10. Renal diseases

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1. INTRODUCTION

- The CFTR protein is expressed in abundance in the kidney but its role is not elucidated.
- Primary renal disease is not a typical feature of CF but
  - CF patients are at risk of developing secondary renal disease, most commonly, as a result of medication-associated nephrotoxicity or CF-related diabetes (CFRD).
  - CF has been associated with nephrolithiasis and nephrocalcinosis.
- The steady increase of the life expectancy of CF patients makes renal protective strategies even more relevant.
- **Supplement S10** provides general and CF-specific information about the assessment of renal function, the definitions, classification and risk factors of renal dysfunction.

2. DRUG INDUCED NEPHROTOXICITY

- Most CF patients are exposed to nephrotoxic drugs repetitively. In many cases administered doses are higher than usual, to compensate the altered drug pharmacokinetics and the malabsorption observed in CF.
- Potentially nephrotoxic drugs frequently prescribed in CF patients, include notably antibiotics such as aminoglycosides and NSAIDs.
- After lung transplantation, immunosuppressive drugs, such as calcineurin inhibitors, but also drug-induced diabetes mellitus and hypertension may result in renal impairment.
- Co-administration of more than one nephrotoxic drugs potentiates the risk of renal damage. Extreme caution is warranted in these cases.

2.1. Antibiotics

2.1.1. Aminoglycosides

- Information on aminoglycosides and their pharmacological properties are presented in **Chapter "*Therapeutic drug monitoring*".**
- Main facts concerning aminoglycoside nephrotoxicity (**Table 3**).
- Tobramycin and amikacin are the aminoglycosides most commonly used in adult CF patients.
- Gentamycin is associated with an increased risk of renal failure and is less active for *P. aeruginosa* (as compared to tobramycin). Its use is **not** recommended in adult CF patients**.**

Table 3: Main facts concerning aminoglycoside nephrotoxicity

Aminoglycosides can cause acute or chronic renal injury
Aminoglycoside nephrotoxicity is dose-related
Toxic levels are close to therapeutic levels
Risk factors of acute renal injury include: volume depletion, sepsis, hypokalemia, advanced age, co-administration of other nephrotoxic drugs, and multiple versus single daily dosing
Repeated IV use is associated with long-term renal damage
Aminoglycoside-associated direct tubular injury (gentamycin > tobramycin) • Proximal damage (more frequent) in the most severe cases acute tubular necrosis • Distal damage e.g. Bartter-like syndrome (hypokalemic metabolic alkalosis, hypomagnesemia, hypocalcemia)

2.1.2. Colistin (Polymyxin E)

- Pharmacological properties, available forms and doses are presented in **Chapter *"Medications"*.**
- The drug is primarily eliminated through the kidneys and may cause direct tubular injury, potentially leading to acute tubular necrosis.

2.1.3. β-Lactams

- Selective toxicity towards renal proximal tubular cells → may cause acute proximal tubular necrosis.

2.2. Other potentially nephrotoxic drugs used in CF

2.2.1. NSAIDs

- Principal mechanism of nephrotoxicity: NSAIDs → inhibition of the enzyme cyclooxygenase → blocking of vasodilator prostaglandins → vasoconstriction of the afferent glomerular arterioles → GFR decrease → eventually acute tubular necrosis.
- NSAIDs may also cause: acute interstitial nephritis or papillary necrosis.

2.2.2. Post-transplantation immunosuppressive drugs

- **Calcineurin inhibitors** such as cyclosporine (Sandimun®) and tacrolimus (Prograf®, Advagraf®) are known for their nephrotoxic properties.
  - Mechanism of nephrotoxicity:
    - Calcineurin inhibitors → endothelial cell dysfunction → decreased production of vasodilators, increased secretion of vasoconstrictors → reduction of renal blood flow → eventually renal failure
    - Rarely they may be associated with hemolytic uremic syndrome

- Regular monitoring of drug levels is used in the current clinical practice to adapt and optimize dosage. The desired levels vary according to the time-point after lung transplantation (higher levels during the first 3 months) and the individual patient characteristics.

