EXTRACORPOREAL NEPHROLOGY GROUP [ECNG]

TUBERCULOSIS IN CKD AND TRANSPLANT RECEPIENTS

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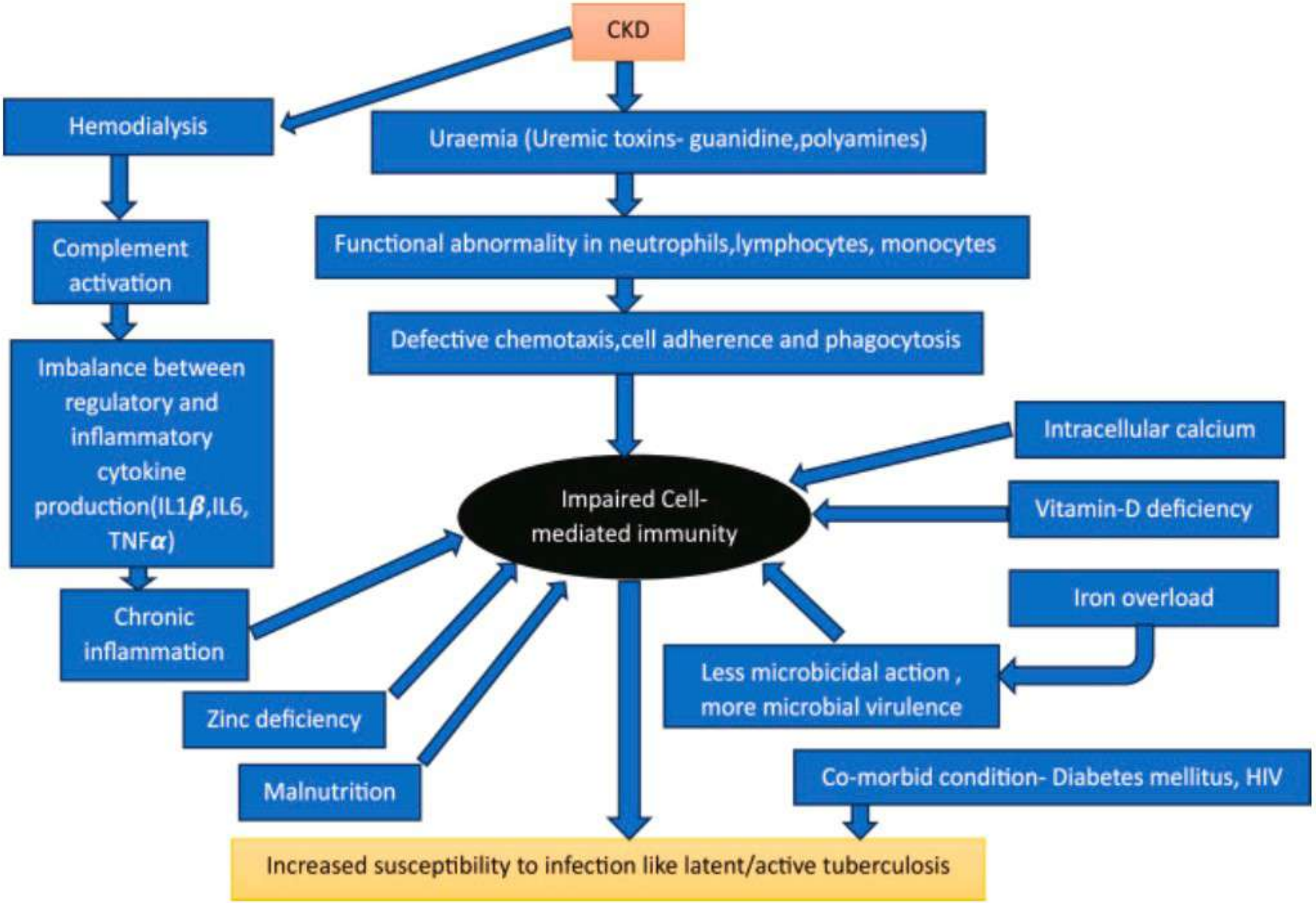
PATHOGENESIS



Clinical Presentation: Diagnostic Challenges

⚠ Clinical presentation is frequently ATYPICAL in CKD and transplant patients — high index of suspicion is essential!

