WHAT YOU ALWAYS ASKED ABOUT ACUTE RHINOSINUSITIS AND NOBODY ANSWERED

Acute Rhinosinusitis under debate

Official Symposium
ERS and ISIAN 2010

23rd Congress of the European Rhinologic Society
29th International Symposium of Infection & Allergy of the Nose

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Dear Friends and Colleagues,

Both Acute and Chronic Rhinosinusitis have increased in prevalence over the last 30 years, representing a serious problem for public health. Chronic Rhinosinusitis can affect the general well-being and quality of life (QoL) of patients, as well as the daily activity of GPs and ENT specialists alike, constituting a considerable economic burden for patients and National Health Systems. This was one of the main topics covered during the 23rd ERS and 29th ISIAN Congress held in Geneva last June.

Given the great quantity of messages I have received since the meeting, the conference should be considered a success. Several important questions were answered at the conference, alongside doubts and new issues that were raised. The high level of interest in Rhinology among the ENTs present was confirmed by their active participation in the scientific sessions. In Geneva we had the opportunity to discuss a variety of topics regarding Rhinosinusitis, thereby challenging our perception and encouraging the proposal of alternatives for yet unsolved problems.

During the symposium on New Treatment Approaches, organized by Hartington Pharma, we had the chance to see several lectures by prestigious scientists from the field of Rhinology. They presented and discussed the latest data on Rhinosinusitis therapy, including some alternative remedies such as phytotherapy, based on proven evidence. A clear example would be *Cyclamen europaeum* L. extract, a therapy for draining sinuses during Rhinosinusitis, which is already available in various countries around the world. Its efficacy and safety were assessed in depth, with the conclusions of said analysis subsequently presented in detail during the Symposium.

At present, scientific researchers and ENTs are investigating the best ways to treat their patients. As a result, different therapies are being tested, all of them based on innovation and differentiation. We should endeavour to move forward every day, improving our knowledge, our daily practice and most importantly, our patients’ health and QoL!

Prof J. Silvain Lacroix, MD, PhD

President of the Organizing Committee
ERS 2010 & ISIAN Congress
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Rhinosinusitis is a significant health problem on the increase, which places a considerable financial burden on society. Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the name commonly used is Rhinosinusitis.

Rhinosinusitis is a highly prevalent disease that, according to estimates, affects up to 16% of the adult population annually. In the European Union, Acute Rhinosinusitis, (ARS) (with symptoms lasting less than 12 weeks), affects between 1-2% of the population, that is to say between 10-20 million people per year. The prevalence of the illness is higher in women and in individuals living in the South. As far as Chronic Rhinosinusitis is concerned, incidence ascends to 10% (more than 50 million people). The prevalence of Rhinosinusitis is increasing on a global scale, making it one of the most common reasons for a physician consultation in primary care. Treatment is aimed at symptom relief, preventing disease progression/recurrence, and most importantly, improving the patient’s quality of life. Currently available therapies often fail to provide adequate symptom relief and new therapeutic options would be a step forward, particularly if they help to avoid the overuse of antibiotics for a disease that is mainly viral in origin.

The 23rd Congress of the European Rhinologic Society (ERS) and the 29th International Symposium of Infection and Allergy of the Nose (ISIAN), the most prestigious International Rhinology meeting, took place in Geneva, in June 2010. Leading figures from the scientific and medical communities came to join the most prestigious scientists and physicians involved in sinonasal disease research. Round table discussions, symposiums, free paper communications and poster presentations contributed to making it an outstanding event.

With the aim of reviewing the pros and cons of Rhinosinusitis therapies, Hartington Pharma Ltd organized and sponsored the symposium, Acute Rhinosinusitis Under Debate, What you always asked about Rhinosinusitis and nobody answered. A range of therapies were debated by internationally renowned specialists, such as Prof. Claus Bachert (Belgium), Prof. Wytske Fokkens (Netherlands), Prof. Ludger Klimek (Germany), Prof. Valerie Lund (UK) and Prof. Joaquim Mullol (Spain). Their lectures included detailed explanations regarding the Pros & Cons of the different therapies for treating Acute Rhinosinusitis. Finally, important questions were raised and answered in a debate on Acute Rhinosinusitis.
Acute Rhinosinusitis Under Debate

What you always asked about Acute Rhinosinusitis and nobody answered

Do we know the important facts?

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The aim of the meeting is to outline the pros and cons of different approved treatments, with Ludger Klimek rounding the event off by presenting the extract of Cyclamen europaeum L. as a new approach to the treatment of Acute Rhinosinusitis.

Figures regarding the main epidemiology of cases of Acute Rhinosinusitis in various European countries show a general increase in the number of cases of Acute Rhinosinusitis. This rise is directly correlated to the total population of the countries studied. The main cause of Acute Rhinosinusitis is a post-viral infection, mainly related to inflammation, but in some cases bacterial infection is present. However, it should be noted that Rhinosinusitis is by no means related to bacterial infection in all cases.

Based on data from recent studies, it is estimated that in the European Union, there are approximately 20 million cases of Acute Rhinosinusitis each year (Fig. 1).

Fig. 1: Prevalence of ARS in the E.U.

Fig. 2: ARS prevalence.
US Census Bureau, International Data Base, 2004
One of the main problems stemming from the treatment of this disease is that in the majority of cases antibiotics are used, thereby adding to data on resistance to antibiotics in Europe (Fig. 2). Given that the cause of bacterial infection has not been proved, this is a surprising fact. The data for countries that use more antibiotics than others, such as France, Spain or Portugal, show that these countries have higher rates of bacterial resistance. A recent study performed in Spain, called the PROSINUS study, highlighted the huge amount of drugs that are given to treat a disease that, in 85% of situations, is self-limiting (Fig. 3). In a comparison between GPs and ENTs, half of them give antibiotics, with mostly GPs prescribing mucolytics, decongestants, saline solutions etc., none of which, or at least not in all cases, have proved their efficacy.

