Whipple's disease

Whipple's disease, caused by *Tropheryma whipplei*, is a rare systemic, often chronic, bacterial infection that presents in a myriad of ways in patients of all ages. Although commonly found infecting the small bowel, its presentation is highly variable; it has also been shown to cause culture-negative bacterial endocarditis and acute pneumonia, as well as skin, joint and eye infections. This review explains when *T. whipplei* should be considered, how to test for its presence, and what treatments can be used to eradicate it.

History of Whipple's disease

American trainee pathologist George Whipple first described the disease in his 1907 autopsy report, published in the *Johns Hopkins Hospital Bulletin* (Whipple, 1907). He attributed the death of a fellow physician to a novel condition he called lipodystrophia internalis or intestinal lipodystrophy. This was typified at the cellular level by granular material (rods) residing within the cells lining the small bowel and the lymph nodes. Although Dr Whipple did not know these rods which he visualized using silver stain were bacteria, clinicians were able to confirm this in 1961 using electron microscopes (Yardley and Hendrix, 1961).

In 1991 nucleic acid amplification and 16s RNA sequencing of duodenal biopsies finally categorized *T. whipplei* as an intracellular bacterial pathogen, part of the aerobic actinomycetes family (Relman et al, 1992). Later that same decade successful culturing in human fibroblast cells (HEL) found this bacillus to be remarkably slow growing – doubling every 18 days (Raoult et al, 2000) (by comparison, *Escherichia coli* doubles within 20–30 minutes).

These relatively recent developments in molecular diagnostics have allowed researchers to better understand how *T. whipplei* affects humans and are increasing the understanding of Whipple's disease epidemiology and treatment. Much of what is known today about treating Whipple's disease has been documented in the past 15 years.

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Epidemiology and pathogenesis

Whipple's disease is a rare opportunistic infection – affecting 1 in 1 000 000 (Schneider et al, 2008) – and predominantly affects Caucasian patients in their fifties (Fenollar et al, 2007) who have been in contact with soil. American data demonstrate a higher prevalence among men (8M to 1F) (Dobbins, 1987), but data from Germany show a higher prevalence among women (von Herbay et al, 1997). Often those affected work in sewers (Keita et al, 2013a) or reside in soiled environments (farmers), but the disease also occurs in clusters of people living in close quarters such as families and in hostels (Fenollar et al, 2012; Lagier et al, 2014). Acquisition of the organism, whether asymptomatic or infectious, appears to be faeco-orally (Lagier et al, 2014). *T. whipplei* is also present in respiratory samples, particularly in HIV-positive individuals, which may indicate colonization or an alternative primary route of infection (Lozupone et al, 2013).

Asymptomatic carriage of *T. whipplei* in Europe ranges between 2% and 11% in general populations (Fenollar et al, 2012; Lagier et al, 2014). Certain populations such as homeless and sewer workers have higher rates of carriage, at 12% and 26% respectively (Schöniger-Hekele et al, 2008; Keita et al, 2013b). Carriage in children appears endemic in children tested in France and Senegal (Fenollar et al, 2007, 2012; Raoult et al, 2010). To date humans appear to be the only reservoir for *T. whipplei*.

The small intestine – specifically the duodenum and jejunum – is most frequently infected. Histologically the villi are flattened, lacteals dilated containing yellow lipid secondary to blocked lymphatics. Biopsied samples demonstrate a lamina propria packed with periodic acid-Schiff-positive macrophages with intracellular bacilli (*Figures 1* and *2*). These changes cause the steatorrhoea and malabsorption leading to

Figure 1. Photomicrograph with periodic acid-Schiff positive ('PAS-positive') inclusions with characteristic purple-stained foamy macrophages.

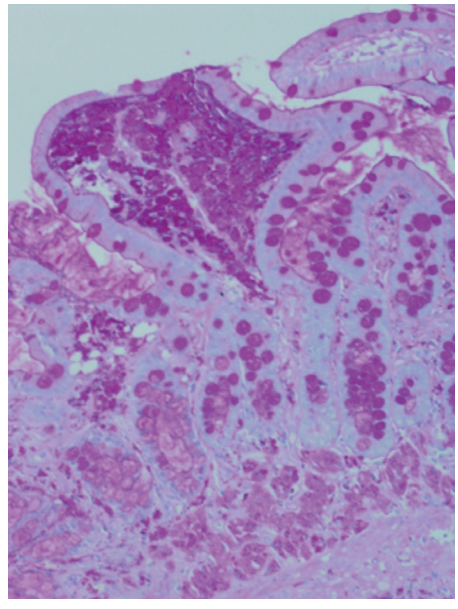

Figure 2. Transmission electron microscopy image of the duodenal biopsy (x10400). Small rod-shaped bacteria of *Tropheryma whippleii* can be seen (arrow).

