Creation of a webpage:
The Microbiology of Cystic Fibrosis

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THE DISEASE:

Cystic Fibrosis (CF) is the most life-threatening genetic disease among the Caucasian population. This disease is caused by a mutation in only one gene, the CFTR (Cystic Fibrosis Conductance Regulator) gene. The CFTR acts as a chloride channel, pumping this ion through the cell membrane of the epithelial cells that produce mucus. This chloride transport controls the water movement, so it infuences the normal mucus production. The lack of the CFTR produces a high reabsortion of water, creating a very sticky and dense mucus that's very difficult to transport. This retention of the mucus leads to recurrent infeccions because the mucus is very rich in nutrients, so it's a perfect environment for the microorganisms to grow [1]. The disease primarily affects the lungs, the digestive and reproductive systems and also the secretory glands [2]. This produces various symptoms such as: persistent coughing, shortness of breath, very salty-tasting skin, poor growth and slow weight gain, greasy stools and frequent lung infections. The most studied effects are the ones that happen in the lung because of their severity and the high mortality rate associated with poor lung function [3].

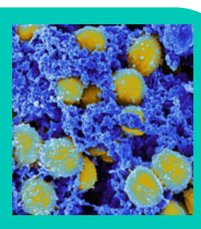
THE MICROORGANISMS:

Bacteria

Pseudomonas aeruginosa:

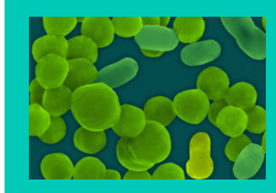
- Gram-negative bacillus with very simple nutritional requirements, and it's the most common pathogen in adult CF patients [4].
- When *P.aeruginosa* infects a CF patient it rapidly adapts and begins to grow in a biofilm form. Problem→antimicrobial tolerance 10-1.000 times higher.
- Acute infection→highly virulent, but its eradication is possible if the antibiotic treatment begins as soon as possible.
- 20% of the acute infections will develope into a chronic infection that can last even a patients lifetime. In this phase, *P.aeruginosa* has a higher antibiotic resistance, and it's much more difficult to eradicate. [1]

Staphylococcus aureus:



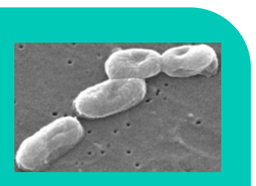
- Gram-positive cocci that agrupates in grape-like clusters, and has a typical yellow-gold pigmentation→most common pathogen in children/teenagers with CF [4].
- It's part of the normal human microbiota, but it's also the most frequent nosocomial pathogen→its prevalence is increasing.
- Transmission=person to person: direct contact/contaminated objects/aerosols…
- It can adapt to the CF lungs, and persist intracellularly (protection from the immune system and antibiotics) [5].
- MRSA= Meticillin Resistant *Staphylococcus aureus*, associated with a decrease in lung function→no consensus about the treatment.

Haemophilus influenzae:



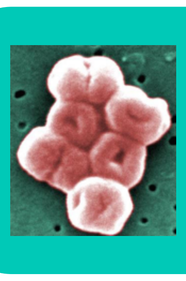
- Pleomorphic gram-negative coccobacillus that's part of the normal human respiratory microbiota, but it's also an important pathogen in respiratory and systemic infections.
- Transmission: direct contact/aerosols.
- It can cause an infection in CF patients, specially in children, but ends up being replaced by *P.aeruginosa* [6].
- There's a vaccine to prevent *H.influenzae* infections, but it doesn't work with the CF patients. However, it's a bacteria that responds well to the antibiotic treatment.

Burkholderia cepacia complex:



- A group of gram-negative bacteria that includes different species with similar features. They have an extreme nutritional versatility.
- *B.cenocepacia, B.multivorans, B.vietnamensis, B.dolosa* and *B.cepacia* can infect CF patients, and they are particularly resistant to antibiotics.
- In 1/3 of the CF patients infected with these bacteria there's a decrease in lung function, and in an even smaller group there's a fast decrease in lung function and in general health causing even the death of the patients [3].

