Reflux and Obstructive Nephropathy

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Reflux nephropathy, or renal parenchymal scarring associated with vesicoureteral reflux (VUR), is an important cause of renal failure. Some studies have shown that in up to 10% of adults and 30% of children requiring renal replacement therapy for end-stage renal disease, reflux nephropathy is the cause of the renal failure. Reflux nephropathy is thought to result from the combination of VUR of infected urine into the kidney by way of an incompetent ureterovesical junction valve mechanism and intrarenal reflux. Acute inflammatory responses to the infection result in renal parenchymal damage and subsequent renal scarring. Loss of functioning renal mass prompt compensatory changes in renal hemodynamics that, over time, are maladaptive and result in glomerular injury and sclerosis.

Clinically, reflux nephropathy may cause hypertension, proteinuria, and decreased renal function when the scarring is extensive. The identification of VUR raises the theoretic possibility of preventing reflux nephropathy. The inheritance pattern of VUR clearly is suggestive of a strong genetic influence. Familial studies of VUR are consistent with autosomal dominant transmission, and linkage to the major histocompatibility genes has been reported. Identification of infants with reflux detected on the basis of abnormalities seen on prenatal ultrasound examinations before urinary tract infection occurs may provide an opportunity for prevention of reflux nephropathy. In persons with VUR detected at the time of diagnosis of a urinary tract infection, avoidance of further infections may prevent renal injury. Nevertheless, the situation is far from clear. Most children with reflux nephropathy already have renal scars demonstrable at the time of the urinary tract infection that prompts the diagnosis of VUR. Most children found to have VUR do not develop further renal scarring after diagnosis, even after subsequent urinary tract infections. Other children may develop renal scars in the absence of further urinary tract infections. The best treatment of
Tubulointerstitial Disease

VUR has not yet been firmly established. No clear advantage has been demonstrated for surgical correction of VUR versus medical therapy with prophylactic antibiotics after 5 years of follow-up examinations. New surgical techniques such as the submucosal injection of bioinert substances may have a role in select cases.

The term obstructive nephropathy is used to describe the functional and pathologic changes in the kidney that result from obstruction to the flow of urine. Obstruction to the flow of urine usually is accompanied by hydronephrosis, an abnormal dilation of the renal pelvis, and calices. However, because hydronephrosis can occur without functional obstruction, the terms obstructive nephropathy and hydronephrosis are not synonymous. Hydronephrosis is found at autopsy in 2% to 4% of cases. Obstructive nephropathy is responsible for approximately 4% of end-stage renal failure. Obstruction to the flow of urine can occur anywhere in the urinary tract and has many different causes.

### Causes of Obstructive Nephropathy

**Intraluminal**
- Calculus, clot, renal papilla, fungus ball

**Intrinsic**
- Congenital:
  - Calyceal infundibular obstruction
  - Ureteropelvic junction obstruction
  - Ureteral stricture or valves
  - Posterior urethral valves
  - Anterior urethral valves
  - Urethral stricture
  - Meatal stenosis
  - Prune-belly syndrome
- Neoplastic:
  - Carcinoma of the renal pelvis, ureter, or bladder
  - Polyps

**Extrinsic**
- Congenital (aberrant vessels):
  - Congenital hydrocalycosis
  - Ureteropelvic junction obstruction
  - Retrocaval ureter
- Neoplastic tumors:
  - Benign tumors:
    - Benign prostatic hypertrophy
    - Pelvic lipomatosis
    - Cysts
  - Primary retroperitoneal tumors:
    - Mesodermal origin (e.g., sarcoma)
    - Neurogenic origin (e.g., neurofibroma)
    - Embryonic remnant (e.g., teratoma)
  - Retroperitoneal extension of pelvic or abdominal tumors:
    - Uterus, cervix
    - Bladder, prostate
    - Rectum, sigmoid colon
  - Metastatic tumor:
    - Lymphoma
    - Inflammatory:
      - Retroperitoneal fibrosis
      - Inflammatory bowel disease
      - Diverticulitis
      - Infection or abscess
    - Gynecologic:
      - Pregnancy
      - Uterine prolapse
      - Surgical disruption or ligation
- Functional
  - Neurogenic bladder
  - Drugs (anticholinergics, antidepressants, calcium channel blockers)

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**FIGURE 8-1**

Obstructive nephropathy is responsible for end-stage renal failure in approximately 4% of persons. Obstruction to the flow of urine can occur anywhere in the urinary tract. Obstruction can be caused by luminal bodies; mural defects; extrinsic compression by vascular, neoplastic, inflammatory, or other processes; or dysfunction of the autonomic nervous system or smooth muscle of the urinary tract. The functional and clinical consequences of urinary tract obstruction depend on the developmental stage of the kidney at the time the obstruction occurs, severity of the obstruction, and whether the obstruction affects one or both kidneys.
Anatomy of Vescoureteric Reflux

**FIGURE 8-2**
Anatomy of the ureterovesical junction. The ureterovesical junction permits free antegrade urine flow from the upper urinary tract into the bladder and prevents retrograde urinary reflux from the bladder into the ureter and kidney. Passive compression of the distal submucosal portion of the ureter against the detrusor muscle as a result of bladder filling impedes vescoureteral reflux (VUR). An active mechanism preventing reflux also has been proposed in which contraction of longitudinally arranged distal ureteral muscle fibers occludes the ureteral lumen, impeding retrograde urine flow [1–3]. (From Politano [4]; with permission.)

