Inflammatory Bowel Disease:

“Clinical updates”

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Princess Alexandra Hospital
Inflammatory bowel disease 2017

• Clinical updates and future directions
  • Pathogenesis
  • Treatment targets
  • Therapeutic agents
  • Individualized therapy
  • Dysplasia surveillance technology
  • Prevention

• Clinical dilemma
  • CMV in acute severe UC
Genetic factors

• Complex polygenic disorder
• >200 susceptibility loci

• NOD2 / CARD15
  • Younger age of onset
  • Small bowel involvement
  • Fibro-stenosing complication
  • Higher risk of surgery

• Limited utility in clinical practice
Monogenic Disorders in very early onset IBD

Uhlig HH Gut 2013
Microbiome in IBD

Reduced diversity

Sommer F Gut 2017
Fecal microbiota transplantation

Neeraj N IBD 2017
Fecal microbiota transplantation

# CRAPSULES

Home DIY FMT Kit
By The Power of Poop
**Figure 3-11: Incidence of CD, 2005**

Incidence - Crohn's disease

- Persons
- Incidence Rate (per 100,000)

Age Group: <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60+

Males, Females, Males (per 100,000), Females (per 100,000)

**Figure 3-12: Incidence of UC, 2005**

Incidence - Ulcerative colitis

- Persons
- Incidence Rate (per 100,000)

Age Group: <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60+

Males, Females, Males (per 100,000), Females (per 100,000)
Clinical manifestations

- Abdominal pain
- Altered bowel habits
- GI bleeding
- Peri-anal complications
- Fistulizing / Stenosing complications
- Malnutrition
- Extra-intestinal manifestations
Natural history

- **Digestive damage (Lemann index)**
  - Disease Initiation; Expansion of auto-inflammatory process
  - Sub-clinical inflammation
  - Early disease
  - Late disease

- **Inflammatory activity (CDAI, CDEIs, CRP)**
  - Stricture
  - Fistula/abscess
  - Surgery

**Window of opportunity**

**Diagnosis**

Colombel JF. Gastroenterology 2017
Treat to target

Symptoms
- QoL

Mucosal healing
- Hospitalisations
- Surgery

Labs
- CRP
- Calpro?

Biologic
- (Deep remission)
- Histologic remission
- Disease modification
Treatment paradigm

Step-up therapy

1. Biologics
2. AZA/6MP/MTX
3. Steroids
4. 5-ASA/SPS

Top-down therapy

1. Biologics
2. AZA/6MP/MTX
3. Combination
4. Steroids
5. Surgery
Therapeutic drug monitoring

Biosimilars
A. MSCs escape immune surveillance

No expression of MHC-II
No expression of co-stimulatory molecules
Low expression of MHC1

B. Immunomodulatory properties of MSCs

Cell-cell contact  Soluble factors  Generation of Tregs

C. Proposed fistula tissue repair properties of MSCs

1. Immune suppression
2. Growth factor production
3. Tissue repair
Diet

• Role in disease development and treatment
  • Ongoing investigation

• Exclusive Enteral Nutrition
  • Induction of remission in Pediatrics

• Low FODMAPs
  • For Irritable bowel syndrome overlay
Diagnosis

Assessment of disease severity

Prediction of disease course

New predictive tools: Omics, serologic markers, serum and fecal biomarkers

Selection of therapy

High risk patients-
   Early combination therapy
   Low risk patients-
   Rapid step up therapy

Predicting response to therapy
   Determining who needs early surgery?

Treat to target: No symptoms and mucosal healing
Tight control: frequent re-assessment / monitoring pharmacokinetics / objective disease monitoring

Currently proposed management strategies
Potential future personalized management strategies
Dysplasia surveillance

Polypoid lesion
Adenomatous
Inflammatory

Targeted biopsy
Quadratic random biopsy
Confocal laser endomicroscopy
Acute severe ulcerative colitis

- **Overall risk colectomy:**
  - 19.9% on first admission
  - 29.0% on second admission
  - 36.6% on third admission
  - 38.2% on subsequent admission