Pulmonary TB (50–60% of cases)

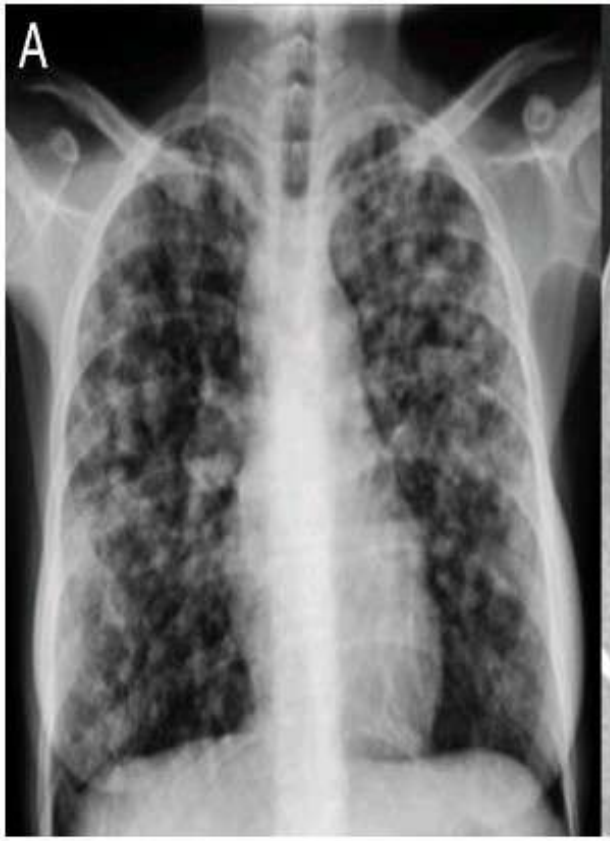
- Cough (often absent or mild)
- Haemoptysis (less frequent)
- Fever — low grade or absent
- Weight loss, anorexia (confused with uremia)
- Atypical CXR: lower lobe involvement, miliary pattern
- Normal CXR in 10–20% of immunosuppressed TB

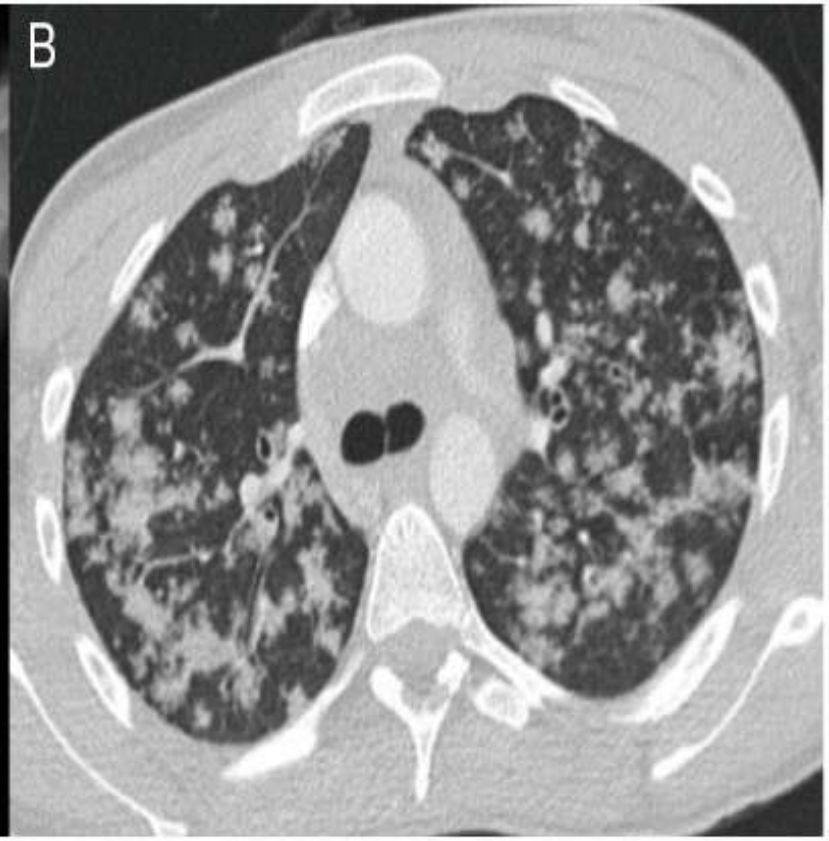
Extrapulmonary TB (40–50% of cases)

