VIRGINIA
EPIDEMIOLOGY BULLETIN

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September, 1993 Volume 93, Number 9

Disseminated *Mycobacterium avium* Complex:

Recommendations on Prophylaxis and Therapy for for Adults and Adolescents Infected with Human Immunodeficiency Virus*

Summary

Mycobacterium avium complex (MAC) causes disseminated disease in up to 40% of patients with advanced human immunodeficiency virus (HIV) disease in the United States. A U.S. Public Health Service Task Force convened to address the prophylaxis and therapy of MAC recommends that patients with HIV infection and <100 CD4+ T-lymphocytes/μL be administered prophylaxis against MAC. The recommended regimen is rifabutin, 300 mg by mouth daily, for the patient's lifetime. If disseminated MAC develops, a treatment regimen containing clarithromycin or azithromycin and at least one other agent is recommended. Diagnosis, therapy, and prophylaxis for HIV-infected children follow similar guidelines.

Introduction

Mycobacterium avium complex (MAC) causes disseminated disease in up to 40% of patients with human immunodeficiency virus (HIV) in the United States, producing fever, sweats, weight loss, and anemia. Disseminated MAC characteristically affects patients with advanced HIV disease and peripheral CD4+ T-lymphocyte counts <100 cells/μL. Effective prevention and therapy of MAC has the potential to contribute substantially to improved quality of life and duration of survival for HIV-infected persons.

Two randomized, placebo-controlled, multicenter studies were recently conducted to study the use of rifabutin for the prevention of disseminated MAC, as defined by positive blood culture. In these studies, rifabutin was shown to reduce the frequency of MAC bacteremia by approximately 50% (48 of 566 patients receiving rifabutin developed MAC, compared with 102 of 580 patients receiving placebo, p <0.001).

On December 23, 1992, the Food and Drug Administration issued the first approval for a prophylactic drug targeted against MAC. Data collected in published and unpublished studies suggest that health-care providers may utilize and their patients may benefit from recommendations for prevention and management provided by a panel of experts drawn from government agencies, universities, practicing clinicians, and the community. The U.S. Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex was convened in Bethesda, Maryland, on December 7-8, 1992, and issued the recommendations in this report.

Indications for Prophylaxis

Patients with HIV infection and <100 CD4+ T-lymphocytes/μL should be administered prophylaxis against MAC. Prophylaxis should be continued for the patient's lifetime unless multiple drug therapy for MAC becomes necessary because of the development of MAC disease.

Clinicians must weigh the potential benefits of MAC prophylaxis against the potential for toxicities and drug interactions, the cost, the potential to produce resistance in a community with a high rate of tuberculosis, and the possibility that the addition of another drug to the medical regimen may adversely affect patients' compliance with treatment. Because of these concerns, therefore, in some situ-

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ations rifabutin prophylaxis should not be administered.

Evaluation before Beginning Prophylaxis

Before prophylaxis is administered, patients should be assessed to ensure that they do not have active disease due to MAC, *M. tuberculosis*, or any other mycobacterial species. This assessment may include a chest radiograph and tuberculin skin test.

Prophylactic Regimens

Rifabutin, 300 mg by mouth daily, is recommended for the patient's lifetime unless disseminated MAC develops, which would then require multiple drug therapy. Although other drugs, such as azithromycin and clarithromycin, have laboratory and clinical activity against MAC, none has been shown in a prospective, controlled trial to be effective and safe for prophylaxis. Thus, in the absence of data, no other regimen can be recommended at this time.

The 300-mg dose of rifabutin has been well tolerated. Adverse effects included neutropenia, thrombocytopenia, rash, and gastrointestinal disturbances.

Diagnosis of MAC

Disseminated MAC is most readily diagnosed by one positive blood culture. Blood cultures should be performed in patients with symptoms, signs, or laboratory abnormalities compatible with mycobacterium infection. Blood cultures are not routinely recommended for asymptomatic persons, even for those who have CD4+ T-lymphocyte counts <100 cells/μL.

