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Clinical Features of Infections Caused by New Nontuberculous Mycobacteria, Part I*

Enrico Tortoli, Sc.D., Regional Reference Center for Mycobacteria, Careggi Hospital, Florence, Italy

Abstract

Many of the mycobacterial species described in the past decade have been involved in human disease. This issue discusses the most frequent pathologies, including respiratory infections in elderly people, cervical lymphadenitis in children, and localized post-traumatic and post-surgical infections at various body sites. Also discussed are disseminated infections, which were frequent in AIDS patients several years ago but are now rare, with the prevalence probably higher in immunocompromised HIV-negative persons. Part II of this article describes *Mycobacterium* species associated with sepsis and other diseases. No substantial differences exist in the number of cases in which slow and rapid growers are involved in disease, with the former more commonly responsible for pulmonary infections and lymphadenitis and the latter preferentially affecting bones, joints, skin, and soft tissues.

The number of known nontuberculous mycobacteria (NTM) has increased steadily during the last decade (1), with, on average, three new species described per year since 1990. Recent developments in mycobacterial taxonomy, however, are often disregarded by clinicians. Their prevalent opinions are that NTM are rarely clinically significant; that even when they are responsible for disease, their identification to species level is of little, if any, medical relevance; and that it is useful only to distinguish the *Mycobacterium tuberculosis* complex from NTM.

Given that such views are not shared by microbiologists, a clinician-oriented survey of the diseases in which NTMs

have been involved may be of use. This review, therefore, focuses on the new mycobacteria, i.e., the species described since 1990. Exhaustive reviews of the species described previously exist (2,3), and a reiteration here is unnecessary.

Unless otherwise stated, the involvement of mycobacteria in the cases reviewed here was clinically relevant; the patients whose HIV status is not detailed should be regarded as HIV negative. The clinical cases are grouped according to the localization of infection. For the reader's convenience, the species are ordered alphabetically within each group.

Respiratory Disease

The respiratory tract is the most frequent target of mycobacterial pathologies. NTM pulmonary infection is usually not distinguishable from tuberculosis, with which it shares a wide spectrum of manifestations ranging from lack of symptoms to cavitary disease.

Although not yet demonstrated for most of the newly described species, the environment is considered the natural reservoir of NTM. The main route

of infection, therefore, is by inhalation, although ingestion and direct inoculation may have roles. Contaminated aerosolized water is thought to be one of the most important sources of mycobacteria.

NTM pulmonary disease is rare in young subjects and in patients without predisposing conditions. The typical patient is older than 50 years and presents with other pulmonary problems, such as silicosis, chronic obstructive pulmonary disease, pneumoconiosis, previous tuberculosis, chronic bronchitis, bronchiectasis, or cancer. Smoking represents an important risk factor. The most frequent symptoms include productive cough, fever, weight loss, night sweats, and weakness. The radiograph may reveal fibrosis, upper lobe cavitations, nodular or parenchymal opacity, and pleural thickening. The progression

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Mailing Address: Dr. Enrico Tortoli, Centro Regionale di Riferimento per la Diagnosi dei Micobatteri, Laboratorio di Microbiologia e Virologia, Piastra dei Servizi, Ospedale Careggi, viale Morgagni 85, 50134 Firenze, Italy. Tel.: ++39 055 4279199. Fax: ++39 055 4279010. E-mail: e.tortoli@libero.it

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of disease is slow. It often takes several years, is accompanied by steadily worsening respiratory insufficiency, and may result in death. Remission is rare in the absence of treatment.

In patients with AIDS, mycobacterial pulmonary disease is acute, evolving in only a few weeks, even in the absence, as a rule, of predisposing conditions. The symptoms are minimal, and the radiological picture is usually normal or, at most, reveals mediastinal or hilar adenopathy. Cavitation is an exceptional finding. The following species are recently described NTM isolated from patients with respiratory disease.

M. branderi

M. branderi has been isolated repeatedly from the sputa of 9 people, including patients with pulmonary cavity disease resistant to drug treatment; however, no clinical information is available about them (4). In another report, a 74-year-old woman presented with lung infiltrates and middle lobe collapse, but the role of *M. branderi*, which was isolated from a bronchial specimen, remains unclear (5).

