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Current Position Of The Management Of Community-Acquired Acute Maxillary Sinusitis Or Rhinosinusitis In France And Literature Review

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1. Introduction

Since the end of the first studies by the SGIS group (Study Group of Infectious Rhinosinusitis), a number of other publications have appeared that have enriched the debate on the management of adult community-acquired acute maxillary rhinosinusitis (AMRS). In particular, the recommendations of the French Health Products Safety Agency (AFSSAPS) have reinforced the conclusions of the SGIS studies. Abroad, other consensus conferences or revised recommendations have given rise to new debates and opened up new possibilities of management, taking into account the development of resistance, the commercialisation of new antibiotics and validated shortened courses of treatment. On the basis of these new data, it appeared necessary to revise the text that had emerged from the SGIS' initial studies, with the group having now been enriched by the inclusion of new general practitioners, infectious diseases specialists and microbiologists. This update has been divided into five sections:

- clinical aspects and management strategy,
- complications,
- bacteriology,
- antibiotic treatments,
- non-antibiotic treatments,

1.1 METHODOLOGY

The SGIS II group (Study Group of Infectious Rhinosinusitis) was set up to consider exhaustively and pragmatically the management of uncomplicated community-acquired adult acute maxillary rhinosinusitis (AMRS). To this end, it is multidisciplinary (bacteriology, infectious diseases, general medicine, ENT).

The principle of operation of the group involved organising plenary meetings and working parties on the specific topics (antibiotic, complications, etc.). The three co-ordinators centralised and summarised the information.

The first stage consisted of a critical review of the 2001 manuscript (Rhinology, Klossek et al. 2001). It was decided to update this text so as to provide greater details about those aspects in which knowledge and practices had progressed.

Four subgroups were established to analyse the literature and put forward a text to the co-ordinators for each of the proposed sections of the new manuscript.

The second stage was to analyse, discuss and modify the first version of the text proposed by the co-ordinators in plenary session. A number of changes were made, ensuring that the contributions were all standardised, so as to obtain a second version that was revised and annotated in plenary session.

The third stage was the validation of this manuscript resulting from the plenary review of the text by the members of SGIS II. The automated literature search involved the MEDLINE and EXCERPTA Medica databanks. The key words used were: Sinusitis and Drug therapy, Drug resistance and *S.pneumoniae*, Drug resistance and *H.influenzae*, Drug resistance and *M. catarrhalis*, Sinusitis and Family practice, Sinusitis and Management, Sinusitis and Complication, Common cold and Clinical trial, Sinusitis and allergy or Asthma or Diabetes or Immunodeficiency or Viral infection or Septal deviation or Gastroesophageal reflux or Tobacco smoke or Air pollution or Environment and Risk factors. In all, more than 500 references were identified, of which the group retained almost 200, and ultimately 127 were used for this study.

The quality of each article was evaluated according to the recommendations of the guide to analysis of the literature published by ANAES (French National Association for Healthcare Quality & Evaluation). The reading grids employed involved the use of responses based on the options yes/no/indeterminate and the items to be completed relate to the study method (comparative, randomised, prospective), the relevance of the clinical variables considered, the suitability of the population treated, the a priori calculation of the population size, the statistical significance, the clinical significance, the existence of an analysis by intention to treat, and the applicability of the treatments under study in routine use. Comparative trials were adopted first of all. Trials for which the antibiotics tested are not or will not be available in France and trials for which the study populations were not homogeneous, combining acute rhinosinusitis and exacerbations of chronic rhinosinusitis, or rhinosinusitis and bronchitis, were excluded.

The grade of the recommendations formulated in this text is therefore directly correlated with the level of scientific evidence of the references cited. When there were insufficient data, or in the absence of studies, a professional consensus was sought, taking into account professional practice.

2. Clinical situations in a general practice consultation

In the majority of situations in general medicine, the diagnosis is presumptive and the treatment empirical. This is particularly true of acute infectious maxillary rhinosinusitis defined as a microbial process affecting the nasal fossae and extending to the maxillary sinuses (Gehanno^a 2003). Sinusitis of dental origin with a specific aetiology does not come within the scope of this study since only maxillary sinusitis of rhinogenic origin is the subject of study.

The problem for the clinician is to distinguish bacterial superinfection from a disease of essentially viral aetiology. In daily practice, faced with a presentation suggestive of maxillary rhinosinusitis, four major clinical situations can be individualised (Cf. below).

The presumptive diagnostic approach of the practitioner must involve the examination of all the arguments in favour of one of these four clinical situations.

The elements of the diagnosis involve primarily the clinical examination and the previous history. For the general practitioner, in fact, the contribution of supplementary examinations, particularly X-rays, is unhelpful, not so much because of the lack of accessibility as specifically the lack of sensitivity and specificity (Laranne et al. 1992, Pfeleiderer et al. 1986, Burke et al. 1994, Druce 1992). In addition, the need for the practitioner who is consulted to define a "pragmatic" treatment reinforces the concept of a primarily clinical approach in order to adapt the treatment of the rhinosinusitis according to its impact on daily life and the risk of complications (Varonen et al. 2004, Linder et al. 2003). A CT scan, considered the reference examination in matters of sinus imaging, is reserved for complications (Mortimore et al. 1999) or in the event of doubt over the diagnosis (pansinusitis, sphenoiditis).

The aim of this presumptive approach is to evaluate the necessity or otherwise of instituting antibiotic treatment, given that the aim of antibacterial therapy is to relieve the symptoms while hastening the cure and theoretically to prevent complications, although this has not been formally demonstrated (Gehanno^a 2003, Lindbaek et al. 1996, Van Buchem et al. 1997).

2.1 The four individualised major clinical situations

1. *Rhinosinusitis indicative of viral rhinitis*

This situation corresponds to the common cold. It is frequent. The signs and symptoms are very different from those of acute bacterial maxillary sinusitis, from which it must be distinguished. Viral rhinitis is manifested by bilateral nasosinus symptoms comprising a clear nasal discharge, non-localised pain and no discharge in the rhinopharynx. These signs develop over the course of less than 72 hours in an often epidemic context and are associated with those of a viral syndrome with fever, general malaise, pharyngitis, myalgia, conjunctivitis, cough and sneezing.

2. *"Doubtful" rhinosinusitis*

In this case, the symptoms present are insufficient to establish a diagnosis of bacterial sinus infection, but do not correspond to those of a common cold. It is a very common situation in general practice, too often resulting in the unnecessary and inappropriate prescription of an antibiotic.

