IBD diagnosis: is biopsy best?

Roger Feakins
Barts Health NHS Trust / QMUL
IBD diagnosis: is biopsy best?

When a patient presents with acute bloody diarrhea, the differential diagnosis is often between acute self-limited colitis and the first attack of idiopathic inflammatory bowel disease, either ulcerative colitis or Crohn's colitis. History and physical examination are not very helpful, although a history of rectal intercourse in male homosexuals raises the possibility of specific intestinal infections such as Neisseria gonorrhoeae, Chlamydia trachomatis, Herpes simplex virus type II, and Treponema pallidum, as well as the usual enteric pathogens (1). Stool cultures grow pathogens in only 40%–60% of patients with the spectrum of acute self-limited colitis (acute infectious-type colitis). Am J Surg Pathol 1982;6:523–9.


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IBD diagnosis: is biopsy best?

Outline

1. Brief history
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1859 - “Ulcerative colitis” first described (S Wilks)

Late 19th C - Rectal biopsy for cancer

1932 - B B Crohn describes “regional ileitis”

1957 - Rectal biopsy for UC and Crohn’s

1969 - Colonoscopy

IBD diagnosis: is biopsy best?

De Dombal FT. Postgrad Med J 1968;44:684
Chronic idiopathic inflammatory bowel disease (IBD)

Clinical, imaging & pathological diagnosis

Two types
• Ulcerative colitis (UC)
• Crohn’s disease

Unclassifiable cases
• Biopsy: Inflammatory bowel disease, unclassified (IBDU)
• Resection: “Indeterminate” colitis (controversial)

BSG IBD biopsy guidelines 1997

Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative

D Jenkins, M Balsitis, S Gallivan, M F Dixon, H M Gilmour, N A Shepherd, A Theodossi, G T Williams

Introduction
Unambiguous interpretation of colorectal biopsy specimens is important for clinical decisions in the investigation of suspected chronic idiopathic inflammatory bowel disease (IBD). Variability of reporting style and terms such as mild inflammatory change and non-specific chronic inflammation is a source of confusion.

Where the prevalence and the nature of the diseases are very different.

Method for development of evidence-based guidelines
The development of the guidelines was based on systematic literature review presented to an expert consensus panel composed of gastroenterologists.
IBD: changes since 1997

Management

- colonoscopic biopsies
- new drugs
- dysplasia
- IBD service standards

Pathology

- mimics of IBD
- effects of time
- variations in anatomical distribution

IBD diagnosis: is biopsy best?

Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines

Roger M Feakins

ABSTRACT
Accurate histopathological assessment of biopsies is important for the diagnosis, subclassification, and management of chronic idiopathic inflammatory bowel disease (IBD). British Society of Gastroenterology (BSG) guidelines for the initial histopathological diagnosis of IBD were published in 1997. Changes since then include: more widespread use of full colonoscopy; greater recognition of the effects of time and treatment; improved documentation of variations in anatomical distribution; better understanding of the mimics of IBD; significant progress in clinical management; and modifications of terminology. Accordingly, an update is required. These revised guidelines aim to optimise the quality and consistency of reporting of biopsies taken for the initial diagnosis of IBD by summarising the literature and making recommendations based on the available evidence. Advice from existing clinical guidelines is also taken into account. Among the subjects discussed are: distinguishing IBD from other colitides, particularly infective colitis; subclassification of IBD (as ulcerative colitis, Crohn’s disease, or IBD undiagnosed); the use of inflammatory bowel disease activity indices; and the role of endoscopy.

To promote consistency of pathologists’ approach to reporting.
To encourage correlation between histological and clinical findings, including discussion at clinicopathological meetings.
To minimise the use of ambiguous or confusing terms.

Process
The advice provided by the BSG at the time of writing was followed, with some exceptions which are mentioned below (see online supplementary appendix 1 for more details).