The resulting expenditure on direct and indirect costs is extremely high. A calculation taken from the PROSINUS study estimates that, with drugs and both direct and indirect costs, each case of Acute Rhinosinusitis accounts for approximately €800. By extrapolating that data, the cost of Acute Rhinosinusitis comes to more than one billion dollars per year in Spain alone (Fig. 4).

In conclusion, it is clear that Acute Rhinosinusitis is commonly an inflammatory disease, the treatment for which is aimed at relieving symptoms, allowing sinus drainage and ventilation, as well as helping to prevent bacterial infection.

So, several questions need to be answered. Should Acute Rhinosinusitis be diagnosed by symptoms and nasal examination? Or by imaging and other diagnostic tools? Do corticosteroids provide effective relief of symptoms caused by sinonasal inflammation, or should they be avoided in Acute Rhinosinusitis? Should antibiotics be used as a first line treatment or should they be reserved for bacterial infection? And finally, can Cyclamen europaeum L. constitute an adjunct treatment for Acute Rhinosinusitis?
What are the main tools that we should use to make a good diagnosis of Acute Rhinosinusitis?

Prof. Valerie J Lund, CBE
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Honorary Consultant ENT Surgeon
Royal National Throat, Nose and Ear Hospital
London

The vast majority of clinicians dealing with Rhinosinusitis do not try to validate a diagnosis arrived at due to the presence of certain symptoms. Her observations were based on the EP3OS document, commonly used as a reference at this meeting and previous events. According to the EP3OS document, when discussing Rhinosinusitis, in essence what we are talking about is inflammation in its many different forms. Sinuses have limited ways of demonstrating the fact that they are inflamed, such as blockage or congestion, producing more mucus–discharged into the front or the back of the nose– and obviously there may be collateral effects on the sense of smell and facial pain or pressure (Fig. 5).

These symptoms are the basis for diagnosing Rhinosinusitis in general practice, or indeed in hospitals, where some specialists, such as paediatricians, will apply these criteria. The anatomy of the nose and sinuses clearly offer good reasons why patients may manifest these symptoms. However, ENT surgeons have the opportunity to look in the nose and to use images. In the case of Acute infection, obviously the focus is on mucopurulent discharge or swelling or oedema within the nose.

The use of imaging to validate these symptoms in an Acute situation is highly unlikely. Formal imaging is not
recommended for every case of Acute Rhinosinusitis, as it is unnecessary in most cases and would expose the patients to an undesirable amount of radiation. A study carried out by Gwaltney on medical students many years ago, for which he was roundly criticised at the time, shows conclusively that even in a viral cold there are definite inflammatory changes occurring within the sinuses (Fig. 6).

The problem when addressing Acute infection is how to define it in the context of duration of symptoms (Fig. 7). Often the medical community will apply arbitrary deadlines of 12 weeks as the break-point, when in actual fact these limits are derived from studies, where they are used just to facilitate the medical trial. The Food and Drug Administration dictates that the information be presented in these formats when studies are conducted. However, one thing does define the Acute episode: the complete resolution of symptoms. These can be organized in terms of severity. These are extremely common problems and the true extent of patients who proceed from a viral cold to a more extensive or severe infection with bacteria is very difficult to gauge. Estimating a level of just 1% or 2%, using data from the United States, encompasses a vast number of people. It does, however, also cover a wide range of problems.

There is a proportion of patients suffering the common cold whose symptoms actually increase after 5 days, or indeed have symptoms that continue for more than 10 days. What happens to these patients and why it happens is something that needs to be considered. These cases are arbitrarily determined to be a bacterial infection, when in actual fact there is often little evidence to support such a diagnosis. All that can be said is that it is an Acute problem that is continuing, which has not improved and that is probably not a virus. This is yet another example of how our definitions are extremely flawed. In order to avoid this problem, the sudden onset of 2 or more symptoms can be used as criteria – as detailed in EP3OS regarding the definition and diagnosis of a condition – such as nasal blockage or discharge, to which facial pain and reduction of sense of smell might be added (Fig. 8).

Facial pain is clearly an important symptom in Acute Rhinosinusitis, for which the nose can be examined and other collateral problems looked for. However, plain X-rays are not recommended due to the many false negatives and false positives they give. A CT scan is not indicated unless there are additional problems present. For example, when the patient has not improved, or they are a special case, such as an immunocompromised patient or indeed that there are signs of regression to severe complications.

In a recent Asian study conducted by Professor Wang, in China, Indonesia, Malaysia, India, Pakistan, etc., the management of Acute Rhinosinusitis was looked at in the real world, studying what was happening in the diagnosis and treatment of this condition out in the field, where people actually come with the problem. Over two and a half thousand questionnaires were sent out, of which 2,524 were evaluable, to GP’s, ENT surgeons acting in this field and paediatricians throughout Asia, who were quizzed on diagnosis management.
From the data that came back, an interesting statistic emerged: 6 to 10% of the patients that were seen, on a daily basis, had Acute Rhinosinusitis (Fig. 9). Moreover, 94% of this group used the same diagnostic criteria as the EP3OS recommendations. Of particular note, 63% said there was no need for radiology in order to make the diagnosis. So broadly speaking, these Asian doctors are working in accordance with EP3OS guidelines.

An analysis of the symptoms most commonly used for diagnosis, taken from the same study, shows that nasal congestion and rhinorrhea are in first position, while rather interestingly, facial pain and pressure, as well as sense of smell, feature much further down the list, outside the top 3 positions (Fig. 10).

While X-ray/CT scan are not recommended, clinicians should always be aware of certain features, such as unilateral symptoms, the sudden onset of various minor symptoms: eyelid swelling, eye redness, displacement of the globe, etc. All those things that might indicate an Acute orbital or intracranial complication is brewing, such as a subperiosteal abscess, Pott’s puffy tumour or indeed a frontal lobe abscess. Complaints that are often present, ostensibly as an Acute Rhinosinusitis, are severe allergic rhinitis, sudden and spontaneous onsets of cerebrospinal fluid leaks and other rather rare conditions that, nonetheless, can be quite Acute in their presentation: vasculitis, invasive fungal disease and indeed tumours such as T-cell lymphoma (Fig. 11).
What are the pros and cons of the use of corticosteroids in Acute Rhinosinusitis?