The signs develop over the course of less than 72 hours in the form of mucous or seromucous nasal discharge, without localised pain and with minor constitutional symptoms. A previous history of rhinosinusitis is often absent.

A coloured discharge bilaterally does not necessarily indicate a **bacterial** superinfection (AFSSAPS 2005).

This situation represents a non-urgent infectious situation. It can regress spontaneously or develop into true bacterial rhinosinusitis.

3. *Infection indicative of acute bacterial maxillary rhinosinusitis*

The previous history and clinical data likely to yield a very probable diagnosis must be investigated in considerable detail (Gehanno^a 2003).

The rhinosinus symptoms develop in an infectious context and are unilateral. They involve:

a/ pain, localised suborbitally, increasing on anteflexion, radiating towards the dental arches and present particularly at night and in the afternoon.

b/ frankly purulent anterior rhinorrhoea.

A history of acute rhinosinusitis, the observation of a posterior mucopurulent discharge in the rhinopharynx or the presence of a purulent discharge in the meatus on rhinoscopic examination reinforce the conviction of a probable acute bacterial maxillary infection.

4. *Rhinosinusitis at the stage of complications*

The complications of maxillary sinusitis are rare, particularly since the era of antibiotics (Gehanno^a 2003). However, all sinusitides, whatever their localisation, may be complicated despite almost systematic antibiotic treatment (Gehanno^a 2003, AFSSAPS 2005, Lindbaek et al. 1996, Van Buchem et al. 1997).

These involve:

a/ Orbital lesions with palpebral oedema and risk of paralysis of the oculomotor nerves.

b/ Maxillary bone lesions manifested in vestibular/gingival bulging or buccal oedema.

c/ Bacterial meningitis, usually pneumococcal.

d/ Suppurative intracranial collections.

Besides these particularly severe developments, the situation of blocked sinusitis due to an ostial obstruction is found more often in daily practice. Following local suppuration and oedema of the mucosa of the nasal fossae, the drainage ostium of the maxillary sinus becomes blocked, thus isolating the pus-filled sinus cavity from the rest of the airways. The pain then becomes intolerable and resistant to analgesics.

2.2 Management strategy

The management of acute rhinosinusitis is dominated by the decision whether or not to institute antibiotic or symptomatic treatment. This decision is not trivial either individually or collectively (occurrence of adverse effects and risk of emergence of bacterial resistance) (AFSSAPS 2005). Pragmatically, each of the situations described previously is matched with a therapeutic strategy that must take account of the potential for progression of the infection and sometimes requires a re-evaluation of the symptoms in the short term.

2.2.1 Suspicion of viral rhinosinusitis

Antibiotic therapy is not justified. Treatment is symptomatic. An antipyretic, analgesic and/or vasoconstrictor for 2 to 3 days are sufficient. The patient must nevertheless be informed of the possible progression of the symptoms to genuine sinusitis, of the justification for abstaining from antibiotic therapy and of the need to visit the doctor again in the event of an unfavourable progression. This approach is reinforced by information campaigns for the general public on the safety of this strategy.

2.2.2 Suspicion of "doubtful" rhinosinusitis

This raises another important practical problem in this situation, the most commonly encountered in daily practice, as there is a great temptation to use an antibiotic for any coloured discharge and/or febrile syndrome. This approach however should be discussed and modified. At this stage, symptomatic treatment is capable of producing a cure in a large number of cases. The use of antibiotics to prevent the occurrence of true bacterial sinusitis is not recommended. It is preferable to give priority to clinical monitoring with the active participation of the patient, which requires information and education as this approach encounters considerable psychological resistance. This decision does not jeopardise the prognosis of the infection, allows the use of appropriate antibiotic therapy at any time and on a larger scale safeguards the interests of the community.

2.2.3 Suspicion of probable bacterial rhinosinusitis

The use of antibiotic therapy is recommended because of the benefit observed in this situation (AFSSAPS 2005). This antibiotic therapy must be appropriate to the microbial epidemiology (causative bacteria, resistance profiles). Since the previous analysis by the SGIS group, some French studies evaluating antibiotic therapy have been published. These prospective studies have been conducted either by comparing antibiotics with one another or in open-label studies.

Antibiotic therapy is instituted in accordance with the AFSSAPS recommendations. It pursues two aims (Gehanno^a 2003): to reduce the intensity and duration of the symptoms and to decrease the incidence of locoregional complications.

Antibiotic therapy is empirical and decided upon at the end of the consultation. In fact, the bacteriological diagnosis requires a sample of pus, either by aspiration from the middle meatus

or by sinus puncture, which cannot be performed in the general practitioner's surgery. In addition, the need to wait for the result would cause an additional delay that is unacceptable to the patient requiring antibiotic therapy.

Because of the current epidemiology in France ascertained through recent studies available there (Gehanno et al. 2002, Pessey et al. 2001), antibiotic treatment must be effective against *Streptococcus pneumoniae* and *Haemophilus influenzae*. These two bacteria are predominant (50%), alongside *Moraxella catarrhalis*, *Streptococcus pyogenes* and more rarely *Staphylococcus aureus* (Gehanno^a 2003). Treatment must allow for the resistance of these bacteria in France. These factors have resulted in amoxicillin alone, macrolides and first generation cephalosporins no longer being recommended as first-line treatment, even if individual successes are observed in the treatment of bacterial AMRS with these antibiotics (Gehanno^a 2003, AFSSAPS 2005). This decision is based on the danger of the large-scale use of antibiotics whose percentage resistance has become worrying for the two bacteria most commonly implicated in AMRS. All these data prohibit an approach which involves the prescription of an antibiotic not in line with the recommendations.

Finally, in accordance with the AFSSAPS recommendations, only the following antibiotics are to be used in the first line:

- the combination amoxicillin-clavulanic acid, in 2 or 3 doses of 19 each for 7 or 10 days.
- cefuroxime axetil, in 2 daily doses of 250 mg each for 5 days.
- cefpodoxime proxetil, administered at a dose of 200 mg twice daily for 5 days.
- cefotiam hexetil in 2 doses of 200 mg each for 5 days.
- pristinamycin, at a dose of 2 g daily for 4 days.
- telithromycin, 800 mg in a daily dose for 5 days.
- pristinamycin and telithromycin are also recommended in the event of beta-lactam contra-indication.

