At the end of this talk, you should be able to

- Understand the significance of GU TB today
- Understand why TB is so virulent
- Understand the pathogenesis of GU TB
- Diagnose GU TB
- Know the clinical manifestations of GU TB
- Manage GU TB including basic medical therapy
History

5000 BC - 1800 AD

- “consumption”
- “phthisis”
- “scrofula” - King’s evil
- vampirism
Industrial Revolution (1700-1900)

- Endemic
- 1/4 deaths in England
- 1880's - contagious
- TB sanitoriums - rich and poor
  - 50% of all who entered died in 5 years
- "white plague"

Guess who???

- Born 1810, Poland
- Child piano prodigy
- Romantic period
- Affair with writer George Sand

Frederik Chopin
died of TB 1849
1882 Koch’s postulates

Mycobacterium tuberculosis

1. Present in every diseased case
2. Isolated and grown in pure culture
3. Reproduced in healthy susceptible host
4. Recoverable from experimentally infected host

Noble prize 1905

Genitourinary tuberculosis

- Medlar 1926 pathologist
  - Microscopic bilateral lesions renal cortex
- Bryant 1870
  - Nephrectomy pyonephrosis
- Antituberculous drugs
  - Streptomycin 1944
  - Para-aminosalicylic acid 1946
  - Isoniazid 1952
  - Rifampicin 1966
Epidemiology

Worldwide

- 1/3 world population infected
  - 2 billion
- 8 million/year become ill
- 2 million/ year die
- >95% cases in developing world
- Single leading cause of death

WHO 2006
Worldwide Incidence

Cases per 100,000. WHO 2006

Global Incidence of TB

Annual number of new reported TB cases. WHO2006.
Why increased incidence?

- HIV/AIDS co-epidemic
- Increased immigration and travel
- Population growth in endemic areas
- Emergence of drug resistant strains
  - Prev tx, non-compliance, country of origin
- Neglect/breakdown of social and health infrastructure

Canada - Incidence

Constant since 2004 ~5 per 100,000
**BC - Incidence**

Higher than national average ~7.4 per 100,000 in 2004
3% overall decrease since 2003

**Sub-Vancouver - Incidence**

Highest in Downtown Eastside
Increase in City Centre, North East
Canada - Age group
Two peaks 25-34 and over 65

Canada - Birthplace

Source: Tuberculosis Prevention and Control, Public Health Agency of Canada
**Risk factors**

- Close contact with known/suspected case
- Immunocompromised
  - HIV/AIDS, steroids, DM, malignancy, renal failure
- Travel/immigration from endemic areas
- “Urban poor”
  - Aboriginal communities, homeless
- Crowded
  - Prisons, refugees, long term care facilities
- Persons who work with any of these groups

**HIV and TB**

- 12-50% HIV deaths caused by TB
- 1/3 HIV co-infected
- 50x more likely to develop active TB in lifetime (10%/year)
  - Non-HIV 10% lifetime
- 90% die within 2-3 mos, if no tx
- “co-epidemic”
Genitourinary TB

- 1.2% primary TB
- 6% extrapulmonary TB (US 2003)
- 15-20% extrapulmonary TB (worldwide 1999)

Microbiology
Mycobacterium species

5 closely related species causing TB:

- **M. tuberculosis**
  - Obligate anaerobe
  - Gram-positive
  - Thick, waxy cell wall
  - Acid-fast
  - **Survive alveolar mφ**
  - Caseous granuloma
  - Divide q15-20 HRS
  - 3-6 weeks culture

- **M. bovis**
  - GI via unpasteurized milk
  - Can be airborne
  - BCG, vaccine
  - No animal reservoirs
  - Airborne

- **M. africanum**
- **M. canetti**
- **M. microti**
**Caseous granuloma**

1° TB Ghon complex = granuloma + enlarged LN

- Caseous necrosis, surrounding epithelioid cells (mços)
- Mature reactive T cells
- Langhan’s giant cells

**Langhan’s giant cell**

- Mycobacterial infections
- Formed by fusion of macrophages (epithelioid cells)
- Multiple nuclei in horseshoe shape
**Miliary TB**

