Apoptosis in Ear, Nose & Throat

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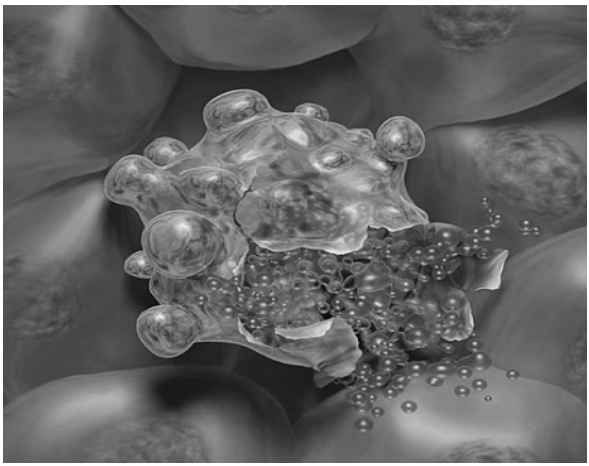
Definition

Apoptosis is a biological process which occurs throughout the body. Apoptosis was first described in 1950 by Sidney Brenner. In the last two decades its importance has increased in the scientific community. Apoptosis is also known as programmed cell death, silent, physiologic, passive and also called cellular suicide (**Figure 1**).

Figure 1. Apoptosis



Features

1.- Generally under genetic regulation
2.- 14 genes related to programmed cell death
3.- Involved in Immune system homoeostasis
4.- Deregulated apoptosis creates immune system dysfunction

Functions

1.- Repairs cellular damage caused by viral infections.
Viral p53 protein produced by human papilloma virus may lead to laryngeal and uterine cancer by inhibition of apoptosis.
2.- Stress or nuclear DNA damage.

Stresses produce cellular damage similar to damage caused by UV rays, ionizing radiations, gamma rays, and X-rays can induce the cell to initiate an apoptosis process. Mitochondria and the nucleus initiate the process.

Parp-1 is the process that maintains genome integrity.

3. – Homeostasis is the equilibrium between life and death, mitosis and cellular death by necrosis or apoptosis.

50 to 70 billion cells die by apoptosis in adults every day, but this loss is balanced by mitotic cellular proliferation.

Many fatal pathologies are related to altered apoptotic activity. Tumors are an example of under active apoptosis.

4.-Tissue Development

Apoptosis plays an important role in developing animal tissues and plants.

Cellular death may be caused by necrosis, which in such cases is initiated by an acute injury or infection, causing the inner part of the cell to empty into the extracellular space.

The cell nucleus is fragmented during apoptosis and macrophages phagocytize them.

During the embryonic period apoptosis is necessary to avoid overproliferation of abnormal cells and to avoid malformations and tumors.

5. - Immune system regulation

Apoptosis plays a role with B and T Lymphocytes

6. - Tissue remodeling

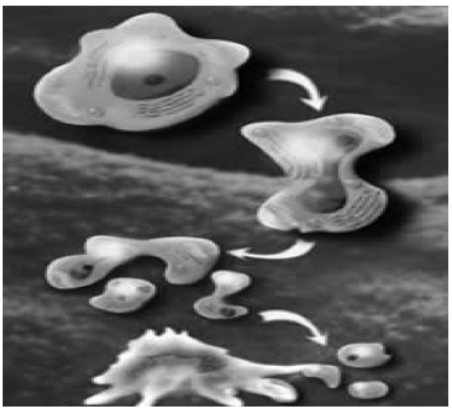
7. - Transitory organ removal

8. - Phylogenetic remains removal

Apoptosis Mechanism (Figure 2)

1. - Induction Phase

Initiator signs for programmed cellular death, pro apoptotic stimuli, cascade signs, calcium channels activation, Daxx, Bad/, Bcl-2 genes.



2. - Effectors Phase

Caspase activation leads to characteristic cellular changes; the regulator process involves mitochondrial action.

3.-Degradation phase with formation of apoptotic bodies

Cytoplasmic events, Caspase cascade activates, DNA nucleus fragmentation, chromatin condensation, phosphatidilserine deposits on membrane, phagocytosis and apoptosis process.

