Moreover, death could occur as a complication of anesthesia or surgery performed to correct VUR. In a patient with renal scarring who develops hypertension which, after a period of being asymptomatic, may result in heart failure or encephalopathy, death could result if treatment were unsuccessful. Women with bilateral renal scarring, even those with no previous symptoms, may exhibit acute deterioration of renal function during pregnancy and require aggressive treatment to prevent death; some of these women regain renal function after delivery, while others do not (Jacobson, Eklof, Eriksson, et al., 1989). Progressive deterioration of renal function over many years in patients with severe bilateral renal scarring is a major cause of ESRD in patients younger than 30 years of age (Arant, 1991; Pistor, Scharer, Olbing, et al., 1985; Salvatierra, Kountz, and Belzer, 1973; Mathew, 1987). The average mortality rate for patients on chronic dialysis in the United States is about 25 percent each year (Bloembergen, Port, Mauger, et al., 1994). Others die as a complication of renal transplantation. While none of these causes of death is the immediate consequence of untreated VUR, the possibility of an association cannot be ignored.

Harms of medical treatment

Adverse drug reactions

Antibiotic prophylaxis. One of the mainstays of the medical management of VUR is antimicrobial prophylaxis. The usual medications administered are trimethoprim/sulfamethoxazole, trimethoprim alone, and nitrofurantoin. The dose prescribed for prophylaxis typically is one-fourth to one-third of the dose recommended for full therapy. The incidence of drug-related adverse effects is lower with reduced dosages. Most reports describing adverse drug reactions pertain to adult patients taking the full dosage of the medication (Lawson and Paice, 1982).

Potential adverse reactions to antimicrobial prophylaxis include minor effects such as nausea, vomiting, abdominal pain, and bad taste in the mouth, as well as more serious side effects (Table 10 on page 42). Very few studies dealing with the medical management of reflux have reported minor effects. Determining whether abdominal complaints are related to medication or some other factor is often difficult. Underreported side effects may contribute to the lack of compliance with medication in some cases, and the need to change antibiotic prophylaxis because of side effects is also probably underreported. Bacterial resistance to antibiotic prophylaxis may also occur and is discussed in the section on UTI (page 36).

Reported side effects of trimethoprim/sufamethoxazole prophylaxis are uncommon. Uhari, Nuutinen,

Table 10. Adverse effects of antimicrobials commonly prescribed for antibiotic prophylaxis in children

Antibiotic	Adverse reactions
Cotrimoxazole	Skin rash/urticaria, nausea, vomiting, anorexia, dental caries (1–4%)
	Rare (<0.1%): serious dermatologic, hematologic, cardiovascular, central nervous system, endocrine, renal, hepatic effects
Trimethoprim	Skin rash/urticaria, nausea, vomiting, anorexia (2.5–7%)
	Rare (<0.1%): serious dermatologic, hematologic, cardiovascular, central nervous system, endocrine, renal, hepatic effects
Nitrofurantoin	Nausea, vomiting, abdominal pain 34% (less with macrocrystals) Headache, dizziness (less with macrocrystals); skin rash/urticaria
	Rare (<0.1%): hematologic, cardiovascular, central nervous system, gastrointestinal, hepatic, respiratory, dermatologic effects

Source: Computerized Clinical Information System, March 1996 (Micromedex, Inc., Denver CO); American Hospital Formulary Service Drug Information, 1995.

and Turtinen (1996) reported that medication was changed because of adverse effects in 15 percent of children receiving sulfonamides and 8 percent receiving trimethoprim. The most common adverse effect is allergic skin reaction, usually from the sulfa, and accounts for 90 percent of nonfatal drug reactions (Lawson and Paice, 1982). Uhari, et al. (1996) reported that 4.5 percent of children receiving prophylaxis developed urticaria, with an incidence of 7.4 events per 100 years at risk. Allergic skin reaction may occur after several weeks or months of therapy, but anaphylaxis is rare. Although neutropenia, thrombocytopenia and/or eosinophilia occur in 12–34 percent of children taking full-dose trimethoprim/sulfamethoxazole for only 10 days (Asmar, Maqbool, and Dajani, 1981), the incidence of these side effects in children receiving prophylactic dosages for periods as long as 1 year ranged from 0 percent (Smellie, Gruneberg, Normand, et al., 1982; Uhari, Nuutinen, and Turtinen, 1996) to 41 percent (Holland, Kazee, Duff, et al., 1982). In the latter study, in children with a white blood count (WBC) less than 5000/mm3, the WBC level normalized by the following visit in all cases. Another potential problem is dental caries related to the fructose in the liquid preparation, but this can be prevented by having the children brush their teeth after taking the drug. Other side effects include nausea, vomiting, abdominal pain, hepatotoxicity, and significant hypersensitivity reaction, but these effects have been reported only anecdotally in children. Although sulfamethoxazole and trimethoprim compete for sequential sites in the metabolic pathway of bacterial folic acid synthesis, children receiving prophylaxis have not developed folic acid deficiency. Trimethoprim/sulfamethoxazole is the most common drug associated with reactions requiring hospital admission, although the drug accounted for only 0.07 percent of hospital admissions (Mitchell, Lacouture, Sheehan, et al., 1988).

Trimethoprim alone has been reported to cause side effects in as many as 27 percent of patients (Brendstrup, Hjelt, Petersen, et al., 1990). Reported side effects included nausea, vomiting, or abdominal pain in 14 percent of patients, bad taste in the mouth in 6 percent, and headache, dizziness, dermatitis and pruritus in 8 percent. Of children receiving trimethoprim prophylaxis, 8 percent changed the drug because of side effects (Uhari, Nuutinen, and Turtinen, 1996). Hematologic and allergic reactions are uncommon (Smellie, Gruneberg, Normand, et al., 1982).

The incidence of side effects associated with nitrofurantoin depends on the drug preparation. Nitrofurantoin suspension is tolerated poorly, and as many as 55 percent of children taking this medication experience a side effect, including nausea, vomiting, or abdominal pain in 34 percent, bad taste in the mouth in 27 percent, and headache, dizziness, dermatitis, pruritus or fever in 12 percent; 30 percent changed the medication because of side effects (Brendstrup, Hjelt, Petersen, et al., 1990). Many of these effects may be eliminated by administering nitrofurantoin macrocrystals. The capsule may be opened and placed in the children's

food if they are unable to swallow the capsules. One group of children using the macrocrystals experienced no adverse effects (Lohr, Nunley, Howards, et al., 1977). Hematologic side effects are infrequent (Holland, Kazee, Duff, et al, 1982). More serious adverse reactions are extremely rare, with 1 study documenting only 40 reports out of 8.6 million uses (Coraggio, Gross, and Roscelli, 1989). Approximately 32 percent of children younger than age 2 years and 10 percent older than 2 years of age taking nitrofurantoin prophylaxis changed therapy because of adverse reactions (Uhari, Nuutinen, and Turtinen, 1996). In that study, it was not indicated whether children were receiving the suspension or macrocrystal preparation.

Anticholinergics. In children with bladder instability and VUR, anticholinergic therapy and timed voiding are often recommended in addition to antibiotic prophylaxis. Although several reports describe the frequency of reflux resolution in these patients, few descriptions of the adverse effects of anticholinergic medications are available. One reason for this lack of information may be that the dosage of anticholinergic medication is usually titrated to the lowest effective dose in each child, providing the maximum therapeutic effect in reducing bladder instability while minimizing the side effects. Facial flushing can be brought on more easily in warm or hot temperatures; thus, a lower dose may be necessary in summer or warm climates. A dry mouth is common. This side effect may be particularly bothersome to some children, yet have minimal effect on others. Table 11 lists possible adverse effects of the most commonly prescribed anticholinergic medications.

Hospitalization of patients receiving medical treatment

Many studies reported occurrences of UTI in children with reflux who received medical therapy, and some distinguished between episodes of clinical pyelonephritis and cystitis (Cardiff-Oxford Bacteriuria Study Group, 1978; Hanson, Hansson, and Jodal, 1989; Weiss, Duckett, and Spitzer, 1992). However, none of the studies reported on the proportion of children experiencing clinical pyelo-nephritis who required hospitalization.

Children with clinical pyelonephritis often have fever, and flank or abdominal pain, and may experience nausea, vomiting, and diarrhea. Decisions about whether to admit a child to the hospital for intravenous antibiotic therapy and rehydration vary, and may depend on duration and severity of symptoms, hydration status, sensitivity pattern of the bacterial strain and the child's age. If a child is hospitalized for pyelonephritis, in 1992 the mean length of stay was 4.1 days (U.S. Department of Health and Human Services, 1993).

Harms of surgery

Ureteral obstruction is a recognized complication following ureteral reimplantation. The other harms of surgical treatment of VUR occur less frequently. Many reports do not describe harms explicitly. Others indicate isolated events within the series, and these reports were used to review the types and approximate frequencies of surgical complications of antireflux surgery. The panel recognizes, however, that due to underreporting, the absence of reported complications in many studies may be misleading and that the actual complication rates may exceed reported values.

Table 11. Adverse effects of anticholinergic medications most commonly prescribed for bladder instability in children

Antibiotic	Adverse reactions
Oxybutynin chloride	Xerostomia (usually dose related) 40–45% vasodilation, facial flushing, mydriasis, decreased sweating, tachycardia, blurred vision, drowsiness, constipation (5–30%)
	Rare (< 0.1%): urinary retention, urticaria, hallucinations
Hyoscyamine	Xerostomia, decreased sweating, mydriasis, drowsiness, restlessness, blurred vision, tachycardia (5–30%)
	Rare (< 0.1%): Central nervous system effects, urinary retention, urticaria, speech disturbances
Propantheline	Xerostomia, constipation, cycloplegia (5–30%)
	Rare (<0.1%): Central nervous system, cardiovascular, endocrine, renal effects

Source: Computerized Clinical Information System, March 1996 (Micromedex, Inc., Denver, CO); American Hospital Formulary Service Drug Information, 1995.

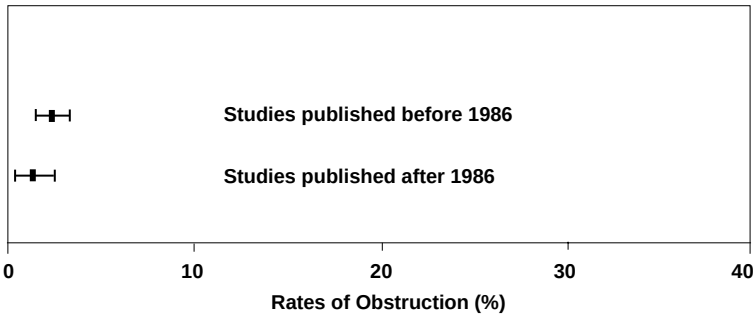

Figure 7. Combined rates of obstruction after surgery

Analysis of 33 studies showed that the rate of obstruction after ureteral reimplantation for VUR was 2 percent in studies after 1986 compared to a rate of approximately 4 percent in studies before 1986.

Obstruction

Thirty-three studies provided rates of obstruction after ureteral reimplantation for VUR (Table E–4, Appendix E). Figure 7 (page 44) shows the rate of obstruction in studies before and after 1986. All studies used either renal ultrasonography or intravenous pyelography to detect hydronephrosis indicative of obstruction. The likelihood of obstruction in the 33 series ranged from 0–9.1 percent, with a combined rate of 2 percent after 1986 (95% CI 1–4). The rate of obstruction was similar for different types of repair. Fourteen studies provided data regarding reoperation for obstruction (Table E-5, Appendix E). The reoperation rate ranged from 0.3–9.1 percent, with an overall incidence of 2 percent. On the basis of these studies, nearly every case of obstruction leads to reoperation so that the best estimate of obstruction is probably the proportion of patients requiring reoperation (2 percent).

Obstruction following endoscopic treatment of reflux. Fifteen series provided detailed information about postoperative ureteral obstruction following the subureteric injection technique as described by O'Donnell and Puri (1984) (Farkas, Moriel, and Lupa, 1990; Sauvage, Saussine, Laustriat, Becmeur, et al., 1990; Dodat and Takvorian, 1990; Puri, 1990; King and Gollow, 1988; Schulman, Pamart, Hall, et al., 1990; Sweeney and Thomas, 1987; Dewan and O'Donnell, 1991; Kaminetsky and Hanna, 1991; Davies and Atwell, 1991; Leonard, Canning, Peters, et al., 1991; Bhatti, Khattak, and Boston, 1993; Frey, Berger, Jenny, et al., 1992; Dewan and Guiney, 1992; Lipsky and Wurnschimmel, 1993). Using renal ultrasound or excretory urography, the incidence of transient dilation was reported in 2 series at 17 and 23 percent (Sweeney and Thomas, 1987; Bhatti, Khattak, and Boston, 1993). The 15 series included a total of 1,741 refluxing ureters treated using either Teflon™ (1,437 ureters) or collagen (304 ureters) as the injected substance. Seven (0.40 percent) persistent obstructions were reported, requiring ureteral reimplantation in 5, ureteral catheter drainage (5 days) in 1, and an unknown treatment in 1 (Dodat and Takvorian, 1990; Puri, 1990; Schulman, Pamart, Hall, et al., 1990; Sweeney and Thomas, 1987; Dewan and O'Donnell, 1991). All persistent obstructions reported occurred in patients with reflux who were treated with Teflon™. The amount of experience with the technique that the centers had gained when the obstructions occurred was not reported. In 10 of the 15 centers, persistent obstructions were not reported.

Bleeding

Although hematoma was reported in only 2 of 771 patients (0.26 percent) undergoing Politano-Leadbetter or Cohen transtrigonal ureteral reimplantation (Brandell and Brock, 1993; Ehrlich, 1985; Ehrlich, 1985; Broaddus, Zickerman, Morrisseau, et al., 1978; Price, Johnson, and Marshall, 1970; Garrett and Switzer, 1966; So, Brock, and Kaplan, 1981; Jonas, Many, Boichis, et al., 1974; Pypno, 1987; Ahmed and Tan, 1982), it occurred in 15 of 1,257 patients (1.2 percent) who received surgery using the Lich-Gregoir method (Arap, Abrao, and Menezes-de-Goes, 1981; Zaontz, Maizels, Sugar, et al., 1987; Funke, Chiari, and Planz, 1980; Marberger, Altwein, Straub, et al., 1978; McDuffie, Litin, and Blundon, 1977; Hampel, Richter-Levin, and Gersh, 1977; Hohenfellner, 1971; Houle, McLorie, Heritz, et al., 1992;

Wacksman, Gilbert, and Sheldon, 1992). In 1 study of the Lich-Gregoir technique, hematoma was reported in 13 of 371 patients (3.5 percent) (Marberger, Altwein, Straub, et al., 1978). Although bleeding from the bladder is thought to be less common after the Lich-Gregoir method than after the intravesical methods (Politano-Leadbetter, transtrigonal Cohen, or Glenn-Anderson advancement), specific data relating to this factor are not available.

Infection

Surgical wound infection following antireflux surgery was reported explicitly in only 2 cases (Garrett and Switzer, 1966). Other series did not report the occurrence or specific absence of this complication.

Bladder injury/voiding dysfunction

Several reports of temporary voiding dysfunction after extravesical ureteral surgery for reflux have been published. The incidence was as high as 15 percent in several series (Houle, McLorie, Heritz, et al., 1992; Wacksman, Gilbert, and Sheldon, 1992; Zaontz, Maizels, Sugar, et al., 1987). In most cases, the voiding dysfunction was associated with bilateral ureteral surgery and was self-limiting. However, intermittent catheterization, which may be problematic for families, was required during the period of voiding dysfunction. Late follow-up suggests that essentially all patients are likely to fully regain voiding efficiency (Fung, McLorie, Jain, et al., 1995). The overall incidence associated with the Lich-Gregoir method was 10 of 125 (8%), in contrast to no reported cases after intravesical techniques.

Contralateral reflux

The occurrence of contralateral reflux (CLR) after unilateral ureteral surgery has been reported in numerous series. It is important to determine not only the initial incidence (usually found at first postoperative cystography) but also the persistence of CLR over time. The presence of resolved VUR in the non-operated ureter has been thought to be a major risk factor for recurrence with contralateral operation, but evidence for this clinical impression is lacking. A recent report demonstrated this relationship in a small group of patients with unilateral antireflux surgery (Ross, 1995).

The incidence and persistence of contralateral reflux were estimated from reports that specifically indicated the occurrence of CLR, including some in which the incidence was zero. By definition this included only unilateral reimplantation or unilateral subureteric injection of Teflon™ in which a contralateral ureter was present. A total of 1,566 ureters were considered at risk, with an overall incidence of 142 reported new CLR (9.07 percent). Not all of these reports included adequate follow-up information, which was used to estimate persistence of the reflux. When specified, the type of surgical procedure was examined in terms of its effect on new CLR.

The rate of new CLR in studies reported before 1986 (13.4 percent) was higher than that reported after 1986 (4.7 percent). Although the reasons for this difference are unclear, an increase in the practice of contralateral reimplantation in case of any suspicion of prior reflux after 1986 and recognition of the influence of voiding dysfunction in reflux management in recent years may also have contributed to the difference. Reflux grade did not significantly affect the rate of contralateral reflux, although the rate was highest for Grade IV reflux at 3.7 percent compared with 1.5 percent for Grades I and II (Table 12). The surgical method of reimplantation did not influence the likelihood of new CLR. The rate of CLR after endoscopic treatment using Teflon™ was 2.9 percent and was not significantly different from that for other open surgical methods of correction.

Table 12. Estimated percentage chance of contralateral reflux for studies reported in 1987 or later (by grade and surgical method)

Factor	Estimate (95% confidence interval)
Grade	
Grade I/II	1.52% (0–5.49%)
Grade III	2.80% (0–12.73%)
Grade IV	3.66% (0–12.67%)
Grade V	2.53% (0–9.77%)
Surgical method	
Politano-Leadbetter	5.21% (1.29–10.31%)
Transtrigonal	1.90% (0.25–4.24%)
Lich-Gregoir	2.33% (0.26–5.39%)
Open surgery - other	5.07% (1.47–9.63%)
Teflon™	2.95% (0–10.58%)

Recent studies have offered some new insight. Ross, Kay, and Nasrallah (1995) reported a high incidence of CLR in ureters with previously demonstrated VUR. Diamond, Rabinowitz, Hoenig, et al. (1996) indicate that CLR is related to the grade of VUR rather than to the surgical technique.

Although uniform duration of follow-up is not available, the overall resolution rate of new CLR was 52.1 percent with 28.7 percent persisting at time of follow-up.

Follow-up was usually 1–2 years after surgical reimplantation; 13.8 percent of patients with new CLR underwent surgical correction at varying points of follow-up. Little follow-up data are available for patients reported after 1986. Clearly, an early decision to operate would mask possible spontaneous resolution.

Postoperative pain

No specific data are available regarding pain after surgical repair of VUR. Recent advances in pediatric pain management have altered the approach to pain management in children after major surgery. The increasingly widespread use of epidural analgesia and patient-controlled analgesia have markedly improved pain control after many surgical procedures (Cain, Husmann, McLaren, et al., 1995). Continuous epidural analgesia is particularly well suited to antireflux surgery because it reduces incisional pain as well as the intensity and frequency of bladder spasms, a common occurrence after reimplantation surgery. Urethral catheterization is necessary while the epidural catheter is in place. Although no objective data are available, these complications appear to be less severe after extravesical reimplantation, in part because of the usually shorter period of catheterization. Several studies have reported the use of intravesical repairs without postoperative catheter drainage (Brandell and Brock, 1993).

Hospitalization after antireflux surgery

The length of hospitalization in children undergoing open antireflux surgery was reported in 10 studies, with a total of 637 patients and 826 ureters (Table 13). The mean stay varied from 2.4 days (Zaontz, Maizels, Sugar, et al., 1987) to 13.9 days (Rezmi, Ozen, Erkan, et al., 1984). The length of stay appeared to vary with the surgical technique and whether postoperative ureteral stents were used.

Following extravesical forms of ureteroneocystostomy (e.g., detrusorrhaphy), Zaontz, Maizels, Sugar, et al. (1987) reported a mean length of stay of 2.4 days. Wacksman, Gilbert, and Sheldon (1992), reporting a similar surgical technique, had a longer hospital stay of 4.2–5.2 days. Patients undergoing intravesical techniques of antireflux surgery (Cohen, Leadbetter-Politano, Glenn-Anderson) had hospital stays averaging 2.7–10.6 days (Brock, 1983; Burbige, 1991; Fort, Selman, and Kropp, 1983).

