Gas gangrene in an immunocompromised girl due to a Clostridium ramosum infection
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Primary Lamivudine Resistance in Acute/Early Human Immunodeficiency Virus Infection

Primary resistance of HIV to zidovudine was first described in 1992 [1] and has since been identified in up to 10% of antiretroviral-naive patients in some centers [2]. Primary resistance to nevirapine [3] has also been reported, but the prevalence of primary resistance to other agents in widespread use in clinical practice is unknown. We now report two cases of primary lamivudine resistance in two antiretroviral-naive patients who presented with acute HIV infection.

Patients with acute/early HIV infection (documented acquisition of infection in the previous 6 months) were recruited as part of an ongoing pilot study, initiated in March 1995. Patients have been recruited from community physicians, street clinics, sexually transmitted disease clinics, cohort studies of gay or bisexual men and intravenous drug users, and high-risk persons admitted to hospital. At the time of the initial evaluation, a blood sample was obtained for measurement of the CD4 cell count and the plasma virus load (Amplicor HIV Monitor kit; Roche Diagnostics, Mississauga, Canada).

For resistance testing, HIV RNA was isolated from the baseline plasma sample and then reverse-transcribed and amplified by use of primer NE1 (5’-CCCACAAGTCTGATGTCATAAACGTCAGCT-3’) and primer A (5’-TGAGTGCACCCCTTAAAATTTCTAGTCTATT-3’), respectively, under standardized conditions. Dilutions of this first PCR product were used as templates for specific PCR-based detection of the M184V mutation characteristic of resistance to lamivudine. This was done with primer 184 (5’-GTAATCCCCACCTCAACAGA-3’) and either primer 184M (5’-CAGACATAGTTACCTATCAACG-3’) or 184W (5’-CAGACATAGTTACCTATCAATACG-3’), designed to selectively amplify viruses with the appropriate mutation at codon 184 (184M) or wild-type HIV (184W). Experimental controls (provided by J. Mellors) consisted of clinical plasma samples known to contain wild-type or mutant virus strains. Selective PCR findings were confirmed by formal sequencing of DNA obtained from the initial reverse transcription–PCR product.

The M184V mutation was identified at baseline in isolates taken from 2 of 35 patient samples. These consisted of 1 of 12 homosexual men (patient A), 0 of 17 injection drug users, and 1 of 6 heterosexual subjects (patient B).

Patient A is a 36-year-old man who presented 60 days after an acute retroviral syndrome that began 2 weeks after receptive anal intercourse with an unknown male partner. At the time of initial evaluation, the patient was well. Physical examination was entirely unremarkable. A test for HIV antibodies was positive. His baseline plasma virus load was 136,000 copies/mL of plasma, and his CD4 cell count was 190/μL (figure 1A). Therapy was initiated with zidovudine (500 mg/day) and lamivudine (300 mg/day). At week 8, the plasma virus load was 8,400 copies/mL. Saquinavir (enhanced oral formulation, 3,600 mg/day) was added at week 10. With this regimen, maximal virologic suppression was achieved (<400 copies/mL) and has been maintained to week 86, the most recent CD4 cell count being 1,020/μL.

Patient B is a 20-year-old man who presented 35 days after an acute illness that followed sexual contact with a female partner. Physical examination revealed oral candidiasis. He received local therapy with nystatin (to which the candidiasis responded), and an HIV antibody test was ordered, which was positive. Prior testing earlier in the year had yielded negative results. His baseline plasma virus load was 3,600 copies/mL, and his CD4 cell count was 380/μL (figure 1B). Therapy was initiated 5 weeks later with zidovudine (500 mg/day) and lamivudine (300 mg/day). By week 3, the virus load had fallen to unquantifiable levels but then increased to 970 copies/mL, and his treatment regimen was changed to stavudine (80 mg/day), didanosine (400 mg/day), and indinavir (2,400 mg/day) and then changed again to stavudine and lamivudine at week 18 because of intolerance. His plasma virus load was <400 copies/mL until week 36 and was then found to be 670 copies/mL after a recurrence of genital herpes. Four months later, while the patient is receiving the same therapy, his plasma virus load is 53,000 copies/mL.

It is not surprising that the first cases of transmission of resistant virus strains involved isolates with decreased susceptibility to zidovudine [1]. Additional cases of primary drug resistance have been slow to be identified but are now being described. The transmission of nevirapine-resistant HIV likely relates to the ease with which high-grade phenotypic resistance may develop in vivo [4]. A parallel can be drawn with lamivudine [5]. This study should not be taken as a measure of the prevalence of primary lamivudine resistance in British Columbia, as our study population was largely unselected. It is of interest that none of 17 injection drug users evaluated had primary drug resistance, and this should be monitored on an ongoing basis.

The prospective mapping of spread of primary drug resistance (to lamivudine and any other agents) may allow us to follow the spread of HIV infection in specific groups or communities. Comprehensive sampling of sentinel populations is being planned at a national level in Canada to begin to address these issues.

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Figure 1. Serial plasma virus load measurements (copies/mL, ■), CD4 cell counts (cells/µL, ○), and antiretroviral therapy administered to patients A and B, HIV-infected patients with virus isolates with primary resistance to lamivudine (ddl = didanosine; D4T = stavudine; IDV = indinavir; SQV = saquinavir; 3TC = lamivudine; ZDV = zidovudine).

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References

Massive Hemoperitoneum: A New Manifestation of Bacillary Peliosis in Human Immunodeficiency Virus Infection

Bartonella henselae and Bartonella quintana are agents recognized to be responsible for bacillary angiomatosis (BA) and bacillary parenchymal peliosis (BPP), two diseases characterized by unique vascular lesions affecting almost exclusively patients who are severely immunocompromised by HIV [1]. Histologic findings in BA consist of lobular proliferations of small blood vessels coated by enlarged endothelial cells. Although BA is most frequently found localized to the skin [1, 2], involvement of virtually every organ system has been reported [1]. Pathologic findings in BPP include dilated capillaries and blood-filled cavernous (peliotic) spaces involving the liver and spleen [1, 3]. We report a case of an HIV-infected patient with massive hemoperitoneum and hypovolemic shock as the main manifestation of hepatic BPP, complications not previously reported in this entity.

A 29-year-old man, seropositive for HIV, was admitted to the hospital because of fever and abdominal pain. The patient had a history of intravenous drug use until a few months before admission. A diagnosis of HIV infection had been made 8 years earlier, but the patient had never sought medical attention. He had had close contact with cats until recently. One month before admission, he was hospitalized because of low-grade fever, blurred vision in the right eye, dysarthria, and right hemiparesis. A CT scan of the brain revealed multiple small hypodense lesions distributed throughout both hemispheres, with no enhancement after administration of iv contrast. Results of CSF testing were normal. His serum was positive for antitoxoplasmic IgG antibodies at a titer of 1:300, and he had a CD4 cell count of 41/µL. The patient rejected a cerebral biopsy. He became clinically stable and was discharged while receiving treatment with pyrimethamine and sulfadiazine.

Six days after discharge, he was readmitted to the hospital because of fever, widespread abdominal pain, vomiting, and anorexia. On physical examination, the patient appeared severely ill, with a temperature of 38.5°C, diffuse abdominal tenderness, and marked hepatomegaly. Neurological findings remained unchanged in relation to those observed in the previous admission. The following laboratory values were noted: alkaline phosphatase, 2,774 U/L (normal range, 91–258 U/L); lactate dehydrogenase, 570 U/L (normal range, 230–460 U/L); WBCs, 1.8 × 10^9/L; neutrophils, 1.2 × 10^9/L; platelets, 28.8 × 10^9/L; hemoglobin, 124 g/L. Bilirubin, aspartate aminotransferase, and alanine aminotransferase levels were normal, as was a chest radiograph. An abdominal CT scan revealed important liver enlargement, with a small hypodense lesion in the right hepatic lobe, and mild spleen enlargement. On the second hospital day, the patient developed hypovolemic shock and abdominal distension. His hemoglobin level...
Persisting Fever as the Only Manifestation of Chronic Coxsackievirus B4 Infection in the Brain of a Human Immunodeficiency Virus–Infected Child

Children with perinatal HIV-1 infection frequently have long-lasting fever. This fever may be sustained by secondary infections.

References


Often, no etiologic agent can be identified, and persistent fever is interpreted as being due to HIV-1 [1]. We report here the case of an HIV-1-infected child, in whom persistent fever was the only symptom of chronic coxsackievirus B4 infection in the brain, preceding by several months the appearance of neurological signs.