Prof. Claus Bachert, M.D., Ph.D.
Chief of Clinics ENT Department
Ghent University Hospital
Ghent

There is no doubt that corticosteroids are recommended in the treatment of Acute Rhinosinusitis, but what is the background to that recommendation? Underlying inflammation is believed to be what drives the disease of Acute Rhinosinusitis. This inflammation causes increased vascular permeability and mucosal oedema. Mucociliary clearance function impairment and increased mucus production are just signs of what is going on in terms of inflammation (Fig. 12).

The objective of medical treatment is the infection, but the use of antibiotics should only be considered if there is strong evidence that bacteria are involved. However, for all the other patients, which is the vast majority of patients with Acute Rhinosinusitis, inflammation should be targeted, thereby relieving congestion, improving drainage and ventilation, as well as sinus clearance. In view of this information, it is easy to build a case for glucocorticosteroid therapy.

Let us review the results of a recent study that compared a glucocorticosteroid to amoxicillin, which is the standard antibiotic treatment, and placebo. The study, data from which was published in the Journal of Clinical Investigation, looked at the time of the disease itself, with a treatment period of 15 days, and a follow-up of the subsequent 15 days to see whether there was any recurrence. The results point to the fact that the glucocorticosteroid did a good job, performing better than amoxicillin, which was no different to the placebo in that group of patients. This data clearly indicates that this is not a bacterial disease in the first place. Some effect was achieved with glucocorticosteroid, and this was dose related. Considering all the symptoms, it had a significant effect on those of congestion, facial pain, headache and rhinorrhea, with the higher dosage proving more effective in all these cases (Fig. 13).
Quality of life issues were studied in an English-speaking sub-group of patients, where yet again no change was perceived between amoxicillin versus placebo, while the higher dosage of the topical glucocorticosteroids did make a significant change for those patients. There is further evidence from studies where glucocorticosteroids are added on to an antibiotic, which support their use (Fig. 14).

So in fact, glucocorticosteroids as a monotherapy or as a combined therapy with antibiotics are recommended by various studies, such as the 2007 EP3OS guidelines. There is even meta-analytic evidence now, steroids for Acute Rhinosinusitis, a hotline meta-analysis actually recommending, or at least supporting the notion that there is more evidence for than against glucocorticosteroids (Fig. 15).

So, are there any arguments against the use of glucocorticosteroids? Well, yes there are. While in just one day the glucocorticosteroids take effect, the extent of the difference they make should be contrasted against the placebo group. The result is a 5% to 7% difference versus placebo, which is rather small.

It should not be forgotten that Acute Rhinosinusitis is a self-healing disease, which means patients are fighting against something that is healing anyway (Fig. 16). Therefore, the difference is just making that process slightly faster. By observing the difference glucocorticosteroids offer as part of an adjunct treatment with the same critical eye, the results also show a somewhat insubstantial difference.

The principal argument against glucocorticosteroids would seem to be that Acute Rhinosinusitis is usually a self-limiting disease, and as such is it really worth treating for such minor improvements to the patient’s condition. In addition, corticosteroids are not well accepted, people have steroid-phobia, and high dosages are required to achieve small treatment effects. In fact, the dosage needed to achieve a significant effect is double that recommended for allergic rhinitis (Fig. 17).
The question of how glucocorticosteroids reach the sinuses is as yet unanswered. The issue of how they actually work has yet to be explained, and even the European Medicines Agency (EMA), the European Health Authorities, have not given an indication for the topical use of glucocorticosteroids in Acute Rhinosinusitis, despite their inclusion in guidelines for treatment.
What are the pros and cons of the use of antibiotics in Acute Rhinosinusitis?

Prof. Wytske Fokkens
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Why do we use antibiotics? What is the evidence to support their use? Why should we use antibiotics much less, and follow instead the management scheme based on EP3OS? In essence, there are maybe two main reasons given for using antibiotics. The first supposition is that Acute Rhinosinusitis is a bacterial disease, the second being that this disease can lead to severe complications. These two presumptions deserve closer examination. ENT specialists often refer to Acute Rhinosinusitis as non-viral Rhinosinusitis, due to the fact that it is frequently unknown whether it is bacterial. According to the EP3OS definition, Acute Rhinosinusitis usually starts with a common cold, and if the symptoms increase after 5 days or persist after 10 days, given that this is not the normal course of a common cold, it is defined as Acute Rhinosinusitis. However, if these patients undergo a CT scan, only a minority of them actually have bacterial disease, while the rest have persistent inflammation for which the cause is unknown.

Data from related literature regarding total nasal blockage indicate that 0.5% to 2% of patients with common colds are affected, and that of this group half is presumed to be caused by bacteria (Fig. 18). More than 10 years ago, the Dutch ENT surgeon Van Buchem published a paper in the Lancet comparing, for the first time, antibiotics to placebo in a normal GP population of Acute Rhinosinusitis, demonstrating that antibiotics did not have any additional effects to placebo (Fig. 19). Similar studies were conducted for Otitis 5 years earlier, also proving antibiotics to have little effect. In spite of this information, antibiotics are still used a great deal, indicating that this is apparently a difficult message to convey.

The Cochrane Review on antibiotics in Acute Rhinosinusitis provides an extremely interesting statistic: the NNT (Number needed to treat) is 7, so we have to treat 7 patients with antibiotics to probably make
We have to treat 7 patients with antibiotics to probably make one better slightly earlier. Clinicians should weigh the moderate benefits of antibiotic treatment against the potential for adverse effects.


one better slightly earlier. Also of note, is that only 32 studies passed the Cochrane limit, despite there being around a thousand in total.


So, is Acute Rhinosinusitis a bacterial disease? Yes, sometimes it is, but thankfully bacterial diseases can be healed. Antibiotics were discovered during the Second World War, but we survived bacteria before that time, so a simple bacterial infection does not need antibiotics (Fig. 20).

