Whipple’s Disease

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Whipple’s disease

- Clinical Relevance and Diagnosis: GI tract and beyond
- Microbiology
- Immunology and Pathogenesis
- Clinical Features
- Therapy
### „Classical“ Whipple’s disease

<table>
<thead>
<tr>
<th>MAJOR SYMPTOMS</th>
<th>%</th>
<th>SPECIFIC ORGAN MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>80-100</td>
<td>Gastrointestinal 90-100</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>70-100</td>
<td>Joints / Muscles 80</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70-85</td>
<td>Heart / Lung 50</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>50-90</td>
<td>CNS 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FREQUENT SYMPTOMS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>40-60</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>40-60</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>35-60</td>
</tr>
<tr>
<td>Hypotension</td>
<td>30-80</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>20-45</td>
</tr>
<tr>
<td>Heart murmurs</td>
<td>30-40</td>
</tr>
<tr>
<td>Occult Blood</td>
<td>20-30</td>
</tr>
<tr>
<td>Myalgias</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal tumors</td>
<td>15-25</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>20</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5-20</td>
</tr>
<tr>
<td>Ascites</td>
<td>10</td>
</tr>
</tbody>
</table>
Whipple’s disease

Time from first symptom to diagnosis in 30 patients

Arthropathy: First symptoms in 2/3 of patients

Arthropathies often vanish with the occurrence of GI symptoms
Whipple’s disease – Joint Manifestations

Often non-destructive migratory oligo- or polyarthritis

Axial Arthritis (Sakroileitis): 30% clinical, 20% radiologic

Xavier Puechal, Curr Op Rheumat, 2001
Infrequent: Destructive Arthritis

Carpal and carpometacarpal ankylosis

Apophyseal joint fusion

Puechel et al, Arthr Rheumat, 2007
Immunosuppressive therapy for unclear arthropathy and diagnosis of WD in the later course

Retrospective study in 133 patients:
- 56 received immunosuppresive therapy
- All patients experienced clinical deterioration
- 57% of patients developed diarrhea soon after immunosuppressive therapy

Lagier, Medicine 2010
Neurological symptoms in WD are not rare. 20% of all WD patients exhibit neurological symptoms:

- Dementia: 57%:
- Ophtalmoplegia: 43%:
- Psychiatric symptoms: 37%:
- Epilepsia/myoclonus: 20%/21%:
- "Oculomasticatory myorhythmia": 17%:
- Ataxia: 17%:

Louis et al., 1996; Gerard 2002

Occurs also as isolated CNS disease, i.e. localized WD

Positive PCR for *T. whipplei* in spinal fluid in 50% of patients at time point of first diagnosis

Flair and T1 sequences

Black et al., AJNR 2010
Whipple’s disease and Heart valves
(WD occurs also isolated, i.e. localized WD)
- Cardiac valves from 1135 pts., 255 with detectable infections

- Most frequently: streptococci, staphylococci, enterococci, **T. whipplei (6.3%)**

- Less frequent: Bartonella, Coxiella, Haemophilus, Actinobacillus, and others

⇒*Tropheryma whipplei* is the most frequent bacterial agent of culture-negative endocarditis
Diagnosis of "Classical" Whipple's disease

Endoscopic aspect

PAS – positive cells

Diagnosis by endocapsule, iscan®, confocal microscopy
Immunohistology of *T. whipplei* control

EM of *T. whipplei*: Size 0.2 x 2 µm

PAS-positive macrophages

FISH: control

Whipple rRNA

Besides histology: *T. whipplei* specific PCR as an important diagnostic technique:

Fredricks et al., JID 2001

Marth et al., Lancet ID 2016
Diagnostic approach to Whipple’s disease

Atypical

Symptoms of Whipple’s disease

PAS test preferentially from duodenal / jejunal tissue
(low specificity if biopsy is taken from extraintestinal tissue)

Negative: WD improbable

Second test for safe exclusion (PCR, IH)

Two negative tests: WD excluded

In atypical cases consider: Stool PCR

Positive: WD possible

Second test for confirmation (PCR, IH)

Two positive tests: WD confirmed

Third test in cases of doubt (IH or EM)

Indication for therapy

Two positive tests: WD confirmed

PCR test from CSF recommended to exclude CNS affection
Whipple’s disease

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GENOME of T. whipplei

1) Reduced genome ("parasitic bacterium")

2) Lack of AA metabolic pathways (e.g. no thioreductine)

3) High variability of surface structures

⇒ dependency from the host

⇒ immune-evasion as possible advantage to survive

Bentley et al, Raoult et al., 2003
Tropheryma whipplei: An environmental antigen with human-to-human transmission

- *T. whipplei* detectable in (waste) water samples  
  Maiwald et al. 1998

- *T. whipplei* in saliva, gastric juice, duodenum in 5-30% of healthy subjects  
  Ehrbar et al. 1999, Zinkernagel et al., 2003