The antipneumococcal fluoroquinolones (levofloxacin and moxifloxacin) are not recommended in France in the first-line treatment of acute maxillary sinusitis. They are reserved for radiologically and/or bacteriologically documented failures of first-line empirical antibiotic therapy. Conversely, they can be used from the outset in the treatment of sinusitis with a high potential for complications (frontal, ethmoidal or sphenoidal) or in a situation of radiologically and/or bacteriologically documented treatment failure (Gehanno^a 2003).

The prescription of non-antibiotic treatments is based on the intensity of the obstructive or painful symptoms. The treatments involve analgesics, antipyretics and vasoconstrictors. The use of systemic corticosteroids can be considered, particularly in the hyperalergic forms in which there is extensive mucosal oedema.

2.2.4 Suspicion of complicated forms

In the case of overt or suspected complicated forms, emergency specialist management is necessary. This is detailed in section 7.3.

2.3 The different outcomes

Once treatment has been instituted, the clinical signs regress over 3 to 10 days. The pain disappears fairly rapidly within 48 hours. The sensation of nasal congestion may persist for longer, together with the discharge and the posterior rhinorrhoea. In all cases, the usual outcome is an improvement without any new symptoms or clinical abnormalities. A return to normal is observed clinically after about 10 days. The patient therefore needs to be informed of this to avoid a change of therapeutic strategy which is totally unjustified. No follow-up X-ray is necessary, particularly as the normalisation of the films takes longer and requires a few weeks (3 to 4 at least).

2.3.1 Relapse

The diagnosis of a relapse implies that the first episode has resolved completely and that there is clinical and radiological disease-free interval between the two episodes. This definition excludes exacerbations when the patient has never recovered from the first episode or situations of infection that reveal an underlying disease.

In a relapse, the symptoms may be identical to those of the previous episode. The clinical examination is similar to that described for the initial episode. Conversely, every attempt must be made to investigate the cause of the relapse. The factor may be local with the presence of a dental focus or a sinus fungal ball. Systemic causes are more exceptional and principally involve disorders of acquired immunity. An X-ray examination should be considered in particular if the relapse is unilateral.

2.3.2 Failure

The definition of a failure remains disputed: for some, it involves the persistence of the symptoms, for others the appearance of new symptoms or the increase in intensity of symptoms already present or the development of complications. Ultimately, in practice this situation appears to come down to the request for a second opinion by the patient. The analysis at this point should attempt to differentiate a normal progression from an actual failure. Apart from the development of clinical complications, there are no symptomatological or radiological features specific to the diagnosis of failure. The use of a bacteriological sample has been little studied in this situation (Brook et al. 2004, Gehanno^c et al. 2003) and would perhaps be a discriminating factor. The analysis of a situation involving a treatment failure must be rigorous in order to identify the cause: poor compliance or adherence to treatment, incorrect choice of antibiotic, dosing error, failure due to bacterial resistance (need for a sample), presence of an underlying disease, etc. The prescription of a new antibiotic may be discussed at the end of this re-evaluation (Gehanno^c 2003).

2.4 Discussion

Acute rhinosinusitis is a fairly seasonal disorder (autumn/winter) encountered very frequently in daily practice. It is often

polymorphic, particularly when the infection is viral, more rarely characteristic and in this case probably due to a bacterial infection. Intermediate situations, which are the source of incorrect and inappropriate prescriptions of antibiotics, are nevertheless the most common.

The specialty of the attending doctor consulted first of all means that, apart from situations involving complications or a relapse, supplementary examinations are random. Likewise, the results of surveys or studies of management of these infections without an antibiotic may currently appear inapplicable in practice. These remarks however should not conceal the place of rigorous symptomatological investigations on which the therapeutic strategy depends.

Recent studies confirm the considerations about the antibiotic therapy. De Bock (2001) for example compares the development of three strategies: surveillance, immediate empirical antibiotic therapy and selective deferred antibiotic therapy. After one week, 91.5%, 94.5% and 93.2%, respectively, of patients in each group were considered cured. Theis et al. (2003) in a retrospective analysis reported that the gain from antibiotic therapy is modest (two to three days relative to placebo treatment). In 2003, on the basis of a retrospective analysis of a study of efficacy of antibiotics in AMRS, Williams et al. tried to evaluate the benefit of this treatment and the type of compounds to be used. From 2058 studies available, only 49 comprising 13,660 patients were retained for analysis by two experts. Their conclusion supports the use of an antibiotic such as penicillin V or amoxicillin. It is difficult however to abide by these results without comment. The first objective of these studies was confined solely to individual parameters such as duration or intensity of the symptoms. Because of the small number of patients included in each of the studies, it is still impossible to postulate about the risk of complications on a large scale.

It is equally restrictive if management is confined to the prescription of an antibiotic. This is part of a wider approach, incorporating in the decision the evaluation of the stage of the disease, the context in which it has developed and the efficacy of symptomatic treatments. At the stage where there is a high probability of bacterial rhinosinusitis - and only at this stage - the recommended antibiotics should be used, i.e. those whose activity has been demonstrated in this disease in which the microbial ecology has developed over the past ten years in France. Incorrect use of antibacterial therapy, whether in the choice of compounds, the incorrect dosages administered or the inappropriate duration, can only be detrimental to the individual treated and to the community (risk of selection of resistant micro-organisms).

In a situation involving a failure or a relapse, the same rigour is essential, with an analysis of compliance and an investigation of a perpetuating factor or a complication. The possible use of another family of antibiotics may prove necessary, once again with due regard to the AFSSAPS recommendations. If necessary, a specialist opinion may prove useful (endoscopy, bacteriological samples, CT scan).

3. Are these predisposing factors?

3.1 Predispositions

3.1.1 Allergy

No study comparing the incidence of acute rhinosinusitis in the general population and in an allergic population is at present available. Savolainen had identified a more frequently allergic population during acute maxillary rhinosinusitis. However, there was no significant difference between the allergic and non-allergic subjects in the number of previous sinusitis episodes. In addition, there was no difference between the two populations in the organisms responsible for the infectious episodes and the duration of the episode (Savolainen 1989).

3.1.2 Immune disorders

HIV infection does not encourage the occurrence of rhinosinusitis, as long as the CD4+ T lymphocyte count remains greater than 200/mm³ (Wurzer et al. 1995, Lacassin et al. 1993, Bernal et al. 2003, Gurney et al. 2003).

3.1.3 Diabetes

There are no new data to confirm whether diabetes represents a predisposing factor for infectious sinus episodes (Jackson et al. 1987).

