Drug-Induced Renal Disease – Prevention Strategies

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ABSTRACT

The easy availability ('over-the-counter') and, at times, inappropriate usage of drugs coupled with burgeoning therapeutic interventions has contributed to the increasing numbers of hapless victims of drug nephrotoxicity. The kidney is an organ susceptible to the injurious effects of the drugs because of its functional properties. Possession of knowledge of the harmful effects of drugs should arm the physician with strategies to prevent the development of renal disease. Recognition of potentially dangerous settings and the adoption of strategies to either prevent or minimize the injury should be the need of the hour. Understanding the mechanisms of nephrotoxicity enables the planning of preventive strategies.

This chapter would serve to identify the risks associated with situations, the mechanisms involved in injury causation and the potential for interventions to prevent or mitigate the injury in the scenario of drug usage. The risks existent in certain patients, at times, may have necessitated the avoidance of the use of that particular drug or have dictated adoption of a particular approach to modify the risk factor. The general principles addressing drug-induced nephrotoxicity include vigilance, identifying patients at risk, adoption of precautions, management of renal failure if it develops and withholding the drug/s if in doubt about the potential risk.

INTRODUCTION

The addition of newer drugs, besides contributing to better therapeutic potential, has added another dimension to the causation of renal disease. The abuse or indiscriminate use of drugs, coupled with easy availability, has taken its toll on the kidneys. The list of drugs incriminated in this process increases day by day. One, however, may wonder why the kidney falls prey to the drug's onslaught. The reason lies in the functional properties of the kidney which makes it susceptible to injury.[1]

The kidney is an organ characterized by a large volume of blood supply (20-25% of the cardiac output) which ensures a high level of toxicant delivery over a period of time. The extensive reabsorptive capacity of the tubule with specialized transporters promotes cellular uptake of the toxicant. Concentrating capability of the tubule produces high concentrations in the medullary lumen and interstitium. High metabolic rates and workload increases the sensitivity to toxicants. Metabolic alteration (biotransformation enzymes) may produce highly toxic metabolites or reactive intermediates.[1]

The nephrotoxic chemicals damage specific portions of the tubule with the brunt being borne by the proximal tubule. Segment specific targets exist for nephrotoxicants. The reasons for segmental specific nephrotoxicity of agents may be attributable to the differences in toxicant delivery, differences in transport and uptake among segments and differences in biotransformation among segments.[1] The end result of the nephrotoxicant effect on the epithelial cells is cell injury and death. Cell death could also be the consequence of ischemia related to a decreased renal blood flow. Intraluminal tubular obstruction (increases the intraluminal pressure and decreases single nephron glomerular filtration rate), "backleak" of tubular infiltrate (due to loss of epithelial cells) and inhibition of cellular repair and regeneration are processes, other than cell death, that could cause drug related acute renal dysfunction.[1]

Drug-related causation was implicated in 18.3% of acute renal failure cases reported in a one year survey.[2] In India, too, a study reported a 20% incidence of drug-induced acute renal failure with a large proportion (40%) being secondary to aminoglycoside usage.[3] Acute renal failure by its manner of presentation is easily recognized. It is well known that drug related renal disorder may have a wide spectrum of presentations, some of which may go unnoticed. Even the development of acute renal failure may have a variety of mechanisms ranging from decreased renal perfusion, vascular or direct tubular injury, allergic interstitial inflammation and glomerular basement membrane injury.[4] The drug toxicity may not be limited to acute presentations only. Chronic renal failure may be the consequence of a chronic interstitial injury and papillary necrosis. Subtle effects on electrolyte, water and

Table 1: Drug-induced toxic renal syndromes

Syndrome	Medication Examples
Acute Renal Failure	
• Prerenal (decreased perfusion)	Diuretics, NSAIDs, ACE Inhibitor
• Intrinsic Renal (direct tubule cell toxicity)	Aminoglycosides, Radiocontrast media, cisplatin
Acute tubular necrosis	
• Hemolysis	Quinine, sulfonamides, hydralazine
• rhabdomyolysis	Lovastatin, ethanol, barbiturate
Acute Interstitial Nephritis	
(immune-mediated)	Penicillin, rifampicin, sulfonamides
TTP-HUS	
(vascular endothelial injury)	Cyclosporin, tacrolimus, quinine
• Obstructive	
Intratubular	Acyclovir, methotrexate, sulfonamides, methysergide, methyldopa,
Ureteral (retroperitoneal fibrosis)	gold, pencillamine, captopril, NSAIDs, mercury
Nephrotic Syndrome (immune-mediated)	
Renal Tubular Dysfunction	
Chronic Renal Failure (interstitial fibrosis)	NSAIDs, acetaminophen, cyclosporine