2.3. Contrast-induced nephropathy

- Information on contraindications, adverse reactions and kidney-protective strategies concerning iodine and gadolinium based contrast media can be found in http://www.esur.org/guidelines/ (ESUR guidelines).

3. NEPHROPROTECTIVE STRATEGIES (TABLE 4)

Table 4: Nephroprotective strategies

Concomitant use of multiple nephrotoxic drugs should be avoided if possible

Dosing: once daily and three times daily intravenous tobramycin appear to be equally effective in the treatment of pulmonary exacerbations. In children once daily dosing has been associated with smaller creatinine changes. Currently single day dosing is the preferable treatment strategy in CF patients.

Route of administration: Nebulized tobramycin and colistin are characterized by increased lung deposition and lower systemic penetration resulting in a lower risk of renal failure compared to intravenous administration.

To prevent and recognize nephrotoxicity, **monitoring of renal function and drug levels (with subsequent dose adjustment) is critical**.

– Monitoring of renal function with plasma/serum creatinine, GFR or cystatine C is mandatory
– Currently, due to lack of evidence, systematic use of renal damage biomarkers such as NAG or NGAL, is not recommended in every-day clinical practice.
– **Therapeutic drug monitoring (TDM):** Serum drug levels should be used to adapt the dosing of antibiotics and notably of aminoglycosides **(see also Chapter "*Therapeutic drug monitoring*")**

4. NEPHROPATHY ASSOCIATED TO CFRD (CYSTIC FIBROSIS RELATED DIABETES)

- CFRD is presented in detail in **Chapter "*CF-related diabetes*"**.
- Patients with diabetes or hypertension are at risk for kidney disease and should be screened for proteinuria and albuminuria.
- Moderately increased albuminuria ('microalbuminuria') has been reported in 4–21% of CFRD cases.
- Patients with CFRD may be at greatest risk of renal tubular damage when exposed to nephrotoxic drugs.

5. OTHER NEPHROPATHIES ASSOCIATED WITH CF

- **Many nephropathies** have been reported (most as case reports) but their co-existence with CF may be incidental. Among them, although rare, IgA-nephropathy is the most frequently reported glomerulonephritis in CF.
- **Secondary amyloidosis**
  - The exact incidence in the CF population is not known but it remains rare.
  - It may result from chronic inflammation and may be associated with proteinuria.
  - The prognosis is generally poor.
- **Pseudo-Bartter's syndrome:** hypokalemic metabolic alkalosis, hypomagnesemia, hypocalcemia.

6. NEPHROLITHIASIS AND NEPHROCALCINOSIS IN CF

- **Incidence:** the prevalence of nephrolithiasis in CF seems to be increased as compared to age-matched controls (3-6% vs 1-2% respectively).
- **The most commonly encountered kidney stones in CF contain calcium-oxalate.**
- Risk factors for kidney stones in CF are summarized in **Table 5.**

Table 5: Risk factors for kidney stones in CF

Dehydration
Hyperoxaluria due to increased interstinal absorption: – Malabsorption due to pancreatic insufficiency → calcium binds to fatty acids in the intestinal lumen rather than to oxalate → more free oxalate available for absorption – Malabsorption → more bile salts reach the colonic lumen → increased colonic permeability to oxalates – Frequent use of antibiotics → destruction of oxalate degrading bacteria (e.g. *Oxalobacter formigenes*) → increased availability of oxalate for intestinal absorption – Excessive consumption of oxalate-rich foods e.g. spinach, rhubarb, mangold, sorrel, cocoa, chocolate, black tea, nuts
Hypocitraturia: chronic metabolic acidosis → hypocitratemia → hypocitraturia
Hyperuricosuria: uncertain role
Hypercalciuria: scant evidence of altered calcium homeostasis in CF, prolonged immobilization, systemic corticosteroids or excessive consumption of salt may favor hypercalciuria

- **Screening and additional diagnostic investigations**
  - Currently, for asymptomatic patients, screening of lithogenic diathesis by spot urine analysis or 24h-urine collection is not recommended (lack of evidence).

