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Tropheryma whippelii pathogenesis

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Tropheryma whippelii and Whipple's disease

1907 First description of Whipple's disease (Metabolic trouble)

1991 Identification of the agent of Whipple's disease
 A rare bacterium causing a rare chronic infection

2000 First establishment of a strain of *T. whippelii*

2013 *T. whippelii*. A common bacterium
 Chronic infections
 Asymptomatic carriage
 Acute infections

-Lagler JC, Fenollar F, Raoult D. From Whipple's disease to *T. whippelii* infections. Med Mal Infect. 2010;40:111-82.
 -Schneider T, Moos V, //, Raoult D. Whipple's disease: New aspects on pathogenesis and treatment. Lancet Infectious Diseases 2008;8:179-90.
 -Fenollar F, Puechal X, Raoult D. Whipple's Disease. N Eng J Med 2007;356:55-66.

Prevalence of *T. whippelii* carriage
-Kaïta AK, Raoult D, Fenollar F. *T. whippelii* as a commensal bacterium. Future Microbiol. 2013;8:57-71.

- Saliva and stools specimens:

- Age
- Exposure
- Geographical area

Population	Young children in France	French general adult population	Underground sewer workers	Homeless people	Adults in rural Senegal	Relatives of <i>T. whippelii</i> patients or carriers	Children in rural Senegal
Prevalence	0%	3%	12%	13%	17.4%	36%	48%
Prevalence	NA	0.2%	3%	3.7%	1.7%	10%	9.5%

- Asymptomatic carriage of *T. whippelii* in saliva : Only observed for people with a carriage in stools

- Duodenal biopsy:

- 0.25%

Acute infections: Pneumonia (2007)

- In the bronchoalveolar lavage fluid (BAL) of a child with pneumonia (USA)
Harris J, De Groot MA, Sagal SD, //, Posner AS. PNAS 2007;104:20529-33.

- In 3% of BAL (210) from patients with pneumonia in intensive care units (Marseille, France)
Boissier S, Prost B, Jeffrey M, Raoult D. 2010;16:259-263

Broad range 16S rRNA PCR detected only *T. whippelii* in the BAL of a patient with pneumonia

Molecular detection of *T. whippelii* in association with other bacteria from the saliva in the BAL of other patients with aspiration pneumonia

Isolation of *T. whippelii* in pure culture from the BAL of a patient with interstitial acute pneumonia
Fenollar F, Ponge T, La Scala B, Lagler JC, Lelebre M, Raoult D. J Infect. 2012;65:275-8.

- Molecular detection of *T. whippelii* in the blood specimens of patients with fever and cough as the main manifestations
Fenollar F, Medjanikov O, Sokolovskiy C, //, Raoult D. Clin Infect Dis 2010;51:515-21.

- *T. whippelii* and HIV?
Lozupone C, Cola-Gomez A, Palmer BE, //, Fontenot AP. for the Lung HIV Microbiome Project. Am J Respir Crit Care Med. 2013 Epub ahead of print.

Acute infections: Gastro-enteritis (2010)

- In 15% of stools of 241 children from 2-4 years-old hospitalized in Marseille (France)
- High bacterial loads (>10⁶/g)
- Absence of *T. whippelii* in stools after patient recovery
- Positive serology in patients significantly higher than in controls

-Raoult D, Fenollar F, Rotain JM, Minocher P, Bosduro E, Li W, Garnier JM, Richet H. EID 2010;16:776-82.

- Murine model with previously inflamed colonic tissues

-Al Moussawi K, Malou N, Mege JL, Raoult D, Desnues B. JID. 2011;204:44-50.

Arguments about the role of *T. whippelii* as an agent of gastroenteritis

	Arguments in favor	Arguments against
Epidemiological	-Very common in the age group of early socialization (15%) in France -Presence of a circulating clone (genotype 3) in diarrheic children; the same genotype causes one-third of the cases during a survey	
Microbiological	-No cases in age-matched controls -High bacterial loads (>10 ⁶ /g) -Absence of <i>T. whippelii</i> in stools after patient recovery -Positive serology in patients significantly higher than in controls	-Presence of asymptomatic cases (2.4%) in French adults -Presence extremely common in healthy children in rural Senegal (Africa) -33% co-infection with identified pathogens
Experimental	-Murine model with previously inflamed colonic tissues	

T. whipplei bacteremia during fever in Senegal (2010)

Fenollar F, Medannikov O, Socolovschi C, Bassene H, Diatta G, Richei H, Tall A, Sokhna C, Trape JF, Raouil D. *T. whipplei* bacteremia during fever in Rural West Africa. Clin Infect Dis 2010;51:515-21.

- Role of *T. whipplei* in febrile patients with a negative test for malaria in rural Senegal?

Prospective study in Dielmo and Ndiop
From November 2008 through July 2009

↓

Blood specimens were collected by finger pricks with a lancet stick

↓

First step of DNA extraction done directly in the village dispensary:

1. Blood digestion, binding and washing of samples with Qiagen columns
2. Columns with the bound and dried DNA inside stored at +4°C

↓

Final elution performed later in France prior to *T. whipplei* PCR

Presence of *T. whipplei* DNA in blood specimens from 13/204 (6.4%) tested samples

T. whipplei bacteremia
12/103 (11.6%)
Stool screening:
Patients without *T. whipplei* bacteremia: 3/6
Patients without *T. whipplei* bacteremia: 1/250

Saliva screening:
Patients with *T. whipplei* bacteremia: 0/7
Patients without *T. whipplei* bacteremia: 0/21

No correlation observed between the presence of *Tw* in the stools and saliva and bacteremia

Table 1. Epidemiologic and Clinical Characteristics of the 13 Patients with *Tropheryma whipplei* Bacteremia and Results of the Systematic Screening to Look for *T. whipplei* in Stool and Saliva Specimens, April 2009.

