

AEROSOLIZED ANTI-INFECTIVE AGENTS

Generic name:	Pentamidine isethionate
Brand name:	NebuPent
Mode of action:	Pentamidine is an antiprotozoal, active against <i>Pneumocystis carinii</i> , the causative organism of <i>Pneumocystis carinii</i> pneumonia (PCP) in patients with AIDS. The exact mode of action is not known, and may be due to multiple actions. Pentamidine blocks synthesis of RNA and DNA, inhibits oxidative phosphorylation and interferes with folate transformation. Resistance to Pentamidine by <i>P. carinii</i> has not been shown and may be due to the multiple effects of the drug on the organism's metabolism.
Indications:	<ol style="list-style-type: none">1. history of one or more episodes of PCP2. peripheral CD4+ lymphocyte count of 200 cells/mm³ or less
Routes of administration:	<p>Pentamidine can be given parenterally or by aerosol, but is not absorbed with oral administration. When given parenterally, it quickly distributes to the major organs where it binds to tissues and is stored for months. After a single intramuscular dose, the drug can be detected in the urine 270 days later. When given by aerosol, the drug first binds to lung tissue, but is then slowly absorbed into the circulation and distributed to body tissues. As a result, prolonged aerosol administration can result in systemic accumulation. Approximately 75% of the drug is excreted in the urine and 25% in feces over the months following administration. The following three reasons provide the rationale for aerosol administration:</p> <ol style="list-style-type: none">1. PCP is located in the alveolar region of the lung and aerosol administration targets drug delivery to the lung.2. Parenteral administration is associated with numerous and serious systemic side effects.3. Aerosolized pentamidine produces substantially higher lung concentrations than IV administration.
Adverse effects:	<p>Local airway effects include: cough and bronchial irritation, SOB, bad taste (bitter or burning), bronchospasm and wheezing, spontaneous pneumothoraces</p> <p>Note: Airway effects can be reduced or prevented by the prior administration of a β_2-adrenergic bronchodilator. Ipratropium has also been shown to prevent bronchoconstriction.</p> <p>Systemic effects include: conjunctivitis, rash, neutropenia, pancreatitis, renal insufficiency, dysglycemia, digital necrosis, appearance of extrapulmonary <i>P. carinii</i> infection</p>
Dosage forms:	Nebupent is supplied as a dry powder, with 300 mg in a single vial. This must be reconstituted with 6 ml of sterile water for injection (not normal saline, which can cause precipitation) added to the vial.
Dosage:	300 mg (the entire contents of one vial) once every 4 weeks for prophylaxis of PCP in AIDS subjects
Administration:	FDA approval was for administration via the Respirgard II nebulizer, a small volume nebulizer fitted with a series of one-way valves and an expiratory filter. The nebulizer should be powered with a flow of 5-7 L/min.
Environmental exposure:	<p>Drug exposure Although one study concluded that health care workers administering pentamidine treatments receive one-millionth of the patient's dose, pentamidine has been reported in low levels in the urine of some workers. Health care workers have complained of conjunctivitis and bronchospasm while administering the drug. This risk can be minimized by the following precautions:</p> <ol style="list-style-type: none">1. Use a nebulizer system with one-way valves and an expiratory filter.

2. Stop nebulization if the patient takes the mouthpiece out of the mouth (a thumb control on the power gas tubing gives more control).

Risk of tuberculosis

The risk of tuberculosis when treating AIDS patients with nebulized pentamidine is due to the following factors:

1. There is an association of tuberculosis with AIDS.
2. Tuberculosis has an airborne mode of transmission.
3. Pentamidine aerosol can cause coughing and expulsion of droplet nuclei containing tuberculosis bacilli.

The following precautions will help minimize environmental contamination from the aerosolized drug or infectious organisms:

1. Use nebulizers producing an MMD of 1-2 μ m to increase alveolar targeting and lessen large airway deposition and cough production.
2. Always use a suitable expiratory filter and one-way valves with the nebulizer.
3. Instruct patients to turn off the nebulizer when talking or when taking the mouthpiece out of the mouth.
4. Screen patients for cough history and pretreat with a β agonist, with sufficient lead-time for effect in reducing the bronchial reactivity.
5. Administer aerosol in a negative pressure room with six air changes per hour, or consider using an isolation booth/hood assembly with an exhaust fan and air directed through a high-efficiency filter.
6. Use barrier protection (gloves, mask, eyewear) for health care workers.
7. Screen HIV subjects for tuberculosis and treat where evidence of infection exists.
8. Do not allow treatment subjects to mix with others until coughing subsides.
9. Health care workers should be periodically screened for tuberculosis.
10. Pregnant women and nursing mothers should avoid exposure to the drug, and all practitioners should limit their exposure to the extent possible.