3.1.4 Asthma

It is still not possible to consider the asthmatic subject as predisposed to sinus infections, although sinusitis is often reported in the analysis of the cost of management of asthmatic patients (Halpern et al. 2000).

3.1.5 Anatomical variations of the middle meatus

While some authors have defended the idea that anatomical variations involving the middle meatus or the nasal septum might encourage the development of acute rhinosinusitis, no recent study currently confirms this hypothesis (Collet et al. 2001, Aktas et al. 2003, Hamdan et al. 2001).

3.1.6 Gastro-oesophageal reflux

The investigation of an association between gastro-oesophageal reflux and chronic rhinosinusitis has been the subject of several recent publications, particularly in children (Ulualp et al. 1999, Phipps et al. 2000, Gilger 2003, Weaver 2003, Loehrl et al. 2004). The level of evidence is usually grade C in favour of the existence of this association. However, there is no publication that confirms the implication of gastro-oesophageal reflux in the occurrence of acute rhinosinusitis.

3.2 Environment

3.2.1 Smoking - Pollution

Lieu et al, in a longitudinal study from 1988 to 1994, showed that active smoking non-significantly increases the risk of developing acute sinusitis (Lieu et al. 2000).

No study on the role of environmental factors in the onset of acute rhinosinusitis is available to date.

In summary, since the publication of the first studies of the SGIS group, no fundamental new data have revealed any predisposing factors.

4. Place of Rhinoscopy

The initial conclusions of the studies of the SGIS group underlined the limited use of rhinoscopy by the general practitioner (GP) in the diagnosis of AMRS. Recent studies by Gehanno (2002) and Pessey (Pessey et al. 2003) have also confirmed that the diagnosis is established purely on the basis of an interview. There is however no study evaluating the value of this examination in this situation compared to interview alone. The aim of rhinoscopy is to check for the presence and nature of endonasal secretions and even their origin. Rhinoscopy is little practised in general medicine, but is possible with an otoscope if there is no septal obstacle.

The technique is performed with the patient seated facing the consultant. Prior blowing of the nose in this case should be avoided as it risks eliminating the stagnant secretions in the nasal cavity. The first look should reveal the presence of any secretions (usually invisible) and their nature (colour, viscosity, location). The second part of the examination identifies the first feature of the lateral wall, which corresponds to the head of the inferior concha. It is easy to observe its size and colour. It is not unusual to observe a difference in size between the two sides, as the alternation of congestion/decongestion is physiological for the mucosa of the inferior concha.

Conversely, a very pale translucent colour often indicates an inflammatory and perhaps allergic problem. The nasal septum can be more or less rectilinear, particularly in its antero-inferior portion, which corresponds to the base of the septum. The presence on either side of the septum of an area rich in small vessels over the first centimetre is also normal: this is the area of the vascular spot.

This examination is not always simple and acquisition of the technique represents a justification for performing this type of investigation regularly to increase one's experience. Anatomical abnormalities can interfere with the procedure, particularly septal deviation. Some tips can be given to facilitate the rhinoscopic examination: spraying a vasoconstrictor (oxymetazoline) after the initial procedure and after blowing the nose.

In summary, the equipment necessary for this rhinoscopic examination is already in the general practitioner's bag in the form of the traditional otoscope. The rediscovery of this simple examination should encourage observational studies to validate its true benefit in this situation (investigation of signs indicative of a bacterial infection).

5. Place of imaging

Since the publication of the first work by the SGIS group, there have been a few studies to confirm its conclusions. The plain X-ray, even when the characteristic features are present (air-fluid level, total opacity, mucosal thickness greater than 5 mm), does not have sufficient specificity and sensitivity to establish the presence of a bacterial infection. The association with clinical abnormalities nevertheless enhances its value and it remains necessary in the context of studies validating antibi-

otic treatment for adult acute sinusitis. In routine use, it does not seem useful in helping the practitioner in his therapeutic decision. A recent study by Reider et al. (2003) also points out this principle in everyday practice. Imaging remains reserved for situations involving treatment failure or complications. At this stage, CT scans are more appropriate. These must be performed using bone and parenchymatous windows to observe potential orbital or encephalic complications.

6. Complications of adult acute Rhinosinusitis

Any rhinosinusitis may spread by anatomical contiguity or vascularly to the neighbouring structures, the eye and brain. The incidence of these complications is difficult to ascertain precisely. Nevertheless, the extended prescription of antibiotics in adult acute maxillary rhinosinusitis (AMRS) has produced a marked reduction in the frequency of complications (Gehanno^b et al. 2003). This fact is still the subject of discussion as there have been no prospective studies to confirm it. It is probable that the improvement of living conditions, and more especially of orodental and nasal hygiene, has also played a role alongside antibiotic therapy. However, Clayman et al. in 1991 reported a particularly high rate of 3.7%.

Maxillary rhinosinusitis has the reputation of being least often responsible for complications, again without any objective study being available to confirm this. The objective of this section is to describe the predictive factors, the clinical forms and their management. This analysis gives rise to a proposal to investigate these complications in the event of any AMRS.

6.1 Predictive factors

6.1.1 Age and sex

One fact common to all the series is the young age of the patients suffering from complications of sinus origin, on average between 20 and 30 years (Clayman et al. 1991, Maniglia et al. 1989, Jones^a et al. 2002, Lang et al. 2001). For Stoll et al. (2004), the mean age in adults is 40 years. This would appear to be due to the fact that in young adults the network of diploic veins is more developed. After the age of 65 years, sinus complications are exceptional. A male predominance to a greater or lesser extent (2/3 to 3/4) is reported by all authors.

6.1.2 Predisposition risk factors

Immunodepression remains a classic factor. However, poorly controlled diabetes, HIV infection (Belafsky et al. 2001), postchemotherapeutic neutropenia or a deficit of granulocyte chemotaxis are reported in a minority of cases. Congenital bone dehiscence or sequelae of trauma are also a factor in the spread of the infectious process through the meninges. In practice, only 10 to 15% of complicated forms involve chronic underlying diseases, surgical procedures on the ENT sphere or the orodental sphere (Dessi et al. 1994, Jones^a et al. 2002).

6.1.3 Localisation

It is the initially frontal, ethmoidal and sphenoidal localisations in isolation or pansinusitis that are at greatest risk of complications. In France, these account for almost a third of cases of sinusitis seen by private ENT specialists (Pessey et al. 2003) or by GPs. The most common maxillary localisations in practice generate fewer complications. Of the 43 cases in the study by Stoll et al. (2004), 4 cases of maxillary sinusitis were identified.

