

Bug of the Month

Ironic Exorcise

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Infections in Medicine is happy to again present "Bug of the Month," which features fictional diagnostic sleuth Dr Schmeckman.

After drinking a cup of coffee in the lounge of St Gimmick Hospital, Dr Schmeckman accompanied one of his students, Mollie Jeanette, who was beginning her rotation through the hospital's infectious diseases service, to the microbiology laboratory.

"Despite all the new-fangled technology that seems to be central to the lab, the technologists still can tell a lot from the culture plates," Dr Schmeckman told Mollie. "Familiarity with the quality of growth of a particular organism, what the colony looks like on different types of agar, and what odors are produced can speed along the diagnosis."

As they walked further into the laboratory, Dr Schmeckman picked up a Petri dish from the nearest workstation and said, "Look at this yet unused plate. It contains MacConkey agar. Culture using MacConkey agar is the classic way to distinguish lactose fermenting from non-lactose fermenting 'bugs.'"

Seeing the confused look on Mollie's face, Dr Schmeckman continued, "Distinguishing between the two helps us characterize the various gram-negative rods that we encounter. MacConkey agar is a very useful initial screening plate for culturing stool samples when looking for evidence of *Salmonella*. Most facultative stool flora are lactose fermenters—*Escherichia coli*, for example, whereas *Salmonella* species are non-lactose fermenters."

Dr Schmeckman picked up a plate of MacConkey agar that had been inoculated the previous day. "As you can see, there are mostly red to pink colonies on the left side of this plate. These are the lactose fermenters. The colorless non-fermenters are on the right." (Figure).

Just then, Dr Schmeckman's cell phone rang. Mollie was surprised that the cell phone's ringtone was "Tubular Bells" by Mike Oldfield, which is the theme song of the movie *The Exorcist*. Dr Schmeckman's call was from Dr

Bridget Kildare, a junior attending physician whom Dr Schmeckman had trained. Dr Kildare had requested that Dr Schmeckman meet her in the emergency department (ED) to discuss a case.

"Why that ringtone?" asked Mollie, with a puzzled look.

Dr Schmeckman smiled. "I've always thought of infectious disease medicine—especially in regard to bacterial infections—as the branch of internal medicine that is closest to surgery because, like our surgical colleagues, we infectious disease specialists separate the patient from his or her disease process like an exorcist removes a demon. For example, while an alien organism, such as group A streptococci, resides within a person, aberrations manifest."

On arrival at the ED, Dr Kildare told Dr Schmeckman and Mollie about the case. A 33-year-old man in whom HIV infection and pneumocystosis were diagnosed 6 years earlier had presented to the referring hospital with a fever (temperature of 40°C [104°F]) and a draining, left-sided neck mass that had persisted for 2 to 3 weeks. The patient had been nonadherent to antiretroviral therapy and had not accessed health care of any kind for several years.

Dr Schmeckman turned to Mollie and said, "Fever and a draining lateral neck mass. What do you think?"

"I think the diagnosis might be lymph node tuberculosis," she replied. "The patient is HIV-positive and probably has a draining lymphadenitis in his neck. I'd do an acid-fast bacillus [AFB] stain on the drained fluid if it hasn't already been performed."

"Doggone it!" Dr Kildare interjected. "That's the heart of the matter. The referring hospital performed at least 8 AFB stains and culture tests of the neck discharge after no organisms grew on the original culture. Every AFB stain was loaded with red snappers, but every culture—even those held for 8 weeks—was negative."

Referring to the transfer records, Dr Kildare related additional information about the patient: "Findings from his chest radiograph were unremarkable. As of last week, his CD4⁺ cell count was 27/μL and his HIV RNA level was 105,000 copies/mL. As mentioned, the results of several AFB cultures of blood and stool were negative."

Dr Schmeckman smiled thoughtfully. "We know that acid-fast bacilli are behind this illness given the consistent smear-positive specimens, even though none of the cultures grew these organisms. How ironic!" Dr Kildare and Mollie looked at each other, being puzzled by the use of the word "ironic" to describe the clinical situation.

