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Drug Resistant Tuberculosis 1

Running head: DRUG RESISTANT TUBERCULOSIS: HARD TO BEAT

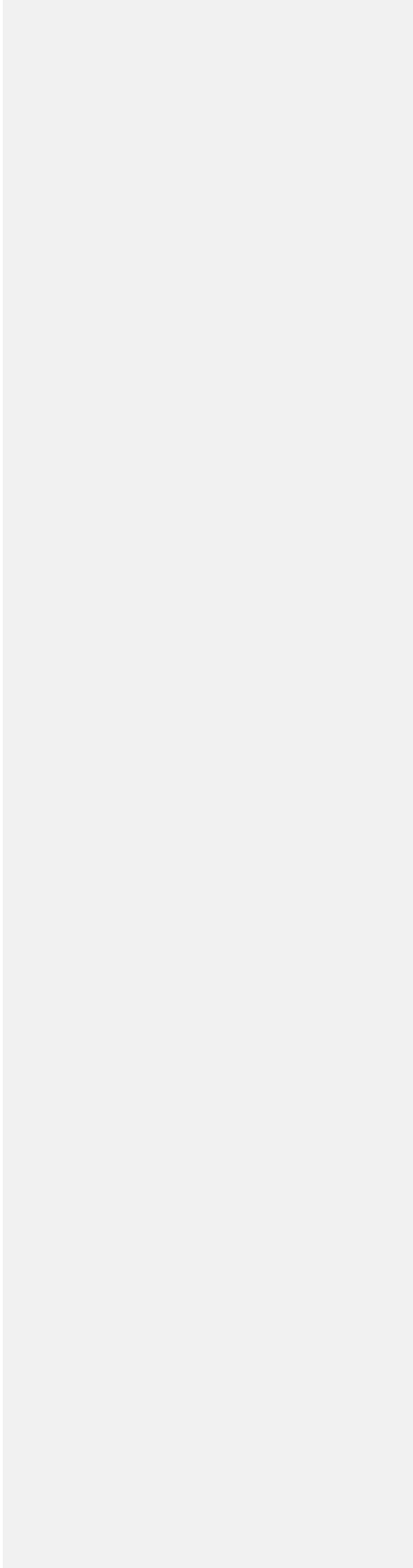
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Drug Resistant Tuberculosis:

A Hard Infection to Beat

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CSU Channel Islands



Drug Resistant Tuberculosis: A Hard Infection to Beat

Usually a global threat invokes thoughts of nuclear weapons and wars. But, as the most common cause of death by infection, tuberculosis is a global threat (Shi, Itagaki, & Sugawara, 2007) Of the 1.86 billion people in the world that have tuberculosis, about 8 million develop active tuberculosis a year and a little fewer than 2 million die. (Khan, Chundru, Rodrigues, Pokharel, & Kansakar, 2007) Drug resistance is making the battle against tuberculosis a hard one. Iew, Pai, Oxlade, and Martin consider resistance to drugs for tuberculosis is one of the "most important threats to global tuberculosis control". (2008) Factors involved in the fight against drug resistant tuberculosis are treatment obstacles and drug resistance with a notable tie between tuberculosis and HIV co-infection. Treatment obstacles include flawed drug regimens, poor drug quality, and unreliable drug supply. Causes of drug resistance includes patient noncompliance and poor infection control. This paper focuses on these factors.

great topic!

Introduction

Tuberculosis is caused by the pathogen *Mycobacterium tuberculosis*. The Mayo Foundation for Medical Education and Research [Mayo Clinic] lists many signs and symptoms for pulmonary tuberculosis including: a persistent cough, weight loss, fatigue, fever, night sweats, chills, loss of appetite, and pain associated with breathing. (2008) According to Carol Porth, the symptoms attributed to tuberculosis are not caused directly by the bacteria but instead the body's hypersensitivity to it. As the body tries to kill off the bacteria, the macrophages release large amounts of lytic enzymes which damage the surrounding tissues. (2007) Pulmonary tuberculosis in the lungs is the most common type of tuberculosis, but it can also affect other parts of the body resulting in a multitude of signs and symptoms depending on the location. (Mayo Clinic, 2008) This paper will be referring solely to pulmonary tuberculosis and it will be referred to by its common name.