Clinical Application:

The results of several studies on aerosol therapy of acute PCP reveal:

1. Hospitalization is less common in those patients treated prophylactically, but the treatment does not lessen the clinical severity of PCP or lessen sensitivity of diagnostic testing for PCP in sputum.
2. The short-term use of pentamidine (600 mg by aerosol once a day for 21 days) to treat active PCP can have positive effects (13 of 15 patients with first time PCP responded to treatment).
3. In a study comparing aerosol administration (600 mg) with IV administration (3 mg/kg) in 45 patients with mild to moderate first episodes of PCP showed the reduced IV dosage to more effective than aerosol to treat mild to moderate PCP.

The results of a long-term study on aerosol therapy for prophylaxis of PCP reveal:

1. During a 1992 study 133 HIV+ patients received TMP-SMX 3 days per week and 125 others received aerosol pentamidine (300 mg) once per month. No patient on TMP-SMX developed PCP during the 2-year study, while 17 patients on the aerosol regimen developed PCP. However, in the TMP-SMX group, 56% of subjects changed drug due to adverse reactions, while only 2% of the aerosol group did so. The study concluded that TMP-SMX is the drug of choice to prevent PCP in these subjects, provided adverse effects are tolerated and clinically acceptable.
2. These results, along with other reports on the adverse effects of aerosol pentamidine therapy, have caused a reevaluation of aerosolized pentamidine for the prophylaxis of PCP.

Generic name:	Ribavirin
Brand name:	Virazole
Mode of action:	<p>The mechanism by which ribavirin exerts its virostatic effect is not completely understood. Its viral inhibition is probably based on its structural resemblance to the nucleosides used to construct the DNA chain. During the formation and assembly of new viral protein within the cell, ribavirin is most likely taken up instead of the natural nucleoside to form the DNA chain. This prevents construction of viable viral particles and subsequent shedding of the virus into the bloodstream. Because of the nature of viral infection, antiviral drug therapy is difficult. In particular, there are three complications in managing viral diseases:</p> <ol style="list-style-type: none"> 1. Attacking the intracellular virus may harm the host cell. 2. Viral replication is maximal before the appearance of symptoms. 3. Viruses have the property of antigenic mutability (i.e., they change their appearance to the immune system).
Indications:	Approved as an inhaled aerosol for management of bronchiolitis and pneumonia caused by RSV. Specifically, it is indicated for use in severe cases of RSV in infants and young children requiring hospitalization and/or supported ventilation, where underlying conditions of prematurity, immunosuppression, congenital heart disease or other cardiopulmonary disease increase the risk of morbidity or mortality from the RSV infection.
Adverse effects:	<p><i>Pulmonary:</i> deterioration of pulmonary function and worsening of asthma or COPD; pneumothorax, apnea, and bacterial pneumonia</p> <p><i>Cardiovascular:</i> cardiovascular instability including hypotension, cardiac arrest and digitalis toxicity</p> <p><i>Hematologic:</i> effects on blood cells reported with oral or parenteral administration, but not with aerosol use; reticulocytosis has been reported with aerosol</p> <p><i>Dermatologic/Topical:</i> rash, eyelid erythema, and conjunctivitis</p>
Dosage forms:	Ribavirin is supplied as a dry powder, with 6 mg in a 100 ml vial. The powder is reconstituted first in the vial with sterile USP water for injection or inhalation, transferred to the large volume (500 ml) reservoir of the nebulizer, and further diluted to a volume of 300 ml with sterile water. This gives a concentration of 6 g/ml, or 20 mg/ml, 2% strength solution.
Dosage:	Ribavirin is given in a 20-mg/ml solution that is administered by nebulizer (SPAG-2) for 12 to 18 hours per day for a minimum of 3, but no more than 7 days.
Administration:	Clinical trials were carried out by using the SPAG. The drug was approved for general use with this aerosol generator.
Environmental exposure:	<p><i>Drug exposure</i></p> <p>Ribavirin has potential for mutagenic and carcinogenic effects. The effect on fertility is uncertain, but the drug has caused testicular lesions in rats. Acute side effects include precipitation on contact lenses and conjunctivitis. Although there are no reports of serious effects from exposure to ribavirin, precautions to limit or avoid exposure are well indicated. Pregnant women, or those wishing to become pregnant should avoid exposure if at all possible. Environmental containment is superior to personnel barrier protection and the drug manufacturer will make a containment system available.</p>
Generic name:	Tobramycin
Brand name:	TOBI
Mode of action:	Tobramycin binds irreversibly to the 30S subunit of bacterial ribosomes. This binding blocks protein synthesis in the bacteria, causing cellular death.
Dosage:	The usual dosage of TOBI is 300 mg bid approximately 12 hours apart and not less than 6 hours apart, for 28 days consecutively, with the following 28 days off of the drug.

