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A General Review of the antibiotics Mupirocin and Cefuroxime on Paronychia caused by S. Aureus and S. Pyogenes species

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Abstract:

This article will focus on the treatment of paronychia with cefuroxime and mupirocin, which are two different types of antibiotics frequently prescribed by medical professionals for the treatment of nail infections caused by common pathogenic bacterial species. Cefuroxime is an antibiotic isolated from a fungus and is characterized as a type of class II cephalosporin that belongs to the class of B-lactam antibiotics that binds to penicillin-binding-proteins in bacteria, therefore inhibiting bacterial peptidoglycan (cell wall) synthesis and kills the cell. Mupirocin (more commonly known as Bactroban) is another antibiotic that is isolated from a fellow bacteria species and works by obstructing bacterial aminoacyl-tRNA synthesis in various species of bacteria that may be susceptible to the mechanism. However, the application of these antibiotics onto infected regions does not guarantee a complete elimination of the pathogens due to the rise of antibiotic resistance genes throughout the bacterial population. A short discussion will follow all the presented materials, as well as the referenced materials.

Keywords: Paronychia, skin infections, cephalosporins, mupirocin, antibiotic resistance

1. Introduction

In general, paronychia is a general term used for the inflammation around the skin area of the nail due to pathogenic infections and affects a significant amount of people yearly in the US. Paronychia is characterized into two types clinically: one may be diagnosed as having acute paronychia, which lasts shorter and is most frequently caused by a bacterial infection, or is diagnosed as having chronic paronychia caused by fungi, mechanical work, constant exposure to irritants, constant exposure to unclean water, manicures, ingrown toenails, sucking or biting the nail… etc. [1][2][3], which all leads to the infection of the local skin area by microbial entries of viruses, bacteria and fungi species. The entry occurs because of a sudden

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breach in the barrier between the nail and the nail fold, thus causing the loss of the normal nail and nail fold interaction (which is to block pathogens from entering internal tissues). [1] Common treatment of paronychia involves soaking the affected area in warm water for 10 to 15 minutes, as well as using prescribed topical or oral antibiotics over the course of around a week. [1] Usually, the infected area would be red, swollen, pus-filled or painful to touch. [2] An abscess may be seen at the trauma site- it may drain by itself or be drained by a medical professional to aid with the process of healing. [4] According to Cleveland Clinic, the medical provider may culture the fluid to see the type of bacteria that is causing the infection. [36] In the worst cases, such as when the infection had spread to parts outside of the skin fold tissue or when there is a possibility of a fungi infection, the nail would have to be removed completely. [5] The article will explore the infection caused by *staphylococcus* and *streptococcus* species (as they are one of the most common species that cause paronychia [6]), as well as the available biosynthetic antibiotics that are available for the treatment of the wound caused by these respective bacterial species. The antibiotics will be described briefly and distinguished regarding their structure, mechanism of action, effectiveness, way of administration and the future for these medicines.

2. Paronychia, Treatments and Responses from the Immune System

The nail (See figure 1) is a hard plate-like structure made of keratin that is found in practically all primates. [7] They grow continuously throughout an individuals' lifetime and exhibit intricate structures when looked closely. The nail bed is located under the nail plate, which undergoes oncogenesis (creating cells) and houses many blood vessels, including arteries and veins. The matrix is where all hard nail-plate cells are generated: it has one end hidden deeper under the proximal nail fold and another end visible to the naked eye. The visible matrix is presented as a white half-moon shaped called the Lunula. The size of the lunula varies from person to person. Special cells called oncocytes come out of the matrix and give the nail plate its rigid shape. The unalive clear layer directly around the nail is called the cuticle, which may be trimmed by a nail painter to enhance the stickiness of the nail polish or ornaments placed on the nail plate. The proximal nail fold (situated on top of the matrix) protects the nail's growing area from microbial invasions. The lateral nail folds are on the sides that also serves a protection purpose. The place where the nail vanishes on the side is called the nail grooves- they help anchor and stable the nail on each side. Additionally, the eponychium is an alive-portion interior to the cuticle. The hyponychium connects the nail plate at the nail bed. The nail horn is the free-growing half-transparent nail beyond the boundary and improves fingertip sensation, as well as motor skills such as picking up objects. Nail nerves are concentrated near the tip to help transmit sensory information to the central nervous system. [8]. Fingernails grow on an average of 3 milliliters per month; toenails grow a bit slower. [9]

