

Genitourinary Tuberculosis

History

5000 BC	Observed in humans
375 BC	Hippocrates described 'phthisis'
1696	Wiseman described 'scrofula & King's Evil'
1882	Koch's postulates organism in disease growth outwith body disease following infection
1882	Ehrlich discovered acid-fastness
1925	Calmette & Guerin generate BCG
1929	Medlar reported asymptomatic renal tubercles in pulmonary TB
1937	Wildbolz coined term 'genitourinary tuberculosis'
1943	Streptomycin discovered
1952	Isoniazid discovered
1966	Rifampicin discovered

Demographics

One third of world's population thought to be infected with tubercule bacillus
 Annual incidence of clinical TB ~ 10 million per year (mainly reactivation)
 Incidence falling in developed countries despite blip in late 80's/early 90's due to HIV/AIDS epidemic esp. in USA
 Incidence in undeveloped world appears to be static/rising, especially in countries with a large HIV burden (ie. Africa)

Worst TB incidence rates per capita in Africa, Cambodia and Haiti

Peak incidence in 20-40 age group worldwide

Male-female ratio 2:1

Aetiologic factors

- Virulence of mycobacterium strain
 - Cord factor - inhibits granuloma formation
 - Sulphatides - impairs macrophage phagocytosis
 - Lipoarabinomannan – inhibits macrophage killing
- Host factors - immunocompromise

Microbiology

Mycobacteria

- 2.4 um long x 0.5um wide
- Non-motile, non-flagellated
- Strict aerobes

Thick cell wall containing 4 complex layers of approx 50% lipids
Very difficult to stain (hot carbol-fuchsin)
Stain is 'fast' to acid or alcohol
Very slow growing – doubling time 16-20 hrs

4 mycobacteria strains cause human tuberculous disease, collectively (and unhelpfully) known as *m. tuberculosis* complex: *m. tuberculosis*, *m. bovis*, *m. leprae* and *m. africanum*. Mycobacteria tuberculosis accounts for most of the disease. Humans are the only reservoir of the disease. In practical terms GU TB is synonymous with *m. tuberculosis* infection.

Other non-tuberculous mycobacteria have only rarely been associated with genitourinary TB (*m. kansasii*, *m. avium intracellulare*)

Immunology

M. tuberculosis infection elicits a highly effective host immune response, characterised by cell-mediated immunity (type IV hypersensitivity).

Almost all *M. tuberculosis* infections are acquired by the inhalation of aerosolized droplet nuclei (1 to 5 µm), which reach the pulmonary alveoli and stimulate an acute inflammatory response. Neutrophils are inadequate to deal with the mycobacteria (thick cell walls resist degradation) which multiply, spreading first by way of the lymphatics and then through the blood stream.

Within about 4 weeks, the rate of multiplication decreases as T helper cells activate macrophages to more efficiently deal with the mycobacteria. This phase is characterised by the appearance of tubercles (fibroblasts surrounding lymphocytes, surrounding activated macrophages and giant cells (Langhans' cells), surrounding caseous necrosis).

What happens next depends upon the infecting dose, the virulence of the organism, and the immune competence of the host. Most persons clear the initial infection and develop no clinical illness. Often the only evidence of primary asymptomatic TB infection is a peripheral Ghon focus on CXR.

Approximately 5% of patients develop primary progressive TB, and a further 5-10% develop reactivation of viable dormant bacilli, which may begin to multiply and produce disease years later. This may occur after debilitating disease, trauma, corticosteroid administration, immuno-suppressive therapy, diabetes, and AIDS.

Extrapulmonary TB most commonly affects kidneys, lymph nodes, bone and intestine. It may develop as part of primary progressive TB in an immunocompromised host (ie HIV), or more commonly arise from reactivation without evidence of co-existing pulmonary TB. Renal involvement accounts for ~20%.

Pathology

Most tissue damage due to hypersensitivity reaction and not organism itself. Chronic inflammation causes fibrosis, scarring and dystrophic calcification.