- Patients already known for kidney stones should be addressed to a nephrologist and undergo a complete metabolic evaluation including
  - 24h-urine collection: Volume, Sodium, Potassium, Creatinine, Calcium, Phophate, Proteins, Magnesium, Chloride, Uric acid, Urea (=BUN), Oxalate, Citrate
  - Analysis of freshly voided urine: urinary pH, urinary sediment searching for crystals, Dipstick, if pathologic → culture
  - Blood sampling: Sodium, Potassium, Creatinine, Calcium (ionized), Phosphate, Albumin, Magnesium, Chloride, Uric acid, Urea (=BUN), Glucose, Alkaline Phosphatase, venous blood gas analysis, blood count, PTH, 25-OH VitD3
  - Imaging studies according to clinical indication, e.g. abdominal ultrasound, CT scan, MRI
  - Analysis of the renal stone if available (use of urine filter to retrieve the renal stone).

- **Management**
  - **Emergency treatment of symptomatic nephrolithiasis (Table 6):**
    - The mainstay of treatment is pain control
    - Conflicting evidence exists on medical expulsive therapy, such as the α1-adrenoreceptor antagonist tamsulosine (the recent RCT of Pickard et al. showed that tamsulosin was not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks).
    - No convincing evidence to support forced IV hydration or high volume strategies.
    - An urgent urologic consultation is warranted in cases of associated renal infection, renal failure and when symptoms persist despite initial treatment.
  - **Metaphylactic treatment (=prevention of recurrence of kidney stones)** should be discussed with a specialist. **Table 7** summarizes the main points to consider.
  - **Monitoring of hyperoxaluria/hypocitraturia:** the frequency of monitoring depends on the severity of hyperoxaluria. During or immediately after metaphylactic treatment, a 24h-urine collection is initially recommended every 3-6 months. Afterwards, the frequency of the 24h-urine analysis may be reduced (e.g. once a year).

Table 6: Emergency pain control treatment for nephrolithiasis

Category	Examples of drugs	Administration	Dosage	Comment
NSAIDs	Ibuprofen	Oral	600-800 mg 3x/ day or 4x/day	
	Novalgin®	IV	0.5-1.0 g 3x/day or 4x/day	
Opioids	Morphine	IM, IV	5 mg 6x/day	If pain relief unsatisfactory with NSAIDs
Spasmolytics	Buscopan®	Oral, IM, IV	10-20mg 3x/day or 4x/day Max 100 mg/day	

Table 7: Metaphylactic treatment (prevention of recurrence)*

Increased fluid intake
Diuresis > 2–2.5 L/day
Fluid intake evenly distributed during 24h (if possible even during the night)

The generally recommended sodium-restricted diet (<100 mmol/day) has not been formally investigated in CF patients with kidney stones. This recommendation may not apply for CF patients due to CFTR related salt wasting.

Specific recommendations depending on the composition of kidney stone and the results of the metabolic investigations.
For calcium oxalate kidney stones:
– In case of hyperoxaluria: avoid or reduce consumption of oxalate-rich foods e.g. spinach, rhubarb, mangold, sorrel, cocoa, chocolate, black tea, nuts
– In case of hypocitraturia: increase consumption of citrate-rich foods e.g. lemon, vegetables

It is important to keep a **normal calcium intake** (1000-1200 mg/day = 25-30 mmol/day): calcium poor diet favors intestinal oxalate absorption

*Consultation with a specialist is recommended

7. REFERENCES

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S10. Renal diseases

1. ASSESSMENT OF RENAL FUNCTION

- **Serum creatinine:** its relationship with the glomerular filtration rate (GFR) is not linear, but inversely proportional.
  - Muscle mass reduction and malnutrition may lower creatinine levels rendering it an imperfect measure of renal function in these situations.
  - Some medications, such as trimethoprim, inhibit tubular secretion of creatinine and thus may increase serum creatinine. The latter results in a decrease of the "calculated" GFR which may not be a "real" GFR decrease and is reversible.
- **Glomerular filtration rate** (**GFR)** depends on age, sex and body size. GFR measurement is cumbersome; hence it is usually estimated using equations. These equations have a decreased accuracy in CF and they should be used with caution as they may underestimate the degree of renal dysfunction, notably during surveillance of drug nephrotoxicity.