A perinatally HIV-1-infected child at 3 months of age developed diffuse lymphadenopathy, hepatosplenomegaly, diarrhea, and failure to thrive. Zidovudine therapy resulted in recovery from diarrhea and a marked weight gain. During the following 4 years, his general condition and growth remained satisfactory, despite the progressive decrease in number of CD4+ cells (723 × 10^6 cells/L at 2 years, 38 × 10^6 cells/L at 4 years). After the identification of a genotype mutation associated with zidovudine resistance,
Postexposure Rabies Vaccination in Patients Infected with Human Immunodeficiency Virus

In general, symptomatic HIV-infected children and adults have suboptimal immunologic responses to several commonly used vaccines [1–5]. Previous studies demonstrated impaired formation of antibodies to T lymphocyte–dependent antigens (such as diphtheria, tetanus, poliovirus, and influenza vaccines) in relation to the number of CD4+ T lymphocytes; however, vaccination of HIV-infected persons with these antigens may induce a normal antibody response when undertaken early in the disease [4–6]. Although HIV-infected persons require special consideration because of concern that their response to vaccine may be abnormal, the vaccination of HIV-infected persons against tetanus, diphtheria, pertussis, poliomyelitis, hepatitis B, influenza, and pneumococcal disease has been recommended [7].

There is little doubt that postexposure rabies vaccination prevents deaths in persons who are exposed to rabies, so it differs from other immunizations in that it represents treatment for a fatal disease. Because the aim of postexposure rabies vaccination is to induce protective immunity, as measured by neutralizing antibody responses to rabies virus, as quickly as possible, we...
in HIV-infected patients after postexposure rabies vaccination was conducted. We identified nine HIV-infected patients without active opportunistic infections, who presented with possible or proven rabies exposure (all except one had severe exposure, WHO category III) [8]. CD4⁺ T lymphocyte counts were determined in venous blood collected from all HIV-infected patients before vaccination (day 0). They were given the WHO-approved Thai Red Cross multidose intradermal postexposure vaccine regimen (2-2-2-0-1-1, TRC-ID) with purified Vero cell rabies vaccine (Verorab; Pasteur Mérieux, Connaught, France; batch L0316 and K0183; potency, 8.8 and 8.9 IU/mL). All except one received purified equine rabies immune globulin (Institut Pasteur Diagnostics, Marnes-la-Coquette, France; batch L 5174; potency, 247 IU/mL, 40 IU/kg). Titers of neutralizing antibody to rabies virus were determined by the method of Smith et al. [9] before vaccination and on days 7, 14, 28, and 90 thereafter. This study was approved by the ethics committee of this institution.

We found that none of the HIV-infected patients died of rabies during the following 6–12 months. Five HIV-infected patients with low CD4⁺ T lymphocyte counts of ≤300/μL (range, 111–250/μL) had a poor or even nondetectable neutralizing antibody response to vaccination (figure 1). However, four HIV-infected patients with CD4⁺ T lymphocyte counts of >300/μL (range, 316–950/μL) had neutralizing antibody titers well above the minimal WHO-recommended level of 0.5 IU/mL, as did nine HIV-seronegative patients (CD4⁺ T lymphocyte count range, 554–1,124/μL) treated in the same manner (data not shown). This preliminary study demonstrated that HIV-infected persons with low CD4⁺ T lymphocyte counts have an impaired (primary) antibody response after receipt of tissue culture rabies vaccines as recommended by WHO. We recommend that it is necessary to check titers of neutralizing antibody to rabies virus in HIV-infected patients after postexposure rabies vaccination with tissue culture rabies vaccine. Higher doses or more frequent booster injections may be considered for HIV-infected patients; however, the response to higher doses of rabies vaccine and the persistence of neutralizing antibodies in these patients have not been evaluated. Recently, we decided to double the dose of tissue culture rabies vaccine in HIV-infected persons exposed to rabies. This practice at our institution is needed to determine whether this will result in an adequate neutralizing antibody response.

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References
Successful Treatment of Multiple Cerebral Histoplasmosas with Itraconazole

Amphotericin B has been suggested as the treatment of choice for cerebral histoplasmosas, but it is effective in only about half of cases [1]. In the review by Wheat et al. [1], no cases of cerebral histoplasmosas resolved without antifungal therapy, and only two were treated with azoles. I am unaware of previous reports of itraconazole use for CNS histoplasmosis.

A 53-year-old woman with a history of type II diabetes mellitus presented with a 3-week history of confusion, dysarthria, right-sided weakness, left-sided eyelid ptosis, weakness of gaze to the right, right-sided hyperreflexia, and left-sided neglect. She denied having chills or sweats and was afebrile.

Four months earlier, she had had a platelet count of 5,000/mm³ and was treated with corticosteroids and intravenous immunoglobulin for idiopathic immune thrombocytopenia. During that time, she had a brief febrile illness; a bone marrow examination revealed noncaseating granulomas, and a chest radiograph showed increased interstitial markings. Her platelet count, fever, and chest radiograph returned to normal after a few days, and corticosteroid treatment was tapered and then discontinued 3 weeks before her neurological symptoms began.

At the time of her neurological symptoms, an MRI scan revealed numerous lesions (diameter, <1 cm) of the grey and white matter of the frontal, parietal, and occipital lobes and lesions within the midbrain and brain stem (figure 1). The lesions enhanced after intravenous injection of gadolinium, and some had surrounding edema. An abdominal CT scan showed the left adrenal to be 3.4 × 3.9 cm with a hypodense center and hyperdense rim. A chest radiograph was normal. A fine-needle adrenal aspirate showed nondiagnostic results. On CSF testing, the following values were noted: glucose, 52 mg/dL; protein, 61 mg/dL; RBCs, 0/mm³; WBCs, 1/mm³ (100% mononuclear). Bone marrow and CSF cultures were negative. The *Histoplasma capsulatum* polysaccharide antigen level in serum was 0.5 U and in CSF was 0.7 U. The patient was negative for IgG antibodies to *Echinococcus* species and HIV and IgM antibodies to *Toxoplasma* species in serum. Her serum was positive for IgG antibodies to *Toxoplasma* species, but the ratio of *Toxoplasma* IgG antibodies to total IgG was twofold greater in serum than in CSF. Her titer of complement fixation antibody to *H. capsulatum* in CSF was 1:2 for the mycelial antigen and 1:4 for the yeast antigen. An open adrenal biopsy revealed extensive necrosis, granulomatous inflammation, and organisms consistent with histoplasmosis. Culture of adrenal tissue yielded *H. capsulatum*.

The patient refused therapy with amphotericin B. She began receiving itraconazole, 200 mg three times daily for 3 days, followed by 200 mg twice daily. Her neurological signs and symptoms improved over the next 3 months, and repeat MRI scans revealed a decrease in the number and size of the lesions and in the surrounding edema. She continued to receive itraconazole for 1 year. Another MRI scan done 4 months after discontinuation of therapy revealed no change from the scan at the end of therapy. More than 2.5 years after discontinuing therapy, the patient remains asymptomatic.

The patient described had evidence of cerebral histoplasmosas, despite the lack of a brain biopsy. *H. capsulatum* was found in the adrenal gland, antibodies to *H. capsulatum* were present in CSF, and the lesions and symptoms responded to antifungal therapy. Negative cultures of CSF and a negative result on CSF histoplasma polysaccharide antigen testing are observed in about half of cases of CNS histoplasmosis [1]. It is likely that her disease was related to the immunosuppressive effects of the corticosteroids, despite discontinuation of corticosteroids 3 weeks before her neurological symptoms began.

Two cases of cerebral histoplasmosas have been successfully treated with ketoconazole after relapse following therapy with intravenous amphotericin B [2, 3]. There has also been a report of treatment failure with ketoconazole therapy for cerebral histoplasmosas [4]. Ketoconazole has been associated with treatment failures in immunocompromised patients with histoplasmosis and has poor penetration into CSF [1]. Two reported cases of CNS histoplasmosis have been treated with fluconazole, which crosses the blood-brain barrier, but the length of follow-up was short [5, 6]. Fluconazole is associated with treatment failures and relapses in both immunocompetent and immunocompromised patients with histoplasmosis and is less active than itraconazole against *H. capsulatum* in vitro [7].

Itraconazole is more active than ketoconazole or fluconazole in non-CNS histoplasmosis [7, 8]. In animal models, concentrations of itraconazole in CSF are negligible, but concentrations in brain
tissue exceed those in plasma, which may explain itraconazole’s utility in cases of cryptococcal and coccidioidal meningitis and cerebral aspergillosis [8–10]. Itraconazole use should be considered for cerebral histoplasmosomas, especially in patients who cannot tolerate treatment with amphotericin B or who have amphotericin B treatment failure.

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References


Successful Treatment of Ventriculitis Due to Carbapenem-Resistant Acinetobacter baumannii with Intraventricular Colistin Sulfomethate Sodium

Over the past 2 decades, Acinetobacter baumannii has developed one of the most alarming patterns of antibiotic resistance ever observed [1]. Nowadays, since an increasing proportion of isolates are resistant to all antibiotics tested routinely, therapy is a serious challenge [2]. In 1992, a large outbreak due to multiresistant A. baumannii was noted in our 1,000-bed tertiary teaching hospital, causing considerable imipenem overuse [3]. In January 1997, two clones resistant to carbapenems emerged: clone D, moderately resistant to imipenem (MICs, 4–16 mg/L) and tobramycin (MIC, 8 mg/L) and susceptible only to sulbactam and polymyxins (MICs, ≤4 mg/L), and clone E, highly resistant to imipenem and sulbactam (MICs, >256 mg/L), moderately resistant to tobramycin (MIC, 8 mg/L), and susceptible only to polymyxins. Since then, five patients have developed catheter-associated ventriculitis due to carbapenem-resistant A. baumannii strains (table 1). Of these five patients, three died of their infection after receiving inadequate therapy (patients 1–3). The other two are, to our knowledge, the first reported to date who survived after treatment with intraventricular colistin sulfomethate sodium (patients 4 and 5).