**FIGURE 8-3**
Tissue sagittal sections (upper panels) and cystoscopic appearances (lower panels) of the ureterovesical junction illustrating varying submucosal tunnel lengths. The length of the submucosal segment of the distal ureter is an important factor in determining the effectiveness of the ureteral valvular mechanism in preventing vescoureteral reflux (VUR). In children without VUR, the ratio of tunnel length to ureteral diameter is significantly greater than in children with VUR [5,6]. (From Kramer [7]; with permission.)

**FIGURE 8-4**
Simple and compound papillae are illustrated [8,9]. Two types of renal papillae have been identified. Simple papillae are the most common type. They have slitlike papillary duct openings on their convex surface. These papillae are compressed by increases in pelvic pressure, preventing urine from entering the papillary ducts (intrarenal reflux). Compound papillae are formed by the fusion of two or more simple papillae. In compound papillae, some ducts open onto a flat or concave surface at less oblique angles. Increased intrapelvic pressure may permit intrarenal reflux. Compound papillae usually are found in the renal poles.
Pathogenesis of Vesicoureteric Reflux and Reflux Nephropathy

FIGURE 8-5
Experimental vesicoureteric reflux in pigs. This pathology specimen demonstrates surgically induced vesicoureteric reflux in a 2-week-old male piglet. Note that the submucosal canal of one of the ureters has been unroofed.

FIGURE 8-6
Experimental vesicoureteric reflux in pigs: cystourethrogram showing intrarenal reflux. Reflux of radiocontrast medium into the renal parenchyma is seen. The pressure required to produce intrarenal reflux is lower in young children than it is in older children or adults, which is consistent with the observation that reflux scars occur more commonly in younger children [10].

FIGURE 8-7
Experimental vesicoureteric reflux in pigs. The polar location of acute suppurative pyelonephritis and evolution of parenchymal scars. In urinary tract infections, reflux of urine from the renal pelvis into the papillary ducts of compound papillae predominantly (Continued on next page)
FIGURE 8-7 (Continued)
located in the poles (intrarenal reflux) provides bacteria access to the renal parenchyma, resulting in suppurative pyelonephritis and subsequent polar scarring [11,12]. Intact (A, C, E) and coronally sectioned (B, D, F) kidneys illustrating the three stages of reflux nephropathy: Hemorrhagic with polymorphonuclear cell infiltrate (A, B); white, not retracted, with prominent mononuclear cell infiltrate (C, D), and retracted scan with prominent fibrosis (E, F).

FIGURE 8-8 (see Color Plate)
Experimental vesicoureteric reflux (VUR) in pigs: mesangiopathic lesions. Reflux of infected urine can result in glomerular lesions characterized by activation of mesangial cells, mesangial expansion, mesangial hypercellularity, and the presence of large granules. The granules test positive on periodic acid–Schiff reaction and are located inside cells with the appearance of macrophages. These glomerulopathic lesions occur by a process that does not require contiguity with the infected interstitium nor intrarenal reflux. These lesions are not related to reduction of renal mass. Similar glomerular lesions have been identified in piglets after intravenous administration of endotoxin. Whether similar glomerular lesions occur in infants or young children with VUR and reflux nephropathy is not known [13].

FIGURE 8-9 (see Color Plate)
Experimental vesicoureteric reflux (VUR) in pigs: 99mTc-Technetium-dimercaptosuccinic acid (DMSA) scan demonstrating reflux nephropathy. Radionuclide imaging using DMSA has been found to be safe and effective in investigating reflux nephropathy [14]. DMSA is localized to the proximal renal tubules of the renal cortex. Parenchymal scars appear as a defect in the kidney outline, with reduced uptake of DMSA or by contraction of the whole kidney. Currently, DMSA radionuclide renal scanning is the most sensitive modality used to detect renal scars relating to reflux. New areas of renal scarring can be seen earlier with DMSA than with intravenous pyelography [15].
Integrative view of pathogenetic mechanisms in reflux nephropathy. Abnormalities of ureteral embryogenesis may result in a defective antireflux mechanism, permitting vesicoureteral reflux (VUR), incomplete bladder emptying, urinary stasis, and infection. Bacterial virulence factors modify the pathogenicity of different bacterial strains. Bacterial surface appendages such as fimbriae may interact with epithelial cell receptors of the urinary tract, enhancing bacterial adhesion to urothelium. Endotoxin is capable of inhibiting ureteral peristalsis, contributing to the extension of the infection into the upper urinary tract even in the absence of VUR. Inoculation of the renal parenchyma with bacteria produces an acute inflammatory response, resulting in the release of inflammatory mediators into the surrounding tissue. The acute inflammatory response elicited by the presence of infecting bacteria is responsible for the subsequent renal parenchymal injury. In addition, it is possible that immune complexes, bacterial fragments, and endotoxin resulting from infection may produce a glomerulopathy.

Even in the absence of urinary tract infection, VUR associated with elevated intravesical pressure is capable of producing renal parenchymal scars. The developing kidney appears to be particularly susceptible. Renal tubular distention resulting from high intrapelvic pressure may exert an injurious effect on renal tubular epithelium. Compression of the surrounding periureteral capillary network by distended renal tubules may produce ischemia. During micturition, elevated intravesical pressure is transmitted to the renal pelvis and renal tubule. This transient pressure elevation may produce tubular disruption. Extravasation of urine into the surrounding parenchyma results in an immune-mediated interstitial nephritis and further renal injury.

The reduction in functional renal mass produced by the interaction of the pathogenetic factors listed here induces compensatory hemodynamic changes in renal blood flow and the glomerular filtration rate. Over time, these compensatory changes may be maladaptive, may produce hyperfiltration and glomerulosclerosis, and may eventually in renal insufficiency. (From Kramer [16]; with permission.)