Table 2: Risk factors for nephrotoxicity

Patient-related factors
- Age, sex, race
- Pre-existent renal disease
- Specific disease (diabetes mellitus, multiple myelome, proteinuric patients, lupus)
- Sodium-retaining states (cirrhosis, heart failure, nephrosis)
- Dehydration and volume depletion
- Acidosis, potassium and magnesium depletion
- Hyperuricemia, hyperuricosuria
- Sepsis, shock
- Renal transplantation

Drug-related factors
- Inherent nephrotoxic potential
- Dose
- Duration, frequency and form of administration
- Repeated exposure

Drug interactions
- Combined or closely associated use of diagnostic or therapeutic with added or synergistic nephrotoxic potential (eg. Radiocontrast agents, aminoglycosides, NSAIDs, cisplatin, ACEI)

acid-base balance, complete the picture. Table 1 shows the drug-induced toxic renal syndromes.

The majority of drugs in common usage have low nephrotoxic potential. Specific certain patients and clinical situations seem to be susceptible to nephrotoxicity. [5] The recognition of the factors that predispose to nephrotoxicity of drugs would enable attempts at limiting or preventing the same. Table 2 has listed risk factors for drug nephrotoxicity.

The occurrence or even the prevention of drug-related renal disease should be approached with emphasis on the above-mentioned risk factors. The risk factors take into consideration factors that range from the patient to the drug-related factors and visualizes the potential of drug interactions in the causation or potentiation of nephrotoxicity.

To the "internist's nephrotoxic quartet" [NSAIDs, ACEIs, radiocontrast media, aminogycosides], labeled thus by Garella[6] probably because of their common occurrence in lists of drugs causing nephrotoxicity, newer drugs, especially finding usage in specific situations, are being continually added to this list. This article addresses the preventive strategies employed in drug-induced renal disease and will not dwell on the pathogenetic mechanisms involved in individual drug toxicity.

The chapter cannot include all the nephrotoxic agents but will deal with the commonly used and commonly encountered nephrotoxic drugs, starting with the "quartet".

NON - STEROIDAL ANTI - INFLAMMATORY DRUGS

The number of patients at risk or affected by the nephrotoxic properties of NSAIDs has increased commensurate with the widespread usage of this class of drugs. The nephrotoxicity associated with these drugs has been now accorded the required importance. The mechanisms of nephrotoxicity relate to the capacity to induce vasomotor changes and a reduction in renal function. Additionally, nephrotic syndrome associated with interstitial nephritis, chronic renal injury and water-electrolyte abnormalities (sodium, potassium and water) are encountered. The common thread through all these syndromes seems to be a disruption of prostaglandin metabolism.[7]

As mentioned above, the occurrence of the nephrotoxic syndromes are related to the presence of risk factors in the subset of patients. The patient with a decreased effective arterial blood volume (congestive heart failure, cirrhosis, nephrotic syndrome, sepsis, haemorrhage, diuretic therapy, 'third-spacing", volume depletion/hypotension) as well as those with a normal or increased effective arterial volume (chronic renal failure, glomerulonephritis, elderly, contrast-induced nephropathy and cyclosporin) are at risk of developing vasomotor renal failure.[7] The association of a nephrotic state with interstitial nephritis characterizes the toxicity of NSAIDs.[5] Analgesic nephropathy has been found to be a consequence of chronic NSAID intake.[7] The use of paracetamol, instead of a NSAID, to prevent analgesic

Table 3: Preventing NSAID nephrotoxicity

- Recognize the potential (situational factors) for causation of nephrotoxicity and take corrective action to minimize nephrotoxic potential
- Avoid chronic (habitual) use of NSAIDs
- Avoid combinations of analgesics
- Monitoring use of drugs when consumption is mandatory
- Low dose aspirin safe (as used for prevention of cardiovascular events)
- All available analgesics have a nephrotoxic potential (except paracetamol?) and should be carefully considered before usage.

