Antibiotics in Non-Tuberculous Pulmonary Diseases*

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The introduction of antibiotics has revolutionized the treatment of pulmonary disease. With the rapid discovery of new antibiotics, an increasing number of inflammatory lung lesions is rapidly being brought under control. It is proposed in this paper to describe the practical use of the antibiotics in non-tuberculous diseases of the chest. The useful antibiotics will be discussed in detail and some of the newer ones mentioned. The treatment of the following pulmonary diseases will be considered: Pneumonia, lung abscess, bronchitis, bronchiectasis and empyema.

Up to the present time over 100 antibiotics have been isolated, but only a few of these have practical value in the treatment of pulmonary disease. Many others will unquestionably be added as refinements in preparation and means of overcoming toxicity are discovered. At this writing, four of the antibiotics are available for treatment of pulmonary diseases, penicillin, streptomycin, aureomycin and chloromycetin.

1. Antibiotics Useful in Pulmonary Diseases

Penicillin: Penicillin is derived from the common mold, Penicillln notatum. It was first discovered by Fleming1,2 in 1928. The most widely used preparation is crystalline penicillin G. readily soluble in water. It is the drug of choice in pulmonary infections caused by the following organisms: 1) Diplococcus Pneumoniae, 2) Streptococcus, 3) Staphylococcus, 4) Actinomyces Bovis, and 5) Spirochaetes.

The drug is non-toxic except for the occasional allergic reactions of dermatitis, urticaria and fever which can be readily controlled with anti-histaminics or by changing the brand of penicillin. Resistance rarely develops following penicillin therapy.

The best method of administration is by the intramuscular route, using 50,000 units of the sodium or potassium salt of penicillin G in aqueous solution every three hours around the clock. This produces quick and adequate plasma concentrations of penicillin. The dosage may be increased to 100,000 units or decreased to 25,000 units depending on the severity or mildness of the infection.

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caine penicillin G is a salt that is relatively insoluble in water and releases penicillin slowly following an intramuscular injection. A single injection of 300,000 units of procaine penicillin gives an adequate blood level for at least 12 to 24 hours, so that two such injections 12 hours apart would be adequate for most infections. The addition of 100,000 units of sodium or potassium penicillin G to the procaine penicillin provides both rapid and prolonged action up to 24 hours. When repeated injections of crystalline penicillin are not feasible, as in home therapy, the longer acting procaine penicillin should be used. Oral penicillin of the sodium or potassium salt of crystalline penicillin may be used when the parenteral method is impossible. However, five times the estimated parenteral dose must be prescribed. While the oral method has received adequate trial with considerable success, it should never be the route of choice in a severe infection.

The inhalation of vaporized solutions of penicillin is of considerable value in the treatment of broncho-pulmonary disease. From 25,000 to 50,000 units of penicillin dissolved in 1 cc. of physiological saline solution are inhaled three to five times daily by means of a vaponefrin nebulizer, preferably attached to an oxygen tank by rubber tubing. Green suggests the use of Laboratory aerosol in the dilutions, and at times epinephrine and pyribenzamine solution. He states that with these solutions, local reactions to penicillin in the nose and throat are eradicated.

Intratracheal solutions of penicillin may be used and have been found to be of value where the drug is indicated. For this, 50,000 units are dissolved in 3 cc. of physiological saline and introduced with a catheter. Penicillin may also be combined with lipiodol, 1,500 units to 1 cc. of oil, and introduced as in ordinary broncho-ography.

Streptomycin: Streptomycin was first described by Schatz, Bugie and Waksman in 1944. It is derived from certain strains of Actinomyces griseus. It is prepared in powder form, readily soluble in water or saline. The chief value of streptomycin lies in its potency against many gram-negative organisms resistant to penicillin. It is the drug of choice in the following infections involving the lungs, either primarily or secondarily: 1) Klebsiella pneumoniae (Friedlander's bacillus), 2) Pasteurella tularensis, 3) Pasteurella pestis, 4) Haemophilus influenzae, 5) E. Coli, 6) Bacillus Pyocyaneus, 7) Brucella species (with sulfonamides).

Streptomycin is more toxic than penicillin, particularly if given over a long period of time. Allergic reactions such as fever and urticaria are usually not severe and can be controlled with antihistaminics. When the drug is given in large doses longer than three weeks, involvement of the eighth nerve may take place caus-
ing vertigo, tinnitus and deafness. Even the severe cases of vertigo however, eventually compensate in spite of irreparable damage to the vestibular system. Resistance develops in the majority of cases if the drug is used a long time, starting approximately five weeks after beginning of streptomycin therapy.

