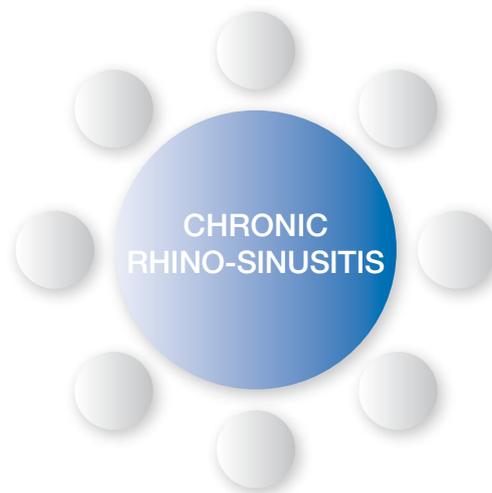


**NASAL DRUG DELIVERY WITH A FOCUS
ON CHRONIC RHINO-SINUSITIS**



■ ■ A scientific roundtable hosted by Aptar Pharma Prescription Division

■ ■ INTRODUCTION AND OBJECTIVES

Aptar Pharma recently hosted a scientific roundtable on "Nasal drug delivery with a focus on chronic rhino-sinusitis". This international scientific forum was held in Paris, France on November 13th 2012. The roundtable was organized to explore and exchange views on the science of various forms of sinusitis and its related unmet medical needs.

It is estimated that around 20% of the population in developed countries suffers at any one time with rhino-sinusitis type symptoms, and the prevalence of CRS (chronic rhino-sinusitis) has been on the increase over the last 30 years^{1,2}.

The roundtable was organized to explore and exchange views on the science of various forms of sinusitis and its related unmet medical needs.

In the US alone this chronic disease is estimated to have an overall cost burden ranging from 4.3 to 5.8 billion dollars per year³. These numbers are likely to be very similar in Europe.

The overall objectives of the meeting were to better understand the science and medical needs with regard to CRS, establish current and future unmet medical needs, and identify potential opportunities for nasal spray or other treatments in this area.

During this one day meeting the experts shared their knowledge and debated several key themes, structured around the following subject areas:

- Anatomy and physiology related to the nasal cavity
- Current approaches to treating CRS including guidance, drugs and therapies
- Patient needs and unmet medical needs

Invited guests came from a variety of backgrounds ranging from front-line clinicians to leading pharmaceutical company and university hospital experts, as well as consultants specialized in nasal drug delivery. All of these hold senior positions either within the industry or in hospitals and many are recognized key opinion leaders. Aptar Pharma would like to thank their guests for their excellent contributions to the roundtable and for helping to make the event both informative and enjoyable.

The summary of some of the discussions held, detailed later in this document, reflects the views of our invited experts and every attempt has been made to reflect the overall consensus of view as accurately as possible.

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■ ■ ANATOMY AND PHYSIOLOGY RELATED TO NASAL THERAPY

Nasal anatomy is already well known to be suitable for delivery of drugs in aerosol or spray form and numerous therapies are successfully given by this route of administration. Examples include:

Locally acting therapies:

- Nasal decongestants, nasal corticosteroids, nasal salines, vasoconstrictors.

Systemically acting therapies:

- Migraine, breakthrough pain relief, osteoporosis, hormone replacement therapy, influenza vaccination.

Access of drug therapies to the sinus cavities (frontal, ethmoid, sphenoid, maxillary - see **Figure 1**) is recognized as a challenge as the openings to the cavities are relatively restricted (1 -3mm) and can become inflamed during infection. The nose is known to have its own clearance mechanism (by use of epithelial cilia) and it is evident that any drug or therapy needs to be absorbed relatively quickly through the nasal epithelium for local applications before clearance takes place. It was also discussed how CRS is a multifactorial disease and different classes of drugs may be needed depending on the underlying source of the infection, e.g. inflammation, bacterial infection, fungal infection etc.