Indications and
Administration:

Inhalation: TOBI is recommended for patients 6 years or older. The intended use is that of managing chronic infections with *P. aeruginosa* in cystic fibrosis (CF)) as follows:

- treat or prevent early colonization with *P. aeruginosa*
- maintain present lung function or reduce the rate of deterioration

TOBI is formulated as a nebulizer solution with 300 mg in a 5-ml ampoule. In clinical trials, the drug was administered using the PARI LC Plus with a DeVilbiss Pulmo-Aide compressor. Other delivery devices should be tested to ensure adequate drug output and particle size. Patients should be instructed not to mix dornase alfa (Pulmozyme) with TOBI in the nebulizer. TOBI should be inhaled after other therapies usual in CF, e.g. CPT and other inhaled medications including bronchodilators or dornase alfa.

TOBI should be stored at refrigerated temperatures of 2-8°C (36-46°F). After removing from refrigeration, or if refrigeration is not available, the pouches in which the drug is provided can be stored at room temperature less than 25°C (77°F) for up to 28 days. Drug ampoules should not be exposed to intense light. The solution may darken with aging if not refrigerated. This does not change drug activity if the manufacturer's guidelines are followed.

Clinical
Application:

The disease state for which aerosolized antibiotics have been used more consistently for pulmonary infections is CF. CF patients are chronically infected with gram-negative organisms, such as *P. aeruginosa* and the gram-positive bacterium *S. aureus*. Chronic *Pseudomonas* infection can lead to recurring acute respiratory infections. Except for quinolone derivatives such as ciprofloxacin (Cipro), antibiotics effective against *Pseudomonas* do not give sufficient lung levels to inhibit bacteria when taken orally, leading to the use of IV or inhaled administration. It is interesting to note that before the introduction of TOBI, tobramycin was often given by aerosol using the injectable formulation with a dose of 80 mg per treatment. During the development of TOBI, dose-response studies indicated that a dose of 300 mg per treatment was needed. This is a clear exception to the rule that a lower dose of a drug can be given with direct pulmonary targeting with aerosol.

Adverse effects:

Parenteral administration:

By the parenteral route, the adverse effects of tobramycin may be similar to those of other aminoglycosides, including:

- ototoxicity
- nephrotoxicity
- neuromuscular blockade
- hypomagnesemia
- cross-allergenicity
- fetal harm

Inhaled administration:

The only adverse experiences reported after the 6-month trial of Ramsey and associates were tinnitus and voice alteration. No hearing loss or changes in serum creatinine were associated with the aerosol administration of TOBI.

Precautions:

Inhaled administration:

- TOBI should be used with caution in pts. with preexisting renal, auditory, vestibular or neuromuscular dysfunction
- Admixture incompatibility exists between β -lactam antibiotics and aminoglycosides when physically mixed in solution. In general, mixing TOBI with other drugs is discouraged
- Factors that increase the risk of hearing damage with the prolonged use of TOBI are renal impairment, concomitant use of parenteral aminoglycosides, dehydration and concomitant use of ethacrynic acid (Edecrin), furosemide (Lasix) or other ototoxic drugs

- Nebulization of antibiotics in the hospital setting should be performed under conditions of containment to prevent environmental saturation and development of resistant organisms in the hospital
- Aminoglycosides can cause fetal harm if administered to pregnant women; exposure to ambient aerosol drug should be avoided
- Local airway irritation with cough and bronchospasm is possible with inhaled antibiotics
- Allergies in patients, staff or family are possible if exposure to the aerosol is not controlled

Generic name: Zanamivir

Brand name: Relenza

Mode of action: Zanamivir is a neuraminidase inhibitor that prevents the spread of influenza A and B viruses, the viruses responsible for the "flu." Neuraminidase is an enzyme that is required by the influenza viruses to spread from infected cells to healthy cells. Zanamivir blocks the action of neuraminidase thereby reducing the spread of influenza. Since the spread of the viruses is prevented, the symptoms and duration of infection are reduced. On average, zanamivir reduces the duration of symptoms by one day if treatment is started within forty-eight hours after symptoms begin.

Indications and Administration:

Zanamivir is indicated in the treatment of uncomplicated influenza illness in adults, during the early onset (within 48 hours) of infection. Zanamivir is available in a DPI (Diskhaler) for oral inhalation. Each blister contains 5 mg. There are 4 blisters in a Rotadisk, and the drug package contains 5 Rotadisks with 1 Diskhaler device. The dose in adults and children 12 years and older is 2 inhalations (2 blisters or 10 mg) bid, approximately 12 hours apart for 5 days. Patients should finish the entire 5-day course of the drug.