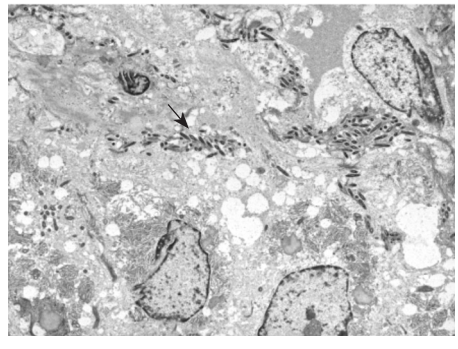

Table 1. Other possible periodic acid-Schiff/polymerase chain reaction positive tissues which can be sent for periodic acid-Schiff or polymerase chain reaction

Heart	Lung
CSF and CNS tissue	Eyes
Vitreous body	Ascites
Bone marrow	Abdominal viscera
Joints and synovium	Lymph nodes
Bone marrow	Endocrine glands

Adapted from Dobbins (1987)

anaemia and weight loss most often seen in the classical form of the disease. Polymerase chain reaction-positive and periodic acid-Schiff-positive macrophages can be seen in other tissue (*Table 1*).

Clinical presentation

Infection with *T. whipplei* can present in many ways (*Table 2*). In the classical form a patient will present with weight loss, diarrhoea and arthropathy, although not necessarily simultaneously. The patient may have fever, lymphadenopathy, melanoderma, abdominal pain, cough or other non-specific signs. A full blood count almost always demonstrates anaemia and hypoalbuminaemia will be notable on the biochemistry.

Acute cases present frequently as a self-limiting diarrhoeal disease (Gautret et al, 2014; Lagier et al, 2014), although pneumonia has been found in a child (Harris et al, 2007) and among HIV-positive adults (Lozupone et al, 2013). Bacteraemias have been reported in Senegal (Fenollar et al, 2010).

CNS infections and endocarditis are localized chronic examples of Whipple's disease. To date endocarditis caused by *T. whipplei* has had fewer than 100 case reports in the literature and can present with cardiac insufficiency or an embolic event. However, this in itself does not differentiate it from other more common causes of bacterial endocarditis. The British Society of Antimicrobial Chemotherapy (Gould et al, 2012), Infectious Disease Society of America/American Heart Association (Baddour et al, 2015) and European Society of Cardiology (Habib et al, 2015) guidelines for culture-negative endocarditis note how rare Whipple's disease diagnoses are and therefore advise testing only if all other infectious causes are excluded. Constrictive pleurocarditis and pericarditis is described although this is more commonly seen at post mortem (Stojan et al, 2013).

Table 2. Signs and symptoms of Whipple's disease

Sign/symptom	Frequency
Weight loss	90%
Arthralgia	85%
Diarrhoea	80%
Abdominal pain	60%
Fever	45%
Peripheral lymphadenopathy	45%
Hyperpigmented skin	35%
Oedema	30%
Cardiac murmur	30%
Myalgia	25%
Intra-abdominal lymphadenopathy	20%
Neurological or ocular signs	15%
Splenomegaly or hepatomegaly	10–15%
Chronic cough	15%
Ascites	10%
Other signs or symptoms	<5%

Adapted from Seguy (2007)

The presentation of CNS infections is variable and can include ataxia, cognitive impairment and supranuclear ophthalmoplegia.

Asymptomatic carriage is common and useful to note for the patient who might become iatrogenically immunosupressed. However, *T. whipplei* is unlikely to be found by chance as it requires a specialist lab and histopathology. However, if it is found, and a patient were to deteriorate or develop symptoms of Whipple's disease then treatment can readily take place. There is no evidence to support eradication in asymptomatic carriers.

Differential diagnosis

As with any disease a list of differentials should be considered. Testing for non-infectious causes (e.g. coeliac, Crohn's disease and malignancies especially lymphoma) should be carried out, in addition to looking for other infectious causes such as *Rhodococcus equi*, *Mycobacterium tuberculosis* and Histoplasma, especially if geographically relevant. Periodic acid-Schiff-positive cells can also be caused by melanosis coli or histiocytosis.

Diagnosis

Where Whipple's disease is suspected the clinical team should involve their local infection specialist before organizing biopsies. This is necessary to consider alternative diagnoses and whether advice from a Whipple's expert should be sought. If the decision is then taken to investigate for Whipple's disease, after careful consideration of the history and examination findings, it is advisable to then collect tissue samples for periodic acid-Schiff testing – most frequently this will be from the small bowel – and inform the pathologist of what is being looked for to guide appropriate staining. Adequate samples must be acquired in order to send for histology and polymerase chain reaction. In the UK there are two laboratories which test for *T. whipplei*. Quantitative real-time polymerase chain reaction can be performed on samples of EDTA blood, histological samples and CSF. Samples are sent via the local microbiology laboratory.

If the periodic acid-Schiff is negative, then Whipple's disease is unlikely, particularly where polymerase chain reaction and/or immunohistochemistry are also negative. If the polymerase chain reaction is positive for Whipple's disease in this scenario, then a third test (such as immunohistochemistry) should be performed. If this is negative then Whipple's disease can be ruled out. If this test is positive then a diagnosis of Whipple's disease can be made (Moos and Schneider, 2011). If the periodic acid-Schiff and polymerase chain reaction are positive, then a diagnosis of Whipple's disease can be made and therapy (discussed below) is indicated.