Renal TB

Renal TB is usually caused by the activation of a prior blood-borne metastatic renal infection. Tubercle bacilli lodge in capillaries close to glomeruli and cause caseating necrosis. The healing process results in fibrous tissue and calcium salts being deposited, producing the classic calcified lesion. Calcified lesions may contain viable mycobacteria in up to 28% (Wong and Lan 1980). The fibrous tissue may cause strictures in the calyceal stem or at the pelviureteral junction. Hypertension may occur as a complication of severe unilateral TB and reduced renal blood flow.

Ureteric TB

Tuberculous ureteritis is always an extension of the disease from the kidney. The site most commonly affected is the ureterovesical junction. This is invariably secondary to extensive disease of the kidney and, if not recognized early, can rapidly cause complete destruction.

Bladder TB

Bladder lesions are without exception secondary to renal TB. The earliest forms of infection start around one or another ureteral orifice, which becomes red, inflamed, and edematous. Tuberculous ulcers may be present, but they are rare. Fibrosis starts around the ureteral orifice, which contracts and can either produce a stricture or become withdrawn, rigid, and dilated, assuming the classic golf-hole appearance. These ureters are usually rigid in the lower third and always give rise to ureteral reflux. Very occasionally fistulae may occur into rectum, prostate etc.

Epididymis TB

The disease usually starts in the globus minor, because it has a greater blood supply than other parts of the epididymis. tuberculous epididymitis may be the first and only presenting symptom of genitourinary TB. The usual presentation is a painful, inflamed scrotal swelling. The globus minor alone is affected in 40% of cases. In extensive disease, there may be generalized epididymal induration with beading of the palpable vas and even involvement of the testis, but this is now rare. In an earlier series (Ross et al, 1961), lesions were bilateral in 34% of cases, but today this presentation is unusual.

Other GU TB

TB testis is almost exclusively due to extension from epididymis. TB prostate, penis and uethra very rare.

Presentation

Often vague presentation with lethargy, malaise, low grade fever and weight loss. Bladder seeding presents with irritative LUTS. Fairly extensive upper tract destruction and stricturing needs to be present to give loin pain and haematuria. Occasionally lone epididymitis.

Examination may reveal thickened epididymis, beaded vas, coarse prostate. Upper abdo bruit in advanced renal destruction.

Diagnosis

Urine

50% microscopic haematuria

80% pyuria

proteinuria common

20% coexisting UTI – does not exclude TB

Urine Smear testing

Waxy coats difficult to get stain through

Ziehl-Neelson method uses hot carbolfuschin (red) with methylene blue or malachite green

Once absorbed stain is acid and alcohol fast

3-5 EMUs recommended

Fresh urine has higher yields

Even then sensitivity 22-81% (Mean 55%)

Worse if on antibiotics for presumed UTI

PCR method has positive predictive value of 95% if smear test positive but only 40-75% if negative – not much help!

Urine Culture

3-5 EMUs required (intermittent production of bacteria)

Each specimen split into 2 aliquots – one slant each

Lowenstein Jensen medium – M. tb, BCG, and other non-tuberculous mycobacteria;

Pyruvic Egg Medium with penicillin – M. bovis (anaerobic growth below medium)

Fresh urine has higher yields

? Better detection rates with auramine/rhodamine fluorescence microscopy, carbon-labelled CO₂

Mycobacteria species can reliably be determined by HPLC

Bloods

Typically ESR is raised in active infection

Tuberculin Testing

Used for the identification of latent TB infection

Mantoux test - Intradermal injection of tuberculin (purified protein derivative of killed cultured TB organisms)

Heaf test – six needles used to drive tuberculin into skin – popular in UK but manufacturer withdrew needles from market in 2005

Inflammatory reaction within 72 hours

Positive reaction indicative of previous infection – cannot be regarded as evidence of active infection

3 thresholds for determination of positivity dependent upon immunocompetence and exposure to mycobacteria

>= 5 mm HIV; organ transplants; contacts of index cases;

>= 10 mm IVDA; multiple medical co-morbidity; mycobacteria lab personnel; multiple co-habitees

>= 15 mm Normal subjects

Tuberculin test most helpful when patients previously known to be negative

False positives may occur with previous BCG vaccination

QuantiFERON TB-Gold

Whole blood assay for IgG produced by lymphocytes sensitised to M. tuberculosis.