People respond differently to tuberculosis. Occasionally, the body is able to fight it off but it usually stays in the body in an inactive form. (Mayo Clinic, 2008) Regrettably in some it becomes active resulting in what is called active disease (AD) status- the form of the disease that can be transmitted. (Amaral et al., 2007) According to Amaral et al., only 5-10% of people who are infected with TB progress to AD status (usually after age 60) but being impoverished, starvation, un-cleanliness, HIV, and war can cause AD status to occur much faster. (2007) This

progression of the disease in the poor is a contributor to the transmission of the disease along with inadequate tools to manage it, as will be discussed later.

People with HIV are the most at risk, and their prognosis is very grim. The National Aids Control Organization (NACO) estimates that over 60% of AIDS patients die of tuberculosis. (Khan et al., 2007) With tuberculosis HIV turns into AIDS much faster and the life of the patient is usually cut short. (National AIDS Control Organisation [NACO], 2007) HIV co-infection is a big factor in the fight against TB. Its impact can be seen in many of the top ics concerning TB.

Comment [CSU1]: Wow!

Comment [CSU2]: Great statement.

Treatment

There are many problems associated with treating *m. tuberculosis*. Tuberculosis is very resilient: it can lay dormant for a long time, it grows slowly and resistance develops easily. *M. tuberculosis* is more resilient than other bacteria, partly because it has a capsule and it can also hide in lesions for a long time before it starts to grow. (Porth, 2007) Because *m. tuberculosis* grows slowly, treatment must be given for long periods of time (between 6 months and two years). (Howland, Mycek, Harvey, & Champe, 2006) As will be demonstrated later, long treatment plans produce a lower rate of patient compliance, a major contributor to resistance in TB. Another problem with treatment is that patients who have been previously treated and those who don't take their medications properly develop resistant strains easily. (Howland et al., 2006) Resistance, as stated before, is a major player in the battle against TB.

Another problem associated with treating TB is the lack of new drugs. Since 1968, there have been no new drugs discovered to fight tuberculosis, which is contributing to the increase in drug resistant strains. (Kahn et al., 2007) The Global Alliance for TB Drug Development is currently researching 5 compounds that would combat drug-resistant tuberculosis. (Khan et al., 2007) Two of them are in clinical trials right now (Global Alliance for TB Drug Development [TB Alliance], 2008). But, it is estimated that a perfect XDR-TB treatment will not be ready until at least 2012. (Khan, et al., 2007) This lack of drugs gives doctors very little choice in treatment options.

Sadly drugs for TB are not easy to come by. Amaral et al. claims that creation of new anti-TB drugs is harder than those of other bacterial infections. (2007) Two reasons for this is that the drugs must be able to get into the cells where the bacterium is living, and also be potent enough to destroy it without being toxic to the patient.

To prevent drug resistance, multiple drugs are used. According to Howland et al., strains that are resistant to a certain drug are caused by treatment with only that one drug so therapies with more than one drug are recommended to delay or prevent these strains. (2006) Patient compliance is always a problem with drug resistance. Unfortunately drug treatment is expected to be continued for a long period after signs of the disease are gone, but compliance is low if patients are expected to take several drugs for more than 6 months. (Howland et al., 2006) Drug therapies must be geared towards patient compliance and effectiveness. So, according to Howland et al., the best "short-course" chemotherapy for tuberculosis is 2 months of INH, RIF, and pyrazinamide, followed by INH and RIF for 4 months, ethambutol and/or streptomycin are sometimes used with them. (2006) Once again, this treatment will only work if the person is not resistant to any of the drugs.

