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Renal Late Effects in Patients Treated for Cancer in Childhood: A Report from the Children's Oncology Group

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Abstract

Background—Improvements in childhood cancer therapy have led to increasing numbers of long-term survivors. These survivors are at risk for a variety of late effects due to the disease itself, treatment exposures (surgery, chemotherapy, and radiotherapy), underlying medical problems, and health behaviors. The *COG LTFU Guidelines* are risk-based, exposure-related recommendations for the identification and management of late effects due to therapies utilized in the treatment of childhood cancer, and are designed for asymptomatic survivors presenting for routine medical follow-up two or more years after completion of cancer therapy.

Procedure—The COG Guidelines Task Force on Urinary Tract Complications conducted an extensive review of the medical literature via MEDLINE. Specific treatment exposures which were reviewed include nephrectomy, chemotherapy regimens known to be nephrotoxic (cisplatin, carboplatin, ifosfamide, and methotrexate) and renal irradiation. Literature sources were ranked according to the strength of evidence and are cited in the review.

Conclusions—This review summarizes the literature that supported the recommendations for cancer survivors at risk for nephrotoxicity previously outlined in the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (COG LTFU Guidelines)*.

Keywords

Wilms' tumor; ifosfamide; cisplatin; methotrexate; radiotherapy; nephrectomy; chronic kidney disease; proteinuria; hypertension

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Introduction

Improvements in childhood cancer therapy have led to increasing numbers of long-term survivors. These survivors are at risk for a variety of late effects due to the disease itself, treatment exposures (surgery, chemotherapy, and radiotherapy), underlying medical problems, and health behaviors. The *COG LTFU Guidelines* are risk-based, exposure-related recommendations for the identification and management of late effects due to therapies utilized in the treatment of childhood cancer, and are designed for asymptomatic survivors presenting for routine medical follow-up two or more years after completion of cancer therapy. More extensive evaluation is warranted for survivors with symptoms suggesting illness or organ dysfunction. Patient education materials called “Health Links” accompany the guidelines; both the guidelines and Health Links can be downloaded from http://www.survivorshipguidelines.org.

Among the late effects of childhood cancer therapy are renal impairment and associated hypertension. Herein, we provide a brief discussion of normal kidney function followed by the evidence supporting the nephrotoxic potential of therapeutic interventions undertaken in the management of childhood cancers and health screening recommended for asymptomatic survivors treated with nephrotoxic therapy by the *COG LTFU Guidelines*.

Methods

To ensure that the *COG LTFU Guidelines* reflect the most current evidence available in the medical literature, multidisciplinary task forces comprised of experts in pediatric and adult subspecialties have been involved in the development and periodic revision of the guidelines. During this process, the COG Guidelines Task Force on Urinary Tract Complications conducted systematic review of the medical literature via MEDLINE (National Library of Medicine, Bethesda, MD) encompassing the years 1970 to 2004. The task force members were: Sheri Spunt, M.D., Chair, Pediatric Hematology/Oncology, Joan Darling, patient advocate, Fernando Ferrer, Pediatric Urology, Dan Green, M.D., Pediatric Hematology/Oncology, Deborah Jones, M.D., Pediatric Nephrology, Anne Mauck, R.N., M.S.N., C.P.N.P., Nursing, Arnold Paulino, M.D., Radiation Oncology, Michael Ritchey, M.D., Pediatric Urology, and Patricia Shearer, M.D., Pediatric Hematology/Oncology. A total of 32 key articles related to kidney late effects following treatment of childhood cancer were retrieved, and formed the basis for the kidney-related *COG LTFU Guidelines*. In 2006, a second literature review was conducted in an identical manner and the *COG LTFU Guidelines* were updated to reflect the new information identified in 10 additional key articles.

A multidisciplinary panel of late effects experts scored the *COG LTFU Guidelines* according to a modified version of the National Comprehensive Cancer Network “Categories of Consensus” system [1]. High-level evidence (category 1) was defined as evidence derived from high quality case control or cohort studies. Lower-level evidence (category 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series, and clinical experience. A category of 2A indicated uniform consensus by the panel, and category 2B indicated non-uniform consensus regarding the appropriate screening recommendation.

