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Chapter 1 : Antifungal Resistance | Fungal Diseases | CDC

Antifungal chemotherapy has improved over the past several decades, first with the introduction of amphotericin B and then with the oral antifungal agents flucytosine, ketoconazole, fluconazole, and itraconazole. More recent advances include the development of less toxic formulations of amphotericin B, liposomal amphotericin B, and amphotericin.

Figure Inhibition of protein biosynthesis by aminoglycosides. Spectinomycin is an aminocylitol antibiotic that is closely related to the aminoglycosides. It binds to a different protein in the ribosome and is bacteriostatic but not bactericidal. It is used to treat penicillin-resistant gonorrhea. Other agents that bind to 30S ribosomes are the tetracyclines Fig. These agents appear to inhibit the binding of aminoacyl-tRNA into the A site of the bacteria] ribosome. Tetracycline binding is transient, so these agents are bacteriostatic. Nonetheless, they inhibit a wide variety of bacteria, chlamydias, and mycoplasmas and are extremely useful antibiotics. Figure Structure of tetracycline showing the area critical for activity and major and minor points of modification. There are three important classes of drugs that inhibit the 50S ribosomal subunit. It inhibits peptide bond formation by binding to a peptidyltransferase enzyme on the 50S ribosome. Macrolides are large lactone ring compounds that bind to 50S ribosomes and appear to impair a peptidyltransferase reaction or translocation, or both. The most important macrolide is erythromycin, which inhibits Gram-positive species and a few Gram-negative species such as Haemophilus, Mycoplasma, Chlamydia, and Legionella. Figure Structure of chloranphenicol. New molecules such as azithromycin and clarithromycin have greater activity than erythromycin against many of these pathogens. Lincinoids, of which the most important is clindamycin, have a similar site of activity Fig. Both macrolides and lincinoids are generally bacteriostatic. Structure of erythromycin prototype or macrolide and clindamycin. Although extremely different in structure, both compounds inhibit protein synthesis by binding to 50S ribosome. Drugs that Inhibit Other Biochemical Targets Both trimethoprim and the sulfonamides interfere with folate metabolism in the bacterial cell by competitively blocking the biosynthesis of tetrahydrofolate, which acts as a carrier of one-carbon fragments and is necessary for the ultimate synthesis of DNA, RNA and bacterial cell wall proteins Fig. Unlike mammals, bacteria and protozoan parasites usually lack a transport system to take up preformed folic acid from their environment. Most of these organisms must synthesize folates, although some are capable of using exogenous thymidine, circumventing the need for folate metabolism. Figure Structure of sulfonamide and trimethoprim with sites of inhibition of folic metabolism. Sulfonamides competitively block the conversion of pteridine and p-aminobenzoic acid PABA to dihydrofolic acid by the enzyme pteridine synthetase. Sulfonamides have a greater affinity than p-aminobenzoic acid for pteridine synthetase. Trimethoprim has a tremendous affinity for bacterial dihydrofolate reductase 10, to , times higher than for the mammalian enzyme ; when bound to this enzyme, it inhibits the synthesis of tetrahydrofolate. Antibacterial Agents that Affect Mycobacteria Isoniazid is a nicotinamide derivative that inhibits mycobacteria. Its precise mode of action is not known, but it affects the synthesis of lipids, nucleic acids, and the mycolic acid of the cell walls of these species. Ethambutol is also an antimycobacterial agent whose mechanism of action is unknown. It is mycostatic, whereas isoniazid is mycocidal. The other antituberculosis drugs, rifampin and streptomycin, affect mycobacteria in the same manner that they inhibit bacteria. Pyrazinamide is a synthetic analog of nicotinamide. It is bactericidal, but its exact mechanism is unknown. Bacterial Resistance Bacteria have proved adept at developing resistance to new antimicrobial agents. There are a number of ways in which bacteria can become resistant Table Most of the early studies of bacterial resistance focused on single-step mutational events of chromosomal origin. Resistance to the early sulfonamides, for example, was the result of a single amino acid change in the enzyme pteridine synthetase that caused sulfonamides to bind less well than p-aminobenzoic acid. Similarly, a single step mutation that altered a ribosomal protein conferred resistance to streptomycin. In the late s, Japanese workers found that enteric bacteria such as Shigella dysenteriae had become resistant not only to sulfonamides but also to the tetracyclines and chloramphenicol. This resistance was due not to a chromosomal change, but rather to the presence of extrachromosomal DNA that was transmissible. This type of resistance is called plasmid-mediated resistance. Table Mechanisms of Resistance.