Clinical Application:

Clinical trials demonstrate that inhaled Zanamivir can shorten the duration of symptoms in influenza by approximately 1 day, and there was no consistent difference in effect with influenza A versus influenza B. There is no data on the efficacy of the drug if administration is started after more than 48 hours of symptoms. Zanamivir is not approved for prophylaxis, nor does it reduce the risk of transmission of the virus. The drug is of no benefit in persons with infections other than influenza and there exists no clinically easy or inexpensive diagnostic tool to confirm the presence of influenza infection. As a result, using symptoms alone to prescribe Zanamivir can result in inappropriate use of antiinfluenza drugs.

Adverse effects:

Bronchospasm and deterioration of lung function:

Patients with underlying respiratory disease such as asthma or COPD may experience bronchospasm after inhaling Zanamivir.

Under treatment of bacterial infection:

Bacterial respiratory infections can appear with influenza-like symptoms and viral respiratory infections can progress to serious bacterial 2° infections. Treatment with antiviral agents is not effective against bacterial infection and could possibly allow progression of such infections to serious illnesses such as pneumonia.

Allergic reactions:

As with any drug, patients should be monitored for allergic reactions with Zanamivir.

Other adverse effects:

Adverse reactions occurring in a small percentage of patients included: diarrhea; nausea; vomiting; bronchitis; cough; sinusitis; ear, nose and throat infections; dizziness and headaches.

AEROSOLIZED ANTIBIOTICS

GENERAL USE OF AEROSOL ANTIBIOTICS

The delivery of antibiotics by aerosol and direct endotracheal instillation date back to the early 1970s. Aerosol delivery of antibiotics has been tried for two general situations: 1) gram-negative pulmonary infections and 2) fungal pulmonary infections. In both situations local targeting of the lung was intended as an adjunct to systemic therapy. In addition, some antibiotics do not give sufficient lung levels to inhibit bacteria when taken orally (poor oral availability). Therefore either IV or aerosol delivery routes must be used.

AEROSOL ADMINISTRATION OF ANTIBIOTICS

Several points should be noted when nebulizing (SVN) antibiotics:

1. Antibiotic solutions such as gentamicin are more viscous than bronchodilator nebulizer solutions and as such may affect nebulizer performance. High flow rates (10-12 L/min) are suggested to produce suitably small particles.
2. Environmental contamination and practitioner exposure to the aerosolized drugs can be reduced by using expiratory filters with one-way valves and a thumb control.
3. Antibiotic aerosols such as polymyxin or gentamicin may irritate the airway and cause bronchospasm. Pretreatment or concomitant use with a β_2 agonist may be needed.
4. Physical incompatibility between some antibiotics has been noted. These drugs should be given in separate nebulizer treatments.
5. Specific written physician orders are needed to administer an antibiotic as an inhaled aerosol if the drug is not FDA-approved for this method of delivery.

NON-AEROSOLIZED ANTI-INFECTIVE AGENTS

Antibiotic: Substance produced by microorganisms (bacteria, fungi, molds) or in a laboratory setting, which is capable of inhibiting or killing bacteria and other microorganisms.

MODES OF ACTION OF ANTIBIOTICS

Inhibition of Cell Wall Synthesis

Bacteria possess rigid cell walls rather than membranes. The rigid wall is necessary due to high internal osmotic pressure. Without this protection, in the relatively hypotonic environment of the body, such cells would explode. Examples of antibiotics that inhibit cell wall synthesis include:

Penicillins	Cephalosporins	Cycloserine
Bacitracin	Vancomycin	

Inhibition of Cell Wall Function

The cytoplasmic membrane that encloses a cell is a selective, functional, and active filter that keeps certain proteins and nucleotides in the cell and allows other substances to enter the cell for metabolism. Disruption of the membrane function upsets this necessary flow and storage of material. Examples of antibiotics that inhibit cell wall function include:

Polymyxins

Inhibition of Protein Synthesis

Protein synthesis is essential to a cell's growth and function, as amino acids are linked to produce protein for structural enlargement, energy storage or enzymes. Many antibiotics interfere with the ribosome's ability to synthesize proteins. Examples of antibiotics that inhibit protein synthesis include:

Chloramphenicol	Erythromycin	Lincomycin	Kanamycin
Tetracyclines	Streptomycin	Aminoglycosides	Gentamicin

Inhibition of Nucleic Acid Synthesis

DNA synthesis is the heart of cellular activity and life, acting as the master code for cell function and structure. Certain of the antibiotics attach to the DNA strands and block further DNA replication or formation of RNA. Examples of antibiotics that inhibit nucleic acid synthesis include:

Actinomycin
Mitomycin
Rifampicin

TERMS DESCRIBING ANTIBIOTIC ACTIVITY

In general, antibiotics are either bactericidal or bacteriostatic. Examples include:

Bactericidal	Bacteriostatic
Penicillins	Chloramphenicol
Cephalosporins	Erythromycin
Cycloserine	Tetracyclines
Vancomycin	Lincomycin
Bacitracin	
Streptomycin	
Kanamycin	
Polymyxins	

Antibiotics are also classified as broad-spectrum or narrow-spectrum. Broad-spectrum antibiotics are useful against a wide range of organisms, both gram-positive and gram-negative bacteria. Narrow-spectrum antibiotics are useful against only a few organisms. Examples include:

Broad-Spectrum	Narrow-Spectrum
Chloramphenicol	Penicillin
Tetracyclines	Streptomycin
Kanamycin	Erythromycin
Cephalosporins	Lincomycin
Ampicillin	Polymyxin B
	Vancomycin

SENSITIVITY AND RESISTANCE

Antibiotics are tested for use in therapy through sensitivity and resistance (S & R) studies. Various antibiotics are impregnated onto paper disks and placed in dishes, each of which is heavily inoculated with a different bacterium. If the organism is susceptible, or sensitive to, the antibiotic on a disk, then a clear zone of inhibited growth will occur around the disk. Broad-spectrum antibiotics can be administered until the results of the S & R are known.

One disturbing development in the use of antibiotics is that of resistant organisms. For example, in a colony of staphylococcal organisms, most individual bacteria may be vulnerable to an antibiotic such as penicillin. However, perhaps 1% is resistant to penicillin. The penicillin will effectively treat the colony, inhibiting growth of 99% of the bacteria and the patient will become free of symptoms. However, the remaining 1% of bacteria continues to grow and reproduce, so that eventually a new population of resistant bacteria exists. This antibiotic is no longer effective against this mutant strain of bacteria.

β-LACTAM ANTIBIOTICS

The β-lactam antibiotics include the penicillins, the cephalosporins, the carbapenem and the monobactam. The agents are bactericidal, through inhibition of cell wall synthesis. Bacterial resistance to the β-lactam antibiotics can occur through the actions of an enzyme, produced by bacteria known as β-lactamase and also known as penicillinase. β-lactamase can be produced by a number of gram-positive and gram-negative bacteria.

Penicillins

The penicillins, which represent one of the oldest classes of antibiotics include both natural and semisynthetic penicillins. Examples include:

Penicillin G	Cloxacillin (Tegopen)	Amoxicillin (Polymox)
Penicillin V	Methicillin (Staphcillin)	Carbenicillin (Geopen)
Oxacillin (Prostaphen)	Ampicillin (Omnipen)	Ticarcillin (Ticar)

The penicillin group is divided into three subgroups: the natural penicillins (e.g. penicillin G), penicillinase resistant agents (e.g. methicillin or oxacillin), and the broad or extended spectrum penicillins (e.g. ampicillin, carbenicillin and ticarcillin).

Mode of action:	The β-lactam antibiotics act by inhibition of cell wall synthesis
Resistance:	Resistance is caused by β-lactamase, which is produced by most strains of <i>Staphylococcus aureus</i> , by the <i>Bacillus</i> species, <i>Escherichia coli</i> , <i>Enterobacter aerogenes</i> , the <i>Proteus</i> species, <i>Pseudomonas aeruginosa</i> and <i>Mycobacterium tuberculosis</i> . There are penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin and cloxacillin) that are effective against <i>S. Aureus</i> . Clavulanic acid is a β-lactamase inhibitor. It can protect penicillin type antibiotics by binding to and inactivating β-lactamase. Clavulanic acid is combined with ticarcillin as the product Timentin and with amoxicillin as Augmentin.
Allergy:	Hypersensitivity reactions are more common with parenteral rather than oral administration and are manifested by anaphylactic shock, urticaria and various skin rashes.
Uses:	This group is useful in managing infections due to streptococcal species, staphylococcal species, <i>Haemophilus influenzae</i> and gonococcal and syphilis causing organisms.

Cephalosporins

This group of antibiotics was originally derived from a fungus, Cephalosporin acremonium, in 1948 and is said to be the most prescribed group of antibiotics in the US. This group is divided into generations based on their spectrum of activity. The first generation is active against gram-positive and a few gram-negative organisms. The second and third generations have better activity against gram-negative organisms.

