EXTENDED REPORT

Standardised work-up programme for fever of unknown origin and contribution of magnetic resonance imaging for the diagnosis of hidden systemic vasculitis

A D Wagner, J Andresen, E Raum, J Lotz, H Zeidler, J G Kuipers, M C Jendro

Background: Fever of unknown origin (FUO) is a diagnostic challenge. Rheumatologists are often in charge of patients with FUO because the vasculitides, especially, are potential and common causes of FUO.

Objective: To evaluate the value of a standardised investigation to identify the cause of FUO.

Methods: A standardised work-up programme for patients with FUO was started at the beginning of September 1999. The rate of identified causes of FUO was compared between all patients with FUO admitted to a tertiary care centre of rheumatology between January 1996 and August 1999 (control group) and September 1999 and January 2003 (work-up group). In January 2002 magnetic resonance imaging (MRI) was added to the investigation.

Results: 67 patients with FUO were identified—32 before and 35 after institution of the work-up programme. Before implementation 25% of all patients with FUO remained undiagnosed, after implementation 37%. After institution of the investigation the percentage of patients with vasculitides increased significantly from 6% (n = 2) to 26% (n = 9, p = 0.047, Fisher’s exact test). This increase could be attributed to the addition of MRI in 2002. When all patients with FUO before 2002 (n = 55) and thereafter (n = 12) were compared the prevalence of systemic vasculitis increased from 11% (n = 6) to 42% (n = 5, p = 0.021).

Conclusion: Implementation of a standardised work-up programme for FUO did not improve the overall rate of diagnosis. Addition of MRI significantly increased the diagnosis of systemic vasculitis as the underlying cause of FUO. MRI should be included in the investigation of patients with FUO when vasculitis is suspected.

The diagnostic investigation of patients with fever of unknown origin (FUO) remains a challenge. In the past, several attempts have been made to outline diagnostic approaches to improve diagnosis of the underlying diseases. However, owing to the plethora of different causes of FUO, the geographical influence on the prevalence of diseases causing FUO, and differences in the prevalence of underlying diseases between patient cohorts, it seems to be impossible to construct general algorithms covering the complete spectrum of FUO. The objectives in designing diagnostic work-up programmes for FUO are twofold: firstly, guidance, so that the decisive diagnostic procedure in the individual patient is performed as fast as possible to limit financial resources and possible harm to the patient and secondly, guarantee, so that harmful and life threatening diseases, at least, can be excluded in patients with FUO whose diagnosis remains unknown.

An interesting approach dealing with both objectives has been developed by the Netherlands FUO Study Group. This approach combines general application of diagnostic procedures to all patients, with special attention to so called potentially diagnostic clues (PDCs). PDCs are valuable suggestive information derived either by history or physical examination to determine the underlying diseases. During initial presentation all patients are thoroughly investigated for the presence of PDCs and the diagnostic procedures of step 1 are performed. When PDCs are present they are followed by adequate further diagnostic procedures. If PDCs are absent or misleading and a final diagnosis cannot be made, the standardised diagnostic programme proceeds to procedures of step 2 and, if not successful, finally, to step 3. The questionnaire of PDCs and the stepwise diagnostic work-up programme, which were applied to our patients who presented with FUO since September 1999, are based on the original publication of De Kleijn et al with minor modifications (see web table W1, available at http://www.annrheumdis.com/supplemental). 1

In January 2002 magnetic resonance imaging (MRI) of the aortic arch and the proximal cervical arteries was added to the diagnostic work-up programme when there was a suspicion of vasculitis. Large vessel arteritis is, especially in elderly patients as giant cell arteritis (GCA), a common cause of FUO. According to Knockaert et al the prevalence of GCA in elderly patients presenting with FUO is 12%. Because of this high prevalence, step 3 procedures already included duplex sonography of temporal, carotid, and subclavian arteries and biopsy of the temporal artery in patients older than 55 years. However, several studies and case reports did demonstrate the value of MRI in the diagnosis of large vessel arteritis. Our hypothesis was that MRI might improve diagnosis of large vessel arteritis in patients with FUO. The final incentive to add MRI was the case of one woman who presented with FUO in July 2001, in whom Takayasu’s arteritis (TA) was exclusively diagnosed by MRI of the aortic arch.