- 25% PCR positive stool samples in 64 sewage plant workers;  
  Schöniger-Hekele 2007

- Relatives of WD patients are frequently (38%) carriers  
  Fenollar, Emerg Inf Dis 2012

- 20% PCR positive stool samples in WD patients after therapy  
  Marth unpublished

- Lifelong susceptibility: Relapses with different *T. whipplei* strains  
  Lagier, 2011

- No hints for reservoir in animals or ticks etc.  
  Dutly 2001, Fenollar 2008

- **In Europe asymptomatic carriage 2-4% (up to 11%)**

- **In Africa: Up to 31% (risk higher depending on hygienic status)**
Transitent and acute Whipple’s disease

205 children with diarrhea:
- in 49 children bacteria/virus in stools
- in 36 cases T. whipplei in stools
- More frequent than Rotavirus

⇒ T. whipplei as most frequent diarrheal antigen
⇒ Transient and acute Whipple’s disease
Transitient and acute Whipple’s disease:
Frequency of *T. whipplei* during diarrhea and fever in Senegal

- **497 stools**, 370 saliva, 454 sera analyzed by quantitative PCR
- Stool PCR:
  - **31% of all patients had *T. whipplei* (TW)+ stool PCR**
  - 49% of diarrheal patients had TW pos. stool PCR
  - **75% of children (0 to 4 years) had TW pos. stool PCR**
  - 30% of children (5 to 10 years) had TW pos. stool PCR
  - 17% of individuals (> 11 years) had TW pos. stool PCR
- Saliva samples were infrequently positive (3,5%)
- Seroprevalence
  - 72% overall, after diarrheal episode
  - 2/3 seroconversion

*Keita et al., Plos.ntds 2011*
Whipple's disease

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Whipple’s disease – hints to a immunological pathogenetic factors

**Epidemiology:**

Ratio m : f = 8 : 1  (new data: 3 : 1)

European cohort (>100 pat.):
DRB1*13, DQB1*06;

**Histopathology:**

Reduced phagocytic capacity, diminished cellular degradation of bacteria in macrophages

=> long intracellular persistence

(Martinetti et al., Gastroenterology 2009)
Decrease of IgA+ plasma cells in duodenum

IgG2 serum concentration (ng/ml)
analysis of 69 WD pts.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treated WD</th>
<th>Untreated WD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51 +/- 9.2</td>
<td>46.6 +/- 11.5</td>
<td>44.4 +/- 9.9 *</td>
</tr>
</tbody>
</table>

* p < 0.0009 vs. control

Geelhaar et al.
Infect Immunity 2010

Humoral immunity in WD
Studies on immunoglobulin levels in WD patients

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>WD patients</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG2 (mg/dl)</td>
<td>292 ± 28</td>
<td>429 ± 107</td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>119 ± 26</td>
<td>155 ± 46</td>
</tr>
<tr>
<td>IgA (mg/dl)</td>
<td>421 ± 63</td>
<td>242 ± 86</td>
</tr>
</tbody>
</table>

Ratio: \( \frac{\text{IgG2} + \text{IgM}}{\text{IgA}} \) = 0.97

For WD patients \( n=29 \) for IgG2, and \( n=27 \) for IgM and IgA.
Th1 / Th2 dysregulation in WD

Marth et al., Gastroenterology 2002
Mucosal level

IFN-γ secretion of LPL stimulated with α-CD2 and α-CD28

Serum IL-12p40 in 40 WD patients

Interleukin-12 in situ

Marth et al., Gastroenterology 1997; 2002

Kalt et al., AJG 2005
Similar for CD4+CD154+

WD Subgroup analysis: no difference;
SEB or other bacteria stimulation: control = Whipple

Moos et al, JI 2006
Reduced Th17 / Th1, increased TGF-β response in WD

Schinnerling et al. JI 2011
Cytokine genetic profile in WD

- Cytokine genes analyzed in 111 German and 22 Italian patients; 341 controls using PCR sequence specific primers
- **High producers of IL-4 (genotype IL4-590T/T):**
  WD 5.34% vs. 1.17% (p<0.01)
- **Low producers of TGF-β1 (genotype TGF-β1+869C/C +915C/C):**
  12.3% vs. 3.8% (p<0.0002)
- No differences cytokine genes of IFN-γ, IL-12
- Profile is skewed toward Th2 responses
- **This favors a M2 macrophage (chronic inflammatory) milieu**
- Low Th1 responses may be secondary

*Biagi et al. Eur J Clin Microbiol Infect Dis 2012*
After contact with *T. whipplei*, intestinal macrophages shift to M2 phenotype and promote Th2 reactions.
Increased alternatively activated macrophages

Summary:

Defective (mucosal) immune responses are insufficient to kill and degrade *T. whipplei* in intestinal macrophages
Whipple’s disease

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Infection with Tropheryma whipplei

Classic WD (CWD)

Localized WD (LWD)

WD associated with immuno-suppression (IS \( \rightarrow \) WD)

Asymptomatic carrier of Tw / WD (AWD)

Transient and acute WD (TWD)
Association of *T. whipplei* infection with immunosuppression

- Genome of *T. whipplei*: „parasitic“ bacterial features
- Mucosal immune defects in classical WD
- Discrepancy: Widespread bacterium, rare clinical symptoms
- Is there an additional trigger for the switch of asymptomatic carriage with the low-pathogenic *T. whipplei* to systemic WD symptoms?
<table>
<thead>
<tr>
<th></th>
<th>Patient group I</th>
<th>Patient group II</th>
<th>Patient group III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>41</td>
<td>61</td>
<td>1059</td>
</tr>
<tr>
<td><strong>Therapy with TNFI</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Therapy with non-biological DMARD</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Signs or symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>percent (patient number)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>85,4 (35)</td>
<td>88,5 (54)</td>
<td>70-90</td>
</tr>
<tr>
<td>Fever</td>
<td>53,6 (22)</td>
<td>44,3 (27)</td>
<td>35-60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>36,6 (15)</td>
<td>42,6 (26)</td>
<td>80-96</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35,3 (18)</td>
<td>54,1 (33)</td>
<td>70-85</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>12,2 (5)</td>
<td>1,6 (1)*</td>
<td>0,16 (17)*</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>12,2 (5)</td>
<td>3,3 (2)</td>
<td>0,08 (9)*</td>
</tr>
<tr>
<td>IRIS</td>
<td>16 (4)</td>
<td>22,9 (14)</td>
<td>0</td>
</tr>
</tbody>
</table>

*[Referenced work: Marth, WJC 2014; APT 2015]*
<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Patient number (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of severe complications</td>
<td>49 (1,88 complications per patient)</td>
</tr>
<tr>
<td>Total number of affected patients</td>
<td>26 out of 41 patients (63%)</td>
</tr>
<tr>
<td>Fever, septic temperatures</td>
<td>16</td>
</tr>
<tr>
<td><em>T. whipplei</em> septicaemia, <em>T. whipplei</em> in blood</td>
<td>6</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>5</td>
</tr>
<tr>
<td>Endocarditis (many with valve replacement)</td>
<td>5</td>
</tr>
<tr>
<td>IRIS</td>
<td>4</td>
</tr>
<tr>
<td>Spondylitis (multisegmental)</td>
<td>4</td>
</tr>
<tr>
<td>Colitis, fistula, perforation</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic symptoms, meningitis</td>
<td>3</td>
</tr>
<tr>
<td>Severe skin manifestation</td>
<td>3</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2</td>
</tr>
<tr>
<td>Severe eye complications, blindness</td>
<td>2</td>
</tr>
<tr>
<td>Ankylosing sacroiliitis</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

Complicated course of WD associated with TNF inhibitor therapy

*Marth, WJC 2014; APT 2015*
IRIS = fever and other symptoms (shortly) following the start of the antibiotics
PCR for *T. whipplei* is negative (no viable bacteria)
15/87 pts with WD developed IRIS

**Table 2. Characteristics of and Laboratory Findings in Patients With and Without IRIS After Treatment of Whipple Disease***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Without IRIS</th>
<th>Patients With IRIS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>57 (11) [55–60]</td>
<td>60 (10) [54–65]</td>
<td>0.43</td>
</tr>
<tr>
<td>Women/men, n/n</td>
<td>16/55</td>
<td>4/11</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>21 (4) [21–22]</td>
<td>23 (3) [21–24]</td>
<td>0.055</td>
</tr>
<tr>
<td>Mean ESR (SD), mm/h</td>
<td>50 (27) [43–58]</td>
<td>32 (23) [12–51]</td>
<td>0.063</td>
</tr>
<tr>
<td>Lymphadenopathy, n/n (%)</td>
<td>23/71 (32.4) [21.8–44.5]</td>
<td>7/15 (46.7) [21.3–73.4]</td>
<td>0.37</td>
</tr>
<tr>
<td>Arthritis, n/n (%)</td>
<td>57/71 (80.3) [69.1–88.8]</td>
<td>14/15 (93.3) [68.1–99.8]</td>
<td>0.45</td>
</tr>
<tr>
<td>Diarrhea, n/n (%)</td>
<td>55/71 (77.5) [66.0–86.6]</td>
<td>5/15 (33.3) [11.8–61.6]</td>
<td>0.002</td>
</tr>
<tr>
<td>CNS infection with <em>Tropheryma whipplei</em>, n/n (%)</td>
<td>19/46 (41.3) [27.0–56.8]</td>
<td>7/9 (77.8) [40.0–97.2]</td>
<td>0.069</td>
</tr>
<tr>
<td>Weight loss, n/n (%)</td>
<td>58/69 (84.1) [73.3–91.8]</td>
<td>5/15 (33.3) [11.8–61.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous immunosuppressive treatment, n/n (%)</td>
<td>11/71 (15.5) [8.0–26.0]</td>
<td>12/15 (80.0) [51.9–95.7]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Feurle et al., J. Ann Intern Med, 2010*