Vesicoureteral reflux and renal dysplasia. An abnormal ureteral bud resulting from defective ureteral embryogenesis may penetrate the metanephric blastema at a site other than that required for optimum renal development, potentially resulting in renal dysplasia or hypoplasia [17].
Reflux and Obstructive Nephropathy

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Diagnosis of Vescoureteric Reflux and Reflux Nephropathy

**FIGURE 8-12**
International system of radiographic grading of vesicoureteral reflux (VUR). The severity of VUR is most frequently classified according to the International Grading System of Vescoureteral Reflux, using a standardized technique for performance of voiding cystourethrography. The definitions of this system are illustrated in Figure 8-4 and are as follows. In grade I, reflux only into the ureter occurs. In grade II, reflux into the ureter, pelvis, and calyces occurs. No dilation occurs, and the calyceal fornices are normal. In grade III, mild or moderate dilation, tortuosity, or both of the ureter are observed, with mild or moderate dilation of the renal pelvis. No or only slight blunting of the fornices is seen. In grade IV, moderate dilation, tortuosity, or both of the ureter occur, with moderate dilation of the renal pelvis and calyces. Complete obliteration of the sharp angle of the fornices is observed; however, the papillary impressions are maintained in most calyces. In grade V, gross dilation and tortuosity of the ureter occur; gross dilation of the renal pelvis and calyces is seen. The papillary impressions are no longer visible in most calyces [18].

**FIGURE 8-13**
Grading of renal scarring associated with vesicoureteral reflux. Reflux renal parenchymal scarring detected on intravenous pyelography can be classified according to the system adopted by the International Reflux Study Committee consisting of four grades of severity. In grade 1, mild scarring in no more than two locations is seen. More severe and generalized scarring is seen in grade 2 but with normal areas of renal parenchyma between scars. In grade 3, or so-called backpressure type, contraction of the whole kidney occurs and irregular thinning of the renal cortex is superimposed on widespread distortion of the calyceal anatomy, similar to changes seen in obstructive uropathy. Grade 4 is characterized by end-stage renal disease and a shrunken kidney having very little renal function [19]. Parenchymal scarring detected by radionuclide renal scintigraphy is classified similarly. A. In grade 1, no more than two scarred areas are detected. B. In grade 2, more than two affected areas are seen, with some areas of normal parenchyma between them. C. Grade 3 renal scarring is characterized by general damage to the entire kidney, similar to obstructive nephropathy. D. In grade 4, a contracted kidney in end-stage renal failure is seen, with less than 10% of total overall function [14].

**FIGURE 8-14**
Voiding cystourethrogram demonstrating bilateral grade 5 vesicoureteral reflux. Voiding cystourethography is performed by filling the bladder with radiocontrast material and observing for reflux under fluoroscopy, either during the phase of bladder filling or during micturition. Contrast material is infused through a small urethral catheter under gravity flow.
Radionuclide cystogram demonstrating bilateral vesicoureteral reflux (VUR). This method using $^{99m}$technetium pertechnetate is useful in detecting VUR. Advantages of radionuclide cystography include lower radiation exposure, less interference with overlying bowel contents and bones, and higher sensitivity in detection of VUR. Radionuclide cystography is useful in follow-up examinations of patients known to have VUR, as a screening test in asymptomatic siblings of children with reflux and girls with urinary tract infections, and in serial examinations of children with neuropathic bladders at risk for developing VUR. Disadvantages of this method include less anatomic detail and inadequacy in evaluating the male urethra, making it unsuitable for screening boys for urinary tract infections [7].

A, Intravenous pyelogram and, B, nephrotomogram demonstrating grade 2 reflux nephropathy. Historically, this testing modality has been the one most commonly used to evaluate reflux nephropathy [7]. Irregular renal contour, parenchymal thinning, small renal size, and calyceal blunting all are radiographic signs of reflux nephropathy on intravenous pyelography [17]. Radiographic changes may not be visible immediately after renal infection, because scars may not be fully developed for several years [20]. The advantages of intravenous pyelography in evaluating reflux nephropathy include precision in delineating renal anatomic detail and providing baseline measurements for future follow-up evaluations, renal growth, and scar formation.

A, Posterior and, B, anterior views of $^{99m}$technetium-dimercaptosuccinic acid (DMSA) renal scan showing bilateral grade 2 reflux nephropathy. This nephropathy is characterized by focal areas of decreased radionuclide uptake predominantly affecting the lower renal poles.
Prenatal detection of vesicoureteral reflux (VUR). A, Ultrasonography showing mild fetal hydronephrosis. B, Postnatal voiding cystourethrogram (VCUG) showing grade 4 VUR. C, Graph showing small renal size in the same infant. Vesicoureteral reflux has been identified in neonates in whom prenatal ultrasonography examination reveals hydronephrosis [21–28]. Normal infants do not have VUR, even when born prematurely [29,30]. The severity of reflux often is not predictable on the basis of appearance on ultrasonography [22,31]. Hydronephrosis greater than 4 mm and less than 10 mm in the anteroposterior dimension on ultrasound examination after 20 weeks’ gestational age has been termed mild fetal hydronephrosis. Mild fetal hydronephrosis is associated with VUR in a significant percentage of infants [26,31]. Despite the absence of a previous urinary tract infection, many kidneys affected prenatally exhibit decreased function [22,24,32,33]. Unlike the focal parenchymal scars seen in infection-associated reflux nephropathy, the parenchymal abnormalities seen in prenatal VUR are most commonly manifested by a generalized decrease in renal size (reflux nephropathy grade 3 or 4) [34,35].
Prenatal detection of vesicoureteral reflux (VUR): gender distribution versus VUR detected after urinary tract infection (UTI). VUR detected as part of the evaluation of prenatal hydronephrosis is most commonly identified in boys. In an analysis of six published studies of VUR diagnosed in a total of 124 infants with antenatally detected hydronephrosis, 83% of those affected were boys [33]. Conversely, VUR detected after a UTI most commonly affects girls. In the International Reflux Study in Children (IRSC) and Southwest Pediatric Nephrology Study Group (SWPNSG) investigations of VUR detected in a total of 380 children after UTI, 77% of those affected were girls [20,36].