- Lymphadenopathy (most common EP site)
- CNS TB / tuberculous meningitis
- Skeletal — spinal (Pott's disease)
- Genitourinary TB (often presenting as CKD)
- Peritoneal TB — PD patients especially
- Hepatic, splenic, adrenal involvement
- Cutaneous TB (rare but documented)

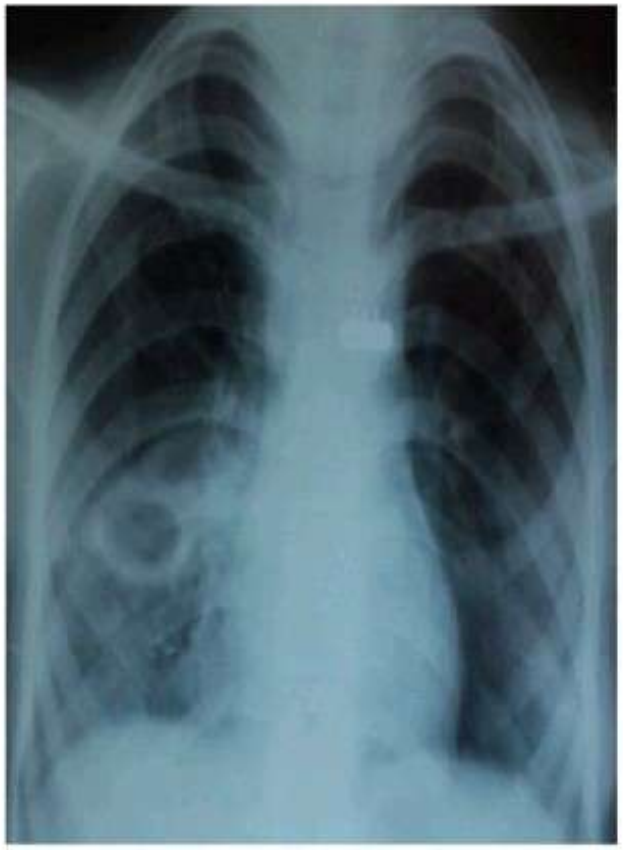
References: Bumbacea D et al. Eur Respir J 2012; Holty JC et al. Chest 2006; KDIGO 2022 Guidelines

