Classification of IBD can only be based on the clinical phenotype

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AKH Wien
...clinical phenotype may be the most immediate and objective method to assess a disease...
Is phenotyping in IBD necessary?

Some suggestions:

- To delineate a reproducible pathogenetic model
- To elaborate a diagnostic standard
- To anticipate the course of disease
- To facilitate the comparison of treatment results
- To customise therapy

Too good to be true!!!
IBD comprises not 2 disorders but a heterogeneous family of inflammatory disorders...

Inconsistencies of genotype phenotype associations highlight the problem inherent to all genetic association studies of complex disease, namely …variable disease definition, populations stratification…
A single gold standard for diagnosis of CD is not available.

The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations.

Diagnostic puzzle may elicit inconsistent results in studies.
Change of diagnosis during 1 year after initial diagnosis

A 10% misclassification rate resulted in up to 40% loss of power to detect a true linkage when using a statistical model for a presumed IBD locus


Diagnosis of Crohn’s disease by surgical material

- 1932 – Crohn, Ginzburg, and Oppenheimer\(^1\): subacute or chronic necrotizing and cicatrizing inflammation involving the terminal ileum alone and predisposing to fistulas; by pathologic inspection of resected specimen

- 1960 – Lockhart-Mummery and Morson\(^2\): CD may affect the colon (regional enteritis of the large intestine); by gross and microscopic appearances in surgical material

\(^1\)Crohn BB et al. *JAMA* 1932;99:1323

\(^2\)Lockhart-Mummery HE and Morson BC. *Gut* 1960;1:87
Distribution of NOD-2/CARD15 variants in Crohn’s disease

<table>
<thead>
<tr>
<th>Locus</th>
<th>Ileal</th>
<th>Colonic</th>
<th>Ileo-colonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD2/CARD15</td>
<td>40%</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>HLA</td>
<td>19%</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>Other loci</td>
<td>30%</td>
<td>30%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Use of classifications/scores in CD

- Lennard-Jones Evaluation of perianal fistulas
- Endoscopic activity index
- Clinical activity index

Reinisch W, et al. Questionnaire on Clinical Diagnosis and Imaging; CD consensus 2004
Application of the Lennard-Jones Criteria for Selection of CD Patients in Genotype Studies

Number (%) of studies in a meta-analysis of 41 genotype studies

Diagnostic criteria of CD

Lennard-Jones*

- Macroscopic discontinuity of disease
- Transmural inflammation
- Fibrosis
- Lymphoid aggregates
- Discontinuous inflammation on histology
- Granulomas

CD established: Granuloma with at least 1 criterion, or in the absence of a granuloma by 3 of 6 criteria

CD probable: 2 criteria without granulomas

Standard criteria describe only a loose combination of investigations which have to be considered specifying those features which have to be considered

Distribution of Diagnosis according to Lennard-Jones at Time of Diagnosis by Standard Criteria

Primary CD Population: n=142

- Non CD: 78/142 (55%)
- Prob. CD: 17/142 (12%)
- CD: 47/142 (33%)
Distribution of ASCA across Strata according to Lennard-Jones at Diagnosis

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Negative</th>
<th>Positive</th>
<th>ASCA-positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prim. Pop.</td>
<td>114/142</td>
<td>28/142</td>
<td>80.3%</td>
</tr>
<tr>
<td>CD</td>
<td>42/47</td>
<td>25/47</td>
<td>87.5%</td>
</tr>
<tr>
<td>Prob. CD</td>
<td>13/17</td>
<td>9/17</td>
<td>76.5%</td>
</tr>
<tr>
<td>Non CD</td>
<td>59/142</td>
<td>83/142</td>
<td>77.1%</td>
</tr>
</tbody>
</table>

p = 0.15

ASCA-positivity defined by positivity for at least IgG or IgA
Proportions of Patients fulfilling the Lennard-Jones Criteria over Time

- **definite CD** (red line)
- **probable CD** (blue line)
- **no CD** (yellow line)

Follow-up (months):
- 0
- 12
- 24
- 36
- 48
- 60
- 72
- 84
- 96
- 108
- 120
- 132
- 144
- 156
- 168
- 180

Counts:
- N = 142
- 133
- 87
- 55
- 32
- 20
Is there a need to classify IBD?