Similar to tuberculin skin testing but simpler and is not a/w false positives with previous BCG injection– requires whole blood for incubation of lymphocytes with purified antigens derived solely from M tuberculosis.

As for tuberculin testing, cannot distinguish between prior or active infection, although degree of IgG response calculated by ELISPOT (enzyme-linked immunosorbent spot) from incubated lymphocytes may indicate likelihood of infection

Radiology

Cardinal features are calcification and distortion

CXR advisable in all cases to determine previous TB

Plain **KUB** important in determining extent of calcification

Lone ureteric calcification extremely rare – TB calcification intraluminal whereas schistosomiasis calcification is intramural

Most ureteric calcification extension from kidney

IVU excellent for delineating calyceal anatomy and distortion. Also provides an assessment of peristalsis and ureteric stricture.

Cystographic phase may show small contracted ‘thimble bladder’.

Computed Tomography not much more helpful over IVU but may help identifying location of early lesions and ruling out co-existent malignant tumours. Occasionally patients may present with papillary necrosis and obstruction (other causes memorised using acronym POSTCARD = pyelonephritis, obstruction, sickle-cell disease, TB, cirrhosis, analgaesics, renal vein thrombosis, diabetes)

Retrograde studies helpful in determining length of ureteric stricture and for lateralising studies

Renography useful for determining split function as a baseline and also for planning surgical intervention

Cystoscopy occasionally helpful. Campbells says biopsy contraindicated in the presence of acute tuberculous cystitis, presumably to reduce risk of extraperitoneal seeding/ haematogenous spread.

Management

Herd immunisation

1925 Calmette and Geurin developed a method of attenuating the virulence of *M. bovis* by repeated subculture – permanently avirulent strain called Bacillus Calmette Geurin.

Herd immunisation used on national scale in some countries including UK until recently. But controversial:

Variable protection (UK 80%, 0% in Southern India and Georgia (US))

Protection only lasts 15 years

Vaccine does not decrease incidence of clinical TB

Significant complication rate (lymphadenitis, lupus, BCGitis)

Due to low rates of infection and above problems, UK immunisation policy changed in Autumn 2005. In the UK, immunisation against TB with the BCG vaccine is offered to:

- Babies living in areas of the UK where there is a high rate of TB. That is, areas where the incidence of TB is 40 cases per 100,000 people per year, or greater.
- Babies whose parents or grandparents have lived in a country with a high rate of TB. That is, countries where the incidence of TB is 40 cases per 100,000 people per year, or greater.
- The following groups of people who have not previously been immunised.
 - Immigrants to the UK from countries where TB is common.
 - People at risk due to their job. For example, health workers, prison staff, etc.
 - Close contacts of people with active TB.
 - People who intend to live for one month or more in countries with a high TB rate.

Note: until 2005, all schoolchildren in the UK were routinely given the BCG vaccine at about the age of 13. The policy changed in Autumn 2005 and those now immunised are in the groups listed above. The policy change was due to the changing patterns of TB in the UK.

Antituberculous Chemotherapy

First-line drugs are isoniazid (INH), rifampicin, pyrazinamide, streptomycin, and ethambutol. First 4 bacteriocidal.