Authorship and review
Draft versions were initially submitted by the author to the pathology section committee of the BSG for review. The content has now been discussed with and approved by the pathology section committee, the clinical services and standards committee of the BSG, and the chair of the IBD section of the BSG. The document is also approved by the BSG editorial board.
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IBD diagnosis: is biopsy best?
Why biopsy?

Guidelines for the management of inflammatory bowel disease in adults

Craig Mowat, Andrew Cole, Al Windsor, Tariq Ahmad, Ian Arnott, Richard Driscoll, Sally Mitton, Tim Orchard, Matt Rutter, Lisa Young, Charlie Lees, Gwo-tzer Ho, Jack Satsangi, Stuart Bloom, on behalf of the IBD Section of the British Society of Gastroenterology

ABSTRACT
The management of inflammatory bowel disease represents a key component of clinical practice for members of the British Society of Gastroenterology (BSG). There has been considerable progress in management strategies affecting all aspects of clinical care since the publication of previous BSG guidelines in 2004, necessitating the present revision.

with inflammatory bowel disease in the United Kingdom. The authors of these guidelines were members of the BSG IBD Committee at the time. This committee is elected by fellow members of the IBD section of the Society. They replace the guidelines published in 2004 by Carter et al. They have been written with close reference to the recent European evidence-based consensus documents on

UC vs. Crohn’s

Dysplasia

Exclude coexistent conditions

<table>
<thead>
<tr>
<th>Biopsy contribution</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of IBD</td>
<td>+++</td>
</tr>
<tr>
<td>UC vs. Crohn’s</td>
<td>++</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>++++</td>
</tr>
<tr>
<td>Exclude other conditions</td>
<td>+++</td>
</tr>
<tr>
<td>Activity</td>
<td>+++</td>
</tr>
<tr>
<td>Extent</td>
<td>+</td>
</tr>
</tbody>
</table>

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IBD diagnosis: is biopsy best?
Clinical setting

Blinded pathologist  
substandard interpretation

Clinical
• First presentation?
• Duration of symptoms, if new?

Endoscopy form
Meetings

IBD diagnosis: is biopsy best?

Stange EF et al. J Crohns Colitis 2008;2:1
Rex DK et al. Am J Gastroenterol 2002;97:1296
Shepherd NA, Valori RM. In press.
Biopsy quality

**Sampling**
- multiple site colorectal + ileal

**Identification of sites**

**Quality of processing**
- cellular detail
- orientation

IBD diagnosis: is biopsy best?

Geboes K et al. Am J Gastroenterol 1998;93:201
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<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Basal plasmacytosis  | ≡ loss of plasma cell gradient  
                       | ≡ transmucosal chronic inflammation  
                       | Plasma cells - easy to see         |
| Crypt distortion     | Includes:  
                       | Loss of parallelism  
                       | Branching  
                       | Irregularity                  |
| Crypt atrophy        | Shortening and / or wide spacing  
                       | Not included in distortion        |
| Granulomas           | >5 macrophages ?                                                       |

IBD diagnosis: is biopsy best?
Pitfalls

- **Basal plasmacytosis**
  - Basal plasma cells normal in caecum / ascending colon

- **Crypt distortion**
  - Anorectal zone
  - Next to crypt abscesses / lymphoid follicles

- **Crypt atrophy**
  - Caecum & rectum – larger spaces

- **Granulomas**
  - Exclude crypt rupture

- **Basal lymphoid aggregates**
  - May resemble normal aggregates

IBD diagnosis: is biopsy best?
Normal mucosa

Caecum / ascending colon - basal plasma cells

Rectal mucosa – crypt spacing

IBD diagnosis: is biopsy best?
Crypt distortion in normal mucosa

Distortion adjacent to lymphoid aggregate / follicle

Branched crypts (up to 2 per biopsy)

IBD diagnosis: is biopsy best?
Basal lymphoid aggregates

Normal lymphoid aggregate  
Lymphoid aggregates in IBD

IBD diagnosis: is biopsy best?
Granulomas

Cryptolytic granulomas

- limited discriminant value
- serial sections may reveal crypt rupture

Granulomas + no other abnormality

- interpret with caution

IBD diagnosis: is biopsy best?
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IBD diagnosis: is biopsy best?
“Controls” for IBD histology studies