Patient 4 was a 16-year-old boy who underwent surgery and the insertion of an external ventriculostomy tube for continuous drainage because of hemangioblastoma of the fourth ventricle. On day 7 after surgery, meropenem at 2 g/8 h was started empirically to treat his fever, although CSF cultures had been sterile. On day 16, his fever increased, and CSF analysis revealed 27,900 cells/mm³ (95% polymorphonuclear cells), and cultures of CSF yielded A. baumannii. Meropenem was discontinued, and intraventricular tobramycin (10 mg/12 h), intravenous tobramycin (5 mg/kg once a day), and intravenous sulbactam (2 g/6 h) were then initiated. On day 19, because CSF cultures remained positive, the ventriculostomy tube was replaced and intraventricular tobramycin was switched to intraventricular colistimethate sodium (5 mg/12 h), intravenous tobramycin was maintained, and intravenous sulbactam was discontinued. Intraventricular colistin was administered in a 5-mL solution of saline serum through the ventriculostomy tube after previous extraction of 5 mL of CSF, and thereafter, the drainage was interrupted for 3 hours. On day 21, cultures of CSF were negative and remained so until colistin sulfomethate sodium therapy was ended on day 39, when a ventriculoperitoneal shunt was inserted. During therapy, CSF, bactericidal titers at 3 hours after colistin sulfomethate sodium administration (peak) were 1/2, and before doses were administered (trough), titers ranged from <1/2 to 1/4. Similarly, CSF bacteriostatic titers at peak were 1/8 and at trough ranged from 1/4 to 1/16. Levels of tobramycin in CSF varied from 7.9 mg/L (peak) to 0.7 mg/L (trough). No adverse reactions were documented during therapy. On day 82, the patient was alert with spontaneous mobilization of the extremities, but he died suddenly of cardiac arrest. Postmortem examination ruled out ventriculitis, and cultures of CSF were negative for A. baumannii.

Patient 5 was a 34-year-old woman who required an external ventriculostomy tube because of subarachnoid hemorrhage with hydrocephalus. The catheter was removed 6 days after insertion; however, 24 hours later, the patient developed high fever and neurological symptoms worsened, with purulent secretion from the catheter insertion site. CSF obtained through a new ventricular drainage site was cloudy, showing 2,000 cells/mm³ (95% polymorphonuclear cells) and short gram-negative rods on gram stain. Cultures from the purulent secretion and CSF yielded A. baumannii. Intraventricular colistimethate sodium (5 mg/12 h), given following the above-mentioned procedures, and intravenous tobramycin (4 mg/kg once a day) were administered without complications. Although a rapid decrease in the bacterial count in CSF

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was observed, cultures of CSF remained positive through the fifth day of therapy. Dosages of colistin sulfomethate sodium were then increased to 10 mg/12 h, and 24 hours later, cultures of CSF yielded negative results (CSF peak bactericidal and bacteriostatic titers were <1/2 and 1/16, respectively). Cultures of CSF continued to be negative until day 30 of the patient’s stay in the intensive care unit (6 days after the end of colistin sulfomethate sodium therapy), when a ventriculoperitoneal shunt was inserted. Two months later, the patient was discharged from the unit, remaining on intravenous therapy, when a ventriculoperitoneal shunt was inserted. Two months later, the patient was discharged from the unit, remaining on intravenous therapy, when a ventriculoperitoneal shunt was inserted.

In view of these results, search for new therapeutic strategies is urgently needed for the treatment of CNS infections due to A. baumannii that is resistant to carbapenems. In the meantime, intraventricular colistimethate sodium may be life-saving in circumstances in which there are no other options.

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References


Table 1. Clinical characteristics of the five patients with carbapenem-resistant Acinetobacter baumannii ventriculitis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Underlying condition</th>
<th>Surgery/ventricular tube*</th>
<th>Clone</th>
<th>Intrathecal colistin¹</th>
<th>Intravenous antibiotics¹</th>
<th>Infection outcome¹</th>
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<td>1</td>
<td>47/F</td>
<td>Subarachnoid hemorrhage</td>
<td>No/yes (7)</td>
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<td>No</td>
<td>Mer (2) + Tm (2)</td>
<td>Died (2)</td>
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<td>Ependymoma</td>
<td>Yes/yes (11)</td>
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<td>No</td>
<td>Sulb (7) + Tm (7)</td>
<td>Died (7)</td>
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<tr>
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<td>Epidermoid tumor</td>
<td>Yes/yes (21)</td>
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<td>No</td>
<td>No</td>
<td>Died (1)</td>
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<td>4</td>
<td>16/M</td>
<td>Hemangioblastoma</td>
<td>Yes/yes (16)</td>
<td>D</td>
<td>Yes (19)</td>
<td>Sulb (3) + Tm (19)</td>
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<tr>
<td>5</td>
<td>34/F</td>
<td>Subarachnoid hemorrhage</td>
<td>No/yes (7)</td>
<td>E</td>
<td>Yes (17)</td>
<td>Tm (17)</td>
<td>Cured</td>
</tr>
</tbody>
</table>

NOTE: Mer = meropenem; Sulb = sulbactam; Tm = tobramycin.

* Parentheses indicate the days from catheter insertion to diagnosis of infection.

¹ Parentheses indicate the days of treatment.

² Parentheses indicate the days from diagnosis of infection to death.

³ Parentheses indicate the days from diagnosis of infection to death.

¹ The patient died of a noninfectious cause, 66 days after treatment ended.
Adult Pneumococcal Cellulitis: Case Report and Review

*Streptococcus pneumoniae* is an infrequent cause of skin infections in adults. Prior reports describe facial cellulitis in children with hypogammaglobulinemia and hemoglobinopathy and in adults with connective tissue disorders [1, 2]. We report a case of pneumococcal cellulitis and bacteremia in an alcoholic patient with diabetes and discuss this disease in adult patients.

A 71-year-old man with a history of alcohol abuse presented with fever and a 4-week history of intermittent and progressive pain in the right lower extremity associated with skin discoloration. He denied any history of trauma or respiratory illness. He had not previously received polyvalent pneumococcal vaccination.

On admission, the patient was febrile to 38°C, lethargic, and confused. Bullae, a violaceous hue, and multiple areas of desquamation were noted on the right foot and lower leg. The lower leg was warm and tender, whereas the foot was cold and pulseless. Significant laboratory values included the following: leukocytes, 30,500/mm³, and creatine phosphokinase, 295 U/L. A chest roentgenogram was unremarkable. Cultures of blood yielded *S. pneumoniae*.

The patient underwent a below-knee amputation. Histopathologic evaluation revealed diffuse polymorphonuclear infiltrates of the soft tissue, gram-positive diplococci, and acute thrombophlebitis with acute inflammatory infiltrates of arterial adventitia consistent with cellulitis. The patient was treated with vancomycin. He underwent a subsequent above-knee amputation because of poor stump healing.

Pneumococcal cellulitis is rare, with ~30 cases reported in the English-language literature. Descriptions range from localized erythema to violaceous or brawny skin discoloration and bullae formation [2–4]. It has been postulated that a toxin may mediate some aspects of local tissue inflammation [2, 3]. The majority of patients had underlying chronic illnesses or were immunocompromised by drug or alcohol abuse [2–5].

There appear to be two distinct clinical syndromes of pneumococcal cellulitis. The first is cellulitis of the limbs that is associated with a history of ethanol abuse, injection drugs, and diabetes mellitus [1, 2, 6]. These patients are at higher risk for limb trauma, which may serve as the portal of entry of bacteria. The practice by some injection drug users of blowing through syringes to establish patency before injection may increase the risk for pneumococcal contamination [6]. In contrast, patients with systemic lupus erythematosus, nephrotic syndrome, and hematologic disorders, including multiple myeloma and macroglobulinemia, commonly present with face and neck cellulitis [1–4, 7]. Pharyngeal colonization has been postulated to be the initiating event for facial cellulitis because of the proximity to the respiratory tract [1]. The age distribution correlated with the patient’s underlying disease. The male-to-female ratio was ~2:1.

Pneumococcal cellulitis was universally associated with bacteremia [2–5, 7]. Penicillin was typically the drug of choice. Thus far, only one reported case was due to penicillin-resistant *S. pneumoniae* [7]. The role of pneumococcal vaccination is difficult to ascertain, since administration was not reported and most patients would be expected to have a poor antibody response.

Suppurative complications were common, and surgical intervention was required in many cases [2–4, 6]. Procedures included debridement, fasciectomy, amputation, and skin grafting. Mortality was ~15% [1–6].

