Inflammatory Bowel Disease
A selected overview

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Consultant Gastroenterologist, Christchurch Hospital
Medical Director, Digestive Health Services Ltd
Medical Advisor, Christchurch Crohn’s and Colitis Support Group
Who am I?

- Gastroenterologist with a passion for IBD
- Born and bred in Christchurch
- House Surgeon Nelson / Christchurch
- Gastroenterology Registrar, Christchurch
- PhD “Aspects of IBD in Canterbury”
- IBD Fellow, Box Hill Hospital, Melbourne
- IBD Researcher, Christchurch
- Nutrition Support Fellowship, St Mark’s, London
Acknowledgements

• Brian Poole

• Pharmaco / Ferring
  – Distributers of Pentasa
Conflicts of Interest

• I have received support to present research at international meetings from
  – Ferring/Pharmaco
  – Pharmatel Fresenius Kabi
  – Schering Plough
  – Abbott
  – Orphan
IBD – a selected overview

- IBD in NZ
  - A New Epidemic?

- What Causes IBD?
  - Insights from your backyard

- Drug Treatment of IBD
  - The battle to get and keep you well

- Diet and IBD
  - Are you what you eat?
IBD in New Zealand

A new epidemic?
Overview

• What is IBD
• Things that can get mixed up with IBD
• IBD International
• IBD in NZ (the past)
• IBD in NZ (now)
• What does the future hold?
Overview

• What is IBD
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• What does the future hold?
Inflammatory Bowel Disease

- Crohn’s disease
- Ulcerative Colitis
- Indeterminate colitis
The Gastrointestinal Tract

Crohn’s disease
Any part of the GI tract
Patchy inflammation
Inflammation affects full thickness of intestine
Perianal disease

Ulcerative Colitis
Colon only
Continuous inflammation
Inflammation starts at the bottom and moves proximally
Inflammation affects inner lining of bowel only (mucosa)
Normal Colon
Inflammatory Bowel Disease

- Abdominal Pain
- Diarrhoea
- Rectal Bleeding
- Weight Loss
- Medication/Surgery
- Colorectal Cancer
Normal v IBD

Why?
Overview

• What is IBD
• Things that can get mixed up with IBD
• IBD International
• IBD in NZ (the past)
• IBD in NZ (now)
• What does the future hold?
IBD Differential Diagnosis

Other causes of GI Sx
- Irritable Bowel Syndrome (IBS)
- Colorectal Cancer
- Diverticular disease
- Microscopic colitis
- Coeliac disease

Other causes of Inflammation
- Infective gastroenteritis
- Drugs (NSAIDS)
- IBD
  - Crohn’s disease
  - Ulcerative colitis
Overview

• What is IBD
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• IBD in NZ (the past)
• IBD in NZ (now)
• What does the future hold?
GEOGRAPHIC DISTRIBUTION OF IBD

[Map showing geographic distribution with color gradient indicating highest to lowest incidence.]
Introduction

IBD epidemiology

The incidence of IBD has risen rapidly over the last 50 years.
Overview

• What is IBD
• Things that can get mixed up with IBD
• IBD International
• IBD in NZ (the past)
• IBD in NZ (now)
• What does the future hold?
Epidemiological studies of IBD in New Zealand

- Wigley, *et al.*, 1962
  - Wellington
- Eason, *et al.*, 1982
  - Auckland
- Schlup, *et al.*, 1986
  - Otago
Epidemiological studies of IBD in New Zealand

<table>
<thead>
<tr>
<th>Wellington</th>
<th>Auckland</th>
<th>Otago</th>
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<td>1962</td>
<td>1982</td>
<td>1986</td>
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</table>

UC is about as common as other places
CD is less common than other places
Very few Maori / Pacific Island people have IBD
**Introduction**
the reality in Christchurch

- clinics full of IBD patients
- most clinically difficult group of patients
- ↑ use of expensive tests/therapies
- CD >> UC
- little understanding of aetiology
How common is IBD in Canterbury?