Table 4: Modifiable and non-modifiable risk factors for aminoglycoside nephrotoxicity

Non-modifiable

- Age, gender, obesity
- Pre-existing liver or chronic renal disease
- Renal hypoperfusion
- Sepsis

Modifiable

- Choice of aminoglycoside (inherent nephrotoxic potential)
- Drug dose – per day, drug interval, duration of therapy
- Volume depletion (most important clinically)
- Hypokalemia and hypomagnesemia
- Metabolic acidosis
- Concurrent drug administration (synergism) – other nephrotoxic agents such as amphotericin B, cephalothin, vancomycin, cisplatin, furosemide, calcium channel blockers, radiocontrast agents, cyclosporin (interactive nephrotoxicity)

nephropathy has recently come under examination, with a report of an increased risk of chronic renal disease even with paracetamol.[8]

Combination of drugs may potentiate the nephrotoxic properties and enhance the risk of toxicity. The NKF consensus panel indicated that aspirin and NSAIDs combinations could produce an increased risk of renal failure and hence are not encouraged. Habitual ingestion of analgesics is also not recommended. If essential, then monitoring of the therapy for renal side effects should be performed. Controlled availability of combinations, labeled should be provided with an explicit warning of the risks of habitual consumption.[9] Table 3 indicates the preventive measures that can be adopted to prevent NSAID nephrotoxicity.

The promise of a reduced nephrotoxic potential of COX-2 inhibitors when compared to other NSAIDs, has not been fulfilled.[10]

ANTIBIOTIC RELATED RENAL FAILURE

Antibiotic associated renal failure is predominantly noted with the use of aminoglycoside antibiotics though it may also occur with beta-lactam, vancomycin, sulfonamides and antifungal antibiotics.[11] Therefore, this class of drugs warrants more attention and will hence be the focus of preventive strategies. Table 4 lists the modifiable and non-modifiable risk factors for aminoglycoside nephrotoxicity.

Besides the listed factors, a few others may also predispose to nephrotoxicity viz., repeated courses of aminoglycosides a few months apart, malnutrition and high trough concentrations.[5]

Table 5: Approach to prevention of Aminoglycoside Nephrotoxicity

- Choice of aminoglycoside
- Dosing as per level of GFR, monitoring of serum levels
- Monitor renal function (creatinine levels every 2-3 days or more frequently depending on renal function
- Single daily dosing (less nephrotoxic with no loss efficacy; 'post-antibiotic effect' & concentration dependent killing. [14-17] Dose to be administered during the early afternoon
- Modifying 'correctable' factors (mentioned in Table 4)
- Avoiding interactive / synergistic nephrotoxic combinations

The nephrotoxic potential of various aminoglycosides differ, with gentamicin being the most toxic, followed by tobramycin, amikacin, netilmicin and streptomycin.[11] Since nephrotoxicity could be associated with aminoglycosides, monitoring of serum drug levels may be warranted in an attempt to prevent nephrotoxicity.

The first step in the prevention of aminoglycoside nephrotoxicity would be the selection of this class of drugs for well-defined situations, choosing the appropriate drug and dose in an effort to achieve therapeutic effect but not at the cost of toxicity.[11] In an attempt to choose the correct dose or drug interval, monitoring of drug levels would seem a rational approach.[12,13] Even though the logical consequence of such an action would be avoidance of toxicity, this may not always be possible. Yet, monitoring of the same still seems to be warranted so that therapeutic concentrations are achieved and toxic concentrations avoided. A certain proportion of patients would still develop nephrotoxicity and the physician should be forewarned that this may still be forthcoming.[14] Renal function tests should be monitored, initially every 2-3 days (every day especially in patients who have raised creatinine at the start). With rising creatinine, aminoglycoside therapy may need to be replaced by appropriate but non-nephrotoxic antibiotics.[11] Table 5 lists the measures that could be adopted to prevent aminoglycoside nephrotoxicity.[14-17]