Resistance-conferring plasmids are present in virtually all bacteria Table For example, resistance to ampicillin appeared in Haemophilus influenzae in and in Neisseria gonorrhoeae in In the last several years, organisms such as enterococci have been shown to contain plasmids that confer resistance to drugs such as ampicillin and aminoglycosides. Table R-Plasmid-Mediated Resistance. Bacteria also contain transposons, which can insert into plasmids and also into the chromosome see Ch. Transposon-mediated resistance to most of the major antibiotics has been found in the past few years. Antimicrobial agents exert a strong selective pressure on the development of both chromosomal and plasmid-mediated resistance, as discussed below. Administration of an antibiotic destroys the susceptible bacteria in a population, but may permit resistant ones to proliferate. From an epidemiologic viewpoint, plasmid-mediated resistance is the most important type, since it is transmissible, is usually highly stable, confers resistance to many different classes of antibiotics simultaneously, and often is associated with other characteristics that enable a microorganism to colonize and invade a susceptible host. Mechanisms of Resistance The basic mechanisms by which a microorganism can resist an antimicrobial agent are 1 to alter the receptor for the drug the molecule on which it exerts its effect ; 2 to decrease the amount of drug that reaches the receptor by altering entry or increasing removal of the drug; 3 to destroy or inactivate the drug; and 4 to develop resistant metabolic pathways. Bacteria can possess one or all of these mechanisms simultaneously. In , Streptococcus pneumoniae strains resistant to penicillin G were encountered in South Africa. Plasmids were not the cause of the resistance. Penicillin-resistant S pneumoniae cells have altered penicillin-binding proteins, which bind penicillin less well. Resistance of S pneumoniae to penicillin has been increasing, and there are now relatively resistant isolates minimal inhibitory concentration [MIC], 0. Staphylococcal organisms resistant to methicillin are resistant to all penicillins, cephalosporins, and carbapenems. Enterococci are resistant to all cephalosporins because of failure to bind to the penicillin-binding proteins. Vancomycin Resistance Certain transposable genetic elements encode special cell wall-synthesizing enzymes which change the structure of the normal D-Ala-D-Ala side chain in the peptidoglycan assembly pathway. The altered side chain D-Ala-D-Lac does not bind vancomycin and allows normal peptidoglycan polymerization to occur in the presence of the drug. Depending upon the nature of the vancomycin resistance gene, high-level resistance can occur to glycopeptides. Thus far, this type of resistance has been found in enterococci but not in multi-resistant isolates of Staphylococcus aureus. Macrolide-lincomycin Resistance Macrolide-lincomycin resistance in clinical isolates of staphylococci and streptococci has been recognized for several decades. This resistance is plasmid mediated, and the resistance is encoded on transposons. Resistance results from induction of an enzyme that is normally repressed. Induction of resistance varies by species, and in most Gram-positive species erythromycin is a more effective inducer of resistance than is clindamycin. The plasmids that mediate macrolide-lincomycin resistance in streptococci and staphylococci have extensive structural similarity, indicating that these plasmids readily pass between these species. Rifampin Resistance The resistance of bacteria to rifampin is caused by an alternation of one amino acid in DNA-directed RNA polymerase, which results in reduced binding of rifampin. The degree of resistance is related to the degree to which the enzyme is changed, but does not correlate strictly with enzyme inhibition. This form of resistance occurs at a low level in any population of bacteria so that resistance develops by natural selection during a course of therapy. Naturally resistant organisms are more common among members of the Enterobacteriaceae, explaining why agents of urinary tract infections rapidly became resistant to rifampin. The resistance of Neisseria meningitides to rifampin appeared in closed military settings in which rifampin has been used for prophylaxis. Sulfonamide-trimethoprim Resistance Sulfonamide can be rendered ineffective by altered or new dihydropteroic synthetase that has poor affinity for sulfonamides and preferentially binds p-aminobenzoic acid. Sulfonamide resistance of this type can result from a point mutation or from acquisition of a plasmid that causes synthesis of the new enzyme. A most serious resistance problem is an increase in resistance to trimethoprim. This plasmid- and transposon-mediated resistance is due to production of an altered dihydrofolate reductase that has markedly reduced affinity for trimethoprim. Quinolone Resistance Resistance to quinolones can be caused by mutations in DNA gyrase subunits A or B, reduced outer membrane permeability in gram-negative cells, or to active efflux transporters found in many bacteria. The highest level of resistance to the newer fluoroquinolones is most frequently associated with chromosomal mutations,

causing amino acid substitutions in a highly conserved region in the A subunit of DNA gyrase. Multiple-mechanisms of resistance can occur in a single isolate of bacteria, leading to a higher level of resistance to many fluoroauinolones. In an initial energy-independent rapid phase, tetracycline binds to cell surface layers and passes by diffusion through the outer layers of the cell. In the second, energy-dependent phase, tetracycline crosses the cytoplasmic membrane, probably by means of a proton-motive force. The precise transport system has not been identified. Tetracycline resistance is common in both Gram-positive and Gram-negative bacteria. In most cases it is plasmid encoded and inducible; however, chromosomal, constitutive resistance is found in some organisms such as Proteus species. Many plasmid-encoded specified tetracycline resistance determinants have been found in enteric bacteria. The most common of these determinants, TetB, is also present in H influenzae. Tetracycline resistance in Staphylococcus aureus is due primarily to small multicopy plasmids; chromosomal resistance is rare. Tetracycline resistance is found on nonconjugative plasmids in Streptococcus faecalis and on the chromosome of S pneumoniae, S agalactiae group B streptococci , and oral streptococci. Clostridium species such as C difficile harbor chromosomal genes for tetracycline resistance. Basically, tetracycline resistance is due to a decrease in the levels of drug accumulation. Decreased uptake and increased efflux both probably participate. Resistant bacteria bind less tetracycline, and the tetracycline they do accumulate is lost by an energy-dependent process when they are in a drug-free milieu. Plasmid-mediated resistance to tetracyclines can be partially overcome in Gram-positive species by modifying the tetracycline nucleus. Hence, achievable concentrations of minocycline and doxycycline, in particular, will inhibit some tetracycline-resistant streptococci such as S pneumoniae, and some S aureus strains. Molecular modification has not been successful in overcoming the tetracycline resistance of members of the Enterobacteriaceae or Pseudomonas or most Bacteroides species. Tetracycline resistance is a major concern because it is located on plasmids near insertion sites, and these plasmids readily acquire other genetic information to enlarge the spectrum of resistance. The widespread use of tetracycline in animal feeds may be a factor in the extensive, worldwide resistance of members of the Enterobacteriaceae, particularly enteric species such as Salmonella, to tetracyclines and subsequently to many other drugs. Not only can tetracycline resistance move among members of the Enterobacteriaceae on plasmids, but plasmids mediating tetracycline resistance have moved between S aureus, S epidermidis, S pyogenes, S pneumoniae, and S faecalis.