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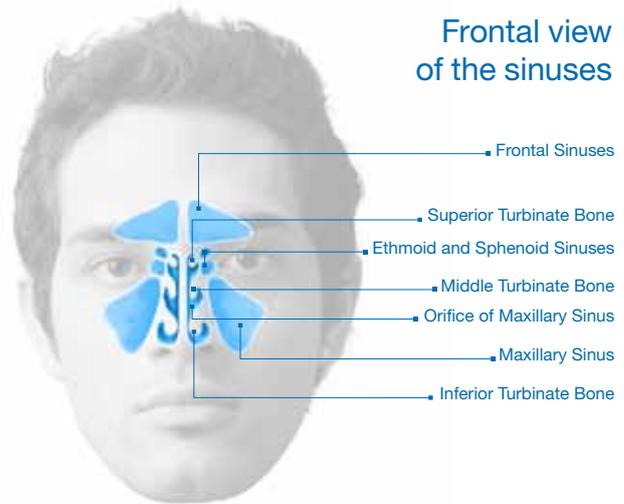


Figure 1: Anatomy of the sinus cavities



■ ■ CURRENT GUIDANCE WITH REGARD TO TREATING RHINO-SINUSITIS

In March 2012 the International Rhinological Society published a position paper in the "Rhinology" journal entitled "European Position Paper on Rhino-sinusitis and Nasal Polyps 2012" (EPOS2012⁴) which stands as the current reference in this field for treating these diseases. This guidance was reviewed in detail and provides extensive information on several key areas including:

- Clinical definitions including acute and chronic
- Pathogenesis of CRS and its multifactorial nature
- Proposed therapies: local, systemic, corticosteroids, antibiotics, and others

- Evidenced-based proposals for selection and recommendations for treatments

- Outstanding research needs for improved medical treatments

There was general agreement that intranasal corticosteroids are still the first line of treatment in this area with saline nasal lavage also being popular with physicians. An example of one of the typical evidenced-based approaches is given below in **Figure 2**.