6.1.4 Chronology

If the complication occurs following a previously diagnosed rhinosinusitis, it is frequently indicative of a sinus focus (Younis^b et al. 2002). Likewise, the prior institution of antibiotic therapy is sometimes noted in the cases reported (Jones^a et al. 2002).

6.2 Clinical forms

In the majority of observations, the orbital or intracranial complication reveals the rhinosinusitis.

Maxillary rhinosinusitis is associated in particular with orbital complications.

As therapeutic emergencies, they always require a specialist opinion and very often immediate hospitalisation for radiological investigations (CT or MRI), parenteral antibiotic therapy and a surgical opinion.

6.2.1 Orbital complications

The anatomical proximity of the sinus cavities and the orbital wall explains these complications.

- Peri-orbital cellulitis (Younis^a et al. 2002) is manifested clinically in a high fever, inflammatory oedema and redness of the upper eyelid causing closure of the eye. The CT scan reveals a process confined to the preseptal region.
- The subperiosteal abscess is the result of the accumulation of purulent secretions beneath the periosteum. There is unilateral oedema of the upper eyelid totally obscuring the eye, with or without chemosis. Exophthalmia is not always easy to demonstrate in view of this oedema which will require the forced lifting of the eyelid, but diplopia is present. Above all, these symptoms develop over a very short period. The existence of homolateral epistaxis with the palpebral oedema is a further diagnostic argument in favour of an extraperiosteal abscess. It involves a risk of blindness. A CT scan will identify the periosteal detachment. In a recent French series, two patients out of six developed secondary blindness (Barry et al. 2000).
- Orbital cellulitis: the infectious process has spread to the orbital fat and the extrinsic muscles of the eye. It is manifested in protrusion of the eyeball (exophthalmia), oedema of the conjunctiva (chemosis) and the limitation of eye movements that can progress as far as ophthalmoplegia. Oculomotor paralysis may be the initial presenting feature.

In summary, the occurrence of oedema of the upper eyelid, exophthalmia, restricted movement of the eyeball and a decrease in visual acuity are all warning signs that indicate an orbital lesion: subperiosteal abscess, peri-orbital cellulitis or orbital cellulitis. They require hospitalisation as an extreme emergency.

6.2.2 Intracranial complications

(Younis^b et al. 2002, Albu et al. 2001, Jones^a et al. 2002)

The mode of onset in neurological complications is often more sudden. The clinical history preceding the neurological presentation is difficult to determine, particularly in meningitis (Younis et al. 2001). However, the study by Jones (Jones^a et al. 2002) on the search for prevention of intracranial complications provides a wealth of information. More than half (55%) of the 47 patients identified had consulted their GP before the neurological complication and were receiving antibiotics. The mean time between the rhinosinus and neurological signs was 15 days (3-39 days). The time between the consultation with the GP and the diagnosis of a complication was 5.5 days (0-17 days). Only 7 patients (15%) had a previous history of rhinosinusitis; for the 40 others, this was an inaugural common acute rhinosinusitis. The sinuses most often responsible were the frontal sinus (42 patients) and the ethmoid sinus (21 patients). These data show that a severe neurological complication may occur a priori from the outset or during purulent rhinitis independently of any pus retention in the sinus in young subjects without a previous history.

The clinical forms:

- Cerebral abscesses: these represent 2/3 of the intracranial complications of sinusitis. They complicate acute frontal or ethmoidal sinusitis in particular. They develop predominantly towards the frontal lobe, a silent zone, which may explain the clinical latency. The triad of fever, headaches and obtundation requires hospitalisation and a cerebral CT scan. Bacteriologically, the flora is usually polymorphic, combining aerobic and anaerobic bacteria.
- Meningitis: meningitis complicating sinusitis has no specific clinical features in relation to other forms of meningitis. Pneumococcus is the predominant bacterium. Cryptococcal meningitis complicating sinusitis is specific to AIDS patients. Sphenoidal sinusitis is usually involved (Younis et al. 2001). Here again, a CT scan or MRI will highlight the sinus origin that has often gone unnoticed. Diffusion of the bacteria may occur via a breach (fracture of the frontal sinus, the lamina cribrosa or the roof of the ethmoid), the sequela of a sometimes former trauma.
- Subdural empyemas: purulent effusion localised between the dura mater and the arachnoid tending to become compartmentalised. The extension often of frontal sinusitis, the clinical presentation, as in cerebral abscesses, combines febrile headaches, disorders of consciousness, epileptic seizures and signs of deficit. In the most recent series of 10 observations, immediate medical and surgical management prevented deaths at the cost of neurological sequelae in 2 cases (Lang et al. 2001).
- Cavernous sinus thrombophlebitis (Soga et al. 2001): this complication of sinusitis has become rare. The orbital infection spreads towards the cavernous sinus. It is often revealed by imaging in an assessment of complications, but it can have an independent clinical expression.

An epileptic seizure can occur suddenly with prolonged post-critical obtundation. This is then followed by usually bilateral orbital signs, the unilateral forms being less common. The orbital signs and symptoms, when they are unilateral, may lend themselves to confusion with an orbital complication; otherwise the palpebral oedema is the same. Chemosis and exophthalmia are usually also present. There is in particular a cavernous sinus syndrome involving in addition to this exophthalmia paralysis of the oculomotor nerves (mydriasis), which may culminate in ophthalmoplegia. These clinical signs and the CT scan will enable the diagnosis to be established, confirming the exophthalmia and, in the venous stage of the angio-MRI, amputation of a cavernous sinus. It is associated in the majority of cases with sphenoidal sinusitis. The micro-organism most often involved is staphylococcus.

6.2.3 Other complications

- Frontal osteomyelitis (Marshall et al. 2000): fever, headaches and cranial bulging reflect the spread of frontal sinusitis to the bony walls.
- Frontal subcutaneous abscess (Pott's Puffy Tumour): this is manifested in inflammatory bulging of the frontal region combined with classic signs of infection. In the series in the study by Stoll et al. (2004), 8 out of 43 patients were sent at this stage.

6.3 Management

The principal prognostic element is to establish the diagnosis of orbital or intracranial complications early, which requires a knowledge of the presenting signs. A true therapeutic emergency, they require immediate hospitalisation.