In summary, pneumococcal skin infections represent two distinctive clinical syndromes: facial cellulitis in persons with systemic lupus erythematosus and hematologic disorders and limb cellulitis in persons with diabetes and substance abuse. Bloodstream invasion, tissue necrosis, and suppurative complications are common. Thus, a clinician should have a high degree of suspicion of pneumococcal cellulitis for patients who present with cellulitis associated with bullae and violaceous color, to allow for the initiation of early, aggressive management.

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**References**


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Recrudescence of Cutaneous Mycobacterium haemophilum Lesions Following Tetanus Immunization

Mycobacterium haemophilum is increasingly recognized as a cause of cutaneous, joint, and pulmonary infections in immunocompromised hosts [1, 2]. We describe a patient with HIV infection and cutaneous lesions due to M. haemophilum who experienced an unusual reaction to a routinely administered tetanus vaccine.

In August 1996, a 51-year-old homosexual man was diagnosed with Pneumocystis carinii pneumonia and treated successfully with trimethoprim-sulfamethoxazole (TMP-SMZ). He declined formal HIV testing, choosing instead to travel in search of nontraditional healing strategies. While in Thailand in April 1997, he noted the subacute onset of tender, erythematous nodules on his extremities. He returned to the United States and presented to the hospital, where he reported intermittent fevers and weight loss. Physical examination revealed a temperature of 39.0°C, temporal wasting, and oral candidiasis. There were multiple violaceous, tender, and fluctuant nodules on his legs (Figure 1). A chest radiograph was normal. The WBC count was 3,000/mm³, and testing for antibody to HIV was positive. The absolute CD4 count was 4/mm³, and the plasma HIV RNA was 432,000 copies/mL.

Aspirates from skin lesions were heavily laden with acid-fast bacilli. The patient was initially treated with isoniazid, rifampin, ethambutol, and pyrazinamide until DNA probes ruled out Mycobacterium tuberculosis. Specimens subcultured on chocolate agar at 30°C yielded growth after 1 month. Gas-liquid chromatographic analysis of the cell-wall fatty acids produced a pattern consistent with M. haemophilum, and the patient was treated with clarithromycin, TMP-SMZ, rifabutin, and ciprofloxacin. He also received the antiretroviral medications stavudine, lamivudine, and nelﬁnavir. By July 1997, the lesions were greatly improved; his CD4 count had risen to 64/mm³, and plasma HIV RNA was undetectable. As part of a routine clinic visit, he was given an intramuscular injection of tetanus toxoid. Within 1 day, he noted the rapid recurrence of the nodular lesions on his legs. Aspirates of these lesions 1 week later again revealed many acid-fast bacilli. However, plasma HIV RNA remained undetectable, and the CD4 count was 95/mm³. The patient was observed while taking the same regimen of antiretroviral and antimycobacterial medications, and after several weeks the lesions again slowly resolved. Cultures from the second aspirate remained negative.

M. haemophilum has been reported as a cause of lymphadenitis in otherwise healthy children, and is now recognized as a pathogen of immunocompromised adults [1, 2]. Because of the organism’s propensity for growth at reduced temperatures, skin lesions are usually found on the extremities. Optimal treatment is unknown, and the prognosis appears to be closely linked to the degree of underlying immunosuppression [1–3]. The rapid recrudescence of such skin lesions has not been reported. Given the slow growth of M. haemophilum and the absence of viable organisms from the recurrent lesions, it is unlikely that this recrudescence represented resurgence of infection. Rather, this case illustrates a previously unrecognized effect of tetanus vaccination in the setting of immune-system restoration.

The phenomenon of inflammatory reactions resulting from newly competent immune cells has been recognized in HIV-infected patients since the advent of potent antiretroviral therapy, and has been particularly noted with mycobacterial infections [4]. In the case presented here, the combined medication regimen initially resulted in successful treatment of both mycobacterial and HIV infections. The return of functional CD4 cells is supported by the near resolution of the M. haemophilum skin lesions, which to date has been rare in AIDS patients [3]. However, the vaccination provided a sudden immune stimulus, presumably secondary to CD4-cell activation by the T-cell dependent tetanus toxoid. The resulting skin lesions, although now sterile, were no less dramatic. The transient increase in HIV viral load that can be seen following tetanus vaccination [5, 6] was likely mitigated by antiretroviral therapy. Despite the temporary setback, the combination therapy again proved to be successful, with no detrimental effect on CD4 count or HIV viral load. Tetanus, and perhaps other vaccines,
while still of great benefit in preventive health care, should also be recognized as nonspecific immune activators. Practitioners who are treating HIV-infected patients should be aware of such acute stimuli and the immune reconstitution syndrome.

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References


Severe Neutropenia During Therapy for Concurrent Primary Human Immunodeficiency Virus and Cytomegalovirus Infections

Treatment of primary HIV infection with antiretrovirals is based on theoretical rationale, limited clinical trial data, and the opinions of experts. We describe a patient with concurrent primary HIV-1 and cytomegalovirus (CMV) infections who had severe neutropenia while receiving antiretroviral therapy.

Serologies for antibodies to CMV and HIV and testing to determine plasma HIV RNA viral load (Amplicor HIV Monitor Test, Roche Diagnostic Systems, Branchburg, NJ) were done with use of commercial kits. A search was performed on MEDLINE and AIDSLine through November 1997 for concurrent acute/primary infections with HIV and CMV. Additional cases were identified by manual searches.

A previously healthy, 32-year-old woman was hospitalized (day 1) because of fever of 12 days duration, headache, skin rash, and enlarged cervical lymph nodes. She had been prescribed acyclovir for suspected genital herpes infection 9 days earlier. Her history revealed two episodes of condom-protected heterosexual intercourse 2 weeks before the fever. She had been HIV-negative 4 months earlier, and she denied other possible exposures to HIV thereafter. On hospital day 1, serologies for antibodies to HIV showed a distinct reaction to envelope protein gp 41 and weak reactions to envelope protein gp 120 and to protein p 17, the plasma HIV RNA viral load was 480,000 copies/mL, and a serology for antibodies to CMV was negative. On day 3, her WBC count was 3.6 × 10^9/L (neutrophils, 1.1 × 10^9/L), hemoglobin level was 127 g/L, and her platelet count was 188 × 10^9/L. On day 5, therapy with zidovudine (600 mg/d), lamivudine (300 mg/d), and indinavir (2,400 mg/d) was instituted, and fluconazole and famotidine were started for oral thrush and retrosternal pain, respectively. On day 8, she had severe neutropenia (WBCs, 0.9 × 10^9/L; neutrophils, 0.05 × 10^9/L), an axillary temperature of 39.6°C, and her condition was deteriorating. Antiretroviral therapy was discontinued, and empirical treatment for sepsis syndrome was started with ceftizoxime and tobramycin. The CD4+ lymphocyte count was 0.180 × 10^9/L on day 9. An esophagogastroduodenoscopy done on day 17 revealed a necrotic esophageal ulcer (1 cm by 10 cm). CMV and HIV were cultured from biopsy material. Neither staining nor culture showed evidence of fungal etiology. CMV inclusion bodies could not be identified. Ganciclovir was started and the retrosternal pain quickly abated.

On day 15, the patient’s WBC count was 3.5 × 10^9/L (neutrophils, 0.36 × 10^9/L) and her plasma HIV RNA viral load was 5,700 copies/mL; zidovudine (600 mg/d) was restarted. Lamivudine (300 mg/d) was added on day 17. Because of the declining neutrophil count (0.13 × 10^9/L), therapy with zidovudine was replaced by that with stavudine (80 mg/d) on day 19. The neutrophil count increased to 1.5 × 10^9/L and the CD4+ lymphocyte count to 0.607 × 10^9/L by day 25, when saquinavir (1,800 mg/d) was added. The patient tolerated stavudine, lamivudine, and saquinavir and was discharged to her home. On day 54, her WBC count was 4.9 × 10^9/L (neutrophils, 2.6 × 10^9/L), CD4+ lymphocyte count was 0.640 × 10^9/L, and her plasma HIV RNA viral load was 2,200 copies/mL. A serology for antibodies to HIV showed strong reactions to gp 41 and gp 120, but no reaction to p34. A serology for IgG antibodies to CMV was positive. Esophagogastroduodenoscopy findings were within normal limits.

The cause of neutropenia in our patient was probably multifactorial; antiretroviral agents, two acute viral infections, and sepsis may have contributed to neutropenia. There was no definite histological proof for CMV causing the esophageal ulcer, but positive culture from biopsy material, CMV seroconversion, and response to ganciclovir supported this diagnosis.

Ten cases of HIV and CMV primary coinfections have been described. In general, HIV infection seemed to progress rapidly, as measured by the decline in CD4 cell counts. Several patients had complications during the primary disease. One patient had CMV and toxoplasma retinitis 5 months after the primary infection [1]. He died 2 months later of lymphoma. Other complications included pancytopenia, hepatitis, and pericarditis [2], CMV colitis [3], and CMV encephalitis [4]. Only one of the

previously described patients was distinctly neutropenic (0.15 \times 10^9/L) during the primary infection [2]. In vitro studies have suggested possible mechanisms for interactions between HIV and CMV including increased expression of both HIV and CMV in coinfected cell lines, or in cells infected by CMV; induction of Fc receptors on cells to facilitate the entry of HIV immune complexes; or expression of a protein that can be used as a co-receptor for HIV entry [5–7].