Erosion into lymphatic or blood vessel leads to lung dissemination

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**Sneaky bugger...**

- Thick cell wall
  - Multiplies in macrophages, not digested
- No known endotoxins or exotoxin
  - No immediate host response to infection
  - 2-12 wks before $10^3$ activates cellular immunity
- Travels via lymphatics to hilar LN -> bloodstream -> distant sites (before cellular immunity develops)
  - Bone, brain, kidney, upper lung - fertile land!!!
  - Liver, spleen, bone marrow - seeded but resistant to multiplication
Pathogenesis

The Natural History of TB Infection

Exposure to TB

Non-Infection (70-90%)

Dormant TB (90%) well
- never develop TB
- NOT infectious

Infection (10-30%)

Active TB (10%) ill
- 5% develop TB within 2 years
- 5% develop TB many years later

Untreated

50% die within 2 years

Treated

Cured
Pathogenesis of GU TB

- Lungs → bacillemia
- Renal cortex
- Medulla
- Calyces, pelvis
- Ureter
- Bladder
- Genital tract

Pathogenesis of GU TB

- Epididymis #1
- Testes
- Prostate #2
- Urethra, perineum (fistula)
- Penis

- Fallopian tubes #1
- Ovaries
- Endometrium #2
- Cervix

Rare
GU TB principles

- Incubation period 13-30 years
- Only 50-70% GU TB have history of TB
- ~25% GU TB have N CXR
- Local, not systemic symptoms
- Clinically unilateral but pathologically bilateral
- Spread by contiguity
- Uncommon in children (long latency)

Clinical Presentation
Clinical Presentation

History - key
- Male (5:3)
- 20-45 yrs, >60yrs
- Intermittent
- Painless frequency, nocturia
- Ureteral colic (flake of Ca or clot)
- Hematuria 10% gross, 50% microscopic
- Females: pelvic pain, infertility, irregular menses

Clinical Presentation

Physical exam
- Usually NO systemic sx
- Chest sx
- Flank mass
- Testicular/epididymal swelling
- Hydrocele
- Perineal sinus
- Beading of spermatic cord
Guess who?

- Born 1903, India
- Aka Eric Arthur Blair
- Author “1984” and “Animal Farm”

George Orwell

died of TB 1950

Diagnosis
Diagnosis

- Hx - symptoms, TB history
- PE
- PPD skin test
- Urinalysis
- Serial AM urine -> AFB, culture
- Urine PCR
- CXR
- Imaging - IVU, CT

Purified Protein Derivative Test

- Mantoux, Pirquet, tuberculin sensitivity test
- Delayed hypersensitivity reaction
- Glycerine extract of tuberculin (Ag)
- Intradermal injection
- Measure induration 48-72hrs later
- 3 cut points to improve specificity
PPD test

- Positive test means TB infection NOT necessarily TB disease
- Negative skin test does NOT r/o TB (88% sens)
- BCG vaccine does NOT make test positive except when administered <5yrs
**BCG Vaccine**

- Live attenuated strain of *M. bovis*
- *Bacille Calmette - Guerin*
  - Albert Calmette and Camille Guerin 1919
- 80% effective, lasts 15 years*
- Deltoid IM injection
  - Local skin reaction, keloid scar, poss abcess

**Urine exam**

- Urinalysis
  - Microscopic hematuria 50%
  - Sterile pyuria classic
- Urine culture and smear
  - 3 to 5 early AM samples
    - Intermittently excreted
  - AFB smear often negative (50% sn, 89% sp)
  - ~20% - 2º bacterial infection (coliforms)
- Culture (65-85% sn, 100% sp)
  - 6-8 wk on solid medium Lowenstein-Jensen
  - 1-3 wk on liquid medium Middlebrook
- **Seminal fluid, vaginal cultures usually negative - unreliable**
Urine PCR

- High sn (96%), sp (98%)
- 6 hours
- Highest sensitivity
  - cultures (37%)
  - bladder biopsies (46%)
  - intravenous pyelography (IVP) (88%)
  - PCR (95%)