6.3.1 In the emergency department

6.3.1.1 Antibiotic treatment

Orbital or cerebral complications necessitate the institution of intravenous antibiotic therapy as soon as the clinical diagnosis is established. Pending the results of the bacteriological samples by puncture or during any surgical procedure on bone, cerebral or sinus foci, this antibiotic therapy must be effective against Gram-positive cocci (streptococci, pneumococci, staphylococci), β -lactamase-secreting *Haemophilus*, enterobacteria and anaerobic bacteria. It must also penetrate and diffuse appropriately into the bone or brain and meninges.

Currently, the preferred approach is to institute a 3rd generation cephalosporin at a high dose, preferably: cefotaxime (Claforan® 200 to 300 mg/kg/day) or ceftriaxone (Rocephine® 70 to 100 mg/kg/day) combined with metronidazole (Flagyl®). The addition of fosfomycin to the previous combination (Fosfocine® 200 mg/kg/day) is recommended in the case of a suspected staphylococcal infection (cavernous sinus thrombophlebitis). Meningitis with clinical signs of severity is an indication for the combination of cefotaxime and vancomycin

(40 to 60 mg/kg/day) on the assumption of a pneumococcus of reduced susceptibility to penicillin. In osteomyelitis of the cranial vault, the combination cefotaxime, metronidazole and quinolone is recommended.

In all cases, antibiotic therapy must be re-assessed in the light of the clinical outcome and the microbiological results. The duration of antibiotic treatment is 4 to 8 weeks, depending on the clinical and radiological outcome.

The sequelae involve blindness in the ophthalmological forms (Barry et al. 2000), epilepsy, permanent paralysis of the cranial nerves (VI, VII, VIII) and sensorimotor deficits or deficits of higher functions (Younis et al. 2001). Mortality remains high at between 2% (Jones^a et al. 2002) and 21% (Maniglia et al. 1989).

6.3.2 Specialist management

6.3.2.1 Extraperiosteal orbital abscess

An emergency intervention involves the evacuation of the abscess even if the patient has not yet undergone a CT scan and if the visual acuity is still normal or only slightly impaired. The intervention should be performed without imaging on the clinical features only (compression of the eyeball for 90 minutes may cause permanent blindness).

Two approaches are possible: an endoscopic endonasal approach or a classic orbitotomy.

6.3.2.2 Orbital cellulitis

Imaging reveals cotton-wool opacities in the whole area of projection of the eyeball. There is no indication for surgery: parenteral antibiotic therapy alone is appropriate. Visual acuity

must be checked twice daily. CT scans should be repeated to check for a possible collection in the orbital fat that might require surgical drainage in association with the ophthalmologists.

6.3.2.3 Cavernous sinus thrombophlebitis

If there is no improvement of the clinical signs and symptoms on antibiotics within 24h-48h despite the antibiotic treatment, surgical drainage should be considered.

6.3.2.4 Meningitis

This requires antibiotic therapy as described previously. In the absence of a clinical improvement, drainage of the sinus or sinuses concerned may be indicated.

6.3.2.5 Cerebral abscesses

Usually, these are treated purely medically, but an evacuation puncture may be necessary, particularly in the case of subdural empyemas.

In summary, the severe ophthalmological or cerebral complications of acute rhinosinusitis occur sporadically and it seems clear that antibiotic therapy can reduce but not eradicate them (Jones^a et al. 2002). Thus, any acute episode of rhinosinusitis requires an investigation of the premises for a potential complication. A careful orbital examination, an investigation for preliminary neurological signs and the explanation to the patient of the risks of complications might prove more effective for early diagnosis and management than a systematic prescription of antibiotics. Emergency imaging in the event of a suspected complication is the key examination.

7. Bacteriology and antibiotics; current situation

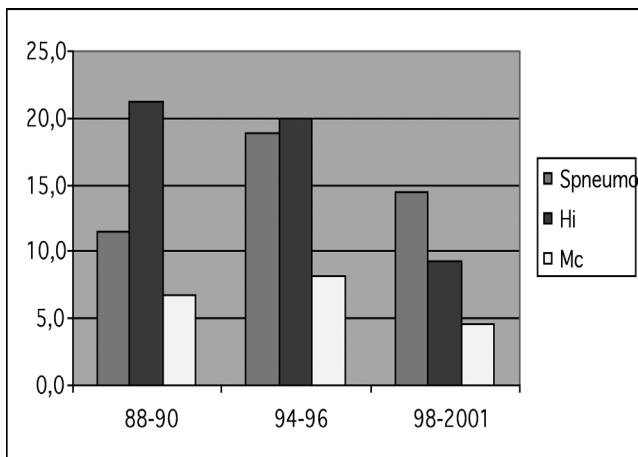
Introduction:

Recent studies provide up-to-date information on microbial epidemiology (distribution of species, state of resistance).

The review of 2076 patients included by the same team of ENT investigators in various clinical trials of antibiotic therapy between 1988 and 2001 provides a particular wealth of information about these different points. Analysis of the bacteriological information of these studies was performed by the same laboratory (Gehanno^b 2004). All patients had samples taken by aspiration with a teflon microcatheter or by swabbing, both procedures being performed under visual surveillance of the middle meatus. The percentage of positive cultures ranged from 61 to 66%.

Histogram No. 1 (after Gehanno^b 2005) shows the distribution of the three main, highly predominant pathogens *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* as a percentage of all cases of sinusitis sampled.

Histogram 1. Maxillary sinusitis, bacteriological outcome 1988-2001.

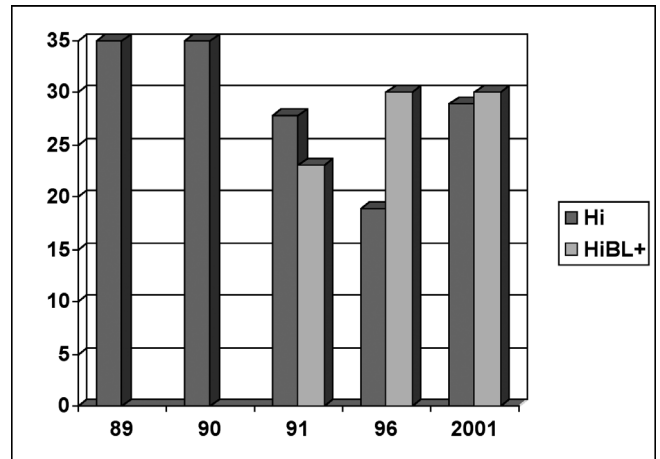


Histograms Nos. 2 and 3 (after Gehanno^b 2005) show the development of resistance for *H. influenzae* and *S. pneumoniae*.