Temporary ureteral stents generally are used after ureteroneocystostomy with tapering, a technique utilized in children with Grade V and some with Grade IV reflux. Some clinicians also use postoperative stents in lower grades of reflux to maintain the patency of the newly-created

Table 13. Mean and range of hospital stay for surgical therapy of vesicoureteral reflux

Study	Patients	Ureters	Reimplantation type1	Mean hospital stay (days)	Hospital stay range with/ without catheterization
Hampel, Richter-Levin, and Gersh, 1977	51	83	LG	4	Not stated
So, Brock, and Kaplan, 1981	52	87	GA, LP	5	3 to 9 days
Fort, Selman, and Kropp, 1983	63		GA, LP, Cohen, Hutch	10.6/9.3	6–12/3–16 days
Remzi, Ozen, Evkan, et al., 1984	89	143	LP	13.94	11.6/15.3 days[2]
Ehrlich, 1985	63	74	Kalicinski	6	Unstated
Pypno, 1987	43	80	Cohen	8.6	5–14 days
Zaontz, Maisels, Sugar, et al., 1987	79	120	Detruss.	2.4	1 to 6 days
Burbige, 1991	120	180	LP, Cohen	4.2/5.6	5–7/3–5 days
Wacksman, Gilbert, and Sheldon, 1992	132	211	Detruss.	4.2–5.2	Not stated
Brock, 1993	34	57	GA, LP, Cohen	5.4/2.7	4–8/2–4 days
Totals	637	826			

[1] GA=Glenn-Anderson; LP=Leadbetter-Politano.
[2] Remzi reports the average stay with a urethral catheter/suprapubic tube. His patients had no ureteral catheters.

ureterovesical junction. In general, patients with ureteral stents have had a longer length of stay (5.4–5.6 days) than nonstented patients (2.7–4.2 days) (Brock, 1993; Burbige, 1991).

Concerns regarding length of stay were not raised in the United States until relatively recently and now are emphasized because of the increasing cost of medical care in this country. In a review of 186 children undergoing ureteroneocystostomy from 1986 to 1994, McCool and Joseph (1995) found that the mean length of stay had decreased from 3.6–2.3 days. It is likely that average lengths of stay for children undergoing open antireflux surgery will continue to decrease.

Most endoscopic interventions for reflux are treated as outpatient procedures or require less than 24-hour in-hospital stays.

Adverse effects of surveillance testing

Risk of urinalysis

Routine urinalysis and urine cultures carry very little risk except skin sensitivity to cleansing agents. There is potential for misinterpretation of urinalysis and/or urine culture due to inappropriate collection and/or contamination that may result in erroneous diagnosis of UTI and therefore inappropriate therapeutic decisions.

Risk of radiologic evaluation

Surveillance evaluation using radiologic techniques represents a major component of follow-up in patients with reflux. Risks of surveillance for the various methods can be divided into risks related to physical manipulation in the performance of the test and risk from contrast or radiation.

Renal imaging

Harms from physical manipulation. All imaging techniques using contrast or radioactive tracer require administration via venipuncture, which may be stressful to infants and children and their parents to a variable degree. In addition, extravasation of the imaging agent into the soft tissues may cause inflammation, particularly with iodinated contrast, but this complication is uncommon. Ultrasonographic studies appear to have little significant impact on children, either from the direct manipulation or from the transmitted sound waves.

Risk of contrast. Adverse reactions to intravenous contrast media are uncommon in the pediatric population. Minor reactions with IVP (ionic contrast media) occur in 6 percent and include nausea, vomiting, urticaria, flushing, pruritus, and headache (Gooding, Berdon, Brodeur, et al., 1975). Major reactions, including cardiac arrest, pulmonary edema, apnea, seizures, bronchospasm,

Table 14. Radiation exposure in upper urinary tract imaging[1]

Study		Kidney	Bladder wall	Ovaries	Testes	Whole body	Typical dose
				Urography (rad/film)			
IVP[2]							
6 mo.	AP	—	—	0.0072	0.00092	0.2[3]	—
	Pelvis	—	—	0.024	0.023		—
4 yr.	AP	—	—	0.011	0.0012	0.3[3]	—
	Pelvis	—	—	0.033	0.055		
12 yr.	AP	—	—	0.035	0.0054	0.5[3]	—
	Pelvis	—	—	0.038	0.075		
				Scintigraphy (rad/mCi)			
Tc-99m-MAG-3 renogram		0.014	0.48	0.026	0.016	0.007	3.25 mCi
Tc-99m-DTPA renogram							
2 hr void		0.090	0.12	0.011	0.007	0.006	9.75 mCi
4 hr void		0.090	0.27	0.015	0.011		
Tc-99m-DMSA renal scan		0.850	0.07	0.014	0.006	0.016	3.25 mCi

[1] References: IVP—Kirks, 1991; MAG-3 and DTPA—Stabin, Taylor, Eshima, et al., 1992; MPI, 1985.
[2] Typical IVP is 2–3 films.
[3] 4 films.

Table 15. Radiation exposure in lower tract imaging (rad)[1]

Study	Kidney	Bladder wall	Ovaries	Testes	Whole body	Typical dose
VCUG[2]	—	—	0.208	—	—	—
VCUG (tailored; low-dose)[3]	—	—	0.029	—	—	—
Tc-99m cystography	<0.001	0.025	0.002	<0.001	<0.001	1 mCi

[1] References: Bisset, Strife, and Dunbar, 1987; Conway, King, Betman, et al., 1972; Kleinman, Diamond, Karellas, et al., 1994; Willi and Treves, 1983.
[2] Exposure variable and depends on fluoroscopy time and number of films taken; Bisset et al., 1987.
[3] Assuming digital fluoroscopic time over the bladder of 3 to 5 seconds; Kleinman et al., 1994.

laryngeal edema, and shock, are rare. In a large group of pediatric patients, the incidence of serious reactions to ionic contrast media was 0.5 percent, but there were no deaths (Gooding et al., 1975). The risk of adverse reaction with nonionic contrast media is significantly less (Bisset, Strife, and Kirks, 1991). There is no risk of allergy to agents used for scintigraphy.

Radiation exposure. The average radiation exposure in children undergoing upper urinary tract evaluation is shown in Table 14, page 47. The average annual radiation exposure in the environment is 0.250 rad (Mettler and Upton, 1995).

Cystography

Harms from physical manipulation and contrast. McAlister, Cacciarelli, and Shackelford (1974) describe atypical cases involving complications of cystography, and suggest ways of avoiding complications in clinical experience. Zerin and Shulkin (1992) studied 228 children who had voiding cystourethrograms or radionuclide cystograms and noted irritative voiding symptoms in 70 (35.1 percent). Three patients developed fever, and urine cultures were negative in all. Sixty-three of 228 patients received no postprocedural prophylaxis, and postcatheterization symptoms were only slightly higher (37 percent) compared with 34.5 percent in the nonantibiotic group. No significant difference in symptoms was reported between children having nuclear cystograms and those having contrast cystograms. There is a risk of inducing a UTI if the procedure is not performed using sterile technique. Individuals allergic to iodinated contrast do not develop an allergic reaction during VCUG.

The psychological consequences of cystographic studies have not been formally addressed, but anecdotal experience suggests that many children sustain varying degrees of psychological trauma from catheterization.

Radiation exposure. The average radiation exposure in children undergoing lower urinary tract studies is shown in Table 15.

Chapter 4: Treatment recommendations

Only a few recommendations can be derived purely from scientific evidence of a beneficial effect on health outcomes (as opposed to intermediate outcomes; see page 20). Evidence of the efficacy of medical management on health outcomes is available only for Grades I–IV reflux. Control data are lacking to compare outcomes for intermittent with those for continuous antibiotic therapy. Open surgical repair, although proven to cure reflux in 90–98 percent of patients, has not been demonstrated to improve health outcomes other than pyelo-nephritis; for this outcome, the evidence suggests that children with Grade III or IV reflux receiving continuous antibiotic prophylaxis are 2.5 times more likely to develop pyelonephritis than children who have undergone successful antireflux surgery. Accordingly, based on health outcomes data alone, health outcomes for medical and surgical treatment can be compared only for children with Grade III or IV reflux. Even for these patients, available outcomes data provide little information on whether the benefits of treatment exceed its potential risks, nor do they aid the clinician in selecting the most appropriate treatment options for initial therapy or for persistent reflux. Thus, evidence-based recommendations provide limited practical guidance for the clinician. The need for further outcomes research is addressed in Chapter 5.

The following more detailed recommendations, which generally lack empirical scientific support, reflect the clinical experience and opinion of the panel. The panel recognizes the limitations of relying on opinion as a basis for generating practice guidelines. This description of practice patterns is instead offered as an aid to clinicians interested in more detailed recommendations and in the perspective of pediatric urologists and nephrologists who specialize in reflux care. Full documentation of the panel's underlying rationale for the recommendations is provided: statements based on opinion are explicitly identified, and evidence-based recommendations are accompanied by appropriate references to outcomes analyses in Chapter 3 (see Rationale for recommendations, page 52).

As outlined in Chapter 2, the recommendations were derived from a survey of preferred treatment options for 36 clinical categories of children with reflux. The recommendations are based on the outcomes analysis presented in detail in Chapter 3 and on the clinical experience and opinion of the panel. Treatment options selected by 8 or 9 of the 9 panel members are classified as guidelines and given the strongest recommendation language. (The word "should" is used to indicate treatment options in this category; e.g., "Children with Grade V reflux should undergo surgical repair.") Treatment options that received 5 to 7 votes are designated as preferred options, and treatment options that received 3 to 4 votes are designated as reasonable alternatives. Treatments that received no more than 2 votes are designated as having no consensus and are not recommended.

Assumptions

The treatment modalities considered included (1) no treatment (including intermittent antibiotic therapy); (2) bladder training; (3) continuous antibiotic prophylaxis; (4) antibiotic prophylaxis and bladder training; (5) antibiotic therapy, bladder training and anticholinergics; (6) open surgical repair; and (7) endoscopic repair. These modalities are described in Chapter 1. The recommendations assume that the patient has uncomplicated reflux (e.g., no breakthrough UTI, voiding dysfunction, duplex systems, or other comorbid conditions); see Special considerations below regarding the care of patients with additional complications. The recommendations apply only to the scope of the topic of this report (see Chapter 2) and therefore do not address diagnosis of reflux, treatment of patients over age 10, management of reflux complicated by other factors (see Special considerations below) or surveillance testing.

Special considerations

The treatment recommendations apply only to patients with uncomplicated reflux. More aggressive treatment interventions may be indicated for children with breakthrough UTI or other medical

complications, such as renal insufficiency, new or progressive scarring, obstructive congenital anomalies of the upper urinary tract (e.g., ureteropelvic junction), solitary kidney, intrarenal reflux, secondary reflux (e.g., neuropathic or iatrogenic reflux, reflux associated with structural urologic anomalies such as ureterocele, ectopic ureter, posterior urethral valves, prune-belly syndrome, or exstrophy), or other medical comorbid conditions. There is limited direct evidence that duplication anomalies increase the risk of developing persistent reflux; surgical cure rates appear to be comparable with duplex and single systems (see Chapter 3, page 26). Treatment options may be countermanded by such factors as antibiotic allergies, intolerance or noncompliance, limitations in surgical skills and inadequate hospital facilities. Finally, the intensity of treatment may need to be modified depending on the nature of the doctor-parent-patient relationship and to accommodate such factors as limited access to care and personal preference.

An important variable in the scope of treatment is the presence of concurrent voiding dysfunction, a common occurrence among children with reflux. Because resolution of voiding dysfunction may be accompanied by resolution or diminution of reflux, such children may require more aggressive treatment with antibiotics, anticholinergics, and bladder training (e.g., timed voiding, biofeedback, parental monitoring of voided volumes). Surgical repair of reflux is less successful in children with voiding dysfunction, and thus a higher threshold is necessary before surgery is recommended in such patients. Children with reflux should therefore be assessed for voiding dysfunction as part of their initial evaluation.

Recommendations

The recommendations that follow emphasize the importance of shared decision-making in the management of reflux. The treatment recommendations are tabulated in Table 16 on pages 52–53.

Recommendations for children without scarring at diagnosis

Age at diagnosis: Infants (<1year)

Initial treatment. Infants with Grades I–IV reflux should be treated initially with continuous antibiotic prophylaxis. In infants with Grade V reflux, continuous antibiotic prophylaxis is the preferred option for initial treatment.

Follow-up treatment. In infants who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (see Duration of medical management, page 51). For patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic therapy, periodic cystography, or surgery. Surgical repair is the preferred option, however, for patients with persistent unilateral Grades III–IV reflux. Patients with persistent bilateral Grades III–IV reflux or Grade V reflux should undergo surgical repair.

Age at diagnosis: Preschool children (ages 1–5 years)

Initial treatment. Preschool children with Grades I–II reflux or unilateral Grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis. Continuous antibiotic prophylaxis is the preferred option in preschool children with bilateral Grades III–IV reflux. In patients with unilateral Grade V reflux, continuous antibiotic prophylaxis is the preferred option for initial treatment, although surgical repair is a reasonable alternative. In patients with bilateral Grade V reflux, surgical repair is the preferred option and continuous antibiotic prophylaxis is a reasonable alternative.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (*see* Duration of medical management, page 51). In children with persistent Grades I–II reflux, there is no consensus regarding the role of continued antibiotic therapy, periodic cystography or surgery. Surgery is the preferred option for children with persistent Grades III–IV reflux. Patients with persistent Grade V reflux should undergo surgical repair.

Age at diagnosis: School children (ages 6–10 years)

Initial treatment. School children with Grades I–II reflux should be treated initially with continuous antibiotic prophylaxis. Continuous antibiotic prophylaxis is the preferred option for initial treatment of patients with unilateral Grades III–IV reflux. In patients with bilateral Grades III–IV reflux, surgical repair is the preferred option, although continuous antibiotic prophylaxis is a reasonable alternative. Patients with Grade V reflux should undergo surgical repair.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (see Duration of medical management, page 51). In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. Surgery is the preferred option for persistent reflux in children with Grades III–IV reflux.

Recommendations for children with scarring at diagnosis

Age at diagnosis: Infants (<1 year)

Initial treatment. Infants with scarring at diagnosis and Grades I–IV reflux should be treated initially with continuous antibiotic prophylaxis. In infants with Grade V reflux and scarring, continuous antibiotic prophylaxis is the preferred option for initial treatment, and surgical repair is a reasonable alternative.

Follow-up treatment. In infants who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (see Duration of medical management). In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. In boys with persistent unilateral Grades III–IV reflux, surgical repair is the preferred option. Boys with persistent bilateral Grades III–IV reflux, girls with persistent Grades III–IV reflux, and boys and girls with persistent Grade V reflux should undergo surgical repair.

Age at diagnosis: Preschool children (ages 1–5 years)

Initial treatment. Preschool children with scarring at diagnosis and either Grades I–II reflux or unilateral Grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis. Antibiotic therapy is the preferred option in children with bilateral Grades III–IV reflux and scarring, and surgical repair is a reasonable alternative. Surgery is the preferred option for patients with unilateral Grade V reflux. Patients with bilateral Grade V disease and scarring should undergo surgical repair as initial treatment.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (see Duration of medical management). In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. Girls with persistent Grades III–IV reflux and boys with persistent bilateral Grades III–IV reflux should undergo surgical repair. Surgery is the preferred option for boys with persistent unilateral Grades III–IV reflux and girls with bilateral Grades III–IV reflux. For patients with persistent Grade V reflux who have not undergone surgery as initial treatment, surgical repair is the preferred option.

Age at diagnosis: School children (ages 6–10 years)

Initial treatment. School children with scarring at diagnosis and Grades I–II reflux should be treated initially with continuous antibiotic prophylaxis. In children with unilateral Grades III–IV reflux and scarring, antibiotic therapy is the preferred option. Patients with bilateral Grades III–IV reflux or Grade V reflux should undergo surgical repair as initial treatment.

Follow-up treatment. In children who continue to demonstrate uncomplicated reflux, antibiotic prophylaxis should be continued (see Duration of medical management). In patients who have persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. Patients with persistent unilateral Grades III–IV reflux who have not undergone surgery as initial treatment should undergo surgical repair.

Duration of medical management

The recommendations refer to "persistent reflux" but do not specify the amount of time that must elapse before VUR is considered persistent. Little scientific evidence exists for determining how long to continue antibiotic prophylaxis before recommending surgical repair, and this decision is therefore left to clinical discretion in consultation with parents. The duration of reflux is an important consideration. As indicated in Table 2 (page 23), which is based on the model described in Chapter 2 and Appendix C, the probability that reflux will resolve spontaneously depends on the duration and grade of reflux. Other factors to consider include the patient's surgical candidacy, comorbidities, tolerance of antibiotics, socioeconomic factors, compliance to medications and follow-up, and parental preferences and concerns.

(continued on page 54)

Table 16. Treatment recommendations

Recommendations were derived from a survey of preferred treatment options for 36 clinical categories of children with reflux. The recommendations are classified as follows:

Guidelines = Treatments selected by 8 or 9 of 9 panel members, given the strongest recommendation language.
Preferred Options = Treatments selected by 5–7 of 9 panel members.
Reasonable Alternatives = Treatments selected by 3–4 of 9 panel members.
No Consensus = Treatments selected by no more than 2 of 9 panel members.

The treatment recommendations apply to both boys and girls with primary vesicoureteral reflux.

Treatment recommendations for children without scarring at diagnosis

Clinical presentation (age at presentation)		**Treatment**					
		Initial (antibiotic prophylaxis or open surgical repair)			**Follow-up[1]** (continued antibiotic prophylaxis, cystography or open surgical repair)		
VUR grade laterality	Age (years)	Guideline	Preferred option	Reasonable alternative	Guideline	Preferred option	No consensus[2]
I-II Unilateral or bilateral	<1	Antibiotic prophylaxis					Boys and girls
	1-5	Antibiotic prophylaxis					Boys and girls
	6-10	Antibiotic prophylaxis					Boys and girls
III-IV Unilateral or bilateral	<1	Antibiotic prophylaxis			Bilateral: Surgery if persistent[3]	Unilateral: Surgery if persistent[3]	
	1-5	Unilateral: Antibiotic prophylaxis	Bilateral: Antibiotic prophylaxis			Surgery if persistent[3]	
	6-10		Unilateral: Antibiotic prophylaxis Bilateral: Surgery	Bilateral: Antibiotic prophylaxis		Surgery if persistent[3]	
V Unilateral or bilateral	<1		Antibiotic prophylaxis		Surgery if persistent[3]		
	1-5		Bilateral: Surgery Unilateral: Antibiotic prophylaxis	Bilateral: Antibiotic prophylaxis Unilateral: Surgery	Surgery if persistent[3]		
	6-10	Surgery					

[1]For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
[2]No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
[3]See Duration of Reflux in the text regarding the length of time that clinicians should wait before recommending surgery.

Table 16. Treatment recommendations (continued)

Recommendations were derived from a survey of preferred treatment options for 36 clinical categories of children with reflux. The recommendations are classified as follows:

Guidelines = Treatments selected by 8 or 9 of 9 panel members, given the strongest recommendation language.
Preferred Options = Treatments selected by 5–7 of 9 panel members.
Reasonable Alternatives = Treatments selected by 3–4 of 9 panel members.
No Consensus = Treatments selected by no more than 2 of 9 panel members.

The treatment recommendations apply to both boys and girls with primary vesicoureteral reflux.

Treatment recommendations for children with scarring at diagnosis

Clinical presentation (age at presentation)		**Treatment**					
		Initial (antibiotic prophylaxis or open surgical repair)			**Follow-up[1]** (continued antibiotic prophylaxis, cystography or open surgical repair)		
VUR grade laterality	Age (years)	Guideline	Preferred option	Reasonable alternative	Guideline	Preferred option	No consensus[2]
I-II Unilateral or bilateral	<1	Antibiotic prophylaxis					Boys and girls
	1-5	Antibiotic prophylaxis					Boys and girls
	6-10	Antibiotic prophylaxis					Boys and girls
III-IV Unilateral	<1	Antibiotic prophylaxis			Girls: Surgery if persistent[3]	Boys: Surgery if persistent[3]	
	1-5	Antibiotic prophylaxis			Girls: Surgery if persistent[3]	Boys: Surgery if persistent[3]	
	6-10		Antibiotic prophylaxis		Surgery if persistent[3]		
III-IV Bilateral	<1	Antibiotic prophylaxis			Surgery if persistent[3]		
	1-5		Antibiotic prophylaxis	Surgery	Surgery if persistent[3]		
	6-10	Surgery					
V Unilateral or bilateral	<1		Antibiotic prophylaxis	Surgery	Surgery if persistent[3]		
	1-5	Bilateral: Surgery	Unilateral: Surgery			Surgery if persistent[3]	
	6-10	Surgery					

[1]For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
[2]No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
[3]See Duration of Reflux in the text regarding the length of time that clinicians should wait before recommending surgery.

Other management recommendations

In children with VUR, at initial evaluation the urine should be assessed for infection and proteinuria, and the child's height, weight, and blood pressure should be measured. If the child shows evidence of renal scarring, hydronephrosis, or has a solitary kidney, or known underlying renal disease, a serum creatinine should also be obtained.

In children with VUR, urethral dilation and internal urethrotomy are not beneficial. In addition, cystoscopic examination of the ureteral orifices does not appear to aid in predicting whether reflux will resolve (see Chapter 1, page 12). Furthermore, evocative cystometry is unnecessary in children with reflux and normal voiding function. However, in children with symptoms of voiding dysfunction, urodynamic evaluation may be beneficial.