Serious adverse events during antiretroviral treatment of acute HIV infection have not been previously reported. We emphasize the role of concomitant pathogens that may modify symptoms and potentially affect the prognosis of HIV disease.

**References**


**Melioidosis Brain and Lung Abscess After Travel to Sri Lanka**

Melioidosis is an infection caused by the soil and water bacterium *Burkholderia pseudomallei*. Melioidosis is endemic in Southeast Asia and Northeast Australia [1]. Occasionally tourists who have traveled for a limited period in an area of endemicity, such as the northern part of Thailand, may develop melioidosis [2]. Herein, we describe a patient who had acute melioidosis, with necrotizing pneumonia and a brain abscess, that occurred after travel to Sri Lanka, a region that was considered nonendemic [1].

A 66-year-old man with a negative medical history traveled in Sri Lanka for 15 days. He returned to Europe 2 days before the onset of fever (temperature, 39°C) and headache. He was treated initially with paracetamol. Ten days after onset of symptoms, the patient was admitted to the hospital because of persisting fever and increasing stupor and disorientation. There was no motal rigidity. A CT scan of the head revealed a frontal lobe mass. A chest radiograph and CT scan showed an infiltrate with central necrosis in the right upper pulmonary lobe. Direct microscopy of a specimen obtained by CT-guided aspiration of the pulmonary lesion revealed polymorphonuclear WBCs; there were no bacteria evident on gram-staining of the aspirate. Culture of the aspirate yielded *B. pseudomallei*. The strain was susceptible to ceftazidime (MIC, 1.0 mg/L), imipenem (MIC, 0.09 mg/L), and ciprofloxacin (MIC, 0.5 mg/L). Serology for *B. pseudomallei* (agglutination assay) performed at the Pasteur Institute (Paris), showed a titer of 1:320. Antibiotic treatment with ceftazidime (2 g iv t.i.d.) was continued for 56 days. Oral maintenance treatment (ofloxacin, 800 mg per day) was administered for 8 months. The patient’s clinical condition improved and the radiological evolution of the pulmonary and brain lesions was favorable. The patient had no recrudescence of melioidosis during 2 years of follow-up.

This case of melioidosis is intriguing because of its clinical presentation and geographic origin. The disease was acquired by a tourist who traveled in a region that was considered nonendemic [1]. Indeed, only very few cases of melioidosis have been reported from the Indian subcontinent or Sri Lanka, despite similarities in geographic location, weather, and environmental conditions with Southeast Asian countries. Melioidosis may, however, be underdiagnosed because of difficulties in culturing the causative microorganism or may be misdiagnosed as plague [3].

The common clinical presentations of acute melioidosis are sepsis and pneumonia. Neurological involvement is infrequent [4]. Only one other case of melioidosis brain abscess acquired during travel has recently been described [5]. The patient we describe, with multiple organ involvement, was treated with ceftaziemid followed by a prolonged maintenance treatment with ofloxacin. Ceftazidime has been shown to halve the mortality rate of acute melioidosis and has become first-choice antibiotic for treatment of severe melioidosis [6, 7]. Fluoroquinolones have been used for treatment of melioidosis, but recent experience indicates that primary treatment failures and relapses are more frequent than with a conventional antibiotic combination [8]. The main reasons for these failures may be the marginal in vitro activity against most isolates of *B. pseudomallei* and the emergence of resistance during treatment. The favorable response of our patient may be due to the lower MIC, the higher dose of the fluoroquinolone, and a longer primary treatment with ceftazidime compared to the experience in the literature.

In conclusion, we described a patient with acute pulmonary and neurological melioidosis acquired during travel in Sri Lanka, a region that was considered nonendemic. Ceftazidime monotherapy followed by long-term maintenance treatment with ofloxacin resulted in complete cure.

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Candida (Torulopsis) glabrata: A New Pathogen Found in an Empyema

A 75-year-old man presented to the emergency department because of epigastric pain, nausea, and vomiting after consuming dinner. On initial presentation he was afebrile. He had diffuse abdominal tenderness with guarding. His physical examination findings were otherwise normal. The WBC count was normal with no left shift. His chest radiograph revealed a small left-lower-lobe infiltrate, for which he was started on intravenous ampicillin/subactam. An abdominal series revealed no evidence of obstruction. An exploratory laparotomy showed no significant pathology. Within 24 hours following the operation, a closed chest-tube thoracostomy was performed because of the development of an expanding massive left pleural effusion with compression atelectasis. Microscopic evaluation of a pleural-fluid specimen revealed a yeast-like organism, and culture of the pleural fluid yielded Candida (Torulopsis) glabrata.

The patient was treated initially with intravenous fluconazole, 1,200 mg over 3 days, for a presumed systemic candidal infection while awaiting the final identification of the yeast. Therapy with fluconazole was discontinued when the organism was identified, and then therapy with intravenous amphotericin B was begun. Video-assisted thoracoscopy revealed a multiloculated fluid collection with massive fibrinous pleuritis and an entrapped lung. The amphotericin B. Despite intense treatment, he died of persistent fever and respiratory compromise.

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Figure 1. A 75-year-old man with empyema due to Candida (Torulopsis) glabrata demonstrating budding yeast cells (arrows) (Gomori’s methenamine silver stain, magnification ×100, oil immersion).
In summary, empyema due to *C. glabrata* has not been reported previously. Early diagnosis and appropriate treatment of infections due to *Torulopsis* species with prompt, adequate drainage of an empyema will reduce morbidity and mortality.

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Gas Gangrene in an Immunocompromised Girl Due to a *Clostridium ramosum* Infection

Clostridia are gram-positive, spore-forming anaerobic rods. A number of *Clostridium* species that are normally present in the commensal flora of the human intestine may cause infections. Severe infection of soft tissue results in gas gangrene or myonecrosis. Such infections occur after traumatic injuries as well as spontaneously. Spontaneous nontraumatic gas gangrene is either locally associated with an intraabdominal focus or a distant spread of infection. These infections occur mainly in immunocompromised hosts. *Clostridium septicum* is the *Clostridium* species isolated most frequently in nontraumatic gas gangrene in patients with malignancies of the gastrointestinal tract and leukemia, and in children with cyclic neutropenia [1, 2]. In patients colonized with *C. septicum*, it appears that neutropenia predisposes to the development of bacteremia. *Clostridium ramosum* is one of the *Clostridium* species that is often isolated from stool samples of children, but has been associated only rarely with severe infections or bacteremia [3, 4]. The number of cultures positive for *C. ramosum* is probably underestimated. The organism can easily be missed in anaerobic cultures, because it usually stains gram-negative instead of gram-positive, and the typical terminally located spores are sometimes hard to detect. We describe a lethal septic episode in an immunocompromised child with spontaneous gas gangrene and cultures of blood yielding *C. ramosum* and *Candida albicans*.

An 11-year-old girl had been receiving chemotherapy for several weeks because of the recurrence of a common acute lymphatic leukemia and was in a neutropenic phase (WBC count, 200 × 10⁹/L). While at home, she developed a severe mucositis, and her condition deteriorated in the days before she was admitted to the hospital. She had fever, chills, myalgia, loss of appetite, and watery, bloody diarrhea. Physical examination at admission revealed a sick, somnolent, dyspneic girl with yellow sclaeae and several greenish necrotic ulcers on the tongue. Her face and neck were swollen with palpable crepitations of the skin. She had a tempera-

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Figure 1. Radiograph of the thorax of an 11-year-old immunocompromised patient with an infection due to *Clostridium ramosum*. Interstitial emphysema is seen in the right axilla (black arrow) and the superior mediastinum (white arrows).
In the pediatric intensive care unit, the girl was treated for septic shock. Vancomycin (40 mg/kg), gentamicin (6 mg/kg), cefazidime (100 mg/kg), and dexamethasone (stress doses) were administered intravenously, and she received circulatory and respiratory support. In spite of maximal treatment she died within 1 hour of admission. The presumptive diagnosis was spontaneous gas gangrene with circulatory failure. The diagnosis could not be confirmed because autopsy was not permitted.

To our knowledge, we have described the first case of a fatal infection due to *C. ramosum* in a child with leukemia and chemotherapy-induced neutropenia. A number of the >30 known clostridial species have been isolated from soft-tissue infections. They are frequently part of polymicrobial cultures and can act synergistically with other pathogens, thereby worsening the clinical outcome. Underlying illnesses such as cancer are believed to facilitate the development of clostridial infections. Our patient presented with spontaneous gas gangrene. This disorder has been reported in patients with colon cancer and leukemia and other forms of neutropenia. *C. septicum* is the *Clostridium* species most frequently isolated from blood cultures and intraabdominal specimens in these patients [1, 2]. *C. ramosum* has been cultured from gastrointestinal abscesses and ear infections. Since many other *Clostridium* species and non-clostridial bacteria are often present in such infections, it is difficult to assess the pathogenic role of *C. ramosum*. On the other hand, there have been a few reports of unusual infections with *C. ramosum* as the sole microorganism isolated [5, 6]. Bacteremia has been described and is occasionally found in leukemic patients [7].

