

## ANTIMICROBIAL TREATMENT OF NASAL INFECTIONS

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Conservative and especially antimicrobial treatment of nasal infection does not differ in principle from that in infections of other parts of the body. This means that antimicrobial treatment should be instituted only when

1. the infection is caused by a micro-organism sensitive to an antimicrobial agent,
2. this agent can reach the site of infection in a concentration at least high enough to inhibit the growth of this micro-organism, but if possible high enough to kill it;
3. the total advantage of the application outweighs possible disadvantages of antimicrobial therapy, as sensitization to the drug, changes in the normal microflora and exchange with resistant micro-organisms.

To start with the last point mentioned you have noticed that the word "seriousness" of the disease is not used, although implicated partly, by the last prerequisite. This is done on purpose. There are many minor infectious diseases of which we do not know the natural history well enough to decide whether and at which moment antimicrobial therapy might be indicated, notwithstanding their primary innocuous appearance. We do know for example that an acute inflammation of the middle ear or a paranasal sinus is preceded in a certain percentage of the cases by an upper respiratory disease as by example the "common cold". We do not know, however, in what percentage this "common cold" as seen by the general practitioner is followed by the disease entities just mentioned.

The cases seen in our out-patient departments or in our hospitals are certainly no real indication of this. They certainly do not represent a random selection from the total group of acute otitis and sinusitis seen by the general practitioner.

We cannot decide therefore whether it is wise or not to institute antimicrobial treatment in every case of coryza which becomes bacterially infected to prevent the occurrence of these complications as we cannot weigh the disadvantages of the use of these antimicrobial agents against the advantage of preventing a more serious affection, which may become chronic and, when aggressive therapy becomes necessary, may then cause especially in children much more mental disturbances than we think of.

I have touched this subject only to show that in these so-called minor diseases there is a large field for co-operative research between the general practitioner and the medical research institutes, which has been neglected for too long a time.

But let us return to the first point, the requirement that the use of an antimicrobial agent is only permissible when the infection is caused by a micro-organism sensitive to it. Although one of the most important of the ten commandments of antimicrobial therapy, it is probably as much broken as the Christian ones. One of the reasons heard to excuse such happenings is that

it is so difficult to diagnose the real nature of the infecting micro-organisms straight away the first time one sees the patient, who is crying for immediate effective treatment.

Although this is true to some extent there are various facts and points, which should help us to stay away from the Devil's arguments.

First of all — and this is meant more for the general practitioner than for the specialist who is credited to be aware of it — the plain fact that a clear and watery nasal secretion is never bacterially infected, the only type of nasal infections against which antibiotics are useful. The secretion in a bacterial nasal infection always shows a colour running the whole scale from a light yellow tinge through yellow, greenish yellow to a full green in fully purulent infections or those caused by *Ps. pyocyanea*.

The only "false positive" in this regard probably could be the secretion in allergic conditions as a secretion rich in eosinophiles may show a slightly yellow colour, even without bacterial infection.

The second point to remember is that there is a definite relation between the type of bacteria, which can invade a certain region and the anatomical and histological structure of that region, provided there are no gross changes in that structure. By example, an acute infection of the urinary bladder will never be caused by *H.-influenzae*, a primary bronchitis never by *E.-coli*.

In this regard it is wise to remember that a large part of the nose, including the paranasal sinusses belongs to the respiratory tract and is covered by a mucus secreting cylindrical and partly ciliated epithelium resembling the epithelium of the lower respiratory tract, while only the vestibulum nasi knows stratified epithelium. For that reason both parts have their own pathogenic flora, on which the choice of the antimicrobial agent to be used can be based.

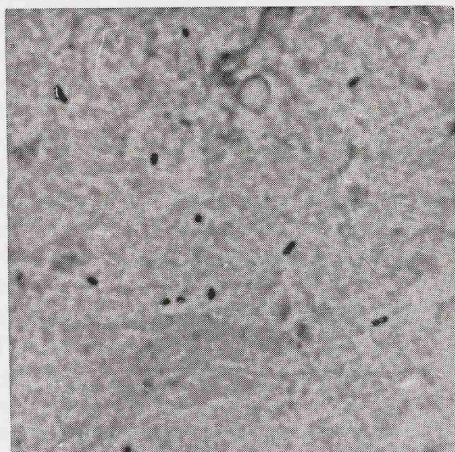
The normal respiratory epithelium can only be invaded by a rather small variety of micro-organisms, namely mainly pneumococci, *H.-influenzae* and beta-hemolytic streptococci and much less frequently *Kl.-pneumoniae*, *N.-catarrhalis* and *N.-meningitides*. *Staphylococcus aureus* does not belong to this group; this micro-organism needs a respiratory epithelium which has been damaged histologically by a viral infection, functionally by an abnormality as allergy or muco-viscoidosis, or anatomically by trauma or the knife of the surgeon before it can get a hold. The results of the bacteriological investigations from the group of Dr. Van Dishoeck here in Leiden and of which he spoke this morning, fit in completely into this picture.

