

Anti TNF Inflammatory Bowel Disease and infection



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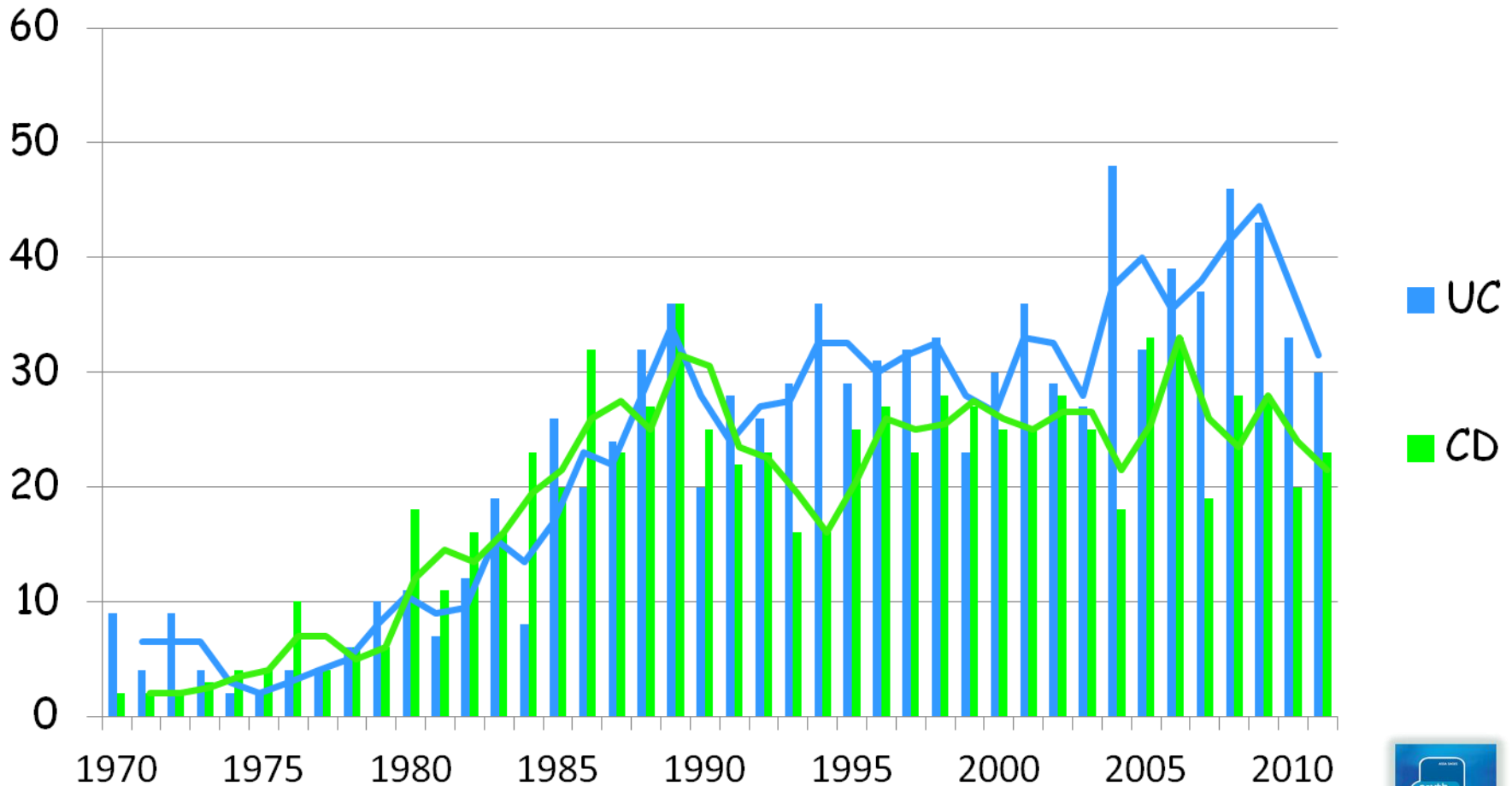
Epidemiology of IBD

- Changed over the past 50 years
- Increase in the incidence of UC and CD
- Initially an increase in cases of UC
- Followed 10-15 years later by CD
- Trend has reached a plateau in the West
- Ongoing in the developing world: SE Asia
- The incidence in children also increasing