Perhaps a more interesting question is whether the liberal use of antibiotics can prevent complications. If that were true then it would be a strong argument for using them. Unfortunately, there is only very little data. An interesting study by Prof. Klossek looked at an estimated study population of 12 million in France, and found 30 complications per year, of which 11 were intracranial. Interestingly, even in France, more than a third of the patients did not have antibiotics before they entered the hospital, and the reason was very clear. When these patients actually commenced their complication, it was the first sign of the disease. So they lost consciousness or had other severe problems, and that was how they found out that they had an Acute Rhinosinusitis. Prior to this, they simply had not known; 44% of the patients actually had antibiotics before the complication, 70% of whom had a proven bacterial infection.

Inspired by these data, a study was carried out in the Netherlands that looked at a full year of the Dutch registration of hospital admissions. The adult population is in the same order as that studied by Prof. Klossek. There were 22 complications per year, of which 11 were also intracranial, while 40% did not have an indication of Acute Rhinosinusitis before they were admitted to hospital, and 43 patients had antibiotics before the complication. The interesting comparison between these two sets of data is that the Netherlands is one of the countries that use the least antibiotics in Europe, while France is the absolute top. It is calculated that there is at least 3 times the amount of antibiotics prescribed in France compared to the Netherlands (Fig. 21). Apparently, this made no difference to the number of severe complications of the disease.

So while Acute Rhinosinusitis can lead to severe complications, unfortunately antibiotics do not seem to prevent these complications.

Why then, is it so important for us not to use antibiotics?

By comparing the sales of antibiotics in the Netherlands, Denmark and Sweden, with those in France and Spain, and then correlating that information with the prevalence of penicillin resistance to normal Streptococcus in those countries, the answer becomes clear.

For that reason the European Community is very active in trying to make ENTs and other medical professionals more aware of the use of antibiotics. It is extremely important to inform the people who prescribe antibiotics for upper airway diseases, because more than half of the antibiotics prescribed in Europe are for respiratory problems, with upper airways accounting for a significant proportion. Consequently, the EP3OS guidelines advise against the use of antibiotics, except in the case of a very severe disease, with high fever and a lot of pain, or when there are signs of complications of Acute Rhinosinusitis (Fig. 22). Evidently, in those situations antibiotics are helpful, but it should be stressed that this is not the case for an extended common cold.

For Acute Maxillary Rhinosinusitis confirmed radiographically or by aspiration, current evidence is limited but supports the use of penicillin or amoxicillin for up to 14 days.

*The EP3OS guidelines advise against the use of antibiotics, except in the case of a very severe disease.*

*More than half of the antibiotics prescribed in Europe are for respiratory problems, especially those involving upper airways.*
What are the benefits and challenges regarding the use of *Cyclamen europaeum* L. as a potential treatment option for Acute Rhinosinusitis

Prof. Dr. Ludger Klimek
Center for Rhinology and Allergology
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On examining the pros and cons of the extract of *Cyclamen europaeum* L. for ARS treatment, one of the main advantages of this treatment is that it offers therapeutically multi-action functions, opening the ostiomeatal complex, and activating the mucociliary system. Consequently, it increases the drainage of mucus retained in the sinonasal area; produces fast dehydration and a detumescent effect (calms and relieves swelling). Unlike other products used in Rhinosinusitis treatment, Nasodren is not indicated for a specific etiology, but rather aimed at improving the symptomatology regardless of the cause that produces it.

This Product has no systemic effect while producing positive effects when treating Acute Rhinosinusitis. To understand how this is possible, it is necessary to look at the way that *Cyclamen europaeum* L. extract acts.

Without being dispersed through the entire mucosa of the nose, and possibly not even entering the sinuses at all, the *Cyclamen europaeum* L. extract produces a positive effect. The main secret that may be behind *Cyclamen europaeum* L. is the saponins, which produce a nociceptive response from the trigeminal nerve. A type of reflex is produced, thereby stimulating secretion and also ciliary transport (Fig.23).

In actual fact, the saponins stimulate the lipid membranes of the neuronal cells in the sinuses, thereby producing a reflex that stimulates secretion. Additional advantages the action of this extract offers in treating Acute and Chronic Rhinosinusitis are helping to dilute secretions, as well as increasing the transport of said secretions. So, finally there are some innovative new treatment options in Rhinosinusitis.

**MECHANISM OF ACTION**

No systemic effect

Saponins in *Cyclamen europaeum* L. extract produce a nociceptive response by stimulating afferent trigeminal nerve endings

Stimulation of secretory response and reactivation of ciliary transport through cholinergic stimulation.

Fig. 23: Mechanism of action.
There have already been a number of studies carried out on this new Product, the most interesting of which have been selected for this presentation to illustrate the effectiveness of *Cyclamen europaeum* L.

One study (Trial code 4334-083) was conducted in the US, in accordance with all the criteria you would expect from a modern trial - randomized, double-blind, placebo-controlled - using *Cyclamen europaeum* L. nasal spray on patients with mild to moderate Acute Rhinosinusitis. For this reason, the *Cyclamen europaeum* L. extract was used as a monotherapy, without any other medication whatsoever.

Patients with symptomatic Acute Rhinosinusitis, between 18-70 years old, with inflammation and mucopurulent secretion on nasal endoscopy and signs of acute sinusitis in the CT scan, were included in the study. Two main outcomes were evaluated, one being subjective: the daily patient-reported Total Symptom Scores (TSS); the other being objective: the percentage of Sinus Occlusion evaluated by CT scan.

The patients were evaluated for the symptoms they had afterwards, but more importantly were also examined radiographically, with three CT scans being performed on all of the patients - on the day of inclusion, day 15 and day 29 of the treatment. The study was carried out on adult patients who had to have symptoms that were not too severe, with mucopurulent secretion and nasal endoscopy, inflammation and a CT scan with the respective signs of Acute Rhinosinusitis. Randomization took place, followed by double-blind treatment for 7 days, with a total of 48 Cyclamen-treated patients in comparison with the placebo-treated patients (Fig. 24).