BACKGROUND

The term “renal function” is typically used to refer to glomerular filtration rate (GFR). With approximately one million nephrons per kidney, there is inherent “renal reserve” so that a significant number of nephrons may be injured or lost before a clinically detectable change

in renal function occurs. In evaluating the potential effects of therapy on GFR, one must consider that the incidence of decreased GFR after exposure to any nephrotoxic agent is affected by the method used to measure GFR [2]. GFR is typically measured by clearance techniques that estimate GFR by measuring the clearance of a substrate which is excreted primarily by glomerular filtration [2].

Glomerular filtration is only one component of renal function [2]. After presentation of plasma filtrate to Bowman's space via the process of glomerular filtration, the filtrate is processed by a highly specialized renal tubular epithelium, which ultimately controls solute and fluid excretion. Nonspecific proximal tubular injury from ischemia or toxins such as ifosfamide often results in the wasting of more than one substrate [3]. For example, in the Fanconi syndrome, which is the clinical syndrome of proximal tubular wasting, urinary excretion of phosphate, bicarbonate, Na, K, glucose and amino acids are inappropriately increased. In addition, polyuria and hypouricemia may complicate proximal tubular dysfunction [3].

The primary role of the kidney in the control of blood pressure is related to 1) regulation of salt and water excretion in response to changes in extracellular fluid volumeand 2) generation of humoral agents which directly increase peripheral vascular resistance [4]. Hypertension may be encountered in cancer survivors as a sequela of renal irradiation, in children with solitary kidneys or renal insufficiency due to nephrotoxic chemotherapy or surgical renovascular insult [5].

Glomerular/Tubular Dysfunction and Hypertension Following Childhood Cancer Treatment

Cancer treatments associated with renal damage and/or high blood pressure later in life include chemotherapeutic drugs (cisplatin, carboplatin, ifosfamide, methotrexate), renal radiotherapy, and nephrectomy. Chemotherapy-induced nephrotoxicity can manifest as acute irreversible renal failure, slowly progressive chronic renal failure or as specific defects in renal tubule cell function [6]. Clinical manifestations of kidney damage include hypertension, proteinuria and varying degrees of renal insufficiency [7]. Table I summarizes recommendations for monitoring children exposed to these potentially nephrotoxic insults; the category given by the committee as to the strength of evidence and consensus of the committee is also found in the table.

Ifosfamide

Ifosfamide can have serious adverse effects on the kidney despite concurrent use of the uroprotectant mesna. The most common manifestation of ifosfamide-induced nephrotoxicity is proximal tubular dysfunction, and less often, decreased GFR [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18]. During therapy, acute renal tubular dysfunction often resolves prior to the next course; however, permanent and potentially progressive kidney damage may also occur [16].

A reduction in GFR (defined by serum creatinine levels at or above 3 times normal) occurred in 25% of patients treated with high dose ifosfamide ($14g/m^2$) [17]. Following administration of more conventional doses, progressive renal insufficiency occurred in 17 - 50% of ifosfamide-treated youngsters [19]. A statistically significant fall in mean GFR of 35 $ml/min/1.73m^2$ was observed after completion of therapy [19]. Although the median GFR at 1 year was no different than that at 10 years follow-up, there are marked differences in the course of individual children [16].

Approximately 30% of ifosfamide-treated children develop a persistent tubulopathy and 5% have clinically significant Fanconi syndrome [8]. This syndrome is caused by a generalized dysfunction of renal proximal tubule cells and is defined by excessive urinary excretion of

glucose, amino acids, phosphate, bicarbonate and other solutes handled by this nephron segment. In many cases, tubular dysfunction is asymptomatic. However, growth failure and rickets are sequelae of this disorder if untreated. Although some children with ifosfamide-induced Fanconi syndrome recover sufficient renal tubular function, approximately one-third continue to have clinically significant renal tubular damage [16]. “Severe” hypertension has been reported rarely (5%) [19]. Both tubular and glomerular function may deteriorate further even after completion of therapy.