Chapter 2 : antifungal chemotherapy | Spoonie Chronicles

Antifungal chemotherapy. Koldin MH, Medoff G. When the decision to treat a fungal infection is made, there are several antifungal agents available for use. AmB.

The problem Medical illustration of fluconazole-resistant Candida Antifungal drugs save lives by treating dangerous fungal infections, just like antibacterial drugs antibiotics are used to treat bacterial infections. Unfortunately, germs like bacteria and fungi can develop the ability to defeat the drugs designed to kill them. This is known as antimicrobial resistance. That means the germs are not killed and continue to grow. When this occurs with fungi that no longer respond to antifungal drugs, it is called antifungal resistance. This is especially a concern for patients with invasive infections like those caused by the fungus Candida , a yeast, which can cause serious health problems, including disability and death. More information is needed about the risk antifungal resistance poses on human health and how many people are sickened by drug-resistant fungal infections each year. CDC and its partners are working to: Better understand why and how antifungal resistance emerges. Increase awareness among medical and public health communities about these infections. Develop better methods to prevent and control drug-resistant fungal infections. Fungal infections are a serious problem in healthcare settings Invasive fungal infections can cause disability and death. Patients can get fungal infections while receiving care for something else in a healthcare facility. For example, the fungus Candida is a leading cause of healthcare-associated bloodstream infections in US hospitals. Antifungal resistance makes infections harder to treat Antifungal resistance is a particular problem with Candida infections. Some types of Candida are increasingly resistant to the first-line and second-line antifungal medications, such as fluconazole and the echinocandins anidulafungin, caspofungin, and micafungin. This is especially concerning as echinocandins are the first-line treatment for Candida glabrata, which already has high levels of resistance to fluconazole. The primary treatment option is Amphotericin B, a drug that can be toxic for patients who are already very sick. Not surprisingly, there is growing evidence to suggest that patients who have drug-resistant candidemia are less likely to survive than patients who have candidemia that can be treated by antifungal medications. Emerging antifungal resistance has been identified in species like Candida auris. However, echinocandin resistance can develop while the patient is being treated. Antifungal resistance in Aspergillus Microscopic view of Aspergillus Although the most common antifungal resistance occurs in Candida species, resistance in other types of less common fungi is also a problem. In Aspergillus a mold infections, emerging resistance to the first-line treatment threatens the effectiveness of life-saving medications. In general, Aspergillus infections are associated with high rates of death, especially in patients with weakened immune systems or underlying disease. Aspergillus is the leading cause of invasive mold infections, with an estimated , cases worldwide every year. This demonstrates that antifungal resistance in Aspergillus is likely acquired before entering the healthcare setting and is partially driven by environmental sources. For example, research shows that agricultural use of azole fungicides to treat crop diseases, which are similar to azole medications like fluconazole, can lead to the growth of resistant strains of Aspergillus in soil and other places in the environment. There is a potential for resistant infections if people with weak immune systems breathe in spores. What causes antifungal resistance? Some species of fungi are naturally resistant to treatment with certain types of antifungal medications. Other species can develop resistance over time due to improper antifungal useâ€”for example, dosages too low or treatment courses that are not long enough. This resistance could occur for a variety of reasons. For example, antibacterial drugs can reduce good and bad bacteria in the gut, which creates favorable conditions for Candida growth. What you can do Antifungal resistance is a growing threat. Everyone has a role to play in preventing fungal infections and reducing antifungal resistance. Tracking trends in antifungal resistance through the Emerging Infections Program by conducting multicenter candidemia surveillance and performing species confirmation and antifungal susceptibility testing on Candida bloodstream isolates. Using genetic sequencing and developing new laboratory tests to identify and understand specific mutations associated with antifungal resistance in Candida. Summarizing antifungal prescribing patterns across different healthcare facilities to understand opportunities

to promote appropriate use of antifungals. Healthcare facility executives and infection control staff can: Assess antifungal use as part of their antibiotic stewardship programs. Ensure adherence to guidelines for hand hygiene, prevention of catheter-associated infections, and environmental infection control. Doctors and other hospital staff can: Prescribe antifungal medications appropriately. Test for antifungal resistance for patients with invasive disease who are not improving with first-line antifungal medications. Document the dose, duration, and indication for every antifungal prescription. Participate in and lead efforts within your hospital to improve antifungal prescribing practices. Follow hand hygiene and other infection prevention and control guidelines with every patient. Be sure everyone cleans their hands before entering your room. If you have a catheter, ask each day if it is necessary. Talk to your healthcare provider about your risk for certain infections, especially if you have a weakened immune system. Learn more about using antibiotics, including when they are needed and when they are not.

Chapter 3 : PPT â€“ ANTIFUNGAL CHEMOTHERAPY PowerPoint presentation | free to view - id: 1b22d4

Aggressive chemotherapy weakens your immune system and can put you at risk for getting a fungal infection. 4 Your hospital stay matters. After your transplant, you may need to stay in the hospital for a long time.