- Normal: limited value
- Infective: the most common comparison
- “Acute self-limiting colitis” / “non-relapsing colitis”: probably mostly infective
- Other inflammatory conditions
- Combinations of the above: Often defined by follow-up

IBD diagnosis: is biopsy best?
Ideal studies
• pre-treatment or “initial”

Longstanding IBD may show
• Discontinuity
• Rectal sparing
• Normality
<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Reliability</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal plasmacytosis</td>
<td>High</td>
<td>Focal in Crohn’s</td>
</tr>
<tr>
<td>Crypt distortion</td>
<td>High</td>
<td>Focal in Crohn’s</td>
</tr>
<tr>
<td>Crypt atrophy</td>
<td>High</td>
<td>Focal in Crohn’s</td>
</tr>
<tr>
<td>Villiform mucosal surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomas</td>
<td>Moderate</td>
<td>Not UC</td>
</tr>
<tr>
<td>Basal lymphoid aggregates</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Basal giant cells</td>
<td>Fair</td>
<td>Often not assessed</td>
</tr>
</tbody>
</table>

IBD diagnosis: is biopsy best?
### IBD > non-IBD in initial biopsies

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Reliability</th>
<th>Reproducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal plasmacytosis</td>
<td>High</td>
<td>Moderate / good</td>
</tr>
<tr>
<td>Crypt distortion</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Crypt atrophy</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Villiform mucosal surface</td>
<td>Moderate</td>
<td>Good</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Moderate</td>
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<td>Moderate</td>
</tr>
<tr>
<td>Basal giant cells</td>
<td>Fair</td>
<td>Moderate / good</td>
</tr>
</tbody>
</table>

**IBD diagnosis: is biopsy best?**
Mild crypt distortion: loss of parallelism

IBD diagnosis: is biopsy best?
Crypt branching

Vertical crypt branching – more discriminant?

Horizontal crypt branching

IBD diagnosis: is biopsy best?

Crypt atrophy

No atrophy

Mild atrophy

IBD diagnosis: is biopsy best?
- No feature is diagnostic in isolation
- Multiple features increase accuracy
- Number needed for a diagnosis not defined

IBD diagnosis: is biopsy best?
IBD > non-IBD in initial biopsies: less reliable

<table>
<thead>
<tr>
<th>Paneth cell metaplasia</th>
<th>Chronicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep crypt abscesses</td>
<td>Limited data</td>
</tr>
<tr>
<td>Crypt neutrophils+++</td>
<td>Limited data</td>
</tr>
</tbody>
</table>
Histology of infective colitis vs IBD

Most reliable

- Absence of basal plasma cells
- Preserved crypts

Less reliable / limited data

- Lamina proprial inflammation acute > chronic
- Superficiality of giant cells and crypt abscesses

Specific pattern 1-10 weeks after onset?

- Mild upper lamina proprial hypercellularity + increase in lamina proprial and crypt epithelial neutrophils

IBD diagnosis: is biopsy best?
IBD vs. other

Infection or IBD

Stool culture

Imaging?

Endoscopy

Symptoms, clinical course

Biopsy histology

IBD diagnosis: is biopsy best?
# IBD diagnosis: is biopsy best?

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UC vs. Crohn’s disease

Why distinguish?