In healthy persons, *C. albicans* is frequently isolated from gastrointestinal tract specimens as part of the normal flora. Fifty to seventy percent of the stool and throat specimens from immunocompromised patients show colonization with *C. albicans* [8].

The finding of a blood specimen positive for *C. ramosum* in the presence of gas gangrene in the neck and thorax implicates a pathogenic role for *C. ramosum* in this patient with severe neutropenia. *C. ramosum* is able to produce IgA1 and IgA2 proteases that may facilitate mucosal penetration [9]. The (oral) mucositis in our patient—a common feature in patients treated with chemotherapy—was most likely the portal of entry and may have enhanced intravascular invasion with *C. ramosum* and probably also with *C. albicans*. Whether the fungemia due to *C. albicans* played a role in the fatal outcome of the acute infection in this patient remains unclear.

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**Disseminated Papulopustular Eruption Due to *Mycobacterium fortuitum* in an Immunocompetent Patient**

Cutaneous infections due to atypical mycobacteria are well known. However, the frequency of rapidly growing mycobacteria is probably underestimated. Cutaneous or soft-tissue infections are the most frequent human diseases caused by these microorganisms. The lesions are usually nodular, ulcerative, or cellulitic. To our knowledge, we describe the first case of a disseminated papulopustular eruption due to *Mycobacterium fortuitum* without associated systemic infection in an immunocompetent patient.

A 45-year-old male marine electrician presented with a progressively spreading papulopustular eruption. The first lesions had appeared 2 months earlier on the right arm and had persisted despite local disinfection. Gradually, the other arm, the trunk, and the neck had become involved (figure 1). There was no pruritus or fever. Oral antibiotics were administered (oxacillin, 2 g per day for 1 week, followed by priminamycin, 3 g per day for 2 weeks) with no improvement. There was no history of previous surgery, trauma, or injection. The clinical examination did not reveal lymph node involvement or hepatosplenomegaly. Blood cell count, lymphocytic phenotyping, profile of ion concentration, hepatic and renal function, as well as chest radiographs and abdominal ultrasonography were normal. A serology for antibodies to HIV was negative. Cultures of two different specimens from two pustules obtained at 2-week intervals both yielded mycobacteria within 5 days. The strain presented characteristics of *M. fortuitum* group [1]: colonies were nonphotochromogenic, grew on MacConkey agar, and were positive for nitrate, iron uptake, and arylsulfatase. As determined by the Etest method (AB BIODISK, Solna, Sweden), the strain was susceptible to clarithromycin, ciprofloxacin, and minocycline.

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and resistant to rifampin. Histological evaluation of a skin biopsy specimen showed an inflammatory infiltrate without tuberculoid granuloma. Doxycycline (200 mg/day) and clarithromycin (3 g/day) were administered. Two months later, the cutaneous lesions had only partially regressed; ciprofloxacin, 1 g/day, was added to the previous regimen. Because the patient continued his usual work, he was asked to protect his skin while working in stagnant water. Three months after the beginning of the treatment, the lesions had improved. However, further follow-up is necessary.

The mycobacteria of Runyon group IV are rapidly growing mycobacteria. The time required for growth is 3 to 7 days at 25°C to 40°C on routine bacteriologic media [2]. In this group, only \textit{M. fortuitum} and \textit{Mycobacterium chelonae} are considered to be pathogenic for humans. Rapid growers are found in soil, dust, and water [3, 4]. More than 90% of cutaneous diseases caused by mycobacteria are due to \textit{M. fortuitum} and \textit{M. chelonae} [2, 5]; cutaneous infections are the most frequent manifestations. \textit{M. fortuitum} is isolated more often from skin lesions, whereas \textit{M. chelonae} is mostly responsible for disseminated infections [5]. The organisms gain entry into a host by inoculation into the skin and subcutaneous tissues during surgery, trauma, or injections. Cutaneous lesions may also follow a systemic infection. Immunocompetent patients develop cellulitic, nodular, or ulcerative lesions. Extensive necrosis and abscess formation are more often encountered in immunocompromised patients. A satellite pathologic lymph node is generally noted.

To our knowledge, only one case of maculopapular eruption due to a rapidly growing mycobacterium has been reported, accompanied by disseminated infection, which was not observed in our case [5]. Therefore, we have described the first case of profuse papulopustular eruption due to \textit{M. fortuitum}, without systemic involvement, occurring in an immunocompetent patient. The particular occupational context (a marine electrician often exposed to microtraumas in stagnant water) probably explains this kind of eruption with its particular disseminated variety. The partial regression of the lesions after 2 months of bi-antimicrobial therapy could be explained by a lower sensitivity of the microorganism in vivo than in vitro. Alternatively, the partial efficacy of the treatment could be related to insufficient skin protection of the patient during his work activities.

The spectrum of primitive cutaneous lesions due to \textit{M. fortuitum} in immunocompetent patients should be extended to disseminated papulopustular eruptions.

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Torovirus Gastroenteritis Presenting as Acute Abdomen

Toroviruses are enveloped, positive stranded RNA viruses that are classified as members of the family Coronaviridae [1]. They have been shown to be etiologic agents of gastroenteritis in cattle, and a porcine torovirus has recently been reported [2, 3]. There have been a number of articles describing the detection of torovirus-like particles in children and adults with gastroenteritis [4–7]. It was further shown in a case-control study that torovirus was definitively associated with hospital-acquired gastroenteritis in children [8]. The detection of toroviruses by use of electron microscopy has been substantiated by EIAs using antisera to Breda virus, a bovine torovirus, and by immunospecific and molecular approaches [5, 7]. Herein we describe two patients who presented with gastroenteritis as well as with signs of acute surgical abdomen. In both patients, the detection of torovirus in the stool specimens was the only finding implicating an etiologic agent. To our knowledge, we describe the first cases of torovirus associated with symptoms and signs of peritonitis.

Patient 1 was a 9-year-old girl with familial Mediterranean fever (FMF), diagnosed at 2½ years of age [9], that was well controlled.

Figure 1. Papulopustular eruption of the neck, trunk, and arm of a 45-year-old man due to \textit{Mycobacterium fortuitum}.
with daily colchicine therapy. She presented with a 1-day history of fever (temperature, to 39°C) that resolved the following day, when she developed recurrent bouts of severe colicky abdominal pain, each lasting 30 to 60 minutes; she was pain free between the episodes. Accompanying the abdominal pain were vomiting and loose watery stools without frank or occult blood. On physical examination, she was afebrile and looked well except during the painful abdominal attacks when she was in significant distress. The abdominal examination revealed generalized tenderness, with involuntary guarding, positive rebound sign, and reduced peristaltic sounds. There was no hepatosplenomegaly. The remainder of the physical examination findings were within normal limits. This patient was not considered to be having an episode of FMF, since the clinical presentation differed from those during her previous attacks. She was afebrile and the pain was intermittent and not consistent as in patients with FMF [9].

The results of the following laboratory tests were normal or negative: CBC with differential and platelet count, erythrocyte sedimentation rate, electrolyte levels, renal and liver function tests, serum amylase level, and urinalysis. Abdominal and chest radiographs were within normal limits. Abdominal ultrasonography revealed free peritoneal fluid. WBCs were seen on microscopic examination of the stool. Stool cultures were negative for bacteria and *Clostridium difficile* cytotoxin. Electron microscopic examination of the stool revealed torovirus. The patient was treated with bowel rest, intravenous fluids, and intravenous meperidine until her symptoms resolved 3 days later. Repeated examination for torovirus in stool 1 month later was negative, and the patient has remained well.

**Patient 2** was a 15-year-old boy who had had severe systemic-onset juvenile rheumatoid arthritis since age 4. His medications at the time of presentation included prednisone, 15 mg a day alternating with 5 mg a day; indomethacin, 25 mg t.i.d.; ranitidine, 150 mg b.i.d.; and methotrexate, 12.5 mg subcutaneously once weekly. He was admitted because of dehydration following 3 days of vomiting and diarrhea, but he was afebrile. His condition improved after receiving intravenous fluids, but on the 7th day after onset of symptoms, he suddenly developed severe colicky abdominal pain and fever (temperature, to 39°C). At physical examination he was in moderate distress. The abdominal examination revealed diffuse tenderness, guarding and rebound; there were no peristaltic sounds. Other than for multiple joint deformities, the remainder of the physical examination findings were within normal limits. Laboratory studies revealed the following values: hemoglobin, 76 g/L; WBCs, $19.2 \times 10^{9}/L$ (increased from $10.6 \times 10^{9}/L$ the previous day) with a normal differential; and platelets, $740 \times 10^{9}/L$. The results of the renal and liver function studies, serum amylase level, and the urinalysis were normal, as was the chest radiograph. An abdominal radiograph revealed a distended stomach and bowel loops. Abdominal ultrasonography revealed fluid-filled bowel loops with minimal free abdominal fluid in the cul-de-sac.

