COMMITTEE RECOMMENDATIONS

Indications for Chemotherapy in the Pulmonary Mycoses

A Report of the Committee on Fungus Diseases,* Subcommittee on Therapy
American College of Chest Physicians

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GENERAL CONSIDERATIONS

Observations over many years have led to the conviction that the systemic mycoses are diseases with a generally chronic course, with disability due to pulmonary or other organ involvement, and for the most part a fatal outcome. It is also well known now that infection is usually acquired via the respiratory route and that a primary focus of disease is established in the lung. It would seem logical, therefore, to treat every infection early in the course of an illness, especially before disease has progressed extensively in the lungs or has disseminated to other organs. Two significant factors, however, have mitigated against such logical management. First, pulmonary infection is often subclinical and difficult to detect, and by the time diagnosis is made, infection may already have disseminated from the primary site. Secondly, for most of the major pulmonary mycoses, the only effective and available agent, amphotericin B, must be administered intravenously and for a period of time measured in months. Furthermore, administration of this agent is accompanied by side effects most distressing to the patient and, in the vast majority of cases, by irreversible renal injury. This damage may be disabling, in some instances even before an otherwise optimal dose is achieved.

Thus it is apparent that amphotericin B cannot be administered to every infected individual in the manner that isoniazid can be employed in all individuals who have been infected by the tubercle bacillus. It is also obvious that the value and hazards of therapy with amphotericin B must be weighed against the potential threat of the infection in each individual case, depending upon the identity of the invading organism and the type of illness which it has produced.

Because of these special considerations the following recommendations are made by the committee in regard to the indications for chemotherapy in the pulmonary mycoses.

Cryptococcosis

During the past several years, there have been an increasing number of reports of patients who have pulmonary cryptococcosis without clinical manifestations of disease. It is beginning to be apparent that many of these patients can be observed over long periods of time without there being progression of illness or evidence of dissemination. Occasionally there is spontaneous disappearance of the micro-organism from the sputum. Although the present indications for therapy are not well settled, it is clear that patients should be treated under the following conditions: a) when pulmonary cryptococcosis appears to worsen during radiographic observation; b) when there is evidence of increasing ventilatory impairment; c) when there is such co-existing disease as leukemia, lymphoma, diabetes mellitus, sarcoidosis, or therapy with corticosteroids...
or immunosuppressive agents; or d) when there is evidence of meningitis or involvement of other organs.

Recent reports have described patients without any clinical or roentgenologic evidence of disease from whose sputum Cryptococcus neoformans has been cultured repeatedly, over a period of months or years. At the present time continued observation alone appears to be the treatment of choice in such cases.

Chemotherapy does not appear necessary in patients who have had a coin lesion removed surgically.

Any patient with pulmonary cryptococcosis or with positive sputum cultures must have a lumbar puncture to rule out asymptomatic cryptococcal meningitis.

Those patients with meningitis or cultural evidence of dissemination elsewhere, e.g. the kidney, should receive a course of therapy.

Histoplasmosis

Pulmonary involvement is seen in all three forms of histoplasmosis: (1) primary acute, (2) severe disseminated, and (3) chronic cavitary.

Primary Acute Disease

There are certain semantic difficulties which arise in regard to the primary acute form. It is now well recognized on the basis of the culture of Histoplasma capsulatum from specimens other than sputum during illness, and from the presence of splenic and less frequently adrenal calcification afterwards, that in this form there is indeed hematogenous dissemination. Despite this fact, however, most instances of first infection with H. capsulatum are asymptomatic, or are accompanied by an illness not otherwise differentiated from influenza or other respiratory viral infections, or are diagnosed by culture studies during or after satisfactory convalescence from a mild to moderately severe illness. However, there have been instances of primary acute disease in which the diagnosis is made during the course of illness, in patients who have had severe disease (manifest by prolonged fever, and debilitation), and who have died during this illness. For such serious disease, chemotherapy seems clearly indicated.

There is no uniformity of opinion at present as to the advisability of chemotherapy routinely as a measure of preventing subsequent chronic cavitary disease.

Severe disseminated histoplasmosis

As the name doubly implies, there are at least two indications for chemotherapy. Without such therapy approximately 80–90 per cent of patients die from such manifestations as ulcerative lesions of the gastrointestinal tract, adrenal insufficiency, endocarditis, meningitis, or progressive pulmonary disease.