The best method of administration is the intermittent intramuscular one. For the average infection, 0.5 gram every 6 hours around the clock is sufficient. As much as 4 grams daily may be necessary in severe infections.

Aerosol streptomycin is of value in infections due to gram-negative organisms. The method is the same one described in aerosol penicillin therapy, using 50,000 units of the drug dissolved in 1 cc. of physiological saline solution and repeated three to five times daily. Direct instillation into the trachea may also be used as described above.

Aureomycin: Aureomycin was isolated by Duggar6 in 1948 from Streptomyces aureofaciens. It is a yellow crystalline powder, soluble in water and contains nonionic chlorine. It is the drug of choice in the following pulmonary infections: 1) Primary atypical (viral) pneumonia. 2) Ornithosis and Psittacosis. 3) Rickettsiae Species. 4) Salmonellae Species. 5) Bacterial pneumonia (pneumococcal, streptococcal, staphylococcal and hemophilus influenza infections, particularly if penicillin and streptomycin have failed). 6) Pasteurella Tularensis. 7) Brucella Species. 8) Endameba Histolytica.

Aureomycin is non-toxic, the only disturbing effects being occasional nausea, vomiting and diarrhea. Aluminum hydroxide offsets the nausea. The reactions may be due to impurities in the drug and do not usually necessitate discontinuing treatment. Development of resistance rarely occurs with aureomycin.

Oral dosage is the best method of administration. One gram every four to six hours for several days or until improvement occurs followed by 0.5 gram every six hours is the optimum dosage. Intramuscular therapy is usually accompanied by pain and induration at the site of injection. Intravenous therapy given in 1 per cent solution slowly may be used.

Chloromycetin: Chloromycetin was isolated by Ehrlich and Burkholder4 from Streptomyces venezuelae in 1947 and can also be prepared synthetically. This compound contains nonionic chlorine. It is the drug of choice in the following infections which may primarily or secondarily involve the lungs: 1) Rickettsial species (especially typhus fever), 2) Ornithosis and Psittacosis, 3) Salmonella species (may be better than aureomycin), 4) Atypical pneumonia, 5) E. Coli infections, 6) Brucella species.

Chloromycetin is relatively non-toxic. It is given by mouth, starting with 1 gram dosage every four hours until clinical im-
provement occurs and later 0.5 gram every six hours. Treatment should be continued for three to five days following drop in fever.

It is noted that both aureomycin and chloromycetin have similar therapeutic effectiveness. It would appear at this time however, that aureomycin should be preferred for atypical pneumonia, the ornithosis-psitticosis group, tularemic pneumonia, Rocky Mountain spotted fever and Q fever infections. Chloromycetin appears to be more effective for typhoid, typhus and the salmonella group of infections. Both are apparently effective in brucellosis.

Some of the more promising antibiotics not yet ready for general use should be mentioned at this time.

Polymixin: Polymixin is derived from soil organism B. Polymixa. It is the most effective drug for gram-negative bacilli but is toxic to the kidney. It is more active than streptomycin against streptomycin sensitive gram-negative organisms, and is also active against streptomycin-resistant gram-negative organisms.7

Subtilin: Subtilin is produced by a strain of B. Subtilis. It is active against gram-positive bacteria, M. Tuberculosis, some of the fungi and E. Histolytica. It has a very low toxicity.

Bacitracin: Bacitracin is derived from strains of B. Subtilis. It is very active against gram-positive bacteria, and has been widely used in surgical infections. Its nephrotoxicity makes it unsuitable for systemic use.

Streptothricin: Streptothricin is derived from strains of Streptomyces lavendulae. It is active against fungi, but is toxic to animals.

Actidione: Actidione is produced by strains of Streptomycyes griseus. It is active against yeasts and fungi, particularly Torula, but has received only limited clinical trial.

Neomycin: Neomycin is derived from Streptomyces fradiae. It is active against mycobacteria and streptomycin-resistant organisms. Its clinical value has not yet been established.

2. Pulmonary Diseases Favorably Influenced by Antibiotic Therapy

The most important application of the antibiotic therapy in pulmonary disease is in the treatment of pneumonia. There is now at hand a specific antibiotic for every form of pneumonia except that type due to the smaller viruses. The drug of choice and dosage is given in the following paragraphs.