A number of risk factors for chronic ifosfamide nephrotoxicity have been proposed. These include cumulative dose (> 60-100 g/m^2) [11] [10] [14] [18,19], age < 3-5 years [14,18], concurrent or previous platinum therapy [14,20], renal irradiation [11] and unilateral nephrectomy [11] or hydronephrosis [9]. GFR was below normal in 42% (n=24) of children with osteosarcoma who were studied a median of 9 months after completion of therapy that included both ifosfamide and cisplatin [21]. Subclinical magnesium wasting was present in 25%. More severe renal toxicity occurred in children who had a reduction in renal mass at the time of chemotherapy [22]. The most important predictive risk factor for toxicity appears to be the cumulative dose of ifosfamide.

Cisplatin and Carboplatin

Kidney damage is the major dose-limiting side effect of cisplatin; treatment protocols may reduce or omit this medication when pretreatment glomerular filtration rate (GFR) is less than 60 mL/min/1.73m^2. Most children receiving cisplatin have some acute loss of renal function, with considerable individual variation in severity. Womer et al [23] found a mean 8% decrease in GFR rate per 100 mg/m^2 dose received. The magnitude of GFR decline directly correlates with peak serum or urine platinum concentrations and cisplatin infusion rates [24].

The outlook for long-term recovery or stability of renal function is generally favorable, although data are somewhat limited. Mean GFR significantly increased from immediately post-treatment compared to one year later (92 ± 8 vs. 104 ± 10 ml/min/1.73m^2) [25]. Of children with reduced GFR at the end of treatment, 92% showed at least some improvement with 46% attaining normal GFR when reassessed at 2½ years [26]. Furthermore, 80% of those with normal end-of-treatment GFR maintained their normal GFR over the course of follow-up.

A magnesium-wasting tubulopathy occurs in virtually every patient treated with cisplatin. It can be severe enough to require magnesium supplementation and cause hypocalcemia and/or hypokalemia. This adverse effect tends to be long lasting. Of children with cisplatin-induced hypomagnesemia, approximately one-third to two-thirds remained hypomagnesemic [26,27]. Use of cisplatin concurrently with other nephrotoxic agents, particularly ifosfamide, increases the risk of renal injury [28].

Carboplatin is a cisplatin analogue with a spectrum of activity similar to cisplatin. It is less nephrotoxic than cisplatin, with myelosuppression being its major dose-limiting side effect; unlike cisplatin, it is not transformed into toxic metabolites by renal tubule cells – hence its decreased nephrotoxicity [29]. Clinically important reductions in GFR and hypomagnesemia are rare following carboplatin. Paradoxically, it is possible that the risk of renal insufficiency and tubulopathies is higher with carboplatin/ifosfamide than with cisplatin/ifosfamide combination therapy [20,30].

Methotrexate

High-dose MTX (HDMTX), in which doses in the range of 1000-33,000 mg/m^2 are used in combination with leucovorin, is associated with acute renal dysfunction in 0-12.4% of

patients, for an overall incidence rate of 1.8% [31]. MTX-induced renal dysfunction results in delayed elimination of the drug and its metabolites. The mechanism for MTX nephrotoxicity is postulated to be precipitation of the drug and metabolites within the renal tubular lumen. Most studies assess acute changes in renal function associated with MTX by measurement of plasma creatinine with various definitions of renal dysfunction. However, a single center study of children who were given HDMTX for ALL noted a significant decline in GFR as measured by inulin clearance over the three days after administration of HDMTX [32]. Mean GFR returned to baseline by 7 days post-treatment. Only 2 of the 58 patients had clinical evidence of renal dysfunction with a doubling of their baseline serum creatinine levels. MTX related nephrotoxicity appears to be entirely reversible, with a median time to recovery of renal function of 16 days (range 4-48 days) [31]. Furthermore, subsequent doses of HDMTX have been successfully given to patients who previously experienced renal dysfunction without recurrence of acute renal failure.

There is a paucity of information regarding the long-term renal sequelae associated with MTX.

Radiation Therapy

Irradiation of the kidney can occur when the primary tumor is located in or near the kidney. In susceptible patients, radiation nephritis or radiation nephropathy arises after a latent period of 3-12 months and is manifest by varying degrees of hypertension, proteinuria, renal insufficiency and anemia [33]. Doses less than 18 Gy to the whole kidney appear to rarely cause severe or long-lasting renal injury while doses greater than 20 Gy result in significant nephropathy [34]. Cohen and Robbins [33] have provided a recent summary of the pathogenesis of this disorder and its treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

Most radiation nephropathy late effects studies have been done in children with Wilms tumor. In general, studies have shown that the risk for renal insufficiency is higher among children receiving higher doses of radiation. [35] [36] [37] In a cohort of children evaluated 5 years after receiving abdominal radiation for Wilms tumor, 7% had hypertension [15].