The other antibiotic that needs to be dealt with is the antifungal antibiotic, amphotericin B, that has earned for itself the epithet 'Ampho-terrible" in view of its potential to produce adverse effects. The adverse effects are related to the daily dose, duration of therapy, pre-existent renal disease (15.4 fold increase in toxicity), renal hypoperfusion, sodium depletion and concomitant drug exposure (diuretics (12.5 fold increase), aminoglycosides, cisplatin, radiocontrast agents and cyclosporin). Daily dose is an important factor with increased nephrotoxicity associated with increasing daily dose (risk increase 1.8 fold with 0.1 mg/kg increase in dose). The solubilising agent, deoxycholate contributes to the tubule toxicity of amphotericin.[11] This belief has provoked investigations into use of alternate vehicles as formulations to reduce toxicity, such as liposomal preparations or other lipid formulations. Sodium loading is another way to limit nephrotoxicity.[14] Dopamine agonists, too, have been tried in an attempt to prevent nephrotoxicity.[18]

Other antibiotics such as beta lactams, vancomycin, sulfonamides exert their innate nephrotoxic potentials especially when in combination with other nephrotoxic agents.

Table 6: Prevention of radiocontrast media nephrotoxicity

- Recognition of the high risk populations
- Limitation of the use of contrast agents – avoid multiple procedures within 24 hours or subsequent days [or substitution with non-contrast requiring imaging methods]
- Minimum contrast media dose (<2ml/kg or max. of 150 ml)
- Use of non-ionic radiocontrast media (vs ionic) especially in patients with cardiovascular morbidity or at a greater clinical risk of nephrotoxicity.
- Hydration with 0.45% saline given @ 1ml/kg /hr fro 12 hours before and after procedure
- Sodium bicarbonate infusion
- No conclusive support for mannitol, frusemide, calcium channel blockers, dopamine or atrial natriuretic peptide.
- Use of N-acetyl cysteine 1200mg/day (before and on the day of procedure) *
- No role for dialysis after the procedure; Hemofiltration unproven role
- Monitor renal function for 48-96 hours after procedure

*Contradictory reports now available.

RADIOCONTRAST MEDIA-INDUCED ACUTE RENAL FAILURE

Radiocontrast media induced injury constitutes the third leading cause of hospital-acquired acute renal failure.[5] Nephrotoxicity is rare in patients with normal renal function (<1%) and, hence, it is not unexpected that the most important clinical risk factor for nephrotoxicity is a pre-existing, often unrecognized, renal insufficiency. In addition to pre-existent renal disease, age, male gender, dehydration/volume depletion, congestive heart failure, proteinuria, abnormal liver function, hyperuricemia, diabetes mellitus with renal insufficiency, multiple myeloma (precipitation of light chains in an intratubular location due to dehydration and intratubular calcium), cardiovascular disease, hypertension, renal transplantation, large doses of radiocontrast or repeated studies, type of contrast media (ionic or non-ionic), injection site-intra-arterial vs intravenous, and concomitant exposure to other nephrotoxic agents are risk factors for nephrotoxicity.[5,19]

Table 6 lists the measures that can be employed to prevent or mitigate radiocontrast media nephrotoxicity. Whereas the role of saline loading has been proven,[20] the role of the anti-oxidant N-acetyl cysteine which had shown promise,[21] has again been challenged in the light of recent published data.[22,23] Fenoldopam, too, has been tried with no strong recommendations for use as of date.[22] Sodium bicarbonate, too, has been shown to have a beneficial effect in radiocontrast media induced injury though it has been postulated that the effect may be related to the volume expansion associated with the accompanying saline infusion.[24]

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Used for renal protection, the ACE inhibitors (and the ARBs albeit to a lesser degree) may produce renal failure. The occurrence of functional acute renal failure correlates with a loss of post-glomerular efferent arteriolar vascular tone and is usually reversible with drug withdrawal.