The stool culture was negative for bacteria and parasites and for *C. difficile* cytotoxin. Torovirus particles were detected in stool by use of electron microscopy. The patient was treated with bowel rest and triple antibiotic therapy (ampicillin, gentamicin, and metronidazole) until the confirmation of negative bacterial cultures, and he recovered gradually in 3 days. Torovirus was detected in the repeated stool examination by electron microscopy 2 weeks later, but could not be detected 1 month after presentation.

Torovirus has been reported in association with human gastroenteritis [6, 8]. These studies showed that the virus can be detected in stool specimens of symptomatic patients by use of electron microscopy and ELISA. Torovirus has recently been shown to be a relatively common agent of diarrhea [6, 8]. Clinically, torovirus-induced gastroenteritis is similar to other types of viral gastroenteritis and presents with abdominal pain associated with vomiting and diarrhea; fever may be present at the onset. The disease is self-limited and resolves within several days, although shedding of the virus may continue for weeks, particularly in immunocompromised hosts [8]. Torovirus was the principal identifiable cause of nosocomial diarrhea in immunocompromised patients and in this regard patient 2, whom we have described, was immunosuppressed [8]. An antibody response to the virus develops in more than one-half of the patients; however, serology for torovirus was not performed on the above patients while they were hospitalized.

The two patients described herein are unique in their clinical features. Both presented initially with common, nonspecific clinical features, namely fever, vomiting, and abdominal pain followed by diarrhea, but then developed severe abdominal pain and acute peritoneal signs. To our knowledge, these signs have not been previously reported in conjunction with a torovirus infection. The thorough investigations excluded other etiologies of acute abdomen, as no bacterial or other etiologic agent was found, and the fact that both patients recovered completely in 2–3 days with conservative treatment alone suggests that this illness was consistent with a torovirus infection [8].

Awareness that torovirus may be associated with acute abdomen is important. More clinical data are needed to further describe the pathogenesis and the clinical features of this potentially common and important pathogen.

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Autoimmune Thrombocytopenia Associated with *Borrelia burgdorferi*

The association of borreliosis and thrombocytopenia remains an issue of controversy [1, 2]. In a recent review, Nadelman and Wormser [3] proposed that thrombocytopenia is not characteristic of Lyme borreliosis per se but suggestive of coinfection with species of *Babesia* or *Ehrlichia*. The few cases of thrombocytopenia associated with borreliosis appear to have been transient, remediable by antibiotic therapy, and a consequence of decreased thrombopoiesis [4]. We describe a patient in whom borreliosis triggered an autoimmune thrombocytopenia in the absence of coinfection with *Babesia* or *Ehrlichia* species.

A previously healthy 49-year-old woman from a rural area in the German state of Baden-Württemberg was admitted for evaluation of a 6-month history of recurrent episodes of fever, malaise, and arthralgia. Easy bruising was not reported. In response to specific questioning, the patient recalled a ring-shaped migrating rash and a tick bite on the upper trunk 18 months previously. Except for occasional acetaminophen tablets, she had not taken any medication. Two years previously, a routine platelet count of 220 × 10^9/L had been recorded by the general practitioner. Physical examination was essentially unrevealing. Laboratory evaluation revealed the following significant values: WBCs, 7.2 × 10^9/L (94% neutrophils); platelets, 20 × 10^9/L; and C-reactive protein, 2.0 mg/dL. The first documented platelet count of below 100 × 10^9/L had occurred 6 months earlier.

ELISA (Enzygnost Borreliosis, Behring Diagnostics, Marburg, Germany) showed IgG antibodies to *Borrelia burgdorferi* (710 U/mL; normal, <10 U/mL). Western blot analysis confirmed IgG binding to a *Borrelia*-specific protein at 18 kDa and 39 kDa, and IgM binding to a 41-kDa protein (Recom Blot, Microgen, Munich). Immunofluorescence testing of serum for antibodies to *Ehrlichia* species and a PCR assay for intracellular *Ehrlichia* antigen were negative. Repeated blood smear staining showed no evidence for intraerythrocytic babesiosis. Serological tests were all negative for hepatitis A, B, and C viruses; influenza and parainfluenza viruses; adenovirus; flavivirus causing seasonal tickborne meningoencephalitis; *Chlamydia*; herpes simplex virus; cytomegalovirus; parovirus B19; Epstein-Barr virus; and HIV. There was no immunopathological evidence for connective tissue disease. Histological evaluation of an iliac crest bone marrow trephine showed hyperplasia of megakaryocytes but no other abnormalities.

Glycoprotein-specific ELISA showed IgG binding to patient and donor platelet glycoprotein IIb/IIIa, allowing the diagnosis of autoimmune thrombocytopenia. Cross-reactivity between *Borrelia*-specific IgG antibodies and platelets was excluded, since the acid eluate of the patient’s platelets containing IgG antibodies did not bind to *Borrelia*-specific proteins in the immunoblot. Furthermore, incubation of the patient’s serum with donor platelets failed to decrease *Borrelia*-specific IgG levels.

Our patient presented with a history and symptoms typical of Lyme borreliosis, confirmed by serological tests. The acute infection probably dates back to one and one-half years ago. Since then, she had developed an autoimmune thrombocytopenia without evidence of bleeding. Before the *Borrelia* infection, platelet counts had been normal. Since we can exclude a causal relationship with drugs and other infectious organisms, in particular *Ehrlichia* and *Babesia* species, we propose that the borreliosis infection triggered the autoimmune thrombocytopenia in this patient.

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Arabinose-Positive *Burkholderia pseudomallei* Infection in Humans: Case Report

*Burkholderia pseudomallei* is the causative organism of melioidosis. The disease is endemic in the tropics, especially in northeastern Thailand [1]. Clinical presentations of melioidosis are pro-
A 16-year-old man was admitted to Srisaket Hospital (Thailand) 20 minutes after a motorcycle accident, with blunt trauma to the abdomen and compound fractures of the right femur and right tibia. Physical examination at admission revealed a temperature of 37°C, a blood pressure of 130/80 mm Hg, a pulse rate of 90/min, a respiratory rate of 32/min, and marked tenderness at the epigastrium. An emergency laparotomy revealed a rupture of the duodenum, and the leakage site was repaired. The compound fracture of his right leg was associated with severe soft-tissue and vascular injuries. An above-the-knee amputation of that leg was carried out 5 days later.

The patient was febrile and clinically septic after admission. However, his condition gradually improved with intravenous cloxacillin and gentamicin treatment and supportive ventilation for 2 weeks. During the third week, he again developed a high fever. Cultures of blood obtained at this time yielded *Pseudomonas* species, and cultures of purulent material from the amputation site yielded *B. pseudomallei*. The patient’s therapy was switched to that with cefazidime, and then to a combination of cefoperazone/ sulbactam because the hospital pharmacy ran out of cefazidime. He was afebrile after 17 days of parenteral treatment, and discharged with oral co-trimoxazole and doxycycline therapy for a total course of 20 weeks. The *B. pseudomallei* strains isolated from his wound were identified on the bases of the characteristic colonial morphology on a differential agar, positive oxidase reaction, and resistance to colistin and gentamicin, and confirmed by a biochemical profile based on the results of API-2ONE (bioMérieux, Marcy l’Etoile, France) [5]. Arabinose utilization was determined by growth on minimal salt agar [6] containing L-arabinose (0.2%). This extended biochemical testing confirmed that the strain was an Ara- *B. pseudomallei*.

In the murine model, there was a striking difference in virulence between Ara+ and Ara- *B. pseudomallei* [7]. The ability to assimilate L-arabinose was found to be more strongly associated with virulence than was ribotype group [4, 8]. Ara- *B. pseudomallei* is currently defined as a nonvirulent strain [7]. The acquisition of *B. pseudomallei* infection in this patient was most likely the result of a very heavy inoculation at the time of his accident. The *Pseudomonas* species strain, which was grown from his blood culture, was not available for further identification and might also be *B. pseudomallei*. Thus, Ara- *B. pseudomallei* can also be pathogenic to humans, as shown in this patient.

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**Aerobic and Anaerobic Microbiology of Mycotic Aortic Aneurysm**

Identification of the organisms infecting aortic aneurysms is important, as these organisms can cause local and systemic infection [1], and can contaminate vascular prostheses [2]. Various organisms have been found in mycotic aortic aneurysms (MAAs), including gram-positive aerobic bacteria such as *Staphylococcus aureus* and gram-negative aerobic bacteria such as *Salmonella*

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from all patients and were inoculated into two bottles, one supportive of aerobic growth and the other of anaerobic growth.

**Microbiology.** Eleven organisms, six facultatively aerobic and five anaerobic, were isolated from the eight patients included in the study (table 1). Aerobic organisms were isolated in only four cases, anaerobic organisms in only three, and mixed aerobic and anaerobic bacteria in one. Polymicrobial infection was present in three (patients 3, 4, and 6). The predominant bacteria were *Staphylococcus* species (3 isolates), *Enterobacteriaceae* (2), and *Peptostreptococcus* species (2). Organisms similar to the ones recovered from the MAA were isolated from the blood of four patients. These included one isolate each of *S. aureus*, *Escherichia coli*, *Bacteroides fragilis*, and *Clostridium perfringens* (table 1).