ShareCompartir As a cancer patient, you may have received a lot of information about your treatment and your journey to recovery. Chemotherapy and radiation cause many changes in the body as they destroy cancer cells. One major change is that these treatments weaken your immune system, which can increase your chances of getting an infection, including a fungal infection. Stem cell transplant patients or those who have a blood hematologic cancer such as leukemia, lymphoma, or myeloma may have different risks for fungal infections. What you need to know about fungal infections Chemotherapy and radiation lower your white blood cell count. As you receive your cancer treatment, your white blood cell count can become very low, also known as neutropenia [PDF - 2 pages]. During this time, your body will have trouble fighting infections, including fungal infections. Some fungal infections are mild skin rashes, but others can be deadly, like fungal pneumonia. Fungal infections can look like bacterial or viral infections. The type of cancer you have can affect your risk. If you have a blood cancer like leukemia or myeloma, you may be at greater risk for getting a fungal infection than people with other types of cancer. Some types of cancer may require stronger chemotherapy medication than others, especially the blood cancers. This is sometimes known as aggressive chemotherapy. Aggressive chemotherapy weakens your immune system and can put you at risk for getting a fungal infection. After your transplant, you may need to stay in the hospital for a long time. While there, you may need to have procedures that can increase your chance of getting a fungal infection. Please see types of healthcare-associated infections for more information. Where you live geography matters. Some disease-causing fungi are more common in certain parts of the world. If you live in or visit these areas and have cancer, you may be more likely to get these infections than the general population. Top of Page Preventing fungal infections in cancer patients Fungi are difficult to avoid because they are a natural part of the environment. Fungi live outdoors in soil, on plants, trees, and other vegetation. They are also on many indoor surfaces and on your skin. However, there may be some ways for you to lower the chances of getting an infection, including a serious fungal infection. Learn about fungal infections. There are different types of fungal infections. Learning about them can help you and your healthcare provider recognize the symptoms early, which may prevent serious illness. Know if your white blood cell count is low. Having a very low white blood cell count neutropenia [PDF - 2 pages] can put you at greater risk of infection. Fungal infections often resemble other illnesses. Visiting your healthcare provider may help with faster diagnosis and may prevent serious illness. Your healthcare provider may prescribe medication to prevent fungal infections. Scientists are still learning about which patients are at highest risk and how to best prevent fungal infections. As you recover from chemotherapy and start doing your normal activities again, there may be some ways to lower the chances of getting a serious fungal infection by trying to avoid disease-causing fungi in the environment. Try to avoid areas with a lot of dust like construction or excavation sites. Stay inside during dust storms. Stay away from areas with bird and bat droppings. This includes places like chicken coops and caves. Wear gloves when handling materials such as soil, moss, or manure. Wear shoes, long pants, and a long-sleeved shirt when doing outdoor activities such as gardening, yard work, or visiting wooded areas. Click here to read more about preventing infections in cancer patients. Fungal infections in cancer patients: Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. Journal of Antimicrobial Chemotherapy ; Fungal infections and the cancer patient. European Journal of Cancer ;33, Supplement 4: Fungal infections in immunocompromised travelers. Clinical Infectious Diseases ; Annals of Hematology ; Recommendations and Reports ;

Chapter 4 : ANTIFUNGAL CHEMOTHERAPY | Free Medical Textbook

ANTIFUNGAL CHEMOTHERAPY Classes of Antifungal Drugs Specific Drugs Amphotericin B Flucytosine Ketoconazole Fluconazole Itraconazole Clotrimazole Griseofulvin Miscellaneous Agents Bibliography Fungi are an important cause of human infection.

Miscellaneous Agents Bibliography Fungi are an important cause of human infection. Some, such as Histoplasma capsulatum and Coccidioides immitis, are indigenous to selected geographic areas and are unlikely to be contracted by persons who do not live or travel there. Others, including Candida species and Cryptococcus neoformans, are more universally distributed and are seen primarily in patients with selected forms of immunosuppression or exposure to broad-spectrum antibiotics. Numerous antifungal agents have been approved, and Table provides typical dosages for many of them. However, data on efficacy, safety, and dosing, as well as on the necessary length of treatment, are much less well established than for most antibacterial agents. Reports of carefully controlled, prospective, and blinded studies are few, and problems regarding the use of most of the antifungals are complicated further by a lack of standards for susceptibility testing and blood level determinations. Dosages of commonly employed antifungal agents Classes of Antifungal Drugs Antifungal agents can be grouped into several classes. The polyenes, which include amphotericin B, nystatin, and candicidin, are characterized by the presence of a hydrophilic region and four to seven double bonds. None is absorbed well after oral administration, and all are considered to be relatively toxic when parenterally administered. Additionally, all are poorly soluble in aqueous solvents. The mechanism of action, probably through binding to fungal ergosterol a component of the fungal cell wall , allows for the formation of channels within the fungal cell membrane, with a resultant loss of vital elements. Lack of binding characterizes the occasionally resistant organism, such as Candida lusitaniae. The azoles imidazoles and triazoles include miconazole, terconazole, fluconazole ketoconazole, and econazole. Imidazoles differ from triazoles by having two rather than three nitrogen atoms in the five-member azole ring. The triazole configuration increases tissue penetration, prolongs half-life, and enhances efficacy while decreasing toxicity. Unlike polyenes, which are active primarily against systemic mycoses, azoles are also effective against dermatophytes. The mechanism of action is through inhibition of intracellular cytochrome P, which is required for demethylation of the ergosterol precursor lanosterol and is generally fungistatic. Specific Drugs Amphotericin B Amphotericin B is the standard treatment for disseminated fungal infections, against which all other agents and combinations are judged. It is active against virtually all pathogenic fungi, although occasional resistance and tolerance are encountered. Pharmacokinetically, the drug is poorly absorbed after oral administration, and it must be given intravenously for systemic infections. Its lack of absorption has made amphotericin B a useful component for bowel decontamination or treatment of candidal overgrowth syndromes in selected clinical situations. The remainder is presumably absorbed by cell membranes and is then slowly released during prolonged periods. The drug can be detected for more than 8 weeks after commonly employed dosages. Nevertheless, occasional cures of central nervous system infections, such as cryptococcal meningitis, have been effected with this drug. The solubility of amphotericin B is poor, and it is marketed with deoxycholate to ensure colloidal dispersion. This formulation cannot be mixed with other solutions, and other compounds should not be admixed. It is no longer necessary to cover the bottle with a paper bag during administration. A mm filter causes partial retention of the agent and should be avoided. Amphotericin B is administered in doses of 0. Larger doses are associated with enhanced toxicity without increased efficacy. If the agent is tolerated, the dose is increased to up to 0. In most cases, the maximum daily dose is 50 mg. Generally, dose escalation is at a rate of 0. Generally, dosage modification for renal dysfunction is not needed. Although anecdotal reports of successful infusions lasting fewer than 4 to 6 hours have been published, occasionally severe adverse reactions, including cardiac arrest, have occurred with more rapid administration. Alternatively, the drug may be administered on alternate days with double the usual daily dose. This is especially useful for outpatients. The length of treatment depends on the disease. Under many circumstances, it may be necessary to render therapy for several months. Dosage in these situations is