### Clinical Course of Vesicoureteric Reflux

Resolution of vesicoureteral reflux (VUR) detected prenatally at follow-up examinations over 2 years. Spontaneous resolution of VUR can occur in infants with reflux detected during the postnatal evaluation of prenatal urinary tract abnormalities. In an analysis of six investigations of VUR detected neonatally with a follow-up period of 2 years, resolution was seen in 50% of infants with grades I and II. High-grade reflux (grades IV to V) resolved in only 20% [33].

Resolution of vesicoureteral reflux (VUR) detected postnatally after urinary tract infection: mild to moderate VUR. The Southwest Pediatric Nephrology Study Group (SWPNSG) prospectively observed 113 patients aged 4 months to 5 years with grades I to III VUR detected after urinary tract infection. The SWPNSG reported on 59 children followed up with serial excretory urograms and voiding cystourethography for 5 years. Mild (grade I and II) VUR resolved after 5 years in the ureters of 80% of these children, and in most cases within 2 to 3 years. Grade III VUR resolved in only 46% of ureters in children with VUR [20].

Resolution of vesicoureteral reflux (VUR) detected postnatally after urinary tract infection at follow-up examinations over 5 years. Mild VUR spontaneously resolves in a significant percentage of children, whereas high-grade reflux resolves only rarely. The Southwest Pediatric Nephrology Study Group (SWPNSG) found that grades I and II VUR resolved in 80% of children with refluxing ureters at follow-up examinations over 5 years. In the Birmingham Reflux Study Group (BRS), International Reflux Study in Children (IRSC), and SWPNSG investigations of high-grade VUR (grades III to V) in children, improvement in reflux severity was seen in 30% to 40% of affected ureters. Spontaneous resolution was rare and occurred in only 16% to 17% of children with refluxing ureters at follow-up examinations over 5 years [20,37,38].
Resolution of grades III to V vesicoureteral reflux (VUR) detected postnataally after urinary tract infection: bilateral versus unilateral VUR. Spontaneous resolution of high-grade VUR is much more likely to occur in unilateral reflux. The International Reflux Study in Children (IRSC) showed that grades III to V VUR resolved in children in whom both kidneys were affected nearly five times as often (39%) as in those in whom VUR was bilateral (8%). In bilateral VUR, spontaneous resolution did not occur after 2 years of observation [38].

Frequency of parenchymal scarring at the time of diagnosis of vesicoureteral reflux (VUR). Many children in whom VUR is detected after a urinary tract infection already have evidence of renal parenchymal scarring. In two large prospective studies the frequency of scars seen in persons with VUR increased with VUR severity. The International Reflux Study in Children (IRSC) studied 306 children under 11 years of age with grades III to V VUR [36]. The frequency of parenchymal scarring or thinning increased from 10% in children with nonrefluxing renal units (in children with contralateral VUR) to 60% in those with severely refluxing grade V kidneys. In another large prospective study, the Birmingham Reflux Study Group (BRSG) reported renal scarring in 54% of 161 children under 14 years of age with severe VUR resulting in ureteral dilation (greater than grade 3 using the classification system adopted by the International Reflux Study in Children group) at the time reflux was detected [39]. Participants in these studies were children previously diagnosed as having had urinary tract infection.

Development of parenchymal scarring after diagnosis of vesicoureteral reflux (VUR). Parenchymal scarring occurs after diagnosis and initiation of therapy as well. The Southwest Pediatric Nephrology Study Group (SWPNSG) followed up 59 children with mild to moderate VUR (grades I to III) diagnosed after urinary tract infection [20]. None of the children studied had parenchymal scarring on intravenous pyelography at the time of diagnosis. Parenchymal scars were seen to develop in 10% of children over the course of 5 years of follow-up examinations, including some children without documented urinary tract infections during the period of observation. In this group, renal scarring occurred nearly three times more commonly in grade 3 VUR than it did in grades 1 and 2 VUR. In the International Reflux Study in Children (IRSC) (European group), a prospective study of high-grade VUR (grades III and IV), new scars developed in 16% of 236 children after 5 years’ observation [40].

Development of new renal scars versus age at diagnosis of vesicoureteral reflux (VUR). The frequency of new scar formation appears to be inversely related to age. The International Reflux Study in Children (IRSC) examined children with high-grade VUR and found that new scars developed in 24% under 2 years of age, 10% from 2 to 4 years of age, and 5% over 4 years of age [40].
Treatment of Vesicoureteric Reflux

Correcting VUR in 97.5% of 231 reimplanted ureters in 151 children randomized to surgical therapy. Medical therapy consisted of long-term antibiotic uroprophylaxis using nitrofurantoin, trimethoprim, or trimethoprim-sulfa. No statistically significant advantage was demonstrable for either treatment modality with respect to new scar formation after 5 years of observation in either study. New scars were identified in 20 of the 116 children treated surgically (17%) and 19 of the 155 children treated medically (16%) at follow-up examinations over 5 years. Those children treated surgically who developed parenchymal scars generally did so within the first 2 years after ureteral repeat implantation, whereas scarring occurred throughout the observation period in the group that did not have surgery. VUR persisted in 80% of children randomized to medical treatment after follow-up examinations over 5 years.