**Clinical Manifestations.** Systemic signs of infection, as evidenced by fever and leukocytosis, were present in most patients. Localized pain was present in four (table 1). Associated conditions were present in all cases: atherosclerosis in six; diabetes in two; and urinary tract infection, gallstones, abdominal abscess, and colonic cancer in one each. In situ grafts were placed in four cases, resection of the MAA was done in three, and abscess drainage in one. Three of the patients died.

This report highlights the importance of anaerobic bacteria in MAA. The recovery of these organisms is not surprising, given the proximity of the aorta to the gastrointestinal tract, where anaerobes predominate and reach 10^12 organisms per gram of stool, outnumbering aerobic organisms in a ratio of 1,000–10,000 to one [7]. The enteric source of these organisms is supported by the recovery of *Enterobacteriaceae, B. fragilis*, and *C. perfringens*, which normally colonize the gut. *B. fragilis, Peptostreptococcus* species, and *Propionibacterium acnes* were recovered from infected aortofemoral and aortic grafts [7, 8], from MAA [3–6], and from femoral artery aneurysms in intravenous drug addicts [9]. Although the recovery of anaerobic bacteria from MAA is rare, it is possible that the incidence of these microorganisms is higher than reported, given that the percentage of negative cultures for MAA is generally >25% [10].

The true incidence of recovery of anaerobes in MAA could not be calculated from our study because of its retrospective nature and because we included only specimens that were cultured for both aerobic and anaerobic bacteria. The true prevalence of these organisms in MAA has yet to be investigated by prospective studies. This is of particular importance, since these organisms are often resistant to the antimicrobials used to treat these infections.

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Fungemia Due to Saccharomyces Species in a Patient Treated with Enteral Saccharomyces boulardii

As a pharmaceutical biotherapeutic agent, Saccharomyces boulardii has been used for years outside of the United States to treat diarrhea [1] and is considered to be safe. Nevertheless, serious side effects can occur.

A 78-year-old immunocompetent woman was admitted to the intensive care unit because of an acute exacerbation of chronic obstructive pulmonary disease. Current treatment consisted of antibiotics (amoxicillin/clavulanic acid), mechanical ventilation, and enteral feeding via a gastric tube. On hospital day 12, diarrhea appeared. Investigation for stool pathogens was negative; loperamide and S. boulardii (Ultra-Levure, 1.5 g/day [Biocodex, Montrouge, France]) were administered via the gastric tube (day 13) for 15 days. On day 18, antibiotic therapy was changed to that with cefazidime and ciprofloxacin because of a nosocomial pulmonary infection. On day 34, the temperature was elevated to 39°C and the WBC count was 8,600/mm³. From day 34 to day 37, seven cultures of blood were positive for Saccharomyces species; the organism was initially identified as Saccharomyces cerevisiae and later as S. boulardii. Cultures of arterial and venous catheters removed on day 35 were negative. A colonoscopy was normal and no parasites were found in the stool. Complete recovery was observed after fluconazole therapy for 15 days.

Routine identification of Saccharomyces species often fails to distinguish S. boulardii from S. cerevisiae [1, 2]. Fungemia due to Saccharomyces species has already been reported in patients receiving high enteral dosages of Ultra-Levure. Transfer of Saccharomyces species from an affected bowel (e.g., ischemic or inflammatory) appears to be the primary origin of these fungemias [3–9], especially when antibiotics effective against anaerobes are given [5–9]; in other cases, infected catheters have been implicated as the source of infection [6]. Patients who develop fungemia due to Saccharomyces species are generally immunocompromised (e.g., patients with AIDS and patients receiving corticosteroid therapy) [3–8]. In all reported cases, therapy has consisted of supportive care, anti-fungal drugs, and the cessation of Ultra-Levure. To our knowledge, we have described the first case of S. boulardii fungemia in a non-immunocompromised patient without bowel disease who was receiving high doses of enteral Ultra-Levure. As is true for the other reported cases, the primary identification of the Saccharomyces species was incorrect, with the usual confusion between S. boulardii and S. cerevisiae [1, 2, 5].

Given that S. boulardii may be initially misidentified as S. cerevisiae, it is likely that S. boulardii is responsible for saccharomyces fungemia in patients receiving enteral Ultra-Levure. High doses of Ultra-Levure associated with antibiotics effective against anaerobes, bowel diseases, and/or immunodeficiency seem to be risk factors for such fungemia; our observation suggests that fungemia due to Saccharomyces species can also occur in immunocompetent hosts without bowel disease. Enteral S. boulardii is widely used in the prevention or treatment of diarrhea; therefore, physicians must be aware of the possibility of potentially serious side effects. The reported occurrence of such side effects is infrequent at present, and no current guidelines exist for their treatment.

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Foscarnet Activity on Human Immunodeficiency Virus Type 1 in the Central Nervous System

Foscarnet, a reverse transcriptase inhibitor, has been shown to decrease HIV-1 replication in vitro [1, 2]. Recently, reports of two studies about the effects of this antiviral agent on HIV replication in vivo were published [3, 4]. Both investigators observed significant reductions of HIV plasma viral loads in patients who were treated with foscarnet. Herein, we report an observation that foscarnet is also active in the CNS when used to treat HIV encephalopathy-related symptoms.

A 55-year-old HIV-1-infected man with a Burkitt’s lymphoma was treated with indinavir (800 mg t.i.d.) and saquinavir (400 mg b.i.d.). Therapy with this combination of two protease inhibitors was started during multidrug chemotherapy for his lymphoma to avoid myelotoxicity induced by nucleoside analogs. Since the platelet count remained low (30,000/mm³) and plasma HIV viral load was undetectable, antiretroviral therapy was not modified after completion of the antineoplastic treatment, which led to complete remission. The CD4+ cell count was 150/mm³.

The patient works as a translator. Six months after beginning therapy with protease inhibitors, he experienced first episode of somnolence, lack of concentration, and inability to work. Brain CT scan and MRI showed no abnormalities. A CSF specimen contained 3 lymphocytes/mm³ and protein levels were normal. Microscopic examination and cultures of CSF were negative for bacteria, parasites, and fungi. A search for neoplastic cells and cryptococcal antigen was negative. A PCR assay of CSF was negative for herpes simplex virus types 1 and 2, cytomegalovirus (CMV), JC virus, and Toxoplasma gondii. The CSF HIV viral load was 4.23 log₁₀ HIV RNA copies/mL, whereas the plasma viral load was still undetectable. Zidovudine at low doses (100 mg t.i.d.) was added to the treatment. After 2 weeks, the patient regained his fluency in six languages, and CSF HIV viral load levels decreased to 2.77 log₁₀ HIV RNA copies/mL.

Three months later, a lumbar puncture was performed because of recurrent drowsiness. An HIV RNA viral load of 4.36 log₁₀ copies/mL was detected in an otherwise normal CSF specimen. A PCR assay of CSF for CMV was negative. Tests for CMV antigen remained negative. Lamivudine (150 mg b.i.d.) was added to the therapeutic regimen, but no clinical improvement was noted after 10 days. Stavudine was not proposed, as the patient previously had a severe peripheral neuropathy induced by this antiretroviral agent. Therapy with intravenous foscarnet (100 mg/kg b.i.d.) was started, leading to complete linguistic recovery and disappearance of detectable CSF HIV RNA after 2 weeks. Foscarnet was then continued for 3 months at maintenance doses (100 mg/[kg·d]). CSF and plasma viral loads remained undetectable.

To improve the quality of life for our patient, we decided to interrupt foscarnet administration without modifying the rest of the treatment. A lumbar puncture performed 2 weeks later showed a detectable HIV RNA viral load at 3 log₁₀ copies/mL. A third episode of mental dysfunction, associated with an important rise in CSF viral load (5.1 log₁₀ RNA HIV copies/mL), occurred 6 weeks after stopping foscarnet. Therapy was switched to that with new drugs available at this time, abacavir, nevirapine, and nelfinavir, with successful clinical and virological response.

Foscarnet has been shown to penetrate the blood-brain barrier [5]. In our patient, foscarnet was highly effective in reducing the CSF HIV viral load and neurological symptoms, and this effect was sustained throughout the 3 months of therapy. The CSF HIV RNA load rebounded 2 weeks after cessation of therapy, and clinical symptoms reappeared a few weeks later.

The CNS is a protected compartment, known to be difficult to reach, since antiretroviral drugs like protease inhibitors do not cross the blood-brain barrier efficiently. This phenomenon is illustrated in the case we described, given the occurrence of neurological symptoms associated with a high CSF viral load despite undetectable HIV RNA in plasma. In our patient, clinical evolution paralleled changes in CSF HIV RNA, indicating that high CSF viral loads can be a marker of HIV encephalopathy. Our observation suggests that foscarnet might be helpful for the treatment of HIV-associated mental deterioration in cases of resistance or intolerance to all antiretroviral drugs known to be active in the CNS.

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