M. celatum

M. celatum has been reported to be responsible for several cases of pulmonary disease. Three reports (6-8) concern infections in non-immunocompromised elderly patients with ages ranging from 61 to 73 years. One of these patients had a history of tuberculosis as an adolescent. Unlike in other NTM respiratory diseases, underlying conditions were not present. The symptoms included cough, night sweats, and weight loss; the radiological picture was characterized by nodules, infiltrates, and cavitations. Among hematological parameters, only the erythrocyte sedimentation rate was clearly abnormal. All the patients were first treated

unsuccessfully with a regimen including rifampin and isoniazid, and one of them died in 10 weeks. When treatment, including clarithromycin and ethambutol, was undertaken, one patient markedly improved, but his sputum was still positive for mycobacteria 1 year later. The third patient was considered recovered after a 19-month treatment regimen.

Five exclusively pulmonary *M. celatum* infections have been reported in patients with AIDS (9-11). The patients, almost all male, were younger than 40 and had CD4 counts of <100/ml. The most prominent symptoms were fever, cough, and dyspnea. Chest radiographs revealed alveolar opacity or interstitial infiltrates with small cavitations. Interestingly, one patient was found to be infected by *M. celatum* after 8 months of rifabutin prophylaxis for a *M. avium* complex infection (9). One patient died after 2 weeks, whereas the others improved following treatment with various antimycobacterial drug combinations.

Many reports of infections due to *M. celatum* emphasize its initial misidentification. In many cases, it has been identified as belonging to the *M. tuberculosis* complex because of cross-hybridizing commercial DNA probes (12) or as *M. xenopi*, with which it shares most biochemical and cultural features. In several instances, such misidentification incorrectly directed treatment. Unlike *M. tuberculosis* and *M. xenopi*, *M. celatum* is consistently resistant to even high concentrations of rifampin (13).

M. elephantis* and *M. goodii

The clinical significance of the one isolation of *M. elephantis* from the sputum of a 79-year-old patient is uncertain (14).

The rapid grower *M. goodii* (part of the *M. smegmatis* group) was considered responsible for respiratory disease in three cases associated with histologic findings of lipoid pneumonia (15) and in two cases characterized by the presence of pulmonary infiltrates and granulomatous disease (16). Four of five patients, whose ages ranged from 18 to 76 years, were males.

M. heckeshornense

A case of pulmonary disease in a 30-year-old non-immunocompromised woman presenting with cough, fatigue, weight loss, and hemoptysis was ascribed to *M. heckeshornense* (17). During a lengthy antituberculosis treatment (more than 3 years), only temporary improvement was obtained. Negative sputum cultures for mycobacteria were achieved only after the patient underwent a bilateral upper lobe resection. Specific treatment was continued after the surgery. A new isolation of *M. heckeshornense* has been reported from a patient with pulmonary disorders (18). Further clinical information, however, was not provided.

M. heidelbergense

M. heidelbergense was isolated from a resected biopsy specimen that showed granulomatous inflammation and caseous necrosis (19). The patient, an 82-year-old woman, had undergone a middle-lobe lung resection because the lung lesion was misinterpreted as a tumor on X ray.

M. immunogenum

M. immunogenum was probably involved in a case of chronic pneumonia in a patient with severe combined immunodeficiency disease (20). More than 100 strains of *M. immunogenum* have been isolated from aerosolized, semisynthetic metalworking fluids

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(20-22). Such aerosols are associated with hypersensitivity pneumonitis, and although not demonstrated so far, the responsibility of this species in initiating this immune disorder has been theorized (23,24).

M. interjectum

M. interjectum was responsible for chronic destructive lung disease in a 73-year-old woman (25). On the basis of smear positivity (culture was not performed), she had been diagnosed with tuberculosis 20 years before and had been treated accordingly. Despite the persistence of cough, radiological improvement was satisfactory. Expectoration of *M. interjectum* was ascertained for the first time 10 years later, but despite treatment with rifampin and ethambutol and subsequently, with aerosolized amikacin, the disease progressed, as evidenced by the presence of interstitial shadows and severe retraction of the right lung. The clinical significance of a *M. interjectum* strain isolated from an elderly male with widespread interstitial lung opacities is not as clear cut (26).