Examples include:

First Generation	Second Generation	Third Generation
Cephalexin (Keflex)	Cefamandole (Mandol)	Cefoperazone (Cefobid)
Cefadroxil (Duricef)	Cefoxitin (Mefoxin)	Cefotaxime (Claforan)
Cephalothin (Keflin)	Cefonicid (Monocid)	Ceftizoxime (Cefizox)
Cephradine (Velocef)	Cefoclor (Ceclor)	Ceftazidime (Fortaz)
Cephapirin (Cefadyl)	Cefmetazole (Zefazone)	Ceftriaxone (Rocephin)
Cefazolin (Ancef)	Cefotetan (Cefotan)	Moxalactam (Moxam)
	Cefuroxime (Zinacef)	

Mode of action: The cephalosporins act by inhibition of cell wall synthesis

Toxicity and Hazards: Nephrotoxicity is a serious effect that can result in acute renal tubular necrosis. IV administration can cause thrombophlebitis, and IM injection can be painful.

Uses: Cephalosporins are used for their broad-spectrum activity against many gram-positive cocci and some of the gram-negative organisms. They do, however, lack efficacy against *P. aeruginosa*, *Bacteroides fragilis* and to some extent *H. influenza*. They are active against the *Klebsiella* species.

Carbapenem

The only product in this group is imipenem-cilastatin (Primaxin). Imipenem is formulated with cilastatin to decrease nephrotoxicity.

Monobactam

The only product in this group is aztreonam (Azactam). This is a synthetic bactericidal and is effective against a wide range of gram-negative aerobic organisms.

AMINOGLYCOSIDES

This is group of chemically similar agents derived from different species of *Streptomyces*. Examples include:

Streptomycin	Amikacin
Gentamicin (Garamycin)	Neomycin (Neosporin)
Tobramycin (Nebcin)	Netilmicin (Netromycin)
Kanamycin (Kantrex)	

Mode of action: The aminoglycosides act by prevention and distortion of bacterial protein synthesis, although this does not explain why this group is bactericidal.

Use: Gentamicin, tobramycin, netilmicin and amikacin are used to treat gram-negative bacillary pneumonias with the exception of *Haemophilus*, but may not be totally effective in gram-negative pneumonias if given systemically, and inhalation of aminoglycosides has been used in conjunction with β -lactam antibiotics. Inhalation of aminoglycosides is also commonly used to control *Pseudomonas* infections in cystic fibrosis. Streptomycin is used in treating *M. tuberculosis*, and neomycin is used for topical wound irrigation

Toxicity: The most noteworthy side effect of the aminoglycosides is nephrotoxicity - ototoxicity can also occur and is manifested by dizziness and nausea. These agents can also produce mild neuromuscular blockade, and increase the blockade of neuromuscular paralyzing agents. Due to this effect, they should be used cautiously in myasthenia gravis

TETRACYCLINES

This group is derived from *Streptomyces* species. Examples include:

Tetracycline (Achromycin)	Methacycline (Randomycin)
Oxytetracycline (Terramycin)	Doxycycline (Vibramycin)
Demeclocycline (Declomycin)	Minocycline (Minocin)

Mode of action: The tetracyclines act by interfering with bacterial protein synthesis. They can be bacteriostatic or bactericidal, depending on dosage.

Uses: This group is useful for managing mycoplasmal and other atypical pneumonias, as well as acute infections superimposed on chronic bronchitis. These agents should be taken before meals and on an empty stomach to promote absorption.

Toxicity and

Hazards: Side effects include GI irritation with nausea, vomiting and diarrhea; bone marrow depression; and hypersensitivity manifested by skin rashes or acute anaphylaxis. These agents may also produce oral or vaginal candidiasis or fulminating diarrhea, all caused by superinfections. The tetracyclines are briefly incorporated in the liver and kidneys and should be used with caution, if at all, in pts. with liver or kidney dysfunction. This group may cause tooth discoloration in children as well as retarded skeletal growth, which is a permanent condition.

FLUOROQUINOLONES

The fluoroquinolones or quinolones are synthetic quinolone derivatives with broad spectrum antibacterial activity - the fluorine molecule provides increased potency against gram negative organisms and broadens the spectrum of activity to include some gram positive organisms. Examples include:

Ciprofloxacin (Cipro)	Enoxacin (Penetrex)
Norfloxacin (Noroxin)	Lomefloxacin (Maxaquin)
Ofloxacin (Floxin)	

Uses: The quinolones are useful in infections associated with chronic bronchitis and cystic fibrosis. They have strong activity against *H. influenza*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Neisseria meningitidis*, *Bordetella pertussis*, and especially in cystic fibrosis, against *P. aeruginosa*. The quinolones have excellent lung bioavailability when given orally, but should be used for only several weeks in cystic fibrosis to avoid bacterial resistance.

MISCELLANEOUS ANTIBIOTIC AGENTS

Vancomycin (Vancocin)

Vancomycin is an antibiotic obtained from an actinomycete. The drug has a bactericidal effect produced by interference with bacterial cell wall synthesis. It has been used to manage staphylococcal respiratory infections resistant to methicillin. Ototoxicity is a possible hazard with the drug.