Hemal et al, Oct 00

Imaging

- High dose IVU - traditional gold standard
- CT - new standard
- Pyelography ante/retrograde - limited use
- Plain Radiographs - important
  - CXR, spine XR, KUB XR
- US - limited value
  - Monitor size of lesions/bladder capacity
  - Scrotum
- Nuclear perfusion scans - function
- MRI, arteriography - little application
**IVU**

- Advantage over CT
  - More sens for urothelial mucosal changes
- Fibrosis/length of stricture
- Ureteral peristalsis, kidney function
- Calyceal distortion
- Calcifications
- Collecting system dilatation
- Bladder volume, filling defects, wall

- Findings NOT specific - “clinical correlation required”

**CT**

- Advantage over IVU
  - identify extrapulmonary manifestations
    - adrenal, prostatic, SV necrosis or caseation
  - More sensitive for calcifications
Retrograde Pyelography

Indications
1. Stricture at lower end of ureter
   - Length/amt of obstruction/dilatation
   - Can place stent at same time prn
2. Ureteral catheterization for selective renal urine cultures

Antegrade Pyelography

- Retrograde access not possible
- Aspirate pelvic urine, cavities
- Placement of nephrostomy tube
Endoscopy

- Rarely indicated
- Monitor response to treatment
- GA w/ muscle relaxant - risk of hemorrhage
- Bx to r/o malignancy
  - not advised prior to medical tx
  - contraindicated in acute TB cystitis
- Ureteroscopy to assess ureteral anatomy

Guess who???

- Born 1783, Caracas
- “El Libertador”
- President of
  Gran Colombia including
  Peru, Bolívia

Simón Bolívar
died of TB 1830
Clinical Manifestations

<table>
<thead>
<tr>
<th>Organ site</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal glands</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Persistent hematuria and pyuria, colic, calcifications, calciuria, renal failure</td>
</tr>
<tr>
<td>Ureters</td>
<td>Scarring, strictures</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Ureteral mental stenosis, lower urinary tract symptoms, contracted bladder</td>
</tr>
<tr>
<td>Prostate and urethra</td>
<td>Urethritis with ulcers, urethral stricture, prostatitis</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Epididymitis and ejaculatory duct scarring, seminal vesicle atrophy</td>
</tr>
<tr>
<td>Penis</td>
<td>Penile ulcers (sexually transmitted)</td>
</tr>
<tr>
<td>Scrotum</td>
<td>Painful scrotal mass with granulomatous epididymitis</td>
</tr>
<tr>
<td>Perineum</td>
<td>Abscess, fistula</td>
</tr>
</tbody>
</table>
Adrenal TB

Clinical
- Adrenal insufficiency (Addison’s diz)

Imaging
- Bilateral and asymmetrical
- Non-specific appearance
- Necrosis of gland
- Calcification, atrophy late
Adrenal TB

Figure 14. Adrenal tuberculosis in a 57-year-old

R adrenal mass
In phase

Maintains signal intensity
Out of phase (non sp)
Upper Tract TB

Kidney
Ureter

Upper Tract TB

Clinical
- Hematuria, pyuria
- Colic
- Renal failure
  - Obstructive uropathy
  - Intrinsic parenchymal infection
**Pathophysiology of Upper Tract TB**

Bacillemia → Renal cortex
- Microscopic foci near glomeruli
  - Reactivation of dormant infection
  - Acute - chronic inflammation
  - Granulomas
  - Langhans giant cells
  - Necrosis, abscess
  - Healing by fibrosis,
  - Deposition of parenchymal Ca^{2+}

→ Renal medulla
  - Papillary ischemia/necrosis
  - Sloughing → Colic

→ Renal papilla
  - Inflammation, mucosal ulcers
  - Total/segmental fibrosis
  - → UPJO, Hydro

→ Calyces
  - Ulcerations
  - Extensive calcification
  - → Renal calculi (24%)
  - Infundibular stenoses
  - → Calyceal abscess