CRSsNP in adults-management scheme for ENT- specialists

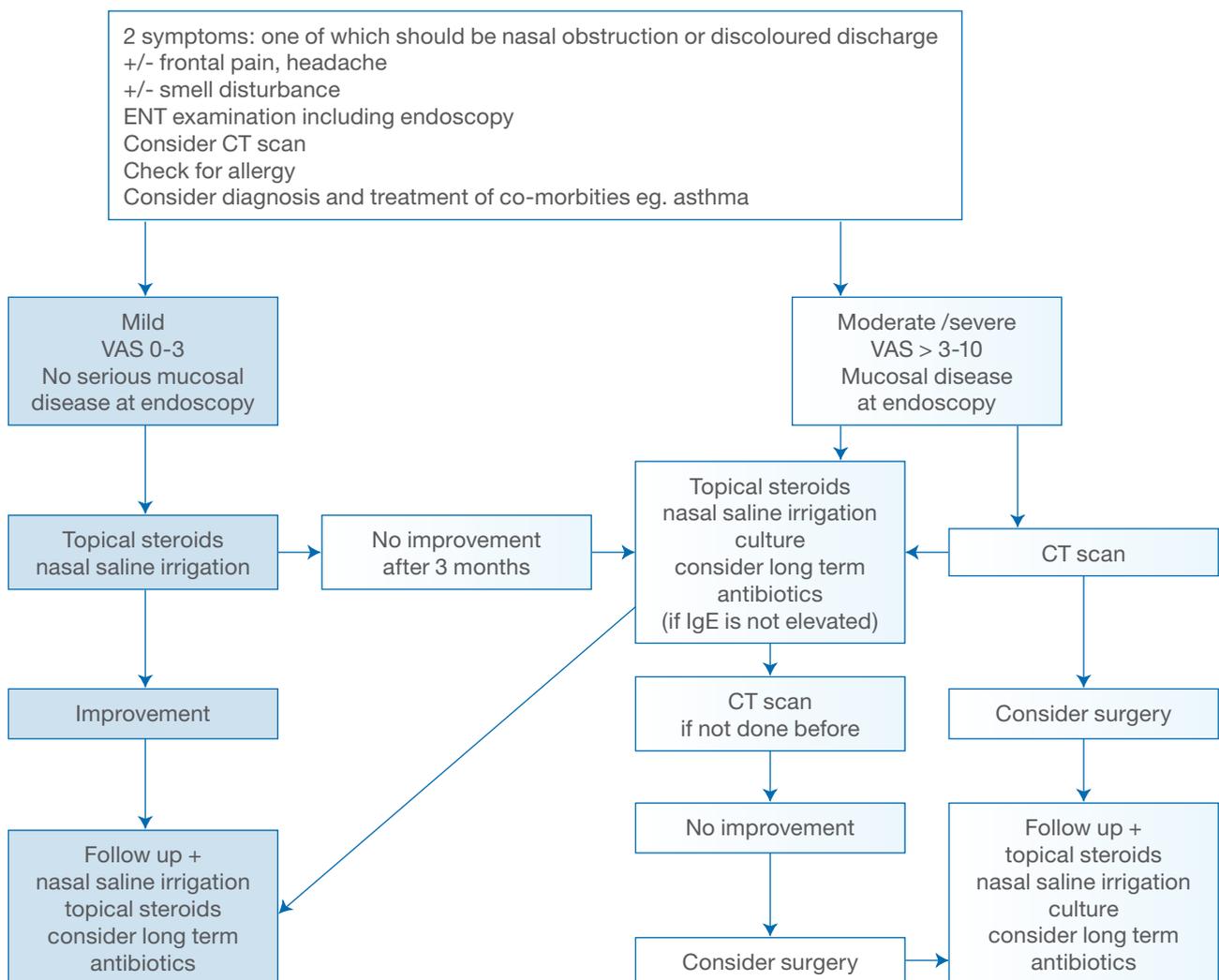


Figure 2: Evidenced-based approach for selection and recommendation for treatment of CRS. CRSsNP – chronic rhino-sinusitis and nasal polyps, ENT – ear, nose and throat, CT – computational tomography, VAS – visual analog scale (nasal obstruction).

■ ■ CURRENT AND EMERGING DRUGS, THERAPIES AND DEVICES

Current therapies proposed for treating CRS are well known: recognized first line therapies include corticosteroids, antibiotics, nasal douches and bacterial lysates. Some other suggested therapies which lack clinical evidence are antimycotics, herbal medicines, probiotics, antihistamines, homeopathic remedies, proton pump inhibitors, surfactants and nasal decongestants. There is also another large group of potential therapies which hold some promise for the future, but today insufficient evidence exists to propose them as proven therapies for CRS. These include anti-IgE, anti-IL5, antihistamines in non-allergic patients, immunosuppressants, furosemide, leukotriene antagonists, aspirin desensitization and capsaicin.

Discussions about some of the techniques used to deliver therapies for CRS revealed a wide range of currently used drug delivery approaches. These include nasal spray pumps, nasal lavage devices and a wide range of nasal nebulizer devices. Preferences are being driven by numerous factors including costs and reimbursement of therapy, convenience, preferences of clinicians in different markets and regions, and geographic and cultural preferences.

Nasal spray pumps have been available for several decades but they still seem to be the most popular and accepted means of delivering intranasal corticosteroids. Discussions around new and emerging therapies or devices revealed several interesting advancements of note. Among these were use of pulsed aerosols^{5,6} to increase the penetration of drug delivery to the sinus cavities (see **Figure 3**), use of novel devices such as bidirectional approaches⁷ and controlled particle dispersion⁸, as well as the emergence of specific medical devices for implant such as stents loaded with corticosteroids⁹. The challenge to reach and significantly penetrate the restricted entries to the sinus cavities still remains to be overcome.