Types of Drug Resistance

Drug resistance is a major factor in the fight against tuberculosis and it is becoming more prevalent. Anti-tuberculosis drug resistance in the world is a report with data from a survey that was done between 2002 and 2006. It was the largest survey ever done with regards to drug-resistant tuberculosis with 90,000 tuberculosis patients from 81 countries and it found the highest rates ever reported. ("Survey Finds Highest Rates of Drug-Resistant TB to Date", 2008) It found extensively drug-resistant tuberculosis in 45 countries and that in some countries, there was two times the amount of multidrug-resistant tuberculosis patients that were co-infected with HIV in comparison with the ones that did not have HIV. ("Survey Finds Highest Rates of Drug-Resistant TB to Date", 2008) After analyzing the data from this report, the World Health Organization estimated that there were almost 500,000 new cases of multidrug-resistant tuberculosis or about 5% of the new cases of tuberculosis each year. In some areas, it was as high as 22.3% of all new cases. ("Survey Finds Highest Rates of Drug-Resistant TB to Date", 2008) These numbers are a good indication that tuberculosis is not under control by any means and that drug resistance is a problem.

There are three different levels of drug resistance: drug-resistant tuberculosis (OR-TB), multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant tuberculosis (XDR-TB). Drug-resistant tuberculosis is defined as being resistant to any anti-tuberculosis drug. (Cobelens et al., 2008) DR-TB is more problematic than non-drug resistant TB. It causes higher mortality rates and treatment is more expensive, has more side-effects, and goes for longer duration. (Lew et al., 2008) Even more serious is MDR-TB.

Multidrug-resistant TB (MDR-TB) is more serious than DR-TB but less than XDR-TB. To be considered MDR-TB, the patient must at least be resistant to INH and RIF, the two most commonly used drugs. (Lew, et al., 2008) MDR-TB is not easily cured. Strains that are multi-drug resistant do not respond well to the current drugs that are available and when treated with second-line drugs, MDR-TB is only cured 65-75% of the time. (Amaral et al., 2007; Cobelens et al., 2008) MDR-TB co-infected with HIV is especially bad. When co-infected with HIV, death occurs almost 100% of the time. (Amaral et al., 2007) Unfortunately, MDR-TB is not the worst.

Extensively drug-resistant (XDR-TB) is tremendously life-threatening and is even worse than MDR-TB. The term extensively drug-resistant tuberculosis was first used in 2006: The Global XDR-TB Taskforce convened by the WHO in October 2006 defined XDR-TB as a form of TB resistant not only to rifampicin and isoniazid, but also to certain second-line drugs (at least one fluoroquinolone, and one of the three injectable drugs kanamycin, amikacin or capreomycin) or as resistant to at least two main first-line drugs and additionally to three or more of the six classes of second-line drugs." (Khan et al., 2007 p. 180) As will be shown later, many places are not set up to test for XDR-TB, so it is often misdiagnosed. A report in 2006 gave an estimate that 7% of MDR-TB samples in the world were in fact XDR-TB or about 0.4% of the TB worldwide. (Khan et al., 2007) In comparison to MDR-TB, XDR-TB has much higher mortality rates, especially if the patient is also HIV positive. (Cobelens et al., 2008) XDR-TB is very serious because it is almost not treatable.

Transmission

Poor infection control is a contributor to the development of drug resistant tuberculosis. Unfortunately, TB is passed very easily. As stated previously, people with active TB are the only ones that are contagious. Their sputum is inhaled by others while they are yelling or coughing, traveling to the alveolar sacs of the newly infected person where they are then phagocytosed by macrophages in the sacs. (Amaral et al., 2007) The bacteria may stay there, or may break out of the macrophages to produce AD status in the newly infected person. (Amaral et al., 2007)

If untreated, each person who has active pulmonary tuberculosis can infect between 10 and 15 people each year. (Khan et al., 2007) In order to lower the spread of drug-resistant tuberculosis, transmission must be prevented. (Cobelens et al., 2008) In some areas, that is not an easy task. In Africa, the number of active TB patients rises about 4% a year. (Kahn et al., 2007) Data suggests that drug-resistant tuberculosis is on the rise because of the high prevalence of HIV in the area. This is mostly because the number of CD4 lymphocytes shrinks

Comment [CSU3]: Not sure I completely agree!