The results of the IRSC paralleled the findings of the Birmingham Reflux Study Group (BRSG) investigation of medical versus surgical therapy for VUR in 161 children. After 2 years of observation, progressive or new scar formation was seen in 16% of children with refluxing ureters in the group treated surgically and 19% in the group treated medically. In contrast to the IRSC, however, new scar formation was rare after 2 years of observation in both groups [37,40].

**FIGURE 8-27**

Effectiveness of medical versus surgical treatment: new scar formation at follow-up examinations over 5 years in children with high-grade vesicoureteral reflux (VUR). The International Reflux Study in Children (IRSC) (European group) was designed to compare the effectiveness of medical versus surgical therapy of VUR in children diagnosed after urinary tract infection. Surgery was successful in correcting VUR in 97.5% of 231 reimplanted ureters in 151 children randomized to surgical therapy. Medical therapy consisted of long-term antibiotic uroprophylaxis using nitrofurantoin, trimethoprim, or trimethoprim-sulfa. No statistically significant advantage was demonstrable for either treatment modality with respect to new scar formation after 5 years of observation in either study. New scars were identified in 20 of the 116 children treated surgically (17%) and 19 of the 155 children treated medically (16%) at follow-up examinations over 5 years. Those children treated surgically who developed parenchymal scars generally did so within the first 2 years after ureteral repeat implantation, whereas scarring occurred throughout the observation period in the group that did not have surgery. VUR persisted in 80% of children randomized to medical treatment after follow-up examinations over 5 years.

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**FIGURE 8-28**

Effectiveness of medical versus surgical treatment: incidence of urinary tract infections. Vesicoureteral reflux (VUR) predisposes affected persons to urinary tract infection owing to incomplete bladder emptying and urinary stasis. Medical therapy with uroprophylactic antibiotics and surgical correction of VUR have as a goal the prevention of urinary tract infection. In three prospective studies of 400 children with VUR (Southwest Pediatric Nephrology Study Group [SWPNSG], International Reflux Study in Children [IRSC], Birmingham Reflux Study Group [BRSG]) treated either medically or surgically and who were observed over 5 years the rate of infection was similar, ranging from 21% to 39%. The rate of infection was no different between the group treated medically and that treated surgically [20,37,39].

**FIGURE 8-29**

Effectiveness of medical versus surgical treatment: incidence of urinary tract infection versus pyelonephritis in severe vesicoureteral reflux (VUR). Although the incidence of urinary tract infections (UTIs) is the same in surgically and medically treated children with VUR, the severity of infection is greater in those treated medically. The International Reflux Study in Children (IRSC) (European group) studied 306 children with VUR and observed them over 5 years; 155 were randomized to medical therapy, and 151 had surgical correction of their reflux. Although the incidence of UTI statistically was no different between the groups (38% in the medical group, 39% in the surgical group), children treated medically had an incidence of pyelonephritis twice as high (21%) as those treated surgically (10%) [41].
Reflux and Obstructive Nephropathy

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Complications of Reflux Nephropathy

FIGURE 8-30
Proposed treatment of vesicoureteral reflux (VUR) in children. This algorithm provides an approach to evaluate and treat VUR in children. In VUR associated with other genitourinary anomalies, therapy for reflux should be part of a comprehensive treatment plan directed toward correcting the underlying urologic malformation. Children with mild VUR should be treated with prophylactic antibiotics, attention to perineal hygiene and regular bowel habits, surveillance urine cultures, and annual voiding cystourethrogram (VCUG). Children with recurrent urinary tract infection on this regimen should be considered for surgical correction. In children in whom VUR resolves spontaneously, a high index of suspicion for urinary tract infection should be maintained, and urine cultures should be obtained at times of febrile illness without ready clinical explanation.

In persons in whom mild VUR fails to resolve after 2 to 3 years of observation, consideration should be given to voiding pattern. A careful voiding history and an evaluation of urinary flow rate may reveal abnormalities in bladder function that impede resolution of reflux. Correction of dysfunctional voiding patterns may result in resolution of VUR. In the absence of dysfunctional voiding, it is controversial whether older women with persistent VUR are best served by surgical correction or close observation with uroprophylactic antibiotic therapy and surveillance urine cultures, especially during pregnancy. Males with persistent low-grade VUR may be candidates for close observation with surveillance urine cultures while not receiving antibiotic therapy, especially if they are over 4 years of age and circumcised. Circumcision lowers the incidence of urinary tract infection. In severe VUR the function of the affected kidney should be evaluated with a functional study (radionuclide renal scan). High-grade VUR in nonfunctioning kidneys is unlikely to resolve spontaneously, and nephrectomy may be indicated to decrease the risk of urinary tract infection and avoid the need for uroprophylactic antibiotic therapy. In patients with functioning kidneys who have high-grade VUR, the likelihood for resolution should be considered. Severe VUR, especially if bilateral, is unlikely to resolve spontaneously. Proceeding directly to repeat implantation may be indicated in some cases. Medical therapy with uroprophylactic antibiotics and serial VCUG may also be used, reserving surgical therapy for those in whom resolution fails to occur.