Review. Scand J Gastroenterol 2001

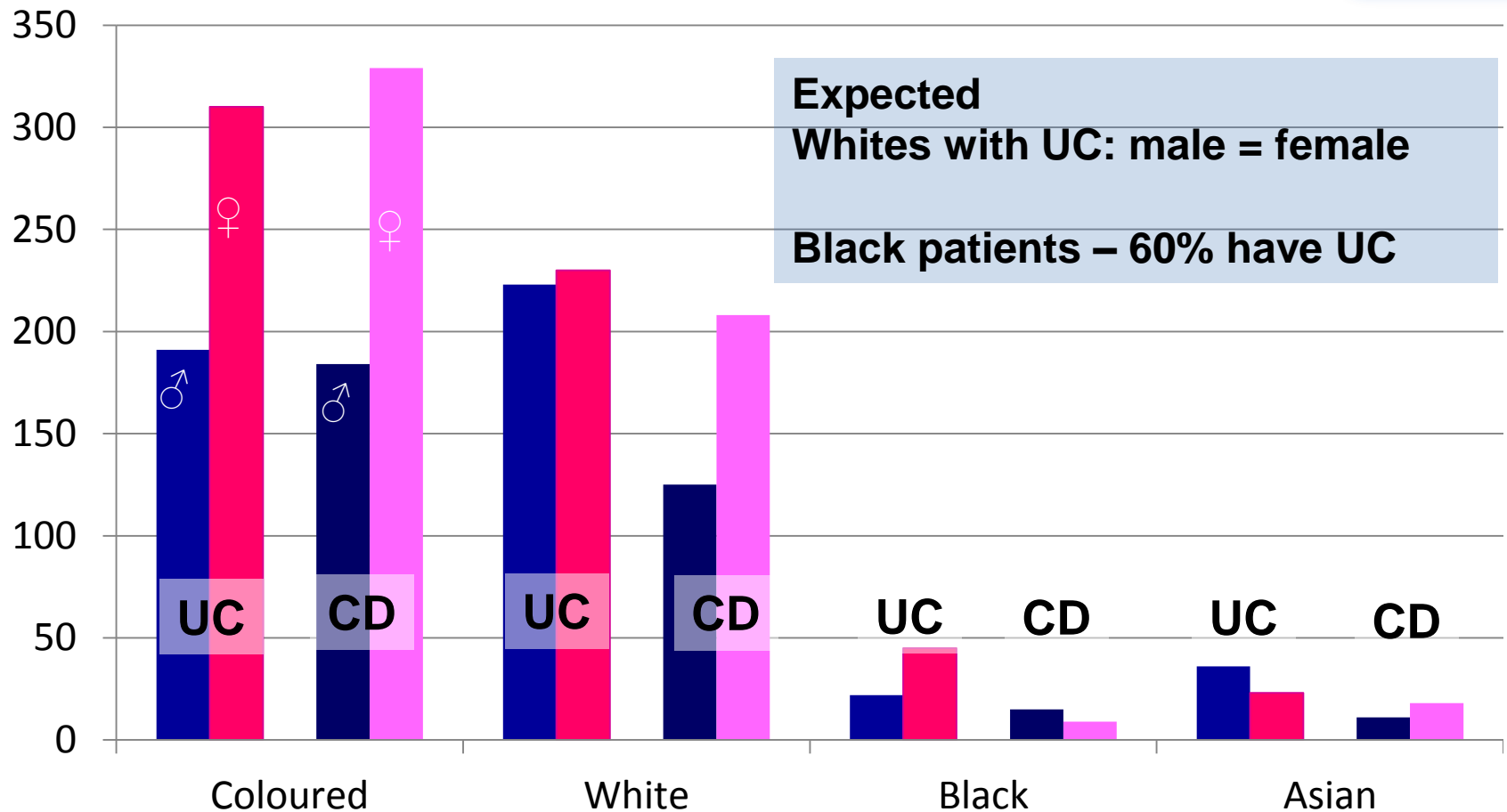
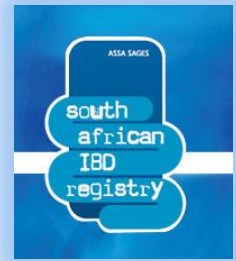
A Critical Review of Epidemiological Studies in Inflammatory Bowel Disease

