Accreditation

This event has been approved as an accredited (Section 1) group learning activity as defined by the Maintenance of Certification program of the RCPSC. It has been produced under RCPSC guidelines for the development of co-developed educational activities between CAG and Abbott.
CanMEDS Roles Covered in this Session:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td>Communicator</td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
</tr>
<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
</tr>
<tr>
<td>Manager</td>
<td>(as Managers, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>(as Health Advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
</tr>
<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
</tr>
<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
</tr>
</tbody>
</table>
# Financial Interest Disclosure:
**John K. Marshall**
(over the past 24 months)

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie, Actavis, Astra-Zeneca, Celltrion, Cubist, Ferring, Hospira, Janssen, Shire, Takeda</td>
<td>Advisory Board</td>
</tr>
<tr>
<td>AbbVie, Actavis, Ferring, Janssen, Shire, Takeda</td>
<td>Speaker</td>
</tr>
<tr>
<td>AbbVie, Centocor, Pfizer,</td>
<td>Research Support</td>
</tr>
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</table>
Learning Objectives

At the end of this session, participants will be able to understand:

• The definitions of various disease states and treatment responses for Patients with moderate to severe UC to better assess the key clinical practice guideline statements that will have the greatest clinical impact.

• Why complete remission is a desirable outcome in UC.

• The role of fecal calprotectin and histology in assessing/monitoring patients with UC.

• The evidence supporting TDM in the management of non-responders to anti-TFN agents in UC
Why CAG Guidelines for UC?

- CAG guidelines for hospitalized UC published 2012
- No prior CAG guidelines for non-hospitalized UC
- Other UC Guidelines:
  - ECCO: 2012
  - BSG: 2011
  - ACG: 2010
  - AGA: N/A
- Evolving strategies:
  - Disease monitoring
  - Treatment monitoring
  - New therapies
Guidelines Development Process

Initiation of process
Identification of steering committee and working group

Development of initial statements by chairs and steering committee

Initial statements posted on CAG web portal
Steering committee linked relevant literature to each statement
First round of voting and commenting by entire consensus group

First revision of statements by steering committee

Revised statements posted on CAG web portal
Second round of voting and commenting by entire consensus group

Second revision of statements by steering committee

GRADE assessment of evidence provided to all participants

Consensus meeting: statements and comments presented to all members of the consensus group for final revisions and voting

Statements finalized and report prepared

November 2013

November 2014

CAG Ulcerative Practice Guidelines

• Co-chairs:
  – Brian Bressler, John Marshall

• Steering Committee:
  – Charles Bernstein, Alain Bitton, Brian Feagan, Jennifer Jones, Reena Khanna, Remo Panaccione, Hillary Steinhart

• Consensus Group:
  – Paul Moayyedi (Chair), Waqqas Afif, Edmond-Jean Bernard, Mark Borgaonkar, Shane Devlin, Richard Fedorak, Geoffrey Nguyen, Robert Penner, Laurent Peyrin-Biroulet, Walter Reinisch, Cynthia Seow, Richmond Sy, Laura Targownik, Peter Thomson, Gert Van Assche, Chadwick Williams

• Methodologists
  – Grigorios Leontiadis, Frances Tse

• Medical Writer
  – Pauline Lavigne

• CAG Office: Louise Hope, Paul Sinclair

• Funding: AbbVie, Actavis, Janssen, Shire, Takeda, CIHR

### Definitions of Remission and Response in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>• Both symptomatic remission and endoscopic healing as defined below</td>
</tr>
<tr>
<td>Endoscopic healing</td>
<td>• Normal mucosa, vascular blurring or chronic changes (e.g. inflammatory polyps, scarring) without friability</td>
</tr>
<tr>
<td>Symptomatic remission</td>
<td>• Normal stool frequency and no blood in the stool</td>
</tr>
</tbody>
</table>
| Symptomatic response           | • Meaningful improvement in symptoms as judged by both the patient and physician in the absence of remission.  
                                | • Not a desirable final outcome but useful to assess early response to treatments |
Definition of Disease Severity

• “Unless otherwise specified, references to mild, moderate, and severe disease activity in this document refer to those disease strata as defined by Mayo score.