Testing the CSF should be considered for all Whipple's disease-positive cases to exclude CNS infection.

Infection control

While no cases of hospital transmission of *T. whipplei* have been reported, studies demonstrate that it can be passed to others. For example, relatives often carry the same genotype when screened (Fenollar et al,

KEY POINTS

- Whipple's disease is an infection caused by the Gram-positive bacterium *Tropheryma whipplei*.
- The incidence is approximately 1 in 1 000 000, and it is found in both sexes across all age groups.
- Whipple's disease presents clinically with pyrexia, malabsorption, unexplained articular pain and diarrhoea.
- *T. whipplei* can penetrate the CNS, cause infective endocarditis and be a cause of normocytic anaemia.
- Diagnosis of Whipple's disease requires positive periodic acid-Schiff staining and/or positive polymerase chain reaction of body fluid or tissue.
- Treatment, including duration, should be discussed with colleagues in infectious diseases or microbiology; it often lasts for a year but can be longer.

2012) and a homeless shelter demonstrated human transmission of a rare genotype of *T. whipplei* among non-related individuals (Lagier et al, 2014). Decisions on isolating a patient known to have *T. whipplei* to a single room with private toilet and handwashing facilities, whether the individual be asymptomatic or infected, should therefore be taken on a case by case basis in discussion with local infection control services.

As noted above, making the diagnosis of Whipple's disease is strengthened with a tissue biopsy. Endoscopes used in acquiring *T. whipplei* samples must not be disinfected using glutaraldehyde as La Scola and colleagues (2003) found that *T. whipplei* was resistant to decontamination with this agent (Raoult et al, 2006). Glutaraldehyde is no longer used in the UK to disinfect endoscopes, but readers elsewhere should check their local endoscope disinfection protocols.

Treatment

T. whipplei is susceptible to a variety of antibiotics including penicillin, streptomycin, trimethoprim-sulfamethoxazole, doxycycline, gentamicin, vancomycin and ceftriaxone (Lagier et al, 2014). While the three latter antibiotics test sensitive, it is important to note that they do not act intracellularly, and this is often where *T. whipplei* is found. Susceptibility tests are not performed on samples sent to labs because of the difficulty in growing the organism and the time it would take to grow and test samples. Empirical therapy is therefore advised.

Selecting an agent to treat the patient requires discussion with the local infection specialist team (microbiology and/or infectious diseases) and, because of its rarity, a Whipple's disease expert. The site of the infection will influence antibiotic choice, as will patient allergy and intolerances and any drug interactions.

A prospective randomized trial (Feurle et al, 2010a) recommended therapy for Whipple's disease as follows:

General Whipple's disease (without evidence of endocarditis and no evidence of CNS involvement)

A 14-day treatment of daily ceftriaxone 2 g or thrice-daily meropenem 1 g intravenously followed by 12 months of twice-daily oral co-trimoxazole (Feurle et al, 2010a). Doxycycline 100 mg 12-hourly plus hydroxychloroquine 200 mg 8-hourly is an alternative oral therapy for those unable to take oral co-trimoxazole.

CNS disease

A 4-week course of intravenous ceftriaxone given 2 g daily is advised, followed by 12 months of oral co-trimoxazole as above. Meropenem can be substituted for ceftriaxone if a contraindication exists.

Endocarditis

A 4-week course of intravenous ceftriaxone given 2 g daily is advised, followed by 12 months of oral co-trimoxazole as described above. Benzylpenicillin 6 g (10 million units) given daily or meropenem can be used if an alternative to ceftriaxone is required.

Lagier et al (2014) advise against using co-trimoxazole, as neither the trimethoprim nor the sulfamethoxazole component show any consistent activity against *T. whipplei*.

All patients should be followed closely – those with small bowel disease should be re-biopsied and samples sent to histopathology and for polymerase chain reaction at 6 months and 1 year while on antibiotic therapy. CSF-infected patients should have similar follow up. If the patient is negative on periodic acid-Schiff and polymerase chain reaction testing at 1 year then antibiotics can be stopped. If either investigation is still positive at a year it is advisable to continue with current therapy.

Immune reconstitution inflammatory syndrome has been documented a few weeks after antibiotic therapy is initiated and can be fatal (Feurle et al, 2010b). Individuals treated with immunosuppressive agents are at particular risk (Biagi et al, 2012). Thalidomide has been proposed as a possible treatment for those developing this condition (Lagier et al, 2010).

Conclusions

Thanks to improved diagnostics *T. whipplei* is more commonly isolated than previously. It can be carried asymptomatically, transmitted among close contacts and, in rare cases, cause Whipple's disease. While Whipple's disease is rare, it should be considered in certain circumstances, particularly in sewer workers and farmers presenting with weight loss, arthropathy and diarrhoea, or culture-negative endocarditis. Much is yet to be learnt about Whipple's disease and molecular techniques are enabling this. Most importantly, if Whipple's disease is suspected in a patient it is advisable to seek the advice of an infection specialist. **BJHM**

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