Figure 2. Apoptosis Mechanisms

Apoptosis in Otolaryngology

1.-Pharynx: Contains great number of lymphocytes which are an important element of immune system.

2. -Ear: Cochlear Hair cells within the neuroepithelium with mitochondria in the cytoplasm.

3.- Nose: Mucosal eosinophils participate in multiple processes that affects the upper airway.

Lymphocyte apoptosis (Figure 3)

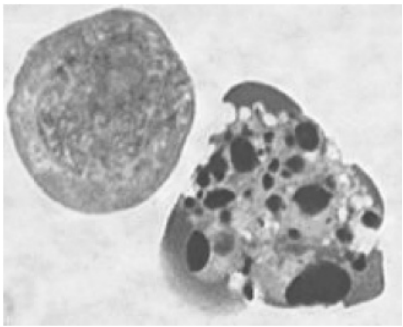
1. - Intrinsic pathway or Mitochondrial pathway

Lack of stimuli leads to release cytocrome and Caspase 9 activation.

2. - Extrinsic pathway or Receptors

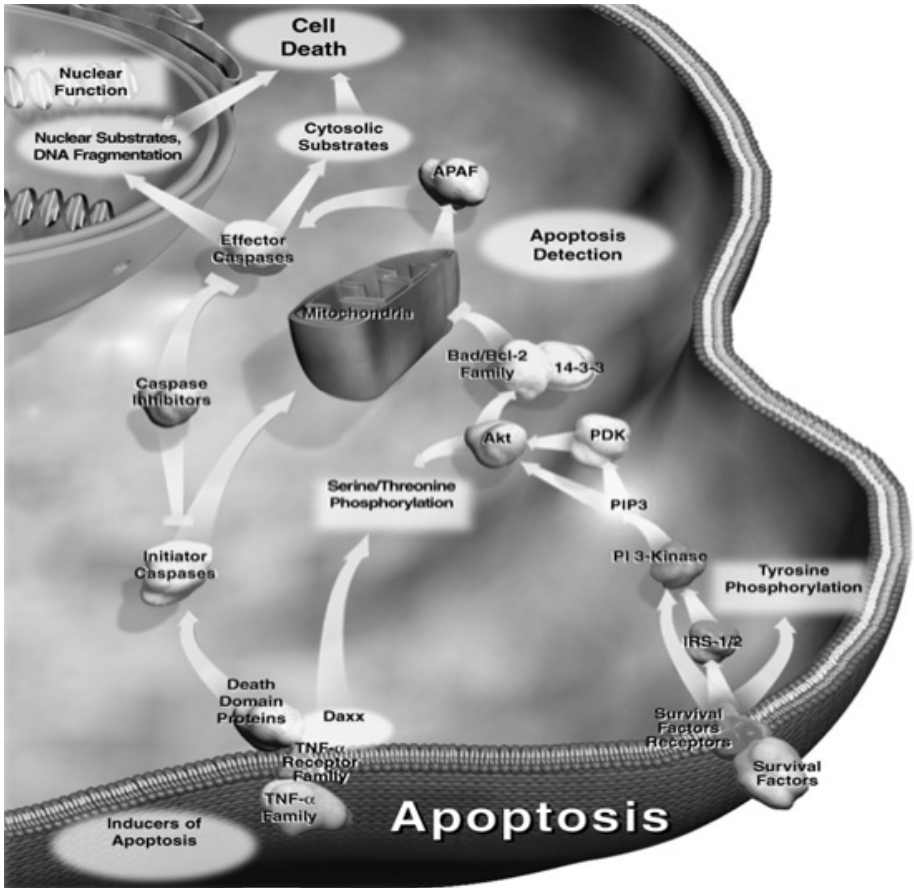
Multiply stimuli of antigens, releases proteins and Caspase 8 activation.

Figure 3. Lymphocyte apoptosis



Caspase (Figure 4) The main effectors of apoptosis, family of cysteine proteases, almost 14 varieties are the first to be activated by different mechanisms. Different types: inactive, active, effectors, inhibitors and independent.