IBD Cases per Year: UC vs. CD 1970 - 2010

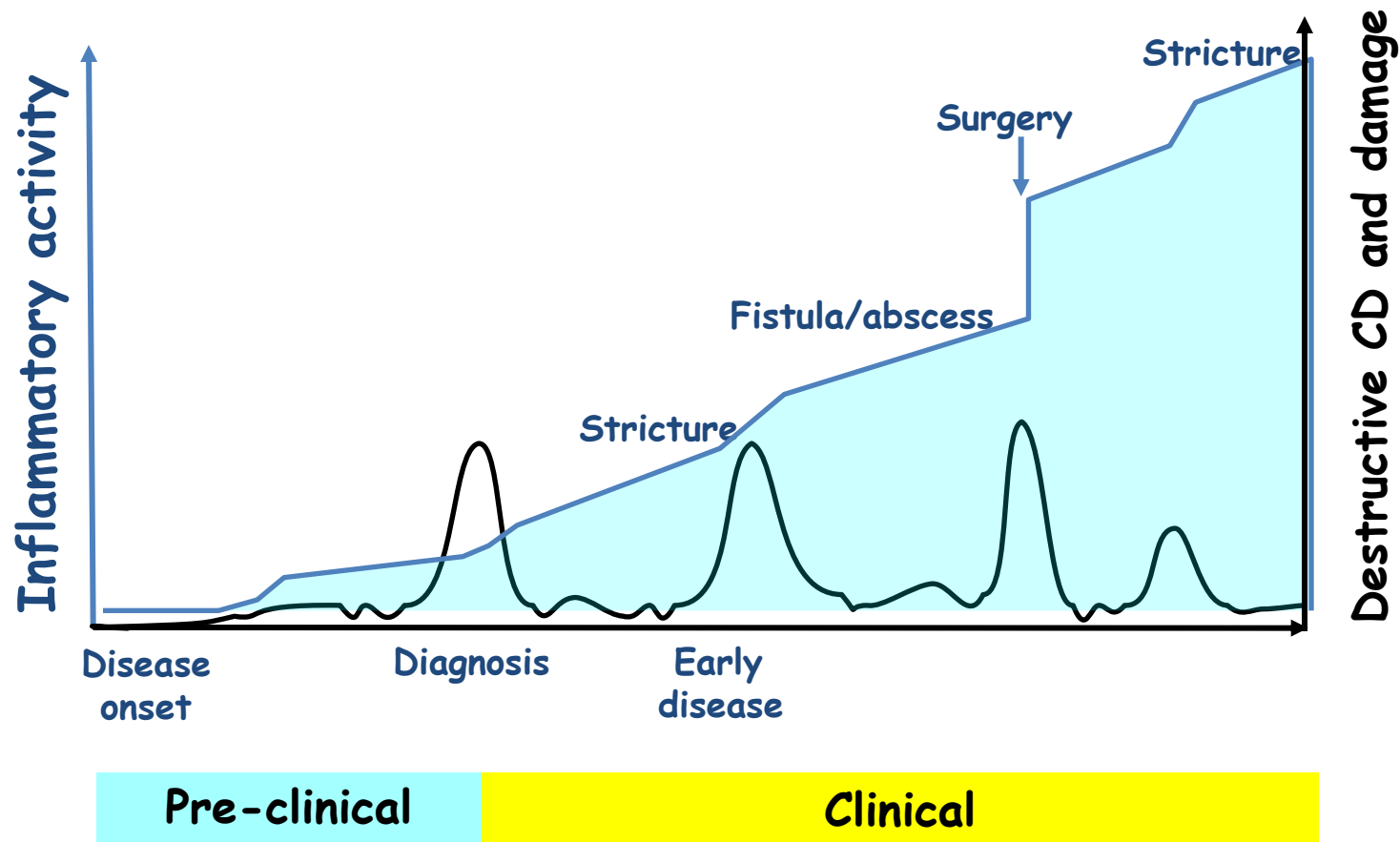


Gender Differences vs. Ethnicity

n = 1,979 08/2013

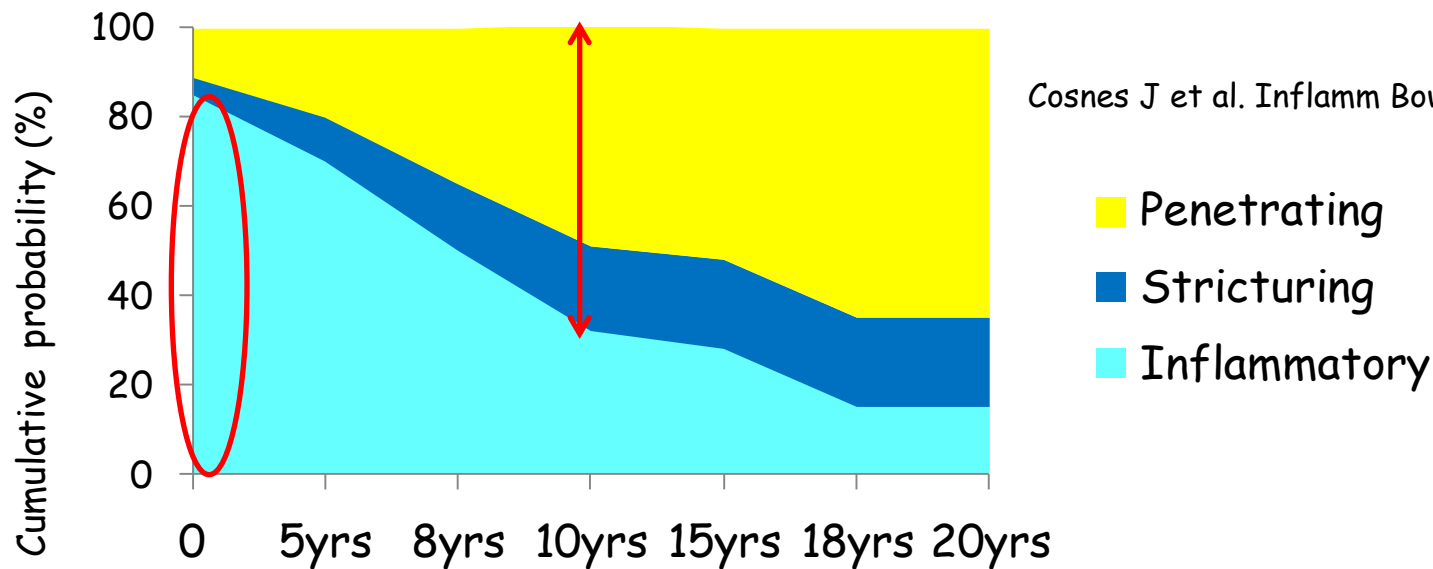


Progression of damage and inflammation



CD is a chronic progressive and destructive disease

Disease behaviour evolves with time.

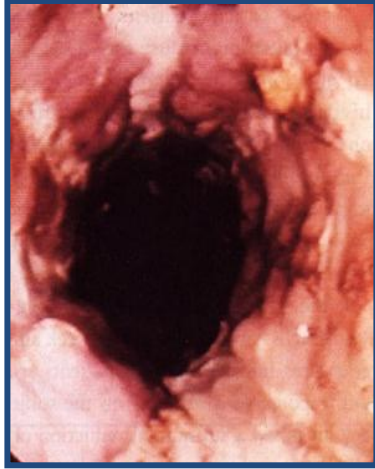


Hospitalisations

At 20 yrs:

80% have had surgery

Biologics in IBD



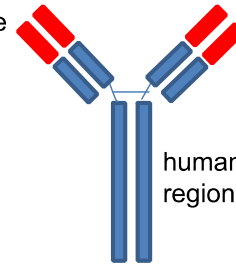
M Hendrick et al

Treatment of Crohn's Disease with Anti- Tumor Necrosis Factor Chimeric Monoclonal Antibody (CA2)