  Online calculators of GFR can be found in
  - ✓ www.kidney.org/professionals/KDOQI/gfr.cfm
  - ✓ touchcalc.com/e_gfr
  - ✓ www.nephron.com
- **Serum cystatin C** has been used for the estimation of GFR. Its levels are not affected by muscle mass, sex or age but they may be affected by inflammation, diabetes and corticosteroid use. Although it appears to be more accurate than creatinine, its clinical superiority is not yet established in the CF population and it is not recommended for routine use.
- **Urine analysis**
  - Detection of **proteinuria** and **albuminuria** in the dipstick should always be confirmed on at least two samples on different days (to rule-out transient proteinuria) and should be quantified to establish the diagnosis.
  - **Proteinuria** is defined as U-protein/U-creat ratio > 15 g/mol. **Transient proteinuria** may be observed during febrile illness or rigorous exercise and does not necessitate any further evaluation.
  - **Albuminuria** is defined as U-albumin/U-creat ratio > 3 g/mol confirmed in two of three random samples obtained during 6 months. *Moderately increased* albuminuria (previously named 'micro-albuminuria') is defined as albuminuria levels between 3-30 g/mol. *Severely increased* albuminuria (previously named 'frank or macro-albuminuria') is defined as albuminuria levels > 30 g/mol.
- **Specific biomarkers of renal damage**
  - Specific urinary or systemic enzymes [such as N-acetyl-ß-D-glucose-aminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1) etc] that may reflect renal tubular damage have been used as non-invasive biomarkers of subclinical renal toxicity.
  - Data are scarce in CF. Normal values and their role as predictors of clinical outcomes are not clearly established in the context of CF, therefore, **none of these biomarkers is recommended in clinical practice for renal toxicity monitoring in CF.**

2. DEFINITION AND CLASSIFICATION OF RENAL DAMAGE (TABLE S1)

- In general terms **acute renal injury** is defined as:
  - An increase in serum Creat of ≥26.5 μmol/L (0.3 mg/dl) within 48h or
  - An increase in serum Creat of ≥1.5 times of baseline or
  - Urine volume <0.5ml/kg per hour for more than 6h.
- In the absence of CF-specific values, severity of **chronic renal dysfunction** (duration >3 months) in CF is evaluated as for the general population.
- Each of these renal dysfunction categories is further characterized according to the level of albuminuria (as mentioned above).
- More details can be found in http://kdigo.org/home/guidelines/

TABLE S1: Severity of renal dysfunction

GFR (mL/min/1.73m²)	Renal function
≥90	Normal or high
60-89	Mildly decreased
45-59	Mildly to moderately decreased
30-44	Moderately to severely decreased
15-29	Severely decreased
<15	Kidney failure

3. RISK FACTORS OF RENAL DYSFUNCTION (TABLE S2)

- As life expectancy of CF patients increases, the accumulation of both non-CF-specific and CF-specific risk factors may contribute to renal dysfunction.

TABLE S2: Risk factors of renal dysfunction

Non-modifiable
Age: decline of GFR with increasing age
Race/Ethnicity: faster rate of GFR decline in African Americans
Gender: males more susceptible to all-cause end-stage renal disease
Genetics: some gene polymorphisms and MHC loci associated with GFR decline
Modifiable
Dehydration
Diabetes

(continued)

Cardiovascular disease
Hypertension
Dyslipidemia
Obesity
Metabolic syndrome
Proteinuria
Various infections (HIV, hepatitis B, hepatitis C, malaria etc)
Malignancy
Nephrotoxic drugs/agents