MILLIARY TB

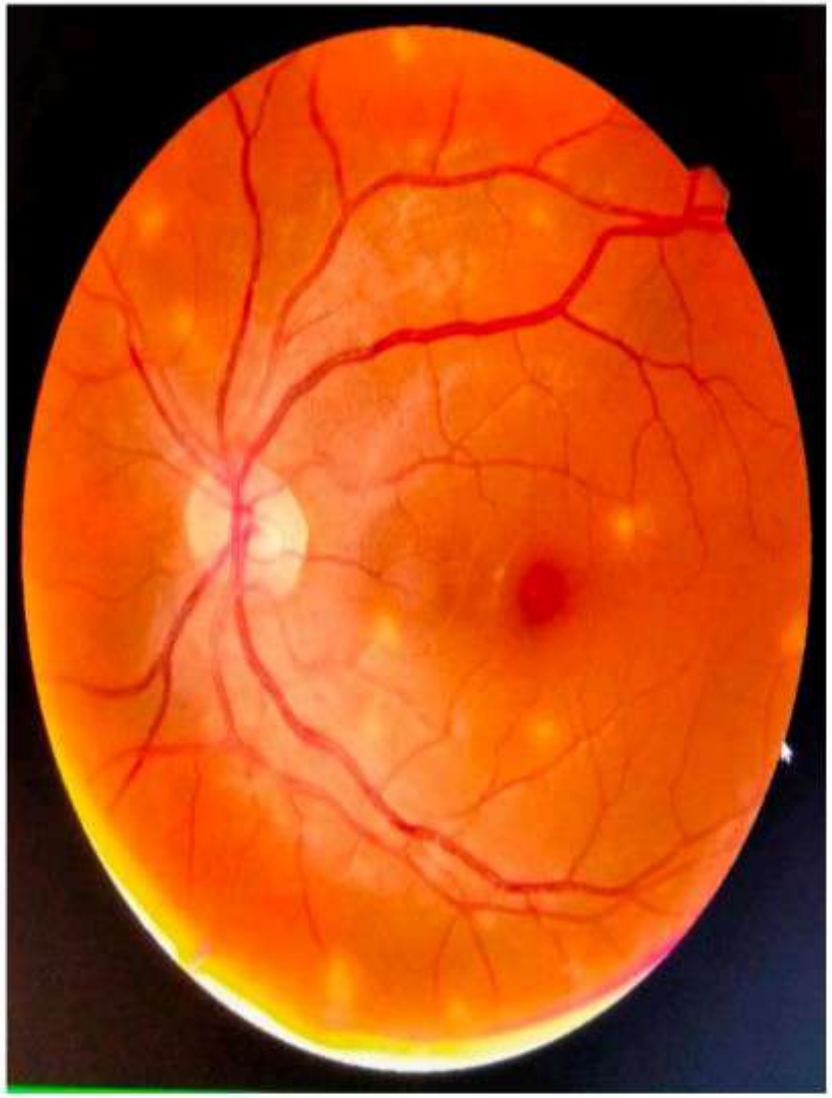




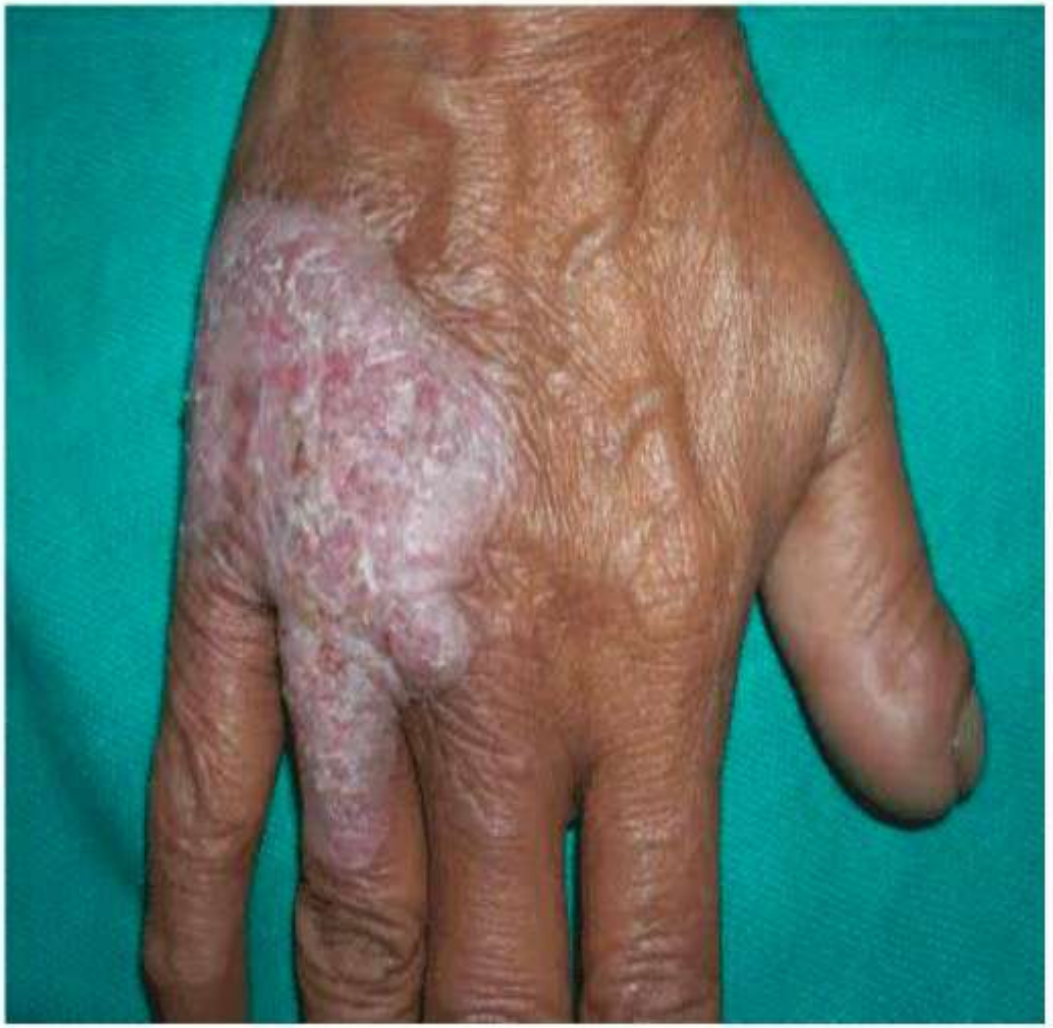
LOWER LOBE - CAVITY



CHOROID TUBERCLES ON FUNDUS



LUPUS VULGARIS - SKIN



Clinical Evaluation: Step-by-Step Approach

1

Detailed History

Prior TB or close TB contact • BCG vaccination history • Country of origin / travel to endemic regions • Immunosuppression type and duration • Symptom timeline (fever, cough, weight loss, night sweats)

2

Physical Examination

Lymphadenopathy (cervical, axillary) • Hepatosplenomegaly (disseminated TB) • Chest auscultation — reduced breath sounds • Neurological assessment (meningeal signs) • Skin: erythema nodosum, lupus vulgaris. Choroid tubercles in the eyes.

