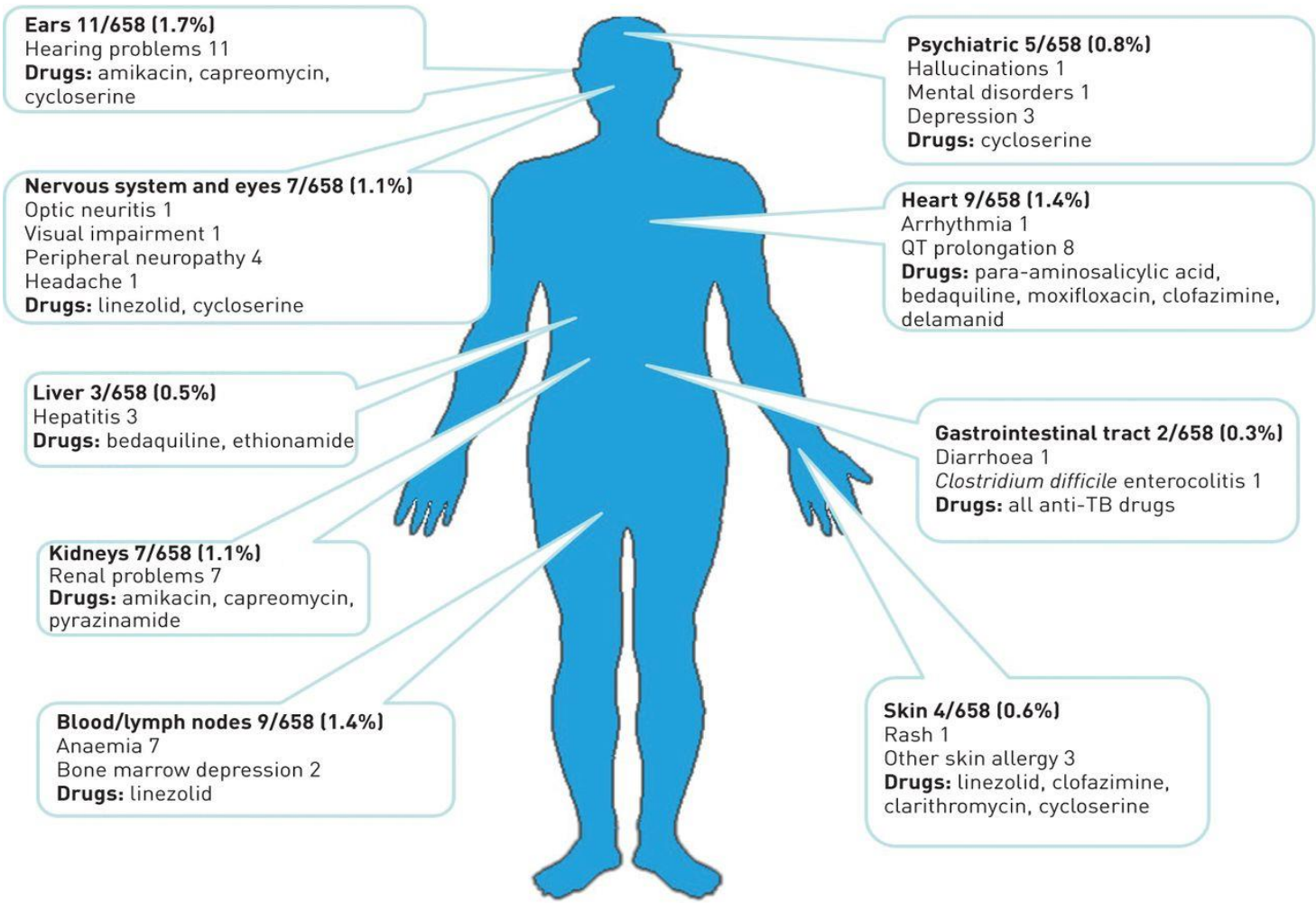
Management of MDR/RR-TB Patients With Renal Failure

Elmira Berikova
Expert, VMC Kazakhstan

Frequency and Type of Adverse Events



Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report
Sergey Borisov, Edvardas Danila, Andrei Maryandyshev, Margareth Dalcolmo et al.