Gastroenterology 1995

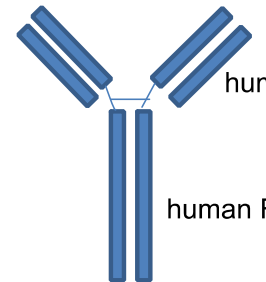


Murine variable region



Infiximab

human constant region



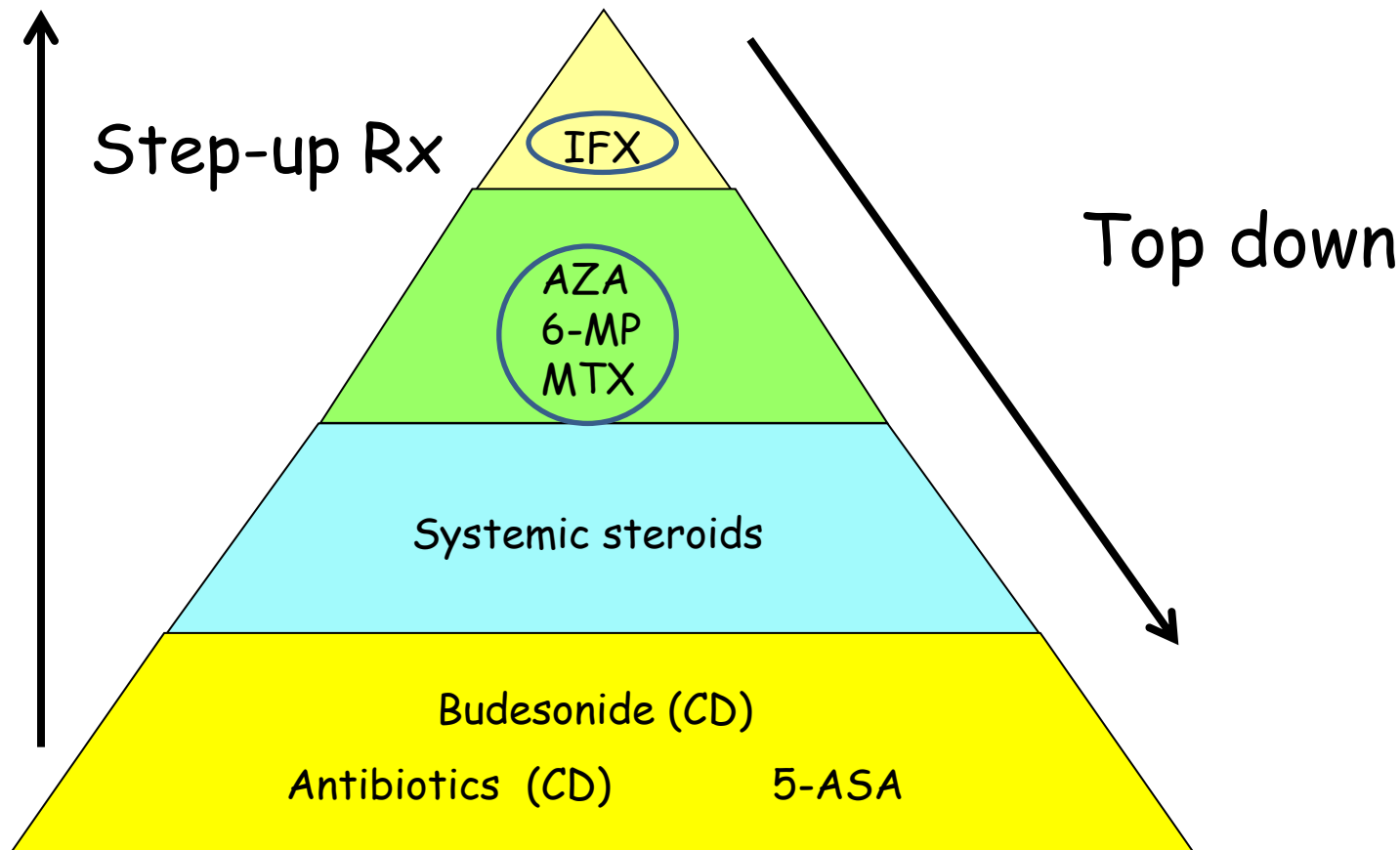
adalimumab

- Potential to modify natural history
- Rapid healing of the mucosa
- Adalimumab and infliximab available: anti-TNFs

Current approach to IBD therapy

Accelerated step-up Rx: anti-TNF within 3/12

Top down RX: anti-TNF at diagnosis (fistulising CD)