Figure 4. Caspase



Cochlear Hair Cells Apoptosis

These cells are primary receptors of the cochlear-vestibular system, belonging to the cochlear neuroepithelium of Central Nervous System. Physical disruption of the organ of Corti happens during apoptosis.

The hair cells are very sensitive to hypoxia and their loss produces sensorineural hearing loss. The elements that leads to apoptosis are: hypoxia, infections, ototoxic drugs, acoustic trauma, presbycussis, and stress.

Mitochondria play an important role in oxygenation, cellular energy and stress related to hearing loss caused by presbyacusis, acoustic trauma, ototoxic and virus injuries. Without mitochondria, apoptosis will not occur.

Eosinophil apoptosis

Eosinophils are cells with a great capacity to produce cytolysis of the respiratory airway. The cells contain cytoplasmic granules, chemical mediators, and the cytokines responsible for chronic sinusitis, tissue remodeling and cellular death. Eosinophils exhibit three different stages: maturation, activation and mediator

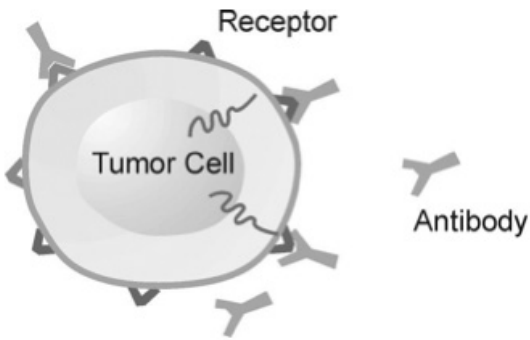
induction. Steroids increase apoptosis improving respiratory symptoms and opposing the function of leukotrienes and interleukins.

Apoptosis and Cancer

Apoptosis plays a role in cancer cell death, leading to cell phagocytosis (**Figure 5**). Genetic errors in cancer cells induce apoptosis inhibiting future cancer growth Apoptosis failure in congenital tumors is due to the inability to prevent tumor cell proliferation.

Apoptosis is more common in skin and blood cells, and less common in the ovary. Apoptosis is enhanced in Parkinson's and Alzheimer's Disease and diminished in tumors.

Figure 5. Apoptosis and cancer



Apoptosis and exercises

Exercise activates and induces signal activation to the mitochondrial level that may lead to violent cell death.

Apoptosis and aging

Stress and free radical release, play an important role in the pathophysiology of aging, capable to produce nuclear DNA damage inducing apoptosis.

Apoptosis and Neurons

Neurodegenerative diseases are related to apoptosis and dopaminergic neurons. Mitochondrial respiratory processes become altered at the *substantia nigra* as in Parkinson's disease. Apoptosis in Alzheimer's Disease happens in the hippocampus.

We must remember: Normal cells may have mutations but will also get sick and die. Mutant cells never suppress apoptosis.

How is Fever and Pain Treated in Children with Acute Respiratory Infections?

Lucia Ferro Bricks

Acute Respiratory Infections (ARI) are the most common diseases in childhood and are generally accompanied by pain and fever. Although analgesics/anti-pyretic (AAP) and non-hormonal anti-inflammatories drugs (NSAIDs) are widely used, there is little information on their efficacy and safety in children.

Besides causing discomfort, fever is the most terrifying clinical manifestation for parents and its presence can be the first indication of severe diseases. Besides, it can cause seizures. Anti-pyretic drugs and NSAIDs are considered safe, but cases with adverse events are not rare, due to errors in their administration (dose and/or interval between doses) or after the regular doses in children with underlying diseases. It is essential that physicians and laymen know the AAP and NSAIDs indications and contraindications.

Main questions related to the use of AAP/NSAIDs in children

1) What is fever?

Fever is the increase in the body temperature mediated by the central nervous system. In general, the thermoregulation center located in the hypothalamus maintains the body temperature around 37°C, with small variations (0.6 to 1.1°C) during daytime. Temperature can be measured in several sites, rectal temperature having the best correlation with the central temperature. Temperatures measured in the rectum are considered an indication of fever when equal to or higher than 38°C. Temperatures are generally lower than centrally when measured in other sites (mouth, axilla, tympanum, skin), and axillary temperatures ≥37.3 °C are therefore considered as elevated.