Serious adverse events in patients on longer MDR-TB regimens

Medicine	Absolute risk of serious adverse event	
	Median (%)	95% Confidence Intervals
Capreomycin	8.4	5.7–12.2
Amikacin	10.3	6.6-17.0
Kanamycin	10.8	7.2-16.1
E/Prothionamide	9.5	6.5-14.5
Pyrazinamide	8.8	5.6-13.2
Streptomycin	4.5	2.3-8.8
Linezolid	17.2	10.1-27.0
Bedaquiline	2.4	0.7-7.6
PAS	14.3	10.1-20.7
Clofazimine	3.6	1.3-8.6
Cycloserine	7.8	5.8-10.9
Levofloxacin	4.1	1.9-8.8
Amoxicillin–clavulanic acid	3.0	1.5-5.8
Moxifloxacin	2.9	1.4-5.6

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, WHO. 2020.

Definition of Nephrotoxicity

- **Nephrotoxicity is a capacity of chemicals to cause structural and functional kidney damage through a non-mechanical action on the body.**
- Nephrotoxicity can manifest as a result of direct action of chemicals (or their metabolites) on the renal parenchyma, and indirect action through changes in hemodynamics, acid-base equilibrium of the internal environment, massive formation of (haemolysis, rhabdomyolysis) products of toxic destruction of cellular elements to be excreted through the kidneys.
- **Nephrotoxic** are substances that directly affect kidneys, to which the sensitivity threshold of kidneys is significantly lower than that of other organs and systems.

Toxicology 101, S. A. Kutsenko, Saint-Petersburg, 2002

High sensitivity of kidneys to nephrotoxic substances is determined by

- high-intensity of renal blood flow and sensitivity to hypoxia;
- the ability to concentrate xenobiotics during urine formation;
- reabsorption of a part of excreted xenobiotics into the cells of renal tubule epithelium;
- biotransformation of xenobiotics, accompanied in some cases by the formation of highly toxic intermediate products.

Patient's Risk Factors

- "Absolute" or "effective" blood volume deficiency
- Age over 60 years
- Diabetes
- HIV
- Simultaneous exposure to more than one nephrotoxin
- Heart failure
- Sepsis
- Renal failure (GFR < 60 ml/min/1.73 m2)

Patient's Risk Factors and Mechanism of Nephrotoxic Effect of Aminoglycosides

Drugs	Risk factors	Mechanism of action
Drugs that have a toxic effect on the epithelium of the renal tubules		
Aminoglycosides, amphotericin B, antiretrovirals (adenovir, cidifovir, tenofovir), cisplatin, contrast agents	Baseline renal failure (prior to drug prescription), treatment duration > 10 days, minimum concentration > 2 mcg/mL, history of concomitant liver disease, hypoalbuminemia, DM and HIV	Renal tubule cells, especially renal proximal tubule cells, are sensitive to the toxic effects of drugs because being involved in the processes of reabsorption of glomerular filtrate and urine concentration, these structures are exposed to circulating toxins in high concentrations. The toxic effects of drugs on the glomerular epithelium are due to impaired mitochondrial function, transport through the tubule wall, increased oxidative stress and the formation of free radicals

Complaints

- nausea
- vomiting
- dehydration
- dyspepsia
- diarrhea
- oliguria/ anuria/ polyuria
- peripheral edema
- dry mouth
- weakness
- hypotension/ hypertension
- allergic reactions (urticaria, Quincke's edema, Lyell's syndrome, Stevens-Jones syndrome, etc.)
- pain in the lumbar region, renal colic
- acute uric acid nephropathy
- hematuria

Laboratory/ Instrumental Parameters

- CBC: eosinophilia, leucocytosis/leukopenia, thrombocytopenia, increased sedimentation rate, anaemia.
- Urine analysis: proteinuria from moderate 0.5 g/day to severe - more than 3.0 g/day, macro/microhematuria, cylindruria, decreased urine relative density.
- Blood chemistry: hypercreatininemia, decreased GFR, electrolyte disorders (hyperkalemia, hyper/hyponatremia, hypocalcaemia)
- Acid-base balance of the blood: acidosis, decreased bicarbonate levels.
- ECG: disorders of rhythm and cardiac conduction.
- Chest X-ray: fluid accumulation in pleural cavities, pulmonary edema;
- Ultrasound of the kidneys and abdomen: increased volume of kidneys, presence of concrements in renal pelvis or urinary tract, diagnosis of various tumours.