The personal preferences of parents (and, at older ages, patients) must be considered in weighing the benefits and harms of treatment options. The clinician should provide parents with information about the known benefits and harms of available options, including continuous antibiotic prophylaxis, surgery, and intermittent antibiotic therapy. The clinician should indicate to what extent the estimates of benefits and harms are based on scientific evidence or on opinion and clinical experience. Given the general lack of direct evidence that any 1 treatment option is superior to another (especially when total benefits, harms, costs, and inconvenience are taken into consideration), parents' and patients' preferences regarding treatment options should generally be honored. To the extent that parents seek physicians' advice on how to proceed, the specific treatment guidelines are offered (Table 16 on pages 52–53).

In children with reflux, a urine culture should be obtained if there are symptoms and/or signs of a UTI. In a child with a suspected UTI, proper specimen collection is important. In girls and uncircumcised boys who are not toilet trained, a urinalysis or urine culture obtained from a contaminated bag specimen may yield an erroneous diagnosis of infection and therefore result in inappropriate management decisions. In such children, a urine specimen obtained by catheterization or suprapubic aspiration is encouraged to minimize the likelihood of a false-positive diagnosis of UTI.

Follow-up evaluation should be performed at least annually, at which time the patient's height and weight should be recorded. In addition, a urinalysis should be performed. If renal scarring has been demonstrated, the blood pressure should also be measured, irrespective of whether the child has reflux that is persistent, resolved spontaneously, or has been corrected surgically.

In deciding how often to obtain follow-up cystography, the clinician should take into consideration the likelihood of spontaneous resolution (see Table 2 on page 23), the risks of continued antibiotic prophylaxis, and the risks of radiologic study. In general, cystography does not need to be performed more than once per year.

In children with reflux who are toilet trained, regular, volitional low-pressure voiding with complete bladder emptying should be encouraged. If it is suspected that the child is experiencing uninhibited bladder contractions, anticholinergic therapy may be beneficial.

In children in whom antireflux surgery is chosen, the panel does not recommend the endoscopic form of therapy because of the lack of proven long-term safety and efficacy of most materials used for injection and the lack of approval of such materials by the U.S. Food and Drug Administration.

Rationale for recommendations

The following recommendations to offer continuous antibiotic prophylaxis as initial therapy are based on limited scientific evidence. No controlled studies have demonstrated that continuous antibiotic prophylaxis achieves better health outcomes in children with reflux than intermittent treatment of UTI. The opinion of the panel, however, is that maintaining continuous urine sterility is beneficial in reducing the risk of renal scarring and that this benefit outweighs the potential adverse effects of antibiotics.[3] Observational data from patients with

[3] The argument for continuous antibiotic prophylaxis is especially compelling during infancy, when diagnosing UTI is difficult. Recommendations to initiate antibiotic therapy when reflux is diagnosed in school children, even when the reflux is mild (Grades I–II), are based on the panel's belief that such children continue to face a risk of scarring and that this risk is independent of grade.

Grades I–III reflux suggest that at least 50 percent of reflux cases resolve within 3–5 years of continuous antibiotic prophylaxis (see Chapter 3). For Grades I–IV reflux, the panel generally favors continuous antibiotic prophylaxis over immediate surgical repair because it is less invasive and is associated with fewer risks over the short term.

Recommendations to proceed to surgery in cases that have not resolved spontaneously while the patient was receiving continuous antibiotic prophylaxis are supported by limited scientific evidence: open antireflux surgery is 95–98 percent effective in correcting reflux, and the risk of pyelonephritis is 2–2.5 times greater in children with Grades III–IV reflux managed medically compared with surgically treated patients. The expert opinion of most panel members is that surgery also reduces the risk of pyelonephritis in girls with Grades I–II reflux and in boys and girls with Grade V reflux. Panel members believe that breakthrough UTI increases the risk of renal scarring. Although the International Reflux Study showed no difference between medical and surgical treatment in the incidence of new renal scarring at 5 years, 80 percent of new renal scars in the surgical group appeared by 10 months after randomization, and thus the rate of new renal scarring between 1 and 5 years following randomization was higher in the medical group. Some panel members believe that with longer follow-up, the incidence of new renal scars in the surgical group will be less than in the medical group. Some panel members also believe that females with unresolved reflux are more likely to experience pyelonephritis during pregnancy than women without reflux, although women who have had antireflux surgery also develop pyelonephritis. The panel believes that the benefits of immediate correction of reflux in patients for whom surgery was recommended, even when coupled with its risks, outweigh the potential harms of continuous antibiotic prophylaxis (e.g., inconvenience of long-term therapy, adverse drug reactions, periodic surveillance testing).

More aggressive recommendations for the treatment of girls than of boys (e.g., for persistent Grades III–IV reflux in school children) are based on epidemiologic evidence that girls face a higher risk of acquiring UTI than do boys (see Chapter 3, page 36). More aggressive recommendations for the treatment of Grade V reflux (e.g., surgical repair as initial therapy) are based on the panel's opinion that such cases are unlikely to resolve spontaneously on antibiotic therapy, that surgery is effective in resolving severe reflux and that these benefits outweigh the potential harms of surgery. More aggressive recommendations for children who have renal scarring at diagnosis are based on the panel's opinion that such patients face a higher risk of progressive scarring and decreased renal functional reserve.

The panel's treatment recommendations are based on its opinion that the benefits of treatment outweigh the potential harms. There is little scientific evidence to confirm these assumptions, however, and therefore clinicians and parents may choose other options if they assign different weights to potential outcomes. For example, some clinicians and parents may not share the panel's opinion that the benefits of one-time surgical correction of persistent reflux, even when coupled with its potential harms, outweigh the inconvenience, cost, and risk of side effects from long-term antibiotic prophylaxis. Choosing continuous or intermittent antibiotic therapy under such circumstances is appropriate given the lack of scientific evidence to suggest otherwise.

Chapter 5: Research priorities

Many aspects of primary VUR remain incompletely understood. The panel identified the following areas as needing further investigation.

Development of VUR: The cause of the maldevelopment of the ureterovesical junction is unknown. Because VUR is often related to voiding dysfunction, research into the development of the autonomic nervous system of the bladder and its effect on morphological bladder development may allow an understanding of the pathoembryology of VUR.

VUR is greater in severity in newborn boys than girls. This phenomenon may be secondary to elevated voiding pressures in the newborn male (Gierup, 1970; Hjalmas, 1976; Sillen, Bachelard, Harmanson et al., 1996). Whether these differences result from dissimilar forms of urethral development and/or autonomic nervous system development is unknown. Investigation of the bud theory of Mackie and Stephens (1975) as applied to VUR is suggested to better understand the relationship between reflux and renal scarring that may be present at birth. Determination of whether fetal reflux has a "water hammer" effect deserves study.

Further investigation of the neurologic changes of the pediatric bladder with maturation that could influence bladder function and physiology, particularly voiding pressures, is needed. Studies should evaluate whether anatomic changes at the bladder neck or a functional disorder of the striated sphincter or bladder neck could account for elevated intravesical pressures.

Reflux resolution: The panel found evidence, based on a few large studies, that resolution of Grades I and II reflux may not depend on patient age or laterality (i.e., unilateral or bilateral). In Grade III reflux, on the other hand, it was suggested that patient age and laterality were important prognostic considerations. In Grade IV reflux, only laterality could be evaluated. Confirmation of these concepts by other large centers would be worthwhile. Furthermore, refinement of predictive criteria for reflux resolution by patient age, reflux grade, and laterality would be useful. In addition, further study of the likelihood of resolution of low-grade reflux during adolescence, as described by Lenaghan, Whitaker, Jensen, et al. (1976) and by Goldraich and Goldraich (1992), is necessary.

Renal scarring: The development of renal scarring in children with reflux is incompletely understood. Further investigation of the roles of bacterial virulence factors and host immune and inflammatory responses in the evolution of renal scarring is necessary. Studies should evaluate methods of affecting the host immune or inflammatory response that could reduce renal scarring during pyelonephritis (Roberts, 1992). Investigation of why younger children, particularly those under 1–2 years of age, appear to be more likely than older children to develop renal scarring from pyelonephritis would be useful.

It is well recognized that pyelonephritis and renal scarring can occur in children without reflux. The extent to which reflux increases the risk of renal scarring and the mechanism of this effect deserve investigation.

The panel attempted to analyze the association between new and progressive scarring in children undergoing medical or surgical treatment for reflux and bacteriuria. Because of extremely limited data, this relationship could not be evaluated. Further investigation into the factors leading to new renal scarring in children with reflux is important. In addition, assessment of whether there are long-term differences in the incidence of new scars in children managed medically and surgically is necessary.

Further analysis of the risk factors for end-stage renal disease, particularly the relative contributions of "congenital" scarring, intervening infection, voiding dysfunction, and hypertension management, would be useful.

More randomized prospective trials comparing the incidence and timing of new scarring, as assessed by DMSA scan, in children with Grades III and IV reflux are important, because previous studies, which used IVP for scar detection, have been difficult to interpret. Whether the risk of new scarring in a child with Grade III or IV reflux decreases as reflux grade decreases or reflux resolves should also be analyzed.

Voiding dysfunction: The role of voiding dysfunction in the pathogenesis of VUR and its risk in reflux complications, such as renal scarring, deserves further investigation. The role of urodynamic studies in infants and children with reflux,

with or without voiding dysfunction, should be evaluated (Sillen, Bachelard, Harmanson, et al., 1996). Matched, controlled studies of anticholinergic therapy and bladder retraining on reflux-related outcomes in children with voiding dysfunction are also necessary.

Medical therapy: A comparative analysis of the efficacy of various forms of antibiotic prophylaxis in preventing infection and renal scarring would be important. Furthermore, studies to assess the duration and dosage of prophylaxis are indicated. An evaluation of the adverse effects of various forms of continuous antibiotic prophylaxis in children and examination of the proportion who do not tolerate prophylaxis or who develop resistance would be important. In addition, compliance with prophylaxis regimens should be evaluated, in particular comparing those who have received prophylaxis for less than 6 months with those who have received therapy for more than 2 years. In addition, a trial comparing reflux-related outcomes in children receiving continuous prophylaxis with those in children receiving intermittent therapy, particularly comparing children younger than age 5 years with older children, would be prudent. Whether anticholinergic therapy is beneficial in children with reflux but no sign of voiding dysfunction should be studied. The short- and long-term risk of stopping prophylaxis in individuals with reflux who have been infection-free deserves evaluation. The efficacy of periodic surveillance, urinalysis, and urine culture in asymptomatic children with reflux should be studied.

Surgical therapy: Development of new techniques of antireflux surgery, particularly minimally invasive techniques, is indicated. Newer materials that can be used for endoscopic subureteral injection and that are safe in children should be studied. Whether current techniques of antireflux surgery cause transient increases in upper tract pressures, potentially resulting in renal injury, should be studied. In addition, the mechanism for new-onset contralateral reflux in children undergoing unilateral antireflux surgery should be studied further, and methods of preventing contralateral reflux should be developed. More effective techniques should be developed for surgical therapy in children with Grade V reflux. In addition, whether early correction of reflux in children with Grade V reflux alters reflux-related outcomes should be analyzed further.

Bladder function/training: Whether bladder training alters reflux-related outcomes deserves study. In addition, whether reflux resolution is enhanced after successful toilet training and maturation of bladder function should be evaluated. Whether pharmacologic manipulation, beyond simple anticholinergic therapy, could be useful in normalizing bladder dynamics should also be studied.

Imaging: The effect of voiding cystourethrography on children should be analyzed, and less traumatic methods of determining whether reflux is present should be developed. Techniques of voiding cystourethrography that result in less radiation exposure, such as the tailored low-dose fluoroscopic method (Diamond, Kleinman, Spevak, et al., 1996), should be developed. Clinicians should refine the ideal duration of time between cystograms in children being treated for reflux. In addition, the role of newer forms of renal imaging, such as SPECT, helical CT and power Doppler ultrasound, in the diagnosis of acute pyelonephritis and renal scarring, should be studied. Furthermore, the indications for obtaining a voiding cystourethrogram in a child with a UTI should be refined. Efforts should be made to determine prognostic criteria for likelihood of reflux resolution based on bladder volume and pressure at which reflux occurs and volume of refluxing urine.

Genetics of reflux: Further evaluation of the genetics of reflux deserves study. The current literature has not separately analyzed the incidence of pure primary sibling reflux and reflux associated with voiding dysfunction. The gene for VUR should be identified.

Screening for reflux: Many groups of children undergo screening for primary reflux, including siblings of offspring of index patients with reflux and children with a multicystic kidney or a solitary kidney. The impact of screening and early intervention (medical or surgical) on reflux-related outcomes should be analyzed.

Circumcision and UTI: Whether circumcision of neonates with prenatally detected VUR diminishes the incidence of UTI and other reflux-related outcomes deserves study.

Reflux and pregnancy: The natural history of VUR in adult women with persistent reflux deserves study, including a comparison of the morbidity of reflux and need for and efficacy of prophylaxis in pregnant and non-pregnant women. Such an analysis should compare various grades of reflux with and without renal scarring. Comparison of the reflux-related outcomes and morbidity of pregnancy in women who had spontaneous reflux

resolution or antireflux surgery during childhood and those with uncorrected reflux is of utmost importance.

Social and economic factors: An analysis of the costs of reflux treatment and surveillance is important, in particular a comparison of the costs associated with medical and surgical therapy of children with various grades of reflux. In addition, studies of how reflux and its treatment and the need for surveillance affect patient/family dynamics and quality of life deserves study.

Randomized controlled trials: Although the International Reflux Study in children was successful in analyzing many reflux-related outcomes, data related to scarring were based on assessment by IVP rather than DMSA renal scan. Further randomized controlled trials studying the role of medical and surgical therapy using DMSA scan for evaluation are indicated. The long-term outcomes (>10 years) of previously randomized children with unresolved reflux at 5 years should be compared with children undergoing successful surgical or medical therapy.

Future clinical studies of children with reflux should analyze specific reflux-related health outcomes and stratify the results by patient gender, age, and reflux grade. Studies should report reflux resolution both by rate of ureteral resolution and patient resolution. Ideally, reports of UTI and renal scarring will analyze these outcomes for 5–10 years after reflux resolution.

References

Aaronson I. Current status of the 'STING': an American perspective. Br J Urol 1995;75:121–5.

Aggarwal VK, Verrier-Jones K, Asscher AW, Evans C, Williams LA. Covert bacteriuria: long term follow up. Arch Dis Child 1991;66:1284–6.

Ahmed S, Tan H. Complications of transverse advancement ureteral reimplantation:diverticulum formation. J Urol 1982;127:970–3.

Allen TD. Modification of the ureteral advancement procedure for vesicoureteral reflux. South Med J 1973; 66:305–7.

Allen TD. The nonneurogenic neurogenic bladder. J Urol 1977;117:232–8.

Allen TD, Bright TC III. Urodynamic pattern abnormalities in children with dysfunctional voiding problems. J Urol 1978;119:247–9.

Amar AD, Singer B, Chabra K. The practical management of vesicoureteral reflux in children. A review of 12 years' experience with 236 patients. Clin Pediatr 1976;15:562–9.

Anderson PA, Rickwood AM. Features of primary vesicoureteric reflux detected by prenatal sonography. Br J Urol 1991;67:267–71.

Arant BS Jr. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol 1992;148: 1683–7.

Arant BS Jr. Vesicoureteric reflux and renal injury. Am J Kidney Dis 1991;17:491–511.

Arap S, Abrao EG, Menezes-de-Goes G. Treatment and prevention of complications after extravesical antireflux technique. Eur Urol 1981;7:263–7.

Asmar BI, Maqbool S, Dajani AS. Hematologic abnormalities after oral trimethoprim-sulfamethoxazole therapy in children. Am J Dis Child 1981;135:1100–3.

Atkins HL, Thomas SR. Dosimetry of radiopharmaceuticals used in nephrologic investigation. In: Nuclear medicine clinical urology and nephrology. Norwalk, CT: Appleton-Century-Croats 1985;31–37.

Atwell JD, Cox PA. Growth of the kidney following unilateral antireflux surgery. Eur Urol 1981;7:257–62.

Atwell JD, Vijay MR. Renal growth following reimplantation of the ureters for reflux. Br J Urol 1978;50: 367–70.

Aubert D, Zoupanos G, Destuynder O, Hurez F. 'Sting' procedure in the treatment of secondary reflux in children. Eur Urol 1990;17:307–9.

Avner ED, Chavers B, Sullivan K, Tejani A. Renal transplantation and chronic dialysis in children and adolescents: the 1993 annual report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 1995;9:61–73.

Bailey RR, Maling TMJ, Swainson CP. Vesicoureteric reflux and reflux nephropathy. In: Schrier RW, Gottschalk CW, editors. Diseases of the kidney. 5th ed. Vol I. Boston: Little, Brown, and Company, 1993; 689–727.

Becker GJ, Ihle BU, Fairley KF, Bastos M, Kincaid-Smith P. Effect of pregnancy on moderate renal failure in reflux nephropathy. BMJ 1986;292:796–8.

Beetz R, Hohenfellner R, Schofer O, Singhof S, Riedmiller H. Long-term follow-up of children with surgically treated vesicorenal reflux: renal growth. Eur Urol 1991;19:39–44.

Beetz R, Schulte-Wissermann H, Tröger J, Riedmiller H, Mannhardt W, Schofer O. Long-term follow-up of children with surgically treated vesicorenal reflux: postoperative incidence of urinary tract infections, renal scars and arterial hypertension. Eur Urol 1989; 16:366–71.

Bellinger MF, Duckett JW. Vesicoureteral reflux: a comparison of non-surgical and surgical management. Contrib Nephrol 1984;39:81–93.

Ben-Ami T, Gayer G, Hertz M, Lotan D, Boichis H. The natural history of reflux in the lower pole of duplicated collecting systems: a controlled study. Pediatr Radiol 1989;19:308–10.

Ben-Ami T, Sinai L, Hertz M, Boichis H. Vesicoureteral reflux in boys: review of 196 cases. Radiology 1989; 173:681–4.

Berg UB. Long-term followup of renal morphology and function in children with recurrent pyelonephritis. J Urol 1992;148:1715–172.

Bhatti HA, Khattak H, Boston VE. Efficacy and causes of failure of endoscopic subureteric injection of Teflon™ in the treatment of primary vesicoureteric reflux. Br J Urol 1993;71:221–5.

Birge RT. The calculation of errors by the method of least squares. Phys Rev 1932;30:207–27.

Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: 5 years' observation. Birmingham Reflux. BMJ-Clinical Research 1987; 295:237–41.

Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. BMJ - Clinical Research 1983;287:171–4.

Bisset GS III, Strife JL, Dunbar JS. Urography and voiding cystourethrography: findings in girls with urinary tract infection. AJR 1987;148:479-82.

Bisset GS III, Strife JL, Kirks DR. Genitourinary tract. In: Kirks DR (editor). Practical pediatric imaging. Diagnostic radiology of infants and children, 2nd ed. Boston: Little, Brown and Company 1991;909.

Blane CE, DiPietro MA, Zerin JM, Sedman AB, Bloom DA. Renal sonography is not a reliable screening examination for vesicoureteral reflux. J Urol 1993; 150:752–5.

Bloembergen WE, Port FK, Mauger EA, Wolfe RA. Causes of death in dialysis patients: racial and gender differences. J Am Soc Nephrol 1994;5:1231–42.

Bourchier D, Abbott GD, Maling TMJ. Radiological abnormalities in infants with urinary tract infections. Arch Dis Child 1984;59:620–4.

Bradic I, Batinica S, Husar J. Primary vesicoureteric reflux treated by antireflux ureterocystostomy at the vertex of the bladder. A 12-year follow-up and analysis of operative fail. Br J Urol 1988;62:1–6.

Brandell RA, Brock JW. Ureteral reimplantation: postoperative management without catheters. Urology 1993;42(6):705–7.

Brendstrup L, Hjelt K, Petersen KE, Petersen S, Andersen EA, Daugbjerg PS, Stagegaard BR, Nielsen OH, Vejlsgaard R, Schou G. Nitrofurantoin versus trimethoprim prophylaxis in recurrent urinary tract infection in children. Acta Paediatr Scand 1990;79: 1225–34.

Broaddus SB, Zickerman PM, Morrisseau PM, Leadbetter GW Jr. Incidence of later ureteral obstruction after antireflux surgery in infants and children. Urology 1978;11:139–41.

Burbige KA. Ureteral reimplantation: a comparison of results with the cross-trigonal and Politano-Leadbetter techniques in 120 patients. J Urol 1991;146:1352–3.

Burge DM, Griffiths MD, Malone PS, Atwell JD. Fetal vesicoureteral reflux: outcome following conservative postnatal management. J Urol 1992;148:1743–5.

Cain MP, Husmann DA, McLaren RH, Continuous epidural anesthesia after ureteroneocystostomy in children. J Urol 1995;154:791–3.