Chloramphenicol (Chloromycetin)

Chloramphenicol represents another antibiotic produced by an actinomycete that has broad spectrum bacteriostatic activity caused by prevention of bacterial protein synthesis. It is effective against salmonellae, penicillinase-producing *S. aureus*, *Klebsiella pneumoniae* and *H. influenza*, but has a risk of causing aplastic anemia. Its use in respiratory infections is limited to severe cases with resistance to less toxic antibiotics.

Erythromycin (Erythrocin, Ilotycin)

Another antibiotic derived from an actinomycete is erythromycin, which acts by inhibition of protein synthesis in bacteria. This agent is bacteriostatic in low doses and bactericidal in higher doses. It is given orally or IV and is relatively safe. It is useful as an alternative for penicillin-allergic patients with pneumococcal pneumonia, and in the management of Legionnaires' disease. Erythromycin is termed a macrolide antibiotic based on its chemical structure. Other macrolide antibiotics include:

Azithromycin (Zithromax)
 Clarithromycin (Biaxin)
 Troleandomycin (Tao)

Polymyxins

There are two antibiotics under the general term polymyxin: polymyxin B and polymyxin E. The polymyxins are polypeptide antibiotics and are derived from *Bacillus polymyxa*. Polymyxin B is very effective against *Pseudomonas* and other gram-negative bacteria. It has been used topically for infections (eye, ear, skin), and because it is not absorbed from the GI tract, it can be given to manage infections of the intestine. It is also given IV, since intramuscular injections are quite painful. Polymyxin B

has also been used as an aerosolized antibiotic. Polymyxin E is known as colistin and is similar to polymyxin B.

Bacitracin

Bacitracin is another polypeptide antibiotic originally obtained from the organism *Bacillus subtilis*. The particular culture used was taken from the wound of a young trauma victim named Tracy, and the name bacitracin commemorates the source of the drug. It is often used for topical management of infections of the mouth, nose, eye or skin. Like the polymyxins, it is not well absorbed from the GI tract for systemic use.

Clindamycin (Cleocin) and Lincomycin (Linococin)

Clindamycin is a derivative of lincomycin, which inhibits bacterial protein synthesis. It is similar to erythromycin against pneumococci, group A streptococci and is active against *S. aureus*, and gram positive and gram-negative anaerobes such as *B. fragilis*. Its pulmonary use is with aspiration pneumonia as an alternative to penicillins. Clindamycin can cause severe diarrhea and associated colitis.

Metronidazole (Flagyl, Metizole)

Metronidazole is active against anaerobic infections, whether pulmonary, intraabdominal, or gynecological.

SYNTHETIC (NONANTIBIOTIC) ANTI-INFECTIVE AGENTS

Sulfonamides

The sulfonamides were the first effective group of chemotherapeutic agents used to treat systemic bacterial infections. *They are not classed as antibiotics*. Before antibiotics, such as penicillin, these were the first line of antibacterial defense. With advent of natural and semisynthetic antibacterial agents, the use of sulfonamides has declined. Examples include:

Sulfisoxazole (Gantrisin)
Sulfacytine (Renoquid)

Sulfamethoxazole (Gantanol)
Sulfamethizole (Thiosulfil)

Mode of action: The sulfonamides are bacteriostatic and act by competitive antagonism to prevent the use of *p*-aminobenzoic acid by bacteria, an effect that ultimately prevents bacterial growth.

Uses: The sulfonamides may be used in the management of intestinal (bacillary dysentery) and urinary tract infections. The most recent interest in sulfonamides has been a combination of sulfamethoxazole with trimethoprim.

Trimethoprim-Sulfamethoxazole (TMP-SMX)

This agent is a compound of two synthetic antibacterial drugs. The compound is not an antibiotic but a laboratory-produced chemical agent. The compound is an attractive antibacterial agent because the two drugs potentiate each other. The compound is used as an anti-infective agent against *P. carinii* pneumonia in patients with AIDS. It is also commonly used to manage acute and chronic urinary tract infections and also respiratory infections.

Nitrofurantoin (Furadantin)

Nitrofurantoin is another synthetic antibacterial agent. It is effective against many gram positive and gram-negative organisms such as *E. coli*, and species of *Proteus*, *Pseudomonas*, *Klebsiella*, and *Enterobacter*. It is used primarily to treat urinary tract infections.

ANTIFUNGAL AGENTS

Amphotericin B

Amphotericin B is a relatively toxic drug obtained from an actinomycete. Its fungicidal action is based on its ability to increase fungal cell membrane permeability. Side effects include nephrotoxicity causing a loss of HCO_3^- , resulting in a metabolic acidosis.

Nystatin

Nystatin is effective against yeast like infections, such as *C. albicans*. It is applied topically to the skin, vulva or mouth for treatment. One brand name is Mycostatin.