3

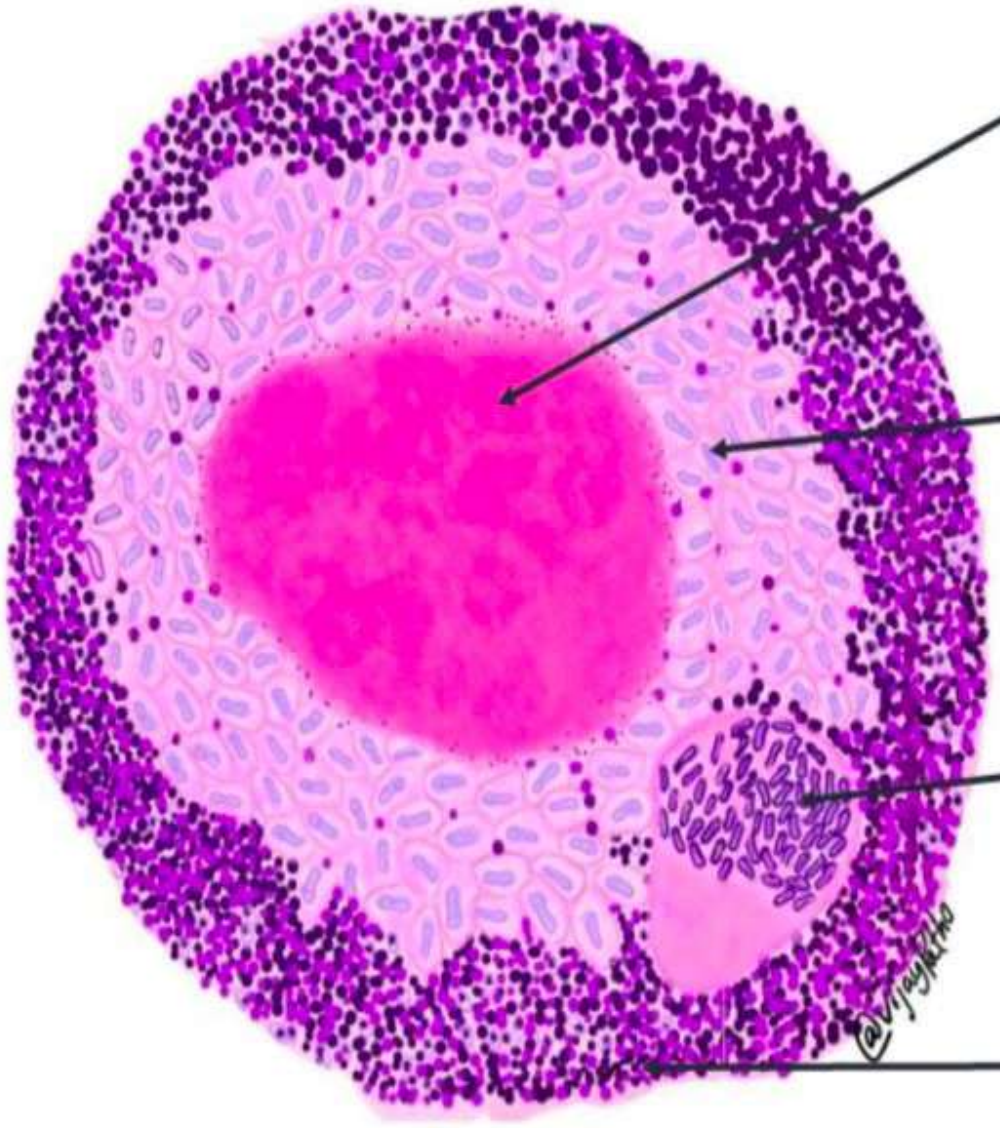
Baseline Investigations

CBC, LFT, RFT, serum albumin • CXR (PA and lateral views) • Sputum AFB smear × 3 (early morning) • Urine AFB (if urogenital TB suspected) • CT chest with contrast (if CXR inconclusive)

References: Getahun H et al. NEJM 2015; Pai M et al. Nat Rev Dis Primers 2016

HISTO PATHOLOGY

TUBERCULOUS LYMPHADENITIS: Necrotizing granuloma



Amorphous granular eosinophilic debritic material
CASEOUS NECROSIS

Modified macrophages with abundant cytoplasm and pale staining "slipper" shaped nuclei
EPITHELOID CELLS

Multinucleated giant cell
LANGHAN GIANT CELL

Collar of lymphocytes surrounding epitheloid cell aggregates

Tuberculin Skin Test (TST) in CKD

Interpretation in CKD / Transplant

≥5 mm	HIV+, transplant, steroids
≥10 mm	ESRD on dialysis, CKD Stage 4–5
≥15 mm	No risk factors

Limitations of TST in CKD:

- False negatives in anergy (30–50% of dialysis pts)
- Requires 48–72 hr return visit
- BCG vaccination confounds results
- Reader-dependent variability
- Cannot distinguish latent from active TB

Two-Step TST Protocol

Recommended for all new dialysis patients and pre-transplant workup in endemic settings

Step 1: Place 5-TU PPD intradermally

Read at 48–72 hours

If negative: repeat test in 1–3 weeks

Step 2: Second TST placed

Positive second result = 'boosted' reaction

Boosting indicates remote TB infection

Used to establish baseline before IS therapy

Anergy panel (Candida/Mumps) no longer routinely recommended (CDC 2005)

References: ATS/CDC/IDSA TB Guidelines 2022; Lewinsohn DM et al. Clin Infect Dis 2017; WHO LTBI Guidelines 2020