(i) Isoniazid (5mg/kg/day)

Isonicotinic acid hydrazide

Inhibits mycolase synthetase – therefore mycolic acid production – unique to mycobacteria

70% renal excretion of acetylated form

Dose reduction in hepatic failure (slow acetylation)

Side effects

Hepatotoxicity (10-20% 'transaminitis')

Occasionally severe hepatic necrosis

Peripheral neuropathy – due to enhanced pyridoxine (B6) excretion – therefore supplementation

- (ii) Rifampicin (10mg/kg/day)
 - From *Streptomyces Mediteraneii*
 - Inhibits DNA-dependent RNA polymerase
 - Lipid soluble therefore enters macrophages
 - Renal elimination
 - Side effects
 - Hepatotoxicity
 - Red discolouration (contact lenses)
 - Significant drug interaction (cytochrome p450)
- (iii) Pyrazinamide (20mg/kg/day)
 - From nicotinamide
 - Inhibits fatty acid synthetases
 - Renal excretion
 - Hepatotoxicity, nausea and vomiting
- (iv) Streptomycin (20mg/kg/day)
 - From *Streptomyces griseus*
 - Aminoglycoside – inhibits bacterial protein synthesis
 - Renal excretion
 - Ineffective against intracellular organisms
 - Ototoxicity
- (v) Ethambutol
 - Effective in resistant forms of the disease
 - Interferes with cell-wall synthesis
 - Renal elimination with high concentrations
 - Occasionally retrobulbar neuritis – heralded by red-green perception difficulty

Combination Chemotherapy

Prognosis before antibiotics dismal

2 year survival with active TB 50%

25% of all deaths in industrial revolution

TB paradigm for multidrug treatment to reduce drug therapy and reduce resistance

Current regimens complicated but all short-course regimes utilise initial treatment with INH, rifampicin and pyrazinamide

Current recommendation for drug-sensitive TB

2 months INH, rifampicin and pyrazinamide

4-7 months of INH and rifampicin (daily, biweekly or thrice weekly)

Impossible to isolate bacilli in urine after 2 weeks of chemotherapy

Multi-drug resistant TB (MDR-TB) declining – typically in failed treatment cases from high risk areas (Russia, India, Dom Rep)

Surgery

Previously surgery was integral to Mx of genitourinary TB

Combination chemotherapy has reduced indications for surgery considerably

Role of surgery in extensive disease remains controversial

Some believe that modern effective chemotherapy will kill all viable organisms and surgery should be reserved for treatment of complications after chemotherapy has halted disease process

Non-functioning symptomatic kidney

?Hypertensive kidney

Obstruction of renal unit

Failure to respond to antituberculous chemotherapy

NB. Lobectomy not routinely performed for residual lung disease post chemo)
However, others believe that despite sterile urine post-treatment, viable organisms remain and complication rates higher than after surgical intervention.

Nephrectomy for calcified non-functioning kidney

Osterhage (1980). Reviewed histological specimens from 300 patients following nephrectomy. 50% had evidence of viable bacteria (on histology only) despite sterile urine. Others report ~25% viable bacteria rate in calcified specimens. Flechner and Gow report increased complication rate in (n=4!) patients who did not have nephrectomy compared with those who did.

Nephrectomy for hypertension

Multiple early observational studies have reported a beneficial effect on hypertension following nephrectomy of a diseased tuberculous kidney

Overall ~ 2/3 patients said to benefit from surgery

However studies small, observational in nature, and ? controlled for chemotherapeutic agent. Campbells raises the possibility of selective renal vein renin sampling before considering nephrectomy in age group with many risk factors for nephrectomy

Ureteric Stricture Disease

VUJ > PUJ > Middle third

VUJ ~9% of patients

Often due to oedema which is satisfactorily treated with Abx

Can add in corticosteroids if necessary

Careful surveillance on chemotherapy – may worsen

Repeated dilatation can temporise (Murphy 1982)

Resection and re-implantation ideally for burnt out stricture

Psoas hitch/ Boari for strictures > 5cm

PUJ Uncommon – usually associated with non-functioning kidney

Temporise with stent whilst on chemotherapy

Careful surveillance

Ideally pyeloplasty for stable stricture after chemotherapy

Mid Stent vs. ??Davis intubation ureterostomy technique

Epididymectomy

Reserved for caseating granulomas not responding to anti-tuberculous

Drugs

Augmentation Cystoplasty

May be considered for severe irritative symptoms in concert with a low volume bladder (< 100 ml – Campbells)