FIGURE 8-31
Development of hypertension in 55 normotensive subjects with reflux nephropathy at follow-up examinations over 15 years. The incidence of hypertension in persons with reflux nephropathy increases with age and appears to develop most commonly in young adults within 10 to 15 years of diagnosis. In a cohort of 55 normotensive persons with reflux nephropathy observed for 15 years, 5% became hypertensive after 5 years. This percentage increased to 16% at 10 years, and 21% at 15 years. The grading system for severity of scarring was different from the system adopted by the International Reflux Study Committee. Nevertheless, using this system, 78% of persons in the group could be classified as having reflux nephropathy severity scores between 1 and 4 [42].
Frequency of hypertension versus severity of parenchymal scarring. The frequency of hypertension in persons with vesicoureteral reflux-related renal scars is higher than in the normal population. In adults with reflux nephropathy the incidence of hypertension can be correlated with the severity of renal scarring. Adding the individual grade of reflux (0–4) for the two kidneys results in a scale ranging from 0 (no scars) to 8 (severe bilateral scarring). Persons with cumulative scores of parenchymal scarring from 1 to 4 have a 30% incidence of hypertension, whereas 60% of those with scarring scores ranging from 5 to 8 have hypertension [42,43].

Glomerular hypertrophy and focal segmental glomerulosclerosis (FSGS) in severe reflux nephropathy. Reflux nephropathy resulting in reduced renal functional mass induces compensatory changes in glomerular and vascular hemodynamics. These changes initially maintain the glomerular filtration rate but are mal-adaptive over time. A–D. Compensatory hyperfiltration results in renal injury manifested histologically by glomerular hypertrophy and FSGS and clinically as persistent proteinuria [44]. In reflux nephropathy, proteinuria is a poor prognostic sign, indicating that renal injury has occurred. The severity of proteinuria is inversely proportional to functioning renal mass and the glomerular filtration rate and directly proportional to the degree of global glomerulosclerosis. Surgical correction of vesicoureteral reflux has not been found to prevent further deterioration of renal function after proteinuria has developed. Hyperfiltration resulting from decreased renal mass continues and produces progressive glomerulosclerosis and loss of renal function. Evidence exists that inhibition of the renin-angiotensin system through the use of angiotensin-converting enzyme inhibitors decreases the compensatory hemodynamic changes that produce hyperfiltration injury. Thus, these inhibitors may be effective in slowing the progress of renal failure in reflux nephropathy.
Reflux and Obstructive Nephropathy

Pathogenesis of Obstructive Nephropathy

Consequences of urinary tract obstruction for the developing kidney in animals. The effects of urinary tract obstruction on the developing kidney depend on the time of onset, location, and degree of obstruction. Ureteral obstruction during early pregnancy results in disorganization of the renal parenchyma (dysplasia) and a reduction in the number of nephrons. Partial or complete ureteral obstruction in neonates causes vasoconstriction, glomerular hypoperfusion, impaired ipsilateral renal growth, and interstitial fibrosis. The degree of impairment of the ipsilateral kidney, in the case of partial unilateral ureteral obstruction, and of compensatory hypertrophy of the contralateral kidney, in the case of partial or complete unilateral ureteral obstruction, is inversely related to the age of the animal at the time of obstruction. The older the animal, the less the impairment of the ipsilateral kidney and the less the compensatory growth of the contralateral kidney. In addition, the recovery of renal function after relief of urinary tract obstruction also decreases with the age of the animal [45].

Renal hemodynamic response to mild partial ureteral obstruction. Renal blood flow and the glomerular filtration rate may not change in mild partial ureteral obstruction, despite a significant reduction in glomerular capillary ultrafiltration coefficient (Kf). This is due to the increase in glomerular capillary hydraulic pressure (Pgc) caused by a prostaglandin E2−induced reduction of afferent arteriolar resistance (Ra) and an angiotensin II−induced elevation of efferent arteriolar resistance (Re). It is likely that other vasoactive factors, such as thromboxane A2, also play a role, particularly in more severe ureteral obstruction accompanied by reductions in renal blood flow and glomerular filtration rate [46]. PGE2—prostaglandin E2; PGI2—prostaglandin I2; Pt—tubule hydrostatic pressure.

A acute renal hemodynamic response to unilateral or bilateral complete ureteral obstruction. In the first 2 hours after unilateral complete ureteral obstruction, there is a reduction in preglomerular vascular resistance and an increase in renal blood flow mediated by increased production of prostaglandin E2 (PGE2), prostacyclin, and nitric oxide (NO). The increase in renal blood flow (RBF) and glomerular capillary pressure maintain the glomerular filtration rate (GFR) at approximately 80% of normal, despite an increase in intratubular pressure. As the ureteral obstruction persists, activation of the renin-angiotensin system and increased production of thromboxane A2 (TXA2) and endothelin result in progressive vasoconstriction, with reductions in renal blood flow and glomerular capillary pressure. The glomerular filtration rate decreases to approximately 20% of baseline, despite normalization of the intratubular pressures. The hemodynamic changes in the early phase (0–2 h) of bilateral ureteral obstruction are similar to those observed after unilateral obstruction. As bilateral obstruction persists, however, there is an accumulation of atrial natriuretic peptide (ANP) that does not occur after unilateral obstruction. The increased ANP levels attenuate the afferent and enhance the efferent vasoconstrictions, with maintenance of normal glomerular capillary and elevated tubular pressures. Despite these differences in hemodynamic changes between unilateral and bilateral ureteral obstruction, the reductions in renal blood flow and glomerular filtration rate 24 hours after obstruction are similar [47–49]. Pgc—glomerular capillary hydraulic pressure; PG12—prostaglandin I2; Pt—tubule hydrostatic pressure; Ra—afferent arteriolar resistance; Re—efferent arteriolar resistance.
**FIGURE 8-37**
Chronic renal hemodynamic response to complete unilateral ureteral obstruction. During complete ureteral obstruction, renal blood flow progressively decreases. Renal blood flow is 40% to 50% of normal after 24 hours, 30% at 6 days, 20% at 2 weeks, and 12% at 8 weeks [48].