Cardiff-Oxford Bacteriuria Study Group. Sequelae of covert bacteriuria in schoolgirls. A 4-year follow-up study. Lancet 1978;1:889–93.

Carpentier PJ, Bettink PJ, Hop WC, Schroder FH. Reflux—a retrospective study of 100 ureteric reimplantations by the Politano-Leadbetter method and 100 by the Cohen technique. Br J Urol 1982;54: 230–3.

Carson CC, Kelalis PP, Hoffman AD. Renal growth in small kidneys after ureteroneocystostomy. J Urol 1982; 127:1146–84.

Claesson I, Jacobsson B, Jodal U. Early detection of nephropathy in childhood urinary tract infection. Acta Radiol 1981;22:315–20.

Claesson I, Jacobsson B, Jodal U, Winberg J. Compensatory kidney growth in children with urinary tract infection and unilateral renal scarring: an epidemiologic study. Kidney Int 1981;20:759–64.

Claesson I, Jacobsson B, Olsson T, Ringertz H. Assessment of renal parenchymal thickness in normal children. Acta Radiol (Diagnosis) 1981;22:305–14.

Cochran WG. Problems arising in the analysis of a series of similar experiments. J R Stat Soc 1937;4: 102–18.

Cohen SJ. Ureterozystoneostomie, eine neue antirefluxtechnik. Aktvel Urol 1975;6:1.

Conway JJ, King LR, Belman AB, Thorson T Jr. Detection of vesicoureteral reflux with radionuclide cystography. AJR 1972;115:720–7.

Coraggio MJ, Gross TP, Roscelli JD. Nitrofurantoin toxicity in children. Pediatr Infect Dis J 1989;8:163–6.

Cunningham FG, Cox SM, Harstad TW, Mason RA, Pritchard JA. Chronic renal disease and pregnancy outcome. Am J Obstet Gynecol 1990;163:453–9.

Cunningham FG, Lindheimer MD. Hypertension in pregnancy. N Engl J Med 1992;326:927–32.

Davies N, Atwell JD. Primary vesicoureteric reflux: treatment with subureteric injection of Polytef paste. Br J Urol 1991;67:536–40.

de Sadeleer C, de Boe V, Keuppens F, Desprechius B, Verbovan M, Piepsz A. How good is technetium-99 in mercaptoacetyl triglycine indirect cystography? Eur J Nucl Med 1994;21:223–7.

Decter RM, Roth DR, Gonzales ET Jr. Vesicoureteral reflux in boys. J Urol 1988;140:1089–91.

Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. J R Stat Soc 1977;38:1–11.

DerSimonian R, Laird N. Meta analysis in clinical trials. Control Clin Trials 1986;7:177–88.

Dewan PA, O'Donnell B. Polytef paste injection of refluxing duplex ureters. Eur Urol 1991;19:35–8.

Diamond DA, Kleinman PK, Spevak M, Nimkin K, Belanger P, Karellas A. Tailored low dose fluoroscopic voiding cystogram for familial reflux screening. J Urol 1996;155:681–2.

Diamond DA, Rabinowitz R, Hoenig D, Caldamone AA. The mechanism of new onset contralateral reflux following unilateral ureteroneocystostomy. J Urol 1996; 156:665–7.

Dodat H, Takvorian P. Treatment of vesicoureteral reflux in children by endoscopic injection of Teflon™. Review of 2 years of experience. Eur Urol 1990;17:304–6.

Drachman R, Valevici M, Vardy PA. Excretory urography and cystourethrography in the evaluation of children with urinary tract infection. Clin Pediatr 1984;23:265–7.

Duckett JW, Walker RD, Weiss R. Surgical results: International Reflux Study in Children – United States branch. J Urol 1992;148:1674–5.

Dunn M, Smith PJB. Results of conservative management of vesicoureteric reflux in children. Br J Urol 1982;54:672–6.

Eddy DM. A manual for assessing health practices and designing practice policies: the explicit approach. Philadelphia: American College of Physicians 1992. 126 p.

Eddy DM, Hasselblad V. FAST*PRO software for meta-analysis by the confidence profile method. Boston: Academic Press 1992. 196 p.

Eddy DM, Hasselblad V, Shachter RD. The statistical synthesis of evidence: meta-analysis by the confidence profile method. Boston: Academic Press 1992. 428 p.

Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. BMJ 1977;2:285–8.

Ehrlich RM. Success of the transvesical advancement technique for vesicoureteral reflux. J Urol 1982;128: 554–7.

Ehrlich RM. The ureteral folding technique for megaureter surgery. J Urol 1985;134:668–70.

Eklof O, Ringertz H. Kidney size in children. A method of assessment. Acta Radiol (Diagnosis) 1976;17: 617–25.

Elder J. Commentary: importance of antenatal diagnosis of vesicoureteral reflux. J Urol 1992;148:1750–4.

Elder JS, Longenecker R. Premedication with oral midazolam for voiding cystourethrography in children: safety and efficacy. AJR 1995;164:1229–32.

Elder JS, Snyder HM, Peters C, Arant B, Hawtrey CE, Hurwitz RS, Parrott TS, Weiss RA. Variations in practice among urologists and nephrologists treating children with vesicoureteral reflux. J Urol 1992;148: 714–7.

Elo J, Tallgren LG, Alfthan O, Sarna S. Character of urinary tract infections and pyelonephritic renal scarring after antireflux surgery. J Urol 1983;129:343–6.

Farkas A, Moriel EZ, Lupa S. Endoscopic correction of vesicoureteral reflux: our experience with 115 ureters. J Urol 1990;144:534–6.

Faure G, Ben-Salah S, dEscoffier PL, Revol M. Bilateral Cohen's antireflux procedure with a single submucosal tunnel. Eur Urol 1982;8:193–5.

Forbes PA, Drummond KN, Nogrady MB. Meatotomy in girls with meatal stenosis and urinary tract infections. J Pediatr 1969;75:937–42.

Fort KF, Selman SH, Kropp KA. A retrospective analysis of the use of ureteral stents in children undergoing ureteroneocystotomy. J Urol 1983;129:545–7.

Frey P, Berger D, Jenny P, Herzog B. Subureteral collagen injection for the endoscopic treatment of vesicoureteral reflux in children. Followup study of 97 treated ureters and histological analysis of collagen implants. J Urol 1992;148:718–23.

Fryczkowski J, Maruszewska A, Paradysz A, Maruszewski W. Evaluation of the course of pregnancy, delivery and the condition of the newborn infant in women operated on for vesicoureteral reflux in childhood. Int Urol Nephrol 1991;23:231–6.

Fung LCT, McLorie GA, Jain U, Khoury AE, Churchill BM. Voiding efficiency after ureteral reimplantation: a comparison of extravesical and intravesical techniques. J Urol 1995;153:1972–5.

Funke PJ, Chiari R, Planz K. Complications after extravesical antireflux operations. Int Urol Nephrol 1980;12: 119–22.

Garrett RA, Switzer RW. antireflux surgery in children. JAMA 1966;195:636–8.

Gierup J. Micturition studies in infants and children. Scand J Urol Nephrol 1970;4:191–207.

Glenn JF, Anderson EE. Distal tunnel ureteral reimplantation. J Urol 1967;97:623–6.

Goldraich NP, Goldraich IH. Followup of conservatively treated children with high and low grade vesicoureteral reflux: a prospective study. J Urol 1992;148: 1688–92.

Gooding CA, Berdon WE, Brodeur AE, Rowen M. Adverse reactions to intravenous pyelography in children. AJR 1975; 123:802–4.

Govan DE, Fair WR, Friedland GW, Filly RA. Management of children with urinary tract infections: the Stanford experience. Urology 1975;6:273–86.

Gregoir W, Van Regemorter GV. Le reflux vesicouretéral congénital. Urol Int 1964;18:122.

Hagberg S, Hjalmas K, Jacobsson B, Sillen U. Renal growth after antireflux surgery in infants. Zeitschrift fur Kinderchirugie 1984;39:52–4.

Hampel N, Richter-Levin D, Gersh I. Extravesical repair of primary vesicoureteral reflux in children. J Urol 1977;117:355–7.

Hanna MK. Early surgical correction of massive refluxing megaureter in babies by total ureteral reconstruction and reimplantation. Urology 1981;18:562–6.

Hannerz L, Wikstad I, Celsi G, Aperia A. Influence of vesicoureteral reflux and urinary tract infection on renal growth in children with upper urinary tract duplication. Acta Radiol 1989;30:391–4.

Hannerz L, Wikstad I, Johansson L, Broberger O, Aperia A. Distribution of renal scars and intrarenal reflux in children with a past history of urinary tract infection. Acta Radiol 1987;28:443–6.

Hanson E, Hansson S, Jodal U. Trimethoprim-sulphadiazine prophylaxis in children with vesico-ureteric reflux. Scand J Infect Dis 1989;21:201–4.

Hasselblad V. Meta-analysis of multi-treatment studies. Med Decis Making (in press).

Hasselblad V. Numerical techniques in distribution fitting. Computing Sci Stat 1994;26:217–21.

Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press, 1985;200–3.

Heidrick WP, Mattingly RF, Amberg JR. Vesicoureteral reflux in pregnancy. Obstet Gynecol 1967;29:571–8.

Hendry WF, Stanton SL, Williams DI. Recurrent urinary infections in girls: effects of urethral dilatation. Br J Urol 1973;45:72–83.

Hinman F Jr. Nonneurogenic neurogenic bladder (the Hinman syndrome)—15 years later. J Urol 1986;136: 769–77.

Hinman F, Baumann F. Vesical and ureteral damage from voiding dysfunction in boys without neurologic or obstructive disease. J Urol 1973;109:727–32.

Hjalmas K. Micturition in infants and children with normal lower urinary tract. Scand J Urol Nephrol 1976;Suppl 37:1.

Hjalmas K, Lohr G, Tamminen-Mobius T, Seppanen J, Olbing H, Wikstrom S. Surgical results in the International Reflux Study in Children (Europe). J Urol 1992;148:1657–61.

Hoberman A, Chao H-P, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. J Pediatr 1993;123:17–23.

Hodson CJ, Davies Z, Prescod A. Renal parenchymal radiographic measurement in infants and children. Pediatr Radiol 1975;3:16–9.

Hodson CJ, Drewe JA, Karn MN, King A. Renal size in normal children. A radiographic study during life. Arch Dis Child 1962;37:616–22.

Hohenfellner R. Therapy of vesicoureteral reflux in children. S Afr Med J 1971;45:1063–4.

Holland NH, Kazee M, Duff D, McRoberts W. Antimicrobial prophylaxis in children with urinary tract infection and vesicoureteral reflux. Rev Infect Dis 1982;4(2):467–74.

Homsy YL, Nsouli I, Hamburger B, Laberge I, Schick E. Effects of oxybutynin on vesicoureteral reflux in children. J Urol 1985;134:1168–71.

Houle AM, McLorie GA, Heritz DM, McKenna PH, Churchill BM, Khoury AE. Extravesical nondismembered ureteroplasty with detrusorrhaphy: a renewed technique to correct vesicoureteral reflux in children. J Urol 1992;148:704–7.

Husmann DA, Allen TD. Resolution of vesicoureteral reflux in completely duplicated systems: fact or fiction? J Urol 1991;145:1022–32.

Hutch JA. vesicoureteral reflux in the paraplegic cause and correction. J Urol 1952;68:457–67.

International Reflux Study Committee. Medical versus surgical treatment of primary vesciourеteral reflux: a prospective international reflux study in children. J Urol 1981;125:277–83.

Jakobsen BE, Genster H, Olesen S, Nygaard E. Vesicoureteral reflux in children. Br J Urol 1977;49:119–27.

Jacobson SH. A 5-year prospective follow-up of women with non-obstructive pyelonephritic renal scarring. Scand J Urol Nephrol 1991;25:51–7.

Jacobson SH, Eklof O, Eriksson CG, Linds LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. BMJ 1989; 299:703–6.

Jodal U, Koskimies O, Hanson E, Löhr G, Olbing H, Smellie J, Tamminen-Möbius T. Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. The International Reflux Study in Children. J Urol 1992;148:1650–2.

Jodal U, Winberg J. Management of children with unobstructed urinary tract infection. Pediatr Nephrol 1987; 1:647–56.

Johnston JH, Farkas A. The congenital refluxing megaureter: experiences with surgical reconstruction. Br J Urol 1975;47:153–9.

Jonas P, Many M, Boichis H, Hertz M. Ureteroneocystostomy in children with vesicoureteral reflux. Experience with 150 reimplanted ureters. Isr J Med Sci 1974;10:603–7.

Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. N Engl J Med 1996;335:226–32.

Jungers P, Houillier P, Forget D, Henry-Amar M. Specific controversies concerning the natural history of renal disease in pregnancy. Am J Kidney Dis 1991; 17:116–22.

Kaplan GW, Sammons TA, King LR. A blind comparison of dilatation, urethrotomy, and medication alone in the treatment of urinary tract infection in girls. J Urol 1973;109:917–9.

Kaplan WE, Nasrallah P, King LR. Reflux in complete duplication in children. J Urol 1978;120:220–2.

Kass EH. Bacteriuria and pyelonephritis of pregnancy. Arch Intern Med 1960;105:194–8.

Kelalis PP. Proper perspective on vesicoureteral reflux. Mayo Clin Proc 1971;46:807–18.

Kim KE, Swartz C. Cardiovascular complications of end-stage renal disease. In: Schrier RW, Gottschalk CW, editors. Diseases of the kidney. 5th ed. Vol III. Boston: Little, Brown and Company 1993;2817–44.

Kincaid-Smith P, Bullen M. Bacteriuria in pregnancy. Lancet 1965;1:395–9.

Kincaid-Smith P, Fairley KF. Renal disease in pregnancy. Three controversial areas: mesangial IgA nephropathy, focal glomerular sclerosis (focal and segmental hyalinosis and sclerosis), and reflux nephropathy. Am J Kidney Dis 1987;9:328–33.

King PA, Gollow I. The endoscopic correction of vesicoureteric reflux. Aust N Z J Surg 1988;58:569–71.

Kirks DR, editor. Practical pediatric imaging. Diagnostic radiology of infants and children, 2nd ed. Boston: Little, Brown and Company; 1991, Appendix 3, p. 1063–4.

Kleinman PK, Diamond BA, Karellas A, Spevak MR, Nimkin K, Belanger P. Tailored low-dose fluoroscopic voiding cystourethrography for the reevaluation of vesicoureteral reflux in girls. AJR 1994;162:1151–4.

Koff SA. Relationship between dysfunctional voiding and reflux. J Urol 1992;148:1703–5.

Koff SA, Kogan B, Kass EJ, Thrall JH. Early postoperative assessment of the functional patency of ureterovesical junction following ureteroneocystostomy. J Urol 1981;125:554–7.

Koff SA, Murtagh DS. The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution. J Urol 1983;130:1138–41.

Kondo A, Otani T. Correction of reflux with the ureteric crossover method. Clinical experience in 50 patients. Br J Urol 1987;60:36–8.

Krober MS, Bass JW, Powell JM, Smith FR, Seto DSY. Bacterial and viral pathogens causing fever in infants less than 3 months old. Am J Dis Child 1985;139: 889–92.

Lacombe A. Ureterovesical reimplantation after failure of endoscopic treatment of reflux by submucosal injection of polytef paste. Eur Urol 1990;17:318–20.

Lawson, Paice BJ. Adverse reactions to trimethoprimsulfamethoxazole. Rev Infect Dis 1982;4(2):429–33.

Lee PH, Diamond DA, Duffy PG, Ransley PG. Duplex reflux: a study of 105 children. J Urol 1991;146: 657–9.

Lenaghan D, Whitaker JG, Jensen F, Stephens FD. The natural history of reflux and long-term effects of reflux on the kidney. J Urol 1976;115:728–30.

Leonard MP, Canning DA, Peters CA, Gearhart JP, Jeffs RD. Endoscopic injection of glutaraldehyde cross-linked bovine dermal collagen for correction of vesicoureteral reflux. J Urol 1991;145:115–9.

Lindberg U, Claesson I, Hanson LA, Jodal U. Asymptomatic bacteriuria in schoolgirls. I. Clinical and laboratory findings. Acta Paediatr Scand 1975;64:425–31.

Lines D. 15th century ureteric reflux. Lancet 1982;2: 1473.

Lohr JA, Nunley DH, Howard SS, Ford RF. Prevention of recurrent urinary tract infections in girls. Pediatrics 1977;59(4):562–5.

Lyon RP. Renal arrest. J Urol 1973;109:707–10.

Mackie GG, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. J Urol 1975;114:274–80.

Maggiolo LF, Lockhart JL, Politano VA. Management of massively refluxing megaureters. Urology 1983;21: 232–5.

Mansfield JT, Snow BS, Cartwright PC, Wadsworth K. Complications of pregnancy in women after childhood reimplantation for vesicoureteral reflux: an update with 25 years of followup. J Urol 1995;154:787–90.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.

Marberger M, Altwein JE, Straub E, Wulff SH, Hohenfellner R. The Lich-Gregoir antireflux plasty: experiences with 371 children. J Urol 1978;120: 216–19.

Martinell J, Claesson I, Lidin-Janson G, Jodal U. Urinary infection, reflux and renal scarring in females continuously followed for 13–38 years. Pediatr Nephrol 1995;9:131–6.

Martinell J, Jodal U, Lidin-Janson G. Pregnancies in women with and without renal scarring after urinary infection in childhood. BMJ 1990;300:840–4.

Mathew TH. Reflux nephropathy as a cause of end stage renal failure. In: Disney APS, editor. Tenth Report of the Australia and New Zealand Dialysis and Transplant Registry. Woodville, South Australia: Queen Elizabeth Hospital;1987:115–21.

McAlister WH, Cacciarelli A, Shackelford GD. Complications associated with cystography in children. Radiology 1974;111:167–72.

McCool AC, Joseph DB. Postoperative hospitalization of children undergoing trans-trigonal ureteroneocystostomy. J Urol 1995;154:794–6.

McDuffie RW, Litin RB, Blundon KE. Ureteral reimplantation: Lich method. Urology 1977;10:19–22.

McLorie GA, McKenna PH, Jumper BM, Churchill BM, Gilmour RF, Khoury AE. High grade vesicoureteral reflux: analysis of observational therapy. J Urol 1990;144:537–40.

McRae CU, Shannon FT, Utley WL. Effect on renal growth of reimplantation of refluxing ureters. Lancet 1974;1:1310–2.

Mettler FA Jr, Upton AC. Mechanical effects of ionizing radiation, 2nd ed. Philadelphia: W.B. Saunders Company;1995:31.

Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. Pediatrics 1988;82(1):24–9.

MPI. DMSA kidney reagent package insert. Medi+ Physics July 1985.

Mulcahy JJ, Kelalis PP. Non-operative treatment of vesicoureteral reflux. J Urol 1978;120:336–7.

Mundy AR, Kinder CH, Joyce MR, Chantler C, Haycock GB. Improvement in renal function following ureteric reimplantation for vesicoureteric reflux. Br J Urol 1981;53:542–4, 1:638–46.

Nasrallah PF, Simon JW. Reflux and voiding abnormalities in children. Urology 1984;24:243–5.

Neuringer JR, Brenner BM. Hemodynamic theory of progressive renal disease: a 10-year update in brief review. Am J Kidney Dis 1993;22:98–104.

Noe HN. The long-term results of prospective sibling reflux screening. J Urol 1992;148:1739–42.

Noe HN. The role of dysfunctional voiding in failure or complication of ureteral reimplantation for primary reflux. J Urol 1985;134:1172–5.

Noe HN, Wyatt RJ, Peedan JN Jr, Rivas ML. The transmission of vesicoureteral reflux from parent to child. J Urol 1992;148:1869–71.

O'Donnell B, Puri P. Endoscopic correction of primary vesicoureteric reflux. Br J Urol 1986;58:601–4.

O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon™. BMJ 1984;289: 7–9.

Olbing H, Claesson I, Ebel KD, Seppanen U, Smellie JM, Tamminen-Mobius T, Wikstad I. Renal scars and parenchymal thinning in children with vesicoureteral reflux: a 5-year report of the International Reflux Study in Children (European Branch). J Urol 1992; 148:1653–6.

Orikasa S. A new antireflux operation. Eur Urol 1990; 17:330–2.

Patel K, Charron M, Hoberman A, Brown ML, Rogers KD. Intra- and interobserver variability in interpretation of DMSA scans using a set of standardized criteria. Pediatr Radiol 1993;23:506–9.

Peppas DS, Skoog SJ, Canning DA, Belman AB. Nonsurgical management of primary vesicoureteral reflux in complete ureteral duplication: is it justified? J Urol 1991;146:1594–5.

Peratoner L, Messi G, Fonda E. Evaluation of kidney growth in vesicoureteral reflux. Int J Pediatr Nephrol 1984;5:83–8.

Pinter AB, Jaszai V, Dober I. Medical treatment of vesicoureteral reflux detected in infancy. J Urol 1988;140: 121–4.

Pistor K, Scharer K, Olbing H, Tamminen-Mobius T. Children with chronic renal failure in the Federal Republic of Germany: II. Primary renal diseases, age and intervals from early renal failure to renal death. Clin Nephrol 1985;23:278–84.