- Try to find every person living in Canterbury ever diagnosed with IBD = Prevalence

- Try to find every person living in Canterbury diagnosed with IBD in 2004 = Incidence
Methods
Case recruitment and prevalence study

- Outpatient clinics
- Inpatients
- Support Groups
- Advertising
- Direct Mail

The Canterbury IBD Study
- Epidemiology
- Genetic studies
- Environmental risk factors
- Drug studies
- Role of microbes
- Effect on people
Canterbury

464,700 people (2005)
75% live in Christchurch
10% of NZ population
Centralised health services
Good public/private health relationships
Canterbury, New Zealand

- CD 16.5 / 100 000
  - Previous highest published 14.6/100 000 (Manitoba, Canada - 1994)

- UC 7.6 / 100 000
  - About average compared to other populations
Worldwide incidence of CD

Figure 1.1A
Incidence of CD in various regions
Worldwide incidence of UC

Figure 1.1B
Incidence of UC in various regions
Prevalence of IBD in Canterbury

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Crohn’s disease</td>
<td>715</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>680</td>
</tr>
<tr>
<td>IBD total</td>
<td>1420</td>
</tr>
</tbody>
</table>
## Prevalence of IBD in Canterbury

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<th>Prevalence</th>
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<td>715</td>
</tr>
<tr>
<td></td>
<td>155 / 100 000</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>680</td>
</tr>
<tr>
<td></td>
<td>145 / 100 000</td>
</tr>
<tr>
<td>IBD total</td>
<td>1420</td>
</tr>
<tr>
<td></td>
<td>308 / 100 000</td>
</tr>
<tr>
<td>Location</td>
<td>Year</td>
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<tr>
<td>----------------------------------------</td>
<td>------</td>
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<tr>
<td>Canada (Mannitoba)</td>
<td>1984</td>
</tr>
<tr>
<td><strong>Canterbury (NZ)</strong></td>
<td>2004</td>
</tr>
<tr>
<td>Britain (Aberdeen)</td>
<td>1988</td>
</tr>
<tr>
<td>Sweden (Orebro)</td>
<td>1987</td>
</tr>
<tr>
<td>USA (Minnesota)</td>
<td>1991</td>
</tr>
<tr>
<td>Germany (Tubingen)</td>
<td>1994</td>
</tr>
<tr>
<td>Denmark (Copenhagen)</td>
<td>1987</td>
</tr>
<tr>
<td>Hungary (Veszprem)</td>
<td>2001</td>
</tr>
<tr>
<td>Israel (Jews – southern)</td>
<td>1992</td>
</tr>
<tr>
<td>Netherlands (Leiden)</td>
<td>1983</td>
</tr>
<tr>
<td>Italy (Florence)</td>
<td>1992</td>
</tr>
<tr>
<td>Faroe Islands</td>
<td>1988</td>
</tr>
<tr>
<td>Iceland (Nation-wide)</td>
<td>1979</td>
</tr>
<tr>
<td>Spain (Granada)</td>
<td>1989</td>
</tr>
<tr>
<td>Puerto Rico (South-west)</td>
<td>2000</td>
</tr>
<tr>
<td>India (Punjab)</td>
<td>2000</td>
</tr>
</tbody>
</table>

World-wide prevalence of IBD (/100,000 population)
CD age of diagnosis

Figure 2.5A
CD age of diagnosis by sex
UC age of diagnosis

Figure 2.5B
UC Age of Diagnosis by Sex
IBD gender split

Crohn’s disease

59% Female
51% Male

$p = 0.042$

Ulcerative colitis

49% Female
51% Male

$p = ns$
How common is IBD in Canterbury?

- In 2004, Canterbury had the highest rate of newly diagnosed CD ever recorded
- There is more CD than UC in Canterbury
- Women are more likely than men to get CD
- People are often diagnosed when young
- IBD - uncommon in Maori / rare in Pacific Islanders
- More medical services will be needed to treat people with IBD
IBD in New Zealand
a new epidemic?

ep·i·dem·ic (p -d m k) or ep·i·dem·i·cal (- k l)
adj.
– Spreading rapidly and extensively by infection and affecting many individuals in an area or a population at the same time, as of a disease or illness.

n.
– An outbreak or unusually high occurrence of a disease or illness in a population or area.

The American Heritage® Stedman's Medical Dictionary
What causes IBD?

Insights from your backyard
What causes IBD?
Insights from your backyard

• Genes

• The “coal face”

• The environment – the forgotten factor
Current concepts of IBD

- Genetic Susceptibility
- Environmental Factors
- Host Immune Response
If you have IBD, you are 5-10x more likely than someone without IBD to have an affected first degree relative.

If you are an identical twin with Crohn’s disease, your twin has a 50% chance of having Crohn’s disease as well.
How much genetic information does each of us contain?