Acinetobacter baumannii:



- Gram-negative coccobacillus common in water and soil, but it can be a parasite of animals, and it's involved in nosocomial infections because it's a frequent causative agent of opportunistic infections (as it happens with the CF patients).
- It's particularly resistant to most antibiotics, so it's essental to study its sensitivity to antibiotics to guide the treatment [7].

Stenotrophomonas maltophilia:

- A gram-negative bacillus, mobile thanks to the presence of polar flagella. It has been isolated with other microorganisms that cause infections in CF patients (primarily in patients 16 to 25 years old).
- It can persist in aqueous, nutrient-poor environments, and it can also live forming biofilms in plastic surfaces such as the nebulizers used in aerosol therapy.
- About an 11% of the CF patients are infected with this pathogen, and a chronic infection caused by this bacterium is associated with a decrease in lung function [8].
- It isn't a highly virulent pathogen, but it's emerging as an important nosocomial bacterium.

Enterobacteriaceae:

- A relatively homogeneous family of gram-negative bacteria. Some of the species are part of the human intestinal microbiota [4].
- They are occasionally isolated from respiratory secretions from CF patients, but they are opportunistic pathogens, and they cause transitory infections that aren't associated with a severe disease.
- The most frequent are: *Escherichia coli, Klebsiella pneumoniae* and *Serratia marcescens.*

New bacteria:

- Genus *Pandoraea*: it contains 5 named and 4 unnamed species, and basically they have only been isolated from respiratory secretions from CF patients. They are gram-negative, and they are being considerated as emerging and multi-resistant pathogens in the CF context. There's few clinical data about the pathogenicity of the bacteria, the course of the infection and the evolution of the infected patients [9].

Fungi

Candida:

- *Candida albicans* and *Candida parapsilosis* are the most frequently isolated yeasts from the CF respiratory secretions. They are part of the normal oral microbiota, so they can migrate and then persist in the airways of the CF patients.
- It's believed that *C.albicans* could be involved in the decrease of lung funtion, and it's frequently associated with *P.aeruginosa* [10].

Aspergillus fumigatus:

- The most common mold that infects the airways of the CF patients, and it's widely distributed in the environment.
- Great esporulating capacity, producing small spores (conidia) that can penetrate in the airways and stimulate a proinflammatory response in the bronchial epithelial cells of the CF patients. This proinflammatory response could serve the mold to escape detection by the immune system of the patient, thereby allowing the colonization of the respiratory tract.
- It can cause severe infections after a lung transplant, but they can be treated with steroids and antifungal agents [11].

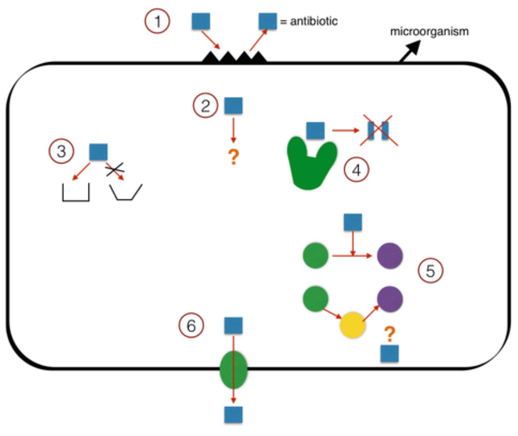
TREATMENT:

Antibiotic therapy: no consensus treatment. Many strategies have been used by changing the route of administration (systemic, oral, inhaled or a combination), the types of antibiotics and the duration of the treatment. Inhaled antibiotics have high bacteria eradication rates due to the direct delivery of a high antibiotic dose to airway space, with limited systemic toxicity. About the oral and intravenous antibiotics, currently fluoroquinolones as ciprofloxacin are the most used (but the use is limited due to the rapid emergence of resistances) [1].