2000 – Vienna classification of CD\textsuperscript{1}: simple classification of CD according to Age at diagnosis, Location and Behavior;

2005 – Montreal modification\textsuperscript{2}: addition of early-onset, allow for co-classification of upper GI and perianal disease – but based on same definitions as VC!!!

By at least both a small bowel examination and a large bowel examination

\textsuperscript{1}Gasché C et al. \textit{IBD} 2000;6:8-15
\textsuperscript{2}Silverberg M et al. Can J Gastroenterol 2005:SA
### “Interobserver agreement” Behavior

<table>
<thead>
<tr>
<th>Interrater agreement</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinhart et al.</td>
<td>0.353</td>
</tr>
<tr>
<td>VC</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Öfferlbauer-Ernst A, et al. DDW 2004
What is the appropriate time to evaluate behavior?

A category “progression” more appropriate?
"Interobserver agreement" Vienna Classification

<table>
<thead>
<tr>
<th></th>
<th>Interobserver agreement</th>
<th>Range in Subgroups</th>
<th>Intraobserver agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>70%</td>
<td>48 - 88%</td>
<td>77%</td>
</tr>
<tr>
<td>Behavior</td>
<td>95%</td>
<td>91 - 97%</td>
<td>97%</td>
</tr>
</tbody>
</table>
“Interobserver agreement”
Impact on genotype phenotype analysis

Proportion (%) of non-significant studies ($p > 0.05$) due to misclassification of location and behavior

<table>
<thead>
<tr>
<th></th>
<th>Location</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement (%)</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>Sample size 150</td>
<td>10.8</td>
<td>63.8</td>
</tr>
<tr>
<td>Sample size 300</td>
<td>0.6</td>
<td>29.7</td>
</tr>
<tr>
<td>Sample size 500</td>
<td>0.0</td>
<td>13.3</td>
</tr>
</tbody>
</table>

The left columns under each phenotype heading denote results for simulations providing a fictive 100% IOA. The right panels depict data as given for the actually observed IOA.
Different methods are performed for disease evaluation

Reinisch W. et al. Questionnaire Clinical Diagnosis and Imaging, CD consensus 2004
Enteroclysis vs CT-Enteroclysis for diagnosis of CD

- Skip-lesions: 34% vs 6%
- Abscesses: 16% vs 0%
- Fistulae: 36% vs 16%
- Strictures: 40% vs 30%

CT-Enteroclysis

N=50

* p< 0.01

Sailer, AJR 2005

Investigations of different sensitivities and specificities

Different IOA

Physicians classifying IBD patients are almost never those who report the radiological, pathohistological, surgical or even endoscopic findings upon which phenotyping is based.

Potential disagreement in primary source reports adds to the variation and may further contribute to inconsistencies.
IBDIS: overall agreement

Sex, diagnosis, age at diagnosis, height, standard weight, behavior, perianal fistula, indication immunosuppressives.

- Poor: Sonography
- Fair: Ankylosing Spondylitis
- Moderate: Nikotin, incontinence histo term. Ileum, joints
- Good: X-Ray term. Ileum, pregnancy, bone density, steroids, infliximab, skip lesion, granuloma
- Very good: Overall agreement

Öfferlbauer-Ernst A, et al. in preparation
### Block A Location

**Editing Datasheet ID: 36**

- **Center:** AKH-Wien
- **Patient:** Smith John
- **Social Security number:** 12345-151759
- **Last Update:** 03.05.2004
- **Diagnosis:** Crohn's disease
- **Age at diagnosis (years):** 40

#### New Examination

**Select method (and technique)**

<table>
<thead>
<tr>
<th>Method</th>
<th>Endoscopy - Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Endoscopy - Histology</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technique</th>
<th>Capsule endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 = Capsule endoscopy</td>
<td></td>
</tr>
</tbody>
</table>

| Examination Date        | 2002 May 8 (Default value: July 15th) |

#### Select Findings by Endoscopy - Histology-capsule endoscopy

<table>
<thead>
<tr>
<th>Segment</th>
<th>Endoscopy-Finding</th>
<th>Histology-Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>&lt;blank&gt;</td>
<td>&lt;blank&gt;</td>
</tr>
<tr>
<td>Jejunum</td>
<td>&lt;blank&gt;</td>
<td>&lt;blank&gt;</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Normal mucosa on macroscopic exam.</td>
<td>Normal mucosa on macroscopic exam.</td>
</tr>
<tr>
<td>Ileum</td>
<td>Consistent with CD discontinuous CD</td>
<td>Chronic inflammation NOS</td>
</tr>
<tr>
<td>Terminal Ileum</td>
<td>Intubation not possible</td>
<td>Intubation not possible</td>
</tr>
<tr>
<td>Nonterminal Ileum</td>
<td>Sera not examined or non-evaluable pathologies</td>
<td>Sera not examined or non-evaluable pathologies</td>
</tr>
</tbody>
</table>