Abbreviations: ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; [18F]FDG-PET, fluorodeoxyglucose positron emission tomography; FUO, fever of unknown origin; GCA, giant cell arteritis; MRI, magnetic resonance imaging; PDCs, potentially diagnostic clues; SE, spin echo; TA, Takayasu’s arteritis; TE, echo delay time

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Additional tables W1–W4 can be found on the web at http://www.annrheumdis.com/supplemental


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This retrospective study aimed at evaluating whether implementation of this stepwise diagnostic programme in clinical practice can increase the rate of determination of the underlying cause of FUO in the cohort examined at our rheumatology tertiary care centre. The second objective was to study whether addition of MRI studies to the original programme can improve the diagnosis of large vessel arteritis.

PATIENTS AND METHODS

Patients

Patients with FUO were retrospectively identified by chart analysis of all inpatients treated at the rheumatology ward of Hannover Medical School between 1 January 1996 and 31 January 2003. Patients were included in the study if they met two criteria: firstly, admission to the rheumatological ward because of FUO between 1 January 1996 and 31 January 2003, and secondly, fulfillment of the criteria for FUO as initially defined by Petersdorf and Beeson and later modified by Durack and Street.10 11 According to this classification fever has to be present for longer than 3 weeks, the fever must be 

\[
38.3\,^\circ\mathrm{C}
\]

on several occasions, and the cause must remain uncertain after three outpatient visits or 3 days of in-hospital investigation. Patients with nosocomial FUO, HIV infection, or neutropenia were excluded because in those patients other causes of FUO prevail and the diagnostic and therapeutic approach is different. GCA, TA, and Wegener’s granulomatosis were diagnosed according to the 1990 American College of Rheumatology (ACR) classification criteria for these diseases.24–26 For microscopic polyangiitis, criteria developed by Zashin et al were used.31

Stepwise work-up programme

The stepwise work-up programme was based on the original publication by De Kleijn et al.13–16 Modifications of the original programme are indicated by bold letters in table W1 (http://www.annrheumdis.com/supplemental). They are mainly related to serological tests for microbiological pathogens where the spectrum of tests was expanded. Instead of \(^{11}\)In IgG scintigraphy, which is not available at our institution, leucocyte scintigraphy was applied. None of the tests originally proposed was omitted. The questionnaire included all valuable PDCs according to the Dutch study. During initial presentation, all patients were thoroughly investigated for the presence of PDCs outlined in the questionnaire on the left side, and in all patients diagnostic procedures of step 1 were performed. When PDCs were present, adequate diagnostic procedures to confirm the suspected underlying diseases were carried out. If PDCs were absent or misleading and a final diagnosis could not be made by the diagnostic procedures, the standardised diagnostic programme proceeded to procedures of step 2 and, if not successful, finally, to step 3. This programme has been used for our patients presenting with FUO since September 1999. Before September 1999 no standardised protocol was used for diagnosing patients with FUO. Application of diagnostic procedures was based on the knowledge of the caring physicians and the individual history of the patients.

MRI studies

Magnetic resonance examinations included axial T1 and T2 weighted spin echo (SE) images as well as T1 weighted SE after application of 0.1 mmol gadolinium/kg body weight (Magnevist, Schering, Berlin, Germany). Fat suppression was applied for T2 weighted images and contrast enhanced T1 weighted images. Peripheral gating was used with T1 weighted images, and respiratory trigger employed for T2 weighted images. Sequence parameters were adjusted to the individual patient according to the field of view and the number of slices acquired. All patients were examined in a 1.5 T system (CV/I or Signa Horizon, both General Electric, Milwaukie, USA) using a phased array surface coil.

