Whipple’s disease revisited

S A Misbah, N P Mapstone

Abstract
Whipple’s disease has traditionally been considered to be a rare multisystem disorder dominated by malabsorption. The recent identification of the Whipple’s disease bacillus has, using polymerase chain reaction based assays, fuelled advances in the investigation, diagnosis, and management of this disease. This leader reviews the aetiology, clinical manifestations, investigation, and treatment of Whipple’s disease in the light of this new information.

(Keywords: Tropheryma whippelii; immune system; polymerase chain reaction)

Whipple’s disease, as described by George Whipple in 1907, a pathologist at John’s Hopkins Hospital, has generally been considered to be a rare multisystem disorder dominated by malabsorption. Whipple’s original patient presented with severe malabsorption associated with mesenteric lymph node enlargement, arthritis, and skin pigmentation. At necropsy, Whipple presciently observed the presence of foamy macrophages and large numbers of argyrophilic rod shaped structures in the lymph nodes. These foamy macrophages were later shown to stain strongly with the periodic acid Schiff reagent (PAS) (fig 1), and this soon became accepted as the diagnostic hallmark of Whipple’s disease. The infective aetiology of this disorder was first proposed in 1952 when a patient with Whipple’s disease, hitherto uniformly fatal, responded to antibiotic treatment. Further support for an infective aetiology arose from the use of electron microscopy to demonstrate that the foamy macrophages in Whipple’s disease were packed with bacillary structures (fig 2), hereafter referred to as the Whipple’s bacillus.

This article will review Whipple’s disease and its protean manifestations in the light of recent advances in the aetiology, diagnosis, and management of this enigmatic disease.

Aetiology
The infective aetiology of Whipple’s disease has always been questioned by purists on the grounds that Koch’s postulates have not been fulfilled. The limitations of Koch’s postulates in relation to unculturable or fastidious microbes that can be identified predominantly by molecular means has been discussed fully by Fredricks and Relman. The growing body of recent molecular and microbiological evidence strengthening the causative role of the Whipple’s bacillus in this disorder is summarised in the ensuing paragraphs.

A major advance in our understanding of Whipple’s disease was the identification of the uncultured Whipple’s bacillus by two groups using the polymerase chain reaction (PCR). Because portions of bacterial 16S ribosomal RNA genes are highly conserved, both groups reasoned that a combination of broad range and specific eubacterial 16S ribosomal primers could be used to amplify uncharacterised organisms such as the Whipple’s bacillus. Analysis of the 16S ribosomal RNA sequence associated with Whipple’s disease suggested that this bacillus was closely related to the actinomycetes group of Gram positive bacteria.
On the basis of its phylogenetic relations and its tendency to cause malabsorption, Relman and colleagues proposed that the Whipple’s bacillus be named Tropheryma whipplei (from the Greek trophe (nourishment) and eryma (barrier) because it causes malabsorption).

After a succession of false starts, the quest to culture the Whipple’s bacillus recently received a major boost when Schoedon et al were able to isolate T whipplei using a novel strategy. Homogenates of infected heart valves from a patient with systemic Whipple’s disease were injected into human mononuclear phagocytes that had been pretreated with interleukin 4 (IL-4), IL-10, and dexamethasone. Within eight to 10 days, diastase resistant, PAS positive inclusions were detected in the mononuclear phagocytes. Subsequent molecular analysis and electron microscopy studies showed that the PAS positive inclusions were T whipplei. If substantiated, this work will be an important advance, which is likely to further our understanding of the immunopathogenesis of Whipple’s disease and pave the way for serological assays.

The immune system and Whipple’s disease

There has been much interest in the possibility that patients with Whipple’s disease have a primary defect in host defense mechanisms, which render them susceptible to this disorder. Several immunological changes have been demonstrated in patients with Whipple’s disease, although it has been difficult to distinguish between primary and secondary effects (fig 3). Any attempt to implicate a host immune defect in the pathogenesis of Whipple’s disease has to take into account the fact that most patients with this disease do not appear to be susceptible to opportunistic infections. Furthermore, Whipple’s disease is not a feature of patients with defective immunity, either cellular or humoral. These clinical observations suggest that any immune defect is likely to be subtle. The idea that such a defect exists has recently been rekindled by evidence of defective in vitro IL-12 and interferon γ (IFN-γ) production by peripheral blood mononuclear cells from patients with Whipple’s disease. IL-12 is a pivotal mediator of cellular immunity, which acts as a trigger for IFN-γ production by T helper type 1 cells. Interestingly, defective cytokine secretion in this study was accompanied by low concentrations of serum IgG2, an IFN-γ dependent IgG subclass. Although it is difficult to comment on the clinical relevance of this finding in the absence of data on immunisation responses, it nevertheless provides a thought provoking link with other reports of IgG2 subclass deficiency and granulomatous disease in some patients with Whipple’s disease.

Epidemiology

The rarity of this disease has meant that precise figures on disease prevalence are not available. Dobbins in his meticulous monograph drew attention to 617 cases reported worldwide between 1907 and 1986, and a further 79 unreported cases. The use of improved diagnostic methods since then suggests that this figure is likely to be a great underestimate. Dobbins also reported a preponderance of farmers and outdoor workers among those afflicted with Whipple’s disease. This observation has recently been strengthened by the demonstration of T whipplei in sewage samples.

Clinical manifestations

Whipple himself described the diverse features of this disease with the exception of neurological involvement. By the time of diagnosis, most (85%) patients have diarrhea on a background of arthralgia, weight loss, lymphadenopathy, fever, and sweats. The gastrointestinal dominance of symptoms at diagnosis is in direct contrast to the early symptoms of disease, which are predominantly articular. Articular involvement is characterised largely by a migratory, symmetrical non-erosive polyarthritis affecting the knees, ankles, and wrists. The non-specific nature of these initial articular symptoms is reflected in the considerable delay in the time taken for diagnosis, with average delays of 72 months. Most case series report an adult male preponderance, with only a few cases presenting in childhood. The rarity of Whipple’s disease in childhood despite the tendency of some children to inadvertently eat soil is unexplained.

Neurological involvement occurs in 21–43% of cases of Whipple’s disease. This may occur either on a background of gastrointestinal symptoms in a patient with known Whipple’s disease or present de novo without gastrointestinal involvement. Many neu-
ologists are familiar with the characteristic triad of dementia, external ophthalmoplegia, and facial myoclonus, which is seen in over a third of patients,14 and would consider the possibility of Whipple's disease in such a situation, even in the absence of gastrointestinal involvement. Claims by some neurologists that certain forms of ocular muscle movement abnormalities, such as oculomastacatory myorhythmia, are on their own sufficient to diagnose Whipple's disease12 (without supporting histology or PCR analysis) should be viewed with scepticism. Despite the relatively high index of suspicion among neurologists for Whipple's disease, rare patients presenting with pure spinal or muscle involvement pose difficult diagnostic problems.15

The presence of systemic granulomatous inflammation in lymph nodes, liver, and spleen in 9% of patients with Whipple's disease not unreasonably leads clinicians to consider the possibility of sarcoidosis.24–26 Over 20 such cases have been documented and illustrate the difficulties in differentiating these two disorders. In some of these cases, raised serum angiotensin converting enzyme concentrations and an increase in gallium 67 uptake on lung scans have also been noted.27 The diagnosis of Whipple's disease only becomes apparent in these cases if PAS positivity is demonstrated in tissue biopsies or if gastrointestinal features supervene.

Cardiac involvement in Whipple's disease can affect any layer of the heart. Rare cases of endocarditis have been reported always on a background of intestinal disease.28–31 A recent report, however, draws attention to four patients with endocarditis caused by T whipplei who presented with cardiac disease de novo with background articular symptoms but with no histological evidence of gastrointestinal disease.32 This report underlines the need for Whipple's disease to be considered as a possible cause of culture negative endocarditis.33

Ocular involvement has been estimated to occur in 2–3% of patients with Whipple's disease.34 A range of ocular manifestations has been described including anterior and posterior uveitis, vitritis, retinitis, and retrobulbar neuritis. Most cases occur on a background of systemic disease. In those rare cases where ocular disease occurs in the absence of gastrointestinal features, considerable delays in diagnosis ensue.35

Investigation of a patient with suspected Whipple's disease

Given its protean manifestations, the diagnosis of Whipple's disease should be considered in a variety of clinical situations (table 1), irrespective of gastrointestinal involvement. The diagnosis is based upon the demonstration of diastase resistant, PAS positive macrophages on tissue biopsies coupled with PCR evidence of infection with T whipplei. The presence of PAS positive foamy macrophages, which has been considered the traditional hallmark of Whipple's disease, can also occur in other infective disorders that closely mimic Whipple's disease (table 2), thus reducing its specificity. Furthermore, PAS positivity can be patchy or deep in the submucosa, and thus missed on single, superficial biopsies. The electron microscopic demonstration of bacilli with a characteristic trilamellar wall (fig 4) has been considered to be specific for Whipple's disease. However, electron microscopy as a diagnostic tool is heavily operator dependent and being eclipsed in many areas of diagnostic pathology by advances in immunocytochemistry and molecular biology. For this reason, histological evidence of PAS positivity should always be complemented by PCR analysis for T whipplei. Two sets of well characterised primers with differing rates of sensitivity (96.6% for W3AF, W4AR and 59% for W3FE, W2RB) are currently available for performing PCR analysis. To maximise its sensitivity, PCR analysis should be performed on more than one tissue substrate. Several recent studies suggest that small intestine, even when histologically normal, yields the highest proportion of positive results followed by other tissues such as lymph node, bone marrow, muscle, synovium, and spinal cord.36 37 PCR positivity in peripheral blood and cerebrospinal fluid (CSF) occurs in approximately 50–80% of samples, respectively, and is a useful method of monitoring response to treatment.38 39 Interestingly, positive PCR results in CSF were reported in seven of 10 patients without neurological

---

Table 1: Clinical situations in which Whipple's disease should be part of the differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained malabsorption on a background of systemic disease</td>
</tr>
<tr>
<td>Unexplained systemic granulomatous disease resembling sarcoidosis</td>
</tr>
<tr>
<td>Neurological disease characterised by myoclonus, dementia, and supranuclear ophthalmoplegia</td>
</tr>
<tr>
<td>Unexplained culture negative endocarditis</td>
</tr>
<tr>
<td>Unexplained uveitis</td>
</tr>
</tbody>
</table>

---

Table 2: List of organisms that stain positively with the periodic acid Schiff reagent

<table>
<thead>
<tr>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomyces</td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
</tr>
<tr>
<td>Mycobacterium avium intracellulare</td>
</tr>
<tr>
<td>Mycobacterium genavense</td>
</tr>
<tr>
<td>Bacillus cereus</td>
</tr>
<tr>
<td>Corynebacterium spp</td>
</tr>
<tr>
<td>Fungi</td>
</tr>
<tr>
<td>Histoplasma</td>
</tr>
<tr>
<td>Rhodococcus equi (previously known as Corynebacterium equi)</td>
</tr>
</tbody>
</table>

---

Figure 4: The appearance of the Whipple's bacillus on electron microscopy (magnification, ×100 000), showing the characteristic trilamellar cell wall (reproduced with permission©).
symptoms before the initiation of antibiotic treatment. This finding underlines the need for the use of antimicrobials with good CSF penetration in the treatment of Whipple's disease (see below).

**Interpretation of PCR results**
The increasing use of PCR for detecting *T. whippelii* has uncovered several PCR positive patients with systemic disease with or without gastrointestinal involvement in the absence of PAS positivity who respond to prolonged antibiotic treatment. These patients had a variety of presentations including diarrhoea, polyarthritis, culture negative endocarditis, and atypical progressive supranuclear palsy. Although this observation calls into question the reliance on PAS positivity as a diagnostic marker for Whipple's disease, recent studies suggest caution in using positive PCR results alone to make a definitive diagnosis. Ehrbar et al found recently that five of 105 patients (4.8%) with no clinical signs of Whipple's disease were PCR positive for *T. whippelii* on duodenal biopsies and 12 patients (11.4%) had positive PCR results on gastric juice. PCR positivity in saliva has also been reported in a high proportion (35%) of healthy individuals. These findings suggest that *T. whippelii* is an oral commensal and accord with its presence in soil. In an anonymous survey of blood donors we found one of 174 individuals to be PCR positive for *T. whippelii*. These data on background positivity in various fluids and tissues are clearly important in assessing the diagnostic importance of PCR for *T. whippelii*.

**Other laboratory abnormalities in Whipple's disease**
As with other infective disorders, over 70% of patients with systemic Whipple's disease exhibit a non-specific acute phase response, as indicated by a raised erythrocyte sedimentation rate. In patients with classic Whipple's disease affecting the gastrointestinal tract, anaemia and hypoalbuminaemia were noted in 75% and 93% of patients, respectively. More interestingly, Lowsky et al found *T. whippelii* as intra-erythrocytic inclusions in two asplenic patients on peripheral blood smears using Wright's stain. In this respect, *T. whippelii* is similar to other haematotropic organisms, such as species of babesia and plasmodium, and may well cause more severe disease in asplenic individuals.

**Management**
The optimal regimen for Whipple's disease has been largely determined by a combination of clinical experience and empiricism. The rarity of this disorder coupled with considerable difficulties in culturing *T. whippelii* have prevented randomised trials of antibiotic treatment being carried out. In managing a patient with Whipple's disease, three important questions should be considered, namely:

1. What is the optimal antibiotic regimen?
2. What should the duration of treatment be?
3. How should the patient be monitored?

**WHAT IS THE OPTIMAL ANTIBIOTIC REGIMEN?**
Beginning with Pauley's use of chloramphenicol, several antibiotics have been used successfully in the treatment of Whipple's disease (table 3). Until the 1970s, the most commonly used regimen was a combination of parenteral penicillin and streptomycin to initiate treatment followed by maintenance oral tetracycline. However, the recognition that central nervous system relapses were an important cause of mortality in patients previously treated with tetracycline, prompted the use of cotrimoxazole, which achieves effective therapeutic concentrations in CSF even in the absence of meningeal inflammation. The superiority of cotrimoxazole over tetracycline in preventing clinical relapses has been shown in a small partially retrospective non-randomised study. To date, this is the only study that has attempted to evaluate antibiotic treatment in Whipple's disease. Taken together with three other studies, the lowest frequency of relapse appears to occur in patients treated with cotrimoxazole when compared with groups treated with tetracycline and penicillin (table 4).

Because of the limited clinical data available, it is important to make a distinction between those patients who have neurological disease at the time of diagnosis and those who do not. In the first group it would be prudent to initiate treatment with parenteral bactericidal antibiotics with good central nervous system penetration (table 3) for a period of two weeks followed by maintenance oral cotrimoxazole. In the second group, oral treatment with cotrimoxazole is recommended on the grounds that this may be more successful in preventing neurological disease.

---

**Table 3** List of antibiotics reported to be effective in the treatment of Whipple's disease

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Ability to penetrate blood-brain barrier</th>
<th>Intracellular penetration</th>
<th>Bactericidal/ static activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>Yes, if meninges are inflamed</td>
<td>Poor</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Excellent, even with uninfamed meninges</td>
<td>Good</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Good, even with uninfamed meninges</td>
<td>Yes</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Limited</td>
<td>Excellent</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Limited</td>
<td>Good</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Penetration limited even with inflamed meninges</td>
<td>Limited</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Yes, if meninges are inflamed</td>
<td>Poor</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Poor</td>
<td>Poor</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Poor</td>
<td>Poor</td>
<td>Bactericidal</td>
</tr>
</tbody>
</table>

Bacteriostatic/static activity refers to in vitro activity of each agent against most conventional pathogens that can be cultured in the laboratory.

**Table 4** Treatment of Whipple's disease: frequency of relapses according to antibiotic regimen

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Keinath&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fleming&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pearle&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Durand&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>21/49</td>
<td>2/16</td>
<td>9/22</td>
<td>5/28</td>
<td>37/115</td>
</tr>
<tr>
<td>Penicillin + Strep</td>
<td>4/20</td>
<td>0/2</td>
<td>0/2</td>
<td>4/34</td>
<td>10/101</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>0/3</td>
<td>0/0</td>
<td>1/8</td>
<td>0/12</td>
<td>1/23</td>
</tr>
<tr>
<td>Others</td>
<td>6/16</td>
<td>0/2</td>
<td>2/11</td>
<td>8/29</td>
<td>27/131</td>
</tr>
<tr>
<td>Total</td>
<td>31/88</td>
<td>2/25</td>
<td>10/30</td>
<td>7/52</td>
<td>50/201</td>
</tr>
</tbody>
</table>

<sup>a</sup> The denominator refers to number of patients treated. Refer to individual references for data on duration of treatment. Strep, streptomycin.
WHAT SHOULD THE DURATION OF TREATMENT BE?
There is no clear consensus in the literature on the duration of antibiotic treatment. Therapeutic success has been achieved with short treatment courses of three months, although it is possible that such patients relapse more frequently. There is some evidence that suggests an increased rate of relapse in patients treated for less than six months in comparison to those treated for 12–24 months.16 At the other end of the scale, some patients have failed to respond to 64 months of continuous tetracycline.48

In view of this lack of clarity, a pragmatic compromise would be to treat all patients for a minimum period of 6–12 months with close clinical and laboratory monitoring (see below).

HOW SHOULD TREATMENT BE MONITORED?
Until the recent advent of PCR based assays for the detection of T whipelli, the response to treatment was monitored using a combination of clinical and histological endpoints. The histological endpoint of eradication of PAS positive cells was not always achieved, with reports of persistent PAS positive cells in the small bowel of patients in clinical remission.54 In contrast, reversion of PCR positivity occurs within two to six months of the initiation of antibiotic treatment and correlates well with the clinical outcome.55 57 Ramzan et al found that a negative post-treatment PCR was good evidence against future relapse, whereas a persistently positive PCR presaged clinical relapse.56

The clear superiority of PCR over histology in monitoring treatment, patients with Whipple’s disease are best followed up in view of the clarity of PCR over histology in monitoring treatment, patients with Whipple’s disease are best followed up using PCR primarily. The selection of which tissues or fluid to perform PCR upon will depend on the initial clinical presentation. We would recommend that a combination of small bowel and peripheral blood be used in most patients as long as these tissues were positive pretreatment. In patients with neurological disease, monitoring CSF in addition to small tissues or fluid to perform PCR upon will be of value.

THERAPEUTIC OPTIONS IN WHIPPLE’S DISEASE
UNRESPONSIVE TO ANTIBIOTICS
IFN-γ has recently been used successfully in the treatment of a patient with a 10 year history of antibiotic resistant Whipple’s disease.11 The choice of IFN-γ as a therapeutic agent is based on the observation of defective IFN-γ and IL-12 production in vitro by mononuclear cells from patients with Whipple’s disease12 and its success in treating other intracellular infections.52 53 Although its therapeutic success in this single case is encouraging, the authors rightly point out that this does not constitute conclusive evidence of a primary defect in IFN-γ production in Whipple’s disease.

Concluding remarks
Much progress has been made in our understanding of Whipple’s disease this century. The recent identification of the putative Whipple’s bacillus has fuelled advances in the use of molecular diagnostic methods, which in turn has helped uncover unusual extra-intestinal modes of clinical presentation. The use of PCR has also helped explain the clinical presentation and management of this disorder on a more scientific footing. It is also becoming apparent that the Whipple’s bacillus is more widely prevalent than was originally thought. The development of clinical disease is likely to be determined by host factors, with the tantalising suggestion of a defective IL-12/IFN-γ pathway in some patients.

Addendum
Since the submission of this leader, Raoult et al have successfully cultivated T whipelli using a human fibroblast cell line that was injected with an aortic valve extract from a patient with Whipple’s disease.58

We thank Dr Kevin Kerr for help with compiling table 3 and critical comments on the manuscript. Fay Storey’s excellent secretarial support is gratefully acknowledged.