Patient	Village	Sex, age	Date of sampling	Temperature, °C	Clinical symptoms	Test results for stool and saliva
A	Ndiop	F, 7 months	18 December 2008	39.2	Thirst, cough	Positive, NA
B	Dielmo	M, 9 months	23 December 2008	38.7	Cough, rhinorrhea	Negative, negative
C	Dielmo	F, 11 months	19 December 2008	38	Headache, thirst, fatigue, sleep disorders	NA, negative
D	Dielmo	F, 1 year	1 January 2009	39.7	Headache, fatigue, cough	NA, negative
E	Dielmo	F, 2 years	3 January 2009	38.7	Headache, fatigue, cough, rhinorrhea	Negative, negative
F	Dielmo	F, 3 years	4 January 2009	38	Low appetite, diarrhea, cough	Negative, NA
G	Dielmo	M, 3 years	5 January 2009	39.1	Headache, fatigue, cough, rhinorrhea	Positive, NA
H	Dielmo	F, 4 years	16 January 2009	38.5	Headache, thirst, low appetite, fatigue, cough, rhinorrhea, sleep disorders	Positive, negative
I	Dielmo	M, 9 years	22 January 2009	38	Cough	Negative, NA
J	Dielmo	M, 1 year	7 January 2009	38.1	Cough, rhinorrhea	Positive, negative
K	Dielmo	M, 15 years	21 April 2009	39.5	Sleep disorders, fatigue, headache, low appetite	Negative, NA
L	Dielmo	F, 39 years	13 April 2009	39.5	Headache, sleep disorders, low appetite, thirst, fatigue, rhinorrhea	Negative, negative
M	Dielmo	M, 49 years	24 April 2009	39.6	Low appetite, cough, sleep disorders, vomiting	NA, NA

NOTE. NA, not available.

- Cough: Significantly more frequent in febrile patients with *T. whipplei* bacteremia (10/13) than in the 191 febrile episodes without *T. whipplei* bacteremia (64/191; $P=0.002$).

Does the presence of *T. whipplei* in blood and the clinical symptoms?

T. whipplei has been recently suggested as an agent of pneumonia

Detection of *T. whipplei* DNA in blood from control groups:
Blood donors: 1/174
French people without WD: 0/973
French stools carriers of *T. whipplei*: 0/18

↓

- Our findings suggest that *T. whipplei* is an agent of unexplained fever in rural West Africa

Looking for *T. whipplei* source and reservoir in Senegal

Kella AK, Medannikov O, Ralmanov P, J, Fenollar F. Am J Trop Med Hyg. 2013;88:339-43.

105 water samples
92 canaris
6 wells
7 water open

317 Ixodid ticks

118 stools of "domestic" animals
Chickens, donkeys, goats, cattle, ducks, domestic pigeons, sheep, dogs

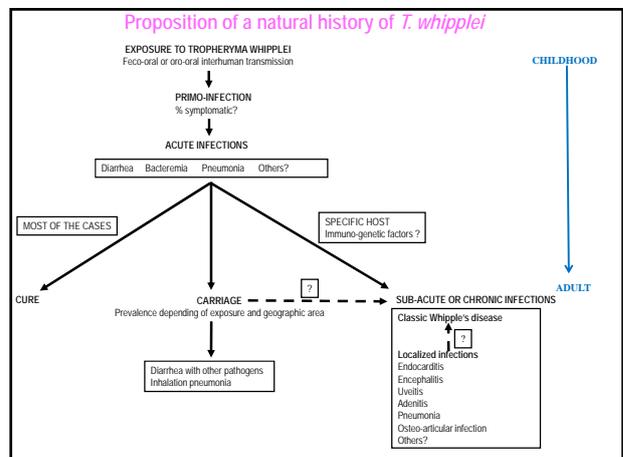
239 fleas

207 dust samples

76 mosquitoes
A. gambiae

44 lice

Humans:
Currently the main identified reservoir and source of *T. whipplei* in these populations



Immunologic factors

Moss V, Schneider T. The role of T cells in the pathogenesis of classical Whipple's disease. Expert Rev Anti Infect Ther. 2012;10:253-5.

- Inadequate stimulation of T-cells
- Dysregulated T-cell functions :
- Persistent decrease or lack of *Tiw*-specific Th1 reactivity (↓ IFN-γ)
- Increase of Th2 activity (↑ IL-10 and ↑ IL-4)



Genetic factors

Keita AK, Raouf D, Fenollar F. *T. whipplei* as a commensal bacterium. Future Microbiol. 2013;8:57-71.
Martinet M, Blagi F, Badulli C, et al. The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. Gastroenterology 2009;136:2289-94.

Besides, currently, several findings suggest a genetic predisposition for Whipple's disease:

- (1) Most of the patients are Caucasian.
- (2) Familial-proved cases of this rare disease have been observed.
- (3) A strong geographical specificity for this disease is also reported.
- (4) A higher frequency of the HLA alleles DRB*13 and DQB1*06 has been detected in patients with classic Whipple's disease than in controls.

Conclusions

- Whipple's disease:

- 1907: Metabolic disease
 1991: Infectious disease caused by a rare bacterium
 2013: Infection caused by a frequent bacterium, *T. whipplei*

T. whipplei is involved in multifaceted conditions

- Main hypothesis:

Many persons in any given population are exposed to *T. whipplei*

AND

Some of those with predisposing immuno-genetic factors
 As yet undefined
 Subsequently develop the disease