Detailed sequence parameters were chosen as follows: SE T1: repetition time (TR) 800 ms (pulse triggered); echo delay time (TE) 14 ms; field of view 280 mm; matrix 256 \times 192; 2 NEX; slice thickness 6 mm, 1 mm gap. FSE T2: TR 4300 ms (respiratory triggered); TE: 88 ms; field of view 280 mm; matrix 256 \times 224; 2 NEX; slice thickness 6 mm, 1 mm gap. Care was taken to completely cover the thoracic aorta, including the proximal parts of the supra-aortic branches, the proximal cervical arteries, and the aortal hiatus of the diaphragm.

Statistics

Statistical analysis employed the SPSS software, version 11.0 for windows (SPSS Science, Chicago, IL, USA). To test whether the prevalence of diagnosed causes of FUO or

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients before and after implementation of the diagnostic work-up programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
</tr>
<tr>
<td>Age at admission (years)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Female (%)/male (%)</td>
<td>19 (59)/13 (41)</td>
</tr>
<tr>
<td>Duration of FUO (year)</td>
<td>1.7 (2.8)</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>55 (32)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>101 (93)</td>
</tr>
<tr>
<td>Final diagnosis:</td>
<td></td>
</tr>
<tr>
<td>FUO (% of final diagnosis)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Autoimmune diseases others than systemic vasculitis (% of final diagnosis):</td>
<td></td>
</tr>
<tr>
<td>Systemic vasculitis (% of final diagnosis):</td>
<td></td>
</tr>
<tr>
<td>With MRI</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Without MRI</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>1</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>1</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td></td>
</tr>
<tr>
<td>Infection (% of final diagnosis):</td>
<td>12 (37)</td>
</tr>
<tr>
<td>Others (% of final diagnosis)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless stated otherwise. p Value as determined by Fisher’s exact test.
clinical characteristics differed between collectives $z^2$ statistics (Fisher’s exact test) were applied. Differences between continuous variables were examined using non-parametric test statistics (Mann-Whitney U test). A value of $p < 0.05$ was considered significant, and $p < 0.01$ was considered highly significant.

RESULTS
Comparison of patients before and after implementation of the work-up programme
A total of 67 patients with FUO were identified and included in the study—32 patients before and 35 after implementation of the standardised work-up programme. Patient age at admission, sex, duration of FUO, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) values were similar for both groups (table 1). Only the percentage of systemic vasculitis as underlying cause of FUO significantly increased after implementation of the programme from 6% (n = 2 patients) to 26% (n = 9, $p = 0.047$, Fisher’s exact test). The percentages of the other underlying causes of FUO like infectious or autoimmune diseases others than systemic vasculitis did not change. (Table W2 (http://www.annrheumdis.com/supplemental) presents a detailed summary of the different causes of FUO.) Application of the programme did not improve the overall rate of successful determination of the underlying cause of FUO. Before the standardised investigation 25% (n = 8) of all patients with FUO and after implementation 37% (n = 13, $p = 0.3$, Fisher’s exact test) remained undiagnosed.

MRI for the diagnosis of systemic vasculitis
In January 2002 MRI of the aortic arch and the cervical arteries was added to the diagnostic work-up programme when vasculitis was suspected. When all patients with FUO before 2002 (n = 55) and thereafter (n = 12) were compared the prevalence of patients with systemic vasculitis identified as the cause of the fever significantly increased from 11% (n = 6) to 42% (n = 5, $p = 0.021$, Fisher’s exact test) (table 2). Most prevalent was large vessel arteritis with GCA in six patients and TA in three patients. Microscopic polyangiitis (n = 1) and Wegener’s granulomatosis (n = 1) were less common. With the exception of patient 3 all patients fulfilled the respective ACR criteria for GCA, TA, or Wegener’s granulomatosis. Microscopic polyangiitis was diagnosed according to Zashin et al. Microangiitis was diagnosed according to Zashin et al. In the patients with large vessel vasculitis, biopsy of a temporal artery was performed and histology was compatible with arteritis only in patient 11. All patients responded promptly to glucocorticoid treatment (1 mg prednisolone/kg body weight). Ten patients were additionally treated with methotrexate or azathioprine and glucocorticoid doses tapered. Before January 2002 four (7%) patients were diagnosed with large vessel arteritis, compared with five (42%) patients after January 2002. All patients with