Dr Schmeckman, sensing their dismay, continued: "No, not ironic as in 'irony.' I mean ironic as in 'iron,' specifically, the ferric form of iron. There is no doubt in

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my mind that incubation of the neck discharge on a culture medium containing ferric ions will yield the pathogen, which I suspect is *Mycobacterium haemophilum*."

Three weeks later, when culture results were available, Dr Schmeckman's prediction proved correct.

Discussion

M haemophilum is a mysterious "blood-loving" organism. How it is spread to humans and its natural habitat are unknown. It is aerobic and can grow in a pH range of 5.4 to 7.4. The optimal temperature for growth in vitro is 30°C to 32°C (86°F to 89.6°F), and growth occurs in approximately 2 to 3 weeks. Most important, it needs growth media that contain ferric iron compounds (specifically, ferric ammonium citrate, hemin, or hemoglobin). It strongly stains with Ziehl-Neelsen, Kinyoun, and auramine-rhodamine acid-fast staining methods. Stains will usually show characteristic short rods that are occasionally curved. The rods may appear either alone or in clumps. Before the nutritional and temperature requirements needed for culturing *M haemophilum* were known, many infections went undiagnosed; thus, the prevalence and clinical significance of *M haemophilum* infection are currently unknown.

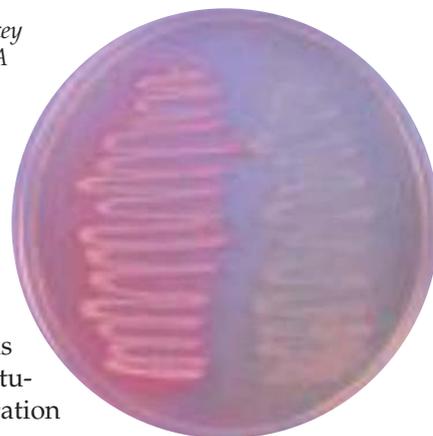
The first documented case occurred in 1978 in a woman with Hodgkin lymphoma and chronic ulcerative skin lesions.¹ Since then, many cases have been documented in immunocompromised adults, including patients with HIV/AIDS; bone marrow, heart, and kidney transplant recipients; and patients with rheumatoid arthritis, myaesthesia gravis, common variable immunodeficiency, and polycythemia vera.

The classic clinical presentation is multiple tender, ulcerating, cutaneous or subcutaneous, nodular skin lesions on extremities and on the top of joints that can subsequently evolve into draining ulcers. More rarely seen manifestations in adults include pneumonitis, sepsis,² septic arthritis, and osteomyelitis.³ In addition, 1 documented case of epididymal abscess has been reported.⁴ In children, however, infection most commonly presents as chronic lymphadenitis in immunocompetent persons. Saubolle and colleagues⁵ observed that the cooler temperature requirements of the organism might explain why lesions frequently appear on the superficial areas of the body, which tend to be cooler than other body sites, although deep-tissue *M haemophilum* infections, such as pyomyositis,⁶ osteomyelitis, and pneumonia,⁵ do occur.

Currently, the most accurate way to diagnosis *M haemophilum* infection is not by culture but by polymerase chain reaction (PCR) assay, real-time PCR assay, or 16S ribosomal RNA gene sequencing.⁷⁻⁹

A goal of treatment is to reverse the immunocompro-

Figure – A MacConkey agar plate is shown. A streak of lactose-fermenting organisms appears on the left and a streak of non-lactose fermenting organisms appears the right.



mised state. This is difficult, and antituberculosis medication is needed. There are no guidelines, and case reviews suggest that different regimens are effective. Single agents such as trimethoprim/sulfamethoxazole, minocycline, erythromycin, and ciprofloxacin, as well as combinations of pyrazinamide, streptomycin, ethionamide, cycloserine, amikacin, doxycycline, clarithromycin, clofazimine, clotrimoxazole, pyridoxine, dapsone, and rifabutin have been used.¹⁰⁻¹³ No head-to-head studies comparing single-drug therapy with combination therapy exist, but because of the possibility of antibiotic resistance, combination therapy with at least 2 medications is recommended.¹⁴ It also has been suggested that patients with chronic immunosuppression should receive lifelong secondary prophylaxis.^{15,16}