2) Does every child with a high temperature have a fever?

No. The rise in temperature can be caused by fever or hyperthermia. In hyperthermia, the elevation of temperature can be caused by conditions that do not involve the thermoregulation center (exposure to heat, hyperthyroidism, use of drugs). It is important to differentiate fever from hyperthermia, as the latter is treated by physical means while fever is treated using AAP/NSAIDs.

3) Is it necessary to treat every child with fever?

No, except when the child has very high temperatures (T > 39.05°C) or there is a risk of overloading the cardiocirculatory system (chronic cardiopathies and pneumopathies). Although the temperature reduction improves the comfort of a child with fever, the high temperature plays an important role in the inflammatory

response, as it increases the migration of neutrophils, production of interferon gamma and other cytokines responsible for the elimination of viruses and bacteria. Although viral ARIs are the main reason for using anti-pyretic drugs in children, there are very few randomized controlled studies on the impact of treating fever on the evolution of these infections. There are no evidences in humans that the temperature reduction will increase the risk of complications.

From the medical point of view, it is more important to investigate the etiology of fever than to reduce the temperature. However, most parents will administer anti-pyretic drugs to their children even when the child has a low fever. Very often, AAP/NSAIDs are given in higher or lower doses than adequate or at very short intervals, as an attempt to maintain the child without fever, even when there are no signs of discomfort. It is necessary to keep in mind that suppressing fever does not mean that a disease is absent and, in some situations, it can make the evaluation and diagnosis of complications more difficult. Besides, drugs (including AAP/NSAIDs) are often responsible for fever being maintained.

Although some NSAIDs reduced the inflammatory response in experimental studies involving otitis, few randomized and controlled studies performed in children with acute otitis media (AOM), otitis media with effusion (OME) and tonsillitis compared the action of paracetamol with ibuprofen or placebo, and both drugs were shown to have comparable effect on resolution of the symptoms. It is important to stress that the inflammatory process in ARIs is self-limited, and the doses of ibuprofen recommended in cases of chronic inflammatory processes are higher (30 to 40 mg/kg) than those used to treat fever (5 to 10 mg/kg).

4) Which is the safest analgesic/anti-pyretic for children younger than six years of age?

The only anti-pyretic drugs presently recommended to treat children with pain and/or fever associated with acute respiratory infections are: paracetamol, dipyrone and ibuprofen. Acetylsalicylic acid is contra-indicated for children younger than six years of age due to its higher toxicity when compared to other anti-pyretic drugs (digestive bleeding, hypersensitivity reactions, Reye's syndrome).

The safety of the drugs will vary according to its type, dose, duration of the treatment, concomitant use of other drugs, nutrition status and previous medical history (peptic disease, respiratory allergy, dehydration, liver or kidney diseases). In every case, all these factors have to be taken into consideration.

Table 1 shows the recommended dose for children and adults, time interval between administrations, and main restrictions to the use of these drugs. It should be stressed that the dose of an NSAID to treat inflammatory processes is generally higher than the dose to relieve pain and fever.

Table 1. Main characteristics of acetaminophen, dipyrone and ibuprofen.

	Acetaminophen	**Dipyrone**	**Ibuprofen**
Characteristics			
Age	From the neonatal period on	After 3 months of age	After 6 months of age
Use	Oral, rectal 1	Oral, rectal, IM, IV	Oral
Dose for adults*	10 to 15 mg/kg 2 g/ day	10 to 20 mg/kg 2 to 4 g/ day	5 to 10 mg/kg / 30 to 40 mg/kg* 800 a 1200 mg/ day
Toxicity	Gastrointestinal Hepatic Hypersensitivity reactions (very rare)	Gastrointestinal Medullary: agranulocytosis/aplasia Hypersensitivity reactions Renal Skin: fixed eruption	Gastrointestinal Reduced platelet adherence Hypersensitivity reactions Renal Skin: exanthema, urticaria, Stevens-Johnson syndrome Bronchospasm
Contra-indications	Acute or chronic liver disease Concomitant use of drugs metabolized by cytochrome P450	Neutropenia Previous hypersensitivity reaction	Peptic disease Platelet alterations Severe asthma or rhinitis Renal disease High blood pressure Previous hypersensitivity reactions to ibuprofen or other NSAIDs Concomitant use of other NSAIDs