Politano VA. Vesicoureteral reflux. In: Glenn JF, editor. Urologic surgery. 2nd ed. New York: Harper & Row; 1975. p. 272–93.

Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol 1958;78: 932–41.

Polk HC Jr. Notes on Galenic urology. Urol Survey 1965;15:2–6.

Poulsen EU, Johannesen NL, Nielsen JB, Jørgensen TM, Andersen AJ. vesicoureteral reflux. II. The long-term outcome of kidney function in non-surgical treatment. Scand J Urol Nephrol (Suppl) 1989;125:29–34.

Price SE Jr, Johnson SH, Marshall M Jr. Experience with ureteral reimplantation in the treatment of recurring urinary infections in childhood. J Urol 1970;103: 485–90.

Puri P. Endoscopic correction of primary vesicoureteric reflux by subureteric injection of polytetrafluoroethylene. Lancet 1990;335:1320–2.

Puri P. Ten year experience with subureteric Teflon™ (polytetrafluoroethylene) injection (STING) in the treatment of vesico-ureteric reflux. Br J Urol 1995;75: 126–31.

Puri P, O'Donnell B. Endoscopic correction of Grades IV and V primary vesicoureteric reflux: 6 to 30 month follow-up in 42 ureters. J Pediatr Surg 1987;22: 1087–91.

Pypno W. antireflux operations without catheter. Int Urol Nephrol 1987;19:141–3.

Ransley PG, Risdon RA. The pathogenesis of reflux nephropathy. Contrib Nephrol 1979;16:90–7.

Ravasini G, Pagano F. Surgical correction of vesicoureteral reflux. Description of technique and results. Urol Int 1973;28:56–64.

Redman JF, Scriber LJ, Bissada NK. Apparent failure of renal growth secondary to vesicoureteral reflux. Urology 1974;3:704–7.

Remzi D, Ozen HA, Erkan I, Kendi S. 15 years of experience in the surgical treatment of vesicoureteral reflux in children. Turk J Pediatr 1984;26:175–9.

Riggs W Jr. Errors in radiographic measurements caused by variations in table top/Bucky tray distance. Radiol 1977;124:844.

Roberts JA. Vesicoureteral reflux and pyelonephritis in the monkey: a review. J Urol 1992;148:1721–5.

Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet Gynecol 1989;73:576–82.

Rosa FW, Bosco LA, Graham CF, Milstien JB, Dreis M, Creamer J. Neonatal anuria with maternal angiotension-converting enzyme inhibition. Obstet Gynecol 1989;74:371–4.

Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. AJR 1984;142:467–9.

Ross JH, Kay R, Nasrallah P. Contralateral reflux after unilateral ureteral reimplantation in patients with a history of resolved contralateral reflux. J Urol 1995; 154:1171–2.

Rushton HG, Majd M. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: a review of experimental and clinical studies. J Urol 1992;148:1726–32.

Sacks SH, Roberts R, Verrier Jones K, Asscher AW. Effect of symptomatic bacteriuria in childhood on subsequent pregnancy. Lancet 1987;2:991–4.

Salvatierra O Jr, Kountz SL, Belzer FO. Primary vesicoureteral reflux and end-stage renal disease. JAMA 1973;226:1454–145.

Sargent MA, Gupta SC. Sonographic measurement of relative renal volume in children: comparison with scintigraphic determination of relative renal function. AJR 1993;161:157–60.

Sauvage P, Saussine C, Laustriat S, Becmeur F, Bientz J, Christmann D, Roy E, Marcellin L. Analysis and perspectives of endoscopic treatment of vesicoureteral reflux in children with a 20-month follow-up. Eur Urol 1990;17:310–3.

Schieve LA, Handler A, Hershow R, Persky V, Davis F. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. Am J Public Health 1994;84:405–10.

Scholtmeijer RJ, Griffiths DJ. The role of videourodynamic studies in diagnosis and treatment of vesicoureteral reflux. J Pediatr Surg 1990;25:669–71.

Scholtmeijer RJ, Griffiths DJ. Treatment of vesicoureteric reflux. Preliminary report of a prospective study. Br J Urol 1988;61:205–9.

Schulman CC, Pamart D, Hall M, Janssen F, Avni FE. Vesicoureteral reflux in children: endoscopic treatment. Eur Urol 1990;17:314–7.

Scott DJ, Blackford HN, Joyce MR, Mundy AR, Kinder CH, Haycock GB, Chantler C. Renal function following surgical correction of vesico-ureteric reflux in childhood. Br J Urol 1986;58:119–24.

Scott JE, Stansfeld JM. Treatment of vesico-ureteric reflux in children. Arch Dis Child 1968;43:323–8.

Selzman AA, Elder JS. Contralateral vesicoureteral reflux in children with a multicystic kidney. J Urol 1995;153:1252–4.

Seruca H. Vesicoureteral reflux and voiding dysfunction: a prospective study. J Urol 1989;142:494–8.

Shah KJ, Robins DG, White RH. Renal scarring and vesicoureteric reflux. Arch Dis Child 1978;53:210–7.

Shindo S, Bernstein J, Arant BS Jr. Evolution of renal segmental atrophy (Ask-Upmark kidney) in children with vesicoureteric reflux: radiographic studies. J Pediatr 1983;102:847–54.

Sillen U, Bachelard M, Harmanson G, Hjalmas K. Gross bilateral reflux in infants: gradual decrease of initial detrusor hypercontractility. J Urol 1996;155:668–72.

Skoog SJ, Belman AB. Primary vesicoureteral reflux in the black child. Pediatrics 1991;87:538–43.

Skoog SJ, Belman AB, Majd M. A nonsurgical approach to the management of primary vesicoureteral reflux. J Urol 1987;138:941–6.

Smellie J, Edwards D, Hunter N, Normand IC, Prescod N. Vesico-ureteric reflux and renal scarring. Kidney Int Suppl 1975;Suppl 4:S65–72.

Smellie JM, Edwards D, Normand IC, Prescod N. Effect of vesicoureteric reflux on renal growth in children with urinary tract infection. Arch Dis Child 1981;56: 593–600.

Smellie JM, Gruneberg RN, Bantock HM, Prescod N. Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children. Pediatr Nephrol 1988;2:12–7.

Smellie JM, Gruneberg RN, Leakey A, Atkin WS. Long-term low-dose co-trimoxazole in prophylaxis of childhood urinary tract infection: clinical aspects. BMJ 1976;2:203–6.

Smellie JM, Normand ICS, Bantock HM. Trimethoprim-sulfamethoxazole and trimethoprim alone in the prophylaxis of childhood urinary tract infection. Rev Infect Dis 1982;4(2):461–6.

Smellie JM, Preece MA, Paton AM. Normal somatic growth in children receiving low-dose prophylactic co-trimoxazole. Eur J Pediatr 1983;140:301–4.

Smellie JM, Ransley PG, Normand ICS, Prescod N, Edwards D. Development of new renal scars: a collaborative study. Br Med J 1985;290:1957–60.

Smith EM, Elder JS. Double antimicrobial prophylaxis in girls with breakthrough urinary tract infections. Urol 1994;43:708–13.

Smyth AR, Judd BA. Compliance with antibiotic prophylaxis in urinary tract infection. Arch Dis Child 1993;68:235-6.

So EP, Brock WA, Kaplan GW. Ureteral reimplantation without catheters. J Urol 1981;125:551–3.

Stabin M, Taylor A Jr., Eshima D, Wooter W. Radiation dosimetry for technetium-99m-MAG3, technetium-99-m-DTPA, and iodine-131-OIH based on human biodistribution studies. J Nucl Med 1992;33:33-40.

Statistics and Epidemiology Research Corporation. EGRET reference manual, Revision 4. Seattle: Statistics and Epidemiology Research Corporation, 1993. 425 p.

Sutton R, Atwell JD. Physical growth velocity during conservative treatment and following subsequent surgical treatment for primary vesicoureteric reflux. Br J Urol 1989;63:245–50.

Sweeney LE, Thomas PS. Evaluation of sub-ureteric Teflon™ injection as an antireflux procedure. Ann Radiol 1987;30:478–81.

Sweet RL. Bacteriuria and pyelonephritis during pregnancy. Semin Perinatol 1977;1:25–40.

Tamminen-Mobius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppanen U, Sixt R. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. J Urol 1992;148:1662–6.

U.S. Department of Health and Human Services. Detailed diagnoses and procedures. National Hospital Discharge Survey, 1993. National Center for Health Statistics. Vital Health Stat 1995;13:122.

Uhari M, Nuutinen M, Turtinen J. Adverse reactions in children during long term antimicrobial therapy. Pediatr Infect Dis J 1996:15:404–8.

van Gool JD, Hjalmas K, Tamminen-Mobius T, Olbing H. Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux. The International Reflux Study in Children. J Urol 1992;148:1699–702.

Wacksman J, Gilbert A, Sheldon CA. Results of the renewed extravesical reimplant for surgical correction of vesicoureteral reflux. J Urol 1992;148:359–61.

Wallace DM, Rothwell DL, Williams DI. The long-term follow-up of surgically treated vesicoureteric reflux. Br J Urol 1978;50:479–84.

Wan J, Greenfield SP, Ng M, Zerin M, Ritchey ML, Bloom D. Sibling reflux: a dual center retrospective study. J Urol 1996;156:677–9.

Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with Grades III and IV primary vesicoureteral ref. J Urol 1992;148:1667–73.

Weiss R, Tamminen-Mobius T, Koskimies O, Olbing H, Smellie JM, Hirche H, Lax-Gross H. Characteristics at entry of children with severe primary vesicoureteral reflux recruited for a multicenter, international therapeutic trial comparing medical and surgical management. J Urol 1992;148:1644–9.

Williams GL, Davies DKL, Evans KT, Williams JE. Vesicoureteric reflux in patients with bacteriuria in pregnancy. Lancet 1968;4:1202–5.

Willscher MK, Bauer SB, Zammuto PJ, Retik AB. Infection of the urinary tract after antireflux surgery. J Pediatr 1976;89:743–7.

Willscher MK, Bauer SB, Zammuto PJ, Retik AB. Renal growth and urinary infection following antireflux surgery in infants and children. J Urol 1976;115: 722–5.

Woodwell DA. Office visits to urologists: United States, 1989-90. Advance data from vital and health statistics; no. 234. Hyattsville (MD): National Center for Health Statistics. 1993:1–9.

Yusef S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Pro Cardiovasc Dis 1985;27:335–71.

Zaontz MR, Maizels M, Sugar EC, Firlit CF. Detrusorrhaphy: extravesical ureteral advancement to correct vesicoureteral reflux in children. J Urol 1987;138: 947–9.

Zerin M, Shulkin BL. Postprocedural symptoms in children who undergo imaging studies of the urinary tract: is it the contrast material or the catheter? Radiology 1992;182:727–30.

Appendix A: Literature review—Papyrus references

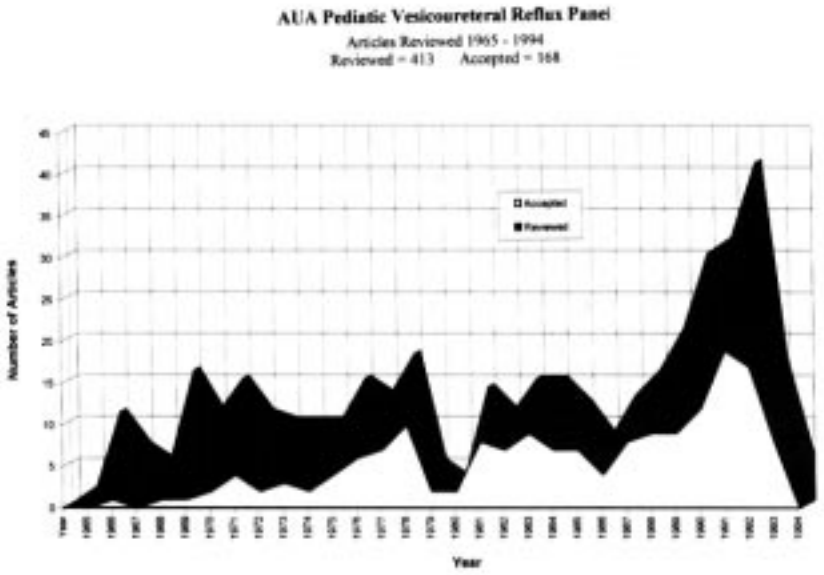

Figure A-1

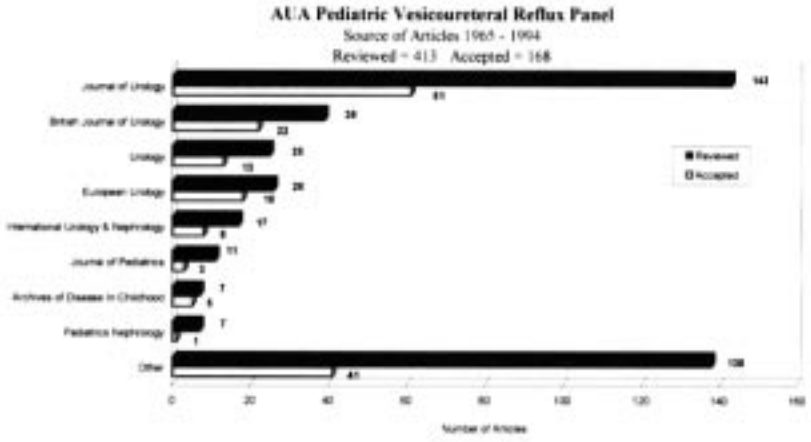

Figure A-2

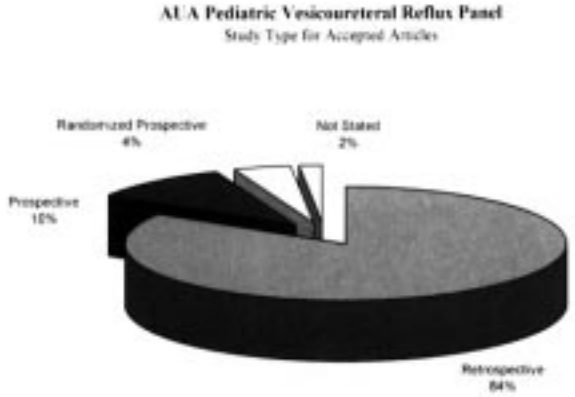

Figure A-3

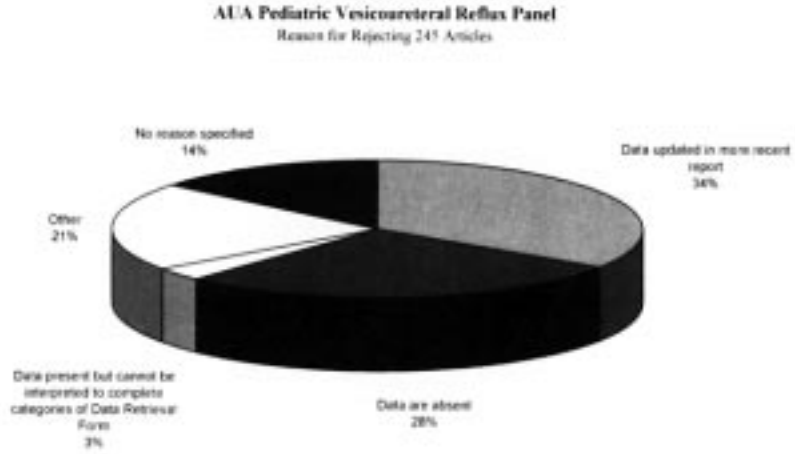

Figure A-4

Table A-1: Papyrus Reference Bibliography—Alphabetic by Author

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
674	Archives of Disease in Childhood	1991	66	1284-6	Covert bacteriuria:long term follow-up	Aggarwal, V.K., Verrier-Jones, K., Asscher, A.W., Evans, C., and Williams, L.A.
252	Journal of Urology	1983	129	787-91	Application of the pull-through technique of transverse advancement ureteral reimplantation	Ahmed, S.
65		1988	140	1092-4	Vesicoureteral reflux in complete ureteral duplication: surgical options	Ahmed, S., Boucaut, H.A.
345	Journal of Urology	1978	120	332-3	Results of ureteral reimplantation in patients with intrarenal reflux	Ahmed, S., Smith, A.J.
301	Journal of Urology	1982	127	970-73	Complications of transverse advancement ureteral reimplantation: diverticulum formation	Ahmed, S., Tan, H.
321	Pediatrics	1980	65	78-80	The conservative management of vesicoureteric reflux: a review of 121 children	Aladjem, M., Biochis, H., Hertz, M., Herzfeld, S., and Raviv, U.
462	Southern Medical Journal	1973	66	305-7	Modification of the ureteral advancement procedure for vesicoureteral reflux	Allen, T.D.
401	Clinical Pediatrics	1976	15	562-9	The practical management of vesicoureteral reflux in children. A review of 12 years' experience with 236 patients.	Amar, A.D., Singer, B., and Chabra, K.
614	British Journal of Urology	1991	67	267-71	Features of primary vesicoureteric reflux detected by prenatal sonography.	Anderson, P.A., Rickwood, A.M.
646	Journal of Urology	1992	148	1683-7	Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group.	Arant, B.S., Jr.
304	European Urology	1981	7	263-7	Treatment and prevention of complications after extravesical antireflux technique	Arap, S., Abrao, E.G., and Menezes-de-Goes, G.
305	European Urology	1981	7	257-62	Growth of the kidney following unilateral antireflux surgery	Atwell, J.D., Cox, P.A.
75	European Urology	1990	17	307-9	'Sting' procedure in the treatment of secondary reflux in children	Aubert, D., Zoupanos, G., Destuynder, O., and Hurez, F.
591	European Urology	1991	19	39-44	Long-term follow-up of children with surgically treated vesicorenal reflux:renal growth	Beetz, R., Hohenfellner, R., Schofer, O., Singhof, S., and Riedmiller, H.
42	European Urology	1989	16	366-71	Long-term follow-up of children with surgically treated vesicorenal reflux: postoperative incidence of urinary tract infections, renal scars and arterial hypertension	Beetz, R., Schulte-Wissermann, H., Troger, J., Riedmiller, H., Mannhardt, W., Schofer, O., and Hohenfellner, R.
209	Contributions to Nephrology	1984	39	81-93	Vesicoureteral reflux: a comparison of non-surgical and surgical management	Bellinger, M.F., Duckett, J.W.

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
46	Pediatric Radiology	1989	19	308-10	The natural history of reflux in the lower pole of duplicated collecting systems: a controlled study	Ben-Ami, T., Gayer, G., Hertz, M., Lotan, D., and Boichis, H.
497	Journal of Pediatric Surgery	1970	5	622-7	Ureteroneocystostomy in refluxing ureteric duplication: indications, technique and results	Bettex, M., Kummer-Vago, M., and Kuffer, F.
630	British Journal of Urology	1993	71	221-5	Efficacy and causes of failure of endoscopic subureteric injection of Teflon in the treatment of primary vesico-ureteric reflux	Bhatti, H.A., Khattak, H., and Boston, V.E.
245	British Medical Journal - Clinical Research	1983	287	171-4	Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children	Birmingham Reflux Study Group
256	Journal of Urology	1983	129	543-4	The use of lower ipsilateral ureteroureterostomy to treat vesico-ureteral reflux or obstruction in children with duplex ureters	Bockrath, J.M., Maizels, M., and Firlit, C.F.
58	British Journal of Urology	1988	62	531-6	Primary vesicoureteric reflux treated by antireflux ureterocystostomy at the vertex of the bladder. A 12-year follow-up and analysis of operative failure	Bradic, I., Batinica, S. and Husar, J.
412	British Journal of Urology	1975	47	525-30	Antireflux ureterocystostomy at the vertex of the bladder	Bradic, I., Pasini, M., and Vlatkovic, G.
789	Urology	1993	42 (12/6)	705-7	Ureteral reimplantation: postoperative management without catheters	Brandell, R.A., Brock, J.W., 3d
359	Urology	1978	11	139-41	Incidence of later ureteral obstruction after antireflux surgery in infants and children	Broaddus, S.B., Zickerman, P.M., Morrisseau, P.M., and Leadbetter, G.W., Jr.
93	Journal of Urology	1989	142	499-500	Open versus endoscopic surgery in the treatment of vesicoureteral reflux	Brown, S.
117	European Urology	1988	314	7-40	Antireflux procedure by Lich-Gregoir. Indications and results	Bruhl, P., van-Ahlen, H., and Mallmann, R.
333	Journal of Urology	1979	121	648-9	Extravesical ureteroplasty	Bruskewitz, R., Sonneland, A.M., and Waters, R.F.
678	Journal of Urology	1991	146	1352-3	Ureteral reimplantation: a comparison of results with the cross-trigonal and Politano-Leadbetter techniques in 120 patients.	Burbige, K.A.
636	Journal of Urology	1992	148	1743-5	Fetal vesicoureteral reflux: outcome following conservative postnatal management	Burge, D.M., Griffiths, M.D., Malone, P.S., and Atwell, J.D.
488	Journal of Urology	1971	106	290-4	Ureteroureterostomy for reflux in duplex systems	Burns, A., Palken, M.
355	Lancet	1978	1	889-93	Sequelae of covert bacteriuria in schoolgirls. A four-year follow-up study.	Cardiff-Oxford Bacteriuria Study Group
181	European Urology	1985	11	181-3	Surgical treatment of vesicoureteral reflux with bilateral medialization of the ureteral orifices	Carini, M., Selli, C., Lenzi, R., Barbagli, G., and Costantini, A.