**FIGURE 8-38**
Development of interstitial cellular infiltrates in the renal cortex and medulla after ureteral obstruction. After ureteral obstruction there is a rapid influx of macrophages and suppressor T lymphocytes in the cortex and medulla (A) that is accompanied by an increase in urinary thromboxane B2 and a decrease in the glomerular filtration rate. The production of thromboxane A2 by the infiltrating macrophages (B) contributes to the renal vasoconstriction of chronic urinary tract obstruction. After release of the obstruction the cellular infiltration is slowly reversible, requiring several days to revert to near normal levels (C) [50,51].
FIGURE 8-39
Pathogenesis of tubulointerstitial fibrosis in obstructive nephropathy. This pathogenesis has been extensively studied. Increased expression of renin, angiotensinogen, angiotensin-converting enzyme (ACE), and the angiotensin II type 1 (AT1) receptor occurs in the obstructed kidney. Angiotensin II can induce the synthesis of transforming growth factor β (TGF-β), a cytokine that stimulates extracellular matrix synthesis and inhibits its degradation. Obstructive nephropathy is accompanied by downregulation of the kallikrein-kinin system and nitric oxide production that can be reversed by administration of a converting enzyme inhibitor or of L-arginine. The rapid upregulation of chemotactic factors such as monocyte chemoattractant peptide 1 (MCP-1) and osteopontin in the tubular epithelial cells, in response to increased intratubular pressure, contributes to the recruitment of macrophages. Macrophages produce fibroblast growth factor and induce fibroblast proliferation and myofibroblast transformation. The downregulation of epidermal growth factor (EGF), Bcl2, and antioxidant enzymes and the increased production of superoxide and hydrogen peroxide (H₂O₂) contribute to an increased rate of apoptosis and tubular dropout [51–57].

PDGF—platelet-derived growth factor; SOD—superoxide dismutase; TIMP—tissue inhibitor of metalloproteinases.

FIGURE 8-40
Recovery of renal function after relief of complete unilateral ureteral obstruction of variable duration. The recovery of the ipsilateral glomerular filtration rate after relief of a unilateral complete ureteral obstruction has been best studied in dogs and depends on the duration of the obstruction. Complete recovery occurs after 1 week of obstruction. The degree of recovery after 2 and 4 weeks of obstruction is only of 58% and 36%, respectively. No recovery occurs after 6 weeks of obstruction [58]. Rare reports of recovery of renal function in patients with longer periods of unilateral ureteral obstruction may represent high-grade partial obstruction rather than complete obstruction or may reflect differences in lymphatic drainage and renal anatomy between the human and canine kidneys [59].
Clinical Manifestations of Obstructive Nephropathy

Clinical correlates of abnormalities of tubular function in obstructive nephropathy. A acute ureteral obstruction stimulates tubular reabsorption, resulting in increased urine osmolality and reduced urine sodium concentration [60]. In contrast, obstructive nephropathy is characterized by a reduced ability to concentrate the urine, reabsorb sodium, and secrete hydrogen ions (H+) and potassium. In unilateral obstructive nephropathy, these functional abnormalities do not have a clinical correlate because of the reduced glomerular filtration rate and immaterial contribution of the obstructed kidney to total renal function. Hyperkalemic metabolic acidosis and, when the intake of free water is not adequate, hypernatremia can occur in patients with partial bilateral ureteral obstruction or partial ureteral obstruction in a solitary kidney. Similarly, postobstructive diuresis can occur only after relief of bilateral ureteral obstruction or ureteral obstruction in a solitary kidney but not after relief of unilateral obstruction [61–67]. ADH—antidiuretic hormone; ANP—atrial natriuretic peptide; ECFV—extracellular fluid volume; Na-K ATPase—sodium-potassium adenosine triphosphatase.
Diagnosis of Obstructive Nephropathy

**FIGURE 8-43**
Diagnosis of obstructive nephropathy. **A**, Diuresis renography. **B**, Doppler ultrasonography. **C, D**, Magnetic resonance urogram utilizing a single shot fast spin echo technique with anterior-posterior projection (**C**) and left posterior oblique projection (**D**). Images demonstrate a widely patent right ureteropelvic junction in a patient with abdominal pain and suspected ureteropelvic junction obstruction. Administration of gadolinium is not required for this technique. Note also the urine in the bladder, cerebrospinal fluid in the spinal canal, and fluid in the small bowel.

Ultrasonography is the procedure of choice to determine the presence or absence of a dilated renal pelvis or calices and to assess the degree of associated parenchymal atrophy.