A third unpublished case is well documented. The patient, a 42-year-old woman in otherwise good health, contacted me through the Internet. She had presented with hemoptysis, and two computerized tomography scans revealed a picture compatible with mycobacterial infection. *M. interjectum* was the only organism grown from two bronchial aspirates; the second had been performed in the hope that it would confirm the hypothesis that the first isolate was a contaminant. After 5 months of treatment with clarithromycin, the patient recovered completely, as confirmed by a normal X-ray picture.

M. interjectum has also been isolated from the sputum of an AIDS patient without any demonstrated clinical significance (27).

M. lentiflavum

M. lentiflavum was involved in one case of pulmonary disease in a 61-year-old immunocompetent woman who had had bronchiectasis since youth (28). She presented with cough, weight loss, slight fever, and radiological evidence of reticulonodular changes and adenopathy. Treatment, based initially on antituberculosis drugs that were subsequently replaced by a combination of rifabutin,

ethambutol, clarithromycin, and ciprofloxacin, was stopped after 3 years because of its evident ineffectiveness; the patient's condition remained stable.

An additional case, in which the role of *M. lentiflavum* isolated from sputum is difficult to interpret, concerns a 59-year-old woman with chronic obstructive pulmonary disease and hemoptysis (29). In this patient, lung cancer had been diagnosed but was unconfirmed.

M. mageritense* and *M. triplex

M. mageritense was isolated from a sinus specimen from a 51-year-old woman with severe sinusitis who was treated with amikacin, ciprofloxacin, and clarithromycin (30).

M. triplex was responsible for two cases of pulmonary infection (31, 32). Both patients had hemoptysis and presented with radiological evidence of small lung nodules. The older, 67-year-old patient had multifocal bronchiectasis, and the 54-year-old patient had parenchymal shadows and infiltrates. The older patient was treated initially with antituberculosis drugs without results but recovered on subsequent 18-month treatment with rifampin, ciprofloxacin, ethambutol, and clarithromycin. The second patient improved following treatment with rifampin, clarithromycin, and isoniazid.

Other *Mycobacterium* spp. in respiratory disease

Strains of *M. alvei* (33), *M. brumae* (34), *M. confluentis* (35), *M. holsaticum* (36), and *M. kubicae* (37) have also been isolated from respiratory specimens. The scanty information available in the published reports seems to exclude them from a pathological role.

Lymphadenitis

Lymphadenitis due to NTM is typically a childhood disease that involves upper cervical lymph nodes. Swelling, which develops in a few days, may vary from barely perceptible to very disfiguring, and pain, if present, is minimal. The infection remains unilateral and localized, without signs of thoracic involvement on X ray. The overlying skin tends to be adherent and erythematous, without increased warmth. The evolution of disease may be characterized by softening of the lymph node mass and by fistula formation with prolonged drainage. No changes in hematologic parameters are found.

Antimicrobial treatment is usually ineffective, but total excision of the involved nodes assures definitive recovery in almost all cases. The route of entry is usually oral, including throat, gingivae, and lips. Tooth eruption has been related to infection. Cases of adult infection and involvement of other nodes, such as inguinal, femoral, axillary, or epitrochlear, are rare.

M. bohemicum

M. bohemicum was responsible for two cases of disease: one in an 11-year-old male (38) and the second in a 2-year-old girl (39). In both cases, treatment, including clarithromycin, was undertaken initially, and subsequent resort to lymph node excision led to complete recovery. A third, similar case, which was diagnosed in our laboratory, is unpublished.

***M. celatum* type I**

M. celatum type I was isolated from pus draining from the incised lymph node of a 15-month-old boy. Cure was obtained by complete surgical removal of the node (40).

M. elephantis* and *M. genavense

M. elephantis is the only mycobacterium species described in the last 15 years that has been reported to be responsible for lymphadenitis localized to a region other than the neck. This organism was isolated from the excised axillary lymph node of a 27-year-old male (41).

M. genavense was isolated from cheesy material in a cervical lymph node removed from a 4-year-old girl with normal immune function (42).