generally 0. Although most cases of this disease are now treated with oral antifungals, selected cases may still require this form of management. In unusual circumstances, amphotericin B can be administered by alternative routes. As an example, selected cases of C. Intraarticular regimens of less than 15 mg per dose have been employed for selected fungal arthritides. Adverse reactions to amphotericin B are common and may be severe. This compound is considered to be a rather toxic agent and should be administered by persons comfortable with its use. Chills, fever, and hypotension may be encountered, especially early in therapy. Such problems usually subside as medication is continued. Concurrent administration of hydrocortisone within the bottle may be beneficial. Premedication with 1 g of acetaminophen or salicylic acid, 30 to 45 minutes before infusion of amphotericin, is also useful. There is often evidence of tubular disease, and proximal renal tubular acidosis may be observed. Renal vasoconstriction and abnormalities of glomerular filtration may also be important. Maintenance of adequate fluid and sodium loading may prove protective. Significant decreases in serum potassium may also be observed with amphotericin B. Profound hypokalemia may occur when amphotericin B is given with other drugs that may also cause this effect. Anemia is routinely observed and is thought to be secondary to either bone marrow suppression or inhibition of erythropoietin production. Thrombocytopenia or neutropenia rarely occurs, and aplastic anemia has not been reported. Adult respiratory distress syndrome has been reported when amphotericin B is used with granulocyte transfusion. The etiology may be related to lysis of aggregates of transfused granulocytes that are trapped in the pulmonary parenchyma. The recommended dose is 1 to 5 mL to mg four times daily for a minimum of 2 weeks. Table summarizes comparative data. No one is distinctly better than the others, but any one may be the therapy of choice for invasive infections with Aspergillus species; use for other fungal infections is uncertain. All have the capacity to cause acute severe reactions, similar to those seen with amphotericin B, and should be administered with a test dose and dose escalation. Fortunately, many of the patients who receive the liposomal preparations will already have had experience of amphotericin B and are less likely to have acute adverse reactions. The liposomal preparations have also been recommended for use in patients with nephrotoxicity from amphotericin B. Expense precludes their routine use, and it is uncertain whether they are beneficial for most fungal infections. Liposomal amphotericin B preparations Flucytosine Flucytosine is a fluorinated pyrimidine related to fluorouracil; it is useful for selected candidal and cryptococcal infections. Its mechanism of action is incompletely understood but is probably related to its conversion to fluorouracil within the fungal cell. It is well absorbed from the gastrointestinal tract and penetrates into most tissues. Renal insufficiency as may be seen with concurrent use of amphotericin B may result in potentially toxic levels of flucytosine unless the dosage is regulated. The compound is supplied in either mg or mg tablets. Flucytosine is relatively safe and usually well tolerated. Bone marrow depression may occur in the presence of renal dysfunction. The cause of this depression is not completely known but appears to be related to the metabolism of the parent compound to 5-fluorouracil. The presence of renal impairment necessitates dosage reduction. One method is to give a dose No nomogram is satisfactory for the anuric patient; however, blood levels can be measured by high-pressure liquid or gas chromatography. Flucytosine is cleared by hemodialysis or peritoneal dialysis, and a single dose of Nausea, diarrhea, and vomiting are occasionally seen but are infrequently severe and rarely necessitate discontinuation of therapy. The use of flucytosine as monotherapy is indicated only in selected patients with candiduria, in whom rapid achievement of high levels may preclude emergence of resistance. It is most frequently employed in combination with amphotericin B for serious cryptococcal infections. For cryptococcal meningitis in the HIV-negative patient, use of the two agents reduces the dose of amphotericin B from 0. In the presence of HIV infection, cryptococcal meningitis is not curable, and the addition of flucytosine may intensify anemia and other adverse reactions. However, some authorities recommend its use for the first 2 weeks of treatment. In a recent study of flucytosine plus fluconazole vs. Other data suggest that the combination may also be useful for the therapy of serious candidal infections. Flucytosine is not effective against infections caused by species of Aspergillus or Mucor. Ketoconazole Ketoconazole is an oral preparation active in vitro against Candida, Coccidioides, Blastomyces, Histoplasma, and most dermatophytes. The usual daily dose is to mg. Ketoconazole is extensively metabolized, and the dosage need not be altered in renal failure. Levels in the cerebrospinal fluid and urine are low, and the drug should not be considered for use