Manifestations of Nephrotoxic Effects

- Blood in the urine (hematuria) due to the damage to the capillary wall of the glomeruli.
- Protein in the urine in the amount of more than 0.5 g per daily sample (proteinuria). Proteinuria may be glomerular, with predominantly high-molecular-weight proteins (more than 40000), and tubular, with predominantly low-molecular-weight proteins (less than 40000) detected in the urine. Glomerular proteinuria indicates destruction of the glomerular blood-brain barrier; tubular proteinuria indicates damage to the proximal parts of the renal tubules.
- Decrease in the amount of excreted urine - less than 600 ml per day (oliguria).
- Increased plasma content of nitrogen-containing low molecular weight substances (urea, creatinine, β2-microglobulins, etc.).
- General edema, which in the absence of heart failure or liver cirrhosis indicates a sharp decrease in blood protein content (hypoalbuminemia).
- Hypertension as a result of glomerulosclerosis.

Main Syndromes of Nephrotoxicity

- Acute renal failure, manifested by azotaemia and oliguria
- Chronic renal failure - renal dysfunction with azotaemia, acidosis, anaemia, hypertension and other disorders
- Tubulointerstitial nephritis (acute or chronic) with signs of tubular dysfunction (proteinuria, acidosis of urine, loss of salts, reduced urine specific gravity, etc.)
- Rapidly progressing glomerulonephritis manifested by haematuria and oliguria

Normal Values: Creatinine, Creatinine Clearance

Age / gender	Normal values
Newborns	20 - 75 µmol/l
Under the age of 1	15 - 37 µmol/l
1 – 3 years	21 - 36 µmol/l
3 – 5 years	26 - 41 µmol/l
5 – 7 years	27 - 51 µmol/l
7 – 9 years	34 - 52 µmol/l
9 – 11 years	33 - 66 µmol/l
11 – 15 years	45 - 75 µmol/l
Above the age of 15	
males	females
62 – 115 µmol/l	53 – 97 µmol/l

Age	Endogenous creatinine clearance ml/min/1.7 m2	
	Males	Females
< 1 years	65-100	65-100
1- 30 years	88-146	81-134
30-40 years	82-140	75-128
40-50 years	75-133	69-122
50-60 years	68-126	64-116
60-70 years	61-120	58-110
> 70 years	55-113	52-105

If blood creatinine is more than 120 µmol/l, urea is more than 35 mmol/l, and creatinine clearance is less than 10 ml/min, then renal dialysis or kidney transplantation may be considered

Prevention of Drug-Induced Nephrotoxicity

- Adjustment of medication doses using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children)
- Pre-treatment renal function assessment with the MDRD formula, renal function check-up prior to prescribing a new medication
- Avoiding combinations of nephrotoxic drugs
- Correction of nephrotoxicity risk factors before treatment initiation
- Providing adequate hydration before and during treatment with potential nephrotoxins
- Prescribing drugs with similar effects that are not nephrotoxic

Formulas for Renal Function Assessment to Adjust Medication Doses

Name	Formula	Use
Cockroft and Gaut	Creatinine clearance= (140 – age)(weight in kg) × (0.85, for female patients) Serum creatinine (μmol/l) × 0,81	Drug dose adjustment depending on renal function in adults
MDRD (Modification of Diet in Renal Disease)	Glomerular filtration rate = 186,3 × (serum creatinine)$^{-1,154}$ × age$^{-0,203}$ × (0.742, for female patients) × (1.21, for patients of color)	Assessment of kidney function and determination of the stage of chronic kidney disease
Schwartz	Creatinine clearance = 88,4 × length in sm в × k Serum creatinine in μmol/l k = 0.45 (newborns 1–52 weeks), 0.55 (children aged 1 to 13 years), 0.7 (boys 14–17 years), 0.55 (girls 14–17 years)	Drug dose adjustment depending on renal function in children