M. heidelbergense

M. heidelbergense was isolated in a more complicated case of a 2-year-old girl with cervical lymphadenitis (43,44). Despite removal of the nodes involved and subsequent treatment with isoniazid, rifampin, and pyrazinamide, a fistula developed. Surgery was found ineffective when a new fistula appeared. Subsequent involvement of the contralateral lymph nodes required neck dissection with removal of both tonsils and several lymph nodes.

M. interjectum

M. interjectum is one of the species most frequently involved in childhood cervical lymphadenitis. Five cases have been reported in three girls and two boys

with ages ranging from 18 months to 3 years (26,45-47). In four cases, one of which required two surgical procedures, total excision of the infected lymph nodes was required for full recovery. In the fifth case, satisfactory results were obtained with drainage of purulent material and thorough curettage of the cavity.

M. lentiflavum

Five cases of infection have also been reported for *M. lentiflavum*. Four boys, with ages between 19 months and 4 years, were cured by means of lymph node excision (28,48,49). In a 3-year-old girl, suppurative cervical lymph nodes were treated with clarithromycin and ethambutol, without improvement in the subsequent 6 months (50). A sixth case of neck lymphadenitis, although unpublished (51), is worth reporting because it concerns a 45-year-old woman. The patient, who had recently been treated surgically for periodontal disease, recovered after lymph node excision. The strain was isolated from the biopsy tissue, which was characterized by a granulomatous inflammatory reaction.

Other *Mycobacterium* species in lymphadenitis

To date, the only strain of *M. palustre* isolated from humans is from a 4-year-old girl with lymphadenitis (52). Despite antimycobacterial treatment, a fistula developed and the patient was subsequently cured surgically.

M. parmense was isolated from liquefied material aspirated from a cervical lymph node of a 3-year old girl. After antituberculosis treatment failed, surgery was successful (53).

Two strains of *M. triplex* were investigated at the time of their description as a new species (54). These strains were isolated from lymph nodes, but no information was provided about the patients and the localization of the infection.

M. tusciae was isolated from the excised lymph node of a 7-year-old boy who had been undergoing steroid treatment since the age of 3 years (55). Following 7 months of ineffective therapy with beta-lactams, he underwent surgical removal of the node.

Cutaneous and Soft Tissue Infections

Traumas and surgical wounds are

frequently the source of soft tissue mycobacterial infections. The clinical manifestation, a nodular granulomatous lesion, develops in the skin or subcutaneous tissue within 1 month, on average. Underlying lymph nodes may be involved, often associated with suppuration, and dissemination of infection is a frequent outcome. Other manifestations include ulcer formation and cellulitis. Even though mycobacteria are often visible in the stained smear of clinical material, their failure to grow in culture is not exceptional.

Mycobacterium species in cutaneous and soft tissue infections

M. bohemicum was isolated from a biopsy specimen in a fatal case in an 85-year-old female with generalized eczema, nummular lesions, and scattered nodules that had spread from her hands over the previous year (56).

A *M. genavense* cutaneous infection limited to the iliac region has been reported in an HIV-negative 38-year-old woman (57). She was lymphopenic because of treatment with corticosteroids for sarcoidosis. The infection resolved after a 12-month treatment with clarithromycin, ethambutol, and ciprofloxacin.

M. goodii was isolated from the breast of a 26-year-old woman after cosmetic surgery and from pacemaker sites of 20- and 91-year-old female patients (16).

Following a liposuction procedure, *M. mageritense* was isolated from the thigh wound of a 37-year-old woman; the patient was cured surgically (30).

M. manitobense was grown from a swab specimen of an ankle ulcer in a 39-year-old male. He presented with swelling, pain, and a clear drainage from the site, despite 2 months of cephalixin therapy (58). After treatment was changed to clarithromycin and doxycycline, to which the mycobacterium was susceptible in vitro, the ulcer healed completely.

A biopsy of a slowly spreading skin granuloma on the hand of a 6-year-old child yielded *M. novocastrense* in culture (59).

M. wolinskyi has been isolated from a 29-year-old woman and a 40-year-old woman, both with post-traumatic cellulitis (16), and from the infected facial wound of a 35-year-old woman who had undergone plastic surgery (60).