Comment [CSU4]: Should be clear

Comment [CSU5]: Good!

as HIV advances, and the immune system cannot fight off the tuberculosis infection, resulting in latent tuberculosis being activated by HIV. (Kahn et al., 2007; NACO, 2007) Active TB is also spread much more easily between people who are immunosuppressed.

Although transmission of MDRTB is more common in healthcare settings with a high number of HIV infected patients, it can also be passed in other settings. Unfortunately, little is known about the management of tuberculosis in the community and homes. Most places do not have the money to prevent transmission and people are often just sent home with their drugs. (Cobelens et al., 2008) Some use preventative therapy of family members with anti-TB drugs. Cobetens et al. states that because there have been minimal studies done for preventive therapies there is no guaranteed prevention method. (2008) Some drug combinations used for TB patients have their own risks, so it is not always advantageous to give them as preventative medicine. (Cobetens et al., 2008) This just goes to show that even if countries implemented preventative medicine to family members, TB could still be spread to others in the community.

Reasons Behind Drug Resistance

There are many reasons for drug resistance in tuberculosis. Drug-resistant tuberculosis is caused by inadequate tuberculosis control in the form of avoidable transmission, flawed therapy courses, poor quality drugs, and poor case management. (Cobelens et al., 2008) According to Cobetens et al., completing a treatment plan for DR-TB is essential for it to be successful but, treatment plans for DR-TB are long and there are often complications. (2008) Many doctors find it is hard to get patients to follow their treatments through until the end. Many patients do not take all of their medications because it causes so many undesirable side-effects, and this non-compliance of patients is the way most antibiotics have become resistant. (Amaral et al., 2007) To prevent non-compliance, the World Health Organization (WHO) recommends using Directly Observed Treatment (DOT). (2008). This means that someone supervises the taking of medications every day. Howland et al. agrees that having someone supervise is a good way to make sure patients are taking all of their medications. (2006) Regrettably, even if patients do take all of their medication, they may not be given the right medication in the first place.

Comment [CSU6]: Good. This is a very important strategy.

Comment [CSU7]: Very true.

In a lot of places, people are not being diagnosed properly. As of June 2008, it was estimated that only 2% of MDR-TB cases were being diagnosed, resulting in improper treatment. (Cobelens et al., 2008; "New Rapid Tests for Drug Resistant TB for Developing Countries", 2008) This leads to greater drug resistance. If MDR-TB is treated incorrectly it could turn into XDR-TB. (Cobelens et al., 2008)

Comment [CSU8]: No need.

MDR-TB wasn't always around. When MDR-TB first started to show up, most places were not set up to test for it. (Amaral et al., 2007) Doctors treated TB the same way they always had. Most treatment plans were with INH and RIF and increased patients on these two drugs increased the incidence of MDR-TB. (Amaral et al., 2007) Kahn et al., maintains that even in developing countries today, most testing programs for drug resistance are inadequate: they use a smear to diagnose the patient, and all are given the same drug regimen with INH and RIF. (2007) The smear test only confirms TB, it does not indicate what kind. Patients whose sputum fails to be negative for the bacterium after 2 or 3 months get tested for resistance and they are usually only tested for resistance to INH and RIF. (Kahn et al., 2007) Up to this point, they would have been receiving improper treatment for 2 or 3 months. If the tests show resistance to INH and RIF, more tests may be done, but usually not for every antibiotic which leads to many patients who are treated with the wrong medicine for their particular strain of tuberculosis, creating even more resistant strains and a longer transmission period. (Kahn et al., 2007) This is bad news for patients. Sometimes, especially if they have HIV, patients will die before getting confirmation of their resistant status and before receiving proper treatment. ("New Rapid Tests for Drug Resistant TB for Developing Countries", 2008) Even if diagnosed with DR-TB, treatment with second-line drugs is hard to get for many patients. In prosperous countries, the availability of the drugs is limited and in poorer countries, they are simply not available. (Cobelens et al., 2008) The unavailability of drugs and poor diagnostics is a huge problem.

