Challenges and Strategies in the management of patients with Haemophilia and Inhibitors A South African Experience

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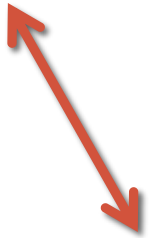
Introduction

- South Africa: a brief perspective of haemophilia care
- Challenges and Strategies
  - Prevention
  - Management
- An illustration from Limpopo Province
- The future



Inhibitors in Haemophilia

- Affect about 20-30% of people with severe haemophilia A
- And 3-5% of people with haemophilia B

- Usually develop within the first 20 exposures to clotting factor concentrate
- High titre ≥ 5 BU/ml, low titre < 5 BU/ml
- High responder, low responder

Haemophilia in South Africa

Expected Epidemiology

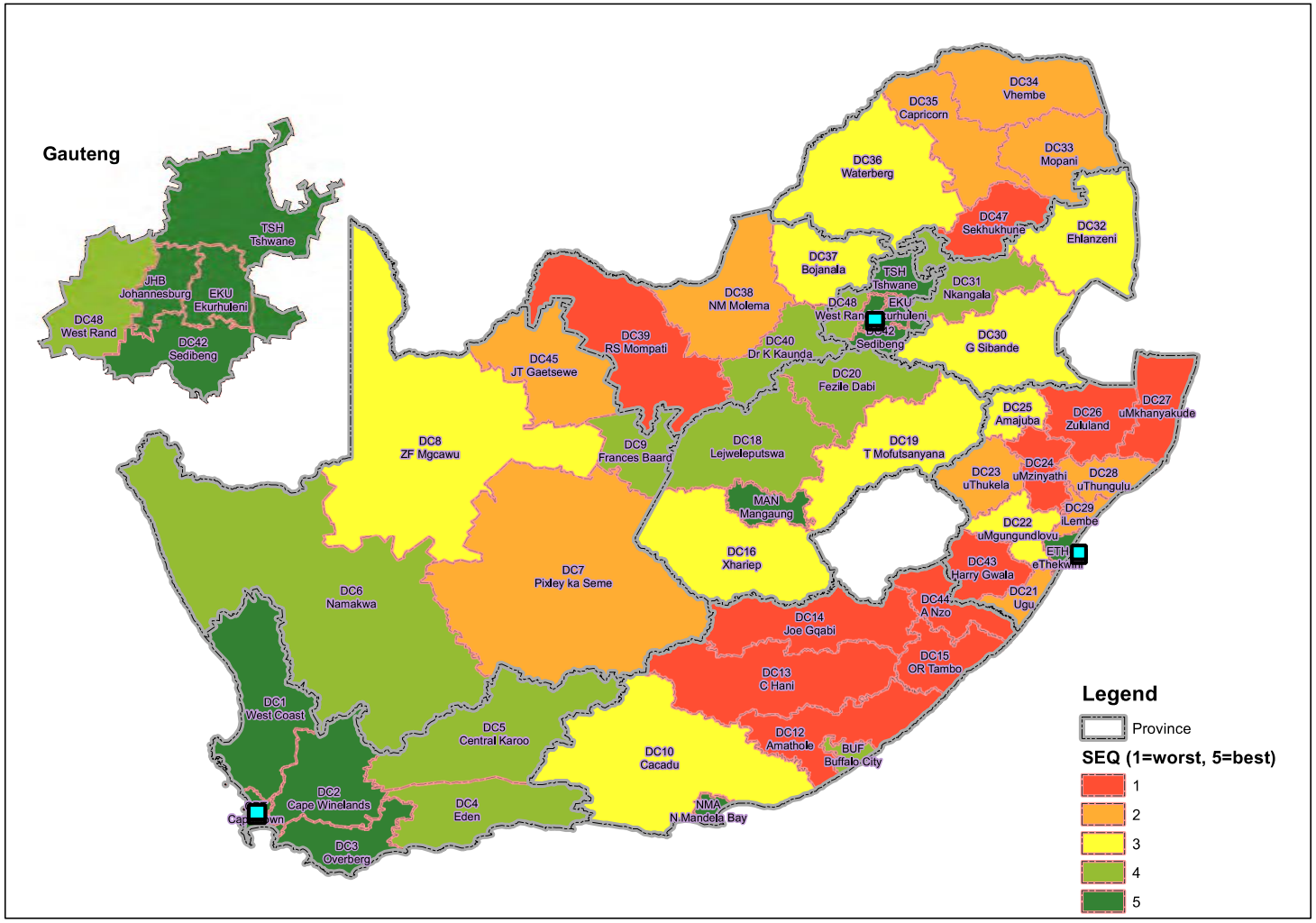
- About 10^6 births/year
- 100 boys with haem/year
- 5000 PWH in total