Interferon-Gamma Release Assays (IGRA) in CKD

QuantiFERON-TB Gold Plus (QFT-Plus)

4th generation; detects CD4 & CD8 T-cell responses. Most widely used globally. Blood-based, single visit.

T-SPOT.TB (ELISpot)

PBMC-based; counts IFN-γ secreting T-cells. May be more sensitive in immunocompromised. Better in lymphopenic states.

IGRA vs TST in CKD / Transplant — Performance Comparison

Parameter	TST	QFT-Plus	T-SPOT.TB
Sensitivity in ESRD	50–60%	72–80%	78–85%
Affected by BCG	Yes	No	No
Anergy risk	High	Moderate	Low

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Affected by BCG	Yes	No	No
Anergy risk	High	Moderate	Low
Single visit	No	Yes	Yes
Cost	Low	Moderate	High
Indeterminate rate in ESRD	—	10–15%	5–10%

References: Sester M et al. Eur Respir J 2014; Diel R et al. Am J Respir Crit Care Med 2011; Pai M et al. Nat Rev Dis Primers 2016

Newer Diagnostics: Molecular Techniques

WHO Endorsed

Xpert MTB/RIF Ultra

- ✓ Detects M. tuberculosis + rifampicin resistance in <2 hours
- ✓ Sensitivity 88–90% (smear-neg: 63–65%)
- ✓ **Uses cartridge-based PCR (CBNAAT)**
- ✓ Approved for sputum, CSF, pleural fluid, tissue biopsies
- ✓ Detects as few as 15 CFU/mL
- ✓ **Preferred first-line test by WHO 2021**

2021 — Latest

Xpert MTB/XDR

- ✓ **Detects resistance to isoniazid, fluoroquinolones, amikacin, kanamycin, capreomycin, ethionamide**
- ✓ **Single cartridge — comprehensive DR-TB detection**
- ✓ Critical for transplant recipients who fail standard regimens
- ✓ Sensitivity: 94% for pre-XDR/XDR strains