We observed a greater reduction in the percentage of sinus occlusion evaluated by the CT scan in the Cyclamen group than in the placebo group (Fig. 25) in the global study population (patients with ARS and CRS with acute exacerbations) on day 29 (endpoint), with a p=0.028. In the subgroup of acute rhinosinusitis patients we observed an important difference in the TSS reduction for the group of Cyclamen-treated patients (Fig. 26), and
a statistically significant difference (percentage-wise) in the reduction of sinus occlusion measured by CT-Scan (p=0.045) compared to placebo (Fig. 27).

The study concludes that *Cyclamen europaeum* L. nasal spray improved both subjective & objective measurements of sinusitis. *Cyclamen europaeum* L. shows an important reduction in the percentage of sinus occlusion in Total Symptom Score, and a significant reduction in Sinus Occlusion when Cyclamen europaeum is compared to placebo in patients with ARS. The placebo effect observed with patient-reported symptom score is not supported by objective measurements. No serious or unexpected adverse events were observed in the study. Despite the relatively small number of patients, the data indicates that there is indeed a clear benefit from treatment with the *Cyclamen europaeum* L. extract (Figs. 28).

Another study (Trial code CYC_E_03), performed at the Centre for Rhinology and Allergology in Germany was carried out on patients with moderate to severe disease. For this reason, antibiotic treatment was included, which came in the form of amoxicillin (500 mg) administered 3 times daily, followed by an add-on with *Cyclamen europaeum* L. in a placebo-controlled way. (Fig. 29).

The study population was about one hundred patients with moderate to severe rhinosinusitis. Randomization was followed by double-blind treatment for 15 days, due to the fact that these patients were more severely diseased. The study was assessed using patient symptoms reported on a visual analogical scale (VAS) for each symptom. The patient must draw a vertical line between 0 and 10 on the VAS (nasal obstruction, mucous secretion, facial pressure or pain (headache), loss of smell); endoscopic signs evaluated by physicians (mucous edema, mucopurulent secretion). Satisfaction with treatment is evaluated by patients and investigator, as is the case for adverse events reporting.

From the study population, most patients were evaluable even after the study period. All of these patients received treatment, that is to say amoxicillin treatment. The study shows that *Cyclamen europaeum* L. nasal spray produces an additional effect over amoxicillin, compared to the control group, presenting a statistically
significant reduction in the percentage of mucous edema (endoscopic signs) (Fig. 31), and greater treatment satisfaction by both patient (p=0.0327) and investigator (Fig. 32 & 33).

*Cyclamen europaeum* L. has also demonstrated a very safe profile, with no serious or unexpected events. Both studies, that of the Centre for Rhinology and Allergology in Wiesbaden and the other performed in the US, also focused on the safety aspects of *Cyclamen europaeum* L., due to the importance of this issue for every Product. Neither of the studies reported any serious adverse events, or indeed unexpected events, with the new Product displaying excellent safety aspects (Fig. 28, 35). However, it should be noted that the treatment might cause some patients to experience some itching or burning sensations from the trigeminal nerve activation. This forms part of the way in which this new Product acts, and as such is not considered to be an undesirable side effect. In other words, these sensations indicate the new treatment is having an effect on the disease. Feedback from our investigators and patients regarding this new Product is very positive, with a strong preference for natural medications over chemical agents.

All clinical results of the studies reviewed and assessed point to a benefit from the effects of Nasodren® in RS, showing relief from symptoms and faster recovery in acute rhinosinusitis due to its sinonasal drainage properties. Nasodren® can contribute to reducing disease progression time, to decreasing the need for antibiotics or to boosting their effects, as well as reducing the number of complications and chronification. Nasodren® is indicated as a first line treatment for rhinosinusitis symptoms in monotherapy, and in combined treatments has shown to be at least of the same efficacy as standard combined treatment. Neither of the studies reported any serious adverse events, or indeed unexpected events, with the new Product displaying excellent safety aspects.

"*Cyclamen europaeum* L. safety aspects:

- No systemic effect
- No serious or unexpected adverse events

Nasodren, due to its mechanism of action, can produce in certain patients some transitory, mild nasal itching, smarting, rhinorrhoea and watery eyes sensation.

Natural treatment: good compliance"

![Cyclamen europaeum L. Safety issues.](image)

![Study CYC-03: Safety.](image)
Valerie Lund pointed out that if most of the patients have a self-limiting disease, even if it is bacterial, then it is not so critical to know whether or not it is bacterial, or indeed which bacteria.

Prof. Ludger Klimek added that even microbiological examination or microbiological staining, if the sample is not taken adequately, may give a high number of false positive or false negative results.

Prof. Claus Bachert defined the problem as a quantitative difficulty, not a qualitative diagnosis, stating that the question should not be whether some bacteria are present or not, but rather “How many are there?” He explained this would be extremely difficult to ascertain and moreover, clinical experience had demonstrated, as was the case in a group of patients with orbital complications in Belgium, that the cause of the disease was totally different. Most complications being on the first, second or, at most, on the third day of the disease itself, with very few exceptions. He concluded that it was safe to say that in most cases antibiotics were not needed, reasoning that the patients with complications coming into the clinic, quite a lot of them, were already on antibiotics, which had not prevented the complication.

Prof. Wytske Fokkens argued that defining moderate as non-bacterial was a mistake, given that in moderate disease there will very often be bacterial disease. She stated that the decision to use high fever or severe pain in defining severe Rhinosinusitis was totally arbitrary, without any data to prove this was the case, but that it was common sense to draw a safe line between moderate and severe disease. She concluded that, in her opinion, a significant amount of patients with the severe disease would also recover without any antibiotic treatment, but there was insufficient data at present to support this.

Prof. Valerie Lund noted that the stratification was based on Visual Analogue Scores and Chronic Rhinosinusitis which had not been validated as Acute, was determined by common sense, a method that was not entirely reliable. For her the distinguishing factor was the amount of other systemic problems – having pyrexia is something that makes the patient feel worse, as opposed to the nasal symptoms themselves being worse. However, she concurred with Prof. Wytske Fokkens on the fact that the area lacked investigation, and that one of the reasons for this was that ENT surgeons do not see mild to moderate patients in most National Health Service Systems.