- Haem A:B = 4:1
- 80 haem A/year
- Fewer than half severe
- Expected inhibitor incidence approx 10/yr

Reality

- Reported data often incomplete
- Approximately 80 new cases per year
- About 2500 PWH in total

South Africa an economic perspective



Map of 52 districts in South Africa as per 2011 demarcation, showing socio-economic quintile

Source: District Health Barometer 2013-14
http://www.hst.org.za/publications/district-health-barometer-201314

Haemophilia in Limpopo

- Haemophilia Treatment Centre opened in 2000
  - Serves approximately 120 patients with Haemophilia A
  - 2001-2015: 4 fold increase in CFC use
  - About half of those 120 diagnosed with severe HA in early childhood since clinic started
  - Standard of care is episodic / on demand factor replacement
  - Just under 20% have developed high titre inhibitors

Haemophilia in Limpopo

- Two brothers diagnosed at 2 and 10 years with severe haemophilia A.
  - Live in a rural village
  - Travel times to HTC can be lengthy
- Both developed inhibitors within 20 EDs
  - Older brother first titre 9 BU, repeat 24 BU
  - Younger brother first titre 1 BU, rose to 9 BU
- Q1: Could this have been prevented ?
- Q2: Now what ?

Case information used with consent

Challenges and Strategies: Prevention

- Modifiable causes of inhibitors may include
  - Nature of CFC
  - Timing and dose of administration of CFC
- RODIN and SIPPET study (results of latter pending)
  - pdFVIII vs rFVIII
  - No significant difference in inhibitor development shown
  - Gouw SC, et al. *N Engl J Med* 2013:368;3
- CANAL and RODIN study
  - Intense exposure a risk factor
  - Prophylaxis protective
  - Gouw SC et al. *Blood* 2007:109;4648-4654
- Low dose prophylaxis & EPIC study
  - Conflicting results regarding the protective effects of low dose prophylaxis together with avoidance of immunologic danger signals
  - Kurnik K et al. *Haemophilia* 2010:16:256-62
  - Auerswald G, et al. *Haemophilia* 2015:21:622-28

Challenges and Strategies: Treatment

- Two main strategies:

- Immune tolerance induction (High dose vs low dose)
- Bypass agents
  - rVIIa
  - APCC

- Both very costly: test the limits of affordability

- For low titre inhibitors FVIII at 2-3x standard dose an option

Challenges and Strategies: Treatment

- International Immune Tolerance Study

- High dose 200IU/kg/day and low dose 50IU/kg 3x/week
  - Both arms achieved similar rates of immune tolerance
  - High dose achieved tolerance slightly faster
  - More bleeding events in low dose cohort

  - Hay CRM, DiMichele DM. *Blood* 2012 119:1335-1344

Challenges and Strategies: Treatment

- Strategy = ITI

- Select good risk patients only
  - Titre < 10 BU at start of ITI
  - Historic peak < 200 BU/ml
  - Within 5 years of diagnosis

- Low dose protocol affordable (?) and most practical accepting possible increased bleed rate
  - 150 IU/kg/week (factor in an up to 50% failure rate)
  - Once tolerized need prophylaxis 75 IU/kg/week

Challenges and Strategies: Treatment

- Strategy no/failed ITI
- Bleed Prevention
  - Target joint
- Try to limit treatment to a single dose of bypass agent
  - Reduce time to treatment
  - Hospitalize for supervision and rehabilitation
- Monitor inhibitor levels: use FVIII when low titres allow

The Future

- Steadily increase the procurement of CFCs for prophylaxis and ITI
- Identify strategies to reduce the time to treatment for patients on therapy with bypassing agents
- Progressive realization of equal access to healthcare
- Availability of more cost-effective medicines

Thank you