- 60,000 genes in the human genome
- 2 metres of DNA in every cell
- many aspects of bodily function require multiple genes
So what are genes?

- Our individual blueprint
- The instructions needed to make proteins
  - Building blocks
  - Enzymes
  - Receptors
  - Cytokines
  - ........
IBD and Bacteria

- Immune system identifies and eliminates foreign organisms and particles
- We are 1% human, 99% bacterial!
- Symbiotic relationship (immune tolerance)
- Dysregulation exacerbates inflammation
IBD Pathogenesis

Intestine

Body

Interaction

With

Immune

System

NOD2

DLG5

TLR4

ATG16L

NCF4
*NOD2* mutations occur more frequently in some types of CD...

- Stricture (narrowing) \(2x\) ↑
- Ileal disease location \(3x\) ↑
- Bowel resection surgery \(4x\) ↑
- Relative with IBD \(1.5x\) ↑
- Diagnosed <17 years \(2x\) ↑
The incidence of IBD has risen rapidly over the last 50 years.
The environment and IBD

- Genes cannot explain the rapid increase in IBD

- Rapid changes in disease incidence

  =

  Changes in environmental factors

“Genes may load the gun, but the environment pulls the trigger”
Case-control study

People with medical condition

People without medical condition

Odds ratio $\frac{4}{2} = 2.0$
Case-control study

People with medical condition

People without medical condition

Odds ratio $\frac{2}{4}$

$= 0.5$
Smoking and IBD

Odds ratio

Increased Risk

Decreased Risk

Crohn's disease
Smoker at diagnosis

Ulcerative colitis
Smoker at diagnosis

Ulcerative colitis
Ex-smoker at diagnosis
Maternal smoking and IBD

Increased Risk

Odds ratio

Crohn's disease

Decreased Risk

Ulcerative colitis
Family history and IBD

Increased Risk

One relative with IBD

Two relatives with IBD

Decreased Risk

Crohn's disease
Ulcerative colitis
Crohn's disease
Ulcerative colitis

Odds ratio
Duration of Breastfeeding & risk of CD

<table>
<thead>
<tr>
<th>Duration of breast-feeding (months)</th>
<th>Increased Risk</th>
<th>Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0.5</td>
<td></td>
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<tr>
<td>3-6</td>
<td>0.0</td>
<td></td>
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<tr>
<td>6-12</td>
<td></td>
<td></td>
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<tr>
<td>&gt;12</td>
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</tbody>
</table>
Duration of Breastfeeding & risk of UC

- **Increased Risk**
- **Decreased Risk**

**Odds ratio (95% CI)**

- 0.0
- 0.5
- 1.0
- 1.5
- 2.0

**Duration of breastfeeding (months)**

- 0
- 0-2
- 3-6
- 6-12
- >12

The graph illustrates the odds ratio for UC risk associated with different durations of breastfeeding.
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<td>2.2-4.1</td>
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<td>7.0</td>
<td>3.3-15</td>
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<td>2.0</td>
<td>1.5-2.7</td>
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<td>1.7</td>
<td>1.2-2.3</td>
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<tr>
<td>Smoker at diagnosis</td>
<td>0.7</td>
<td>0.5-0.9</td>
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<tr>
<td>Ex-smoker at diagnosis</td>
<td>1.8</td>
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Do environmental factors play an important role in IBD?

- Environmental factors are very important
- Some environmental factors may be modifiable
- Associations give us clues as to why IBD occurs
- Many risk factors may occur in infancy / childhood
Causes of IBD are Multifactorial
The effect of IBD

- Important to measure the effects of disease
  - Resource allocation
    - New treatments
    - Medical /nursing staff
    - Community support
  - Prognostic information for patients
The effects of IBD (1)

Does a health problem or condition you have (>6 months) cause you difficulty with or stop doing everyday activities that people you age can usually do?
Average number of days away from usual activities
The Canterbury IBD Study
Conclusions

• IBD is not rare in Canterbury; CD is very common
• IBD in Canterbury is similar to elsewhere
• Genes are important – but not the whole story
• Environment is important – but difficult to unravel
• IBD has a significant impact on the lives of many Cantabrians
• The Canterbury IBD Study provides a unique tool for ongoing population-based research
Drug Treatment of IBD

the battle to get and keep you well
Overview

- Treatment for IBD
- Medical treatment for IBD
- Medical treatment for severe IBD
- Remicade (Infliximab)
- Humira (Adalimumab)
- Costs and implications
- Future directions
- ACCA document
Treatment for IBD

