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Streptococcus pneumoniae's flaw

There is no doubt that, some time or another, you will have been in contact with *Streptoccus pneumoniae*. For behind this name, lies a bacterium at the origin of several common diseases. In the past few years, the medical world has been alarmed by the emergence of strains resistant to classical antibiotics. And now a miracle remedy - or rather a miracle protein - has proved it can conquer the bacteria that were fast becoming invincible. A new therapeutic strategy – which is applicable to other pathogens as well – is being developed.

This is a very seasonal topic since it deals with sinusitis, pneumonia and other such winter delights. In our climates, influenza is of course public enemy No 1. But did you know that pneumonia is one of the principal causes of death in Europe? Did you know that it has become more and more difficult to treat because of the emergence of bacteria that are resistant to antibiotics? What is more, did you know that the problem is spreading and that other fearful diseases are reappearing such as the bubonic plague which was thought to have been eradicated forever. No? Then read on … just for the thrill.

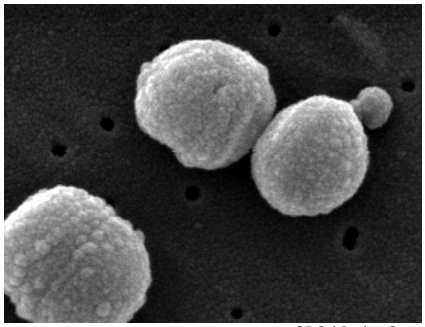
Streptococcus pneumoniae – a child snatcher

Streptococcus pneumoniae, also known as *pneumococcus*, is a bacterium that causes common diseases such as sinusitis, septicemia, otitis, pneumonia and even meningitis. It affects the very young or the elderly, whose immune system is impaired, or whose spleen is either inoperative or absent[1]. Every year, *Streptococcus pneumoniae* takes the life of more than a million children all over the world.

Even if you are in good health, your upper respiratory tract may well be harboring a few *Streptococci pneumoniae*. This "healthy carrier" status can last a long time. The illness only develops when the pneumococci spread beyond the upper respiratory tract. If the contamination remains local, it will cause pharyngitis, otitis midia (the most frequent form of ear inflammation in children) or sinusitis. But if it reaches the pulmonary alveoli, it could develop into a pneumococcal pneumonia – a serious illness that is widely spread and can be fatal. Other bacteria can also cause pneumonia. But only in the US, 25'000 people die of pneumoccal pneumonia every year. If the infection spreads to the surrounding tissues,

[1] The spleen plays a fundamental role in the elimination of certain bacteria found in the blood and which have managed to bypass the immune system.

it can cause pleurisy or even pericarditis[2]. Finally, if the bloodstream is contaminated, septicemia could ensue[3] or the pneumococci could reach other parts of the body and cause, for example, meningitis or infections in the joints. Hence, a pneumococcal infection can have various consequences, ranging from paralysis to cerebral lesions, and even death if no treatment is given or if the strain is resistance to any.



CDC / Janice Carr

Fig.1 *Streptococcus pneumoniae*

Taking up arms

The transmission of *Streptococcus pneumoniae* from one person to another requires close contact, i.e. a maximum distance of two meters between the two. The bacteria can be inhaled as such but more often than not they are propagated at the same time as a viral infection such as the common cold or 'flu'. In short, with every cough or sneeze, we literally shower our close neighbors with a few pneumococci!

There are several types or "strains" of pneumococci. Amongst the 84 listed, only 23 are at the root of most pneumococcal infections. A number of strains have a 'capsule' composed of polysaccharides (sugars), whilst others have none. The strains with capsules are responsible for the most serious illnesses since their capsules – precisely – protect them from our immune system. As a result, the bacterium does not owe its pathogenic powers to the secretion of a particular toxin but to its capacity to proliferate and to the physicochemical structure of its capsule.

Vaccination is a preventive measure against pneumococcal infections. A number of vaccines have been developed in the last 20 years and have been relatively successful in spite of the number of different strains of the bacterium which of course makes it difficult to obtain a really effective vaccine. The difficulty is that people who are most at risk are not systematically vaccinated, despite the very real threat of pneumococcal pneumonia.

As a result, year after year, thousands of people die of pneumococcal infections, and are treated with antibiotics such as penicillin – the choice antibiotic.

The rise in resistance

An antibiotic is a natural substance produced by fungi or bacteria found in the soil. Like a bio-weapon, antibiotics fight off other species of bacteria, either by doing away with them altogether or by slowing down their reproductive process. The latter is carried out via 4 choice methods: 1) the antibiotic can disrupt the fabric of the bacteria's outer layer (the external membrane), 2) it can block the production of proteins, 3) it can modify their energy metabolism or 4) prevent the duplication of their DNA. Fortunately, antibiotics are not toxic for humans when administered in very small doses.

As a consequence, in order to protect themselves, bacteria develop their own natural mechanisms of defense against harmful antibiotics. There are two mechanisms which can neutralize an antibiotic. The most frequent mechanism involves a protein known as an "enzyme" that lacerates the foreign antibiotic thus inactivating it. In more rare instances, the antibiotic remains intact but has no effect on its target because the bacterium has either become "impermeable" to it or because the target itself is no longer recognized by the antibiotic. A bacterium becomes resistant in two ways: either a mutation in its DNA can "produce" the gene which will engender the bacterium's resistance or it can "receive" the resistance gene by way of another bacterium that is already resistant. The last alternative is of greater importance than it was thought to be and gives an idea of the speed at which the phenomenon of resistance evolves in the world of bacteria.