Tuberculosis and Anti-TNF Therapy: South African Considerations

WHO Global TB Report 2012

8.7 million new cases of TB

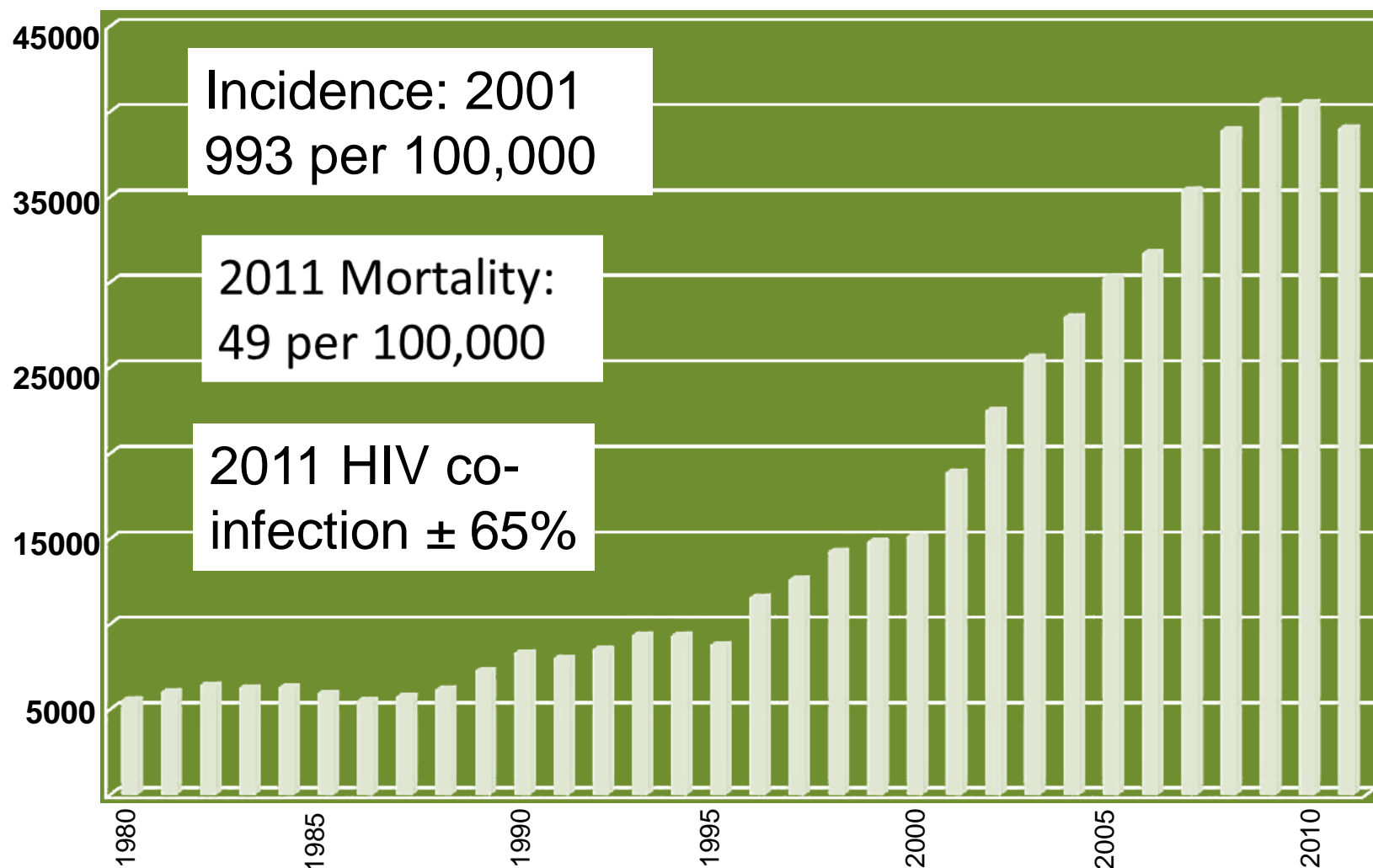
13% HIV co-infected

1.4 million TB deaths

2 billion people with latent TB

Trends in TB Notifications in SA: 1980- 2010

Mvusi L., Department of Health, April 2013



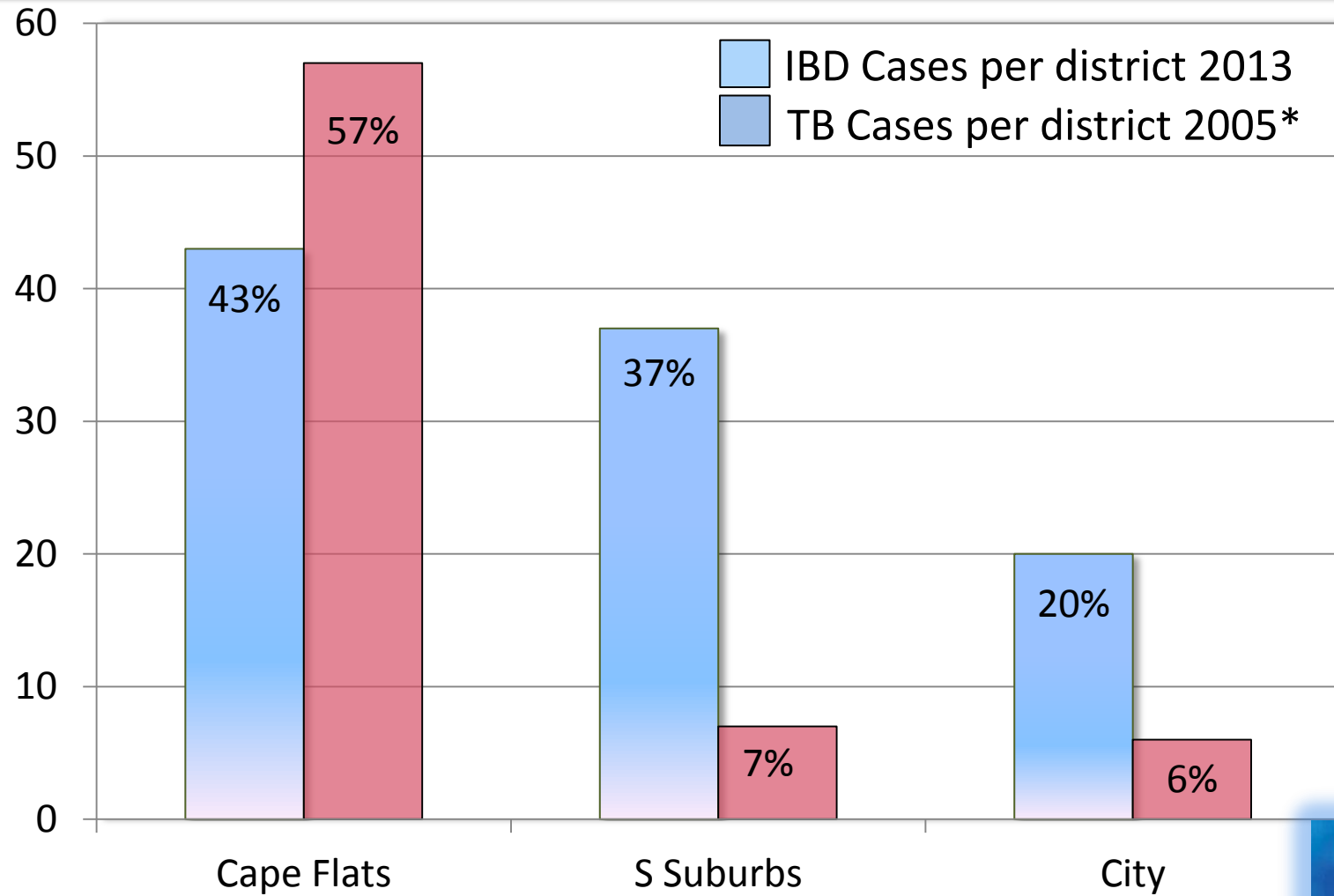
A descriptive study of Tuberculosis in an inflammatory bowel disease cohort from Cape Town

- Retrospective study of 615 IBD patients
 - History of TB treatment
 - x-ray evidence of TB,
 - histology and microbiology
- **72 patients (11.7%)** had TB

Half occurred before the diagnosis of IBD
Coloured ethnicity only risk factor for TB