•Anti-inflammatory dose recommended for children with arthritis and myositis

The most common adverse events associated with AAP/NSAIDs are pain and abdominal discomfort (10 to 30%), but the specific toxicity of the drugs is related to their class. Paracetamol and dipyrone are analgesics and anti-pyretic drugs with no anti-inflammatory activity. The NSAIDs, on the other hand, are generally weak acids that act by inhibiting the cyclo-oxygenases (COX).

COX are enzymes that convert the arachidonic acid into prostaglandin PGH2, that is unstable and, later on, is transformed into stable prostanoids (PGD2, PGE2, PGF2 and PGI2) and thromboxane (TBA2). Prostaglandins (PGs) are associated with inflammation and fever, but also play important physiological functions. Thus, the drugs that lead to their inhibition can also cause several damages to the body.

There are at least two isoforms of cyclo-oxygenase (COX-1 and COX-2) that have 60% homology. The NSAIDs act in a more selective or specific way on COX-1 or COX-2. Aspirin, ketoprofen, indomethacin, ibuprofen, and fenoprofen are potent COX-1 inhibitors. Diclofenac, nimesulide and piroxicam are considered selective COX-2 inhibitors, and the coxibs (rofecoxib and celecoxib) are specific COX-2 inhibitors.

COX-1 is present in almost every tissue, has a citoprotective action in the GI tract, is present in the kidneys and the endothelium, where it acts inhibiting the formation of TBA2 (a substance that favors blood clotting). Thus, drugs with potent inhibitory action on COX-1 damage the GI tract, cause bleeding and renal problems. The bleeding risk depends not only on the drug but also on the dose, time of use and presence of peptic disease. The concomitant administration of aspirin (even in low doses) and other NSAIDs can double or triple the risk of gastrointestinal bleeding.

When compared to acetylsalicylic acid, ibuprofen has a lower specific action on COX-1 and causes less damage to the gastrointestinal tract. If used in high doses, however, the risk of bleeding is increased.

The specific COX-2 inhibitors were developed with the objective of avoiding bleeding and other damages to the gastrointestinal tract, as it is not present in the digestive tract and platelets. Studies in adults showed that the use of specific COX-2 inhibitors was associated with thromboembolic events in these patients. This effect is due to the presence of COX-2 in the vascular endothelium and in the kidneys, where it inhibits the neutrophils adherence to vessel walls and causes vasodilation. As coxibs can cause vasoconstriction, edema, high blood pressure and thromboembolism, their use in children was not approved by the FDA.

The hypersensitivity reactions can occur after exposure to any kind of drugs, but are more frequent in patients with severe asthma, nasal polyps or with previous history of hypersensitivity reaction to aspirin. These reactions can be life-threatening and a new exposure to the drug that caused it is contra-indicated, as well as to other anti-pyretic drugs that can have cross-reactions. Among all AAP/NSAIDs, paracetamol is responsible for less hypersensitivity reactions. Although paracetamol is considered as one of the safest drugs to be used in children and adults, the ingestion of excessive doses of this drug has caused several deaths due to acute liver failure. Most adverse reactions in adolescents and adults are due to intentional overdose. In infants, however, the main cause of toxicity is related to errors in its administration.

Although ibuprofen is considered as safe as paracetamol for children older than six years of age, this drug should be used very carefully in patients with a history of atopia, allergic reactions to other NSAIDs, risk of peptic or renal disease. Some studies have shown that the administration of ibuprofen to newborns with persistent ductus arteriosus is as safe and effective as the use of indomethacin. However, the number of cases is small, and it is necessary to be cautious when prescribing this drug, as the data on its pharmacodynamics is very limited in newborns. During the neonatal period, the clearance of paracetamol and ibuprofen is reduced. While hepatotoxicity cases are rarely associated with the use of paracetamol, ibuprofen reduces the renal function by 20% in these children.