**SAVE**
“Inter- vs. intraobserver agreement”
Location: VC vs IBDIS

Öfferlbauer-Ernst A, et al. submitted
Distribution of Montreal Classification at diagnosis

Location of CD

N = 242

Behavior of CD

Schenk C, et al. In prep
Distribution of Montreal Classification at diagnosis

N = 242

Behavior of ileum

Behavior of colon

Schenk C, et al. In prep
...clinical phenotype may be the most immediate and objective method to assess a disease...by means of a standardized, validated documentation...
…Classification is a condition of knowledge, not a condition of itself, therefore knowledge dissolves a classification…

Horkheimer & Adorno 1944
Is there a need for the establishment of a documentation standard in CD

Reinisch W. et al. Questionnaire Clinical Diagnosis and Imaging, CD consensus 2004
Aim of IBDIS

To harmonise and standardise documentation of IBD patients
Selection of IBD relevant parameters

Definition of parameters and its variables

Validity Testing by "Interobserver agreement"

Inclusion of patients one year after diagnosis in data-base and longitudinal follow-up

Platform for epidemiologic, pathogenetic and prognostic studies

Health educational and economic consequences

IBDIS (Inflammatory Bowel Disease Information System)
IBDIS: Selection of parameters

- 4/99-4/01 27 representatives of Austrian IBD study group selected in 3 consensus conferences IBD-relevant parameters

- Parameters grouped: epidemiology, diagnosis, complications, risk factors, pregnancy, surgical and conservative therapy

- Data-sheet, tested for practicability, completeness, and acceptance in > 300 patients with IBD
# IBDIS: Data-sheet

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>18</td>
</tr>
<tr>
<td>Continuous</td>
<td>8</td>
</tr>
<tr>
<td>Binary</td>
<td>50</td>
</tr>
<tr>
<td>Ordinal</td>
<td>86</td>
</tr>
<tr>
<td>Nominal</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>186</td>
</tr>
</tbody>
</table>
IBDIS: Definitions of parameters and variables

- Basis for reproducible applicability and quality of data-base

- IBDIS includes > 200 definitions:
  - Used or challenged current definitions
  - Consented on uniformed definitions if many were available e.g. steroid-dependency, IC
  - Created new definitions if none were available
IBDIS: “Interobserver agreement”

- 16 charts of IBD patients were provided from centers in Austria
- Evaluation by 18 observers with data-sheet encompassing 186 IBD-relevant parameters according consented definitions
- 24494 single data were obtained for analysis of “interobserver agreement” of parameters and its variables
### Block G Therapy

**Editing Datasheet ID: 30**

**Center:** AKH-Wien  
**Patient:** smith john  
**Social Security number:** 12345-151759  
**Last Update:** 03.05.2004  
**Diagnosis:** Crohn's disease  
**Age at diagnosis (years):** 40

#### Immunosup. (=Immunosuppressives)

<table>
<thead>
<tr>
<th>Immunosuppressives</th>
<th>From</th>
<th>To</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>04.03.2000</td>
<td>06.07.2001</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Selected Immunosuppressive

- **Immunosuppressives:** Azathioprine

#### Time period

- **From:** 2000  
  - Mar.  
  - 4
- **To:** 2001  
  - Jul.  
  - 5

- **Indication:** Maintenance of remission after infliximab in a chronic act...
- **Outcome:** Clinical remission, defined as in 1 without complete disc...
Standardized IBD documentation in Europe

- IBDIS a tool to standardize documentation
- By means of a validated, electronic documentation program
- Currently an European interobserver agreement study on the IBDIS program is ongoing as ECCO project
Future prospects: Customized medicine?
Short History of Crohn’s Disease