Therapy of Disseminated MAC

Although studies have not yet identified an optimal regimen or confirmed that any therapeutic regimen produces sustained clinical benefit for patients with disseminated MAC, the Task Force concluded that the available information indicated the need for treatment of disseminated MAC. The Public Health Service therefore recommends that regimens be based on the following principles:

- Treatment regimens outside a clinical trial should include at least two agents.
- Every regimen should contain either azithromycin or clarithromycin; many experts prefer ethambutol as a second drug. Many clinicians have added one or more of the following as second, third, or fourth agents: clofazimine, rifabutin, rifampin, ciprofloxacin, and in some situations amikacin. Isoniazid and pyrazinamide are not effective for the therapy of MAC.
- Therapy should continue for the lifetime of the patient if clinical and microbiologic improvement is observed.

Monitoring Patients Receiving Therapy for Disseminated MAC

- Clinical manifestations of disseminated MAC —such as fever, weight loss, and night sweats—should be monitored several times during the initial weeks of therapy. Microbiologic response, as assessed by blood culture every 4 weeks during initial therapy, can also be helpful in interpreting the efficacy of a therapeutic regimen.
- Most patients who ultimately respond show substantial clinical improvement in the first 4-6 weeks of therapy. Elimination of the organisms from blood cultures may take somewhat longer, often requiring 4-12 weeks.

Recommendations for HIV-Infected Children

HIV-infected children <12 years of age also develop disseminated MAC. Some age adjustment is necessary when clinicians interpret CD4+ T-lymphocyte counts in children <2 years of age. Diagnosis, therapy, and prophylaxis should follow recommendations similar to those for adolescents and adults.

**Adapted from: Centers for Disease Control and Prevention. Recommendations on Prophylaxis and Therapy for Disseminated* Mycobacterium avium *Complex for Adults and Adolescents Infected with Human Immunodeficiency Virus. MMWR 1993;42(No. RR-9):17-20.*

Diagnosis of Tuberculosis by Nucleic Acid Amplification Methods Applied to Clinical Specimens*

CDC and the Food and Drug Administration (FDA) have received inquiries from health-care providers about rapid assays for detecting *Mycobacterium tuberculosis* in clinical specimens. These assays, currently being offered by several commercial diagnostic laboratories, are based on DNA or RNA amplification procedures, such as the polymerase chain reaction. The false-positive rate, false-negative rate, reproducibility, and predictive value of these tests are not fully understood. In addition, none of the tests have been reviewed or approved by FDA, and their usefulness in patient management and public health practices has not been established. For the diagnostic evaluation of persons suspected of having tuberculosis, the Public Health Service advises clinicians to continue to rely on established techniques: medical history, physical examination, chest roentgenogram, tuberculin skin test, acid-fast stains of clinical specimens, standard or radiometric procedures for cultures and antimicrobial susceptibility testing, and nucleic acid probes for species identification of *M. tuberculosis* isolates.

**Reprinted from: Centers for Disease Control and Prevention. Diagnosis of Tuberculosis by Nucleic Acid Amplification Methods Applied to Clinical Specimens. MMWR 1993;42(35);686.*

Update: Influenza Activity — North America and Europe, 1993*

From October 1992 through February 1993, influenza activity was reported at moderate levels worldwide. Epidemic or outbreak levels of influenza activity were associated with either influenza B or influenza A(H3N2) in many parts of the world. Isolation of influenza A(H1N1) occurred less frequently.