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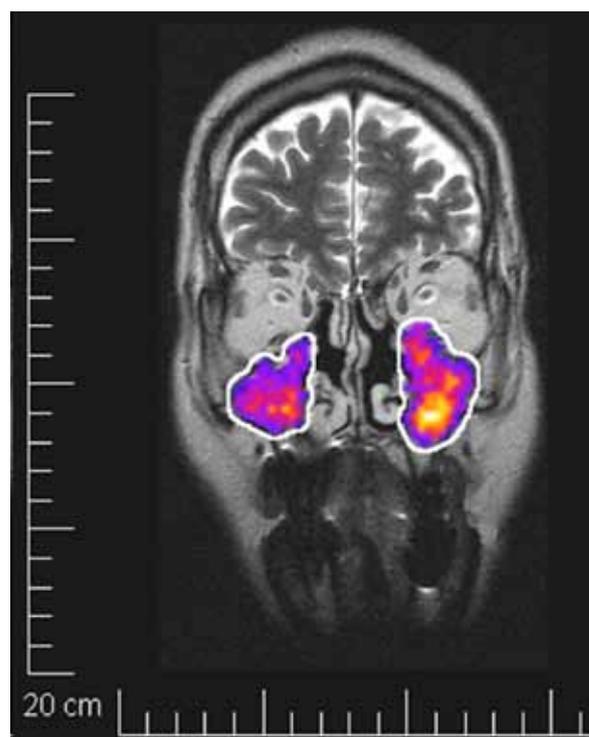


Figure 3: Evidence of aerosol penetration to the maxillary sinus cavities⁵

■ ■ UNMET MEDICAL NEEDS

This subject generated much discussion and it appears that current treatments are not good enough to treat all patients in all cases and there is a need to provide appropriate therapy to all patients. Numerous new potential therapies have been identified but they require further clinical evidence before they become accepted.

Opportunities clearly exist for novel devices and approaches which could be a way forward, and exciting possibilities lie ahead in this area.

There is also potential to better match patients to a suitable therapy by identifying their disease endotypes or phenotypes so that they can receive the appropriate specific therapy. Again much work needs to be done here to identify the various sub-groups of CRS patients and even to develop suitable biomarkers. Several participants referred to the use of 'off label' therapy or devices and this points to a clear unmet need which could bring more options for future treatments if some of these off label approaches are proven clinically safe and efficacious. Other unmet needs were identified in the area of both patient education and adherence to therapy and it appears that there is significant scope for progress which could be made in this area too.

All these elements taken together offer the possibility to improve treatments for CRS. From the drug delivery device perspective, opportunities clearly exist for novel devices and approaches which could be a way forward, and exciting possibilities lie ahead in this area.

■ ■ IN SUMMARY

Although suitable approaches to treating CRS exist today as well as comprehensive guidance documents on how to best treat the disease, this scientific roundtable revealed that several opportunities for improvements also exist in this therapeutic area.

A number of potential drugs and therapies require further work in order to prove their clinical efficacy for treating certain aspects of CRS.

There are also some interesting innovations in the delivery device area as witnessed by some of the recent publications in this field, although they have some way to go before they reach front line therapy.

Unmet needs pointed to areas such as addressing off label uses, and matching patient sub-groups to specific therapies, as well as patient education and adherence. All the above areas offer opportunities for progress to better meet future needs for treating this common chronic disease.

■ ■ SOME QUOTES FROM OUR EXPERTS

«« There is often a selection to be made with regard to experienced-based vs. evidence-based medicines. »»

«« Dosage form for CRS is often an underestimated factor. »»

«« There are at least 10 hypothesis for the role of the sinus cavities (but none seem to stand up as witnessed by the fact that a patient can undergo surgery to remove the sinus structure and still live normally). »»

«« Current treatments are not good enough to treat all patients in all cases – we need to provide appropriate therapy to all patients. »»

■ ■ PARTICIPANTS



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