Fortunately, there are many programs in place now that are trying to help. In June 2008, the World Health Organization, the Stop TB Partnership, UNITAID, and FIND (Foundation for Innovative New Diagnostics) announced new initiatives to increase the amount of people being treated for MDR-TB by 15% that will result in a faster diagnosis for people with MDR-TB and increase the drug supply for them. ("New Rapid Tests for Drug Resistant TB for Developing Countries", 2008) The initiatives should cut down diagnosis time to 2 days by introducing a new way to diagnose MDR-TB called a line-probe assay. ("New Rapid Tests for Drug Resistant TB for Developing Countries",

2008) Diagnosing people faster will get people on the proper drug regimen before they can become more resistant. The goal is to get 16 countries to use these tests within the next 4 years. ("New Rapid Tests for Drug Resistant TB for Developing Countries", 2008) Another part of the initiatives will lower the price of second-line anti-tuberculosis drugs up to 20%. ("New Rapid Tests for Drug Resistant TB for Developing Countries", 2008) This will increase the drug supply for patients with MDR-TB.

Hopefully, new cures will be discovered soon and programs like this will cut down on the amount of drug resistance in the world. Until then, tuberculosis with all of its drug resistant forms will remain a global threat. Drug resistance and treatment programs will remain a concern, along with the high prevalence of HIV co-infection.

References

- Amaral, L., Martins, M., & Viveiros, M. (2007, September). Phenothiazines as Anti-Multi-Drug Resistant Tubercular Agents. *Infectious Disorders- Drug Targets*, 7(3), 257-265. Retrieved October 15, 2008, doi:NO_DOI
- Cobelens, F., Høidal, E., Kimerling, M., Mitnick, C., Podewils, L., Ramachandran, R., et al. (2008, July). Scaling Up Programmatic Management of Drug-Resistant Tuberculosis: A Prioritized Research Agenda. *PLoS Medicine*, 5(7), e150. Retrieved October 15, 2008, from Academic Search Premier database.
- Global Alliance for TB Drug Development [TB Alliance] (2008) *TB Drug Portfolio*. Retrieved November 8, 2008, from <http://www.tb Alliance.org/new/portfolio.php>
- Howland, R., Mycek, M., Harvey, R., Champe, P. (2006). *Pharmacology*. Baltimore, MD: Lippincott Williams & Wilkins.
- Khan, S., Chundru, S., Rodrigues, G., Pokharel, N., & Kansakar, P. (2007, October). From mono, multiple to extensive drug resistant TB: Where are we heading for?. *International Journal of Risk & Safety in Medicine*, 19(4), 179-185. Retrieved October 15, 2008, from Academic Search Premier database.
- Lew, W., Pai, M., Oxlade, O., Martin, D., & Menzies, D. (2008, July 15). Initial Drug Resistance and Tuberculosis Treatment Outcomes: Systematic Review and Meta-analysis. *Annals of Internal Medicine*, 149(2), 123-133. Retrieved October 15, 2008, from Academic Search Premier database.
- Mayo Foundation for Medical Education and Research [Mayo Clinic] (2008). *Tuberculosis: Symptoms*. Retrieved November 14, 2008, from <http://www.mayoclinic.com/health/tuberculosis/DS00372/DSECTION=symptoms>
- National AIDS Control Organisation [NACO] (2007). *FAQs: HIV-TB Co-infection*. Retrieved November 1, 2008, from http://www.nacoonline.org/Quick_Links/FAQsJ#HIV-TB%20Co-infection
- NEW RAPID TESTS FOR DRUG-RESISTANT TB FOR DEVELOPING COUNTRIES. (2008, June). *Indian Journal of Medical Sciences*, Retrieved October 15, 2008, from Academic Search Premier database.
- Porth, C. (2007). *Essentials of Pathophysiology Concepts of Altered Health States*. United States: Lippincott Williams & Wilkins.
- Satti, H., Seung, K., Keshavjee, S., & Furin, J. (2008, June). Extensively Drug-Resistant Tuberculosis, Lesotho. *Emerging Infectious Diseases*, 14(6), 992-993. Retrieved October 15, 2008, from Academic Search Premier database
- Schofield, C. (2008, June). Polish up on past pestilence and present pathogens. *MLO: Medical Laboratory Observer*, 40(6), 20-25. Retrieved October 15, 2008, from Academic Search Premier database.
- Shi, R., Itagaki, N., & Sugawara, I. (2007, November). Overview of Anti-Tuberculosis (TB) Drugs and Their Resistance Mechanisms. *Mini Reviews in Medicinal Chemistry*, 7(11), 1177-1185. Retrieved October 15, 2008, doi:10.2174/138955707782331740
- SURVEY FINDS HIGHEST RATES OF DRUG-RESISTANT TB TO DATE. (2008, February). *Indian Journal of Medical Sciences*, Retrieved October 15, 2008, from Academic Search Premier database.