272	British Journal of Urology	1982	54	230-3	Reflux--a retrospective study of 100 ureteric reimplantations by the Politano-Leadbetter method and 100 by the Cohen technique	Carpentier, P.J., Bettink, P.J., Hop, W.C., and Schroder, F.H.
300	Journal of Urology	1982	127	1146-8	Renal growth in small kidneys after ureteroneocystostomy	Carson, C.C., Kelalis, P.P., and Hoffman, A.D.
495	Journal of Urology	1971	105	720-4	Management of reflux in total duplication anomalies	Daines, S.L., Hodgson, N.B.
612	British Journal of Urology	1991	67	536-40	Primary vesicoureteric reflux: treatment with subureteric injection of Polytef paste	Davies, N., Atwell, J.D.
688	Journal of Urology	1991	146	636-8	Effectiveness of trigonoplasty to treat primary vesicoureteral reflux	De-Gennaro, M., Appetito, C., Lais, A., Talamo, M., Capozza, N., and Caione, P.
66	Journal of Urology	1988	140	1089-91	Vesicoureteral reflux in boys	Decter, R.M., Roth, D.R., and Gonzales, E.T., Jr.
673	Urology	1992	39	162-4	Endoscopic correction of primary vesicoureteric reflux in children	Dewan, P.A., Guiney, E.J.
592	European Urology	1991	19	35-8	Polytef paste injection of refluxing duplex ureters	Dewan, P.A., ODonnell, B.
17	European Urology	1990	17	304-6	Treatment of vesicoureteral reflux in children by endoscopic injection of Teflon. Review of 2 years of experience	Dodat, H., Takvorian, P.
642	Journal of Urology	1992	148	1674-5	Surgical results: international Reflux Study in Children--United States branch	Duckett, J.W., Walker, R.D., and Weiss, R.
260	British Journal of Urology	1982	54	672-6	Results of conservative management of vesicoureteric reflux in children	Dunn, M., Smith, P.J.
370	Journal of Urology	1977	118	826-8	Ipsilateral ureteroureterostomy for vesicoureteral reflux in duplicated ureters	Duthoy, E.J., Soucheray, J.A., and McGroarty, B.J.
459	Journal of Urology	1973	109	888-90	Vesicoureteral reflux in children: a computerized review	Dwoskin, J.Y., Perlmutter, A.D.
373	British Medical Journal	1977	2	285-8	Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children	Edwards, D., Normand, I.C., Prescod, N., and Smellie, J.M.
180	Journal of Urology	1985	134	668-70	The ureteral folding technique for megaureter surgery	Ehrlich, R.M.
267	Journal of Urology	1982	128	554-7	Success of the transvesical advancement technique for vesicoureteral reflux	Ehrlich, R.M.
670	British Journal of Urology	1992	69	294-302	Comparison of DMSA scintigraphy with intravenous urography for the detection of renal scarring and its correlation with vesicoureteric reflux	Elison, B.S., Taylor, D., Van-der-Wall, H., Pereira, J.K., Cahill, S., Rosenberg, A.R., Farnsworth, R.H., and Murray, I.P.
257	Journal of Urology	1983	129	343-6	Character of urinary tract infections and pyelonephritic renal scarring after antireflux surgery	Elo, J., Tallgren, L.G., Alfthan, O., and Sarna, S.
284	Scandinavian Journal of Urology & Nephrology	1981	15	243-8	The role of vesicoureteral reflux in paediatric urinary-tract infection	Elo, J., Tallgren, L.G., Sarna, S., Alfthan, O., and Stenstrom, R.

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
6	Journal of Urology	1990	144	534-6	Endoscopic correction of vesicoureteral reflux: Our experience with 115 ureters	Farkas, A., Moriel, E.Z., and Lupa, S.
620	Journal of Urology	1991	145	542-6	The detection of reflux nephropathy in infants by 99mtechnetium dimercaptosuccinic acid studies.	Farnsworth, R.H., Rossleigh, M.A., Leighton, D.M., Bass, S.J., and Rosenberg, A.R.
274	European Urology	1982	8	193-5	Bilateral Cohen's antireflux procedure with a single submucosal tunnel	Faure, G., Ben-Salah, S., dEscoffier, P.L., and Revol, M.
477	Journal of Urology	1972	107	862-4	Vesicoureteral reflux and ureteral duplication in children	Fehrenbaker, L.G., Kelalis, P.P., and Stickler, G.B.
816	International Urology & Nephrology	1993	25 (2)	141-6	Primary vesicoureteral reflux in children under one year of age: the case for conservative management.	Fichtner, J., Iwasaki, K., Shrestha, G., and Ikoma, F.
255	Journal of Urology	1983	129	545-7	A retrospective analysis of the use of ureteral stents in children undergoing ureteroneocystotomy	Fort, K.F., Selman, S.H., and Kropp, K.A.
657	Journal of Urology	1992	148	718-23	Subureteral collagen injection for the endoscopic treatment of vesicoureteral reflux in children. Followup study of 97 treated ureters and histological analysis of collagen implants.	Frey, P., Berger, D., Jenny, P., and Herzog, B.
684	International Urology & Nephrology	1991	23	231-6	Evaluation of the course of pregnancy, delivery and the condition of the newborn infant in women operated on for vesicoureteral reflux in childhood.	Fryczkowski, M., Maruszewska, J., Paradysz, A., and Maruszewski, W.
141	International Urology & Nephrology	1986	18	397-402	Operative treatment of bilateral vesicoureteral reflux by our own method of ureter reimplantation	Fryczkowski, M., Paradysz, A.
310	International Urology & Nephrology	1980	12	119-22	Complications after extravesical antireflux operations	Funke, P.J., Chiari, R., and Planz, K.
566	Journal of the American Medical Association	1966	195	636-8	Antireflux surgery in children	Garrett, R.A., Switzer, R.W.
150	Journal of Pediatric Surgery	1986	21	697-701	Follow-up of renal morphology and growth of 141 children operated for vesicoureteral reflux: a retrospective computerized study	Ginalski, J.M., Michaud, A., and Genton, N.
184	Journal of Urology	1985	134	304-7	Transverse ureteral advancement technique of uretero neocystostomy (Cohen reimplant) and a modification for difficult cases (experience with 121 ureters)	Glassberg, K.I., Laungani, G., Wasnick, R.J., and Waterhouse, K.
675	Archives of Disease in Childhood	1991	66	1282-3	Imaging in urinary tract infection	Gleeson, F.V., Gordon, I.
641	Journal of Urology	1992	148	1688-92	Followup of conservatively treated children with high and low grade vesicoureteral reflux: a prospective study	Goldraich, N.P., Goldraich, I.H.
418	Urology	6	1975	273-86	Management of children with urinary tract infections: the Stanford experience	Govan, D.E., Fair, W.R., Friedland, G.W., and Filly, R.A.
222	Zeitschrift fur Kinderchirugie	39	1984	52-4	Renal growth after antireflux surgery in infants	Hagberg, S., Hjalmas, K., Jacobsson, B., and Sillen, U.
383	Journal of Urology	117	1977	355-7	Extravesical repair of primary vesicoureteral reflux in children	Hampel, N., Richter-Levin, D., and Gersh, I.

249	Journal of Urology	129	1983	1022-3	Management of unilateral reflux by ipsilateral ureteroneocystostomy--is it sufficient?	Hanani Y., Goldwasser, B., Jonas, P., Hertz, M., and Many, M.
288	Urology	18	1981	562-6	Early surgical correction of massive refluxing megaureter in babies by total ureteral reconstruction and reimplantation	Hanna, M.K.
90	Acta Radiologica	30	1989	391-4	Influence of vesicoureteral reflux and urinary tract infection on renal growth in children with upper urinary tract duplication	Hannerz, L., Wikstad, I., Celsi, G., and Aperia, A.
54	Scandinavian Journal of Infectious Diseases	21	1989	201-4	Trimethoprim-sulphadiazine prophylaxis in children with vesico-ureteric reflux	Hanson, E., Hansson, S., and Jodal, U.
294	Urology	18	1981	241-3	Bilateral or unilateral ureteroneocystostomy for unilateral reflux	Harty, J.I., Howerton, L.W., Jr.
368	Birth Defects Original Article Series	13	1977	367-71	Contralateral reflux: the rationale for a conservative approach	Hirsch, S., Fitzgerald, J.
643	Journal of Urology	148	1992	1657-61	Surgical results in the International Reflux Study in Children (Europe)	Hjalmas, K., Lohr, G., Tamminen-Mobius, T., Seppanen, J., Olbing, H., and Wikstrom, S.
483	South African Medical Journal	45	1971	1063-4	Therapy of vesico-ureteral reflux in children	Hohenfellner, R.
177	Journal of Urology	134	1985	1168-71	Effects of oxybutynin on vesicoureteral reflux in children	Homsy, Y.L., Nsouli, I., Hamburger, B., Laberge, I., and Schick, E.
658	Journal of Urology	148	1992	704-7	Extravesical nondismembered ureteroplasty with detrusorrhaphy: a renewed technique to correct vesicoureteral reflux in children	Houle, A.M., McLorie, G.A., Heritz, D.M., McKenna, P.H., Churchill, B.M., and Khoury, A.E.
616	Journal of Urology	145	1991	1022-3	Resolution of vesicoureteral reflux in completely duplicated systems: fact or fiction?	Husmann, D.A., Allen, T.D.
376	British Journal of Urology	49	1977	119-27	Vesico-ureteral reflux in children	Jakobsen, B.E., Genster, H., Olesen, S., and Nygaard, E.
22	British Journal of Urology	65	1990	413-17	Results of surgical treatment of severe vesicoureteric reflux. Retrospective study of reflux grades 4 and 5	Jansen, H., Scholtmeijer, R.J.
650	Journal of Urology	148	1992	1650-2	Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. The International Reflux Study in Children.	Jodal, U., Koskimies, O., Hanson, E., Lohr, G., Olbing, H., Smellie, J., and Tamminen-Mobius, T.
426	British Journal of Urology	47	1975	153-9	The congenital refluxing megaureter: experiences with surgical reconstruction	Johnston, J.H., Farkas, A.
438	Israel Journal of Medical Sciences	10	1974	603-7	Ureteroneocystostomy in children with vesicoureteral reflux. Experience with 150 reimplanted ureters	Jonas, P., Many, M., Boichis, H., and Hertz, M.
594	Urology	37	1991	244-7	Endoscopic treatment of vesicoureteral reflux in children with	Kaminetsky, J.C., Hanna, M.K.
346	Journal of Urology	120	1978	220-2	Reflux in complete duplication in children	Kaplan, W.E., Nasrallah, P., and King, L.R.
666	Archives of Disease in Childhood	67	1992	506-8	Vesicoureteric reflux and renal scars in asymptomatic siblings of children with reflux	Kenda, R.B., Fettich, J.J
68	Australian & New Zealand Journal of Surgery	58	1988	569-71	The endoscopic correction of vesico-ureteric reflux	King, P.A., Gollow, I.

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
586	International Urology & Nephrology	22	1990	531-5	Surgical management of vesicoureteral reflux by modified Gil-Vernet method	Kliment, J., Fetisov, I., and Svitac, J.
230	Journal of Urology	130	1983	1138-1	The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution	Koff, S.A., Murtagh, D.S.
214	Contributions to Nephrology	39	1984	211-20	The uninhibited bladder in children: effect of treatment on vesicoureteral reflux resolution	Koff, S.A., Murtagh, D.
135	British Journal of Urology	60	1987	36-8	Correction of reflux with the ureteric crossover method. Clinical experience in 50 patients	Kondo, A., Otani, T.
15	European Urology	17	1990	318-20	Ureterovesical reimplantation after failure of endoscopic treatment of reflux by submucosal injection of polytef paste	Lacombe, A.
687	Journal of Urology	146	1991	657-9	Duplex reflux: a study of 105 children	Lee, P.H., Diamond, D.A., Duffy, P.G., and Ransley, P.G.
394	Journal of Urology	115	1976	728-30	The natural history of reflux and long-term effects of reflux on the kidney	Lenaghan, D., Whitaker, J.G., Jensen, F., and Stephens, F.D.
622	Journal of Urology	145	1991	115-19	Endoscopic injection of glutaraldehyde cross-linked bovine dermal collagen for correction of vesicoureteral reflux	Leonard, M.P., Canning, D.A., Peters, C.A., Gearhart, J.P., and Jeffs, R.D.
51	European Urology	16	1989	200-3	Lich-Gregoir anti-reflux operation: a surgical experience and 5-20 years of follow-up in 149 ureters	Linn, R., Ginesin, Y., Bolkier, M., and Levin, D.R.
692	British Journal of Urology	18	1993	52-5	Endoscopic treatment of vesicoureteric reflux with collagen. Five years' experience	Lipsky, H., and Wurnschimmel
417	Quarterly Journal of Medicine	44	1975	481-9	Childhood urinary infection associated with vesico-ureteric reflux	MacGregor, M.E., Freeman, P.
254	Urology	21	1983	232-5	Management of massively refluxing megaureters	Maggiolo, L.F., Lockhart, J.L., and Politano, V.A.
347	Journal of Urology	120	1978	216-19	The Lich-Gregoir antireflux plasty: experiences with 371 children	Marberger, M., Altwein, J.E., Straub, E., Wulff, S.H., and Hohenfellner, R.
372	Urology	10	1977	19-22	Ureteral reimplantation: Lich method	McDuffie, R.W., Litin, R.B., and Blundon, K.E.
5	Journal of Urology	144	1990	537-40	High grade vesicoureteral reflux: analysis of observational therapy	McLorie, G.A., McKenna, P.H., Jumper, B.M., Churchill, B.M., Gilmour, R.F., and Khoury, A.E.
443	Lancet	1	1974	1310-12	Effect on renal growth of reimplantation of refluxing ureters	McRae, C.V., Shannon, F.T., and Utley, W.L.
195	Journal of Urology	133	1985	388-90	Reoperative ureteroneocystostomy: review of 69 patients	Mesrobian, H.G., Kramer, S.A., and Kelalis, P.P.

840	European Urology	23 (3)	1993	379-81	Effects of submucosal Teflon paste injection in vesicoureteric reflux: results with 1-and 2-year follow-up data.	Michael, V., Davaris, P., Arhontakis, A., and Androulakakis, P.A.
817	European Urology	24 (1)	1993	111-15	Endoscopic correction of vesico-ureteric reflux in duplex systems.	Miyakita, H., Ninan, G.K., and Puri, P.
344	Journal of Urology	120	1978	336-7	Non-operative treatment of vesicoureteral reflux	Mulcahy, J.J., Kelalis, P.P.
286	British Journal of Urology	53	1981	542-4	Improvement in renal function following ureteric reimplantation of vesicoureteric reflux	Mundy, A.R., Kinder, C.H., Joyce, M.R., Chantler, C., and Haycock, G.B.
205	Urology	24	1984	243-5	Reflux and voiding abnormalities in children	Nasrallah, P.F., Simon, J.W.
637	Journal of Urology	148	1992	1739-42	The long-term results of prospective sibling reflux screening	Noe, H.N.
176	Journal of Urology	134	1985	1172-5	The role of dysfunctional voiding in failure or complication of ureteral reimplantation for primary reflux	Noe, H.N.
534	British Journal of Urology	41	1969	6-13	Vesico-ureteric reflux in infants and children: results of supervision, chemotherapy and surgery	ODonnell, B., Moloney, M.A., and Lynch, V.
144	British Medical Journal - Clinical Research	293	1986	1404-6	Endoscopic correction of primary vesicoureteric reflux: results in 94 ureters	ODonnell, B., Puri, P.
649	Journal of Urology	148	1992	1653-6	Renal scars and parenchymal thinning in children with vesicoureteral reflux: a 5-year report of the International Reflux Study in Children (European Branch)	Olbing, H., Claesson, I., Ebel, K.D., Seppanen, U., Smellie, J.M., Tamminen-Mobius, T., and Wikstad, I.
12	European Urology	17	1990	330-2	A new antireflux operation	Orikasa, S.
798	British Journal of Urology	72 (9/3)	1993	373-5	Intravesical ureteric plication and reimplantation for megaureters in children.	Ozen, H.A., Tekgul, S., Erkan, I., and Bakkaloglu, M.
403	Urology	7	1976	276-8	Reflux in opposite ureter after successful correction of unilateral vesicoureteral reflux	Parrott, T.S., Woodard, J.R.
677	Journal of Urology	146	1991	1594-5	Nonsurgical management of primary vesicoureteral reflux in complete ureteral duplication: is it justified?	Peppas, D.S., Skoog, S.J., Canning, D.A., and Belman, A.B.
204	International Journal of Pediatric Nephrology	5	1984	83-8	Evaluation of kidney growth in vesico-ureteral reflux	Peratoner, L., Messi, G., and Fonda, E.
107	Journal of Urology	140	1988	121-4	Medical treatment of vesicoureteral reflux detected in infancy	Pinter, A.B., Jaszai, V., and Dober, I.
25	Scandinavian Journal of Urology and Nephrology	125	1989	29-34	Vesico-ureteral reflux. II. The longterm outcome of kidney function in non-surgical treatment	Poulsen, E.U., Johannesen, N.L., Nielsen, J.B., Jrgensen, T.M., and Anderson, A.J.
21	Lancet	335	1990	1320-2	Endoscopic correction of primary vesicoureteric reflux by subureteric injection of polytetrafluoroethylene	Puri, P.
115	Journal of Pediatric Surgery	22	1987	1087-91	Endoscopic correction of grades IV and V primary vesicoureteric reflux: six to 30 month follow-up in 42 ureters	Puri, P., ODonnell, B.
124	International Urology & Nephrology	19	1987	141-3	Antireflux operations without catheter	Pypno, W.
182	British Journal of Urology	57	1985	406-9	Unilateral ureteric reimplantation for primary vesicoureteric reflux in children. A policy re-evaluated	Quinlan, D., ODonnell, B.

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
332	Urology	13	1979	248-52	Primary massive reflux in children	Rabinowitz, R., Barkin, M., Schillinger, J.F., Jeffs, R.D., and Cook, G.T.
461	Urologia Internationalis	28	1973	56-64	Surgical correction of vesicoureteral reflux. Description of technique and results	Ravasini, G., Pagano, F.
183	Turkish Journal of Pediatrics	26	1984	175-9	15 years of experience in the surgical treatment of vesicoureteral reflux in children	Remzi, D., Ozen, H.A., Erkan, I., and Kendi, S.
356	Urology	11	1978	231-6	Megaureters in children	Retik, A.B., McEvoy, J.P., and Bauer, S.B.
827	European Journal of Pediatrics	152 (6/6)	1993	523-5	Primary vesicoureteral reflux in infants with a dilated fetal urinary tract.	Ring, E., Petritsch, P., Riccabona, M., Haim-Kuttnig, M., Vilits, P., Rauchenwald, M., and Fueger, G.
679	International Urology & Nephrology	23	1991	437-40	Screening of asymptomatic siblings of patients with vesicoureteral reflux	Sahin, A., Ergen, A., Balbay, D., Basar, I., Ozen, H., and Remzi, D.
680	International Urology & Nephrology	23	1991	31-5	The fate of contralateral ureter after ipsilateral reimplantation in unilateral vesicoureteric reflux	Sargin, S.Y. Ergen, A., Ozen, H.A., Ozkardes, H., Tekgul, S., Erkan, I., and Bakkaloglu, M.
16	European Urology	17	1990	310-13	Analysis and perspectives of endoscopic treatment of vesicoureteral reflux in children with a 20-month follow-up	Sauvage, P., Saussine, C., Laustriat, S., Becmeur, F., Bientz, J., Christmann, D., Roy, E., and Marcellin, L.
685	Child. Nephrol. Urol.	11	1991	29-32	Treatment of vesicoureteric reflux: results after 3 years in a prospective study	Scholtmeijer, R.J.
18	Journal of Pediatric Surgery	25	1990	669-71	The role of videourodynamic studies in diagnosis and treatment of vesicoureteral reflux	Scholtmeijer, R.J., Griffiths, D.J.
114	British Journal of Urology	61	1988	205-9	Treatment of vesicoureteric reflux. Preliminary report of a prospective study	Scholtmeijer, R.J., Griffiths, D.J.
74	European Urology	17	1990	314-17	Vesicoureteral reflux in children: endoscopic treatment	Schulman, C.C., Pamart, D., Hall, M., Janssen, F., and Avni, F.E.
128	Journal of Urology	138	1987	950-2	Endoscopic treatment of vesicoureteral reflux in children	Schulman, C.C., Simon, J., Pamart, D., and Avni, F.E.
157	British Journal of Urology	58	1986	119-24	Renal function following surgical correction of vesico-ureteric reflux in childhood	Scott, D.J., Blackford, H.N., Joyce, M.R., Mundy, A.R., Kinder, C.H., Haycock, G.B., and Chantler, C.