→ Pelvis

→ Ureter

- Early "moth-eaten" calyces
- Cavitations of papillary necrosis
- Filling defects (calcified)
- Hydro/pyonephrosis
  - Papillary necrosis → Debris in collecting system
- Calyceal dilatation, infundibular stricture/stenosis
  - "phantom calyx"
  - Total calyceal stricture

**Renal TB**

- Early "moth-eaten" calyces
- Cavitations of papillary necrosis
- Filling defects (calcified)
- Hydro/pyonephrosis
  - Papillary necrosis → Debris in collecting system
- Calyceal dilatation, infundibular stricture/stenosis
  - "phantom calyx"
  - Total calyceal stricture
Renal TB

IVU faint outline of enlarged kidney
L autonephrectomy!

RP: calyceal dilatation, infundibular stenoses, contracted pelvis

Renal TB

CT of same pt
- Calyceal dilatation
- Marked cortical thinning
- L psoas abcess
- Multiple Ca$^{2+}$
Renal TB

Late atrophic, dystrophic calcification - putty kidney

Ureteral TB

- Extension from kidney
- Fibrosis, stricture

- Most common site
  UVJ then distal ureter
- UVJ stricture usually <5cm

- Rare UPJ, midureter
Ureteral TB

- Initial dilatation and ragged irregularity of lumen
  "sawtooth appearance"
- Mucosal erosions, ulcers

• Later, ureter may become straight rigid tube
  "pipestem ureter"
  - Fibrosis, calcification wall (rare)
  - Shortens

Ureteral TB

- Healing with associated fibrosis may produce a "beaded" or "corkscrew" ureter
**Lower Tract TB**

- Bladder
- Urethra

**Bladder TB**

- Starts around orifice (descending infection)
- Inflammatory bullous edema
- Follow by granulation
- “Golf-hole orifice”
  - Withdrawn, fibrotic, dilated
- Ulcers rare
Bladder TB

- Calcification in wall
- Thick, reduced capacity bladder
  "thimble bladder"

R U/O stricture
Thimble bladder
**Urethral TB**

- Rare despite constant exposure to infected urine
- Usu from *prostate*

- Initial urethral discharge
- Beefy redness of inflamed urethra
- Superficial ulcerations
- Dilatation of prostatic urethra
- Urethral strictures

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**Male Genital TB**

- Epididymis
- Testis
- Prostate
- Penis
Epididymal TB

- Rare but #1 site of genital TB
- May be first and only site of GU TB
- 50-75% genital TB will have abnormal urinary tract - MUST INVESTIGATE!

- Hematogenous primarily
- Globus minor alone affected in 40%
  - Most blood supply

Epididymal TB

- Young, sexually active males (infertile)
- 70% have previous TB history
- Infertility
- Hematospermia
- Painless epididymal nodule or thickening
- Painful swelling of scrotum
  - Acutely usually epididymorchitis
**Epididymal TB**

- Diffusely/nodularly enlarged hetero/homogeneously hypoechoic lesions (granulomas)

**Testicular/Scrotal TB**

- Usually assoc with TB epididymitis
- Direct extension from epididymis
  - Sinuses/fistulae to scrotum
    - “watering can” scrotum
    - Abscesses
    - Thickened skin
  - Calcifications
  - Hydrocele
**TB Epididymo-orchitis**

- Nodular enlargement head, tail epididymis
- Caseous granulomas
- Heterogeneously hypoechoic lesions in testis

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**Epididymal TB & Infertility**

- Obstructive azospermia
  - Epididymal scarring
  - Multiple vasal obstructions
- Not amenable to surgery
- IVF/ICSI required
- Sperm retrieval and ICSI in non-TB vs TB obstructive azospermia similar outcomes:
  - Embryo quality, pregnancy (Moon et al 99)
Prostatic TB
- Uncommon
- Incidental finding post TURP
- Hematogenous primarily

- “Golf hole” dilatation of prostatic duct
- Nodular prostate - mimic ca
  - Disappears after adequate tx
  - Cavitation -> perineal sinus, fistulae

Penile TB
- Uncommon
- Routes
  - Hematogenous
  - Ritual circumcision (pulm)!
  - Conjugal spread