Table 7: Some other nephrotoxic agents and prevention strategies

Drug	Prevention strategies
• Sulfonamides[11]	Maintain adequate hydration (~3 l/day) Alkalinisation of urine (6-12 g soda bicarb) Detect hematuria / perform sonography
• Indinavir[14]	Hydrate Establish high urine flow
• Cisplatin[26]	Achieve solute diuresis (12-24 hr before) Hydrate with normal saline Cisplatin infusion in normal saline (divide daily dose over 5 days Post infusion normal saline or mannitol for 24 hours Possibly give thiosulphate Use less nephrotoxic drugs platinum compounds e.g.carboplatin
• Lithium[27]	Monitor levels and renal function Amiloride might prevent nephrogenic diabetes insipidus Avoid concurrent neuroleptic therapy
• Cyclosporin[11,28]	Follow drug levels Avoid nephrotoxic drugs or drug interactions which raise levels

Prevention of ACEI and ARB nephrotoxicity is dependent on anticipation of its occurrence depending on the existence of risk factors. Recognition of risk factors, vigilant monitoring and volume management are important to this. "Diuretic holiday" may be prescribed, especially in the first few days after ACEI therapy initiation. [14] Another option is the initiation of therapy with a short-acting ACEI like captopril, titrating the dose upward in response to blood pressure and renal function.[5] With renal function stable, switch to a long-acting ACE inhibitor.[5,14] The initial days after ACEI (or ARB) therapy is initiated, there is a need to monitor renal function, weekly for the first four weeks, later monthly and three monthly thereafter. If the creatinine rise is <30%, then the therapy could be a beneficial trade-off for a better long term outcome.[14] In addition to an elevation in creatinine, significant elevations may be noted in patients on ACEI or ARB, necessitating termination of therapy. [5]

In the present scenario, a sizeable proportion of the patients having chronic tubulointerstitial nephritis and reaching ESRD could well be related to the consumption of drugs.[25] The present chapter has concentrated on the infamous nephrotoxic "quartet" from amongst the seemingly unending list of nephrotoxic drugs. In Table 7, a few other selected drugs (not an exhaustive list) and the approach to preventive strategies is outlined.

If one were to formulate general guidelines for preventing drug-induced nephrotoxicity, the following could be enunciated.

- Acceptance that drug-induced renal injury can occur especially in patients at risk.
- Be vigilant and aware of the nephrotoxic potential of specific drugs
- At-risk patients (elderly and those with renal insufficiency, dehydration, salt-retaining states, diabetes, multiple myeloma) identified

- Assess benefits of radiologic procedures and prescribed drugs in relation to potential risk
- Choose diagnostic procedures or therapeutic measure without nephrotoxic potential
- Avoid dehydration
- Limit total daily dosage and duration of treatment with certain drugs
- Monitor renal functions in all patients on nephrotoxic agents (early detection)
- Modify daily dosage according to GFR
- Avoid a combination of potentially nephrotoxic drugs
- When in doubt about the cause of renal failure, hold all potentially offending drugs.

In the patient with pre-existent renal insufficiency, adoption of a step-wise approach would be helpful in avoiding nephrotoxicity. After recording the history and performing a physical examination, determine the degree of renal insufficiency through laboratory tests. Medication review should be followed by choice of a less nephrotoxic agent. Loading doses permit early achievement of therapeutic levels and subsequent maintenance doses (either reduction of dose or the interval extension method). Measurement of levels definitely help. Constant reassessment for efficacy and need as well as toxicity is essential.[29]