Pneumococcal Pneumonia: Penicillin is so highly specific against the pneumococcus, that it is the drug of choice in the treatment of pneumococcal pneumonia. The sulfonamides are relegated to second choice because of their potential toxicity and somewhat lesser potency. Penicillin is best administered by three
hourly intramuscular injections of 50,000 units of crystalline penicillin. Therapy should be maintained for five to seven days after the crisis. Intramuscular administration of 300,000 units of aqueous penicillin or procaine penicillin G. at 12 hour intervals give just as good results. It is likely that much smaller doses would be adequate in the average case of pneumonia, but it would be unwise to chance inadequate therapy.

**Streptococcal Pneumonia:** Penicillin is highly effective in the treatment of streptococcal pneumonia. Treatment should be intensive and the doses of penicillin high.

**Staphylococcal Pneumonia:** Penicillin is the drug of choice in staphylococcal pneumonia. Large doses should be used. Aureomycin may be of value in those cases in which the organisms have been found to be penicillin-resistant. Children with staphylococcal infections associated with pancreatic fibrosis who did not respond to penicillin were markedly benefited by aureomycin.9

**Friedlander's Pneumonia:** Friedlander's bacillus is sensitive to streptomycin and should be used in all cases. The dose should be large at the onset, usually 4 gms. daily, 1 gm. given intramuscularly at six hour intervals. The dose should be cut down to 2 gms. daily as soon as a therapeutic effect is obtained.

**Hemophilus Influenzae Pneumonia:** Pneumonia due to hemophilus influenzae responds promptly to streptomycin. Two to 4 gms. of the drug are given daily for approximately 10 days. Aureomycin has been found to be effective in infections due to hemophilus influenzae and should be used if streptomycin fails.

**Viral Pneumonia:** The pneumonias due to filtrable viruses may be classified into primary atypical pneumonias of unknown etiology and viral pneumonias of known etiology. In the latter group are included: 1) Influenzal pneumonia, 2) Ornithotic pneumonia, the best known example being psittacosis, 3) Rickettsial pneumonias comprising typhus, Rocky Mountain spotted fever and Q fever.

Aureomycin and chloromycetin are the first drugs known to be effective against any of the viral pneumonias. Aureomycin is apparently specific in the treatment of primary atypical pneumonia, ornithotic pneumonia and the Rickettsial diseases, especially Rocky Mountain spotted fever and Q fever. Chloromycetin has a similar effect and is thought to be preferable in typhus infections. So far as is known, none of the antibiotics have any influence on influenazl pneumonia. The dosage of both aureomycin and chloromycetin has been previously given.

**Pneumonia Associated with Specific Infections:**

**Tularemia:** Streptomycin is specific in its effect on tularemic pneumonia. The dosage is 2 gms. daily for approximately a week.
The result is dramatic within two to three days after the start of therapy. Aureomycin also has a favorable effect on the course of tularemia. In view of the striking results with streptomycin and greater general experience with the drug, the latter should still be the drug of choice.

**Brucellosis:** Pulmonary infections are rare complications of brucellosis. Aureomycin and chloromycetin are equally effective in the treatment of brucellosis, both appearing to be better than the previously used combination of streptomycin and sulfadiazene.

**Pulmonary Infections due to Fungi:** Several antibiotics are effective against the fungi, being both fungistatic and fungicidal in vitro. Most of them are still in the experimental stage, being too toxic for use in man. It is quite likely that some of these antibiotics will soon be available.

Penicillin is said to be valuable in the treatment of actinomycosis\(^1\) and streptothricosis.\(^1\) It should be used along with the other well established measures in combating fungus infections. Dosage should be large and continued for several weeks.

Actidione has been used in cryptococcosis with apparently favorable results.

Up to this time, there have been no favorable clinical reports on the use of antibiotics in histoplasmosis, coccidiomycosis or any of the other fungi.