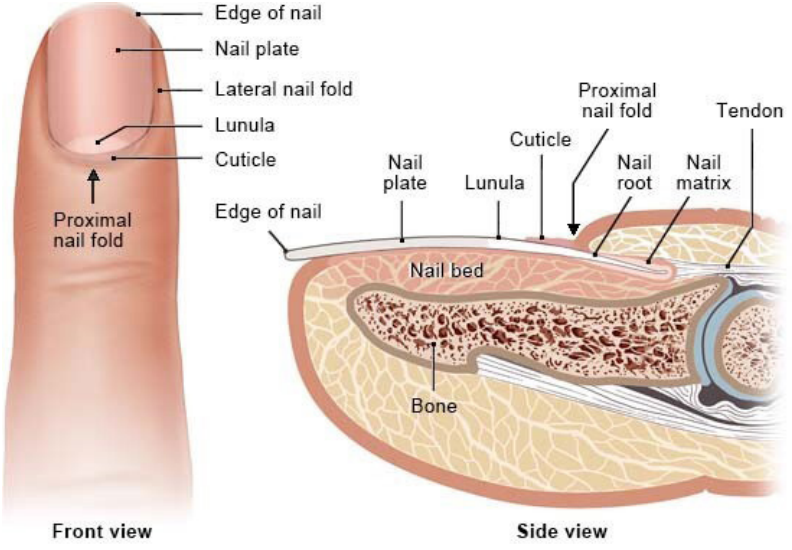

Figure 1.: Cross section of a nail [9]

Bacteria are prokaryotic organisms that may be categorized by the structure of their protective layers. There are generally two types of bacteria based on this specification: gram-negative and gram-positives. Gram-negative bacteria have an inner layer of peptidoglycan and another outer membrane. Gram-positive bacteria only have one inner

membrane, but a much thicker layer of peptidoglycan. [10] It's relatively harder for medications, such as antibiotics to get into the targeted sites of a gram-negative bacteria because of its double membrane. Most pathogenic bacterium are unable to do any real harm inside a human body because of the suppression of these species by the human immune system. A brief overview of the innate immune system is that it consists of the body's natural response to invading pathogens that is rapid but non-specific. In humans, it includes surface barriers (e.g. Skin, mucus, tears…), inflammation (swelling), the complement system (protein cascade that complement the killing of pathogens by after the antibodies had marked them), as well as the recruitment of granulocytes and leukocytes to the infected area that either secretes substance toxin to the pathogen or perform phagocytosis on the foreign particle. [11] The adaptive (or acquired) system is the pathogen-specific response that provides long-term immunity to the body. The T cells differentiate into activate T cells, cytotoxic T cells and memory T cells. The B cells differentiate into "activated" plasma B cells that secretes antigens (or antibodies) into the blood stream, which (the antibodies) may bind to the corresponding receptor proteins on the pathogen, resulting in opsonization (meaning to tag the particle by opsonin so it may be better recognized by phagocytotic cells) and coagulation of the pathogen population. Autoimmune diseases are usually because of when the body has a loss of tolerance for its own produced antigens, which prompts a "destructory" immune system. [12]

Cytokines are chemotactic cytokines that are proteins produced by some cells that's utilized for the signaling between other cells specifically by the immune system in response to foreign pathogens. The nomenclature of cytokines is a "IL" (meaning interleukin) followed by a number. Mature CD4 cells and CD8 (CD8 is also known as the "cytotoxic" T cell) can encounter antigen precenting cells that display MHC class II or MHC class I molecules and interact with these molecules respectfully. The T cells are then said to be activated. The activated CD4 cells can differentiate into either 2 types of T-helper cells: Namely, Th1 (T-helper 1) or Th2 (T-helper 2) cells. These T helper cells can then trigger more cellular defense mechanisms from the infected cells. Proteins like TNF-α and TNF-β is used for cell death effectors. TNF-α can bind to the lipopolysaccharide present on the surface of various bacterial pathogens to induce apoptosis in some targets. [13] The humoral immune response is an event when antigens produced by B plasma cells cause the destruction of pathogens in extracellular spaces. These antibodies that bind to pathogens are recognized by Fc receptors on phagocytotic cells, which enhances phagocytosis. Also, when the antibody binds to the protein, the complement system is activated upon the site of infection. [14]