Drug Resistant Tuberculosis 11

Rubric for Research Paper

Task Description: Write a research paper (6-8 pages) on the topic dealing with the Pathophysiological concepts learned in this course, include secondary sources. Total points= 200

	Student's Name		
	Excellent	Competent	Needs Work
1. Thesis Statement 10% 20 points	Consistently does almost the following: Presentation is centered around a thesis which is highly developed and goes beyond what was presented in class	Does the following most of the time: Presentation is centered around a thesis which is highly developed and goes beyond what was presented in class	The presentation shows no central thesis statement
POINTS 20			
2. Organization 20% 40 points	Consistently does all or most of the following: Paper includes an introduction, body and conclusion which shows support of the thesis statement through research which is thorough and goes beyond what is covered in class.	Does the following most of the time: Paper includes an introduction, body and conclusion which shows support of the thesis statement through research which is thorough and goes beyond what is covered in class.	The paper shows no analytical structure including an introduction, body and conclusion and no support through research. Covers only what is covered in class
POINTS 40			
3. Assertions 20%	Consistently does all or most of the following: Major points are supported by meaningful examples. Identifies salient arguments (reasons and claims)	Paper does not show support of thesis by research and meaningful examples arguments (reasons and claims)	
POINTS 40	<i>Be clear + accurate</i>		
4. Knowledge/Understanding 20% 40 points	Consistently does all or most of the following: Identifies salient points related to the topic and thoughtfully analyzes and evaluates the topic	Does the following most of the time: Identifies salient points related to the topic and thoughtfully analyzes and evaluates the topic	Shows no understanding and knowledge of the topic other than what was presented in class
POINTS 40			
5. Critical thinking 20% 40 points	Consistently does all or almost all of the following: Accurately interprets evidence, statements, graphics, questions etc. Fair-mindedly follows the evidence and presents in a balance manner	Does the following most of the time: Accurately interprets evidence, statements, graphics, questions etc. Fair-mindedly follows the evidence and presents in a balance manner	Offers biased interpretation of evidence, statements, graphics, questions, information or point of view of others. Does not justify results or facts nor explain rationale.
POINTS 40			
6. APA Style 10% 20 points	Consistently does all or most of the following: uses APA Style guidelines to construct: Title page, format, references, appendix and editorial style including grammar, spelling, punctuation	Does the following most of the time for the following: uses APA Style guidelines to construct: Title page, format, references, appendix and editorial style including grammar, spelling, punctuation	Shows limited to no understanding of APA style format in construction of paper
POINTS 20			
TOTAL POINTS 200			

Comment [CSU9]: Watch how you present the data. Be clear and accurate.