Griseofulvin

Griseofulvin is used primarily to treat tinea (ringworm) infections.

Other Antifungal Agents

Flucytosine (Ancobon)

Miconazole (Monistat)

Fluconazole (Diflucan)

Ketoconazole (Nizoral)

Itraconazole (Sporanox)

ANTITUBERCULOSIS AGENTS

Management of Tuberculosis

Effective management of TB began with the discovery of streptomycin in 1944. Prior to this, TB was “managed” by quarantine and isolation. However, the use of streptomycin alone was quickly found to lead to resistant strains of the bacillus *M. tuberculosis*. This necessitated the use of multiple drug therapy, a concept still in use today. The standard approach consists of multiple-first-line drugs for 9 months. Isoniazid and rifampin are given for 9 months. In an initial period of 2-8 weeks, these 2 drugs are supplemented with one of the following: ethambutol, streptomycin or pyrazinamide. With these combinations, a relapse rate of only 0-4% has been seen. Efforts are also being made to reduce the 9-month period to 6 months, with use of 4 drugs (isoniazid, rifampin, pyrazinamide and either ethambutol or streptomycin) for 2 months followed by 4 months of isoniazid and rifampin.

Streptomycin

Streptomycin was the first drug available for effective management of TB. The route of administration is IM.

Isoniazid

Isonicotinic acid hydrazide (INH) was found in the early 1950s to be effective against TB and to be superior to streptomycin. It has remained as one of the primary drugs for management of TB and is easily absorbed from the GI tract with oral administration. There is a risk of severe or even fatal hepatitis and the risk increases with age. It is effective against all clinical forms of TB, however, resistance to the drug can develop.

Rifampin

Rifampin, or rifampicin, is a semisynthetic derivative of the antibiotic rifamycin. Its primary role is the management of mycobacterial infections, and is often used in conjunction with isoniazid. It is usually given orally and is best absorbed on an empty stomach.

Ethambutol

Ethambutol is a synthetic tuberculostatic agent. Resistance of the bacillus to this drug can occur rapidly. The drug is given orally and is fairly safe. However, it may impair vision, an effect that reverses with discontinuance of the drug.

Pyrazinamide

Pyrazinamide is a synthetic analogue of nicotinamide, whose mechanism of action is not well understood. The drug is given orally in tablet form. The most common side effect is liver injury.

Other Antituberculosis Agents

The following agents are considered second-line drugs in the management of TB:

Ethionamide

Capreomycin

Viomycin

Kanamycin

Cycloserine

ANTIVIRAL AGENTS

Mode of action: The mode of action of antiviral agents is not completely known for every agent in use. However, many of the antiviral agents structurally resemble nucleoside precursors of the nucleoside building blocks of DNA strands. As an example, ribavirin resembles the nucleoside guanosine. Phosphates attach to nucleosides to form nucleotides, which assemble to form DNA strands. Each nucleotide has one of four bases, which form the pairs when DNA strands pair: adenine, guanine, cytosine and thymine. Antiviral drugs that are nucleoside analogues (e.g. ribavirin, zidovudine, didanosine, vidarabine, acyclovir, ganciclovir and zalcitabine) substitute for natural nucleosides and interrupt the process of viral gene development and replication.

Antiviral agents and their labeled use in the United States

Drug	Use*
Acyclovir (Zovirax)	HSV 1 and 2
Amantadine (Symmetrel)	Influenza A
Didanosine, ddI (Videx)	HIV
Foscarnet sodium (Foscavir)	CMV retinitis in AIDS
Ganciclovir (Cytovene)	CMV retinitis
Idoxuridine (Herplex)	HSV eye infections
Ribavirin (Virazole)	RSV respiratory infections
Rimantadine (Flumadine)	Influenza A
Vidarabine (Vira-A)	HSV encephalitis, ocular infections
Zalcitabine, ddC (Hivid)	HIV
Zidovudine, AZT (Retrovir)	HIV
* HSV = herpes simplex virus; HIV = Human Immunosuppressant virus; CMV = cytomegalovirus; RSV = respiratory syncytial virus	

**Management of
HIV Infection:**

The management of HIV infections continues to evolve. Didanosine, ddI (Videx); zalcitabine, ddC (Hivid); and zidovudine, AZT (Retrovir) are targeted directly at the AIDS virus. Foscarnet sodium and ganciclovir are used for infections associated with AIDS (i.e. cytomegalovirus retinitis). TMP-SMX and pentamidine isethionate (aerosol and parenteral formulations) are used to manage *P. carinii* pneumonia, a nonviral infection. Currently, there are over 60 potential drugs in various phases of clinical trials for use in AIDS, including vaccines, immunomodulators and antiviral agents.