In **Chart 1** are listed the main conditions in which the use of NSAIDs should be avoided in children

Chart 1. Main conditions in which the use of NSAIDs should be avoided in children

1. Presence of:
- Signs and symptoms of renal, peptic and cardiac disease, diabetes
- Hypovolemia, dehydration (> 10% total body weight)
- High blood pressure
- Clotting alterations
- Nasal polyps, angioedema and bronchospasm
2. Previous medical history:
- Allergic reaction to NSAIDs
- Peptic disease
- Renal disease
- Congestive heart failure
- Diabetes
3. Concomitant use of drugs:
- Other NSAIDs (including low doses of ASA)
- Drugs with anticoagulant action
- Corticosteroids
4. Viral disease (ASA)
5. Use of alcohol

Dipyrone is widely used in Brazil, Spain, Austria, Belgium, Italy, The Netherlands, Switzerland, South Africa, Russia, Israel and India, but its use was banned in the US, Canada and some European countries as Sweden, due to the risk of medullary toxicity. Agranulocytosis (1.1 to 4.9 per million) and medullary aplasia (0.7 to 4.1 per million) are rare events, and it is difficult to determine if there is or not a causal relationship between the exposure to dipyrone and the appearance of these reactions. As there are large regional variations in the occurrence of agranulocytosis and medullary aplasia, it is believed that other factors (genetic, environmental) are involved in medullary toxicity.

5) Which AAP is the most effective in treating pain and fever in children?

There are few well-designed studies to compare effectiveness and safety of different anti-pyretic drugs in children. The effect of a single dose of ibuprofen (4-10 mg/kg) is comparable to a single dose of acetaminophen (7-15 mg/kg) in relieving pain in children. However, a study involving children with trauma showed that pain relief was higher after the administration of ibuprofen. In relation to fever, a 10 mg/kg dose of ibuprofen is more effective when the child has a rectal temperature ≥ 39°C, but with lower temperatures its effectiveness is comparable to that of paracetamol.

6) What are the advantages of using different AAP/NSAIDs simultaneously?

A randomized controlled study showed that the simultaneous administration of paracetamol and ibuprofen reduced the temperature by less than 0.5°C. Thus, the simultaneous use of these drugs is not recommended.

7) Is there any advantage in alternating the use of different anti-pyretic drugs?

Results of two randomized controlled studies designed to evaluate the alternate use of anti-pyretic drugs showed that alternately using ibuprofen and paracetamol was more effective than monotherapy in maintaining a child afebrile. No study was found in the literature comparing the alternate use of these anti-pyretic drugs and dipyrone. As these drugs are metabolized by different pathways and there is no interaction between them, we consider it appropriate to alternate the use of different drugs when the child has high temperatures, but the same drug should not be given in a time interval less than 4 hours. However, **it is necessary to be very cautious when prescribing these drugs, as they are given at different doses and time intervals and any confusion must be avoided.**

Errors in the administration of AAP/NSAIDs are quite common, as well as the concomitant administration of cough syrups or decongestants associated with the anti-pyretic drugs. It is essential to question the parents about the previous use of drugs, including over-the-counter drugs.

8) What are the effectiveness and the risks associated with the use of AAP/NSAIDs to relieve the post-surgery pain in otorhinolaryngological procedures?

Tonsillectomy and placement of ventilation tubes in the mid-ear are common surgeries in children, but the effects of the AAP/NSAIDs have not been extensively studied. There are few well designed studies comparing the various AAP/NSAIDs to evaluate their effectiveness and safety in children.

A meta-analysis was performed to evaluate the risks of bleeding before, during and after surgery and it was found that patients treated with NSAIDs had a **two-fold increase in the risk of bleeding** when compared to patients receiving opioids. **In every 60 patients treated with NSAIDs, there was one case of bleeding.** On the other hand, patients treated with NSAIDs had less nausea and vomiting, and it is estimated that one out of every nine patients treated with opioids will have nausea and vomiting in the port-surgery period.

A recent study published in Canada showed that the action of paracetamol given by oral administration was as effective as the topic use of lidocaine in reducing pain associated with the insertion of ventilation tubes in the middle ear.