Table 2 Characteristics of patients with vasculitis

<table>
<thead>
<tr>
<th>Patient-No</th>
<th>Diagnosis</th>
<th>Diagnostic criteria a</th>
<th>Decisive diagnostic clue</th>
<th>Decisive diagnostic procedure</th>
<th>Value of MRI</th>
<th>Part of the diagnostic programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Takayasu’s arteritis</td>
<td>3/6</td>
<td>Claudication of the arms</td>
<td>Angiography</td>
<td>Not done</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Giant cell arteritis</td>
<td>3/5</td>
<td>Claudication of the legs</td>
<td>CT chest</td>
<td>Not done</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Giant cell arteritis</td>
<td>2/5</td>
<td>Thoracic pain</td>
<td>CT chest</td>
<td>Not done</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Microscopic polyangiitis</td>
<td>5/8</td>
<td>Oedema</td>
<td>pANCA, kidney biopsy</td>
<td>Not done</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Wegener’s granulomatosis</td>
<td>2/4</td>
<td>Oedema</td>
<td>cANCA</td>
<td>Not done</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Takayasu’s arteritis</td>
<td>3/6</td>
<td>Claudication musculos masseter</td>
<td>MRI aortic arch</td>
<td>Diagnostic</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Giant cell arteritis</td>
<td>4/5</td>
<td>Claudication musculos masseter</td>
<td>Duplex sonography carotis artery</td>
<td>MRI normal</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Giant cell arteritis</td>
<td>3/5</td>
<td>Claudication musculos masseter</td>
<td>MRI carotis artery</td>
<td>Diagnostic</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Giant cell arteritis</td>
<td>3/5</td>
<td>Claudication musculos masseter</td>
<td>MRI aortic arch</td>
<td>Diagnostic</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Giant cell arteritis</td>
<td>3/5</td>
<td>None</td>
<td>MRI aortic arch</td>
<td>Diagnostic</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Takayasu’s arteritis</td>
<td>3/6</td>
<td>Aortic aneurysms</td>
<td>CT chest</td>
<td>MRI not possible</td>
<td>because of prosthesis</td>
</tr>
</tbody>
</table>

*Diagnoses were made according to the ACR criteria for GCA, TA, or Wegener’s granulomatosis. Microscopic polyangiitis was diagnosed according to Zashin et al.15

Figure 1 (A) Axial $T_2$ weighted SE image. Initial examination. Significant oedema and an increase in wall thickness is demonstrated in the descending aorta. (B) The inflammatory changes are confirmed in the $T_1$ weighted images after injection of contrast media.
vasculitis were female. In four of the five patients with vasculitis where MRI was used, intramural disease suggestive of arterial wall inflammation was detected.

Figure 1 shows the MRI results for patient 10 (table 2). On initial examination, significant oedema and an increase in wall thickness was demonstrated in the descending aorta. After initiation of treatment improvement was confirmed by reduction in wall thickness and by near normal wall signal levels (fig 2). MRI of the cervical arteries was normal in only one patient, whereas duplex sonography detected suspicious vasculitic lesions (table 2, patient 7). Without application of MRI to the work-up programme four cases of systemic vasculitis would have remained undiagnosed. The most important PDC for suspicion of systemic vasculitis was claudication. Five out of 11 patients with systemic vasculitis presented with claudication due to vasculitic arterial stenosis.