Ileal pouch anal anastomosis

Pouch failure: Crohn’s 30-45% UC < 10%

Drugs

Adalimumab for Crohn’s disease
Ciclosporin for UC

Prognosis

IBD diagnosis: is biopsy best?
UC > Crohn’s disease (initial biopsies)

- **Reliable**
  - Diffuse crypt abnormalities within & between sites
  - Crypt atrophy; crypt distortion; villous surface
  - Mucin depletion (esp. severe)
  - Absence of ileal inflammation

- **Reliable in some studies**
  - Diffuse transmucosal chronic inflammation (& synonyms)

- **Less evidence**
  - Widespread cryptitis / crypt abscesses
  - Changes more prevalent distally than proximally

IBD diagnosis: is biopsy best?
diffuse crypt changes
absence of ileal disease
Crohn’s disease > UC (initial biopsies)

Reliable
- Granuloma (non-cryptolytic)
- Focal or patchy chronic inflammation
- Focal or segmental crypt distortion
- Ileal involvement

Fairly reliable
- Decreasing proximal to distal gradient of changes
- Normal mucosal surface

IBD diagnosis: is biopsy best?
Crohn’s disease
UC vs. Crohn’s: unproven features

- Paneth cell metaplasia
- Disproportionate submucosal inflammation
- Focality of activity
- Eosinophils

IBD diagnosis: is biopsy best?
UC: discontinuity and rectal sparing

Discontinuity within and between sites
- Common in longstanding UC (58%)

Rectal sparing
- Common in longstanding UC
- Rare in new UC; children > adults (?)

Caecal patch
- Adjacent segment of normal bowel
- Common in new UC (75%?)
- Periappendiceal initially

IBD diagnosis: is biopsy best?
Effect of drugs on histology

- Patchiness, rectal sparing, etc. in post-treatment disease
  - caused by time, treatment, or both?
- Drug trials: specific histological changes
### Frequency of UGI abnormalities
- Crohn’s > UC
- Earlier > later
- Children > adults

### Is the inflammation actually due to IBD?
- Difficult - unless there are granulomas

### Significance of granulomas in known IBD
- IBD >> other
- Crohn’s >>> UC
- +/- lower GI granulomas

---

**IBD diagnosis: is biopsy best?**
“Specific” patterns in upper GI IBD

Focally enhanced gastritis
- not specific
- in children: predictive of IBD?

Gastric histology in UC
- focal gastritis
- patchy mixed basal inflammation
- superficial plasmacytosis

IBD diagnosis: is biopsy best?

Lin J. Am J Surg Pathol 2010;34:1672
“Specific” patterns in upper GI IBD

Lymphocytic oesophagitis
- Lymphocytosis +++
- Association with IBD??
- Crohn’s > other in children?

Diffuse duodenitis in known UC
- Rare
- All post-colectomy
- Associated with pouchitis

IBD diagnosis: is biopsy best?

Lin J. Am J Surg Pathol 2010;34:1672
IBD diagnosis: is biopsy best?

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Initial (pre-treatment) histology is not uniform
• depends on duration of symptoms
Pre-treatment IBD

Duration of symptoms

- Basal plasma cells
- Crypt distortion
- Crypt atrophy
- Villous surface

Granulomas: not before 25 days
Pre-treatment IBD

Duration of symptoms

1-15 days  16-30 days  31-120 days  121-300 days

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

- Basal plasma cells
- Crypt distortion
- Crypt atrophy
- Villous surface

Granulomas: not before 25 days
Pre-treatment IBD

Duration of symptoms

1-15 days 16-30 days 31-120 days 121-300 days

Granulomas: not before 25 days

- Basal plasma cells
- Crypt distortion
- Crypt atrophy
- Villous surface
Pre-treatment IBD

![Graph showing the percentage of basal plasma cells, crypt distortion, crypt atrophy, and villous surface over different duration of symptoms (1-15 days, 16-30 days, 31-120 days, and 121-300 days).]
Pre-treatment IBD

Granulomas: not before 25 days

Duration of symptoms

- Basal plasma cells
- Crypt distortion
- Crypt atrophy
- Villous surface

Timing: 3 categories?

- < 4 weeks of symptoms
- > 4-6 weeks of symptoms
- Longstanding / treated disease

IBD diagnosis: is biopsy best?

Stange EF et al. J Crohns Colitis 2008;2:1
IBD diagnosis: is biopsy best?

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8. **Activity**
9. Terminological considerations
Activity

Assessment traditionally based on endoscopy

Histological estimation

- cancer risk categories
- response to treatment in trials: “histological healing”

IBD diagnosis: is biopsy best?