Nephrectomy

Survivors of childhood cancer who have undergone nephrectomy are at risk for various complications including renal insufficiency, hyperfiltration injury, hypertension, and hydrocele. Compensatory hypertrophy of the remaining kidney is a well-documented finding after nephrectomy [38]. Although this adaptation may initially increase glomerular filtration capacity, glomerulosclerosis [39] [40] and interstitial injury [41] may ultimately lead to deterioration of renal function. For childhood cancer survivors, other nephrotoxic insults such as chemotherapy (e.g., cisplatin, carboplatin, ifosfamide), other drugs (e.g., aminoglycoside antibiotics, amphotericin, cyclosporine) and abdominal radiotherapy may also contribute to impaired renal function.

Renal function studies in Wilms tumor survivors may be divided into those in which renal function is assessed either months or years after nephrectomy. In the few small studies focusing on renal function in survivors of Wilms' tumor, clinically relevant reductions in glomerular filtration rate after nephrectomy have been seen in only a minority [39,42,43]. However, the method used to assess GFR may affect the prevalence rates of renal insufficiency. One study reported no statistically significant differences in mean GFR between children who underwent nephrectomy for Wilms tumor or neuroblastoma (median follow-up after nephrectomy, 12 months and 9 months, respectively) and children of comparable age who underwent nephrectomy for non-malignant disease (median follow-up

after nephrectomy, 23 months) [44]. However, 50% of the childhood cancer survivors who underwent nephrectomy had chronic renal insufficiency (defined as GFR < 90 mL/min/1.73 m^2). A comparison between children with Wilms tumor who did or did not receive irradiation, demonstrated lower GFR in the irradiated group (73% of normal) than in the non irradiated group (95% of normal) [45]. In this study, prevalence of chronic renal insufficiency was 34%.

GFR and renal compensatory growth were assessed a minimum of 5 years after nephrectomy in 22 children with Wilms tumor who had received abdominal radiation and 15 children who underwent nephrectomy for congenital hydronephrosis [46]. The estimated size of the remnant kidney was increased by 25–29% in the Wilms tumor group compared to 42% in the hydronephrosis group. Mean GFR was significantly lower in the Wilms tumor group than that of the hydronephrosis group (82% and 92% of healthy controls, respectively) and chronic renal insufficiency was present in 73% of the Wilms tumor group. Long-term follow-up of children (mean 12.9 ± 3 years after therapy) with Wilms tumor found a low GFR (less than 80 mL/min/1.73 m^2 as measured by ^{51}Cr EDTA clearance) in 19% [47]. Children whose GFR measurements were decreased were more likely to have received higher doses of radiation, and demonstrated poorer renal growth as measured by renal ultrasound [47].

The frequency of microalbuminuria, which is indicative of glomerular hyperfiltration, following nephrectomy is less clear. This complication has been reported to be present in 5% to 84% of cases [43,48]. Diastolic hypertension may also be a late effect of treatment that includes nephrectomy. In an analysis of 1,171 children treated for Wilms tumor whose blood pressure was measured 5 years after diagnosis, 83 (7%) had a diastolic blood pressure above the 95th percentile for age [49]. However, a substantial proportion of patients with diastolic hypertension had also received abdominal radiotherapy; therefore, the relative contribution of nephrectomy to this complication is unclear. Hydrocele has recently been recognized to be a sequela of nephrectomy. Sixteen percent (9 of 57) of male survivors of Wilms tumor were found to have hydroceles, all on the same side as the nephrectomy. Only 2 of these patients had received abdominal radiotherapy. [49]

It should be noted that many childhood survivors of Wilms tumor who develop chronic renal failure have syndromes accompanying *WT1* mutations or deletions that predispose to renal disease. Breslow et al [50] recently assessed the risk of end-stage renal disease (ESRD) in Wilms tumor survivors and found that, although the overall incidence was 1% for unilateral tumor and 12% for bilateral tumors, patients with Denys-Drash syndrome, Wilms tumor aniridia syndrome or associated genitourinary anomalies had ESRD risks as high as 90%.