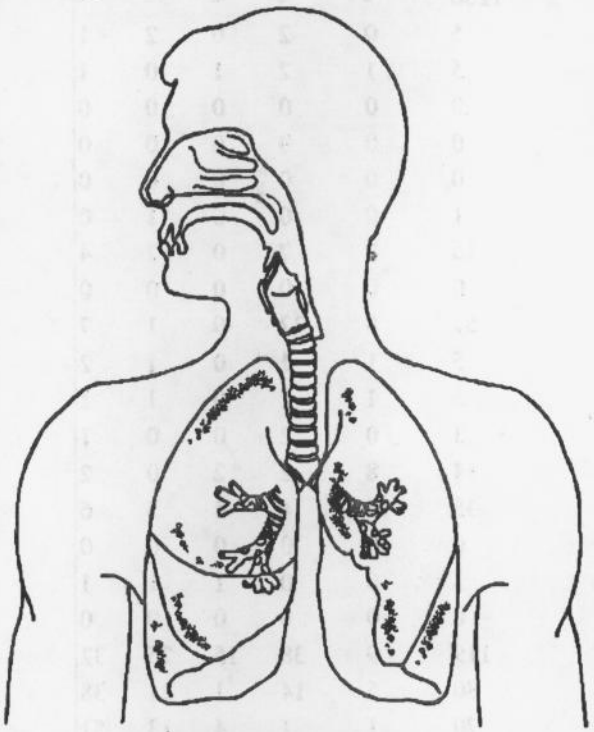
North America and Europe. In most countries, influenza activity peaked in late February or early March and was associated with isolation of influenza B viruses. In March, an increase in the isolation of influenza A(H3N2) that began in mid-January continued throughout the rest of the season. Canada reported influenza A(H3N2) or influenza B outbreaks in nursing homes and other institutions from March through April and detection of sporadic infections caused by influenza A continuing through July. In the United Kingdom, sporadic cases of influenza A(H3N2) were reported during July and August.

In the United States, influenza A(H3N2) was isolated during outbreaks in nursing homes and other institutions during March-May; sporadic isolation of influenza A(H3N2) continued through June. During August, laboratory-confirmed influenza A(H3N2) outbreaks were reported in two nursing homes and among workers on a dredging barge in southern Louisiana. Influenza A(H3N2) viruses from the Louisiana outbreaks are antigenically similar to the A/Beijing/32/92 strain.

Editorial Note: Circulation of influenza A/Beijing/32/92(H3N2)-like viruses late in the 1992-93 season and the association of this virus strain with outbreaks in August suggest that influenza A(H3N2) viruses may be the predominant circulating viruses in the United States during the 1993-94 influenza season. Since the emergence of influenza type A(H3N2) in 1968, influenza seasons during which this strain has predominated have been accompanied by a concomitant increase in the proportion of influenza-associated deaths, particularly among persons aged ≥65 years.

Although sporadic cases of influenza can occur at any time, outbreaks rarely occur during the summer in the United States. Sporadic cases of influenza are often first detected during October or November, but outbreaks usually do not begin until December. Although it is unknown whether the outbreaks investigated in Louisiana indicate an early influenza season this year, in the past, similar outbreaks have been followed by early influenza activity in other parts of the United States. Therefore, CDC recommends that, if possible, vaccination providers complete vaccination programs by the end of October 1993 rather than conducting routine vaccination programs through mid-November, as is usually recommended.

The Advisory Committee on Immunization Practices recommends vaccination against influenza for:



- persons aged greater than or equal to 65 years;
- persons who reside in nursing homes or other chronic-care facilities;
- persons with chronic cardiovascular or pulmonary disorders, including children with asthma;
- persons who required medical follow-up or hospitalization during the past year because of chronic metabolic disease, renal dysfunction, hemoglobinopathies, or immunosuppression;
- children and teenagers who are receiving long-term aspirin therapy and, therefore, may be at risk for developing Reye syndrome after influenza; and,
- health-care workers and other persons who are in close contact with persons in high-risk groups, including household members.

The 1993-94 trivalent influenza vaccine contains virus strains of the three distinct groups of influenza viruses in worldwide circulation: A/Texas/36/91-like (H1N1), A/Beijing/32/92-like (H3N2), and B/Panama/45/90-like. Most influenza viruses isolated since March 1993 are closely related to the 1993-94 influenza vaccine.

Even though the vaccine and circulating virus strains appear to be closely matched, antiviral agents can still be a useful adjunct to vaccination. Rimantadine hydrochloride, approved for marketing in September by the Food and Drug Administration, and amantadine hydrochloride are specifically active against influenza type A viruses and can be used for prophylaxis or for treatment of influenza A infections in certain situations, including:

- as a control measure when influenza outbreaks occur in institutions — both for treatment of ill persons and as prophylaxis for others;
- as short-term prophylaxis for high-risk persons vaccinated after influenza activity has begun and who need protection for the 2-week period during which immunity is developing;
- as prophylaxis during peak influenza activity for persons for whom vaccine is contraindicated or for immunocompromised persons who may not produce protective levels of antibody in response to vaccination; and
- as prophylaxis for unvaccinated health-care workers and household contacts of high-risk persons either during peak influenza activity or until immunity develops after vaccination.