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Bacterial Interference

Frida Scharf de Sanabria

Bacterial colonization of the mucous membranes is initiated after delivery. It evolves competitive interactions between various micro-organisms and it occurs when these micro-organisms compete to establish themselves and dominate their environment. Some of these interactions are synergistic while others are antagonistic (bacterial interference) which helps to maintain a normal balance between the members of the endogenous flora. This allows for the organisms to interfere with the growth of every other member and compete for their ecological space.

Bacterial interference can have a major role in maintaining the normal flora quantities in skin and the mucous membranes by preventing the colonization and subsequent invasion of potential pathogenic bacteria, which translates in preventing certain bacterial infections.

The mechanisms proposed in order to fulfill bacterial interference are:

1. the normal bacterial flora occupies certain sites en the epithelial surface cells which prevents the adherence of pathogens to these cells;
2. changes in the bacterial micro-environment;
3. production of antagonistic substances by some bacteria;
4. competition for the needed nutritional substances.

These mechanisms are carried out due to the mediators of bacterial interference, which include bacteriophages and the production of complex materials by the micro-organisms such as bacteriocins, or bacteriolytic enzymes and less complex molecules such as hydrogen peroxide, fatty or lactic acids, and ammonia.

Bacteriocins are bactericidal proteins that are generated by bacteria and extra cellular toxins that selectively kill other bacteria of the same species or a species closely related, promote colonization and are resistant to the bacteriocins that they themselves produce. These are unlike traditional antibiotics that have a broad or narrow activity spectrum.

Its method of action is to adhere to the receptor of the specific membrane, which is present in the susceptible cells. They are thereafter translocated to their specific targets within this cell. This is followed by morphologic and biological changes in the targeted bacterial cell and probably also in the bacteriocin particle.

Therapy with antibiotics can also affect the balance between pathogens and normal flora by disrupting the ecological balance and that way facilitating recurrent respiratory infections. The recent worldwide emergence of increasing resistance to antimicrobial agents has generated an interest in bacterial interference as a means of controlling the problem, substituting the use of antimicrobial therapy with artificial implantation into the normal micro flora bacterial strains of low virulence that are potentially capable of interfering with colonization and subsequent infection with more virulent organisms.

The alpha-streptococci (*Streptococcus viridans*) are part of and predominate in the normal flora of the respiratory tract just as the non-hemolytic streptococci, *Prevotella*, *Peptostreptococcus* and *Neisseriae* sp, and have capabilities of inhibiting colonization other pathogens such as *Streptococcus pneumoniae*, Group A beta-hemolytic *Streptococcus* (GABHS) also known as Group A *Streptococcus viridans* (GAS) and *Staphylococcus aureus*, and protect in the infection or colonization by GAS.

The interactions between the GAS and other bacteria have been studied for 30 years. Crow demonstrated that children that are colonized by GAS were less colonized by flora inhibitory or bactericidal for GAS, than those that were not colonized by this microorganism. This means that the interfering bacteria (such as *Streptococcus viridans)* is diminished in patients who did not respond to a therapeutic course of penicillin.

Sanders demonstrated that oral therapy with penicillin induced a decline in the number of interfering organisms, a decrease that lasted for at least 20 days after therapy.

The reports of interfering bacteria demostrate how the *Streptococcus viridans* play an important protective role in preventing the colonization and subsequent infection by GAS. This also supports that their absence can lead to failure of penicillin therapy.

The growth of certain bacteria can be suppressed utilizing nutrients in the nasopharynx, essential to the colonization of potential pathogens. This way, the use of interfering bacteria can be an option to the failure of treatments due to bacterial resistance. Therefore, implanting these strains in patients with recurrent GAS infections can be a method of preventing recurrences.

The role of the aerobic and anaerobic organisms is to interfere with the growth of GAS, in such a way that the children with GAS have less aerobic and anaerobic organisms. This was demonstrated with a group of children whom were given treatment for GAS for 10 days. One group was given four known strains of *Streptococcus viridans* and none presented a new episode of tonsillitis, while the ones that did not receive the strains, did present a second episode. This will be, maybe the future of the treatment of recurrent tonsillitis.

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