- 1761 – Morgagni described a patient with “ileal passion”
- 1806 – Drs. Coombe and Sanders presented first case of Crohn’s to the Royal College of Physicians, England
  - Patient with lifelong history of abdominal complaints
  - At autopsy was found to have thickened, inflamed, stricture ileum
- 1913 – Dalziel reported nine cases of intestinal jejunitis, ileitis and colitis¹

¹Dalziel TK. BMJ 1913;2:1068
Diagnostic dilemma of IBD

Unified documentation system for IBD patients in international cooperations is required:

- For homogeneous recruitment of patients in clinical studies
- Correct interpretation of epidemiologic data
- Revelation of environmental and genetic determinants
„Intestinal inflammation ... Will remain a test of clinical acumen, drawing on relevant history, attentive physical examination, judicious laboratory testing, and detailed review of radiographic, endoscopic and pathologic date“
Guidelines on imaging reflect the gastroenterologist perceptions on the appropriateness of radiological methods and might differ from the views of a radiologist society!!!

Idea: distribution of the Imaging questionnaire among the latter; C. Bartram offers help
Diagnostic dilemma of IBD


- Analysis of misclassification in 1096 patients referred for participation in an IBD genetics study
- By reviewing the medical records 68 individuals (6.2%) had a change of diagnosis
- A 10% misclassification rate resulted in up to 40% loss of power to detect a true linkage when using a statistical model for a presumed IBD locus
Potential Pitfalls of Vienna classification (VC)

- Lack of standards for documentation apparent at VC
  - Established on 2 population and 3 referral center based data sets
  - No uniformed catalog of parameters
  - No uniformed definitions of included parameters
- VC includes 3 disease parameters not tested by IOA
- Additional parameters included in present data-bases w/o homogenous definitions
“Interobserver agreement” w/o definitions

General Hospital Vienna 1999, observer n = 5, cases n = 11
IBDIS: overall agreement
IBDIS: Endo-/Histo-agreement
“Inter- vs. intraobserver agreement”

\[
\text{inter\%} = \text{intra\%} - 18.6\%
\]

\[R^2 = 0.55\]

**Behavior**

**Histo Rectum**

- Sono C. ascendens
"Interobserver agreement" Learning by doing
"Interobserver agreement"
Problems of recognition

Ankylose
Gelenke
Knochendichte
falsch  richtig
fehlt
nicht unters.
Walter
The use of imaging findings from novel methods may support classification of a given disease, more objective and reproducible e.g. inflammatory vs fibrotic stricture.

Maglinte DDT et al. Maccioni et al 2000
Topical therapies, oral or systemic therapies may result in patchy healing depending on the timing of endoscopy or completeness of response.

The most accurate diagnosis may be made at the earliest evaluation, before anatomy and histology have been confounded by treatment, however diagnosis not stable within the first year !!!

Walter
IIBDIS provides a validated and reliable tool for obtaining results on prospective studies aiming to classify IBD!!

IIBDIS does not re-invent the wheel, but delivers the tyres which fit on our wheels!!!
I shall tell you what paths of inquiry alone there are for thinking:

#1. The one: that it is and it is impossible for it not to be.

This is the path of Persuasion, for it accompanies Objective Truth.

Parmenides 540 – 480 BC
„Nature has buried truth deep in the bottom of the sea“

„In truth we know nothing, for truth lies in the depth“

Democritus 460 – 400 BC
Classification of IBD

Our knowledge can only be finite, while our ignorance must necessarily be infinite.

Sir Karl Popper
A History to diagnose Crohn’s Disease II

- 1975 – Farmer, Hawk, and Turnbull\(^1\): on a combination of clinical features, procto-sigmoidocopic and roentgenographic findings, and when available histologic data (biopsy or operative) 4 initial anatomic involvements of CD (ileocolic, ileal, colonic amd anorectal)

- 1988 – Greenstein AJ et al\(^2\): on surgical specimen perforating and non-perforating indications of indications for operations discriminated

\(^1\) Farmer G et al. *Gastroenterology* 1975;68:627
“Interobserver agreement” in IBD

Steinhart AH, et al. IBD 1998;

- 15 experts evaluated 12 cases according to behavior by radiological, surgical and pathological reports.

- "Interobserver Agreement" was only fair with \( \kappa = 0.353 \) (<0.2 = poor agreement, 0.81-1.0 = very good agreement).

- Authors conclude: „concerns regarding applicability of behavior in studies of genotype/phenotype associations”.