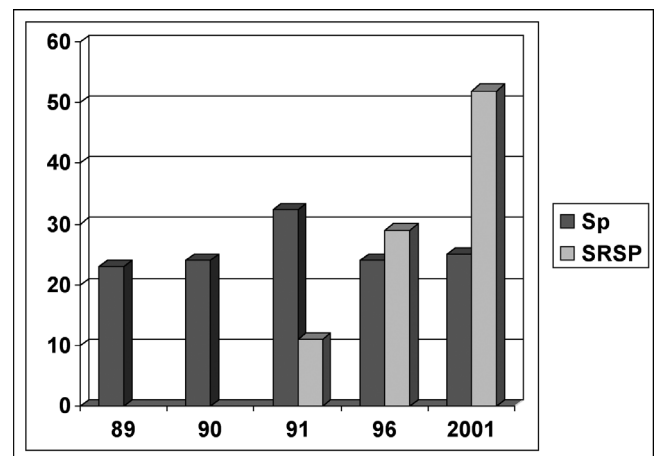
In histogram No. 2, the appearance of β -lactamase-producing *H. influenzae* can be observed at an appreciable level followed by a plateau at about 30%.

In histogram No. 3, a significant increase can be observed in strains of pneumococcus of reduced susceptibility to penicillin G (PRSP), reaching 50% of strains in 2001. This follows the curve observed in paediatric otitis with a lag time of 5 to 6 years.

Histogram 2. *H. influenzae* and beta lactamase-producing Hi.



Histogram 3. *S. pneumoniae* and SP of reduced susceptibility to penicillin.



7.1 State of resistance to antibiotics in *Streptococcus pneumoniae*

7.1.1 β -lactams

Amoxicillin and the injectable third generation cephalosporins have retained good activity against PRSP. These β -lactams have often been studied simultaneously. For the oral cephalosporins, there are fewer bacteriological studies and comparisons are rarely made with aminopenicillins and injectable cephalosporins.

7.1.1.1 Penicillins and injectable 3rd generation cephalosporins

Pneumococci are naturally very susceptible to β -lactams, with very low minimum inhibitory concentrations (MIC) for penicillin G, amoxicillin, ceftriaxone and cefotaxime.

The resistance mechanism derives from modifications of the β -lactam targets, PBP (penicillin-binding proteins). These modifications cause an elevation of the MIC values of all β -lactams,

but the amplitude of this increase varies with the compounds. The MIC of penicillin G are β 0.06 mg/L for sensitive strains (pen-S), between 0.12 and 1 mg/L for intermediate strains (pen-I) and MIC > 1 mg/L for resistant strains (pen-R). Any non-susceptible strain of pneumococcus is referred to as being of reduced susceptibility to penicillin (PRSP).

While there is a large amount of data on resistance to β -lactams, it should be pointed out that few studies distinguish the strains from sinusitis. Usually, data specific to bacteria isolated from the sinus are found in clinical studies of sinusitis.

The percentages of strains resistant to penicillin G (pen-R) in France and in Spain are between 25 and 30% (Jones^b et al. 2002).

The percentage resistance to ceftriaxone and cefotaxime is identical at about 1%. Differences are observed between these two antibiotics, but derive only from the difference in the pen-R strains (Karlowsky^a et al. 2003).

On the basis of all these values, the following points may be highlighted for all pneumococci:

- good homogeneity in the percentage resistance to β -lactams indicated in French studies
- a high level of PRSP which continues to increase, reaching 51 to 55% in 2001 (Drugeon^a et al. 2003, Vergnaud et al. 2003) vs 39.8% in 1999 (Laurans et al. 2001); this corresponds essentially to a greater proportion of pen-R strains. Although this antibiotic is not used in community practice, there should be an awareness of the level of reduced susceptibility (I) and resistant (R) strains in that the reduction in susceptibility to this antibiotic is accompanied by a high level of resistance to macrolides and cotrimoxazole (Cf. multiresistance).
- A low resistance rate for amoxicillin < 5%
It should be noted, however, that resistant strains are more numerous than in 1999 and that 17% of strains resistant to penicillin G are also resistant to amoxicillin (Drugeon et al. 2002).
- A low rate of resistance to third generation cephalosporins < 1%.
- A higher rate of PRSP in children than in adults: 71% vs 46%.

7.1.1.2 Oral 2nd and 3rd generation cephalosporins

The oral cephalosporins usable in this situation are cefpodoxime, cefotiam hexetil and cefuroxime axetil. When the MIC of a cephalosporin is greater than 2 mg/L, the strain of pneumococcus is classified as resistant (except for cefuroxime, MIC > 4 mg/L).

The MIC of cefpodoxime are similar to those of amoxicillin, while those of cefuroxime are two to four times higher (Drugeon et al. 2002, Table 1).

For any strain of PRSP, the MIC of cefixime are equal to or greater than 8 mg/L.

In the study by Schito (2002), the MIC₉₀ of cefuroxime are equal to 2 or 4 mg/L depending on the country for pen-I strains and 8 mg/L for pen-R strains.

In the study by Gehanno, no failure was observed in the treatment of adult acute maxillary sinusitis by cefpodoxime proxetil (Gehanno et al. 2002). In a third of cases, a pneumococcus was concerned, 48.6% of these being PRSP. The MIC of cefpodoxime were determined par the E test method; the MIC₉₀ values of cefpodoxime were respectively 0.06, 1.5 and 3 mg/L for strains susceptible, intermediate and resistant to penicillin G. Although some strains are intermediate or resistant, clinical failures are rare, including in sinusitis (Cohen 2002).

Table 1. MIC of three β -lactams for *S. pneumoniae* in 2001 (Drugeon et al. 2002).

	MIC 50/90 mg/L			
	Total strains: No.	Pen-S strains	Pen-I strains	Pen-R strains
	675	331	191	153
penicillin G	0.12/2	0.015-0.06	0.5-1	2/4
amoxicillin	0.6/2	0.015/0.03	0.5/1	2/4
cefpodoxime	0.06-4	0.03/0.06	0.5/2	2/4
cefuroxime	0.25/4	0.03/0.12	2/4	4/16

A recent evaluation of 965 French strains shows that the activity of cefpodoxime is stable over time (Drugeon 2004).