3. The Pathogenicity of S. Aureus and S. Pyogenes

The pathogenicity of *S. Aureus* is greatly contributed by its ability to spread using its AGR quorem sensing system [15][16]. Staphylococcus species also form an extracellular polymeric biofilm that protects itself against environmental stresses. Drugs are becoming less penetrable due to the layer of biofilm: the biofilm is made of water, protein, polysaccharides and eDNA (extracellular DNA plasmids) [17][18]. EPS is a polysaccharide intercellular adhesin that helps the bacterium adhere to itself, therefore helps in colonization, resistance to antibiotics and resisting the immune system [19]; it exhibits some other proteins which all helps the species attach and facilitate their colonization on host's cells such as fib (fibrinogen-binding gene) fnbA, clfA just to name a few [20]. eDNA sometimes codes for irreversible attachment (to the host), horizontal gene transfer between cells and much more. In a summary written for the pathogenesis of this species, Staphylococcus species is described as excreting TSST1 causes toxic shock syndrome. It may secrete Eta, causing scalded skin syndrome. Other toxins include hemolysin and leukotoxin, which cause pore formation on the cell membrane and cause it to be in host cells. Some toxins may even deactivate the host's immune system. Exoenzymes that are associated with the AGR system cause tissue destruction to the infected regions and deactivate immunomodulators (drugs that change someone's immune system to treat various cell diseases, such as cancer). Anti-biofilm substances that are found to be useful for the degradation the biofilm include DNA degrading enzymes, particles of heavy metal, DNase I, dispersin B and α-amylase. [21]

The 35 species of the *Streptococcus* genus have been identified to be sources of invasive infections in humans. *S. pyogenes causes around 700 million infections per year and, consequently,* the death of 500,000 people. The main underlying mechanism of its pathogenicity is its polysaccharide envelope, which is now being targeted by polysaccharide antigens to aid to the prevention of the disease. *Streptococcus* species have an amazing ability for genetic flexibility because they exhibit a lot of recombination when they replicate themselves. The bacterium excretes exotoxin B, which has the activity of cysteine proteases. [23] *S. Pyogenes* can invade human epithelial cells. The bacterium secretes a variety number of proteins that aid in its virulence in its host. The proteins necessary for invasion are the M and Sfbl (fibronectin-binding) proteins. The cysteine protease SpeB cleaves the immunoglobulin

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IgG (an antigen excreted by activated B lymphocyte cells. Notably, Cpa1 and Cpa45 are collagen-binding proteins isolated from *S. pyogenes* that serve the purpose of intracellular adhesion, like the EPS biofilm present in *S. aureus*. This species is covered by an outer hyaluronic acid capsule that can render it resistant to phagocytosis. The capsule is otherwise an important adherence factor to the larynx through the presence of a CD44 protein binding to the human epithelial cells. [24] Additionally, *Pyogenes* is in the category of beta-hemolytic bacteria, meaning it causes the complete lysis of red blood cells that results in a colorless zone surrounding and under the color when grown on a petri dish enriched with blood agar. [25]

4. Cefuroxime

The peptidoglycan is a structure unique to bacteria that can withstand intracellular pressure and provide the bacteria with a rigid shape. The penicillin-binding protein (PBP) allows for the process of disassembling the peptidoglycan and remaking it again for the purpose of cell elongation. The last stage of peptidoglycan synthesizing enzymes are sensitive to B-lactam antibiotics as it impairs their cross-linking capacity. [26] PBPs can be characterized as low-molecular-mass (LMM) enzymes that are nonessential, monofunctional or as high-molecular-mass (multimodular, HMM) enzymes that have multiple functional roles. In HMM PBPs, the cytoplasmic C-terminal domain binds to penicillin and catalyzes peptidoglycan cross-linking, and the juxtamembrane N-terminal domain participates in transglycosylation. The HMM transpeptidase is based on a lysine residue located in a catalytic motif, whereas the other motifs govern the carboxypeptidase activity (and is the target of B-lactam antibiotics directed at staphylococci). The B-lactam-PBP acyl adduct is stable and results in irreversible inhibition of PBP function.