377	British Journal of Urology	49	1977	109-18	The management of ureteric reflux in children	Scott, J.E.
540	Archives of Disease in Childhood	43	1968	323-8	Treatment of vesico-ureteric reflux in children	Scott, J.E., Stansfeld, J.M.
94	Journal of Urology	142	1989	494-8	Vesicoureteral reflux and voiding dysfunction: a prospective study	Seruca, H.
354	Archives of Disease in Childhood	53	1978	210-17	Renal scarring and vesicoureteric reflux	Shah, K.J., Robins, D.G., and White, R.H.
618	Pediatrics	87	1991	538-43	Primary vesicoureteral reflux in the black child	Skoog, S.J., Belman, A.B.
130	Journal of Urology	138	1987	941-6	A nonsurgical approach to the management of primary vesicoureteral reflux	Skoog, S.J., Belman, A.B., and Majd, M.
611	Pediatric Nephrology	2	1988	12-17	Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children	Smellie, J.M., Gruneberg, R.N., Bantock, H.M., and Prescod, N.
389	British Medical Journal	2	1976	203-6	Long-term low-dose co-trimoxazole in prophylaxis of childhood urinary tract infection: clinical aspects	Smellie, J.M., Gruneberg, R.N., Leakey, A., and Atkin, W.S.
313	Journal of Urology	125	1981	551-3	Ureteral reimplantation without catheters	So, E.P., Brock, W.A., and Kaplan, G.W.
105	European Urology	14	1988	214-15	Correction of vesicoureteral reflux by the Gil-Vernet procedure	Solok, V., Erozenci, A., Kural, A., and Oner, A.
96	British Journal of Urology	63	1989	245-50	Physical growth velocity during conservative treatment and following subsequent surgical treatment for primary vesicoureteric reflux	Sutton, R., Atwell, J.D.
116	Annales de Radiologie	30	1987	478-81	Evaluation of sub-ureteric Teflon injection as an antireflux procedure	Sweeney, L.E., Thomas, P.S.
648	Journal of Urology	148	1992	1662-6	Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children	Tamminen-Mobius, T., Brunier, E., Ebel, K.D., Lebowitz, R., Olbing, H., Seppanen, U., and Sixt, R.
212	Contributions to Nephrology	39	1984	238-46	Unstable bladder activity and the rate of resolution of vesico-ureteric reflux	Taylor, C.M.
262	British Journal of Urology	54	1982	494-8	Micturition symptoms and unstable bladder activity in girls with primary vesicoureteral reflux	Taylor, C.M., Corkery, J.J., and White, R.H.
131	British Medical Journal - Clinical Research	295	1987	237-41	Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group	The Birmingham Reflux Study Group
246	Journal of Urology	129	1983	1198-9	Initial results with the Cohen cross-trigonal ureteroneocystotomy	Wacksman, J.
348	Journal of Urology	119	1978	814-6	Management of vesicoureteral reflux	Wacksman, J., Anderson, E.E., and Glenn, J.F.
660	Journal of Urology	148	1992	359-61	Results of the renewed extravesical reimplant for surgical correction of vesicoureteral reflux	Wacksman, J., Gilbert, A., and Sheldon, C.A.

Papyrus Reference	Journal	Year	Volume	Pages	Title	Author
327	British Journal of Urology	50	1978	479-84	The long-term follow-up of surgically treated vesicoureteric reflux	Wallace, D.M., Rothwell, D.L., and Williams, D.I.
479	Journal of Urology	107	1972	466-8	Unilateral ureteroneocystostomy: the fate of the contralateral ureter	Warren, M.M., Kelalis, P.P., and Stickler, G.B.
647	Journal of Urology	148	1992	1667-73	Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children.	Weiss, R., Duckett, J. and Spitzer, A.
396	Journal of Urology	115	1976	722-5	Renal growth and urinary infection following antireflux surgery in infants and children	Willscher, M.K., Bauer, S.B., Zammuto, P.J., and Retik, A.B.
388	Journal of Pediatrics	89	1976	743-7	Infection of the urinary tract after anti-reflux surgery	Willscher, M.K., Bauer, S.B., Zammuto, P.J., and Retik, A.B.
129	Journal of Urology	138	1987	947-9	Detrusorrhaphy: extravesical ureteral advancement to correct vesicoureteral reflux in children	Zaontz, M.R., Maizels, M., Sugar, E.C., and Firlit, C.F.
640	Journal of Urology	148	1992	1699-1702	Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux. The International Reflux Study in Children	van Gool, J.D., Hjalmas, K., Tamminen-Mobius, T., and Olbing, H.

Total Number of Articles = 168

Appendix B: Data extraction form

VUR Data Retrieval Page 1 of ____

Cover Sheet - A_VUR.DB

Reference No.

Journal:

Year: Vol: Pages:

Author(s):

Title:

Institution:

1. STUDY TYPE (Enter from list, Appendix 1) Acquisition years

Accepted/Rejected: (circle one) A / R

If Rejected, Why ? (circle one or explain)
D = Data updated in more recent report
A = Data are absent
U = Data present but cannot be interpreted to complete categories of Data Retrieval Form
O = Other

Study Quality

	Worst - Best (0 - 10)		(Y or N)
Well defined Patient groups		Exclude Voiding Dysfunction	
Well defined Outcomes		Follow-up Rate > 50%	
Well defined Exclusions		Prospective / Randomized	
Definition of Norms		> 50 patients total	
		Cystoscopy used for Dx	

Overall Study Comments (Use to identify biases to internal and external validity, or other issues which may be of interest to the panel - see instructions for details. Continue on back, if necessary)

List References (or attach bibliography):

Keywords: (Enter number, see Appendix 1)

Reviewer:

Time to Complete: *(minutes)*

Date:

(Reviewer 1 - Red)
(Reviewer 2 - Blue)
(Composite - Yellow)

VUR Data Retrieval Page 2 of ____

Cover Sheet - C_VUR_R*.DB

Reference No.

2.DEMOGRAPHICS - TOTAL Population

TOTAL Patients: Indicate Number TOTAL Renal Units: Indicate Number

Intervention	Patients 1° Rx	Patients 2° Rx	Ureters 1° Rx	Ureters 2° Rx	Inclusion Criteria
Medical					
Surgery					
Endoscopic					
Control					

The following data should reflect the entire study population.

**** 1 ****
Sex Male Female
Age <1 1 to 5 >5 Mean Min Max

**** 2 ****
Presentation UTI PNDx Sib Incid
Complete Duplication Single Dupl
Upper Pole Reflux only
Lower Pole Reflux only
Reflux into both Systems
Unilat/Bilat Unilat Bilat Solitary Kidney
Voiding Dysfunction Pres None Not Stated
IRR Pres None Not Stated
Mode of Dx: VCUG RNC

Reflux Classification Code (see appendix 1)

Reflux Grade:	Patients %	Patients x	Patients y	Ureters %	Ureters x	Ureters y
Grade:						
Grade:						
Grade:						
Grade:						
Grade:						
Grade:						

**** 1 *** If outcomes are analyzed in separate groups characterized by one or more these parameters, a separate set of sheets (pp 4-7) should be filled out for each group.

**** 2 **** The following group of parameters will usually be qualifiers and not segregators. If outcomes are analyzed in separate groups characterized by one or more these parameters, a separate set of sheets (pp 4-7) should be filled out for each group

VUR Data Retrieval Page 3 of ____

Cover Sheet - C_VUR_R*.DB

Reference No.

Define the various groupings that are detailed on the attached sheets. (pp. 4-7)
Each Group should have a separate set of sheets (pp. 4-7). See Appendix 2 for Codes.

	Sex	Age	Dupl	Grade	Uni/Bi	1° Rx	2° Rx	AV	F/U (years)	F/U Code	Other (Describe)
Group 0											
Group 1											
Group 2											
Group 3											
Group 4											
Group 5											
Group 6											
Group 7											
Group 8											
Group 9											
Group 10											
Group 11											
Group 12											
Group 13											
Group 14											
Group 15											
Group 16											
Group 17											
Group 18											
Group 19											
Group 20											
Group 21											
Group 22											
Group 23											
Group 24											
Group 25											
Group 26											
Group 27											
Group 28											
Group 29											
Group 30											

VUR Data Retrieval Page 4 of ____

Dx & Rx Data - D_VUR_R*.DB

Reference No. Group

2.DEMOGRAPHICS - of PARTICULAR Group

TOTAL Patients: (this group) Indicate Number TOTAL Renal Units: (this group) Indicate Number

Intervention	Patients 1° Rx	Patients 2° Rx	Ureters 1° Rx	Ureters 2° Rx	Inclusion Criteria
Medical					
Surgery					
Endoscopic					
Control					

*(*** see 1 on page 2, bottom)*
Sex Male Female
Age <1 1 to 5 >5 Mean Min Max

*(*** see 2 on page 2, bottom)*
Presentation UTI PNDx Sib Incid
Complete Duplication Single Dupl
Upper Pole Reflux only
Lower Pole Reflux only
Reflux into both Systems
Unilat/Bilat Unilat Bilat Solitary Kidney
Voiding Dysfunction Pres None Not Stated
IRR Pres None Not Stated
Mode of Dx: VCUG RNC

3. INITIAL	Patients %	Patients x	Patients y	Ureters %	Ureters x	Ureters y	Definition
Scarring							
Infections							
Hypertension							
Proteinuria							
Impaired Function							
Mean CrCrClr							
ESRD							
Small Kidney							
Short stature							
Voiding Dysfunction							
Other							

Comments

Appendix B (continued)

VUR Data Retrieval Page 5 of ____

Reference No. ____ Group ____

4.1 Medical (Y or N)

Cont Prophylaxis ____ Agent(s) ____ TMX/SUL ____ NF ____ Cef ____ PCN/TR ____ GNT ____

Intermit Prophylaxis ____ NotSp ____

Anticholinergics ____ Agent(s) Ditropan ____ Other ____

4.2 Surgery (Y or N)

OPEN

P-L ____ G-A ____ T-T ____ L-G ____ Pag ____

G-V ____ Detrus ____ B. Neck ____ Tapering ____

Not Stated ____ Other ____

ENDOSCOPIC

Teflon ____ Collag ____ Ivalon ____ Blood ____ Fat ____

Not Stated ____ Other ____

DUPLICATION

Ureteroureterostomy ____ Partial Nephrectomy ____ Common Sheath Reimplant ____

Reimplant of Lower Pole Ureter only ____ 2° Excision of Stump ____

Not Stated ____ Other ____

OTHER

Nephrectomy ____ Nephroureterectomy ____

Not Stated ____ Other ____

Mean Hospital Stay (Days) ____

Comments: ____

VUR Data Retrieval Page 6 of ____

Outcomes Data - O_VUR_R*.DB

Reference No. ____ Group ____

4.3 OUTCOMES

Resolution data is: (circle one) A. Actual B. Actuarial C. Kaplan-Meier

Spontaneous Resolution	Patients %	Patients x	Patients y	Ureters %	Ureters x	Ureters y	Definitions
1 year							
2 years							
3 years							
4 years							
5 years							
>5 years							
All Not spec							
Reduced							
Worsened							
Cross Over to Surgery							
Surgical Cure							
New Scarring							
Progr Scarring							
Infections (NS)							
Cystitis							
Febrile 1							
2 to 3							
>3							
Febrile (Unknown number)							
Asymptomatic							
No of Breakthru							
Hypertension							
Proteinuria							
Impaired Function							
Mean CrCrClr							
ESRD							
Impaired Growth							
Kidney							
Somatic							
Voiding Dysfunction							
Side Effects (Medical Rx)							
None							
Total Number							
Allergic							
Hematologic							
Alter Rx							
Other							
Not Stated							
Complications (Surgical - 3 mo perioperative)							
New Contralateral VUR							
Ipsilateral VUR							
Disappears with time							
Persists req Surgery							
Persists not req Surgery							
REOP Obstruction							
Obstruction no REOP							
Infection (UTI)							
Other							
Not Stated							

VUR Data Retrieval Page 7 of ____

Outcomes Data - O_VUR_R*.DB (con't)

Reference No. ____ Group ____

Relationship of Scarring to Bacteriuria, if known for this particular group:

Bacteriuria (since Rx)	New or Progressive Scarring Y	New or Progressive Scarring N
Y		
N		

(Enter the number of Patients in each box)

Outcomes Comments: ____

Follow-up Data

5. FOLLOW-UP

Mean	Min	Max

VCU	RNC	U/S	IVP	C/S	CrClr	Interval
						Initial
						Subsequent

Detection of Scarring DMSA ____ IVP ____ U/S ____

Measurement of Renal Growth Planimetry ____ Length ____

Measurement of Renal function Serum Cr ____ CrClr ____ EDTA ____ DMSA ____

Comments ____

Appendix C: Methodology for combining parameters

Combining relative risks from several different studies is problematic. Several meta-analytic techniques can be used. A fixed effects analysis assumes that the studies all estimate the same parameter (relative risk). The opposite of a fixed effects model is a random effects model. In a random effects model, the parameter does not remain constant from study to study, but rather varies randomly, and the center of the distribution of the parameter of interest must be estimated. This methodology is especially appropriate for combining relative risks from pediatric reflux studies, because the populations used by each study have different mixes of grades, laterality and gender.

One standard method of combining parameters using random effects models is the empirical Bayes (EB) method (Hedges and Olkin, 1985). For this method, we assume that each θ_j estimates a different parameter, θ_j, with known variance, σ_j^2. The θ_j's are assumed to be a sample from a normal distribution with mean μ and variance τ^2. That is, mother nature chooses parameters for each study at random from a normal distribution with mean μ and variance τ^2. The likelihood is proportional to

$$L \propto \exp\left[-\sum_{j=1}^{m} [(\theta_j - \mu)^2 / (\tau^2 + \sigma_j^2) + \ln(\tau^2 + \sigma_j^2)] / 2 \right].$$

Maximum likelihood estimates can be calculated directly using a modified Gauss-Newton algorithm (Hasselblad, 1994) or the EM Algorithm (Dempster, Laird, and Rubin, 1977).

For dichotomous outcomes, such as rates of renal scarring, the same model can be used for the parameters, but the underlying distribution of the parameters is assumed to be binomial instead of normal. This can be accomplished by fitting a multiple logistic regression model with random effects. The EGRET software package (Statistics and Epidemiology Research Corporation, 1993) can be used to estimate such models. This model can be generalized to include multiple variables of interest.

The following example illustrates the use of the method to estimate the effect of both treatment and grade on renal scarring. A dataset was created for each subgroup of each renal scarring study when the study gave results by grade (see Table C-1). Dummy variables were created for each grade to indicate the effect of grade. Grades IV and V were combined because there were so few subjects. Some studies gave their results for a group of grades, and these presented special analysis problems. For those studies, the fraction of subjects in each grade was used in place of the dummy variables. To understand this, assume that one study had 40 percent in grade II and 60 percent in grade III. Then each individual in grade II should be assigned a one for the dummy for grade II and a zero for the other dummies. If this was actually done for all subjects in both grades and the dummy variables were then averaged, the result would be the fraction for each dummy as proposed. A small number of studies did not give a grade distribution, and for these studies an average grade distribution was assigned.

The data in Table C-1 were analyzed using multiple logistic regression analysis. The model assumes that the effects of each content factor are additive (in the log-odds space). Thus, the analysis results must be converted back to probabilities and relative risks. The results for this example are shown in Table C-2.

TABLE C-1. Dataset Created from the Medical and Surgical Studies of New Scarring (per Ureter)

Study	New Scars	Sample Size	Grade I	Grade II	Grade III	Grade IV/V	Surgery (1=yes)
Ben-Ami, Sinai, Hertz, et al., 1989	0	4	1	0	0	0	0
	0	28	0	.5	.5	0	0
	3	5	0	0	0	1	0
Scholtmeijer and Griffiths, 1988	0	12	1	0	0	0	0
	1	36	0	1	0	0	0
	1	31	0	0	1	0	0
	0	12	0	0	0	1	0
Birmingham Reflux Study Group, 1987	5	111	0	.1	.4	.5	0
Homsy, Nsouli, Hamburger, et al., 1985	0	53	.09	.06	.15	.15	0
Bellinger and Duckett, 1984	1	165	.15	.55	.18	.12	0
Koff and Murtagh, 1983	3	47	.06	.23	.36	.34	0
	2	55	.21	.25	.25	.26	0
Shah, Robins, and White, 1978	1	13	0	1	0	0	0
	4	47	0	0	.40	.60	0
Cardiff-Oxford Bacteriuria Study Group, 1978	0	28	1	0	0	0	0
	1	41	0	1	0	0	0
	1	12	0	0	.40	.60	0
Edwards, Normand, Prescod, et al., 1977	2	121	.15	.18	.49	.14	0
Jakobsen, Genster, Olesen, et al., 1977	0	193	.21	.35	.17	.25	0
Husmann and Allen, 1991	13	142	0	1	0	0	0
Burge, Griffiths, Malone, et al., 1992	0	6	1	0	0	0	0
	0	3	0	1	0	0	0
	0	14	0	0	1	0	0
	0	17	0	0	0	1	0
	0	4	0	0	0	1	0
Arant 1992	1	11	1	0	0	0	0
	5	40	0	1	0	0	0
	9	33	0	0	1	0	0
Aggarwal, Verrier-Jones, Asscher, et al., 1991	0	10	1	0	0	0	0
	0	10	0	1	0	0	0
	2	11	0	0	.40	.60	0
Beetz, Schulte-Wissermann, Tröger, et al., 1989	9	264	.09	.52	.31	.10	1
Scholtmeijer and Griffiths, 1988	2	10	0	0	1	0	1
	1	24	0	0	0	1	1
Birmingham Reflux Study Group, 1987	4	104	0	.1	.4	.5	1
Scott, Blackford, Joyce, et al., 1986	0	97	0	.1	.4	.5	1
Carpentier, Bettink, Hop, et al., 1982	0	100	.35	.5	.28	.12	1
Burge, Griffiths, Malone, et al., 1992	0	21	.14	.05	.28	.53	1
Hjalmas, Lohr, Tamminen-Mobius, et al., 1992	20	237	0	0	.11	.89	1

TABLE C-2. Results of the Multiple Logistic Regression Analysis With Random Effects Using the Data in Table C-1

Variable	Coefficient	Std.Err.Beta	p-value	Odds/Odds ratio
Grade I	-6.125	(1.57)	<.001	.002187
Grade II	-3.739	(.397)	<.001	.02377
Grade III	-3.332	(.770)	<.001	.03573
Grade IV or V	-2.841	(.538)	<.001	.05836
Surgery	-.02613	(.452)	.954	.9742
Random effect term	1.368	(.316)		

The combination of rates, such as complication rates, is a special case of the analysis just described. The general use of a linear model with random effects can be applied to either continuous or dichotomous data. Most standard meta-analytic methods, such as inverse variance weighting and the Mantel-Haenszel method, are special cases of the methods just described.

References for Appendix C

Aggarwal VK, Verrier-Jones K, Asscher AW, Evans C, Williams LA. Covert bacteriuria: long term follow up. Arch Dis Child 1991;66:1284–6.

Arant BS Jr. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study. J Urol 1992; 148:1683–7.

Beetz R, Schulte–Wissermann H, Tröger J, Riedmiller H, Mannhardt W, Schofer O. Long-term follow-up of children with surgically treated vesicorenal reflux: postoperative incidence of urinary tract infections, renal scars and arterial hypertension. Eur Urol 1989;16:366–71.

Bellinger MF, Duckett JW. Vesicoureteral reflux: a comparison of non-surgical and surgical management. Contrib Nephrol 1984; 39:81–93.

Ben-Ami T, Sinai L, Hertz M, Boichis H. Vesicoureteral reflux in boys: review of 196 cases. Radiology 1989;173:681–4.

Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux. BMJ 1987;295:237–41.

Burge DM, Griffiths MD, Malone PS, Atwell JD. Fetal vesicoureteral reflux: outcome following conservative postnatal management. J Urol 1992;148:1743–5.

Cardiff-Oxford Bacteriuria Study Group. Sequelae of covert bacteriuria in schoolgirls. A four-year follow-up study. Lancet 1978;1:889–93.

Carpentier PJ, Bettink PJ, Hop WC, Schroder FH. Reflux—a retrospective study of 100 ureteric reimplantations by the Politano-Leadbetter method and 100 by the Cohen technique. Br J Urol 1982;54:230–3.

Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. BMJ 1977;2:285–8.

Hjalmas K, Lohr G, Tamminen-Mobius T, Seppanen J, Olbing H, Wikstrom S. Surgical results in the International Reflux Study in Children (Europe). J Urol 1992;148:1657–11.

Homsy YL, Nsouli I, Hamburger B, Laberge I, Schick E. Effects of oxybutynin on vesicoureteral reflux in children. J Urol 1985;134:1168–71.