Distribution of IBD and TB Cases per District

n = 1,395



* Cloete K, Western Cape TB & HIV Programme Report 2006

Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening

- Single centre Spanish study 2000 - 2011
- 423 patients on anti-TNF
- 6.9% tested positive for latent TB → prophylaxis
 - 7 patients (1.6%) developed TB
 - 6 screened negative for TB
 - 1 had a positive TST and developed TB on INH prophylaxis

Only 3 patients restarted anti-TNF therapy at a later stage

Tuberculin Skin Testing (TST)

Sensitivity reduced

- Malnutrition
- Active TB
- Crohn's disease*
- Immune suppression

Specificity reduced

- BCG vaccination
- Non-TB mycobacteria

In addition

- 2 healthcare visits – 10% drop out
- Variability = SD 3mm
- Boosting



*Verrier Jones J *et al Gut* 1969

Latent Tuberculosis in Cape Town

- 77 asymptomatic volunteers
- No active TB
- HIV negative
- 66% TST \oplus cut-off 5mm
- 64% TST \oplus cut-off 10mm
- 58% TST \oplus cut-off 15mm



World Health
Organization

www.who.int/tb

TUBERCULOSIS

IGRA TB TESTS

Policy Statement 2011

**The use of TB Interferon-Gamma Release Assays
(IGRAs) in Low- and Middle-income Countries**

“IGRS’s and TST appeared to have only modest predictive value and did not help identify those who were at highest risk of those who are at risk of progression of disease”

Testing prior to initiating anti-TNF testing

Low prevalence TB

High prevalence TB

CONCOMITANT MEDICATION

Steroids, biological therapies,
Azathiaprine and Methotrexate

DEMOGRAPHIC INFORMATION

BCG vaccination,
Residence in a high TB
prevalence country

TST Tuberculin Skin Test

CHEST X-RAY

GAMMA INTERFERON ASSAY

Positive > 5 mm

Negative < 5 mm

Positive nodules,
fibrotic scars, calcified
granulomas and basal
pleura

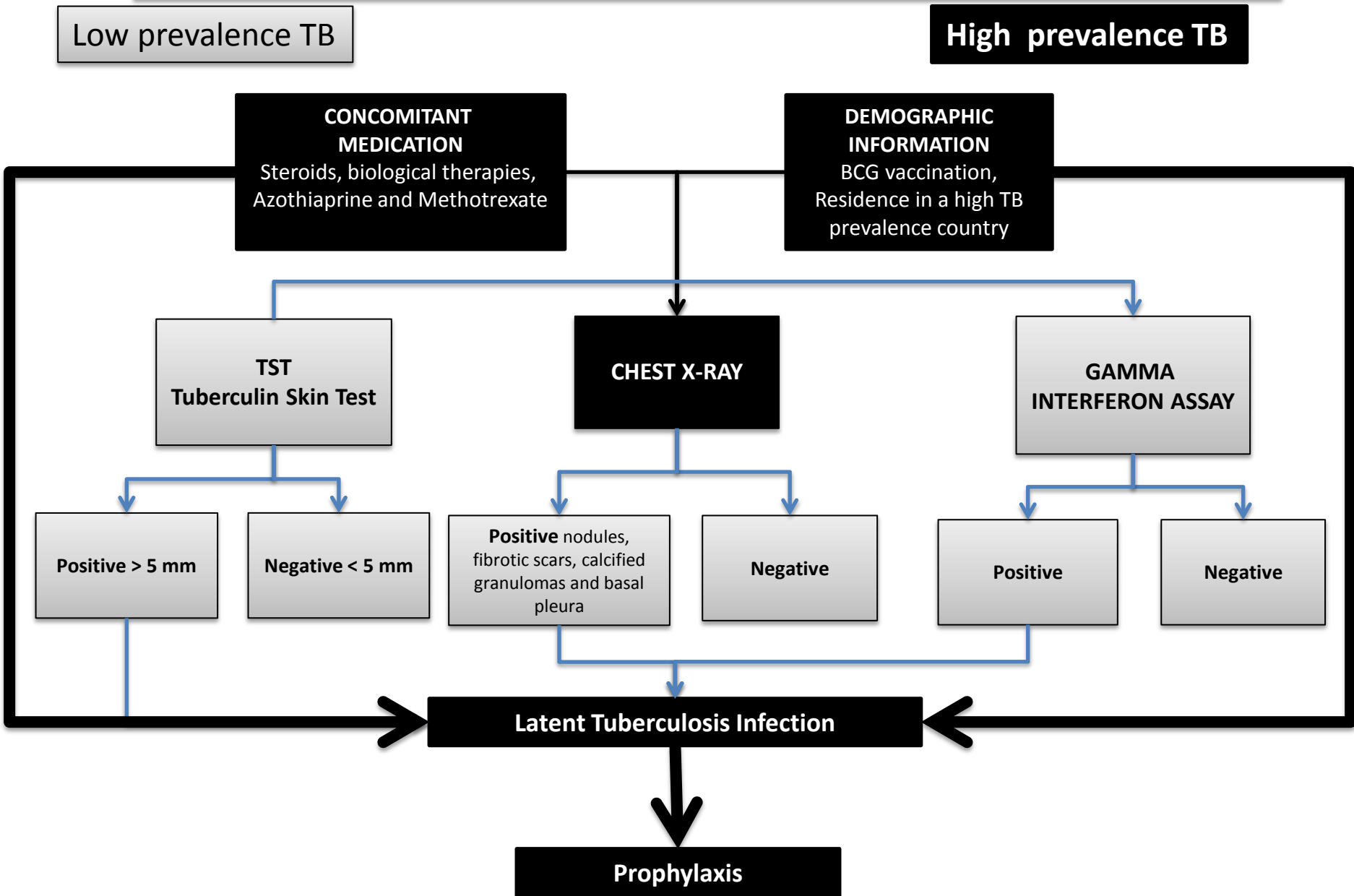
Negative

Positive

Negative

Latent Tuberculosis Infection

Prophylaxis



Isoniazid for preventing tuberculosis in the non-HIV infected person

Method

- 11 trials involving 73,375 patients
- Broad spectrum of patients
- INH prophylaxis 6 and 12 months vs. Placebo
- Outcomes active TB, TB death, INH toxicity

Results

- 60% reduction in active TB over 2yrs
- Treat 35 6 months to prevent 1 case of active TB
- 1 in 200 will develop drug induced hepatitis

Treatment of latent TB infection in HIV infected persons

- Method
 - 12 trials, 8,578 participants
 - TB preventative Rx vs. Placebo
 - Participants could be TST positive or negative
- TB prophylaxis a 32% lower risk of active TB
 - RR 0.68, 95% CI 0.54 to 0.85
- Benefit similar with all TB prophylaxis regimes used.