Diagnostic procedures decisive for diagnosis
Diagnoses could be established by procedures which are part of the work-up programme in 31/45 (69%) cases, whereas diagnostic procedures not part of the diagnostic programme were decisive in 14/45 (31%). (Table W3 (http://www.annrheumdis.com/supplemental) presents further details.)

Before implementation of the diagnostic work-up programme, the contribution of diagnostic procedures and many of them are already commonly used in university centres. Only the application of these diagnostic procedures had already been applied before implementation of the programme. Before September 1999—that is, before implementation, 92% of all successfully diagnosed cases of FUO were determined by procedures not part of the work-up programme. The high percentage of 92% implies that most of the diagnostic work-up programme does not include new diagnostic methods that the work-up programme does not include new diagnostic methods.

Implementation of this stepwise, very sophisticated work-up programme for the diagnosis of FUO neither increased the overall rate of successful determination of the underlying cause of FUO nor changed the distribution of the different causes in the cohort as originally hypothesised. At first glance it is surprising that the rate of successful determination of causes of FUO by the diagnostic procedures of the work-up programme was reduced after implementation of the programme. Before September 1999—that is, before implementation, 92% of all successfully diagnosed cases of FUO were determined by procedures of the diagnostic work-up programme, and after that date only 45% were thereby successfully diagnosed. This means that 55% were diagnosed by procedures not part of the programme. The high percentage of 92% implies that most of the diagnostic procedures had already been applied before implementation of the work-up programme. The reason is that the work-up programme does not include new diagnostic procedures and many of them are already commonly used in university centres. Only the application of these procedures is standardised.

The reduction from 92% to 45% after implementation is mainly due to a more frequent application of MRI studies and bone scintigraphy, which are not part of the programme. After implementation, 12 cases were successfully diagnosed by these procedures, seven by MRI and five by bone scintigraphy, whereas before only one patient was diagnosed by MRI and none by bone scintigraphy. Bone scintigraphy was performed instead of leucocyte scintigraphy as part of

Figure 2  Same patient after treatment. Success of treatment is confirmed by the obvious reduction in the wall thickness of the descending aorta in both T2 (A) and T1 (B) weighted images after contrast media injection. Wall signal returned to near normal levels.

endoprosthesis of the hip (n = 1). Angiography was decisive for TA (n = 1).

Differences between patients with undiagnosed and diagnosed FUO
When the clinical characteristics of both patient groups were compared, significant differences were apparent for age at admission and CRP values. (Table W4 (http://www.annrheumdis.com/supplemental) presents details.) Patients in whom the cause of FUO could be determined were older (difference between mean ages 11 years, p = 0.016, Mann-Whitney U test) and had higher CRP values (p = 0.025, Mann-Whitney U test).

DISCUSSION
Our study demonstrates that improvement in diagnosing FUO can only be achieved when new diagnostic methods such as MRI are included in the diagnostic work up. Implementation of this stepwise, very sophisticated work-up programme for the diagnosis of FUO neither increased the overall rate of successful determination of the underlying cause of FUO nor changed the distribution of the different causes in the cohort as originally hypothesised.

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The reduction from 92% to 45% after implementation is mainly due to a more frequent application of MRI studies and bone scintigraphy, which are not part of the programme. After implementation, 12 cases were successfully diagnosed by these procedures, seven by MRI and five by bone scintigraphy, whereas before only one patient was diagnosed by MRI and none by bone scintigraphy. Bone scintigraphy was performed instead of leucocyte scintigraphy as part of
the programme, because PDCs suggested bone involvement. Bone scintigraphy has to be rated as a modification of the diagnostic programme and not as an entirely new diagnostic approach. It is questionable whether bone scintigraphy is indeed better for diagnosing FUO than leucocyte scintigraphy. However, the more frequent application of MRI seems to be valuable in diagnosing FUO. Diseases diagnosed by MRI include large vessel vasculitis (n = 4) as detailed below, spondylodiscitis (n = 2), multifocal aseptic osteomyelitis (n = 1), and polymyositis (n = 1).