- Superficial ulcer of glans
- Solid nodule
- Can cause cavernositis with urethral involvement
- R/o ca, other infections
Female Genital TB

- Fallopian tubes
- Ovaries
- Uterus
- Cervix

Female Genital TB

- Amenorrhea
- Menstrual irregularities
- Pelvic pain
- Infertility
Female Genital TB

- Hydro/pyosalpinx
- Tuboovarian abcess
- Hysterosalpingogram
  - Ca\(^{2+}\) tubes, ovaries
  - “beaded” and “rigid pipe” tubes
- Tubal obstruction
  - most common
- Tubal dilatation
- Peritubular adhesions
- Endometrial adhesions

Management

Medical
Surgical
Medical

- MULTI-DRUG therapy!!
  - Decrease length of course
  - Decrease drug resistance
- Treatment as for pulmonary TB and other extrapulmonary TB
- 6-9 months of therapy
- 6 month = 9 month except for TB osteomyelitis, TB meningitis, disseminated TB

ACTIVE TB - standard “short course”
- 3-4 drugs for 2 months (RIPE); foll by 2 drugs for 4 months
  - Rifampin
  - Isoniazid (INH)
  - Pyrazinamide
  - Ethambutol or Streptomycin
- Foll by INH and Rifampin - 2-3x/wk
- LATENT TB - 6-9 mos isoniazid only
Follow-up

- Considered cured by 6 mos
  - ~ 2-3% relapse rate
- F/U 3, 6, 12 mos AFTER chemotx
- 3 consecutive AM samples cultured at EACH visit
- LFTs
- IVP
**Corticosteroids**

- Use anecdotal
- ↓ inflammation, stricture formation
- Only proven for TB meningitis, TB pericarditis
- Prednisolone 20mg tid, taper 4-8 wks

**Response**

- Sterile urine after 2 wks chemotx for renal TB
- But 50% show active TB on histology
- High response to short course 2°
  1. Fewer bugs in renal TB than pulmonary
  2. High concentrations RIPS urine
  3. INH, rifampin pass freely into renal cavities in high concentrations
  4. All first-line drugs reach adequate levels in kidneys, ureters, bladder, prostate
Drug resistance

- MDR-TB - resistant to INH AND rifampin
- XDR-TB “extensively” DR=MDR-TB + quinolone resistance + resistance to kanamycin, capreomycin, amikacin (HIV)
- Mortality 80%
- 2% (97 WHO), 1.6% (05 Canada)

Guess who???

- Born 1841
- 7th prime minister (1896-1911) $5 bill
- Quebec born
- Longest consecutive tenure as PM 15yrs

Sir Wilfred Laurier
died of TB 1919
**Rifampin**

- Bactericidal
- Inhibits RNA transcription (blocks RNA polymerase)

Side effects
- Significant drug interactions (CYP450)
  - ↑ metabolism OCP, warfarin, cyclosporine, tacrolimus
- Anti-retroviral interactions
- Hepatotoxic, flu-like sx
- CNS effects - headache, fever, ataxia
- Orange bodily fluids (stain contacts)

**Isoniazid**

- Isonicotinic acid hydrazide (INH)
- Bactericidal
- Inhibits mycolic acid synthesis

Side effects
- 10-20% hepatitis in 6-8 wks tx
  - transaminases prior to chemotx
- Peripheral neuropathy, encephalopathy
  - Pyridoxine supplementation
**Pyrazinamide**

- Bactericidal
- Inhibits fatty acid synthesis

Side effects
- Hepatotoxic #1 culprit in cocktail
- Arthralgia - most common
- Hyperuricemia - gout

**Ethambutol**

- Bacteriostatic - (the only one)
- Inhibits cell wall synthesis

Side effects
- Optic neuritis - colour blindness, blurred vision (reversible early)
- Hyperuricemia (like P) - gout
Streptomycin