The recommendations in SARAA ?

"Treatment choice for latency"

- INH - RIF combination x 3 months
- INH alone for 6 to 9 months.
- Combination
- Rifampicin - INH for 3 months is advised in certain circumstances only.

Anti-TNF and Hepatitis

- Hepatitis B
- Worsening
 - those with evidence of active viral replication,
- Reactivation
 - those who had evidence of quiescent infection
 - Incidence <2%
 - Fulminant hepatic failure

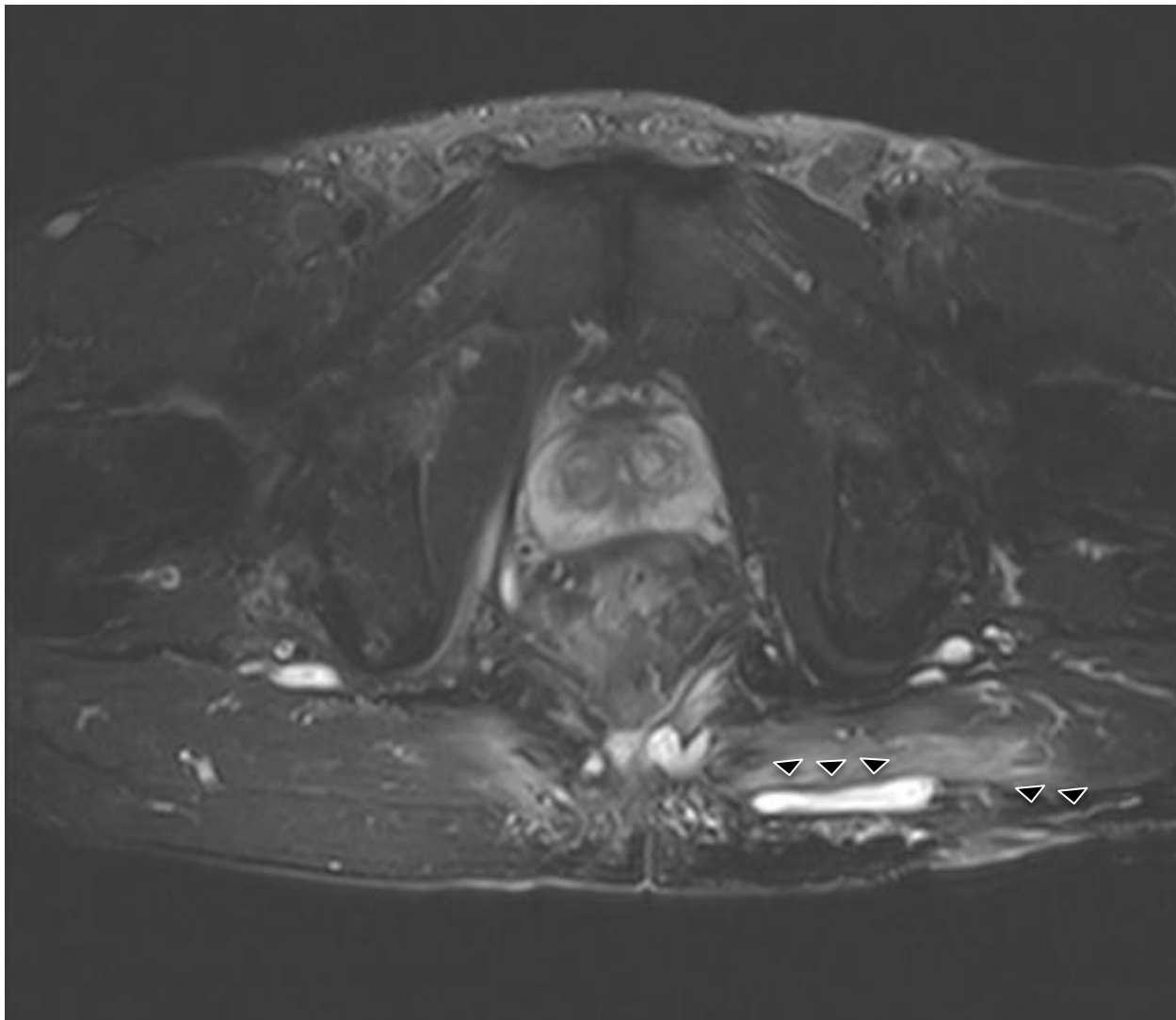
Hepatitis C No risk

Serious Infection Risk with Anti -TNF

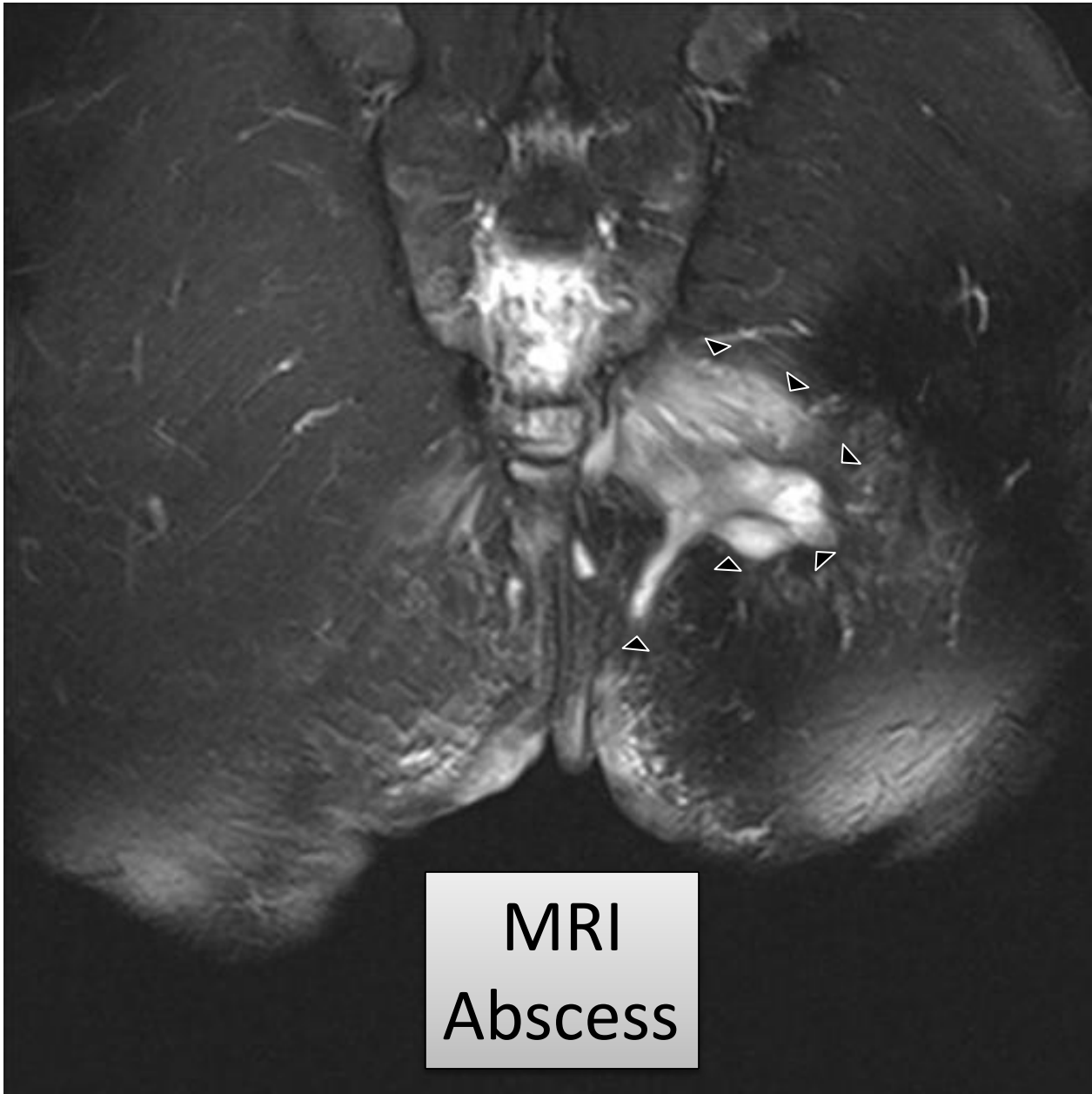
- Infection requiring intravenous antibiotics or hospitalization.
- This rate expressed as patient-years of follow-up.
 - 42/100,000 in the anti-TNF group
 - 32/100,000 in the naive group.
- Greatest Risk
 - the over 60's
 - first 6 months of treatment
 - Corticosteroid therapy

Perianal Disease and Infection Risk





MRI
Fistula



Suspected sepsis in the surgical candidate

- Assess for collections.
 - Aspiration
 - Drain
 - Image guided or surgical.
- Clinical and further imaging
 - confirm the resolution
- Prior to Biological Therapy.

Risk of Surgery **USA** a cohort

151 urgent colectomies

only 17 had received infliximab

- Complications rate
- 37% who received infliximab
- 27% in those who did not. no difference
- Five patients who received additional cyclosporin and anti TNF had an 80 % complication rate .

Risk of Surgery

Dutch Cohort Urgent and Elective

- 72 patients
 - 33 who underwent a 1-stage procedure
 - 39 who had a 2-stage surgery.
- In the 2-stage group (12 months prior to surgery)