The moderator asked whether a specific tool was needed that would verify, in a relatively quick reliable way, if the infection of bacteria was present or not? Or were the tools currently available more than sufficient?
very similar results, the vast majority of cases with complications having taken a rather dramatic course.

Ralph Mösges, attending the symposium, commented on the point that Nasodren does not enter the paranasal sinuses, raised earlier by Ludger Klimek, stating that this was in fact quite normal. Referring to a computer model of real patients’ noses, as opposed to an idealistic model, he pointed out that the results of studying many corticosteroids, nasal decongestants and other substances show that these never enter the paranasal sinuses.

Prof. Claus Bachert explained the mechanism in question was totally different to that of general reflexes, and that by inducing something in the nose by reflex mechanisms you are very likely to have an effect in the sinuses, without the need to go into them. Ludger Klimek affirmed that was exactly the case with Cyclamen europaeum L., highlighting that this mechanism was one of the great advantages of this treatment.

The moderator then prompted for comments on summary questions, everything counts for children, etc.

Prof. Claus Bachert on the question of corticosteroids in children stated that no single study of topical glucocorticosteroids in children had been performed, and that to his knowledge there was no evidence and certainly no indication for their use in children. Remarking on an earlier point regarding other means of decongestion, he explained that while there was evidence that decongestants obviously decongest the nose, they had very limited or no effect on the sinuses. He concluded that for symptomatic treatment the use of decongestants was not an option.

Prof. Joaquim Mullol ended the meeting by asking the speakers for their opinion on a natural extract of Cyclamen europaeum L. that is being used in many countries, like Germany, Italy, Spain and others. Specifically he asked the speakers if they thought there was a place, or role, for this Product that acts symptomatically, either as an adjunct treatment or monotherapy in Acute Rhinosinusitis.

Prof. Valerie Lund pointed out that patients had already voted and that millions of units of the Product had already been sold around the world, clearly demonstrating a need existed. She said that she believes there is a need for the extract of Cyclamen europaeum L. at a point in time where conventional medication did not offer a satisfactory solution, provided that there was clinical evidence of the safety and effectiveness of Cyclamen europaeum L. extract.

Prof. Claus Bachert agreed with Prof. Valerie Lund on the issue of safety, and commented that he had tried the preparation himself, experiencing the slight burning sensation mentioned in the studies but no other adverse effect. He reminded the meeting that to his knowledge no safety concerns had been reported in any of the studies carried out with the Cyclamen europaeum L. extract.

Prof. Ludger Klimek confirmed that no other side effects had been encountered, and that the slight to moderate burning sensation occurring in some patients was expected.

In answering the question on whether the extract of Cyclamen europaeum L. has a role in treating Acute Rhinosinusitis, he explained that a patient who has ARS symptoms, expects from the doctor a safe and effective remedy for their disease. The patient wants the doctor to do something, to help in some way. He concluded that as the Cyclamen europaeum L. extract could reduce the patient’s symptoms and shorten the time period the disease lasted, it was worth trying it. He further supported its use by suggesting it would reduce the number of patients using antibiotics and avoid doctors prescribing them, thereby performing another important role.
The opinion from the invited experts

Prof. Claus Bachert
Chief of Clinics ENT Department Ghent University Hospital.
Belgium

- We know, that in the long term a specific form of inflammation can cause asthma. So if you have sinus disease, which is a severe form of inflammation, you will be more susceptible to having asthma. Evidently, there is a clear need for more research, so we can have at least a hypothesis, indicating the importance of treating chronic inflammation in sinusitis.

- The primary problem that affects the quality of life of the patient is that they are unable to sleep, or to concentrate, so their work performance drops and their social life also suffers. So, it is extremely clear that diseases that affect the sinuses, whether or not they become chronic, can have a major effect on daily life conditions.

- Antibiotics are only to be used in severe cases, which means if the disease is longer than 5 days or more. Moreover, in Chronic Rhinosinusitis antibiotics are also used, as well as anti-NFκB activity or anti-metalloproteins. The objective in the treatment of these diseases is mainly the anti-inflammatory component, restoring ventilation and drainage, especially in Chronic Rhinosinusitis, but also in Acute Rhinosinusitis, and opening the ostia.

Prof. Wytske Fokkens
Professor and Chairman of the Department of Otorhinolaryngology
Academic Medical Center, Amsterdam.
Netherlands

- In the EP3OS Guidelines we advise antibiotics be reserved only for patients with severe disease, defining severe as patients who have symptoms for at least 10 days, or more than 5 days with fever and/or severe facial pain. Consequently, antibiotics are indicated for patients with severe disease and for all the other patients either a symptomatic treatment or an anti-inflammatory one.

- There is a very good correlation between asking the patient to fill in the severity of his symptoms on a Visual Analogue Scale, for example, and dividing that into mild, moderate and severe disease. If we compare that to quality of life questionnaire data, such as SNOT 20, you can see there is a very good correlation, and those patients with severe or moderate to severe Acute Rhinosinusitis are more prone to suffer a dramatic impact on their quality of life.

Prof. Andrey Lopatin
Director - ENT Clinic Sechenov Moscow Medical Academy.
Russian Federation

- Since the Cyclamen europaeum L. extract Nasodren has been on the market, it has been administered for the treatment of Acute and Chronic Rhinosinusitis, based on the evidence of two studies we have performed. The first study shows that Cyclamen europaeum L. extract works as a Product that stimulates mucus drainage, and even increases blood flow in the nasal area. In the second study we saw how it stimulates the parasympathetic system, opening the ostia and improving sinus drainage. The
study group and the control group were using typical antibiotics and *Cyclamen europaeum* L. extract. We showed that the results of the adjunct treatment with *Cyclamen europaeum* L. extract significantly improved the Total Symptom Score of the patient.