Evaluation of Childhood Cancer Survivors Treated with Nephrotoxic Therapy

Assessment of childhood cancer survivors for late renal sequelae is aimed at detection of hypertension, or other evidence of chronic renal injury. Measurement of blood pressure as part of the routine physical examination allows detection of abnormal blood pressure. Currently, the definition of hypertension is: BP level at or above the 95th percentile on at least three occasions. If the BP level meets the definition of hypertension, evaluation and treatment is indicated.

Finding significant proteinuria on urinalysis prompts concern about renal damage from prior therapy or the acquisition of new renal disease. Proteinuria is first detected by urinary dipstick, which primarily detects albumin. False positive urine protein may be caused by alkaline urine, antiseptic cleanser, radiocontrast agents, or a highly concentrated sample. Children with very dilute urine may have significant proteinuria, which may not be detected by dipstick alone. Finding of protein in the urine should prompt the clinician to consider

other signs or symptoms of urinary tract disease, such as hypertension, voiding dysfunction, polyuria or systemic symptoms. If the patient is otherwise asymptomatic, then the urinalysis may be repeated in several weeks to confirm that the proteinuria is persistent. In normal individuals small amounts of protein are present in the urine but not usually detected by dipstick. Persistent proteinuria of ≥2+ protein on dipstick warrants referral to a nephrologist. However, significant proteinuria may be present in the setting of a dilute urine with less than 2+ protein by dipstick.

Abnormal glomerular filtration rate is most often detected by elevated serum creatinine concentrations. Even mild elevations should be noted since as much as 50% of renal parenchymal loss must occur before detectable changes in the creatinine occur. Since early renal insufficiency is often asymptomatic, measurement of creatinine may be the only way to detect its presence. Patients with renal insufficiency should be referred for nephrology consultation. Patients at risk for renal sequelae should be counseled to avoid lifestyles that put them at risk for renal injury such as tobacco use, excessive NSAID use, excessive alcohol consumption, and dehydration. In addition, avoidance of obesity and treatment of hyperlipidemia will also offer some renal protective effects.

The *COG LTFU Guidelines* related to kidney dysfunction are outlined in Table I. The guidelines specify the particular renal complications that may result from childhood cancer therapy, along with the particular risk factors that have been linked to each condition. Baseline screening recommendations for asymptomatic survivors of potentially nephrotoxic therapy include blood pressure measurement, serum electrolytes including Ca, Mg, and P, BUN/creatinine, and urinalysis. After the baseline evaluation, annual follow-up includes blood pressure measurement and urinalysis. Male patients who have undergone nephrectomy should also have an annual testicular exam to evaluate for hydroceles. Progressive renal insufficiency, proteinuria, or hypertension should prompt referral to a nephrologist. Urology referral may be appropriate for large or growing hydroceles. Patients with a single kidney should be counseled about risks to the remaining kidney. The most common causes of renal injury in children are motor vehicle accidents and sports injuries (bicycling, skiing, American football, baseball, basketball, ice hockey, and wrestling) [51] [52] [53] [54]. However, severe injury necessitating nephrectomy is rare. Thus, decisions about participation in contact or collision sports may be individualized [51] [55]. Use of a kidney protector can be considered for individuals who choose to participate in activities that carry a risk of renal damage.

Conclusions

Many individuals treated for childhood cancer are at risk for renal late effects, and these late effects may require ongoing medical management. Function and quality of life may be impaired. Exposure-based risk assessment is key for identification of long-term renal complications. Timely and appropriate treatment, often coordinated with a nephrologist, may diminish symptoms and/or prevent further damage, and may improve function and quality of life. Counseling the survivor regarding timely reporting of worrisome symptoms, prevention of further kidney damage and compliance with medical recommendations is an important component of good long-term care. The *COG LTFU Guidelines* delineate exposure-based risks related to potentially nephrotoxic modalities used in the treatment of childhood, adolescent and young adult cancers accompanied by health screening recommendations. This resource, which can be accessed at the website www.survivorshipguidelines.org, is available free of charge to all clinicians managing the care of childhood cancer survivors.