First day antibiotic therapy of acute catarrhal infections of the nasopharyngeal region when necessary can therefore be directed with confidence against the first three micro-organisms mentioned above. Of these pneumococci and beta-hemolytic streptococci are and will continue to be very sensitive to Penicillin-G, Penicillin-V and Pheniticillin and these are still the best antibiotics against these infections.

*H.-influenzae* gives more trouble, as it is not sensitive to Penicillin-G, Penicillin-V and Pheniticillin. A quick recognition of its presence can therefore be of value. In this regard a Gram-stain of the nasal secretion can give a quick orientation, a fact which is forgotten too often in practice. Even a very small child is able to blow his nose over an open Petri-dish and one needs only a small flake of the purulent secretion to make a preparation on

a slide for staining. One can even make a better preparation from such a small flake than from the well known cotton swab on which the secretion dries out and thus not allow anymore a good spreading of the leucocytes. This method can even be helpful in cases of acute otitis, following an infected coryza, as there is quite often a direct correlation between the nasopharyngeal flora and that of acute otitis.

The next slide gives an impression of such a preparation.



H. - influenzae in nasal secretion after a respiratory viral infection in a child aged 12 years.

H. - influenzae dans la sécrétion nasale après une infection respiratoire virale dans un enfant de 12 ans.

The choice of the antibiotic to be used in these cases is based on the sensitivity to H.-influenzae for various antibiotics, which is given in table I.

As one can see it is very sensitive to Chloramphenicol and reasonably sensitive — although with exceptions — to the Tetracyclines. Both are certainly useful but although without absolute proof we have nevertheless strong indications that the use of bactericidal drugs in respiratory infections would be preferable. H.-influenzae, however, is as mentioned already insensitive to the action of Penicillan-V and Phenticillin, which antibiotics should never be used against this micro-organism. Furthermore it is only moderately sensitive to Penicillin-G of which rather high doses, in the order of  $4 \times 10^6$  U a day by injection, are necessary but then quite effective.

It is possible that Ampicillin (Penbritin) to which H.-influenzae is quite sensitive, might give a solution to this problem. It has proven to be effective in chronic bronchitis in which H.-influenzae plays an important role and this may be true also for acute and chronic otitis media, and acute and chronic sinusitis when H.-influenzae is the causative agent. In this regard it is worthwhile to remember that Streptomycin is very effective against H.-influenzae

Table I

Sensitivity to 8 antibiotics of H.-influenzae, isolated from patients with chronic bronchitis (in Units/ml for Penicillin-G and Penicillin-V, in gamma/ml for other antibiotics).

Sensibilité à 8 antibiotiques de H.-influenzae, isolés chez des patients avec une bronchite chronique (en Unités/ml pour Pénicillin-G et Pénicillin-V, en gamma/ml pour les autres antibiotiques).

Sensitivity Antibiotic	strains Nr. of tested	in U/ml or gamma/ml									
		0.25	0.5	1	2	4	8	16	32	> 32	
Penicillin-G	30	0	1	15	4	2	0	0	0	0	
Penicillin-V	26	0	0	4	5	2	7	2	5	1	
Streptomycin	30	n.t.*	9	12	4	2	1	0	0	2	
Chloramphenicol	30	1	26	3	0	0	0	0	0	0	
Tetracyclin	30	n.t.*	10	13	4	2	1	0	0	0	
Erythromycin	30	0	2	1	12	9	6	0	0	0	
Kanamycin	30	n.t.*	2	10	9	6	1	2	0	0	
Ampicillin	10	1	9	0	0	0	0	0	0	0	

\* not tested

but when used alone causes a quick rise in resistance in many cases. Used together, however, with Penicillin-G it gave us personally very good results in chronic bronchitis and the combination with Ampicillin might be worth trying, especially in sinusitis and in chronic, recurrent otitis media, caused by H.-influenza, both still problems in the way of a definite cure.

The region of stratified epithelium i.e. the vestibulum nasi and the skin, has a definite other spectrum of pathogenic flora. In itself, a healthy stratified epithelium is no easy port of entrance to any micro-organism, except for virulent staphylococci, which may enter the hairfollicels and cause the well known folliculitis and furuncles, of which especially the latter one are dreaded for the possible complications of thrombosis of the sinus cavernosis.

Today, even in general practice 20—30% of the staphylococci may be resistant to Penicillin-G and, if there has been a recent contact with a hospital

in any form, some of them may be also resistant to other antibiotics. The latter is certainly true when the staphylococcal infection occurs in hospital. In infections, which may threaten life it is therefore best to start treatment with one of the new penicillinase-resistant Penicillins, preferable Methicillin (Celbenin, Staphcylin).