in infections at these sites. Orally administered ketoconazole requires gastric acid for absorption, and this product must be given with food. In achlorhydric patients, administration with 8 oz of orange juice, cola, or ginger ale will improve absorption. Ketoconazole has been successfully used to treat candidal infections involving mucous membranes, including esophagitis. It is inferior to fluconazole for esophageal candidiasis in AIDS patients, but its early use may prove initially less expensive. Outcomes in the treatment of thrush in patients with HIV infection are similar for the two agents. Ketoconazole has also been reported useful in the management of coccidioidomycosis, histoplasmosis, cryptococcal infection nonmeningeal , sporotrichosis, and blastomycosis. Chronic relapsing forms of coccidioidomycosis and paracoccidioidomycosis appear to be stabilized with low doses of this agent given for up to 1 year. Side effects of ketoconazole are minor, although hepatitis may occur and should be considered in patients on long-term, high-dose therapy.

Chapter 5 : Antifungal chemotherapy.

**Binds to membrane sterols, preferentially to the primary fungal cell membrane sterol, ergosterol *Disrupts osmotic integrity of the fungal membrane by forming pores in the cell membrane thus resulting in leakage of intracellular potassium, magnesium, sugars, and metabolites leading to cellular death.*

Enzymes related to cell division Intermediate metabolism Bacteria have short generation timesâ€”fast de novo evolution of resistance Resistance genes exist in producers of antibioticsâ€”can spread to pathogenic bacteria by gene transfer We will start our exploration of chemotherapeutic agents with those that act on bacteria, which are the most common class of pathogens. Most antibacterial drugs are antibiotics, that is, natural compounds isolated from other microbes, or derivatives thereof. While penicillin was famously isolated from a mold, most antibioticsâ€”for example, tetracyclins, aminoglycosides like streptomycin, and macrolides like erythromycinâ€”are actually produced by Streptomyces species or related soil bacteria. Since these producer bacteria must be resistant to their own poisons, it follows that mechanisms and genes for bacterial resistance must exist for any of these natural antibiotics. Such genes may migrate to clinical pathogens and spread among them if we apply the proper selection pressure through the medical use and misuse of those antibiotics. Some antibacterial compounds are indeed fully synthetic; we have already seen sulfonamides and trimethoprim as examples. With both natural and synthetic antibiotics, an important strategy to prevent, or at least delay, the emergence of resistance is combination therapy. When several drugs are combined that each alone are able to kill the pathogen, and each of which addresses a different target, the pathogen would have to simultaneously modify all targets in order to survive. With increasing number of agents simultaneously applied, this rapidly becomes unlikely. Given the right selection conditions, multiple resistance transposons may wind up on a single plasmid molecule. Such a plasmid will then confer resistance to several unrelated antibiotics all at once, and the use of any single one of these drugs will cause this multiple resistance to spread further. The first such multiresistance plasmids were observed in the late s, only about ten years after the start of the antibiotic era. While these cell walls may protect the bacteria from antibiotics, they also provide targets for chemotherapy. Note that some bacteriaâ€”mycoplasmas, and the vegetative forms of rickettsias and chlamydiasâ€”have no cell wall at all and therefore are not susceptible to the agents discussed in this section. Gram-negative bacteria have a comparatively thin peptidoglycan layer blue that is surrounded and protected by an outer membrane. The outer leaflet of this lipid membrane consists mostly of lipopolysaccharide LPS, green , which is also known as endotoxin. Multidrug resistance MDR proteins that extrude antibiotics from the cell may be located in the cytoplasmic membrane alone or span both membranes. The lack of an outer membrane makes them more amenable to penicillin see slide 1. The mycolic acids act as anchors for a particularly thick, wax-like and impenetrable outer membrane. Because of their sturdy cell wall, 74 mycobacteria have always been among the most difficult microbes to treatâ€”although decades of selection have bred some real champions of resistance among the Gram-positives and Gram-negatives also. It inhibits the synthesis of mycolic acids, the long-chain fatty acids that are characteristic and essential components of the mycobacterial cell wall. This inhibition arises in a rather unique manner. The adduct inhibits InhA, an enoyl-CoA reductase involved in mycolic acid synthesis. Inhibitors of various enzymes in the murein synthesis pathway are active against member species of all three classes. The synthetic pathway involves the following stages: Phosphoenolpyruvate PEP supplies a lactate residue Lac that is attached to N-acetylglucosamine, which yields N-acetyl-muramic acid 1. Onto the latter, a pentapeptide is built in a series of ATP-activated reactions. The free end of this peptide contains two d-alanine residues that are supplied by alanine racemase 2 and d-alanine ligase 3. This nascent building block is transferred to the lipid carrier undecaprenol phosphate 4 and subsequently extended by another molecule of N-acetylglucosamine and five glycine residues. The completed precursor molecule, named lipid II, is flipped across the cytoplasmic membrane 5. The glycopeptide moiety is transferred from lipid II to a growing murein strand in the transglycosylase reaction 6. The final transpeptidase reaction 7 cross-links the new subunit to an adjacent murein strand, releasing the terminal d-alanine residue. The transglycosylase and transpeptidase activities are both located on the same enzyme protein, variously referred to as muramyl-transpeptidase or