REFERENCES

1. Cummings BS, Schnellmann RG. Pathophysiology of Nephrotoxic Cell Injury. Ed. Schrier RW. Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1071-1091
2. Kleinknecht D, Landais P, Goldfarb B. Drug associated acute renal failure: A collaborative study of 81 biopsied patients. *Adv Exp Med Biol* 1987;212:125-8
3. Jha V, Chugh KS. Drug induced renal disease. *J Assoc Physicians India* 1995;43:407-21
4. Choudhury D, Ahmed Z. Drug-induced nephrotoxicity. *Med Clin North Am* 1997;81(3):705-17.
5. Thatte L, Vaamonde CA. Drug-induced Nephrotoxicity. The crucial role of risk factors. *Postgrad Med* 1996;100(6):83-4, 87-8,91.
6. Garella S. Drug-induced renal disease. Hosp Practice (Off ED) 1993;28 (4):129-40.
7. Palmer BF, Henrich WL. Nephrotoxicity of Non-steroidal Anti-inflammatory Agents, Analgesics, and Angiotensin-Converting Enzyme Inhibitors. Ed. Schrier RW. Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1189-1209.
8. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs. *N Engl J Med* 1994;331:1675-9.
9. Henrich W, Agodoa L, Barrett B, et al Analgesics and the kidney : summary and recommendations to the scientific advisory board of the NKF from an ad hoc committee of the NKF. *Am J Kidney Dis* 1996;62-5
10. Singh NP, Ganguli A, Prakash A. Drug-induced Kidney Diseases. *JAPI* 2003;51 Oct : 970-9.
11. Kaloyanides GJ, Bosmans J-L, De Broe ME. Antibiotic- and Immunosuppression-Related Renal Failure. Ed. Schrier RW . Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1137-1175.
12. Bartal C, Danon A, Schlaeffer F, Reisenberg K, Alkan M, Smoliakov R, Sidi A, Almog Y . Pharmacokinetic dosing of aminoglycosides: a controlled trial. *Am J Kidney Dis* 2003;114 (3):194-8.
13. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin North Am* 2003;17(3):503-28.
14. Guo X, Nzerue C. How to prevent, recognize, and treat drug-induced nephrotoxcity. *Clev Clin J Med* 2002;69 (4):289-290, 293-4,296-7,312.
15. Olsen KM, Rudis MI, Rebuck JA, Hara J, Gelmont D, Mehdin R, Nelson C, Rupp ME. Effect of once daily dosing vs multiple daily dosing of tobramycin on enzymatic markers of nephrotoxicity. *Crit Care Med* 2004 August; 32(8):1678-82.
16. Livornese LL Jr, Slavin D, Gilbert B, Robbins P, Santoro J. Use of antibacterial agents in renal failure. *Infect Dis Clin North Am* 2004;18 (3):551-79.
17. Winston L, Benowitz N. Once- daily dosing of aminoglycosides:how much monitoring is truly required? *Am J Med* 2003 Feb;114(3):239-40
18. Reiner ME, Thompson WL. Dopamine and saralasin antagonism of renal vasoconstriction and oliguria caused by amphotericin B in dogs. *J Infect Dis* 1979;140:564-75.
19. Brezis M, Cronin RE. Radiocontrast Media-Induced Acute Renal Failure. Ed. Schrier RW. Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1211-1223.
20. Barrett BJ, Parfrey S. Prevention of Nephrotoxicity Induced by Radiocontrast Agents. N Engl J Med 1994;331(21):1449-50.
21. Safirstein R,Andrade L, Vieira JM. Acetylcysteine and Nephrotoxic Effects of Radiographic Contrast Agents – A New Use for an Old Drug. *N Engl J Med* 2000;343(3):210-2.
22. Asif A, Epstein M.Prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 2004;44(1):12-24.
23. Fung JWH, Szeto CC , Chan WWM, Kum LCC, Chan AKY, Wong JTH, Wu EB,Yip GWK, Chan JYS, Yu CM, Woo KS, Sanderson JE. Effect of *N*-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. Am J Kidney Dis 2004; 43(5):801-8.
24. Merten GJ, Burgess WP, Gray LV, Hollemann JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, ,Simonton CA 3rd Ritasse RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate. *JAMA* 2004;291:2328-34.
25. Ronco PM, Flahault A. Drug-Induced End-Stage Renal Disease. *N Engl J Med* 1994;331(25):1711-2.
26. Safirstein RL. Renal Disease Induced by Antineoplastic agents. Ed. Schrier RW. Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1175-1188.
27. Neugarten J, Gallo GR, Baldwin DS. Nephrotoxicity secondary to drug abuse and Lithium Use. Ed. Schrier RW . Diseases of the Kidney and the Urinary Tract. Philadelphia, Lippincott Williams & Wilkins. 2001, pp 1225-1254.
28. Smith JM, Nemeth TL, McDonald RA. Current immunosuppressive agents: efficacy, side effects, and utilization. *Pediatr Clin North Am* 2003;50(6):1283-300.
29. Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. CMAJ 2002;166(4): 473-7.