References: Dorman SE et al. Lancet Infect Dis 2018; WHO 2021 Updated Recommendations; Boehme CC et al. NEJM 2010

Latent TB Screening: Pre-Transplant Protocol

All Transplant Candidates — Mandatory LTBI Screening [suspected / at risk patients]

IGRA (QFT-Plus or T-SPOT)

Preferred in CKD — not affected by BCG, single visit

→

TST (if IGRA unavailable)

Two-step protocol; ≥5mm cutoff for transplant candidates

→

Dual testing (IGRA + TST)

Recommended in high-endemic regions (India, sub-Saharan Africa)

LTBI Treatment Indications

- **Positive IGRA or TST with no evidence of active TB** → treat LTBI pre-transplant (preferred).
- **Prior history of untreated/inadequately treated TB** — treat regardless of IGRA result
- **Donor IGRA/TST positive** → recipient should receive LTBI prophylaxis
- **Preferred regimen: Isoniazid 5 mg/kg/day (max 300 mg) × 9 months + Pyridoxine 25–50 mg/day**
- **Alternative: 3HP (Rifapentine + Isoniazid weekly × 12 doses)** — NOT recommended in transplant (drug interactions)
- **4R (Rifampicin × 4 months):** avoid in CNI-based regimens (enzyme induction → ↓ CNI levels critically)

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References: WHO LTBI Guidelines 2020; KDIGO Transplant Guidelines 2022; Subramanian AK et al. Am J Transplant 2019

TB meds for CKD/HD patients (advanced)*

*CrCl<30 ml/min or hemodialysis

Needs to change in frequency	Dose Recommendation	NO Adjustment
Pyrazinamide	25–35 mg/kg/dose 3 times/wk	Isoniazid
Ethambutol	20–25 mg/kg/dose 3 times/wk	Rifampin
Levofloxacin	750–1000 mg/dose 3 times/wk	Moxifloxacin
Cycloserine	250 mg daily, or 500 mg/dose 3 times/wk	Linezolid
Amikacin	15 mg/kg/dose 2-3 times/wk	Bedaquiline
Imipenem	CrCl 20-40: 750 mg q12h CrCl<20: 500 mg q12h	Clofazimine
Para-aminosalicylic acid	4 g/dose twice daily	Ethionamide
Streptomycin	15 mg/kg/dose 2-3 times/wk	Rifabutin**
		Rifapentine

**50% reduction may be used

ATS/IDSA/CDC Clinical Practice Guidelines 2016: Treatment of Drug-Susceptible Tuberculosis
The Spectrum of Tuberculosis from Infection to Disease, TB at a Glance 3rd edition

World Health Organization

WHO TB Guideline: April 2025

New WHO Anti TB Drug Regimens

1. Adult Regimens (≥12 years) – Drug-Susceptible TB

	6 months Regimen (Recommended)	4 months Regimen (Conditionally Recommended)
Intensive Phase (2 months)	1. Isoniazid 2. Rifampin 3. Pyrazinamide 4. Ethambutol	1. Isoniazid. 2. Rifapentine 3. Pyrazinamide 4. Moxifloxacin
Continuation Phase	1. Isoniazid (4 months) 2. . Rifampin (4 months)	1. Isoniazid (2 months) 2. Rifapentine (2 months) 3. Moxifloxacin (2 months)

ATT Dose Adjustments by CKD Stage

Drug	CKD 1–3 (GFR >30)	CKD 4–5 (GFR <30)	Hemodialysis	CAPD
Isoniazid	Standard dose (300 mg OD)	Standard dose + pyridoxine 50 mg	Standard dose (post-HD); pyridoxine 50 mg	Standard dose + pyridoxine
Rifampicin	Standard dose (600 mg OD)	Standard dose	Standard dose (not removed by HD)	Standard dose
Pyrazinamide	Standard dose (25 mg/kg)	25 mg/kg 3× weekly	25–35 mg/kg 3× weekly (post-HD)	25 mg/kg 3× weekly
Ethambutol	15–25 mg/kg OD	15 mg/kg 3× weekly	15–25 mg/kg 3× weekly (post-HD)	15 mg/kg 3× weekly
Streptomycin	Avoid if possible	Avoid; if needed: 12–15 mg/kg 3× weekly	12–15 mg/kg 3× weekly (post-HD)	Avoid
Levofloxacin	750 mg OD (standard)	500–750 mg OD	500 mg 3× weekly	500 mg OD

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Key Principle: Avoid fixed-dose combinations (FDC) in CKD — individual drug dosing allows dose titration to GFR.