PBP2 in *staphylococcus* species allow for transglycosylase and transpeptidase activities. Peptidoglycans need to be cleaved and reformed again to allow for continuous cell growth and division; inhibition of PBP2 leads to restrained (peptidoglycan) elongation and bacterial cell lysis. PBP3 has possibly influenced the perceived "correct" shape and size of cells. PBP4 is a carboxypeptidase and is needed for the secondary cross-linking of peptidoglycan; overexpression of this gene leads to an increase in B-lactam resistance due to greater peptidoglycan cross-linkage. [27]

Antibiotics may be natural compounds isolated from their respective organisms, semi-synthetic compounds made from structurally modified natural materials, or synthetic compounds completely. Natural compounds exhibit a relatively high level of toxicity compared to semi-synthesized or synthesized compounds. [28] Cephalosporin are β-lactam antibiotics that are semi-synthetic and derived from a substance produced by the mold Cephalosporium. [29] In all, Cephalosporins are inactive against enterococci, MRSA (except for cefazoline and ceftobiprole) and anaerobic gram-positive bacilli (except for cefotetan and cefoxitin). There is a total of 5 generations of Cephalosporins, each stemming from the structure in the previous compound with newly innovated properties. The compound in this discussion relates to the second-generation cephalosporin- cefuroxime. Second generation cephalosporins are semisynthetic and used against polymicrobial (simultaneous infection of multiple species of bacteria) that include gram-negative bacilli and gram-positive cocci. Cefuroxime, like every other β-lactam antibiotic, bind to the penicillin-binding proteins in the bacteria, therefore inhibiting cell wall (peptidoglycan) synthesis and causing cell lysis from autolytic enzymes. All native, non-mutative PBPs are inactivated by the β-lactam antibiotics. [30]

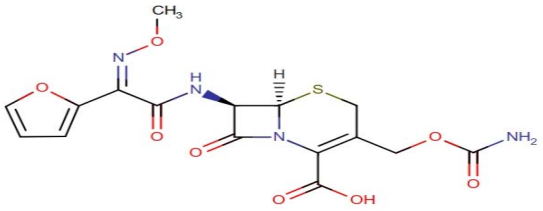

Figure 2. Structure of Cefuroxime $C_{16}H_{16}N_4O_8S$; IUPAC name: (6*R*,7*R*)-3-(carbamoyloxymethyl)-7-[[(2*Z*)-2-(furan-2-yl)-2-methoxyiminoacetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid [31]

The brand names for Cefuroxime is generally Ceftin and Zinacef. It is prescribed for a variety of bacterial infections. It is bactericidal (kills bacteria and cause a decrease of population). [31] Cefuroxime (whether 200mg or 500mg) is to be taken once or twice daily for an adult dosage, but the administration of different methods should

not be interchangeable.[32] Cefuroxime axetil is absorbed from the gastrointestinal track and had shown to have increased absorption when taken with food. Around 50% of cefuroxime bind to serum protein. Cefuroxime is metabolized to acetaldehyde and acetic acid, but not secreted. Tablet products of Ceftin is taken orally and made by 250mg or 500mg per tablet. It can be mixed with other substances such as Clavulanic acid. It belongs to a class of organic compounds called cephalosporin 3'- carbamates. Cefuroxime can also be administered using injection (intramuscularly), with oral suspension. The cost for a Ceftin branded 20 500mg tablet bottle is around $436.36. [31]

In the past, new β-lactam antibiotics, such as methicillin and oxacillin are produced to counter penicillin antibiotic resistance (namely caused by the resistance enzyme β-lactamase) in 1959. β-lactamases can hydrolyze the β-lactam ring of the antibiotics and deactivate them. Strains of S. aureus that is susceptible to β-lactam antibiotics only have 2 class B PBPs. Resistance to B-lactam antibiotics have an additional PBP- PBP2a which has low sensitivity to the antibiotic. [34] The reason it has decreased sensitivity is because the active site of PBP2a is imbedded in a close conformation, which the antibiotic is unable to interact with. [33] The gene mecA codes for PBP2a, which allows for normal peptidoglycan synthesis even when other PBPs are inhibited. The good news is, PBP2a is shown to have high affinity for the recently approved cephalosporin, ceftaroline. [34]