• Though such a scoring system is desirable for accurate and consistent assessment of disease activity, it is often necessary to make management decisions in the absence of endoscopic information while considering the subjective aspects of disease presentation not captured by the full Mayo Score.

• In such circumstances, the partial Mayo score (which omits the endoscopic subscore) can be informative.”

Comprehensive UC Assessment

Disease Activity
- Symptoms
- Objective markers

Disease Impact
- Frequency of hospitalization
- Need for surgery
- Ability to work
- Participation in leisure
- Response to medications

Risk Profile
- Older age
- Elevated CRP/ESR
- Extent of disease
- Need for steroids
- Hospitalization

GRADE Statements

• Quality of Evidence:
  – **High**: Further research very unlikely to change confidence in the estimate of effect
  – **Moderate**: Further research likely to have an important impact on confidence in the estimate of effect and may change the estimate
  – **Low**: Further research very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
  – **Very low**: Any estimate of effect is very uncertain

• Strength of Recommendation:
  – Quality of evidence
  – Uncertainty about balance between desirable and undesirable effects
  – Uncertainty or variability in values and preferences
  – Uncertainty about whether intervention represents wise use of resources
  – **Strong**: “We recommend”
  – **Weak**: “We suggest”

Guyatt GH. BMJ 2008;336:924-6
In patients with mild-to-moderate active ulcerative proctitis, we recommend rectal 5-ASA, at a dose of 1g daily as first-line therapy to induce symptomatic remission.

GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree 57%; agree 30%; uncertain 9%; disagree 4%.

5ASA Therapy

• In patients with mild-to-moderate active UC of any disease extent beyond proctitis, we recommend an oral 5-ASA preparation, at doses between 2.0-4.8g per day, as an alternative first-line therapy to induce complete remission.
  
  GRADE: Strong recommendation, moderate-quality evidence
  Vote: strongly agree 52%; agree 43%; uncertain 4%

• In patients with mild-to-moderate active UC of any disease extent beyond proctitis, we suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone as an alternative first-line therapy to induce complete remission.
  
  GRADE: Weak recommendation, low-quality evidence
  Vote: strongly agree 43%; agree 57%

• In patients with mild-to-moderate active left-sided UC, we recommend 5-ASA enemas, at a dose of at least 1g daily as an alternative first-line therapy to induce complete remission.
  
  GRADE: Strong recommendation, moderate-quality evidence
  Vote: strongly agree 52%; agree 48%

5ASA Therapy

- **5ASA Failure:**
  - Inability to achieve and maintain complete corticosteroid-free remission despite optimal treatment with oral, rectal or combination 5-ASA therapy.

We recommend that patients with ulcerative colitis be evaluated for lack of symptomatic response to oral/rectal 5-ASA induction therapy in 4 to 8 weeks to determine the need to modify therapy.

**GRADE:** Strong recommendation, very low-quality evidence.

**Vote:** strongly agree 35%; agree 57%; uncertain 4%; disagree 4%.

5ASA Therapy

- In patients with oral or rectal 5-ASA-induced complete remission of mild-to-moderate active left-sided ulcerative colitis or proctitis, we **recommend** the same therapy be continued to maintain complete remission.
  
  *GRADE: Strong recommendation, moderate-quality evidence.*
  
  *Vote: strongly agree 48%; agree 52%.*

- In patients with oral 5-ASA-induced complete remission of mild-to-moderate active ulcerative colitis of any disease extent, we **recommend** continued oral therapy of at least 2 grams per day, to maintain complete remission.
  
  *GRADE: Strong recommendation, moderate-quality evidence.*
  
  *Vote: strongly agree 57%; agree 43%.*

- When using oral 5-ASA to induce or maintain complete remission of ulcerative colitis, we **suggest** once-daily over more frequent dosing.
  
  *GRADE: Weak recommendation, moderate-quality evidence.*
  
  *Vote: strongly agree 52%; agree 43%; uncertain 4%.*

5ASA Failure

- In patients with ulcerative colitis who have failed oral 5-ASA we **recommend against** switching to another oral 5-ASA formulation to induce complete remission.
  
  *GRADE: Strong recommendation, low-quality evidence.*
  
  *Vote: strongly agree 39%; agree 57%; uncertain 4%.*

- In patients with mild-to-moderate active ulcerative colitis failing 5-ASA therapy, we **recommend** oral corticosteroids as second-line therapy to induce complete remission.
  