References: Malone RS et al. AJKD 2007; RNTCP/NTEP Guidelines India 2022; BTS Guidelines TB Management 2019

ATT in Renal Transplant Recipients: Key Challenges

⚠ **CRITICAL: Rifampicin–Calcineurin Inhibitor (CNI) Interaction**

Rifampicin induces CYP3A4 → ↓ Tacrolimus/Cyclosporine levels by 80–90% → Acute rejection risk. Requires 3–5× CNI dose increase with very close monitoring (daily trough levels initially). 2 weeks after stopping Rifampicin: reduce CNI dose back. Alternative: use Rifampicin-free regimen where feasible.

Management Strategies

Option 1: Rifampicin-containing regimen (preferred)

- 2HRZE / 7–10 HR: 9–12 months total duration
- Increase CNI dose 3–5× with daily trough monitoring
- Weekly LFTs first 4 weeks; monthly thereafter
- Close collaboration between nephrology and ID team

Option 2: Rifampicin-free regimen

- 9HZE + Levofloxacin (or Moxifloxacin): 12–18 months
- Avoids CNI interaction but reduced bactericidal potency
- Consider in rejection-prone patients or those with very labile CNI levels
- Requires careful monitoring for fluoroquinolone toxicity

MILD TO MOD : INH +PZA+ETB+LEVOFLOX

SEVERE CASES : RIFAMPICIN

References: Subramanian AK et al. Am J Transplant 2019; Meije Y et al. Clin Infect Dis 2021; KDIGO 2022 Transplant Guidelines

BEAT TUBERCULOSIS TRIAL

6-Month All-Oral Regimen Noninferior to Standard Treatment for Rifampicin-Resistant TB

Full Phase 3 BEAT Tuberculosis Trial Results

DR SACHIN ZAMBARE
NEPHROLOGIST

BOTTOM LINE

A 6-month, all-oral regimen of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine was **noninferior** to the standard treatment in participants with rifampicin-resistant tuberculosis.

Participants	Treatment Duration	Sites	Result
1,455 with rifampicin-resistant TB	6 Months	109 in 25 Countries	Noninferior to standard treatment

EXPERIMENTAL ARM (6 Months)

BPaL(M) Regimen

Bedaquiline (Bdq) + Linezolid (Lzd) + Delamanid (Dlm) + Levofloxacin (Lfx) or Clofazimine (Cfz)

- All-oral regimen
- Shorter duration (6 months)
- Simplified treatment
- Designed to improve adherence and reduce toxicity

VS

STANDARD CARE ARM (18–20 Months)

Investigator's Choice Regimen

Multiple Drugs + Longer Duration + More Complex + Higher Risk of Side Effects

- 18–20 months of treatment
- Varied drug combinations
- Greater pill burden
- Higher risk of toxicity and dropouts

PRIMARY OUTCOME RESULTS

Favorable Outcome at 6 Months After Treatment Completion

EXPERIMENTAL ARM (BPaL(M))	DIFFERENCE	STANDARD CARE ARM
89.8%	−1.1% (95% CI: −4.4 to 2.1)	83.7%

Noninferiority Margin: −9%
The upper limit of the 95% CI was well within the noninferiority margin.

The 6-month BPaL(M) regimen was **NONINFERIOR** to the standard treatment.

SAFETY PROFILE

Fewer participants in the experimental arm experienced serious adverse events compared to the standard care arm.

Key Adverse Events Reduced:

- Hepatotoxicity
- Nephrotoxicity
- Gastrointestinal Events
- Treatment Discontinuation

WHY THIS MATTERS

- Shorter treatment means better adherence
- Fewer side effects improve quality of life
- Can transform TB care globally, especially in high-burden settings
- A major step toward ending drug-resistant TB

KEY TAKEAWAY

A 6-month, all-oral regimen of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine is an effective, safer, and shorter alternative to the standard treatment for rifampicin-resistant TB.

REFERENCE
Full Phase 3 BEAT Tuberculosis Trial Results
https://nej.md/4w7aekw

Advancing Evidence. Improving Lives. Ending TB.