Drugs

CAMs

Stress

Diet

Support

Surgery

Knowledge

Lifestyle
Medical Treatment for IBD
Disease flare

- Biologicals
- Immunomodulataters (Azathioprine, 6-MP, Methotrexate)
- Steroids
- 5-ASAs (Sulfasalazine, Pentasa, Asacol)
Medical Treatment for IBD
Maintenance of remission

- Biologicals
- Immunomodulators (Azathioprine, 6-MP, Methotrexate)
- 5-ASAs (Sulfasalazine, Pentasa, Asacol)

No role for long term steroids in maintaining remission in IBD
Medical treatment for severe IBD (requiring admission to hospital)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Intravenous steroids (5-7 days given 6 or 8 hourly)</td>
</tr>
<tr>
<td>Biological Agents (Remicade / Humira)</td>
</tr>
<tr>
<td>Only for UC - IV Cyclosporin (rarely)</td>
</tr>
<tr>
<td>Only for CD Exclusive Enteral Nutrition (paediatrics)</td>
</tr>
<tr>
<td>Surgical Opinion</td>
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## Medical therapy for IBD

<table>
<thead>
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<th>Treatment</th>
<th>UC</th>
<th>CD</th>
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<tr>
<td></td>
<td>relapse</td>
<td>remission</td>
</tr>
<tr>
<td>5-ASA/SSZ</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Steroid</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Aza/6MP/MTX</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Biological Agents</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Biological Therapies
what are they?

- Designer drugs
- Aimed at specific molecules in the inflammatory cascade
- Also known as “MABs” – Monoclonal AntiBodies
- New drug - ?long term safety…
- At least as effective as anything we have now
- Fewer obvious side effects
- Very expensive …
Remicade (infliximab)

• Monoclonal antibody to TNF-α
  – Central cytokine in the inflammatory / immune response
• Given Weeks 0, 2, 8 then 8 weekly
• 97% human sequence / 3% mouse sequence
• Given as a 2-3 hour infusion
• Rapid onset of action
• Infection / ? Lymphoma / Allergy

• www.remicade.com
Remicade for Perianal Disease

- 68% v 26% had >50% of fistulas closed
- 55% v 13% had all fistulas close
- Well-tolerated

- But if you stop taking it – they come back!!
Remicade for Luminal CD

• Remission at 4 weeks
  – 33% v 4%

• Improvement at 4 weeks
  – 81% v 17%

• Maintenance of remission (1 year)
  – 39% v 21%
Remicade for UC
Remicade for UC

![Graph showing response rates in UC patients treated with Placebo, 5 mg of infliximab, and 10 mg of infliximab.](image)

- **ACT 1**: Placebo 37.2%, 5 mg of infliximab 69.4% (p<0.001), 10 mg of infliximab 61.5% (p<0.001).
- **ACT 2**: Placebo 29.3%, 10 mg of infliximab 69.2% (p<0.001).
HUMIRA (Adalimumab)

- Fully human monoclonal antibody (IgG1)
  - specifically neutralizes TNF-α
- Self-administered sub cut injection
- RA / PsA / AS dose
  - 40 mg every other week (eow)

- Crohn’s Disease:
  - Induction 160mg week 0 / 80mg week 2
  - Maintenance 40 mg eow
- >180,000 patients currently being treated worldwide
CLASSIC I Trial: Results at Week 4

- Clinical Remission:
  - Placebo/placebo: 12%
  - Adalimumab 40/20: 18%
  - Adalimumab 80/40: 24%
  - Adalimumab 160/80: 36%

- Response, Δ70:
  - Placebo/placebo: 37%
  - Adalimumab 40/20: 54%
  - Adalimumab 80/40: *59%
  - Adalimumab 160/80: †59%

- Response, Δ100:
  - Placebo/placebo: 25%
  - Adalimumab 40/20: 34%
  - Adalimumab 80/40: 40%
  - Adalimumab 160/80: ‡50%

- Clinical Remission = CDAI < 150
- Clinical response Δ70 or Δ100 = CDAI decrease from baseline ≥ 70 or ≥ 100

*p<0.05; †p=0.003; ‡p=0.002
# CLASSIC I: Treatment-Emergent Serious Adverse Events Summary