After the sensitivity of the *Staphylococcus* has become known, one may change to another effective antibiotic if possible. This should be seriously considered as Methicillin-therapy seems to be followed in a rather high percentage by superinfections with Gram-negative bacteria, even more so than after the use of other antibiotics.

The picture we have just given of what we would call in some way "normal pathogenic" flora of the nose, can change entirely when the superficial outer lining of the nose has been damaged by a viral infection, a metabolic disorder, a traumatic or a surgical wound. As well the region covered by cylindrical epithelium, as that covered by stratified epithelium are than open to a wide variety of bacteria of which the sensitivity cannot be predicted at first sight.

In these circumstances a bacteriological examination is absolutely necessary; a Gram-stain for quick orientation and a culture for a full determination of the organism and antibiotic sensitivity.

When infected material can be obtained and urgency is requested, a preliminary indication of the sensitivity of the micro-organism can quite often be obtained within 6—12 hours, provided the hospital has its own bacteriological laboratory, an absolute prerequisite to-day to my opinion. This leaves only the few "panic" cases in which there is really no time to wait for any answer in which the choice of antibiotic treatment cannot be based on facts, but on a balanced guess. In these cases we prefer personally the combination of Kanamycin, provided renal function is good and in a dosage not exceeding 1 gramme a day, and Chloramphenicol 2—3 grammes a day, as this combination covers the widest range of micro-organisms. Only when an impaired renal function is suspected or shock is present, we substitute Kanamycin in this combination by Methicillin in a dosage of 6 grammes a day.

When one can wait for the answer from the bacteriological laboratory one can say to-day that with all the antibiotics available there are not many circumstances left where there is no antibiotic to meet the need. The semi-synthetic penicillins Methicillin, Oxacillin (Prostaphlin, Penstapho) and Chloraxillin (Orbenin) have solved the problems raised by the infections with "hospital"-staphylococci to a great extent.

Infections with Gram-negative bacteria can be met mostly by the use of one of the Tetracyclines, Chloramphenicol, Kanamycin or Sulfonamides. The increasing number of infections with *Ps. pyocyanea* still cause an anxiety which has not been solved entirely by the discovery of Colistin (Colimycine), the less toxic brother (or sister?) of Polymyxin. Although quite effective in vitro against *Ps. pyocyanea* the results in tissue-infections are less good than in urinary infection, may be due to the fact that the large molecule of this antibiotic does not diffuse into the tissue as well as hoped for.

The solution of this problem probably lies more in the field of prevention, by adherence to strict hygienic measures and the restriction of the use of

broad-spectrum antibiotics, which cause a too rigid suppression of the normal bacterial flora, allowing *Ps. pyocyanea* to take the field.

I do fully realize that I have been able to touch in the short time available only some general points, which most of you probably know already. So I do not blame you when you went to sleep during this paper as it then still will give me the satisfaction that I offered you the opportunity for a much needed rest-pause in the rather heavily loaded programme of this "Boerhaave"-course.

## LE TRAITEMENT ANTIMICROBIEN DE L'INFECTION NASALE

Après une brève énumération des règles de base d'une thérapie aux antibiotiques, valables dans les infections du nez et des fosses nasales, l'auteur relève qu'on ignore encore s'il est souhaitable de traiter les infections soi-disant mineures, elles-même inoffensives, comme par exemple le «common cold», avec une thérapie antimicrobienne afin d'éviter des complications plus graves, comme une sinusite ou une otite. Les chiffres procurés par la médecine générale, les seuls valables en cette matière, ne sont pas connus.

Tant que la structure histologique et la fonction de la muqueuse du nez ne sont pas atteintes, on n'a, dans le choix d'une thérapie aux antibiotiques, qu'à tenir compte d'un nombre restreint de microbes, à savoir les pneumocoques, les streptocoques bêta-hémolytiques et les hémophilus influenzae.

Seul le traitement des infections aux hémophilus influenzae donne des difficultés. L'auteur mentionne la sensibilité de ce micro-organisme pour les différents antibiotiques. La sensibilité pour l'Ampicilline (Penbritine) est signalée.

Dès que la structure histologique ou la fonction de la muqueuse sont altérées par n'importe quelle lésion (virale, métabolique, traumatique, opératoire), une infection avec n'importe quel micro-organisme pathogénique peut se produire. Dans ces cas le choix de la thérapie aux antibiotiques doit être conditionnée par l'antibiogramme du micro-organisme.

Il résulte de ceci que dans presque tous les cas un traitement réel et dirigé est possible. Les infections aux *pseudomonas aeruginosa* (pyocyanique) restent néanmoins encore difficiles à combattre malgré la Colistine.

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