- Aminoglycoside (like gentamicin)
- Bacteriocidal
- Inhibits protein synthesis

Side effects
- Ototoxic - vestibular
- Nephrotoxic

Surgical

- Adjuvant to medical therapy
- Organ preservation and reconstruction rather than excision
- Only after 4-6 wks chemotx
Excisional techniques

- Nephrectomy
- Partial nephrectomy
- Abscess drainage
- Epididymectomy

Nephrectomy

Indications
1. Extensive disease in whole kidney, with HTN and UPJO
2. Coexisting renal carcinoma
3. Non-functioning kidney +/- calcification

50% of nephrectomy specimens show active TB despite sterile urine after chemotx (Osterhage et al, 1980)
**Nephrectomy**

- Open approach most common
- Inflammation, scarring
- Increased perihilar LN and abnormal hilum 55% (Manohar et al, 07)
- Laparoscopy possible in experienced hands (Hemal et al, 00)
- Comparable OR time, blood loss, convalescence to other simple lap nx (Chibber et al, 05)

**Partial Nephrectomy**

**Indications**

1. Localized polar lesion with calcification which fails to respond after 6 wks intensive chemotx
2. Area of calcification slowly increasing in size and threatening to destroy whole kidney

Not justified in absence of calcification - can treat effectively with chemotx
Abscess Drainage

- Open drainage not necessary
- Percutaneous drainage adequate with medical therapy

Epididymectomy

Indications for scrotal exploration:
1. Caseating abscess not responding to chemotx
2. Firm swelling unchanged or slowly increased in size despite antibiotic or anti-TB chemotx
6% risk of testicular atrophy
5% risk of orchiectomy
Scrotal approach
Reconstructive Surgery

- Ureteral strictures
- Augmentation cystoplasty
- Urinary conduit diversion
- Orthotopic neobladder

Ureteral Strictures

- Decompress acutely and during medical therapy
  - Stent/PCN
- Recur often
  - Regular imaging f/u
- UPJ
- Mid - rare
- Distal #2
- UVJ #1
**Ureteral Strictures**

Stent/PCN during medical rx
- ↓ renal loss, ↑ chance of reconstruction

- Ureteral strictures in 84 renal units (Shin et al 02)
  - Meds alone (37 RU)
  - Meds + stent (28 RU)
  - Meds + PCN (19 RU)

- Nephrectomy rate
  - 73% meds alone vs 34% stent/PCN
- Reconstruction rate
  - 8% meds alone vs 49% stent/PCN
- Spontaneous resolution of stricture ~19% both

---

**UPJ strictures**

- Perc NT advantage - can irrigate meds into pelvis
  - Rarely necessary since UPJ stricture associated with complete kidney destruction
- Endopyelotomy/dilatation
- Pyeloplasty
**Mid/distal strictures**

- Edema - can resolve with chemotx alone
- Monitor with IVU or CT during tx
- No change
  - after 3 wk chemo -> try steroids
  - after 6wks chemo -> dilatation or reimplantation

**Distal ureter/UVJ**

- UVJ obstruction - 9% GU TB
- <5cm starting at UO
- Excise entire stricture
- Reimplantation
  - Non-refluxing technique
  - Submucosal tunnel >2cm
  - Difficult in TB cystitis bladder (contracted)
- >5cm -> psoas hitch, boari flap
- Avoid diseased bladder (usu periorifice)
Bladder augmentation

- Indications
  - Intolerable frequency with pain, urgency, hematuria
  - Capacity < 100cc
  - Creatinine clearance > 15ml/min

Urinary Diversion

- Indications for permanent conduit diversion
  - Intolerable diurnal sx with incontinence not responsive to chemotx or bladder dilatation
  - Psychiatric disturbance or obvious subnormal intelligence (precludes augment)
  - Enuresis not related to small capacity

- Orthotopic diversion possible in select population
Take home messages

TB or not TB?

The answers...

- High incidence, prevalence TB
- GU TB uncommon, 1° immigrants
- “The Great Pretender”
- Serial am urine samples x 3
- Granulomas, calcification, fibrosis
- Can’t go wrong with CT (except testes)
- Medical Rx (RIPES) #1 - good response
- Surgery adjunct
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