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=74</th>
<th>40/20 mg EOW n=74</th>
<th>80/40 mg EOW n=75</th>
<th>160/80 mg EOW n=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE*, n (%)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td><strong>3 (4)</strong></td>
</tr>
<tr>
<td>Serious infections</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Perianal abscess</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
CHARM Co-Primary End points

Primary Responders
CHARM Secondary End points – steroid weaning

![Bar chart showing patients in steroid-free clinical remission at Week 26 and Week 56.](chart.png)
## CHARM: SAEs of Interest
### All Adalimumab-treated Patients

<table>
<thead>
<tr>
<th>n (%)</th>
<th>4-week OL n=854</th>
<th>Post randomization (weeks 4–56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=261</td>
<td>40 mg EOW n=535</td>
</tr>
<tr>
<td>Infections and infestations*</td>
<td>10 (1.2)</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td><strong>Infectious SAEs of Interest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>7 (0.8)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>TB</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other opportunistic infections</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Wound infection, sepsis, post-operative infection</td>
<td>3 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Serum Sickness</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

GAIN: Efficacy Outcomes at Week 4

*P<0.001, †P<0.01, both vs. placebo.

Outside the square

- Children
  - Remicade
    - Used effectively
    - Safety data
    - Clinical trial data

- Pregnancy
  - Remicade
    - Contraindicated
    - Pregnancy may occur on the drug

- Breastfeeding
  - Remicade
    - Not advised
Costs and Implications

• These drugs only work if you keep taking them
  – Need to have a viable alternative option in the future (eg azathioprine or methotrexate)
  – No other alternative available (including surgery)
• Long term safety data are lacking
Costs and Implications

• Remicade cost $1175/ 100mg vial
  – 5mg/kg is the standard dose
  – 5 X 60kg = 300mg ($3525/dose)
  – 3 X induction doses then 8 weekly = $31725 per year
  – 3 X induction doses only = $10575

• Humira cost $900/ 40mg injection
  – 160mg / 80mg / 40mg eow
  – 3 X induction doses then 40mg fortnightly = $27000 per year
  – 3 X induction doses only = $6300
Costs and Implications

• Current use at Christchurch Hospital

• Remicade
  – July-Sept 2005 $70500
  – July-Sept 2006 $185395
  – July-Sept 2007 ...

• No Humira data as yet
Implications

Inflammatory bowel disease

25.2 / 100 000

Crohn’s disease

16.5 / 100 000

Ulcerative colitis

7.6 / 100 000

Indeterminate colitis

1.1 / 100 000

Gearry et al, *Inflammatory Bowel Diseases*, 2006
Implications
Sex and age of onset

Crohn’s Disease
Female > Male ($p=0.042$)
Peak age onset $\sim$25 years
Second peak $\sim$55 years
Median age onset 29.5 years

Ulcerative colitis
Male > Female (ns)
Peak age onset $\sim$30 years
Median age onset $\sim$36.5 years
Future directions

• New Mabs mean competition
• Competition lowers price

• Lobbying Pharmac / Politicians
• NZSG / Gastroenterologists / Patients

• Signalling high cost to hospital managers
Key Messages

• Mabs are not magic bullets
• Long term safety data is lacking
• Effective alternative in specific situations
• Costs are high
• National disparity in access
• Pressure on Pharmac and Politicians
• Joint approach is advocated
ACCA IBD Document

- Economic cost of IBD = $2.7 billion (includes a financial cost of $500 million + net cost of lost wellbeing $2.2 billion)
- Lost productivity accounts for > half cost ($266.7 million)
- Estimated cost of absenteeism for IBD patients = $52.3 million
- Costs to the health system = $79 million
- 939,000 hours of informal care provided to IBD patients ($23.5 million)
- Estimated out of pocket expenses for IBD patients = $35.8 million

www.acca.net.au (media page)
IBD Drug Treatment Summary

• UC – 5ASA is the best option

• CD – less evidence for 5-ASA

• CD – immunomodulators key for maintenance

• Steroids – no long term role

• Biologicals – the missing link
Canterbury IBD Study
research team

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• Bruce Chapman
• Michael Burt
• Judith Collett
• James Yeo

Gene Structure & Function Lab
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• Rebecca Roberts
• Nick Bockett
• Melanie Allington
• Aliison Miller

Epidemiology / Statistics
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• Andrew Dodgshun
• Megan Reilly
• Charlotte Duncan
• David Tan