Nephrotoxicity Control Measures

- Repeat clinical urine tests for abnormal urine sediment findings (cylinders, protein, leukocytes)
- Every 3 days - control of blood plasma creatinine level, blood plasma urea level, calculation of GFR
- If GFR decreases by 50% or more, discontinue the injectable drug
- Consider intermittent use of the injectable drug or reduction of the dosage

Laboratory Monitoring Of Adverse Events

Laboratory tests														
CBC/urinalysis	✘		✘	✘	✘	✘	✘	✘	Monthly	✘				
Liver functions tests (AST, ALT)	✘		✘	✘	✘	✘	✘	✘	Monthly	✘				
Serum creatinine and GFR	✘		✘	✘	✘	✘	✘	✘	Monthly	✘				
Serum potassium	✘		✘	✘	✘	✘	✘	✘	Monthly	✘				

Key Therapeutic Principles

- Most drugs that are excreted through the kidneys do not require dose adjustment until creatinine clearance drops below 50 mL/min.
- Adequate hydration is very important to maintain renal perfusion and to avoid drug-induced damage to the renal tissue.
- Before starting treatment with nephrotoxic drugs, blood volume should be assessed and corrected.
- Severe blood volume deficit is manifested by orthostatic hypotension, blood pressure below 90/60 mm Hg, decreased skin turgor and loss of more than 5% of initial pre-treatment body weight.
- In general drug-induced renal damage is manageable. Renal function is fully restored if the complication is detected in time and the drug that causes toxicity is withdrawn.
- Changes in serum creatinine level - an increase by 50% of the initial level or by more than 0.04 mmol/l with the initial values less than 0.180 mmol/l- is a biochemical criteria for ARF.

Management Strategy

- At the first signs of renal failure, the exposure to the causative factor should be stopped immediately if possible, or its effect should be minimized (dose reduction or intermittent administration).
- During treatment, special attention should be paid to maintaining water-electrolyte homeostasis, blood acid-base balance, and blood pressure.
- It is possible to use crystalloid isoosmolar solutions containing sodium chloride/glucose, sodium bicarbonate solution, loop diuretics, antihypertensive drugs.
- Conservative treatment is aimed at etiological, pathogenetic, symptomatic aspects.

Anti-TB Drugs Dosage Adjustment in Renal Failure

Drug	Recommended dose and frequency for patients with creatinine clearance <30 mL/min or patients on hemodialysis
Levofloxacin	750-1000 mg/kg/dose 3 times a week
Moxifloxacin	Adjustment not required
Cycloserine	250 mg once daily, or 500 mg/dose 3 times a week [a]
Terizidone	No recommendations
Clofazimine	Adjustments not required
Linezolid	Adjustments not required
Bedaquiline	Patients with mild to moderate renal failure do not need dose adjustment (for severe renal failure the dosage is not defined, use with caution)
Delamanid	Patients with mild to moderate renal failure do not need dose adjustment (for severe renal failure the dosage is not defined, use with caution)

Anti-TB Drugs Dosage Adjustment in Renal Failure

Drug	Recommended dose and frequency for patients with creatinine clearance <30 mL/min or patients on hemodialysis
Pyrazinamide	25-35 mg/kg/dose 3 times a week
Etambutol	15-25 mg/kg/dose 3 times a week
Ethionamide	Adjustment not required
Streptomycin	12-15 mg/kg/dose 2 or 3 times a week[b]
Amikacin	12-15 mg/kg/dose 2 or 3 times a week[b]
PAS	4 g/dose, twice daily maximum dose[c]
Amoxicillin/clavulanate	In creatinine clearance 10-30 ml/min, the dose of amoxicillin 1000 mg twice a day, in creatinine clearance <10 ml/min, the dose of amoxicillin 1000 mg once a day
Delamanid	Patients with mild to moderate renal failure do not need dose adjustment (for severe renal failure the dosage is not defined, use with caution)
Imipenem/cylastatin	For creatinine clearance 20-40 ml/min, dose 500 mg every 8 hours; for creatinine clearance <20 ml/min, dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min, dose 750 mg every 12 hours; for creatinine clearance <20 ml/min, dose 500 mg every 12 hours
High dose isoniazid	500 mg daily dose