Cairns SR et al. Gut 2010;59:666
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IBD diagnosis: is biopsy best?
Terms to avoid

Non-specific (chronic) colitis

- May be misinterpreted as meaning UC
- Qualify

Colitis

Colitis

Incipient crypt abscess

- Can mean anything
- Risk of misinterpretation

Consistent with / in keeping with / compatible with

IBD diagnosis: is biopsy best?
Ambiguous terms: evidence?

Ambiguous / equivocal: definition

• “capable of being understood in two or more ways”

Demonstrably ambiguous terms:

• Compatible with
• Consistent with
• Not excluded
• Cannot exclude
  • i.e. the degree of certainty attributed to the terms differed significantly between groups

IBD diagnosis: is biopsy best?

Idowu MO, AJSP 2013;37:1722
“In keeping with ulcerative colitis”
Is the mucosa inflamed?

- No
  - No histological features of IBD
    - IBDU
    - Crohn’s disease
      - Crohn’s disease definite or very likely
    - UC
      - UC definite or very likely
      - UC favoured over Crohn’s disease

- Yes
  - IBD definite or very likely*

*In conjunction with the clinical setting

Summaries and examples
IBD diagnosis: simplistic approach

Basal plasmacytosis + Architectural changes → IBD very likely* (in conjunction with clinical setting)
IBD diagnosis: simplistic approach

- No basal plasmacytosis
- No architectural changes

IBD cannot be diagnosed

IBD diagnosis: is biopsy best?
IBD - subclassification

Diffuse architectural changes within and between sites

- No ileal disease
- No granulomas
- Worse distally

UC very likely

IBD diagnosis: is biopsy best?
IBD subclassification

- Granulomas (non-cryptolytic)
- Patchy or focal architectural changes
- Ileal inflammation
- Worse proximally

Crohn’s disease very likely

IBD diagnosis: is biopsy best?
Case 1

- 26 year old man
- Acute diarrhoea & abdominal pain.
- Granularity and ulcers, rectum to splenic flexure. Relatively continuous.
- Diagnosis: UC
Is the mucosa inflamed?

- No
  - No histological features of IBD
    - UC definite or very likely
    - UC favoured over Crohn’s disease
    - IBDU**
    - Crohn’s disease definite or very likely

- Yes
  - IBD definite or very likely*
    - In conjunction with the clinical setting
      - Crohn’s disease favoured over UC
      - Crohn’s disease definite or very likely

*In conjunction with the clinical setting

**IBD unclassified

IBD diagnosis: is biopsy best?
Case 2

- 28 yo man
- Diarrhoea
- Endoscopic diagnosis of UC

Colonic and rectal biopsies

All biopsies had the above features
Is the mucosa inflamed?

- No
  - No histological features of IBD
    - UC definite or very likely
      - UC favoured over Crohn’s disease
      - IBDU**
      - Crohn’s disease favoured over UC
      - Crohn’s disease definite or very likely
  - IBD favoured over other causes
    - IBD definite or very likely*

- Yes
  - IBD definite or very likely*
  
*In conjunction with the clinical setting

**IBD unclassified

IBD diagnosis: is biopsy best?
Case 3

23 yo man; “assessment of IBD.”
Vague endoscopic details

IBD diagnosis: is biopsy best?
**IBD diagnosis: is biopsy best?**

Is the mucosa inflamed?

- **No**
  - No histological features of IBD
  - UC definite or very likely

- **Yes**
  - IBD favoured over other causes
    - IBD definite or very likely*
    - UC favoured over Crohn’s disease
    - IBDU**
    - Crohn’s disease favoured over UC
    - Crohn’s disease definite or very likely

*In conjunction with the clinical setting

**IBD unclassified**
Is biopsy best?

Yes, it can be if you have:
- clinical details
- endoscopy report
- meetings
- adequate biopsy
- knowledge of:
  - pitfalls
  - discriminant features
  - effects of time on histology
Thank you