penicillin-binding protein PBP. Most bacterial species have several PBP subtypes that may differ in susceptibility to penicillins and related antibiotics. Considering its structure, it may not surprise you to hear that the reaction with the target enzyme is covalent and involves the thiol group of a cysteine residue [88]. For uptake across the cytoplasmic membrane, fosfomycin piggybacks on a transport protein that mediates uptake of glycerophosphate. This transporter is not essential for the bacterial cell; therefore, mutations that inactivate the transporter tend to cause rapid development of resistance under therapy. Fosfomycin can therefore only be used in combination with other antibiotics that are less prone to rapid evolution of resistance. It is used mostly against mycobacterial infections, though active in principle against other types of bacteria also. Interestingly, d-cycloserine is also a partial agonist at the sole glycine-specific subunit of the NMDA-type glutamate receptor see section 6. As such, it has been tried therapeutically in various neurological and psychiatric conditions [89]. The class comprises penicillins, cephalosporins and a few other variants. The enzyme is unable to free itself from the covalent modification and remains irreversibly inactivated. These enzymes fall into two major functional classes. The Dmitrienko group in the UW chemistry department is working on the synthesis of such inhibitors [90]. To counter this resistance mechanism, semisynthetic drugs such as methicillin were developed, which escape cleavage by the enzyme through steric obstruction. This obstruction also renders such drugs about ten times less active against the muramyl-transpeptidase target, but because of the generally very high therapeutic index of the penicillins, this does not compromise their clinical utility. Through horizontal gene transfer from another staphylococcal species, these strains have acquired a peculiar variant of the transpeptidase that no longer binds methicillin and related compounds. Ampicillin was the first penicillin derivative with useful activity against Gram-negatives such as Escherichia coli, and ticarcillin the first one to be active against Pseudomonas. Imipenem lacks the sulfur atom in the ring and is therefore referred to as a carbapenem. Natural cephalosporins are produced by fungal species that belong to the genus Cephalosporium. Cephalosporins differ from the penicillins in the structure of the central nucleus. The cephalosporin nucleus is amenable to semisynthetic derivatization and variation in two positions. Cefotaxime has broad activity against both Gram-negative and Gram-positive bacteria; the more recently introduced ceftobiprole has the added bonus of being active against MRSA. Moxalactam is an interesting cephalosporin analog with very good activity against some difficult Gram-negative pathogens, but it was retired due to interference with the plasmatic blood coagulation cascade. It has strong activity against Pseudomonas species. However, with clavulanic acid, this initial reaction is followed by a sequence of reactions that traps a second serine residue in the active site. The modification of serine means that the active site remains blocked even after serine 70 is freed by hydrolysis. Reaction scheme simplified after [91]. However, it does so in a very different and rather unusual manner: Instead of binding to the enzyme, the antibiotic binds to the terminal d-alanine dipeptide on one of the two substrates. Vancomycin is active on Gram-positives but not Gram-negatives. The structure rendered from 1gac. The antibiotic is shown in stick representation, while the peptide moiety of lipid II is shown as spheres. The uppermost part of the peptide consists of the two linked d-alanine residues. Compared to most other antibiotics, resistance took a long time to develop, which may be related to its unusual mode of action that precludes simple point mutations as a resistance mechanism. However, vancomycin-resistant staphylococci and enterococci have emerged and are spreading. Again through horizontal gene transfer, these resistant bacteria have acquired an enzyme that replaces the terminal d-alanine residue with d-lactate. This removes one hydrogen atom and breaks one of the hydrogen bonds between vancomycin and the substrate, which substantially lowers affinity. Interestingly, high-affinity binding to the d-alanineâ€”d-lactate substrate can be restored by introducing an amidine group into the vancomycin molecule opposite the ester oxygen in the substrate [92]. Reportedly, the amidine derivative inhibits both vancomycin-sensitive and -resistant bacteria. If a practical and cost-effective method can be found to produce this derivative, it should be of great clinical value. Schemes redrawn after reference [92]. The letter R denotes several different substituents that have been omitted here for simplicity.

Chapter 6 : Chemotherapy of infectious diseases

Antifungal Chemotherapy The treatment of disease by the use of chemical substances, especially the treatment of fungal diseases by cytotoxic and other drugs. 3. Chemotherapy Types 1.