**Pneumonia of Unknown Etiology**

It may frequently be impossible to determine the exact cause of a pneumonic process, particularly early in the course of the disease. This often applies to the patient who for one reason or another is unable to get hospital care, or in whom adequate laboratory tests may not be possible. Even in a modern hospital, early differential diagnosis between such diseases as viral pneumonia, coccal pneumonia, Friedlander's pneumonia and tularemia may be difficult at the onset. To wait for bacteriological confirmation or to put too much faith in the height of a white count may lose valuable time. This is particularly true in Friedlander's and typhoid pneumonia. In any seriously ill patient therefore, it is advisable to start at once with both penicillin and streptomycin, and if no improvement takes place within a short time, aureomycin and/or chloromycetin should be added. Indiscriminate use of the antibiotics should naturally be deplored as there may be development of sensitization phenomena and resistant organisms. However, when there is serious unknown pulmonary disease present, combined antibiotic therapy is indicated until the exact diagnosis can be made. In this connection, it should be stated that following the use of penicillin in pulmonary infections, penicillin-resistant...
organisms, chiefly gram-negative bacilli may grow and produce
disease after penicillin-sensitive organisms have been controlled.\textsuperscript{12}
This situation would necessitate the use of streptomycin, providing
bacteriological evidence of new infections is found.

\textit{Diseases of the Bronchi}

The antibiotics are of considerable importance in inflammatory
diseases of the bronchi. In acute or chronic bronchitis which does
not respond to the usual measures, a course of antibiotics should
be given, particularly if sensitive organisms are found. Penicillin
and streptomycin are the drugs of choice. These are best used by
the aerosol method, and in severe infections, particularly in the
presence of fever, supplementary parenteral therapy should be
added.

In bronchiectasis, penicillin and/or streptomycin should be used
for acute exacerbations, secondary pneumonia and in preparation
for lung surgery. Both aerosol and parenteral methods of adminis-
tration are effective. The drugs do not cure the disease, but the
amount of expectoration can be considerably reduced, and often
may be changed from purulent to a thin mucoid sputum. Periodic
courses of antibiotics should be given depending on the character
of the sputum.

\textit{Lung Abscess}

Every case of lung abscess should have a thorough trial with
antibiotic therapy. Penicillin is the drug of choice when gram-
positive bacteria predominate in the sputum, and streptomycin
should be used for infections due to gram-negative bacteria. Large
doses of penicillin or streptomycin should be used both paren-
terally and by the aerosol method. Direct instillation of the anti-
biotics into the tracheobronchial tree in conjunction with bron-
choscopy may prove to be of considerable value. The best results
are obtained with the acute lung abscess. In chronic pulmonary
abscess, antibiotics should also be used with the other well-known
methods of therapy. Prior to operation, several days of antibiotic
therapy makes the convalescence much smoother.

A course of aureomycin or chloromycetin may prove to be of
value in lung abscesses not improved by penicillin or streptomycin.

\textit{Empyema}

The organisms most commonly found in empyema are the pneu-
mococcus, streptococcus and staphylococcus. Penicillin is there-
fore the drug of choice. When gram-negative organisms are present,
streptomycin should be used. All acute cases should have a short
trial of repeated aspirations and instillations of penicillin. Fifty
thousand units of penicillin dissolved in 50 cc. of isotonic saline
are instilled daily following aspiration of the exudate. When streptomycin is used, 500,000 units are dissolved in 50 cc. of saline. Sterile saline should be used to wash out the pleural cavity if the pus is difficult to evacuate with a needle. Parenteral therapy must be continued throughout. If the infection rapidly improves as evidenced by the character of the aspirated fluid, negative culture and general improvement of the patient, then antibiotic therapy is continued. If however, no improvement takes place within a week's time or if the exudate is thick, immediate surgical drainage should be instituted. Delay of operation may result in a thickened pleura and a non-expansile lung. The intrapleural instillation of streptokinase, a fibrinolytic substance, as suggested by Drs. Hillet and Sherry, liquefies the exudate and fibrin deposits on the pleura, allowing easy removal of the purulent exudate. This procedure in combination with the antibiotics would appear to be the ideal therapy for empyema and may eventually supplant surgical drainage.

Antibiotic therapy is rapidly supplanting all forms of chemotherapy in inflammatory pulmonary disease. There is available at the present time a specific antibiotic for most pulmonary infections, except those due to the smaller viruses and the fungi. It is highly probable that in the near future, the newer antibiotics will prove to be effective against the other hitherto irremediable infections of the lungs.

SUMMARY

Penicillin, streptomycin, aureomycin and chloromycetin are all invaluable in the treatment of pulmonary infections.

*Penicillin* is the drug of choice in all coccal pneumonias, suppurative diseases of the lungs, bronchiectasis, spirochaetal infections and actinomycosis of the lung. It is best given by the intramuscular route, using 50,000 units of crystalline penicillin G every three hours. When repeated injections are not feasible, 12 hourly injections of 400,000 units of penicillin containing 300,000 units of procaine penicillin G and 100,000 units of sodium or potassium penicillin G should be used. In suppurative lung lesions and bronchial infections, aerosol penicillin should be added, using 50,000 units of penicillin dissolved in 1 cc. of saline solution, three times daily, preferably with an oxygen tank. In empyemas, direct daily instillation of 50,000 units of penicillin dissolved in 50 cc. saline into the pleural cavity may be curative.

