# Whipple’s Disease

## **1. Overview & Taxonomy**

* **Agent**: *Tropheryma whipplei*
  + Gram-positive actinomycete (order *Actinomycetales*), related to *Actinomyces*.
  + **PAS-positive** foamy macrophages in tissues.
  + Non-motile, non–acid-fast, slow-growing, fastidious.
  + Intracellular
  + aerobic
* Named after George Hoyt Whipple (1907).
* **Epidemiology**:
  + Rare (~1/million/year).
  + Middle-aged Caucasian men (M:F ≈ 8–10:1).
  + Found in environment (sewage, soil); asymptomatic carriage possible, especially in endemic settings.
  + Possible occupational link: farmers, sewage workers.

## **2. Laboratory Microbiology**

### **A) Morphology**

* Small, rod-shaped Gram-positive bacilli (weakly Gram-staining).
* **PAS-positive, diastase-resistant** material in lamina propria macrophages.
* Non–acid-fast on Ziehl–Neelsen (differentiates from *Mycobacterium avium* complex and *Nocardia*).

### **B) Culture**

* **Fastidious**: requires **human fibroblast cell lines** (e.g., HEL cells) or other eukaryotic systems.
* No growth on standard bacteriological agar.

### **C) Histology**

* **Small bowel biopsy (duodenum/jejunum)**:
  + Villous blunting, lamina propria expanded by foamy macrophages packed with PAS-positive, diastase-resistant granules (glycoprotein-rich bacterial cell wall remnants).
  + Lymphatic dilation may be present.
* **Special stains**: PAS key;
* Immunohistochemistry with *T. whipplei*-specific antibodies improves sensitivity in equivocal PAS cases.

### **D) Molecular Diagnostics**

* **16S rRNA PCR** (1991) or RT-PCR
* **Best specimens**:
  + Intestinal mucosa (highest yield)
  + CSF (for CNS disease)
  + Synovial fluid
  + Heart valve tissue
  + Aqueous humour

### **G) Antimicrobial Susceptibility**

* No standardised AST — requires intracellular culture.
* In vitro susceptible to beta-lactams, tetracyclines, macrolides, co-trimoxazole.
* Beta-lactams (esp. ceftriaxone, penicillin G) are bactericidal and penetrate tissues; co-trimoxazole and doxycycline penetrate CNS — basis for recommended regimens.

## **3. Clinical Microbiology – Syndromes**

### **A) Classic (Intestinal) Whipple’s Disease**

* **Triad**:
  + Chronic diarrhoea/malabsorption (steatorrhoea, weight loss)
  + Arthralgia/arthritis (often migratory, large joints; may precede GI symptoms by years)
  + Fever (intermittent)
* Other: abdominal pain, lymphadenopathy, hyperpigmentation, anaemia.

### **B) Extraintestinal Disease**

* **Arthropathy**: often initial presentation; non-erosive.
* **Cardiac**: culture-negative endocarditis (important differential with *Bartonella*, *Coxiella*).
* **Neurological**:
  + Cognitive impairment/dementia-like syndrome
  + Supranuclear ophthalmoplegia
  + Myoclonus, seizures, ataxia
  + Untreated CNS involvement → high mortality.
* **Ocular**: uveitis, vitritis, keratitis, retinitis.
* **Pulmonary**: pleuritis, chronic cough.

## **4. Pathogenesis**

* Chronic infection linked to **defective Th1 immunity** (reduced IFN-γ response).
* Organism survives in macrophages → chronic granulomatous/foamy macrophage infiltrates.

## **6. Treatment**

**Principles**:

* Initial bactericidal IV phase → prolonged oral maintenance with CNS-penetrating agent to prevent relapse.

### **A) Standard regimen**

1. **Initial (2 weeks)**:
   1. **IV ceftriaxone 2 g od**  
       **OR**
   2. **IV penicillin G** 2–4 MU q4h + streptomycin 1 g IM od
2. **Maintenance (≥12 months; ≥24 months in CNS disease)**:
   1. **Co-trimoxazole 160/800 mg bd**

### **B) Alternatives**

* **Doxycycline 100 mg bd + hydroxychloroquine 200 mg tds** for ≥12–18 months.

### **C) Monitoring**

* PCR on follow-up biopsy or CSF if initially positive.
* Late relapse possible years after apparent cure.

## **Quick Reference Table**

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| **Feature** | ***Tropheryma whipplei*** |
| Gram stain | Weak Gram-positive coccobacillus |
| Acid-fast | Negative |
| Special stains | PAS-positive, diastase-resistant macrophages |
| Culture | Cell culture only (reference/research) |
| Common presentation | Malabsorption, arthritis, fever |
| Extraintestinal | CNS, cardiac, ocular, pulmonary |
| Diagnosis | Biopsy histology + PCR |
| First-line treatment | IV ceftriaxone × 2 wks → co-trimoxazole ≥12 mo |
| Prognosis | Fatal if untreated; CNS relapse risk high |