Bone and Joint Infections

Mycobacterial infections of synovia, tendon sheaths, bursae, and bone tissue almost always have a traumatic or post-surgical origin and frequently evolve to osteomyelitis. Tenosynovitis involves the tendon sheaths and causes loss of function, swelling, and, at times, fistulization. Granulomatous lesions accompanied by bone necrosis characterize the osteitis. Chronic rheumatism and steroid treatments are other important predisposing conditions.

Mycobacterium species in bone and joint infections

In one case of tenosynovitis involving the right hand of a 52-year-old woman, *M. branderi* was isolated from tissue obtained by surgical debridement of ulcerative subcutaneous nodules (5). After a dramatic initial improvement on treatment with ciprofloxacin and clarithromycin, the infection resolved gradually over 19 months.

In studies describing *M. goodii*, 9 of 28 strains investigated were responsible for osteomyelitis (15,16), 3 for cellulitis and osteomyelitis (15,61) and 2 for cellulitis alone (15). Most of the patients were young, with only three of them older than 30 years. A fracture, often open, or a penetrating trauma were the most frequent precedents of infection; two cases of sternal osteomyelitis and one of femoral osteomyelitis had surgical origins. *M. goodii* was also isolated from two consecutive aspirates from a patient with olecranon bursitis (62). The infection was cured with 2 months of therapy with doxycycline and ciprofloxacin.

M. immunogenum was detected in synovial fluid aspirated from the hand of an immunocompetent patient with a septic joint (20).

M. lacus was grown from the synovia of a 68-year-old woman presenting with bursitis of the elbow following a slight trauma (63). Excision of the bursa revealed caseating granulomas. No antimicrobial treatment was required for cure.

In one case of spondylodiscitis in an 85-year old woman, *M. lentiflavum* was isolated from a granulomatous biopsy specimen; the patient improved markedly following 9 months of antituberculosis treatment (64).

One case of knee osteomyelitis due

to *M. mageritense* has been reported in a 25-year-old man who had recently undergone open reduction of a femur fracture (30). Surgery, along with treatment with amikacin and imipenem, produced improvement.

Two cases of post-traumatic osteomyelitis with cellulitis due to *M. wolinskyi* have been reported in a boy and in a 55-year-old woman (15). In a third case of osteomyelitis attributable to the same mycobacterium, infection in a 69-year-old woman was related to cardiac surgery (15).

Disseminated Disease

Disseminated mycobacterial infections are limited to patients with impaired immune systems. The most important risk factors are HIV infection, hematologic disorders, organ transplantation, and protracted steroid treatment. Mycobacterial bone disease and endocarditis may also be responsible for dissemination.

Particularly in AIDS patients, the most frequent symptoms are long-lasting, often high, fever; weight loss; abdominal pain, usually related to adenopathy; and splenomegaly. Pulmonary manifestations are limited, and radiological signs are lacking.

Several newly described mycobacterial species have been reported to be responsible for disseminated infections in HIV-negative patients.

Disseminated disease caused by *Mycobacterium* species in HIV-negative patients

M. conspicuum was isolated from the sputum of a 27-year-old man with a non-HIV cellular immunodeficiency who had presented initially with pneumonia (65). Despite uninterrupted treatment with various combinations of antimycobacterial drugs, the man died of disseminated infection. The same organism was isolated from multiple skin lesions, pleural fluid, and feces.

Two disseminated infections due to *M. genavense* have been reported in HIV-negative patients. A 47-year-old female presenting with bronchospasm and confluent, nodular dermal infiltrations was considered to have an unclassified systemic autoimmune disorder and was treated with steroids (66). Some months later, she developed a high fever and pancytopenia and died. *M. genavense* was isolated from her

bone marrow and pulmonary secretions. An 80-year-old woman undergoing treatment for a long-standing B-cell chronic lymphocytic leukemia presented with cough, lymphadenopathy, and splenomegaly (67). A bone marrow biopsy specimen revealed multiple granulomas containing acid-fast bacilli, which, along with cultures of peripheral blood, yielded *M. genavense*. The woman's condition improved during a 6-month treatment regimen with clarithromycin and ethambutol, and the blood cultures became negative. Twenty months later, however, the patient's condition worsened and *M. genavense* was isolated again from blood and bone marrow specimens. When, at her request, the resumed antimicrobial treatment was stopped, she died.