Nevertheless, obstruction rarely can occur without hydronephrosis, when the ureter and renal pelvis are encased in a fibrotic process and unable to expand. In contrast, mild dilation of the collecting system of no functional significance is not unusual. Even obvious hydronephrosis in some cases may not be associated with functional obstruction [70]. Diuresis renography is helpful when the functional significance of the dilation of the collecting system is in question [71,72]. Renal Doppler ultrasonography before and after administration of normal saline and furosemide also has been used to differentiate obstructive from nonobstructive pyelocaliectasis [73]. Other techniques such as excretory urography, computed tomography, and retrograde or antegrade ureteropyelography are helpful to determine the cause of the urinary tract obstruction. The utility of excretory urography is limited in patients with advanced renal insufficiency. In these cases magnetic resonance urography can provide coronal imaging of the renal collecting systems and ureters similar to that of conventional urography without the use of iodinated contrast. RI—resistive index. (C, D, Courtesy of B. F. King, M.D.)

**FIGURE 8-44**
Diagnosis of obstructive nephropathy by postnatal renal ultrasound, showing hydronephrosis in ureteropelvic junction obstruction. Renal ultrasonography is a sensitive test to detect hydronephrosis. The absence of ureteral dilation is consistent with obstruction at the level of the ureteropelvic junction.
FIGURE 8-45
Mercaptoacetyltriglycine-3 renal scan with furosemide in a newborn with left ureteropelvic junction obstruction. A diuretic renal scan using 99mTc-mercaptoacetyltriglycine (99mTc-MAG-3) showing differential renal function (47% right kidney; 53% left kidney) at 1 to 2 minutes after radionuclide administration is seen. A significant amount of radionuclide remains in each kidney 15 minutes after administration. After administration of furosemide, however, the isotope is seen to disappear rapidly from the right kidney (t1/2 of radioisotope washout in 4.9 minutes) but persists in the hydronephrotic left kidney (t1/2 in 50.1 minutes). A t1/2 of the radioisotope in less than 10 minutes is thought to reflect a lack of significant obstruction. A t1/2 of over 20 minutes is suggestive of obstruction. Intermediate values of washout are indeterminate. The most appropriate therapy for infants with delayed renal pelvic radioisotope washout and diagnosis of ureteropelvic junction obstruction is controversial. Some authors advocate pyeloplasty to alleviate the obstruction based on renal scan results, whereas others advocate withholding surgery unless renal function deteriorates or hydronephrosis progresses.
Posterior Urethral Valves

**FIGURE 8-46**
Posterior urethral valves. **A**, Illustrative diagram. **B**, Pathology specimen. Valvular obstruction at the posterior urethra is the most common cause of lower urinary tract obstruction in boys. Anatomically, the lesion most commonly is comprised of an oblique diaphragm with a slitlike perforation arising from the posterior urethra distal to the verumontanum and inserting at the midline anterior urethra. (From Kaplan and Scherz [74]; with permission.)

**FIGURE 8-47**
Excretory urogram of a patient with posterior urethral valves. Bladder outlet obstruction results in bladder wall thickening, trabeculation, and formation of diverticula. Increased intravesical pressure may result in vesicoureteral reflux, as is seen on the left. Obstruction resulting in increased intrarenal pressure may result in rupture at the level of a renal fornix, producing a urinoma, or perirenal collection of urine, as seen on the right.

**FIGURE 8-48**
Voiding cystourethrogram (VCUG) demonstrating posterior urethral valves and dilation of the posterior urethra. Urethral valves are best detected by VCUG. The obstructing valves are seen as oblique or perpendicular folds with proximal urethral dilation and elongation. Distal to the valves the urinary stream is diminished. Alleviating the bladder outlet obstruction is indicated, either by lysis of the valves themselves or by way of vesicostomy, in small infants until sufficient growth occurs to make valve resection technically feasible.
Ureterovesical Junction Obstruction

**FIGURE 8-49**
Excretory urogram showing ureterovesical junction obstruction in a 2-year-old girl.

Retroperitoneal Fibrosis

**FIGURE 8-50**
A–H, Idiopathic retroperitoneal fibrosis: computed tomography scans of the abdomen before (left panels, note right ureteral stent and mild left ureteropyelocaliectasis) and 7 years after ureterolysis (right panels, note omental interposition). Retroperitoneal fibrosis is characterized by the accumulation of inflammatory and fibrotic tissue around the aorta, between the renal hila and the pelvic brim. Most cases are idiopathic; the remainder are associated with immune-mediated connective tissue diseases, ingestion of drugs such as methysergide, abdominal aortic aneurysms, or malignancy. Idiopathic retroperitoneal fibrosis can be associated with mediastinal fibrosis, sclerosing cholangitis, Riedel’s thyroiditis, and fibrous pseudotumor of the orbit. In the clinical setting, patients with idiopathic retroperitoneal fibrosis exhibit systemic symptoms such as malaise, anorexia and weight loss, and abdominal or flank pain. Renal insufficiency is often seen and is caused by bilateral ureteral obstruction. Laboratory test results usually demonstrate anemia and an elevated sedimentation rate. The treatment is directed to the release of the ureteral obstruction, which initially can be achieved by placement of ureteral stents. Administration of corticosteroids is helpful to control the systemic manifestations of the disease and

(Continued on next page)
often to reduce the bulk of the tumor and relieve the ureteral obstruction. Administration of corticosteroids, however, should be considered only when malignancy and retroperitoneal infection can be ruled out. As in other chronic renal diseases, administration of corticosteroids should be kept at the minimal level capable of controlling symptoms. Surgical ureterolysis, which consists of freeing the ureters from the fibrotic mass, lateralizing them, and wrapping them in omentum to prevent repeat obstruction, is often necessary. Other immunosuppressive agents have been used rarely when the systemic manifestations of the disease cannot be controlled with safe doses of corticosteroids. In most cases the long-term outcome of idiopathic retroperitoneal fibrosis is satisfactory [75–77].