- Colectomy rate has not changed in 40 years despite advancement in therapies

<table>
<thead>
<tr>
<th>Bloody stools/day</th>
<th>Pulse</th>
<th>Temperature</th>
<th>Haemoglobin</th>
<th>ESR or CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 or 4 or more if ≥6 and</td>
<td>&lt;90 bpm</td>
<td>≤37.5 °C</td>
<td>&gt;11.5 g/dL</td>
<td>≤20 mm/h</td>
</tr>
<tr>
<td></td>
<td>≤90 bpm</td>
<td>≤37.8 °C</td>
<td>≥10.5 g/dL</td>
<td>≤30 mm/h</td>
</tr>
<tr>
<td></td>
<td>&gt;90 bpm or</td>
<td>&gt;37.8 °C or</td>
<td>&lt;10.5 g/dL or</td>
<td>&gt;30 mm/h or</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate ‘in between mild and severe’</td>
<td>Haemoglobin</td>
<td>or CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

- Number of criteria in addition to a bloody stool frequency >6/day | Colectomy risk

<table>
<thead>
<tr>
<th></th>
<th>Colectomy risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>31%</td>
</tr>
<tr>
<td>3</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>45%</td>
</tr>
</tbody>
</table>
Day 1-3: Steroids iv

Methylprednisone iv 60 mg/d or hydrocortisone 100 mg every 6 hours iv

Systematic review 1991 patients:
• Response rate to steroids in ASC of 67%


Day 3: salvage therapy needed?

Predicting outcome: day 3 Oxford criteria

> 8 stools/day
> 2 stools/day + CRP > 45 mg/l

85% chance of emergency colectomy

Travis et al. 1996

Day 4-7: Incomplete responders

Medical rescue therapy or colectomy

Infliximab Vs. Cyclosporin Vs. Surgery


Endoscopic assessment and exclusion of CMV
Cytomegalovirus

• Herpesviridae family
• Primary versus reactivation
• Immunocompromised
• CMV infection versus disease
• UC >> CD
## Detection methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology</td>
<td>-</td>
<td>-</td>
<td>Time delay with seroconversion</td>
</tr>
<tr>
<td>Peripheral pp65 antigenemia</td>
<td>60-100%</td>
<td>83-100%</td>
<td>Does not differentiate latent infection versus active disease / intestinal involvement</td>
</tr>
<tr>
<td>PCR DNA - blood</td>
<td>65-100</td>
<td>45-92%</td>
<td>Better viral quantification Monitor treatment response ? Better correlation with active disease</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>10-87%</td>
<td>92-100%</td>
<td>Gold standard for active disease</td>
</tr>
<tr>
<td>IHC</td>
<td>78-93%</td>
<td>92-100%</td>
<td>Gold standard for active disease</td>
</tr>
<tr>
<td>PCR DNA – tissue</td>
<td>92-96.7%</td>
<td>93-98.7%</td>
<td>Poor correlation with active disease / histology</td>
</tr>
<tr>
<td>Viral culture</td>
<td>45-78%</td>
<td>89-100%</td>
<td>Time delay</td>
</tr>
</tbody>
</table>
Cytomegalovirus in Ulcerative colitis

- Increased hospitalization
- Reduced response to infliximab therapy
- Higher cumulative colectomy rates
Conflicting data

• Detection of CMV in blood and tissue not necessarily result in poor outcome
• Treatment with infliximab not necessarily associated with poor outcome
• Innocent bystander
  • Reflection of severity of disease and immunotherapy

• Data limited by quality / detection method and classification

Lawlor G Inflamm Bowel Dis 2010
Predictors of unfavorable outcome

- Age > 30
- Resistance to steroid / immunosuppressive therapy
- Acute severe ulcerative colitis
- +/- endoscopic severity
- Density of viral infection
  - H&E versus IHC
  - 4 – 10 viral inclusions
  - >250 copies / mg of tissue
  - ? Blood PCR DNA level

Park SC Korean J Intern Med 2017
Refractory ulcerative colitis
Age > 30 yr

Quantification of CMV density in colonic tissue

No CMV reactivation

Low-grade density

High-grade density

No stigmata of severe disease

Stigmata of severe disease

Intensification of immunosuppressive therapy

Ganciclovir therapy associated to anti-TNF Mabs
Summary

• Promising developments
  • Elucidation of pathogenesis
  • Treatment targets and therapeutic options
  • Individualization of therapy
  • Early detection

• Management of CMV in ASUC remains challenging
  • Viral burden may provide guidance to therapy