Chronic cavitary histoplasmosis

In the chronic cavitary form of the disease, the case fatality rate is significantly lower (30 per cent), and dissemination does not occur during or after illness. However, there is ample evidence that this form is associated with progressive destruction of the lungs, increasing ventilatory impairment, and disability. Thus, chemotherapy is indicated in all patients with active disease of this type.

Special Considerations

In patients who have had a coin lesion removed at surgery, there appears to be general agreement that chemotherapy is not necessary.

Despite the apparent reasonableness of the proposition and the strong advocacy by some groups, there is no general agreement that chemotherapy is indicated solely as "coverage" during resectional therapy.

Coccidioidomycosis

As with the other mycoses, chemotherapy is indicated in any patient who has disseminated infection.

In primary acute coccidioidomycosis, therapy is recommended under the following six conditions: (1) infancy; (2) debilitated, elderly state; (3) a "susceptible" population group (e.g., Mexican, Filipino, or patients with diabetes mellitus, pregnancy, corticosteroid or immunosuppressive therapy); (4) rising or persistent high titers (1:32 or more) with serologic complement-fixation tests; (5) progressive pulmonary disease; and (6) persistent hilar or mediastinal lymphadenopathy associated with clinical activity.

In those patients who have had a coin lesion removed at surgery, chemotherapy does not seem indicated.

In patients with cavitary or other pulmonary disease requiring surgery, there is no agreement that chemotherapy is indicated solely as "coverage" during resectional surgery.

Blastomycosis

Despite the chronic course of disease and the lack of progression in some instances, patients with
active pulmonary blastomycosis should have a
course of treatment.

Coin lesions due to B. dermatitidis are rare, but
after their surgical resection, disease has spread
locally in some patients and also hematogenously in
others. In such patients and those with cavitary
or other disease requiring surgery, chemotherapy
appears advisable.

Sporotrichosis

There have been a small number of patients re-
ported who have had pulmonary sporotrichosis ei-
ther with or without the cutaneous-lymphatic form
of disease. These infections have been considered
to be severe and to require chemotherapy.

Candidosis (Moniliasis or Candidiasis)

Various species of Candida are so frequently en-
countered as commensals of the respiratory or the
gastrointestinal tract of man that isolation of this
fungus from sputum can be related only with great
difficulty to any disease present. Chemotherapy for
pulmonary illness would seem indicated only when
there is histologic evidence of tissue invasion, or
when there is present another disease, such as leu-
kemia, where infection frequently and fatally
spreads from a pulmonary lesion.

Aspergillosis

As in the case of candidosis, various species of
Aspergillus are frequently seen in sputum of pa-
tients who have chronic underlying pulmonary dis-
ease. Relationship of this isolation to disease visible
on chest film is problematic. Because this fungus
is a frequent cause of a fatal illness in patients
with leukemia, chemotherapy would appear indi-
cated in those patients who have pulmonary disease
and sputum from which an Aspergillus species has
been cultured.

When a characteristic "fungus ball" is present,
chemotherapy is probably not indicated, as there is
frequently no tissue invasion and little evidence of
response to chemotherapy.

Mucormycosis (Phycomycosis)

Mucormycosis is almost invariably seen only in
patients receiving antileukemic therapy or in com-
pany with diabetic acidosis. It is almost always a
severe and frequently a fatal infection. In the occa-
SIONAL illness that begins or is clinically manifest in
the lung, as well as in the greater number that
begin in the nose, sinus, or orbit, chemotherapy
is recommended.

Actinomycosis and Nocardiosis

Chemotherapy is indicated in all patients with
pulmonary actinomycosis.

Recently there have been some interesting re-
ports of the frequent culture of Nocardia asteroides
from sputum specimens submitted to various large
laboratories. Many of these isolates have come from
patients who have no recognizable pulmonary
pathology. It is not clear at this moment whether
such patients need to be treated. When Nocardia
infection in the lungs is clear-cut, chemotherapy is
indicated.

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A CONCEPT OF TIME

According to the definition of the famous German
philosopher Kant (1724–1804), time is not something
that subsists by itself, nor does it inhere in things as an
ideal relational structure which is presupposed when-
ever we observe them. It is merely a form of intuition
"built into" the mind in such a way that we must see
phenomena as temporal very much as we must see
things as red when we are wearing red glasses. Time is
not a property of things but a property of the instru-
ment by which we view things. And since we have no
instrument other than mind for observing them, we are
compelled to see the world as temporal.

Benjamin, A. C. in Fraser, J. T.: The Voices of Time, Braziller,
New York, 1966