Because amantadine and rimantadine are effective only against influenza type A, use of a rapid diagnostic test for influenza A may assist in determining influenza-control measures.

Information regarding influenza surveillance is available through the CDC Voice Information System (influenza update), telephone (404) 332-4555, or through the CDC Information Service on the Public Health Network electronic bulletin board. From October through May, the information is updated at least every other week. In addition, periodic updates about influenza are published in MMWR, and information on local influenza activity is available through county and state health departments.

**Adapted from: Centers for Disease Control and Prevention. Update: Influenza Activity — United States and Worldwide, 1993 MMWR 42(38);752-755.*

Cases of Selected Notifiable Diseases, Virginia, August 1 through August 31, 1993.*

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
	State	Regions					This Yr	Last Yr	5 Yr Avg
		NW	N	SW	C	E			
AIDS	194	12	121	3	19	39	1240	425	369
Campylobacteriosis	82	12	28	12	18	12	467	429	412
Gonorrhea†	1206	-	-	-	-	-	8070	11129	10793
Hepatitis A	5	0	2	0	2	1	96	75	172
Hepatitis B	5	1	2	1	0	1	94	135	173
Hepatitis NANB	0	0	0	0	0	0	22	26	38
Influenza	0	0	0	0	0	0	1020	122	1177
Kawasaki Syndrome	0	0	0	0	0	0	15	16	16
Legionellosis	1	0	0	0	1	0	4	12	9
Lyme Disease	15	2	7	0	2	4	47	80	61
Measles	0	0	0	0	0	0	1	14	56
Meningitis, Aseptic	57	8	32	9	1	7	171	157	159
Meningitis, Bacterial‡	5	1	1	0	1	2	62	85	103
Meningococcal Infections	5	1	2	0	1	1	31	47	40
Mumps	3	0	2	0	0	1	19	46	78
Pertussis	14	8	2	2	0	2	38	10	17
Rabies in Animals	35	16	4	4	5	6	250	222	193
Reye Syndrome	0	0	0	0	0	0	1	0	1
Rocky Mountain Spotted Fever	3	0	0	1	1	1	8	12	11
Rubella	0	0	0	0	0	0	0	0	2
Salmonellosis	119	9	38	15	25	32	612	613	832
Shigellosis	80	6	14	1	21	38	448	154	233
Syphilis (1° & 2°)†	70	1	1	4	13	51	433	522	490
Tuberculosis	32	4	11	0	9	8	299	248	244

Localities Reporting Animal Rabies: Albemarle 1 skunk; Augusta 1 cat, 2 skunks; Bath 1 skunk; Botetourt 1 skunk; Chesterfield 1 cat; Clarke 2 raccoons; Essex 1 cat; Fairfax 3 raccoons; Frederick 1 bat; Hanover 1 skunk; Henrico 1 fox; Isle of Wight 1 cat; Lancaster 1 raccoon; Loudoun 1 fox; Louisa 1 raccoon, 2 skunks; Mecklenburg 1 raccoon; Montgomery 1 bat, 1 skunk; Page 2 skunks; Powhatan 1 skunk; Pulaski 1 raccoon; Rappahannock 1 cat, 1 raccoon; Rockingham 1 cat; Suffolk 1 raccoon; Virginia Beach 1 cat, 1 raccoon.

Occupational Illnesses: Asbestosis 23; Carpal Tunnel Syndrome 81; Coal Workers' Pneumoconiosis 17; Lead Poisoning 2; Loss of Hearing 13.

*Data for 1993 are provisional. †Total now includes military cases to make the data consistent with reports of the other diseases. ‡Other than meningococcal.

Published monthly by the
VIRGINIA HEALTH DEPARTMENT
Office of Epidemiology
P.O. Box 2448
Richmond, Virginia 23218

Telephone: (804) 786-6261

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