5. Mupirocin

The aminoacyl-tRNA synthetases are an essential player in protein synthesis by pairing the tRNAs (each with a slightly different structure) with their corresponding amino acids so that the mRNA can be translated correctly with respect to its codons. Synthetases ensure that the pairing is done without error by using highly accurate substrate recognition techniques and then further proofreading of any possible wrong products. The synthetase has an extremely difficult task since it must discriminate between the correct tRNA isoaccepter from a pool of tRNAs and select the one amino acid among hundreds of other proteinogenic or non-proteinogenic amino acids. [35] Pseudomonic acids are short-chained fatty acids (originally a polyketide) and the fermentation metabolite of Pseudomonas fluoresens. Pseudomonas are gram-negative bacillus found in nature. A characteristic of this species is that a substance called pyoverdine (a green pigment) is produced when there is an iron deficiency. The metabolite is a mixture of four Pseudomonic acids, different from each other through a variable R group. [39] The topical antibiotic mupirocin is synthesized from these metabolites and is utilized for managing various skin infections. [36A] In short, the antibiotic works by obstructing bacterial protein and aminoacyl tRNA synthesis. [39] It is most active against beta-hemolytic streptococci. The natural antibiotic that is derived from Pseudomonic acid is called Mupirocin. The clinically applicable product is made from 2% mupirocin in polyethylene glycol ointment. [37] The mechanism in which it obstructs protein synthesis is that mupirocin has a side chain like the bacterial isoleucyl-tRNA synthetase' binding site. When mupirocin binds to the synthetase, isoleucyl-tRNA (the original product) cannot be made, causing bacterial death. [38] On a molecular level, the C-14 to C-11 terminus of monic acid resembles the side chain of isoleucine, which then interacts with the active site of isoleucine tRNA-synthase. The pyran ring interacts with the ATP binding site of IleS. [39]

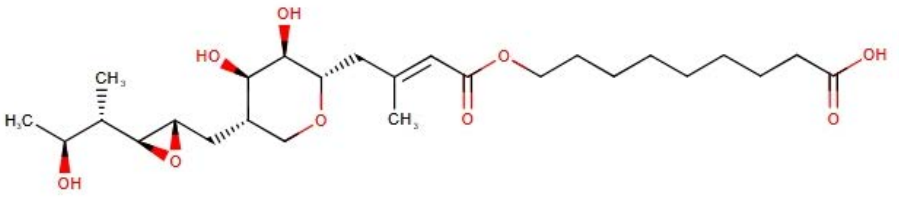

Figure 3. Structure of Mupirocin: $C_{26}H_{44}O_9$, IUPAC Name: 9-[(*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)-3-[(2*S*,3*S*)-3-hydroxybutan-2-yl] oxiran-2-yl]methyl]oxan-2-yl]-3-methylbut-2-enoyl]oxynonanoic acid [40]

The brand names for the antibiotic mupirocin are Bactroban, Centany and Pirnuo. It is bacteriostatic at lower concentrations but exerts bactericidal effects long-term that kill over 99% susceptible bacterial over 24 hours. It would be metabolized to monic acid after systemic circulation and then eliminated through renal excretion. It is found to be excreted in human milk. It can be combined with other substances such as Clotrimazole or Mometasone furoate to make other topical drugs such as Derma Q Crema Topica. The price of mupirocin is dependent on how many grams are purchased; generally, a tube containing 30 gm of 2% Bactroban ointment costs around $77.00. [40]

The transportation of mupirocin into sensitive bacteria is an energy-independent and temperature-dependent process

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(decreased uptake at lower temperatures). More molecules of isoleucyl-tRNA synthetase (target of mupirocin) is shown to cause greater accumulation of mupirocin in the intracellular areas. [41] Lower level of intracellular mupirocin is a result of a mutation in the chromosome that reduces the affinity of the tRNA synthase to mupirocin. The mupA gene is associated with high-level resistance for its production of a novel IleS, being transposable as part of other plasmids, self-transmissible and gives resistance to other antibiotics. In some experimental studies, mupirocin is shown to promote wound healing by increasing human keratinocyte proliferation and growth factor production. At higher concentrations, Mupirocin is shown to improve cell viability compared to the control [42]

6. Conclusion

Paronychia remains one of the most common skin infections around the nail that continues to affect hundreds of thousands of people in the US each year. With the development of more and more antibiotics that are targeted at common pathogens that affect humans, physicians also have greater freedom in choosing which medicine is best suited for each affected individual. However, bacteria strains are becoming increasingly resistant to antibiotics due to the overuse of respective antibiotics- in fact, innovations are needed desperately in today's time. Understanding what antibiotics really are, how they function, and how they kill off pathogenic enemies can perhaps help foster a greater appreciation for the scientists who worked tirelessly to develop newer and better medicines for patients who needed them.

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