  *GRADE: Strong recommendation, low-quality evidence.*
  
  *Vote: strongly agree 57%; agree 43%.*

- In patients with mild-to-moderate active left-sided ulcerative colitis or proctitis failing rectal 5-ASA therapy, we **suggest** rectal corticosteroids as second-line therapy to induce complete remission.
  
  *GRADE: Weak recommendation, overall very low-quality evidence.*
  
  *Vote: strongly agree 26%; agree 61%; uncertain 13%.*

Mild to Moderate Active UC

Left-Sided Colitis

Rectal 5-ASA ≥1g/day*
or Oral 5-ASA 2.0-4.8g/day ± Rectal 5-ASA ≥1g/day

Extensive Colitis

Oral 5-ASA 2.0-4.8g/day*
± Rectal 5-ASA ≥1g/day

ASSESS IN 4-8 WEEKS FOR SYMPTOMATIC RESPONSE

NO

Optimize 5-ASA Therapy

ASSESS FOR COMPLETE REMISSION†

NO

Oral or Rectal Corticosteroids

YES

Continue Oral or Rectal 5-ASA

See Moderate-Severe Ulcerative Colitis Algorithm

Corticosteroid Therapy

- In patients with moderate-to-severe active ulcerative colitis, we recommend oral corticosteroids as first-line therapy to induce complete remission.
  
  *GRADE:* Strong recommendation, moderate-quality evidence.
  *Vote:* strongly agree 70%; agree 30%.

Corticosteroid Therapy

- **Corticosteroid Resistance:**
  - Lack of a symptomatic response despite a course of oral prednisone of 40-60 mg/day (or equivalent) for a minimum of 14 days

- **Corticosteroid Dependence:**
  - Inability to withdraw (within 3 months of initiation) oral corticosteroid therapy without a recurrence of symptoms
  - Symptomatic relapse within three months of stopping corticosteroids
  - Need for two or more courses of corticosteroids within one year

Corticosteroid Therapy

• We **recommend** that patients with UC be evaluated for lack of symptomatic response to corticosteroid induction therapy within 2 weeks to determine the need to modify therapy.
  
  **GRADE:** Strong recommendation, very low-quality evidence.
  
  **Vote:** strongly agree 65%; agree 35%.

• In patients with UC, we **recommend against** the use of oral corticosteroids to maintain complete remission as they are ineffective for this indication and their prolonged use is associated with significant adverse effects.
  
  **GRADE:** Strong recommendation, moderate-quality evidence
  
  **Vote:** strongly agree 96%; uncertain 4%

• In selected 5-ASA naïve patients with UC who have achieved symptomatic remission on oral corticosteroids, we **suggest** an oral 5-ASA preparation of at least 2g/day while being assessed for corticosteroid-free complete remission.
  
  **GRADE:** Weak recommendation, very low-quality evidence.
  
  **Vote:** strongly agree 9%; agree 78%; uncertain 13%.

Immunosuppressant Therapy

• In patients with ulcerative colitis, we **recommend against** the use of thiopurine monotherapy to induce complete remission.
  
  *GRADE: Strong recommendation, low-quality evidence.*
  
  *Vote: strongly agree 52%; agree 43%; uncertain 4%.*

• In selected patients with ulcerative colitis who have achieved symptomatic remission on oral corticosteroids, we **suggest** thiopurine monotherapy as an option to maintain complete corticosteroid-free remission.
  
  *GRADE: Weak recommendation, low-quality evidence.*
  
  *Vote: strongly agree 22%; agree 78%.*

• In patients with ulcerative colitis, we **recommend against** the use of methotrexate monotherapy to induce or maintain complete remission.
  
  *GRADE: Strong recommendation, low-quality evidence for induction & very low-quality evidence for maintenance.*
  
  *Vote: strongly agree 65%; agree 26%; uncertain 9%.*
Biologic Therapy

• Anti-TNF Monoclonal Antibodies
  – Adalimumab
  – Golimumab
  – Infliximab

• Anti-Integrin Monoclonal Antibodies
  – Vedolizumab

Anti-TNF Therapy

• In patients with UC who fail thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission.
  