- There are some studies that show the deterioration of the quality of life in patients with Chronic Rhinosinusitis is even greater than in other diseases, more serious diseases, like ischemic heart disease or chronic pulmonary obstructive disease. So we must be aware of the influence of Chronic and Acute Rhinosinusitis symptoms on the quality of life of our patients.
- It is important to be aware of, and pay special attention to, symptoms like rhinorrea or those of nasal blockage in patients, as they could progress in to serious disease.

**Prof. Ludger Klimek**  
Center for Rhinology and Allergology, Wiesbaden.  
Germany  

- An excellent symposium. We have learned a great deal about Acute Rhinosinusitis in general and received information on the options concerning corticosteroids as an adjunct treatment or a monotherapy. We have also been told a great deal about antibiotics, which is extremely important given that, for many countries, it is the standard treatment for Acute Rhinosinusitis.
- The treatment options include the use of glucocorticosteroids, which have demonstrated efficacy but are still not considered as a standard treatment. Nasal douche may be interesting, despite the fact that it has not been examined in great depth. However, studies show that it may be an interesting alternative. And the new treatment with *Cyclamen europaeum* L., which has several interesting aspects: improving mucociliary transport, improving the secretions themselves, and getting them all out of the sinuses. There is an increasing body of data regarding this Product, and I feel sure it will make its way, becoming a very common Product in the future for use in Acute Rhinosinusitis treatment.
- Modern lifestyle, and other factors we are unaware of, have probably been important elements in producing an increase in Rhinosinusitis in recent years.

**Prof. Valerie J Lund**  
Professor of Rhinology University College London.  
Honorary Consultant ENT  
Surgeon Royal National Throat, Nose and Ear Hospital, London.  
United Kingdom

- With respect to what determines progression of the inflamed sinus we know that most common colds get better, but a proportion of them will go on to be bacterially infected, after which the bacterial infection may persist. In fact, this only happens in perhaps 2% or 3% of individuals, but that still constitutes a very large group of patients, and there may be many determinants - related to the host, genetics, environment and the virulence of the bacteria.
- Chronic Rhinosinusitis has a profound impact on the patient’s quality of life, whether you look at it with a general health quality of life instrument, such as the SF-36, or with a more specific tool such as the SNOT 20 or SNOT 22. So all the domains of general social functioning and general health are affected, as well as the specific ones related to the nose and sinuses.

**Dr. Joaquim Mullol**  
Rhinology Unit & Smell Clinic, ENT Department, Hospital Clinic, Senior Researcher, IDIBAPS, Barcelona.  
Spain

- We have recent data, including the PROSINUS study, that shows patients affected by Acute Rhinosinusitis experience an improvement in the quality of life after treatment, even when this treatment only lasts one or two weeks.
- The use of *Cyclamen europaeum* L., will probably be a good adjunct treatment of Acute Rhinosinusitis to reinforce, or to stimulate, the natural defences, mainly improving clearance or producing new antibacterial products from secretory glands that will help, combined with other products, to reduce the duration of the disease.
- *Cyclamen europaeum* L., which is being tested by evidence-based medicine and with more studies soon to be released, has shown an efficient effect on the treatment and quality of life of Acute Rhinosinusitis patients.
Dr. Antony Papavassiliou
Ex-President of the European Rhinological Society
President Of the Greek Association of ENTs.
Greece

- The clinical evidence that was obtained from my study in Greece shows that with *Cyclamen europaeum* L. extract, the Nasodren spray, we have a rapid decrease of symptomatology. That means better quality of life quicker and of course, less cost in treating these patients.
- *Cyclamen europaeum* L. extract can cure Acute Rhinosinusitis, so that when you stop the Acute phase, there is no chronic stage.
- We are going back to the roots of human society, as we are now able to treat Acute Rhinosinusitis without antibiotics or any other treatments, just with *Cyclamen europaeum* L. spray alone. I say this because I had the experience of organising a study for this treatment in Greece.
Despite the fact that ARS shows an increasing prevalence in European countries, it remains enigmatic in terms of its physiopathology, reliability of diagnosis or even in elaborating an effective, optimal treatment strategy. Perhaps even more surprising is the fact that direct and indirect costs for one episode of ARS treatment are extremely high, approximately €800 according to the PROSINUS study. Considering that more than 20m Europeans are deemed to be affected at least once a year by an episode of ARS, that brings the cost of ARS treatment for the Health Authorities to more than €16bn per year.

Throughout these pages, the key topics related to ARS have been discussed by the most prestigious ENTs in Europe.

Dr. Mullol pointed out that the main cause of ARS is a post-viral infection, and all lecturers agreed that ARS is an inflammatory disease, with the aim of treatment being symptom relief, thereby allowing sinus drainage and ventilation.

But how can ARS be diagnosed? An interesting study presented by Prof. Lund shows that practitioners essentially use the same diagnosis criteria as the EP3OS recommendations. That is to say, symptoms are the basis for Rhinosinusitis diagnosis, while X-ray and CTscan are not recommended at daily practice.

Moving on to available treatments, EP3OS guidelines recommend use of oral antibiotics only for the most complicated cases, where high fever and pain are present.

In most patients, inflammation can be controlled if treated by topical corticosteroids. However, as Prof. Bachert outlined, high doses of corticosteroids are required to achieve a significant effect and, moreover, EMA have not approved a Rhinosinusitis indication for them.

Of particular note is the fact that half of the prescriptions for antibiotics in European countries are for Upper Respiratory Tract Infection. While Prof. Fokkens pointed out that, unfortunately, antibiotics do not seem to prevent ARS complications. A Cochrane Review on antibiotics in ARS provides quite an indicative statistic: we have to treat 7 patients to, probably, make one better slightly earlier.

Increasingly, patients from around the world are looking for safer, more effective Products for managing their disease. Could that be one of the reasons why *Cyclamen europaeum* L. extract is being administered more and more to relieve the symptoms of ARS sufferers?