One of the objectives of developing diagnostic programmes for FUO is to minimise the amount of time needed for diagnosis and the cost. However, because of the study design appropriate data could not be obtained to examine this question. The influence of the work-up programme on these measures cannot be determined and the value of the stepwise work-up programme in diagnosing FUO for our purposes cannot be ultimately judged. However, our personal experience is that colleagues, especially those less experienced, are comfortable with the programme and continue to use it.

The most important finding of our study is that application of MRI of the aortic arch and the proximal cervical arteries seems to be promising for diagnosing large vessel arteritis in patients presenting with FUO. By addition of MRI to the diagnostic investigation in 2002, diagnosis of this disease significantly increased from 7% to 42%. Surprisingly, in addition to patients with GCA, patients with TA were also frequently detected, despite the low prevalence of TA in northern Germany. The prevalence of GCA in patients older than 50 years is 240 per 100 000 people in northern Germany, but in the same study in a cohort of 900 000 people from northern and southern Germany no case of TA could be detected. The annual incidence of TA in Sweden is 0.12 cases per 100 000 people, whereas the annual incidence of GCA in Olmsted county, Minnesota, for patients older than 50 is 17.8 cases per 100 000 inhabitants. GCA alone is one of the most common causes of FUO in elderly patients. Its prevalence ranges between 12 and 16%, predicting a high pretest probability for this disease in patients with FUO. MRI possesses a high sensitivity and specificity in diagnosing GCA resulting in a high post-test probability of this method for diagnosing FUO. According to our results, application of MRI might also be valuable in younger patients for detecting TA as a cause of FUO. However, the prevalence of TA in patients with FUO in northern Europe remains to be determined in a prospective study. Physicians in Germany are much more familiar with GCA than with TA, which might have caused an overrepresentation of TA in the cohort, because a high percentage of patients with FUO were referred from other physicians.
Because of the high costs for MRI, application of this diagnostic procedure should be limited to patients in whom large vessel arteritis is suspected. The most important anamnestic clue for suspicion of systemic vasculitis was claudication. Five of 11 patients with systemic vasculitis presented with claudication due to vasculitic arterial stenosis. Those patients should be preferentially screened by MRI. When the clinical characteristics of the patients in whom the cause of FUO could be determined and the patients who remained undiagnosed were compared, we found that in older patients and patients with high CRP values a diagnosis could be made more frequently.

In view of these preliminary data and published reports we propose the following diagnostic approach for the detection of large vessel arteritis in patients with FUO (fig 3).

Screening should be performed for patients with FUO when the following criteria are met: clinical suspicion for arteritis, especially claudicatio, myalgia, new onset headache, scalp pain, and/or raised CRP or ESR values. Because most studies report a high sensitivity (70–100%) and specificity (61–86%) of duplex ultrasonography for the diagnosis of GCA and because of its low cost, duplex ultrasonography of temporal, occipital, subclavian, and cervical arteries is the first line diagnostic procedure. If duplex ultrasonography is not decisive, patients older than 50 should undergo biopsy of the temporal artery according to the data of Salvarani et al.17 18 In younger patients, because GCA is less common and TA is more likely, biopsy is less promising and is not proposed. MRI of the aortic arch should be applied to older patients with negative biopsy findings or to patients younger than 50. One major advantage of MRI is the possibility of examining additional arteries not accessible by ultrasonography.

The final diagnostic procedure for the detection of large vessel vasculitis [18F]fluorodeoxyglucose positron emission tomography ([18F]FDG-PET) might be applied.22 23 [18F]FDG-PET may be even better than MRI; in a study of Meller et al22 MRI of the aortic arch should be applied to older patients with negative biopsy findings or to patients younger than 50. One major advantage of MRI is the possibility of examining additional arteries not accessible by ultrasonography.

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REFERENCES


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