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Table I

Nephrotoxic Therapy Potential Late Effects and Screening Recommendations Reviewed in the *Children's Oncology Group Long Term Follow-Up Guidelines*[*]

Therapeutic Exposure	Potential Late Effect	Risk Factors	Highest Risk Factors	Health Counseling/Further Considerations
Ifosfamide	**Renal toxicity** Glomerular toxicity (decreased GFR) Tubular toxicity (renal tubular acidosis, hypophosphatemia, hypokalemia, hypomagnesemia, Fanconi syndrome, rickets)	**Host factors** Younger age at treatment Single kidney **Treatment factors** Higher cumulative dose Combined with other nephrotoxins: -Cisplatin -Carboplatin -minoglycosides -Amphotericin -Immunosuppressants -Methotrexate -Radiation impacting the kidney **Medical conditions**: Tumor infiltration of the kidney Pre-existing renal impairment Nephrectomy	**Host factors** Age < 5 years at time of treatment **Treatment factors** Ifosfamide dose ≥60 mg/m^2 Renal radiation dose ≥15 Gy	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria or progressive renal insufficiency Category = 1
Carboplatin **Cisplatin**	**Renal toxicity** Glomerular injury Tubular injury Renal insufficiency	**Host factors** Single kidney **Treatment factors** Combined with other nephrotoxins: -Ifosfamide -Aminoglycosides -Amphotericin -Immunosuppressants -Methotrexate -Radiation impacting the kidney **Medical conditions**: Diabetes mellitus Hypertension Nephrectomy	**Treatment factors** Cisplatin dose ≥ 200 mg/m^2 Renal radiation dose ≥ 15 Gy	In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis. Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria or renal insufficiency. Category = 1
Methotrexate	**Renal toxicity** Acute toxicities predominate	Host factors **Single kidney** Treatment factors **Combined with other nephrotoxins:**	Treatment factors **Treatment before 1970**	**Nephrology consultation for patients with hypertension, proteinuria, or renal insufficiency**. Category = 2A

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Therapeutic Exposure	Potential Late Effect	Risk Factors	Highest Risk Factors	Health Counseling/Further Considerations
		-Cisplatin/carboplatin **-Ifosfamide** **-Aminoglycosides** **-Amphotericin** **-Immunosuppressants** **-Radiation impacting the kidney**		
Radiation -whole abdomen -All upper abdominal fields -TBI	**Renal toxicity** Renal insufficiency Hypertension	**Host factors** Bilateral Wilms tumor Single kidney **Treatment factors** Radiomimetic chemotherapy Radiation dose ≥10 Gy TBI combined with radiation to the kidney Combined with other nephrotoxins: -Cisplatin -Carboplatin -Ifosfamide -Aminoglycosides -Amphotericin -Immunosuppressants **Medical conditions:** Diabetes mellitus Hypertension Nephrectomy	**Treatment factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction TBI ≥ 12 Gy fractionated	Nephrology consultation for patients with hypertension, proteinuria or renal insufficiency. Category = 1
Nephrectomy	**Renal toxicity** Renal insufficiency Hypertension Proteinuria **Hydrocele** (males only)	Treatment factors **Combined with other nephrotoxins:** **-Cisplatin** **-Carboplatin** **-Ifosfamide** **-Aminoglycosides** **-Amphotericin** **-Immunosuppressants** **-Methotrexate** **-Radiation impacting the kidney**		**Discuss contact sports, bicycle safety (e.g. avoiding handlebar injuries) and proper use of seatbelts (i.e. wearing lap belts around hips). Counsel to use NSAIDS with caution.** **Nephrology consultation for patients with hypertension, proteinuria or renal insufficiency.** Category = 1

[*] Guideline score refers to the degree of consensus: High-level evidence (category 1) was defined as evidence derived from high quality case control or cohort studies. Lower-level evidence (category 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series, and clinical experience. A category of 2A indicates that is uniform consensus by the panel, and category 2B indicates that there is non-uniform consensus regarding the appropriate screening recommendation.

Recommended screening for all nephrotoxic exposures includes: 1) Annual BP measurement, 2) Baseline measurement of BUN, creatinine, Na, K, Cl, CO_2, Ca, Mg, PO_4. If abnormal, repeat as clinically indicated, and 3) Annual urinalysis. Additional screening post-nephrectomy includes screening for development of hydroceles.