A number of studies, some of them highly pioneering, have been carried out to demonstrate the clinical effectiveness of *Cyclamen europaeum* L. extract. Said efficacy is mainly due to its high saponin content. Once sprayed into the nostrils, saponins, in addition to a local surfactant effect, stimulate the nervous system of the nasal mucosa inducing both a nociceptive and cholinergic response, hence stimulating glandular secretion and cilia movement.

So, as Prof. Klimek highlighted, there is finally an innovative and effective treatment option for ARS. *Cyclamen europaeum* L. extract will clean and drain mucus away from the sinonasal area in a physiological way. One final point, but by no means of lesser importance, we have heard how *Cyclamen europaeum* L. extract has generated some very positive feedback from patients.
1. NAME OF THE PRODUCT: NASODREN, Powder for the preparation of a nasal spray. 2. QUALITATIVE AND QUANTITATIVE COMPOSITION: Ingredient: Lyophilized powder from the juice and the natural aqueous extract from fresh tubers of Cyclamen europaeum L., 50 mg. The powder is porous, hygroscopic and cream-coloured. Excipients: No excipients, no preservatives or chlorides. Purified water 5 ml, as solvent for reconstitution of the lyophilized powder. Each dose of nasal spray releases 0.13 ml (2-3 drops) of solution (pH 5.3-6.8). This quantity corresponds to 1.3 mg powder. The finished solution produces 38 doses to be applied for a maximum of 16 days. 3. CLINICAL PARTICULARS: 3.1 Therapeutic indications: NASODREN is indicated for the symptomatic relief and treatment of diseases of nasal and paranasal cavities, and of the middle ear: Acute or chronic recurrent inflammation of the paranasal sinuses (rhinosinusitis): catarrhal or purulent maxillary rhinosinusitis, frontalitis, ethmoiditis, sphenoiditis, or combined rhinosinusitis. Acute purulent rhinosinusitis, accompanied by generalized infection or orbital complications. In case of orbital complications or generalized infection, NASODREN should be administered in combination with antibiotics. Acute exudative or purulent otitis media, chronic exudative, Acute secretory otitis media or purulent otitis media. In case of fever, NASODREN should be administered in combination with antibiotics. In postoperative care, after nasal or sinusal surgery. 3.2 Posology and method of administration: Posology in adults and children 5 years and above: The solution is sprayed daily only once into each nostril, preferably at the same time of day, approximately 2 hours before bedtime. Increasing the daily dose does not result in an increased effect. The treatment normally lasts 7-10 days when being used daily but may be extended to 12-16 days if necessary. A significant improvement or total symptomatic relief is achieved after 6-8 applications; however, headaches often associated with the condition may reduce or stop completely after only 3-5 applications of NASODREN. Nevertheless, treatment should be continued for the recommended duration of 7-10 days. In cases which are complicated by purulent infection, concurrent systemic antibiotic treatment is recommended. If a second treatment is necessary in severe or chronic cases, this should only be initiated 7-10 days after completion of the previous course. If a dose of the treatment is forgotten, the patient should continue with the treatment the next day as recommended. 3.3 Contraindications: Individual hypersensitivity against Cyclamen, Primula and other Primulaceae. Polyposis of the nose and the paranasal sinuses that can block the meatus and secretion. 3.4 Special warnings and special precautions of use: Apply only one spray per day into each nostril. Avoid inhaling during application. Avoid eye contact. Contact of the Product with the eyes may result in irritation and symptoms of Acute conjunctivitis. Take note of the section 3.5 Interaction with other Products and other forms of interaction. If necessary, other nasal Products can be administered 1.5-2h before or after NASODREN. Undesirable effects are related to the specific mechanism of action, and may include some itching, sneezing, a brief sensation of mild to moderate burning in the nasopharynx, reflex salivation and, more rarely, a brief lacrimation and flushing of the face (especially in patients treated with antihypertensive medication). However, these are manifestations of the positive response to the Product. When prescribing NASODREN, it is suggested that the physician explains these effects to the patients as being due to the stimulation of N. trigeminus and N. facialis. All these effects usually diminish during the course of treatment. In some isolated cases a mild temporary headache or pale pink discharge may appear. It is not necessary to stop treatment in these cases. Accidental use by patients allergic to Cyclamen, Primula and other Primulaceae, which could lead to swelling of the nasal mucosa, eyelids and/or face. 3.5 Interaction with other Products and other forms of interactions: Simultaneously administered parasympatholytic drugs acting either directly (e.g. carbachol, pilocarpine, betanechol), or indirectly (cholinesterase inhibitors like neostigmine, ambenonium etc) will potentiate the effect of NASODREN (due to amplification of released acetylcholine action in the respective synapses). After application of NASODREN, a slight issuing of red blood cells in the nose was observed in some patients. Therefore, treatment with anticoagulants (e.g. coumarin derivatives, acetylsalicylic acid) should be suspended and the application of NASODREN commenced, taking into account the rate of elimination of the particular anticoagulant. 3.6 Pregnancy and lactation: There is no experience regarding the administration of NASODREN during pregnancy and breast-feeding in humans. Therefore, NASODREN should not be administered during pregnancy and breastfeeding, especially during the first trimester. 3.7 Effects on ability to drive or to operate machinery: Driving or operating machinery is not recommended for 2 hours after using the spray. 3.8 Adverse Reactions: In very rare cases of prolonged lacrimation or salivation lasting more than 2 hours, give atropine or other anticholinergics such as scopolamine to stop the secretory response. 3.9 Overdose: Exceeding the required dose may cause a severe burning sensation in the nasal mucosa or nasopharynx, without serious consequences. In case of an accidental overdose irrigation of the nasal cavity through the nostrils with warm water, and pharyngeal gargling with warm water can be useful. 4. PRODUCT PROPERTIES: 4.1 Incompatibilities: NASODREN is incompatible with anticholinergics (such as atropine, tropicamide etc.). Date of revision: September 2010
New approach in rhinosinusitis symptomatic treatment

Lyophilized extract from Cyclamen europaeum L.

- Fast symptom relief from the first dose
- Once daily, during 7 to 10 days
- For adults and children over 5 years

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