**Biagi et al. 2012:**
- IRIS in Whipple’s disease is correlated with the HLA DQB1*06 allele
- HLA alleles DR1 and DQB1 also overrepresented in leprosy (characterized by IRIS)
- all are associated with a lack of cell-mediated immunity against the infectious agent
Association of *T. whippelii* infection with immunosuppression

- Diarrhea after the start of immunosuppressives (initiated because of unclear arthropathies)
- Localized WD and complicated WD after TNF blockers (initiated because of unclear arthropathies)
- Immune-reconstitution-inflammatory syndrome (IRIS) in WD patients who received immunosuppressives

=> Possible expansion of the pathogenetic concept !?
Clinical features and pathogenetic factors in *Tropheryma whipplei* infection: The "Second Hit"-Hypothesis

Problem in the old pathogenetic concept of WD: Discrepancy of widespread bacterium, but rare clinical presentation

- **TWD** = Transient and acute (short-term) WD, e.g., diarrhea, fever
- **AWD** = Asymptomatic WD / carrier of *T. whipplei* (e.g., family member, after antibiotic therapy)
- **LWD** = Localized WD (isolated organ symptoms)
- **IS → WD** = WD associated with immuno-suppression
- **CWD** = Classical WD
  - Systemic state
  - Steady state
  - Prodromal state

Mucosal immune defect, HLA-association

Second hit: Immuno-Modulation
Whipple’s disease

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## Therapy of Whipple’s disease

### Frequency of Relapse

<table>
<thead>
<tr>
<th>Initial treatment with</th>
<th>percent relapses</th>
<th>no. of treated pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclin</td>
<td>32.2 %</td>
<td>115</td>
</tr>
<tr>
<td>Penicillin / Streptomycin</td>
<td>11.8 %</td>
<td>34</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>4.3 %</td>
<td>23</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>27.6 %</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>25 %</td>
<td>201</td>
</tr>
</tbody>
</table>

*Misbah et al., 2000*
Therapy in 27 patients

TCN = tetracycline
CTM = cotrimoxazol

Feurle und Marth, 1994
51 patients registered

42 patients meet inclusion and exclusion criteria

Ceftriaxon

Meropenem/Imipenem

21

21

diagnosis not confirmed
diagnosis not confirmed

death from myocardial infarction
death from aspiration

1

1

20

20

1

1

19

19

2 weeks iv

1 year cotrimoxazol po

Feurle, Junga, Marth
Gastroenterology 2010
SIMW - Results

- 42 pts:
  - 2 excluded: no WD
  - 2 died of aspiration, myocardial infarction
  - All remaining 38 patients achieve clinical remission

- 3 years after termination of therapy
  - No CNS relapse
  - No other clinical relapse

- No difference between meropenem and ceftriaxone

- Very good treatment results in study patients!
Therapy of Whipple’s disease

Two positive diagnostic tests: WD confirmed
Indication for therapy

Induction therapy (ceftriaxone iv) for two weeks
(alternative: meropenem)

Long-term therapy (cotrimoxazole p.o.) for one year
(alternative: doxycycline plus hydroxychloroquine)

Follow-up:
Endoscopy and PAS test after 6 and 12 months.
In unclear cases additional PCR (or ICH).
Long-term follow-up (relapsing cases!).
Conclusions I

- Broad spectrum of *T. whipplei* infection:
  NOT only a rare systemic infection (Classical WD)

- WD occurs on a specific host background caused by an environmental and „parasitic“ bacterium

- Defective *Tw* specific immune responses in patients

- Macrophage infiltration with *T. whipplei* promotes mucosal Th2 responses

- Immunosuppression leads to progression of infection (Second hit)
Conclusions II

- **WD diagnosis:**
  - Duodenal biopsy if suspected, also in unclear arthropathy, CNS symptoms, endocarditis
  - PAS stain plus PCR (or immunohistochemistry)
  - CSF analysis at time of first diagnosis

- **WD therapy:**
  - Ceftriaxone 2 wks iv, Cotrimoxazole 1 yr po
  - Alternative: doxycycline plus hydroxychloroquine
  - Prolonged / individual therapy: endocarditis, CNS disease
  - Only positive PCR without symptoms: No therapy
Thank you !