It is a fact that we are now facing what is called a "rise" in resistance. The first incriminating factor stems from the mistaken and frequent use of antibiotics prescribed in the event of…viral infections[4]. Several studies on the subject have shown that an increase in bacterial resistance is due to the excessive use of antibiotics, compounded by treatments that are either too short or too long, and doses which are occasionally incorrectly prescribed. In only 20 years, the intake of antibiotics per person and per year has doubled. Besides applications in both human and veterinary medicine, antibiotics are also used as

[2] Inflammation of the membrane which surrounds the heart.
[3] Generalized infection.

[4] Antibiotics only have an effect on bacterial infections.

growth factors in animal rearing, as protective agents in plant cultures and very recently in genetically modified organisms (cf. Protéines à la "Une", Issue 4).

It is obvious that frequent exposure to antibiotics results in the selection of resistant bacteria by eliminating the sensitive ones. What is more, under such selective pressure, bacteria evolve by constantly developing new mechanisms in order to elude the action of antibiotics. And as a bacterium's resistance increases, novel antibiotics are tested…which only favor novel resistance. It's a vicious circle accompanied both by medical and – naturally – economical consequences.

Meanwhile, antibiotic research in the pharmaceutical industry has rested on its laurels, or rather on its huge therapeutic arsenal which was thought to be sufficient. Indeed, no novel family of antibiotics has been discovered in the last 25 years. The development of a new antibiotic is not only a long drawn-out process – about 12 to 15 years – but is also very complex and costly. Good enough reasons for this apparent negligence!

In recent years, the emergence of resistant strains of bacteria has complicated the treatment of infections due to *Streptococcus pneumoniae* considerably: 40% of pneumococcal strains have become resistant not only to penicillin but also to cephalosporins and erythromycin. A further disturbing phenomenon is the emergence of multi-resistances. For instance, resistance both to penicillin and erythromycin is combined in one same strain of *Streptococcus pneumoniae* in 70% of the cases. This resistance is particularly high in France: from 4% in l987, it reached 48% in l997.

A bacteriophage to the rescue

The time came to find a novel treatment . And it seems that a team of researchers at Rockefeller University in New York has done just that. Their work has recently been published. The results are impressive. And to make them, they took advantage of the properties of what are called "bacteriophages".

A bacteriophage is nothing more than a virus that infects only bacteria. Also designated as a "phage", a bacteriophage is very choosy as to the species of bacteria it selects. Once it has bound to the surface of a specific bacterium, it injects its genetic material (either DNA or RNA). As a result, the virus can multiply borrowing all the complex mechanisms of the bacterium cell. Once it has multiplied sufficiently, it can then use various tactics to destroy the bacterium it has just been squatting. The newly formed viruses are free to proceed and infect other bacteria. Like every respectable bacteriophage, phage Dp-1 – which is specific to *Streptococcus pneumoniae* – has a way of "escaping" at the opportune moment. This is done by way of an enzyme – or amidase – termed 'Pal' and that can "digest" the bacterial wall.

The University of New York research team exposed *Streptococcus pneumoniae* bacteria to purified Pal proteins. Within seconds of exposure, 15 common strains of the bacterium were destroyed via ingestion of their outer membrane, including strains that were extremely resistant to penicillin. In the second stage of their experiment, the researchers checked Pal's capacity to eliminate *Streptococcus pneumoniae* "in vivo", i.e. inside a living organism which, in this case, was a mouse. Following the first administration of Pal to infected mice, all trace of infection had disappeared from their nasal mucus after only 5 hours. They concluded that pneumococci found on the nasal or pharyngeal mucous membrane must be extremely sensitive to the action of Pal. A few days later, pneumococci which had survived the treatment reappeared in a few animals. These bacteria however were unable to re-colonize the mice's pharynx. What is more, resistant strains to Pal did not appear even after repeated exposure to weak doses of the amidase. Best of all, this particular enzyme seems to have little or no effect on the microorganisms whose natural habitat happens to be the human pharynx.

Antibiotherapy: plans for the future

Truly a revolution in the treatment of infectious diseases, antibiotherapy has saved many lives. However, resistance to antibiotics – itself linked to the natural evolution of bacteria – has reached an alarming peak. Cases of multi-resistance – i.e. bacteria which are resistant to several families of antibiotics at the same time – are increasing. And so are therapeutic failures… Diseases we thought were eradicated are reappearing. Respiratory infections, meningitis and sexually transmissible diseases are gaining ground as the effectiveness of treatments are dwindling. The bacterium which causes tuberculosis – also thought to be a thing of the past – is making a comeback. In the face of this global problem, the promising results obtained in the battle against *Streptococcus pneumoniae* are a glint in the dark. Indeed, the existence of specific bacteriophages that are lethal to practically all bacteria is a fact. As a consequence, antibiotherapy could be applied to other pathogens. Could it be that the world may owe its salvation to viruses in the future?

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For further information

On the internet:

- Fondation pour la Recherche Médicale (FRM) : http://www.frm.org/Scientifique/Sujetsfond/Antibiotiques/cadantib.htm

A little more advanced:

- Loeffler J.M. et al., "Rapid Killing of Streptococcus pneumoniae with a Bacteriophage Cell Wall Hydrolase", Science 294:2170-2172(2001) PMID: 11739958

Illustrations:

- Heading illustration, Source: http://fr.wikipedia.org/wiki/Achille

At UniProtKB/Swiss-Prot:

- Lysin (PAL), Bacteriophage Dp-1: O03979

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