We were anticipating and preparing for months for the trip, and it was over so fast, but not without plenty of pain and suffering. The beginning of my mold treatment has been tough. A web of an unforgiving, often invisible disease called mycotoxicosis. At least I am now on the right road. Before I was lost, just barely getting through my days, completely in the dark as to why I was so very sick. I wondered why I kept getting worse despite so many treatments and therapies over the years. I agonized over the family and friends I lost due to them doubting, or not understanding why I was always sick, why it was always one thing or another. My family had lived in many water damaged homes throughout my life that were infested with mold, including black mold. Most of it was invisible, and we had no idea of the dangers of mold. My progressive symptoms over the years lead me to dozens and dozens of specialists, but none could figure out what was wrong with me. Some would say it was just a flu a never ending flu? Many were just puzzled as to what was causing all my symptoms including debilitating migraines, chronic fatigue, gastrointestinal problems, body wide muscle and joint pain, vertigo, cognitive dysfunction, chronic severe allergies, breathing problems, ringing in my ears, insomnia, anxiety, heat sensitivity, low grade fevers and many more. When I was 13 I had a benign tumor in my breast and stayed about a week in the hospital when they had it removed. At that same time my dad was in the hospital fighting several types of cancer, including prostate cancer, and bone cancer. He later died from brain cancer. Then my mother got cervical cancer and thank god, she beat it. It seemed everyone in our house seemed to be terribly ill. Anemia, chronic leukopenia, fibrocystic breast disease, dysmenorrhea, and chronic infections plagued my teen years, and continue on today. At 23 I got the long awaited fibromyalgia diagnosis, and then later chronic fatigue syndrome also long overdue. At 24 I found out I had hypoxia, which I believe I had for many years prior, but no dr had thought to test for oxygen levels before. There were a few instances growing up where I suddenly stopped breathing, and my parents told me I would turn blue. I felt I lost a big chunk of my brain that summer and I will never forget the bizarre an terrifying experience I had on the evening of July, 26th, in Bethlehem you can read about it here. I have damage to my prefrontal cortex, neurotransmitter, brain stem, and severe hypothalamus damage, which can explain my autonomic dysfunction. At 25 I began suffered from painful chronic liver and kidney infections would come and go. After years of severe pelvic pain I was diagnosed with interstitial cystitis, and like usual the pain meds I was given did absolutely nothing for my pain. Throughout my life I battled several addictions, OCD, and behavioral issues, not knowing there were dangerous toxins poisoning my brain. I was diagnosed with thyroid disease and most recently POTS, a severe form of dysautonomia. There have been times I stopped breathing once I was out. This happens when my blood pressure drops dramatically and fails to pump up enough blood to my heart and brain, which can result in fainting to immediately raise the blood back to the vital organs. So terrifying until I knew what was wrong. I became more ill, and more disabled as time went on, and I had to quit school, a job that I loved, and any bit of a social life I had left was taken away from me. I got a misdiagnosis of chronic neurological lyme disease, and was taking several antibiotics for over 6 months, only to get much worse. Still, the antibiotics destroyed my digestive system as it killed the little bit of good bacteria I had in my gut. Jan, 6, , after weeks of getting very little sleep or food in due to searing pain in my side, I ended up in the hospital with a mass in my large intestines. When I was discharged from the hospital was in severe pain, vomiting, and weaker than ever before. The feeling of desperation now burning like a wildfire. I started twitching uncontrollably at night, and my restless legs and body got more painful. I was never able to sleep more than a few hours at night and when I was able to sleep I woke up many times from my pain, coughing, or twitching. I needed assistance going to the bathroom, showering, getting dressed. It was so hard to accept that I had NO control of my body, and whatever was taking the life from me was acting faster as time moved on. I watched myself deteriorate before my eyes, and there was nothing I could do about it. And thank goodness she did. Little did I know my home that I spent so much time in was killing me slowly. The

levels of the toxic molds were so high, my dr. The hardest to part with were the books my dad had written, and published for me when I was 4, and knowing I will never see them again still tears me up a great deal inside. This was incredibly hard and stressful time for me, and our family. The move was extremely challenging, and exhausting in my physical state. After we moved I was still very sick, but it seemed I was getting a little better in the following months. However, I still had numerous symptoms, and several months later new symptoms emerged, and I slipped back into the sicker-than-sick state but this time I was worse than before. I was coughing up blood, and I felt as if my body was constantly running a marathon. False negatives could be another reason mycotoxicosis goes so undiagnosed, in addition to the wildly inadequate lack of knowledge of environmental illness, let alone long-term mold illness. The environmental physician I met with at the center explained to me that mycotoxins are a serious, highly unrecognized, detrimental health crisis. It takes years to rid the body of mycotoxins, and some are harder to kill than others. The problem is the body has such a hard time differentiating itself from the mycotoxins at a cellular level. The longer the exposure, the longer the treatment and recovery process will take. In some cases, usually after long-term exposure, the damage to the organs and cells may result in death, and even aggressive treatment will be ineffective, as it is already too late. This will make it even more of a challenge in my treatment. To start the treatment process, I have to reduce my total load. This so called total load refers to toxicity, infections, allergies, and stress. Once I become more stable I can move on to stage 2 which for me will be an intensive in-patient 4 week long treatment program where we will continue immunotherapy I got too sick to complete the antigen injections during my stay at the center , and start a more aggressive detox protocol which will include daily oxygen therapy, IV therapy, hyperthermia therapy, infrared massage, and physical therapy. Not entirely sure what stage 3 consists of yet, but one thing I do now is it will be an uphill battle from here. I will get worse before I get better due to herxheimer reactions die-off from toxins , especially from the sauna, but hyperthermia therapy is the only proven way to pull mycotoxins from the brain. I am hopeful that this road will eventually lead me to the life I had always dreamed of having, a life worth living. I count my lucky stars I am here today. It was a total of over 26 years I was exposed to deadly mycotoxins. I will continue to fight until I reclaim my body as MY body, not the body that is a slave to this dreadful disease. As one of my dr.

Chapter 7 : Antifungal-Chemotherapy Drug Interaction Update - MPR

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Chapter 8 : Cancer Patients and Fungal Infections| Fungal Diseases | CDC

The labeling update under Warnings and Precautions states that concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and.

Chapter 9 : Magic mouthwash: Effective for chemotherapy mouth sores? - Mayo Clinic

Antifungal Agents and Resistance Compared with antibacterial agents, relatively few antimicrobials are available for treatment of fungal infections. Many substances with antifungal activity have proved either to be unstable, to be toxic to humans, or to have undesirable pharmacologic characteristics, such as poor diffusion into tissues.