The weak in vitro activity of cefuroxime against PRSP is confirmed by other studies. In that of Alos et al. (2001), 88% of strains resistant to penicillin G were resistant to cefuroxime. It should be noted that only 17.1% of 372 strains of pneumococci of reduced susceptibility were susceptible to cefuroxime (Decousser et al. 2002). In the study by Decousser (2002), the resistance rates to penicillin G and cefuroxime were 55.5 and 54.4%. For Jones, 47.3% of the 547 French pneumococci were resistant to cefuroxime (Jones^b et al. 2002).

The susceptibility to cefotiam of 158 strains of pneumococcus has recently been evaluated (Soussy^a et al. 2003).

The susceptibility to oral cephalosporins and to amoxicillin was determined in 100 PRSP strains, of which 50 were resistant to penicillin G. The results are fairly comparable, except for cefuroxime for which the resistance rates are higher (Drugeon^b et al. 2003, Table 2).

Table 2. Activity of β -lactams against 100 PRSP strains, 50 of which resistant to penicillin G (Drugeon^b et al. 2003).

% sensitivity	cefuroxime			cefpodoxime			amoxicillin		
	S	I	R	S	I	R	S	I	R
Pen-I	26	28	46	52	30	18	66	34	0
Pen-R	0	2	98	2	46	52	8	50	42

The correlation between in vitro resistance and clinical failure in acute sinusitis is not strictly established.

7.1.2 Macrolides and related substances

At present, the percentage of pneumococci isolated from an ENT focus resistant to macrolides is between 45 and 60%

(Chardon et al. 2002, Drugeon^a et al. 2003, Vergnaud et al. 2003).

The MIC of erythromycin for a susceptible pneumococcus are between 0.01 and 0.06 mg/L. In France, the most common resistance mechanism is methylase production. When the bacterium produces a methylase, high-level resistance is observed (MIC > 64 mg/L); this resistance is crossed for all macrolides and lincosamides (clindamycin). This resistance currently spares pristinamycin (streptogramin) and telithromycin (ketolide) (Drugeon^d 2003).

Efflux, another mechanism which at present is rare in France, affects the 14-carbon (erythromycin, roxithromycin, clarithromycin) and 15-carbon macrolides (azithromycin); the MIC of erythromycin are then of the order of 8 to 16 mg/L.

Resistance to pristinamycin is extremely rare. Intermediate or resistant strains in the standard antibiotic sensitivity test are totally susceptible to this antibiotic when the MIC is determined subsequently by a dilution method. Any resistance to pristinamycin must be checked.

None of the 675 strains isolated in France in 2001 (Drugeon^a et al. 2003) nor any of the 965 strains isolated in 42 centres in 2002 (Drugeon 2004) is resistant to telithromycin or to pristinamycin, irrespective of any resistance to penicillin G and/or macrolides.

7.1.3 Fluoroquinolones

Among the commercially available fluoroquinolones, levofloxacin and moxifloxacin have in vitro antipneumococcal activity (FQAP).

7.1.3.1 Resistance mechanisms

Resistance occurs by efflux or following mutations: mutation in the DNA gyrase subunits (GyrA, more rarely GyrB) or in the type IV topoisomerases (ParC and secondarily ParE). Not all the resistance mechanisms of this family of antibiotics are known.

In pneumococci, the mutations succeed one another and cause an elevation of the MIC in successive stages; each mutation globally multiplies the MIC by a factor of 4. The first mutation occurs in the principal target of the fluoroquinolone. Thus, the preferential target of ciprofloxacin, levofloxacin and norfloxacin is ParC, while that of sparfloxacin, moxifloxacin and gatifloxacin is GyrA (Houssaye et al. 2002).

7.1.3.2 State of resistance to FQAP

The resistance to levofloxacin varies from 0 to 1.8% in the different European countries, including France. Resistance ranges from 0.5 to 3.9% in Asia, with the exception of Hong Kong where it is 8% (Soussy^b 2003, Jones^b et al. 2002).

7.1.3.3 Resistance mechanism and clinical failure

The bacteriological/clinical correlations between resistance and clinical failure are not documented in sinusitis.

7.1.3.4 Frequency of ParC and GyrA mutations in France

Among 2325 strains, a resistance mechanism was demonstrated for 39 strains i.e. 1.7% resistance with a known mechanism. The higher-level resistant strains correspond to the double mutation ParC + GyrA. The ParC mutation alone was observed 17 times, i.e. 0.8% of the 2325 strains studied.

A study conducted at the pneumococcal reference centre showed that, in France, the first mutation occurs with ParC. These mutants can be detected routinely. If a second mutation were to occur during treatment, that might result in a clinical failure.

7.1.4 Multiresistance

Strains of reduced susceptibility to penicillins (PRSP) are frequently resistant to one or more families of antibiotics. Thus, the resistance rate of strains susceptible to penicillin vs PRSP strains are as follows: erythromycin 30.1% vs 82.2%, cotrimoxazole 17% vs 73%, tetracycline 18.3% vs 48.5% and chloramphenicol 10.8% vs 39.8% (Laurans et al. 2001). Simultaneous resistance to penicillin G and to erythromycin is observed in 80% of cases (Drugeon^a et al. 2003). All the studies confirm greater resistance in PRSP to the different families mentioned above.

From July 1999 to April 2000, 16 nasal swabs were taken during episodes of rhinosinusitis (Sokol 2001, Table 3). Greater resistance to penicillins and/or macrolides was significantly associated with the consumption of antibiotics by patients in the three months preceding the episode of rhinosinusitis.

Table 3. Correlation between the susceptibility of pneumococci to antibiotics and consumption of antibiotics within the previous 3 months (Sokol 2001).

Susceptibility	No antibiotic taken	β -lactams taken	Macrolides taken
Penicillin			
S	67% (340/505)	45% (25/55)	48% (14/29)
I	19% (97/505)	20% (11/55)	31% (6/29)
R	13% (66/505)	35% (19/55)	21% (6/29)
Erythromycin			
S	72% (365/505)	49% (27/55)	15% (13/29)
I	0.4% (2/505)	0	0
R	27% (136/505)	51% (28/55)	55% (16/29)

7.2 State of resistance to antibiotics in *Haemophilus influenzae*

H. influenzae is a commensal bacterium of the oropharynx with a carriage rate of more than 40% in young children (Dellamonica et al. 2002, Offredo et al. 2003, Talon et al. 2000). