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The Immune Reconstitution Inflammatory Syndrome in Whipple Disease

A Cohort Study

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Background: Whipple disease, which is caused by infection with *Tropheryma whipplei,* can be treated effectively with antimicrobials. Occasionally, inflammation reappears after initial improvement; this is often interpreted as refractory or recurrent disease. However, polymerase chain reaction for *T. whipplei* in tissue is sometimes negative during reinflammation, indicating absence of vital bacteria, and this reinflammation does not respond to antimicrobials but does respond to steroids.

Objective: To demonstrate that the immune reconstitution inflammatory syndrome (IRIS) occurs in patients treated for Whipple disease.

Design: Cohort study. (International Standard Randomised Controlled Trial Number Register registration number: ISRCTN45658456)

Setting: 2 academic medical centers in Germany.

Methods: 142 patients treated for Whipple disease out of a cohort of 187 were observed for reappearance of inflammatory signs after effective antibiotic therapy. Definitions of IRIS in HIV infection, tuberculosis, and leprosy were adapted for application to Whipple disease.

Results: On the basis of study definitions, IRIS was diagnosed in 15 of 142 patients. Symptoms included fever, arthritis, pleurisy, erythema nodosum, inflammatory orbitopathy, small-bowel perforation, and a hypothalamic syndrome. Two patients died. There was a positive correlation with previous immunosuppressive treatment and a negative correlation with previous diarrhea and weight loss.

Limitations: The study was observational and thus has inherent weaknesses, such as incomplete and potentially selective data recording.

Conclusion: The immune reconstitution inflammatory syndrome was diagnosed in about 10% of patients with Whipple disease in the study cohort; the outcome varied from mild to fatal. Patients who had had previous immunosuppressive therapy were at particular risk. An immune reconstitution syndrome should be considered in patients with Whipple disease in whom inflammatory symptoms recur after effective treatment. Early diagnosis and treatment with steroids may be beneficial; prospective studies are needed.

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Whipple disease (1) is a chronic multisystemic infection caused by *Tropheryma whipplei* (2). Immunogenetic host factors seem to predispose to this infection: Whipple disease is associated with the HLA alleles DRB1*13 and DQB1*06 (3), and unspecific and *T. whipplei*–specific Th1 reactivity is impaired (4, 5). Clinical manifestations of Whipple disease, such as arthritis, diarrhea, and inflammatory signs, usually resolve promptly after treatment with appropriate antimicrobial agents (6–8).

In some patients, a paradoxical reappearance of clinical and laboratory findings occurs after initial improvement after effective treatment with antimicrobials. This inflammatory flare-up has been interpreted as refractory or recurrent Whipple disease (9–14). We have observed, however, that during these flare-ups, *T. whipplei* DNA was not detectable in the tissue by polymerase chain reaction (PCR) and that use of steroids, but not antimicrobials, led to cessation of inflammation. These findings may indicate that patients are experiencing the immune reconstitution inflammatory syndrome (IRIS), as has been described in such infections as HIV, tuberculosis, and leprosy (15–20). Preliminary reports on 2 of our patients and a patient from France have been published (21–23).

We sought to establish or refute the hypothesis that IRIS occurs in patients with Whipple disease. Because there is no single test or a set of measurements that supports the diagnosis of IRIS, our results are based on a clinical definition of IRIS in Whipple disease that we adapted from the definitions of IRIS in HIV and mycobacterial infections (15–20).

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Appendix Tables
Conversion of graphics into slides

METHODS

Study Design and Setting

A cohort of 187 patients with Whipple disease was registered in the European Whipple's Disease Project. Eighty patients with untreated Whipple disease who met the inclusion criteria were prospectively enrolled in thera-

peutic trials (40 patients are described in a published study [8], and information on 40 patients has not been published). The remaining 107 patients with Whipple disease who did not meet the inclusion criteria for the therapeutic trials were registered but not admitted; 62 of them were followed and 45 were lost during follow up (**Figure**). There is evidence that these 45 patients were lost at random, because the female–male ratio ($P = 0.23$), age ($P = 0.81$), and date of diagnosis (between 1999 and 2009) did not differ significantly from those of the 142 patients who were followed. Most patients were from Germany and Austria; some came from Switzerland, Italy, and France.

Permission for the therapeutic trials was obtained from the ethics committees of the Landesärztekammer Rheinland Pfalz, Mainz, Germany, and Charité, Berlin, Germany. All participants gave written informed consent.

Participants

In the 80 patients enrolled in the prospective therapy studies, recurring and new symptoms during and after antibiotic treatment were recorded as adverse events. All patients were asked to report to the treating physician if they developed fever or other symptoms after treatment was started. Follow-up information was obtained by structured questionnaires and telephone interviews. The clinical course after treatment was recorded in all patients in the trials and in the 62 unenrolled patients. Median follow-up was 75 months (range, 11 to 123 months) for the 80 enrolled patients, 24 months (range, 7 to 120 months) for the 62 unenrolled control patients, and 32 months (range, 6 to 110 months) for the 15 patients who developed IRIS after antimicrobial treatment.

Case Definitions

Whipple disease was considered present when infection with *T. whipplei* caused clinical symptoms. Colonization with *T. whipplei* but without invasion and clinical symptoms was not considered to be Whipple disease (8, 24).

To test the hypothesis that IRIS occurs in Whipple disease, we adapted the published definitions of IRIS in HIV infection, tuberculosis, and leprosy (15–20). We defined IRIS in Whipple disease as 1) an initial clinical response of symptoms to antimicrobial treatment (cessation of diarrhea and fever, relief of arthritis, and normalization of C-reactive protein level) within 3 weeks of treatment; 2) recurrence of systemic or local inflammation, with or without fever, lasting more than 1 week, after exclusion of hospital-related conditions (such as allergic reaction, catheter infection, *Clostridium difficile* colitis, other infections, and unrelated conditions that included hidden autoimmune diseases or undetected or newly emerging malignant diseases); and 3) effective antimicrobial treatment of Whipple disease (8). Efficacy of treatment was determined by histologic examination as defined elsewhere (25) and by a negative tissue PCR result for *T. whipplei* while IRIS was manifest (26). The presence of all 3 criteria was required for the diagnosis of IRIS.

Context

Patients with Whipple disease can develop signs of inflammation after antibiotic therapy. This is usually considered refractory or relapsed disease.

Contribution

The investigators observed that some patients who seemed to have relapsed or refractory Whipple disease had no organisms in tissue, and the disease responded to steroids. Applying a case definition for the immune reconstitution inflammatory syndrome (IRIS), they postulated that IRIS occurs in about 10% of patients with Whipple disease.

Caution

The case definition was developed and tested in the same cohort.

Implication

When patients with Whipple disease show new signs of inflammation after antibiotic treatment, IRIS should be considered.

—The Editors

Measurements

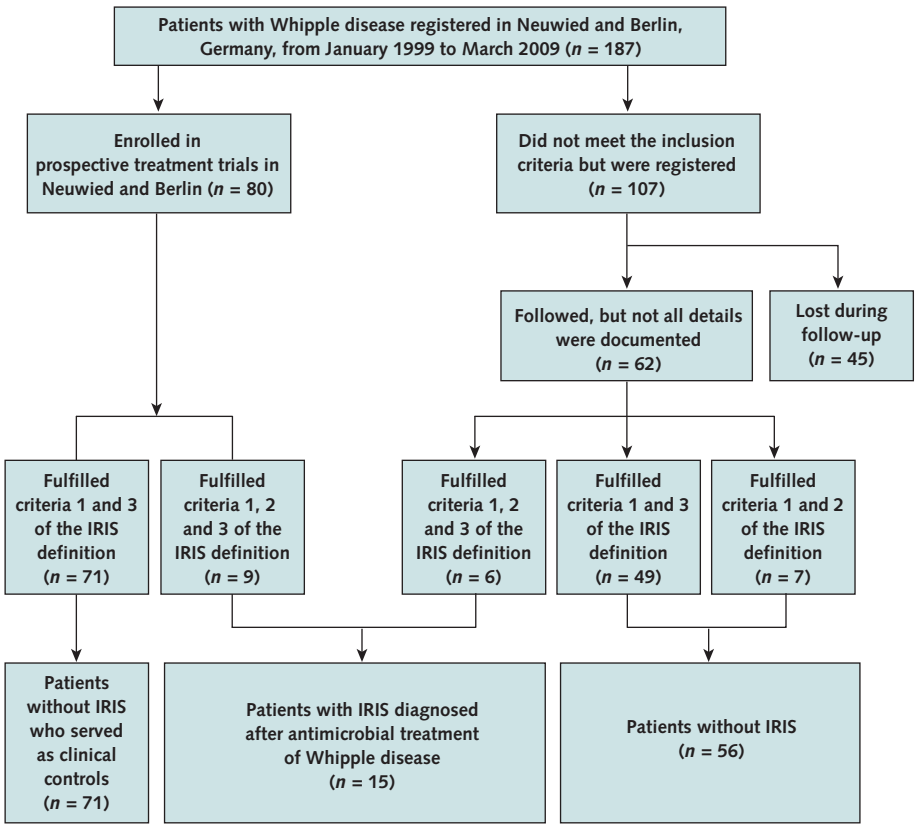
PCR

Tropheryma whipplei–specific PCR was performed from fresh and paraffin-embedded specimen once while IRIS was manifest to exclude persisting infection with *T. whipplei*. The DNA was extracted by using the AMPLICOR Respiratory Specimen Preparation Kit (Roche Molecular Systems, Branchburg, New Jersey) according to the manufacturer's protocol. Likewise, DNA was extracted from paraffin sections after xylene–ethanol treatment. Detection of *T. whipplei* was performed by *T. whipplei*–specific amplification of the 16-strand ribosomal RNA gene as described elsewhere (26), followed by semi-nested PCR in negative cases and sequencing of the PCR products. Amplicons were analyzed on an automated capillary DNA sequencer (CEQ 8000; Beckman Coulter, Krefeld, Germany) and compared with those of all currently available sequences from public databases (European Molecular Biology Laboratory and GenBank). A negative PCR result indicates absence of *T. whipplei* or a concentration of *T. whipplei* DNA below the detection limit.

Histologic Examination

Intestinal mucosal biopsy samples were obtained from all patients and were fixed in formaldehyde and stained with periodic acid–Schiff (PAS) reagent. Biopsies in the prospective treatment trials were performed at predefined intervals (8). In the 62 patients who were registered but not enrolled, the initial biopsy was followed by at least 2

Figure. **Study flow diagram.**



"Fulfilled criteria 1 and 3" indicates effective antibiotic treatment of Whipple disease; "fulfilled criteria 1 and 2" indicates ineffective treatment of Whipple disease; and "fulfilled criteria 1, 2, and 3" indicates effective treatment of Whipple disease and IRIS. IRIS = immune reconstitution inflammatory syndrome.

samplings during follow-up. Morphology was determined from at least 3 biopsies per sampling as the mean cell count of 10 high-power fields of 0.237 mm^2 each.

Statistical Analysis

Clinical variables in patients with IRIS and control patients without IRIS were compared by using the Fisher test. All *P* values were 2-sided; those less than 0.05 were considered significant. The 95% CIs for single proportions were calculated by using the binomial exact test, using the normal approximation to *t* tests for means.

Role of the Funding Source

The study was supported by the European Commission and Deutsche Forschungsgemeinschaft. The funding sources had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation or review of the manuscript; or decision to submit the manuscript for publication.

RESULTS

Frequency of IRIS

In 15 of the 142 patients who had follow-up after initiation of treatment, IRIS was diagnosed according to our study definition (9 of the 80 patients enrolled in the treatment trials and 6 of the 62 unenrolled patients) (**Figure**). The frequency of IRIS in patients treated for Whipple disease in this series was 10.56% (95% CI, 6.03% to 16.82%). The 71 well-documented patients from the 80 trial participants who had no evidence of IRIS served as controls for the clinical findings. We describe here the 15 patients who met our case definition of IRIS.

Risk Factors for IRIS

Table 1 shows the time course of clinical characteristics of patients with IRIS diagnosed after antimicrobial treatment of Whipple disease. Baseline characteristics of patients with and patients without IRIS were similar (**Table 2**). Previous immunosuppressive treatment was positively associated with IRIS ($P < 0.001$), and a course of Whipple disease that manifest predominantly with diarrhea and weight loss was negatively associated with IRIS ($P = 0.002$ and $P < 0.001$, respectively) (**Table 2**).

Clinical Presentations

Fever

The most common symptom of IRIS was fever, occurring in 13 of the 15 patients. In 5 patients, fever (with

Table 1. **Course of Whipple Disease in 15 Patients With IRIS**

Patient	Sex	Age at Diagnosis	Characteristics Before Diagnosis of WD		Test Results*	IRIS After Start of Antimicrobial Treatment of WD†	
			Presenting Symptoms and Their Duration	Immunosuppressive or Disease-Modifying Treatment		Presenting Symptoms	Outcome
1	Male	61	Skin disease, lymphadenopathy, endocarditis, polyarthritis, uveitis, sarcoid-like lesions, fever over 6 y	Steroids and azathioprine for 2 y	Positive	Fever, ataxia, uveitis	Steroid therapy for 24 mo, persisting ataxia; otherwise recovered
2	Male	65	Fever, polyarthritis, diarrhea over 7 y	Steroids, MTX, and hydroxychloroquine for 7 y	Negative (after short antibiotic treatment)	Fever, pneumonia	*Candida* bloodstream infection; died of stroke after 3 mo
3	Female	63	Polyarthritis, tenosynovitis, fever over 12 y	Steroids, azathioprine, MTX, cyclophosphamide, chloroquine, and leflunomide for 10 y	Positive	Fever, ataxia, arthritis, pleuritis	Persistent brainstem symptoms, otherwise recovered; steroid therapy for 18 mo
4	Male	51	Seronegative polyarthritis, sacroiliitis, coxitis, tenosynovitis, lymphadenopathy over 18 y	Steroids and infliximab for 13 y	Positive	Fever, inflammatory pseudotumor orbitae	Blindness in 1 eye, jejunal perforation after 38 mo; still receiving steroids at 4 y
5	Male	42	Fever, polyarthritis, sacroiliitis, tenosynovitis, replacement of both femoral heads over 12 y	Gold and sulfasalazine for 10 y	Positive	Fever, erythema nodosum, pleuritis, leukocytosis ($>50 \times 10^9$ cells/L), inflammatory orbitopathy	Receiving steroids and azathioprine at 1 y; recovered
6	Male	76	Polyarthritis, lymphadenopathy, fever over 16 y	Steroids, MTX, and etanercept for 1 y	Positive	Fever, arthritis, leukocytosis	Receiving steroids at 3 y
7	Male	74	Polyarthritis, fever over 8 y	Steroids, gold, MTX, leflunomide, cyclophosphamide, infliximab, etanercept, cyclosporine, and radiosynoviorthesis for 8 y	Not examined	Fever	Steroid therapy; died 3 y after diagnosis; other diagnoses were osteoporosis, stroke, myocardial infarction
8	Male	43	Polyarthritis, lymphadenopathy, ascites, *Pneumocystis jiroveci* pneumonia, ulcerative enteritis, fever over 3 y	MTX, leflunomide, sulfasalazine, hydroxychloroquine for 3 y	Not examined	Fever, small-bowel perforation in 2006	Received steroids and cyclophosphamide for 7 y; high-grade small-bowel lymphoma in 2009
9	Female	60	"Collagenosis," arthralgia, polymyalgia, uveitis, episcleritis over 10 y	Steroids, MTX, and cyclosporine	Not examined	Fever, polyarthritis	Received steroids for 6 y; recovered
10	Male	57	Arthritis, scleritis, uveitis, hyponatremia, lymphadenopathy, fever over 12 y	Steroids for 6 mo	Not examined	Afebrile orbitopathy	Received acetaminophen for 14 d; recovered
11	Female	68	Arthritis, fever, diarrhea, anisocoria over 10 y	None	Negative	Headache, inflammatory orbitopathy	Received steroids for 8 mo; recovered
12	Male	67	Weight loss, diarrhea, polyneuropathy over 1 mo	None	Positive; protein level in the normal range; no cells	Fever, urinary incontinence, confusion, gait ataxia, hyponatremia (sodium level, 119 mmol/L); CSF findings: lymphocyte count of 0.046×10^9 cells/L, protein level of 688 mg/L, negative PCR, 1 PAS-positive macrophage	Received steroids for 6 mo; recovered
13	Male	56	Polyarthritis, diarrhea over 9 y	Steroids, MTX, and leflunomide for 9 y	Not examined, cytology negative	Fever, diarrhea, skin disease	Recovered; still receiving low-dose steroids at 2 y
14	Male	59	Diarrhea, polyarthritis, fever over 10 y	MTX and steroids for 3 y	Negative	Fever, arthritis	Receiving steroids at 3 y
15	Female	51	Polyarthritis, lymphadenopathy, weight loss over 7 y	MTX and steroids for 5 y	Negative	Fever, skin disease	Receiving steroids at 1 y

CSF = cerebrospinal fluid; IRIS = immune reconstitution inflammatory syndrome; MTX = methotrexate; PAS = periodic acid–Schiff; PCR = polymerase chain reaction; WD = Whipple disease.

* By PCR of cerebrospinal fluid for *Tropheryma whipplei* and other CSF findings.

† 13 patients were treated with intravenous ceftriaxone followed by oral trimethoprim–sulfamethoxazole; patient 8 received long-term oral trimethoprim–sulfamethoxazole, and patient 9 received intravenous ampicillin followed by oral trimethoprim–sulfamethoxazole.

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

Characteristic	Patients Without IRIS	Patients With IRIS	*P* Value
Mean age (SD), *y*	57 (11) [55–60]	60 (10) [54–65]	0.43
Women/men, *n/n*	16/55	4/11	0.74
Mean BMI (SD), kg/m^2	21 (4) [21–22]	23 (3) [21–24]	0.055
Mean ESR (SD), *mm/h*	50 (27) [43–58]	32 (23) [12–51]	0.063
Lymphadenopathy, *n/n (%)*	23/71 (32.4) [21.8–44.5]	7/15 (46.7) [21.3–73.4]	0.37
Arthritis, *n/n (%)*	57/71 (80.3) [69.1–88.8]	14/15 (93.3) [68.1–99.8]	0.45
Diarrhea, *n/n (%)*	55/71 (77.5) [66.0–86.6]	5/15 (33.3) [11.8–61.6]	0.002
CNS infection with *Tropheryma whipplei*, *n/n (%)*	19/46 (41.3) [27.0–56.8]	7/9 (77.8) [40.0–97.2]	0.069
Weight loss, *n/n (%)*	58/69 (84.1) [73.3–91.8]	5/15 (33.3) [11.8–61.6]	<0.001
Previous immunosuppressive treatment, *n/n (%)*	11/71 (15.5) [8.0–26.0]	12/15 (80.0) [51.9–95.7]	<0.001

BMI = body mass index; CNS = central nervous system; ESR = erythrocyte sedimentation rate; IRIS = immune reconstitution inflammatory syndrome.
* Data in square brackets are 95% CIs.

rigors in 2 patients) commenced within 24 hours after start of intravenous antimicrobial therapy; in 8 patients, onset was during the oral phase of treatment or thereafter. In all 13 patients, fever persisted intermittently unless steroid therapy was given. Two patients, both of whom had painful orbitopathy, did not develop fever. Fever that abated after 48 hours and did not recur was not considered to be due to IRIS.

Among the 71 patients without IRIS, self-limited fever was recorded in 13 patients within 24 hours after antimicrobial treatment; in 2, it was preceded by rigors. In this group, fever lasted for less than 48 hours and did not recur.

Arthritis

Recurrent arthritis was the presenting symptom in 13 of the 15 patients with IRIS. Joint pain responded quickly to oral steroid therapy. Recurrent arthritis after treatment of Whipple disease was not observed in any of the control patients.

Orbitopathy

Inflammatory orbitopathy occurred in 4 patients with diagnosed IRIS (patients 4, 5, 10, and 11) (**Table 1**). Patients 10 and 11 reported orbital pain during movement of the eyes without fever. In patients 4 and 5, orbital inflammation was severe, manifesting as pseudotumor orbitae with local pain; ocular, periocular, and generalized inflammatory signs; exophthalmus; and diplopia. Patient 4 lost vision in his right eye despite treatment with high doses of steroids.

Small-Bowel Perforation

Patients with Whipple disease primarily affecting the muscle layer of the small-bowel wall may be at risk for small-bowel perforation once IRIS develops. Small-bowel perforation occurred in 2 of the 15 patients with IRIS in Whipple disease.

Patient 4 developed spontaneous perforation of the jejunum while he receiving low-dose steroids for inflammatory orbitopathy, 36 months after treatment of Whipple disease (**Table 1**). This patient still had PAS-positive material in macrophages of the jejunal submucosa, typical of past infection with *T. whipplei,* whereas the PCR for *T. whipplei* in these biopsies was negative.

Patient 8 was previously treated extensively with steroids and leflunomide for polyarthritis (**Table 1**). In 2002, the patient's CD4 count was less than 0.05×10^9 cells/L and *Pneumocystis jiroveci* pneumonia developed, for which the patient received trimethoprim–sulfamethoxazole for 2 years. Results of HIV tests were negative. In 2006, the patient developed acute abdomen with near-perforation of the ileum; computed tomography at this time showed that the thickness of the small-bowel wall had increased to 15 mm. The highly inflamed ileum was surgically resected, and Whipple disease was diagnosed in this tissue by PAS staining and *T. whipplei*–specific immunohistochemistry that revealed a massive infiltration in the muscular layers of the ileum, with marked structural damage. The PCR result for *T. whipplei* was negative. Thus, *T. whipplei* had apparently been eradicated by treatment of *Pneumocystis jiroveci* infection. During later follow-up, the patient had relapse of the inflammatory process whenever the doses of steroids and cyclophosphamide were reduced.

Central Nervous System Effects

Patient 12 had asymptomatic cerebrospinal infection indicated by a positive PCR result for *T. whipplei* and normal cell count and protein concentration in the cerebrospinal fluid. He developed fever, confusion, urinary incontinence, and hyponatremia 4 weeks after antimicrobial treatment (**Table 1**). The cerebrospinal fluid showed pleocytosis and an increased protein concentration, and PCR for *T. whipplei* had converted to negative. Treatment with steroids led to a complete and sustained recovery.

Skin Disease

A skin disease appeared after treatment of Whipple disease in patients 1 and 5 (**Table 1**). In patient 5, the disease resembled erythema nodosum. The PCR result for *T. whip-*

plei was negative in skin biopsies. In a third patient, rash associated with fever and arthritis was considered unspecific.

Pleuritis

Patients 3 and 5 developed painful and febrile pleuritis that responded well to treatment with oral prednisone.

Death

Patient 2 was receiving long-term parenteral nutrition and intravenous antimicrobial treatment under the assumption that refractory Whipple disease was present; he died of nosocomial infection and stroke in the intensive care unit due to bloodstream infection with *Candida* (**Table 1**). The reason for the death of patient 7 is less clear: He died at home during steroid treatment of IRIS, and postmortem examination was not performed (**Table 1**).

Clinical Events Other Than IRIS

In 15 of 127 control patients for whom outcome data were available, complications that included drug intolerance, refractory infection, a fatal nosocomial complication, persisting central nervous system defects, and continuing joint pain were observed.

DISCUSSION

The immune reconstitution inflammatory syndrome is a complex clinical syndrome that was first described in HIV infection, after the introduction of antiretroviral therapy (16). Later, it was recognized to be a complication during the treatment of mycobacterial infections (17). Because a definitive laboratory test for IRIS is lacking, the diagnosis relies largely on clinical judgment, and various research groups have proposed slightly differing definitions for IRIS (15, 20). Accordingly, our study has limitations. First, we observed only 15 patients who were considered to have developed IRIS. Second, our study is observational, with all of the inherent weaknesses of this design, such as incomplete and potentially selective data recording (**Appendix Table 1**, available at www.annals.org). Moreover, some degree of circular reasoning was unavoidable because we first defined IRIS, then diagnosed it in the same group of patients.

Another limitation was the simultaneous occurrence of other inflammatory reactions during treatment of Whipple disease that mimicked the symptoms of IRIS. Clinical symptoms of Whipple disease recede slowly during the first weeks after successful antimicrobial treatment (8). At the same time, symptoms of IRIS may gradually develop. Because the symptoms of both diseases are similar, there may be an interval when their symptoms overlap and the differential diagnosis is difficult. In addition, patients with Whipple disease are elderly and frequently have comorbid conditions. In such patients, other inflammatory conditions, such as allergic reactions, catheter infection, *C. difficile* colitis, unrelated infections, autoimmune diseases, or previously undetected or newly emerging malignant disease, can obscure the diagnosis of IRIS.

Concomitant drug effects also have important effects: Analgesics, nonsteroidal anti-inflammatory drugs, and steroids suppress inflammatory reactions, and when treatment with these drugs is stopped, rebound of inflammatory signs may occur. In addition, inflammatory signs may appear at the start of treatment with antibiotics or as late as several months after the end of antibiotic treatment (**Appendix Table 1**). Therefore, diagnosis of IRIS requires longer-term clinical scrutiny and judgment.

The effect of varying the time frames of 3 criteria on the sensitivity and specificity of diagnosis of IRIS is conspicuous (**Appendix Table 2**, available at www.annals.org); however, our understanding of the further ramifications of this variance is limited. Because the time frames are empirical and are not yet sufficiently validated, clinical judgment and careful observation are indispensable in diagnosing individual cases. Changing the time frames may mean that spontaneously reversible febrile reactions (criterion 2) or ineffective treatment of Whipple disease (criteria 1 and 3) are mistaken for IRIS, resulting in overdiagnosis of IRIS. Conversely, other time frames could lead to an underdiagnosis or delayed consideration of IRIS; the latter may result in organ damage.

Fever that arises within 24 hours after antimicrobial treatment and subsides promptly may be a Jarisch–Herxheimer febrile reaction, described in patients with Whipple disease (7, 27, 28). Jarisch–Herxheimer febrile reaction in Whipple disease seems to be a self-limited febrile reaction that does not require specific treatment.

In our cohort, 15 of 142 patients met the criteria for our case definition for IRIS. Nine of the 15 patients were recruited from the 80 patients enrolled in treatment trials, and 6 were recruited from the control group of 62 unenrolled patients for whom follow-up data were available. Our definition of IRIS revealed a frequency of IRIS in Whipple disease of 10.56% (CI, 6.03% to 16.82%), which is in the range of IRIS after treatment of tuberculosis or HIV infection (15, 16, 19).

Recurrent infection with *T. whipplei* in the 15 patients with diagnosed IRIS was considered highly unlikely. In the intestinal mucosa, PCR for *T. whipplei* at the time of IRIS was negative, histologic examination and PAS staining revealed remission in all patients (8, 25), and the median follow-up without evidence of recurrent disease was 32 months.

The development of IRIS was strongly associated with immunosuppressive or immune-modifying treatment before diagnosis of Whipple disease (**Table 2**). Immunosuppressive therapy is often given in patients with severe arthritis as the leading symptom as long as Whipple disease has not been diagnosed (29, 30). Of note, however, patient 5 (who had severe orbitopathy) was previously treated exclusively with gold, and patient 13 (who had a hypotha-

lamic presentation of IRIS) had never received immunosuppressive or immune-modifying treatment (**Table 1**). These observations indicate that IRIS can occur also in patients who did not previously receive immunosuppressive drugs. The mechanism of excessive immunosuppressive treatment facilitating IRIS remains undetermined, but it may promote the development of IRIS by aggravating T-cell dysfunction and $CD4^+$ T-cell depletion.

Patients with a diarrhea-predominant course were less likely to receive immunosuppressive treatment and were thus at lower risk for IRIS. Diarrhea was not a symptom of IRIS, and the frequency of IRIS may vary depending on clinical presentation of patients with Whipple disease.

Susceptibility to IRIS in Whipple disease also seems to be determined by immunogenetic factors. According to a recent study (3), IRIS in Whipple disease is correlated with the HLA DQB1*06 allele, which is in linkage disequilibrium with the alleles DRB1*13 and DRB1*15. The HLA alleles DR1 and DQB1 are also overrepresented in leprosy (a condition characterized by the occurrence of IRIS), and in lepromatous leprosy (similar to Whipple disease) they are associated with a lack of cell-mediated immunity against the infectious agent (17, 31, 32). We made similar observations in our patients with IRIS in Whipple disease (data not shown). A reversible, unspecific inflammatory reaction initiated by deficient regulatory T-cell activity may be of greater importance.

Treatment of IRIS in our patients was not prespecified, and management was at the local physician's discretion. On our advice, treatment was initiated with oral corticosteroids. Fever usually responded within 24 hours. Immunosuppressive agents were added when necessary (**Table 1** and **Appendix Table 1**). Formal recommendations for the treatment of IRIS in Whipple disease cannot be developed from our study; a prospective trial is needed to establish treatment measures. Our conclusions are useful to generate a hypothesis about IRIS in Whipple disease to be tested in a future protocol.

Our estimated frequency of IRIS in Whipple disease may be biased because follow-up data were lacking in 45 patients. We assume that these 45 patients were lost at random. The frequency of IRIS in our cohort would stay within the 95% CI of 6.03% to 16.82% if no case of IRIS occurred (yielding a frequency of 8.02%) and if up to 15 cases (frequency of 16.04%) had occurred among patients lost to follow-up. We do not know whether the total number of 187 patients is a representative sample of the entire population with Whipple disease in central Europe. In other regions, immunosuppressive therapy in undiagnosed chronic arthritis may have been prescribed less frequently, resulting in a lower incidence of IRIS. However, our study may increase awareness of this syndrome and may therefore lead to an apparent increase in frequency.

Although it remains unclear whether our findings can be generalized to other populations, they indicate that IRIS in Whipple disease as defined may run a severe course and even be fatal if antimicrobial treatment of Whipple disease is continued on the premise of antibiotic resistance. Thus, diagnosis of IRIS and prompt treatment, probably with oral steroids, should be considered in all patients with Whipple disease who, after a transitory clinical response to antibiotic treatment, develop fever or other unexplained organ manifestations lasting for more than 1 week. Other causes of recurrent inflammation must be excluded, but administration of steroids should not be delayed while waiting for biopsy and PCR results.

Because there is no established laboratory test for IRIS in Whipple disease, diagnosis is made by clinical observation. Anticipation of the diagnosis in all patients, particularly in at-risk patients previously treated with immunosuppressive drugs, and early treatment with steroids may be organ- and life-saving. Further prospective studies are needed to elucidate IRIS in Whipple disease.

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Note: Drs. Feurle and Moos contributed equally to this study.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Feurle (e-mail, g.e.feurle@t-online.de). *Statistical code:* Available from Dr. Jansen (e-mail, Andreas.Jansen@ecdc.europa.eu). *Data set:* Available from Dr. Moos (e-mail, verena.moos@charite.de).

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Appendix Table 1. **Characteristics of Patients With IRIS in Whipple Disease, With Approximate Time Frames for Criterion 2**

Patient	Sex	Age	Report of Symptoms and Duration*
1	Male	61	Fever was reported in the outpatient clinic 3 mo after initiation of antibiotic treatment and persisted until treatment with steroids was started.
2	Male	65	Fever was reported 1 wk after start of antibiotic treatment and continued until death.
3	Female	63	Fever was reported in the first week after antibiotic treatment was begun and persisted until treatment with steroids was started.
4	Male	51	The timing of onset of fever is not known exactly, but severe right ocular symptoms developed 17 mo after the start of antibiotic treatment, resulting in blindness. Flare-up occurred as soon as the steroid dose was reduced.
5	Male	42	Fever was reported 1 mo after beginning antibiotic treatment; 1 mo later, skin involvement developed and persisted until steroid treatment was started. Flare-up occurred as soon as the steroid dose was reduced.
6	Male	76	Fever recurred in the first 2 wk after starting intravenous antibiotic treatment, and treatment with steroids could not be stopped.
7	Male	74	The timing of onset of fever is not known exactly; fever persisted until treatment with steroids was started.
8	Male	43	Prolonged subfebrile elevated temperature started 1 wk after the start of antibiotic treatment; 24 mo later, the patient had inflammatory signs (elevated C-reactive protein level and ESR) and was in very poor condition; 48 mo after starting antibiotic treatment, the patient developed the full clinical picture of IRIS, which persisted until steroid treatment was started.
9	Female	60	The timing of onset of fever is not known exactly; fever persisted until treatment with steroids was started.
10	Male	57	Orbital pain developed in the first 2 wk of intravenous antibiotic treatment; the pain was treated with acetaminophen, and arthritis subsided.
11	Female	68	Orbital pain was reported by the patient 6 mo after start of antimicrobial treatment in the outpatient clinic; the pain was quickly relieved by treatment with steroids.
12	Male	67	Fever and hypothalamic symptoms developed in the first 2 wk after antimicrobial treatment was begun and persisted until steroid treatment was started.
13	Male	56	Fever began in the first week after onset of antibiotic treatment, whereas arthritis subsided; fever persisted until treatment with steroids was started.
14	Male	59	Inflammatory polyarthritis reappeared when treatment with steroids was stopped 16 mo after antimicrobial treatment was started, and it could be remedied only by treatment with steroids.
15	Female	51	Fever developed slowly and was reported 6 wk after antimicrobial treatment was begun; fever persisted until treatment with steroids was started.

ESR = erythrocyte sedimentation rate; IRIS = immune reconstitution inflammatory syndrome.
* Symptoms may have begun earlier.

Appendix Table 2. **Effect of Varying Time Frames of All IRIS Criteria on Sensitivity and Specificity for the Diagnosis**

Criterion	Variation of Time Frame	Effect on Results	Possible Effect in Future Cases of IRIS in WD
1: Improvement within 3 wk	Removed	No effect, because the diagnosis of WD was established in all patients.	Patients with misdiagnosis of WD could be included.
	Reduced to 2 wk	No effect; all 15 patients with IRIS responded to antibiotic treatment within 2 wk.	Severe cases of WD may respond more slowly to the treatment and thus would be excluded.
	Extended to >3 wk	No effect; all 15 patients with IRIS responded to antibiotic treatment within 2 wk.	Reassessment of patients with misdiagnosis of WD could be delayed.
2: Recurrence lasting for more than 1 wk	Removed	Overdiagnosis of IRIS: IRIS would be diagnosed in 135 of the 142 patients with WD (95.07% [95% CI, 90.10%–97.99%]). Only 7 patients who did not fulfill criterion 3 (**Figure 1**) would not receive an IRIS.	Overdiagnosis of IRIS: All patients with WD who received a correct diagnosis and were treated effectively would receive an IRIS diagnosis.
	Reduced to <1 wk	A reduction to 6 d or 5 d would not affect our results. However, a reduction to <3 d would increase the number of IRIS cases to 28 (19.72% [CI, 13.52%–27.22%]), including the 13 patients with self-limited fever from the control group, which results in overdiagnosis of IRIS.	A reduction to <3 d would lead to overdiagnosis owing to inclusion of patients with self-limited fever, such as in those with hospital-related conditions or Jarisch–Herxheimer reaction.
	Extended to 2 wk	No effect on the number of patients, but delayed diagnosis and treatment of IRIS might have caused more severe tissue damage.	The diagnosis of IRIS could be considered too late, which might result in damage to affected tissues.
	Extended to 3 wk	The number of patients with IRIS would decrease from 15 to 14 (9.86% [CI, 5.49%–15.99%]), because orbitopathy in patient 10 resolved within 3 wk without immunosuppressive treatment. In the other patients, diagnosis and treatment would have been delayed.	The diagnosis of IRIS could be considered too late, which might result in damage to affected tissues.
3: Effective treatment	Removed	7 patients from the control group who had recurrent WD but fulfilled criteria 1 and 2 would erroneously be included among patients with IRIS, increasing the number of patients with IRIS to 22 (15.49% [CI, 9.97%–22.51%]) and resulting in overdiagnosis.	Patients with ineffective treatment or recurrent WD could be erroneously considered to have IRIS.

IRIS = immune reconstitution inflammatory syndrome; WD = Whipple disease.