Gene therapy: it could be the treatment to cure CF, because its target is the very cause of CF, rather than just treating the symptoms and the opportunistic infections. Researchers are currently testing aerosol delivery of the normal CFTR gene using nebulizers [12].

Alternative therapy: plant essential oils (cinnamon, clove and thyme) have shown antibacterial activity against *S.maltophilia*, but their toxicity against respiratory epithelial cells has yet to be tested [8]. Another alternative is phage therapy, but it hasn't been used yet.

ANTIBIOTIC RESISTANCE:



Why are microorganisms resistant to certain antibiotics?
6 main reasons:

1- The microorganism may be impermeable to the antibiotic.
2- The microorganism may lack the structure that is inhibited by the antibiotic.
3- The microorganism may change the target of the antibiotic, so it can't exert its effect.
4- The microorganism can alter the antibiotic inactivating it.
5- The microorganism can develop an alternative biochemical pathway, and therefore, become resistant to the antibiotic.
6- The microorganism may be capable of pumping outwards an antibiotic that has penetrated into the cell. [4]

References:

[1]: Sousa A, Pereira M. *Pseudomonas aeruginosa* Diversification during Infection Development in Cystic Fibrosis Lungs—A Review. Pathogens [Internet]. 2014 Aug 18 [cited 2014 Nov 18];3(3):680–703. [2]: Das RR, Kabra SK, Singh M. Review Article Treatment of *Pseudomonas* and *Staphylococcus* Bronchopulmonary Infection in Patients with Cystic Fibrosis. The Scientific World Journal. 2013;2013(June). [3]: Cystic Fibrosis Foundation. About Cystic Fibrosis [Internet]. 2014. Available from: http://www.cff.org/AboutCF/ . [4]: Madigan MT, Martinko JM, Dunlap P V., Clark DP. Brock, biología de los microorganismos. 12th editi. Pearson educación; 2009. 892-899 p. [5]: Windmüller N, Witten A, Block D, Bunk B, Spröer C, Kahl BC, et al. Transcriptional adaptations during long-term persistence of *Staphylococcus aureus* in the airways of a cystic fibrosis patient. Int J Med Microbiol [Internet]. Elsevier GmbH.; 2014 Oct [cited 2014 Nov 20]. [6]: King P. *Haemophilus influenzae* and the lung (*Haemophilus* and the lung). Clin Transl Med. 2012;1(1):10. [7]: Prats G. Microbiología y Parasitología médicas. 1st editio. Editorial Médica Panamericana; 2013. 399-407 p. [8]: Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. Clin Microbiol Rev [Internet]. 2012 Jan [cited 2014 Nov 14]; 25(1):2–41. [9]: Kokcha S, Bittar F, Reynaud-Gaubert M, Mely L, Gomez C, Gaubert J-Y, et al. *Pandoraea pulmonicola* chronic colonization in a cystic fibrosis patient, France. New microbes new Infect [Internet]. 2013 Nov;1(2):27–9. [10]: Delhaes L, Monchy S, Fréalle E, Hubans C, Salleron J, Leroy S, et al. The airway microbiota in cystic fibrosis: A complex fungal and bacterial community-implications for therapeutic management. PLoS One. 2012;7(4). [11]: Reihill J a., Moore JE, Elborn JS, Ennis M. Effect of *Aspergillus fumigatus* and *Candida albicans* on pro-inflammatory response in cystic fibrosis epithelium. J Cyst Fibros [Internet]. Elsevier B.V.; 2011;10(6):401–6. [12]: National Human Genome Research Institute. Learning About Cystic Fibrosis. 2013. **Images:** *P.aeruginosa, B.cepacia, S.maltophilia, A.baumannii and A.fumigatus* : Public Health Image Library (PHIL) http://phil.cdc.gov/phil/details.asp , *S.aureus* and *E.coli*: National Institute of Allergy and Infectious Diseases (NIAID), *H.influenzae*: http://www.historyofvaccines.org/content/haemophilus-influenzae ,