 - 17 had previous infliximab therapy
- Complication rates
 - total infectious, non-infectious and pelvic sepsis
 - similar for infliximab and the naive patients.

Risk of Surgery

Dutch Cohort Urgent and Elective

- 72 patients
 - 33 who underwent a 1-stage procedure
 - 39 who had a 2-stage surgery.
- 1-stage group anti-TNF (7 months before surgery)
 - 21 anti-TNF patients
 - five developed pelvic sepsis
 - 12 naive group.
 - No pelvic sepsis
- Non-infectious complications.
 - Also commoner in those receiving anti-TNF

Risk of Surgery

Danish National Study

- Over 10 years
- 2293 surgery for Crohn's disease
- 214 of whom were exposed to anti TNF therapy.
- No increase
 - death
 - abscess drainage
 - anastomosis leakage
 - reoperation within 30 days.

Risk of Surgery

Danish National Study

Over 10 years

2293 surgery for Crohn's disease

214 of whom were exposed to anti-TNF therapy.

Sub-analyses

No increased risks when anti-TNF agents were given within 14 days prior to surgery

Nørgaard BM, Nielsen J, Qvist N. et al. Pre-operative use of anti-TNF-alpha agents a nationwide cohort study Aliment Pharmacology Therapeutics 2013

Surgery and Anti-TNF

- Adopt a cautious approach
- Elective surgery
 - longest window possible without anti-TNF therapy
- Salvage surgery
 - be vigilant for complications surgery is required when these drugs fail when used for salvage therapy.

Conclusion

- Treatment paradigms
- Risks
 - The TB Risk
 - Prophylaxis
- Exclude infection prior to use.
- Vigilant for infection when surgery performed.
- Need a medical gastroenterologist