Husmann DA, Allen TD. Resolution of vesicoureteral reflux in completely duplicated systems: fact or fiction?. J Urol 1991;145:1022–3.

Jakobsen BE, Genster H, Olesen S, Nygaard E. Vesico-ureteral reflux in children. Br J Urol 1977;49:119–27.

Koff SA, Murtagh DS. The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution. J Urol 1983;130:1138–40.

Scholtmeijer RJ, Griffiths DJ. Treatment of vesicoureteric reflux. Preliminary report of a prospective study. Br J Urol 1988;61:206–9.

Scott DJ, Blackford HN, Joyce MR, Mundy AR, Kinder CH, Haycock GB, Chantler C. Renal function following surgical correction of vesico-ureteric reflux in childhood. Br J Urol 1986;58:119–24.

Shah KJ, Robins DG, White RH. Renal scarring and vesicoureteric reflux. Arch Dis Child 1978;53:210–17.

Appendix D: Recommendations questionnaire—Sample page

American Urological Association, Inc.
Vesicoureteral Reflux Guidelines
Panel Survey Questionnaire

NAME:

Question No.

Age: **Grade:** **Characteristics:**

A. What would be your initial treatment? (check one)

Boys	Girls	
_____	_____	a. Intermittent treatment
_____	_____	b. Continuous Antibiotic Prophylaxis (go to B)
_____	_____	c. Surgery

How strongly do you feel about this recommendation? (circle one)

Boys:	low	medium	high
Girls:	low	medium	high

B. If uncomplicated reflux persists, you would continue prophylaxis until age:
(boys) _____ (girls) _____ , and then:

Boys	Girls	
_____	_____	a. discontinue treatment and cystography
_____	_____	b. discontinue treatment and continue cystography until age: (boys) _____ (girls) _____
_____	_____	c. operate
_____	_____	d. discontinue treatment: continue cystography and, if reflux persists until age: (boys)_____ (girls) _____ , then operate.

How strongly do you feel about this recommendation? (circle one)

Boys:	low	medium	high
Girls:	low	medium	high

Appendix E: Data presentation

TABLE E-1. RESOLUTION OF REFLUX AFTER OPEN SURGERY

Author/ Papyrus #	Number of Patients	Number of Ureters	Surgical Procedure[1]	Surgical Success (Patients)	Surgical Success (Ureters)	Grade I/ Total	Grade II/ Total	Grade III/ Total	Grade IV/ Total	Grade V/ Total
Linn 51	60	101	L-G	55/60						
Beetz 42	189	242	L-G		238/242					
Jansen 22	80	106	Mix,P-L,C,L-G	96/106						
Fryczkowski 14	50	103	Author's own		103/103		8/8	48/48	44/44	3/3
Bellinger 209	207	338	Mix,P-L,G-A,C	197/207		?/12	?/80	?/102	?/115	?/26
Glassberg 184	60	101	C		101/101	1/1	10/10	23/23	32/32	35/35
Remzi 183	89	143	P-L		118/143					
Quinlan 182	51	51	Mix, L-P, C		50/51					
Sutton 96	22	22	P-L		22/22		1/1	8/8	13/13	
Solok 105	14	22	G-V		18/22		4/4	9/9	4/5	1/4
Decter 66	30		Mix P-L,G-A,C	30/30		1/1	5/5	10/10	9/9	5/5
Carini 181	14		G-V	13/14			3/3	8/9	2/2	
Ehrlich 120		31	K		31/31					
Scott 157	56	97	C	52/56						
Kondo 135	32	64	C		57/57		12/12		45/45	
Zaontz 129	79	120	D		111/120		57/58	42/47	15-Dec	
Birmingham 131	77	107	L-P, C		105/107		105/107			
Breuhl 117	146	190	L-G		188/190		46	106	32	6
Pypno 124	43	80	C		80/80		6	53	10	
Bradic 58	618	792	Anterior D		792/824		43	378	403	
Hanani 249	105		P-L, G-A	98/105						
Faure 274	136	272	C		270/272					
Carpentier 272	200	100	P-L		88/100	8	46	31	10	5
Carpentier 272		100	C		97/100	12	55	25	8	0
Ehrlich 267	135	229	C		226/229			74	102	53
Maggiolo 254	15	28	TH		24/28					24/28
Ahmed 252	28	38	C		37/38			4/4	12/12	21/22
Wacksman 24	36?	52	C		51/52	5/5	6/6	24/24	11/11	5/6
Hagberg 222	13	15	P-L		14/15					
Jakobsen 376	80		L-P Bischoff (2)	68/80						
McDuffie 372	51	78	L-G		73/76					
Retik 356	8	9	TH		9/9					
Marberger 347	371	429	L-G		419/429					
Wachsman 348			P-L			10/1	62/67	50/54		
Wachsman 348			G-A			2/2	39/40	25/26		
Wachsman 348			P				8/8	7/7 misc	10/19	
Harty 294	35	35	L-P		35/35	2/2	6/6	23/23		
Hanna 288	13	22	TH		21/22					21/22

[1]L-G = Lich-Gregoir; P-L = Politano-Leadbetter; C = Cohen (transtrigonal); G-A = Glenn-Anderson; K = Kalicinski; D = Detrusorrhaphy; TH = Tailoring Hendren; P = Paquin; G-V = Gil-Vernet; U = Ureterostomy; H = Hutch

TABLE E-1. RESOLUTION OF REFLUX AFTER OPEN SURGERY (continued)

Author/ Papyrus #	Number of Patients	Number of Ureters	Surgical Procedure[1]	Surgical Success (Patients)	Surgical Success (Ureters)	Grade I/ Total	Grade II/ Total	Grade III/ Total	Grade IV/ Total	Grade V/ Total
Scott 540	31	46	? type		38/46					
Bradic 412	90	106	Anterior D		91/93					
Hohenfellner 4	96		L-G	92/96						
Parrott 403		253	P		253/253					
Hampel 383	51	83	L-G		78/83					
Scott 377	163		Mod. P-L	157/163						
Duckett 642	87	154	C, P-L		153/154			18/153	135/153	
Burbige 678	33		C	33/33						
Burbige 678	37		P-L	37/37						
Brandell 789	34		Mixed,G-A,P-L,C	57/57	7/7	12/12	20/20	8/8	5/5	
Oezem 798	11	11	Starr Plic		5/11					5/11
Wacksman 660		202	D		202/202	1/1	63/63	112/112	22/22	4/4
De Gennaro 6	47	69	G-V		68/69		25/25	39/39	3/4	
Houle 658	45	65	D		62/65	6/6	16/16	23/23	13/14	4/6
Garrett 566	58	96	P-L		95/96					
Kliment 586	60	96	G-V	54/60						
Bettex 497	27	29	P-L		25/29					
Ravasini 461	22	37	Mod. G-A		37/37					
Jonas 438	86	150	Mix P-L, G-A		132/150					
Hjalmas 643	151	237			191/237					
Hjalmas 643	83	131	P-L							
Hjalmas 643	39	59	L-G							
Hjalmas 643	27	41	C							
Hjalmas 643	2	4	G-A							
Hjalmas 643	1	2	Mod. H							
Willscher 388+	223	342	P-L		338/342					
Hirsch 368	61	91	Unknown		84/91					
Broaddus 359	40	73	P-L		73/73	6/6	28/28	15/15	13/13	2/2
Rabinowitz 332	54	80	TH		25/25					25/25
So 313	52	87	Mix G-A, P-L		82/87					
Funke 310	142	176	L-G		168/176					
Atwell 305	112	106	P-L		106/106	14/14	16/16	43/43	33/33	
Arap 304	300	520	L-G		514/520	29/29	307/307	184/184		
Ahmed 301	205	296	C		294/296	13/13	101/101	119/121	61/61	
Carson 300	200		Unknown	194/200						
Mundy 286	73	80	Mix P-L,C		80/80					
Elo 284	49		P-L	47/49						
Brockrath 256	11	13	U		11/13					
Fort 255	63		Mix,G-A,P-L,C,H	47/50						
Govan 418	61	105	H		88/105					
Govan 418			P-L		14/17					
Burns 488	15		U		6/6					
Burns 488			H		7/9					

[1]L-G = Lich-Gregoir; P-L = Politano-Leadbetter; C = Cohen (transtrigonal); G-A = Glenn-Anderson; K = Kalicinski; D = Detrusorrhaphy; TH = Tailoring Hendren; P = Paquin; G-V = Gil-Vernet; U = Ureterostomy; H = Hutch

TABLE E-1. RESOLUTION OF REFLUX AFTER OPEN SURGERY (continued)

Author/ Papyrus #	Number of Patients	Number of Ureters	Surgical Procedure[1]	Surgical Success (Patients)	Surgical Success (Ureters)	Grade I/ Total	Grade II/ Total	Grade III/ Total	Grade IV/ Total	Grade V/ Total
Lee 687	23		P-L for duplex	18/23						
Scholtmeijer 685		49	Unknown		46/49	1/2	3/3	6/10	21/23	6/7
Sargin 680	30	30	MixP-L,G-A,C,P,		30/30			12/12	18/18	
Allen 462	20	29	Mod. G-L	18/19						
Mc Rae 443	39	63	Mix H,P,L-P		40/53					
McGregor 417	4		Unknown	4/4						
Amar 401	111		Mod. P-L	109/111						
Brown 93	51	79	C		75/76	18	18	15/15	40/3	
Johnston 426	17	29	TH		16/29					
Peratoner 204	38	50	Unknown		50/50		2/2	17/17	31/31	
Ginalski 150	141	229	Mix P-L, C		229/229	10/1	87/87	106/106	26/26	
Nasrallah 205	9	16	Unknown		4/16					
Fehrenbaker 4	16		Unknown duplic		13/16					
Marra 969	3	3	Unknown		3/3			1/1	2/2	

[1]L-G = Lich-Gregoir; P-L = Politano-Leadbetter; C = Cohen (transtrigonal); G-A = Glenn-Anderson; K = Kalicinski; D = Detrusorrhaphy; TH = Tailoring Hendren; P = Paquin; G-V = Gil-Vernet; U = Ureterostomy; H = Hutch

TABLE E-2. GRADE V REFLUX: RESOLUTION AFTER OPEN SURGERY

Author/ Papyrus #	Number of Patients	Number of Patients	Surgical Procedure[1]	Surgical Success (Ureters)	Grade V/ Total
Johnston 426	17	29	TH	16/29	
Rabinowitz 332	54	80	TH	25/25	25/25
Oezem 798	11	11	Starr Plic	5/11	5/11
Hanna 288	13	22	TH	21/22	21/22
Retik 356	8	9	TH	9/9	
Maggiolo 254	15	28	TH	24/28	24/28
Ehrlich 120		31	K	31/31	
Total	118	210		131/155	75/86
Percent				84.50%	87.2

[1]TH = Tailoring Hendren; K = Kalicinski

TABLE E-3. RESOLUTION OF REFLUX AFTER OPEN SURGERY

Author/ Papyrus #	Number of Patients	Number of Ureters	Surgical Procedure[1]	Surgical Success (Patients)	Surgical Success (Ureters)	Grade I/ Total	Grade II/ Total	Grade III/ Total	Grade IV/ Total	Grade V/ Total
Scholtmeijer 685		49	Unknown		46/49	1/2	3/3	6/10	21/23	6/7
Brown 93	51	79	C		75/76	18	18	15/15	40	3
Ahmed 301	205	296	C		294/296	13/13	101/101	119/121	61/61	
Burbige 678	33		C	33/33						
Wacksman 246	36	52	C		51/52	5/5	6/6	24/24	11/11	5/6
Ahmed 252	28	38	C		37/38			4/4	12/12	21/22
Ehrlich 267	135	229	C		226/229			74	102	53
Carpentier 272		100	C		97/100	12	55	25	8	0
Faure 274	136	272	C		270/272					
Pypno 124	43	80	C		80/80		6	53	10	
Kondo 135	32	64	C		57/57		12/12		45/45	
Scott 157	56	97	C	52/56						
Glassberg 184	60	101	C		101/101	1/1	10/10	23/23	32/32	35/35
Total	**815**	**1408**		**85/89**	**1288/1301**	**19/19**	**117/117**	**185/187**	**116/116**	**61/63**
Percent				**95.50%**	**99%**	**100%**	**100%**	**98.90%**	**100%**	**96.80%**
Politano-Leadbetter Procedure										
Lee 687	23		P-L for duplex	18/23						
Govan 418			P-L		14/17					
Elo 284	49		P-L	47/49			5/6	28	8/9	
Atwell 305	112	106	P-L		106/106	14/14	16/16	43/43	33/33	
Broaddus 359	40	73	P-L		73/73	6/6	28/28	15/15	13/13	2/2
Willscher 388+396	223	342	P-L		338/342					
Bettex 497	27	29	P-L		25/29					
Garrett 566	58	96	P-L		95/96					
Burbige 678	37		P-L	37/37						
Scott 377	163		Mod. P-L	157/163						
Harty 294	35	35	L-P		35/35	2/2	6/6	23/23		
Wachsman 348			P-L			10/10	62/67	50/54		
Hagberg 222	13	15	P-L		14/15					
Carpentier 272	200	100	P-L		88/100	8	46	31	10	5
Sutton 96	22	22	P-L		22/22		1/1	8/8	13/13	
Remzi 183	89	143	P-L		118/143					
Total	**1091**	**961**		**259/272**	**928/978**	**32/32**	**118/124**	**139/143**	**67/68**	**2/2**
Percent				**95.20%**	**94.90%**	**100%**	**95.20%**	**97.20%**	**98.50%**	**100%**
Lich-Gregoir Procedure										
Zaontz 129	79	120	D		111/120		57/58	42/47	12/15	
Breuhl 117	146	190	L-G		188/190		46	106	32	6
Hampel 383	51	83	L-G		78/83					
Wacksman 660		202	D		202/202	1/1	63/63	112/112	22/22	4/4
Allen 462	20	29	Mod. G-L	18/19						
Arap 304	300	520	L-G		514/520	29/29	307/307	184/184		

TABLE E-3. RESOLUTION OF REFLUX AFTER OPEN SURGERY (continued)

Author/ Papyrus #	Number of Patients	Number of Ureters	Surgical Procedure[1]	Surgical Success (Patients)	Surgical Success (Ureters)	Grade I/ Total	Grade II/ Total	Grade III/ Total	Grade IV/ Total	Grade V/ Total
Funke 310	142	176	L-G		168/176					
Houle 658	45	65	D		62/65	6/6	16/16	23/23	13/14	4/6
Hohenfellner	96		L-G	92/96						
Marberger 347	371	429	L-G		419/429					
McDuffie 372	51	78	L		73/76					
Beetz 42	189	242	L-G		238/242					
Linn 51	60	101	L-G	55/60						
Total	**1550**	**2235**		**165/175**	**2053/2013**	**36/36**	**443/4431**	**361/361**	**47/51**	**8/10**
Percent				**94.30%**	**97.60%**	**100%**	**100%**	**100%**	**92.20%**	**80%**
Gil-Vernet Procedure										
Solok 105	14	22	G-V		18/22		4/4	9/9	4/5	1/4
Carini 181	14		G-V	13/14			3/3	8/9	2/2	
De Gennaro 688	47	69	G-V		68/69		25/25	39/39	3/4	
Kliment 586	60	96	G-V	54/60						
Total	**162**	**187**		**67/74**	**86/91**		**29/29**	**48/48**	**7/9**	**1/4**
Percent				**90.50%**	**94.50%**		**100%**	**100%**	**77.70%**	**25%**
Paquin Procedure										
Wachsman 348			Paquin				8/8	7/7 misc.	10/19	
Parrott 403		253	Paquin		253/253					
Total		**253**			**253/253**					
Percent					**100%**					

TABLE E-4. STUDIES OF OBSTRUCTION AFTER OPEN SURGERY

Study	Rate (By ureter)	Estimate (95% Confidence Interval)
Orikasa, 1990	0/92	0.000 (0.000, 0.032)
Ehrlich, 1985	1/78	0.013 (0.000, 0.039)
Bellinger and Duckett, 1984	7/338	0.021 (0.007, 0.038)
Hagberg, Hjalmas, Jacobsson, et al., 1984	1/15	0.067 (0.000, 0.206)
Maggiolo, Lockhart, and Politano, 1983	0/28	0.000 (0.000, 0.105)
Carpentier, Bettick, Hop, et al., 1982	3/200	0.015 (0.001, 0.036)
Ahmed and Tan, 1982	11/304	0.036 (0.016, 0.060)
Arap, Abrao, and Menezes-de-Goes, 1981	5/520	0.010 (0.002, 0.020)
Broaddus, Zickerman, Morrisseau, et al., 1978	4/73	0.055 (0.009, 0.119)
Hampel, Richter-Levin, and Gersh, 1977	0/83	0.000 (0.000, 0.036)
Willscher, Bauer, Zammuto, et al., 1976	4/342	0.012 (0.002, 0.026)
Govan, Fair, Friedland, et al., 1975	8/105	0.076 (0.028, 0.135)
Jonas, Many, Boichis, et al., 1974	3/150	0.020 (0.002, 0.048)
Garrett and Switzer, 1966	4/96	0.042 (0.007, 0.090)
Duckett, Walker, and Weiss, 1992	0/154	0.000 (0.000, 0.019)
Wacksman, Gilbert, and Sheldon, 1992	0/211	0.000 (0.000, 0.014)
Burbige, 1991	1/180	0.006 (0.000, 0.021)
Bradic, Batinica, and Husar, 1988	10/824	0.012 (0.005, 0.021)
Sutton and Atwell, 1989	3/36	0.083 (0.007, 0.197)
Pypno, 1987	0/80	0.000 (0.000, 0.037)
Zaontz, Maizels, Sugar, et al., 1987	0/120	0.000 (0.000, 0.025)
Birmingham Reflux Study Group, 1987	0/107	0.000 (0.000, 0.028)
Kondo and Otani, 1987	2/100	0.020 (0.000, 0.056)
Ehrlich, 1982	0/229	0.000 (0.000, 0.013)
Faure, Ben-Salah, dEscoffier, et al., 1982	1/272	0.004 (0.000, 0.011)
Mundy, Kinder, Joyce, et al., 1981	0/17	0.000 (0.000, 0.171)
Hanna, 1981	1/22	0.045 (0.000, 0.139)
McDuffie, Litin, and Blundon, 1977	1/78	0.013 (0.000, 0.039)
Johnston and Farkas, 1975	3/33	0.091 (0.008, 0.214)
Ravasini and Pagano, 1973	0/37	0.000 (0.000, 0.080)
Allen, 1973	0/29	0.000 (0.000, 0.102)
Hjalmas, Lohr, Tamminen-Mobius, et al., 1992	8/237	0.034 (0.012, 0.060)
Houle, McLorie, Heritz, et al., 1992	0/65	0.000 (0.000, 0.046)

TABLE E-5. STUDIES OF REOPERATION FOR OBSTRUCTION

Study	Rate (By ureter)	Estimate (95% Confidence Interval)
Ehrlich, 1985	1/78	0.013 (0.000, 0.039)
Bellinger and Duckett, 1984	7/338	0.021 (0.007, 0.38)
Hagberg, Hjalmas, Jacobsson, et al., 1984	1/15	0.067 (0.000, 0.206)
Ahmed and Tan, 1982	1/304	0.003 (0.000, 0.010)
Broaddus, Zickerman, Morrisseau, et al., 1978	4/73	0.055 (0.009, 0.119)
Govan, Fair, Friedland, et al., 1975	6/105	0.057 (0.016, 0.110)
Jonas, Many, Boichis, et al., 1974	3/150	0.020 (0.002, 0.048)
Garrett and Switzer, 1966	4/96	0.042 (0.007, 0.090)
Burbige, 1991	1/180	0.006 (0.000, 0.021)
Bradic, Batinica, and Husar, 1988	10/824	0.012 (0.005, 0.021)
Sutton and Atwell, 1989	3/36	0.083 (0.007, 0.197)
Hanna, 1981	1/22	0.045 (0.000, 0.139)
Johnston and Farkas, 1975	3/33	0.091 (0.008, 0.214)
Hjalmas, Lohr, Tamminen-Mobius, et al., 1992	7/237	0.030 (0.009, 0.055)

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Notes

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This report on the Management of Primary Vesicoureteral Reflux was developed by the Pediatric Vesicoureteral Reflux Clinical Guidelines Panel of the American Urological Association, Inc.

This report is intended to furnish to the skilled practitioner a consensus of clear principles and strategies for quality patient care, based on current professional literature, clinical experience and expert opinion. It does not establish a fixed set of rules or define the legal standard of care, pre-empting physician judgment in individual cases.

An attempt has been made to recommend a range of generally acceptable modalities of treatment, taking into account variations in resources and in patient needs and preferences. It is recommended that the practitioner articulate and document the basis for any significant deviation from these parameters.

Finally, it is recognized that conformance with these guidelines cannot ensure a successful result. The parameters should not stifle innovation, but will, themselves, be updated and will change with both scientific knowledge and technological advances.

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