Two cases of disseminated cutaneous infections caused by *M. immunogenum* have been reported, one in a liver transplant patient and the second in a patient with severe combined immunodeficiency disease (20).

A disseminated infection due to *M. lentiflavum* has been described in a 52-year-old woman with a long history of steroid therapy (68). The initial manifestation, a painful swelling on her right wrist, received open surgical drainage. Despite nonspecific empirical antimicrobial treatment, the patient developed a right knee effusion and inflammatory skin plaques on both lower extremities. Biopsy specimens of wrist synovia and of the cutaneous lesions revealed granulomatous reactions and focal necrosis. *M. lentiflavum* was isolated in culture. The patient was placed on antituberculosis treatment but died following a rapid worsening of her general condition, with development of wasting syndrome and new joint effusions. Antimicrobial susceptibility testing revealed that the strain was resistant to almost all antimycobacterial drugs, confirming a previous report (28).

M. triplex was isolated from a long-term-immunosuppressed 13-year-old girl who had undergone four liver transplantations (69). The patient presented with generalized edema, which a computerized tomography scan revealed as pericardial and peritoneal effusions. Even though *M. triplex* was isolated from both fluids, no antibiotic treatment was undertaken. The effusions were drained, and the edema resolved rapidly

without any relapse of mycobacterial infection.

Disseminated disease caused by *Mycobacterium* species in HIV-positive patients

Reports of disseminated infections in AIDS patients are much more numerous than in HIV-negative patients. Nine cases due to *M. celatum* have been reported. Most patients were males, ranging in age from 25 to 37 years. All presented with fever, and almost all with weight loss and cough. Except for one patient, their CD4 cell counts were less than 50/ml. In six of the nine patients, *M. celatum* was responsible for pulmonary infection in addition to disseminated disease. The patients were treated with various combinations of antimycobacterial drugs, with only clarithromycin in common. Improvement and defervescence were seen, although most of the patients had very short survival times. Death was almost never ascribed to the *M. celatum* infection (9-11,70-73).

In contrast, *M. conspicuum* was responsible for the fatal outcome of a disseminated infection in a 24-year-old male with AIDS. The patient presented with fever, weight loss, and pancytopenia, and *M. conspicuum* was isolated from his blood and sputum. Treatment with rifabutin, ciprofloxacin, and ethambutol produced a transient improvement followed by death after 2 months (65).

About 100 disseminated infections due to *M. genavense* have been reported in the literature, with the majority of cases diagnosed in the years preceding the introduction of antiretroviral therapy (74). The patients were males in 60% of the cases, young (mean age, 34 years), and had CD4 cell counts below 25/ml; fever, weight loss, and diarrhea were the most frequent symptoms. Most of the isolates were obtained from blood, but others were from biopsy specimens of lymph nodes, spleen, and duodenal mucosa. Treatment with three or four drugs, most frequently clarithromycin, amikacin, ethambutol, ciprofloxacin, and rifampin, produced improvement in the majority of cases.

One case of disseminated *M. lentiflavum* infection has been reported in a 49-year-old HIV-positive male with a CD4 cell count of 40/mm³ (75). The patient presented with fever, cough, and weight loss. Following the isolation of

M. lentiflavum from three blood cultures and one bronchoalveolar lavage specimen, treatment was begun with clarithromycin, rifabutin, ethambutol, and a new antiretroviral regimen. The patient recovered fully.

A disseminated *M. triplex* infection has been reported in a highly immunocompromised, 40-year-old AIDS patient who, while on antiretroviral therapy for 1 year, complained of fever, night sweats, weight loss, and articular pain in both knees (76). *M. triplex* was isolated from synovial fluid and tibia and bone marrow specimens. Treatment with clarithromycin and ethionamide, which were active in vitro, produced initial improvement, but subsequently, when the same mycobacterium was isolated from a colliquative knee abscess, the patient's condition slowly worsened.

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Paul A. Granato, Ph.D.
Dept. of Microbiology & Immunology
WH 2204
SUNY Upstate Medical University
750 E. Adams St.
Syracuse NY 13210 USA
Tel.: 315-464-7653
e-mail: granatop@upstate.edu

Editors:

Mary Jane Ferraro
Paul A. Granato
Josephine A. Morello
R.J. Zabransky

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