Management Strategy

- Regimen: bed rest for the first 24 hours, then general regimen based on patient's condition.
- Diet: restriction of table salt (mainly sodium) and fluids. In the presence of edema, content of table salt is limited to 0.2-0.3 g per day, daily dietary protein consumption is limited to 0.5-0.6 g/kg of body weight, mainly through the restriction of animal proteins.
- In hyperkalemia - potassium antagonist - calcium gluconate/chloride 10% 20 ml IV for 2-3 minutes #1 (if there are no changes on ECG, repeat injection in the same dose, in the absence of response - hemodialysis).
- 20% glucose 500 ml + 50 IU of short-acting soluble human insulin IV fluid drip.
- 15-30 units every 3 hours until normalization of blood potassium level.
- In acidosis - sodium bicarbonate 4% IVFD. Dose calculation by formula: X= BE (base deficit)*weight (kg)/2, Sodium bicarbonate 8.4% IVFD. Calculation of the dose according to the formula: X= VE*0.3* weight (kg) 5% dextrose 500 ml IVFD until blood volume deficit is replenished. The highest adult dose of sodium bicarbonate is approximately 315 mL of 4% solution per day at the drip rate of 60 drops/minute.
- Sodium chloride 0.9% IVFD 500 ml/10% 20 ml IV 1-2 times a day - until the blood volume deficit is compensated.
- Furosemide 200-400 mg IV, starting at a rate of 5-10 mg/hour, with hourly urine output monitoring.

Management Strategy

- The use of glucocorticoids in the treatment of renal failure has failed to show efficacy in restoring renal function, and therefore is not recommended in most cases.
- GCSs are recommended when renal function does not improve after cessation of the causative factors.
- There is no need for additional interventions in patients with minimal elevation of blood creatinine/ recovery of renal function within 3-7 days.
- Glucocorticoid therapy may be initiated in patients with a confirmed association between the development of acute tubulointerstitial nephritis and exposure to the drug, if renal biopsy is not possible.
- GCS therapy: prednisolone 1 mg/kg/day (up to 40-60 mg/day maximum) for a minimum of 1-2 weeks, starting dose tapering when creatinine returns to near basal levels, with a full treatment duration of 2-3 months.

Indications For Renal Replacement Therapy:

- 58% of cases need renal replacement therapy
- Renal output ≤200 ml/12h or anuria, azotemia with plasma urea level ≥36 mmol/l, hyperkalaemia ≥6.5 mmol/l and/or ECG changes; hypermagnesemia ≥4 mmol/l and/or no deep tendon reflexes, acidosis pH≤7.15, refractory edema, complicated extrarenal pathology
- Renal replacement therapy methods in acute renal injury are subdivided into extracorporeal (intermittent, prolonged, extended) and intracorporeal - manual and automated peritoneal dialysis (PD)
- Intermittent methods are performed daily for 2-4 hours. They include hemodialysis, hemofiltration, hemodiafiltration
- Continuous methods, which are carried out almost around the clock for several days or even weeks

Conclusion

- Treatment of MDR-TB is a major challenge because of the long duration of therapy, high cost, and adverse events associated with complex treatment regimens.
- Adverse events are more common with MDR-TB treatment compared to standard treatment of drug-susceptible TB, which can lead to poor patients' adherence and unfavourable treatment outcomes.
- Therefore, close monitoring and proper management of MDR-TB patients to prevent unfavourable outcomes and amplification of drug resistance is important.
- Regarding nephrotoxicity, ubiquitous switch to all-oral treatment regimens for MDR-TB will significantly reduce the incidence of this adverse event.
- Overall, reducing the duration of DR-TB treatment with transition to shorter regimens will improve treatment tolerance and adherence to treatment.

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