*Streptomycin* is the drug of choice in gram-negative infections of the lung. It is highly specific for pneumonias and pulmonary infections due to Friedlander's bacillus, B. tularensis, B. pestis, hemophilus influenzae and E. coli. It is best given by intramuscular
injection of $\frac{1}{2}$ gram every six hours until the infection is under control. In suppurative diseases of the lungs and bronchiectasis, aerosol streptomycin in conjunction with penicillin should be used.

**Aureomycin** is the drug of choice in atypical pneumonia, ornithotic pneumonia, tularemia, Rocky Mountain spotted fever, Q fever infections and brucellosis. The drug is given orally, using 1 gram every six hours for several days, and then $\frac{1}{2}$ gram every six hours. Bacterial pneumonias not responding to penicillin and streptomycin may respond to aureomycin.

**Chloromycetin** is the drug of choice in pulmonary infections due to typhus, salmonella group, E. coli and brucella organisms. The drug is given by mouth, using 1 gram every four to six hours until improvement takes place, then $\frac{1}{2}$ gram every six hours.

**Combined Therapy:** In pulmonary infections of unknown etiology, it is often invaluable to use both penicillin and streptomycin at once, and if in a short time improvement does not occur, aureomycin and/or streptomycin should be added.

**Other Antibiotics:** Several of the newer antibiotics show great promise in the treatment of hitherto incurable lesions, such as fungus and viral infections. Most of these are still toxic to animals, but it is very likely that with further refinements in preparation, they will soon prove to be effective in a still wider range of pulmonary infections.

**RESUMEN**

En el tratamiento de las infecciones pulmonares la penicilina, la estreptomicina y la aureomicina son de valor inapreciable.

La penicilina es la droga de elección en todas las infecciones neumónicas por cocos, supuraciones del pulmón, bronquiectasias, infecciones por espiroquetas y actinomicosis pulmonar.

Es mayor daria por vía intramuscular usando 50,000 unidades de penicilina cristalina G. cada tres horas. Cuando no es posible inyectar con frecuencia puede usarse Penicilina G. potásica 100,000 unidades asociada a penicilina procainica 300,000 unidades cada doce horas. En las lesiones supurantes y bronquiales el aerosol de penicilina usando 50,000 unidades en 1 cc. de solución fisiológica tres veces al día puede usarse mediante un tanque de oxígeno. En los empiemas la instilación directa diariamente de 50,000 unidades en 50 cc. de solución salina en la cavidad pleural puede curar.

La Estreptomicina es la droga de elección en las infecciones del pulmón por gérmenes Gram negativos. Es altamente específica para las neumonias y las infecciones pulmonares por bacilo de Friedlander, bacilo tularensis, pestis, hemofilo de la influenza y E. coli. Es mejor inyectarlo intramuscular a razón de medio gramo cada seis horas hasta que la infección se domine.
En las supuraciones de los pulmones y en bronquiectasias el aerosol de estreptomicina combinado con el de penicilina deben usarse.

La aureomicina es la droga preferible en las neumonías atípicas, neumonía psitacosta, tularémica, en la fiebre de las Montañas Rocallasas, en la fiebre Q. y en la brucelosis.

La droga se usa oralmente dando un gramo cada seis horas por varios días y después medio gramo cada seis horas. Las neumonías bacterianas que no responden a penicilina y estreptomicina pueden responder a la aureomicina.

La cloromicetina es la droga preferible en la tifoidea, el grupo de salmonedas, el tifo, la brucelosis y la E. coli. Se dá por vía oral un gramo cada seis horas hasta que se presente mejoría y después medio gramo cada seis horas.

Terapéutica combinada: En las infecciones de naturaleza desconocida es a menudo útil usar tanto penicilina como estreptomicina y si después de corto tiempo no ocurre la mejoría deben usarse la aureomicina y la cloromicetina.

Otros antibióticos: Varios de los más nuevos antibióticos son prometedores en el tratamiento de lesiones hasta ahora incurables. La mayoría de estas drogas son aún tóxicas para los animales, pero es posible que su refinamiento las haga útiles en otras infecciones pulmonares.

REFERENCES