  **GRADE:** Strong recommendation, high-quality evidence.
  
  **Vote:** strongly agree 70%; agree 30%.

• In patients with UC who are corticosteroid dependent, we recommend anti-TNF therapy to induce and maintain complete corticosteroid-free remission.
  
  **GRADE:** Strong recommendation, very low-quality evidence.
  
  **Vote:** strongly agree 52%; agree 48%.

• When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission.
  
  **GRADE:** Strong recommendation, moderate-quality evidence for AZA & very low-quality evidence for MTX.
  
  **Vote:** strongly agree 26%; agree 65%; uncertain 9%.

Anti-TNF Therapy

• We recommend that patients with UC, be evaluated for lack of symptomatic response to anti-TNF induction therapy in 8 to 12 weeks to determine the need to modify therapy.
  
  GRADE: Strong recommendation, low-quality evidence.
  Vote: strongly agree 43%; agree 57%.

• In patients with ulcerative colitis who respond to anti-TNF induction therapy, we recommend continued anti-TNF therapy to maintain complete remission.
  
  GRADE: Strong recommendation, very low-quality evidence for infliximab and adalimumab & high-quality evidence for golimumab.
  Vote: strongly agree 65%; agree 35%.
Biologic Failure

• **Primary failure:**
  – Inability of the patient to achieve corticosteroid-free complete remission despite dose optimization

• **Secondary failure:**
  – Inability of the patient to maintain corticosteroid-free complete remission after having achieved a symptomatic response

Anti-TNF Therapy

• In patients with UC who have a suboptimal response to anti-TNF induction therapy, we **recommend** dose intensification to achieve complete remission.
  
  **GRADE:** Strong recommendation, very low-quality evidence.
  **Vote:** strongly agree 39%; agree 61%.

• In patients with UC who lose response to anti-TNF maintenance therapy, we **recommend** optimizing dose to recapture complete remission.
  
  **GRADE:** Strong recommendation, very low-quality evidence.
  **Vote:** strongly agree 61%; agree 39%.

• We **recommend** dose optimization for patients with UC be informed by therapeutic drug monitoring.
  
  **GRADE:** Strong recommendation, low-quality evidence.
  **Vote:** strongly agree 61%; agree 35%; uncertain 4%.

Vedolizumab Therapy

- In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission.
  
  GRADE: Strong recommendation, very low-quality evidence.
  
  Vote: strongly agree 48%; agree 43%; uncertain 9%.

- In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on TDM results to induce complete corticosteroid-free remission.
  
  GRADE: Strong recommendation, very low-quality evidence.
  
  Vote: strongly agree 43%; agree 57%.

- In patients with moderate-to-severe active UC who fail corticosteroids or thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission.
  
  GRADE: Strong recommendation, moderate-quality evidence.
  
  Vote: strongly agree 70%; agree 26%; disagree 4%.

Vedolizumab Therapy

- We **recommend** that patients with ulcerative colitis be evaluated for lack of symptomatic response to vedolizumab induction therapy in 8 to 14 weeks to determine the need to modify therapy.
  
  **GRADE:** Strong recommendation, very low-quality evidence.
  Vote: strongly agree 35%; agree 65%.

- In patients with ulcerative colitis who respond to vedolizumab, we **recommend** continued vedolizumab therapy to maintain complete corticosteroid-free remission.
  
  **GRADE:** Strong recommendation, moderate-quality evidence.
  Vote: strongly agree 87%; agree 13%.

Steroid Resistant/Dependent UC

Other Therapies

• In patients with UC, we **recommend** against fecal microbial transplant to induce or maintain complete remission outside the setting of a clinical trial.
  
  GRADE: Strong recommendation, low-quality evidence.
  
  Vote: strongly agree 70%; agree 30%.

• In patients with UC, we **recommend** against probiotics to induce or maintain complete remission outside the setting of a clinical trial.
  
  GRADE: Strong recommendation, very low-quality evidence.
  
  Vote: strongly agree 48%; agree 43%; uncertain 9%.
Summary

• First Canadian clinical practice guidelines for management of ambulatory ulcerative colitis
• First global clinical practice guidelines to include new therapeutic classes
• Next steps:
  – Clinical practice guideline dissemination
  – Knowledge transfer
  – Assessment of impact
  – Additional CAG clinical practice guidelines