Total excision of the affected lymph node and infected tissue alone may cure localized lymphadenitis in children. However, this intervention can lead to scarring. Indeed, incision and drainage are not recommended because of possible scarring and also a higher chance of recurrence and chronic drainage from the lesion site.^{17,18} The role of antimicrobial therapy in children has not been well studied. Erythromycin failed to elicit a therapeutic response in 2 pediatric cases of *M haemophilum* infection reported in 1991,¹⁰ but clarithromycin and rifabutin therapy resulted in complete eradication of oculofacial lesions caused by *M haemophilum* infection in 4 months in another, more recent case report.¹⁹

Because of the increase in use of immunosuppressive therapies for malignancies, use of long-term corticosteroid therapy for various ailments, and the persistence of HIV infection in the general population, *M haemophilum* infection should be part of the differential diagnosis in patients with skin lesions, especially if those lesions are associated with an organism that responds to acid-fast staining techniques but does not grow on regular media used for mycobacteria. Treatment of *M haemophilum* infection is similar to that of other nontuberculous mycobacterial infections. ❖

continued

**Dr Schmeckman's Questions
for the House Staff**

1. Sorbitol MacConkey agar is used to distinguish *Escherichia coli* O157:H7 from other *E coli* strains. O157 does not ferment sorbitol and other *E coli* do. Which statement is not true about enterohemorrhagic *E coli* (EHEC)?
 - a. The initial recognized outbreak of EHEC was associated with undercooked ground beef.
 - b. The infection can result in hemolytic-uremic syndrome, especially in young children.
 - c. All EHEC are O157:H7.
 - d. The toxins produced by EHEC are very similar to *Shigella* toxins.
2. Which statement is not true about scrofula, or mycobacterial infection of cervical lymph nodes?
 - a. In both children and adults, most cases are due to nontuberculous mycobacteria.
 - b. In the Middle Ages, it was believed that "royal touch"—the touch of the sovereign of England or France—could cure the disease. Scrofula was therefore also known as the King's Evil.
 - c. Granulomata are found in the lymph nodes.
 - d. The word comes from the Latin word meaning brood sow.
3. A rise in CD4⁺ cell count can occur during anti-retroviral therapy. Which statement is true regarding CD4⁺ cells in persons with HIV infection?
 - a. A rise in number always accompanies a treatment-related fall in viral load.
 - b. The risk of pneumocystosis is independent of the CD4⁺ cell count.
 - c. A fall in number may occur with an HIV viral load remaining below detectable levels.
 - d. All patients with HIV infection will have low CD4⁺ cell counts within 5 years of onset of infection.

Answers to Dr Schmeckman's Questions for the House Staff

1. c. Although the *Escherichia coli* O157:H7 serotype is the classic enterohemorrhagic *E coli*, a number of other serotypes also can cause the disease. In the fall of 2008, an outbreak of *E coli* infection involving the O111 strain occurred in Oklahoma. Almost 300 persons were affected, and 1 person died.
2. a. Most cases of scrofula in adults are caused by *Mycobacterium tuberculosis* complex.
3. c. Indeed, as an example, CD4⁺ cell counts in patients with HIV infection who receive external beam radiation for cancer will drop, returning to pretreatment levels after therapy ends.

**Therapeutic agents
mentioned in this article**

Amikacin	Erythromycin
Ciprofloxacin	Ethionamide
Clarithromycin	Minocycline
Clofazimine	Pyrazinamide
Clotrimoxazole	Pyridoxine
Cycloserine	Rifabutin
Dapsone	Streptomycin
Doxycycline	Trimethoprim/sulfamethoxazole

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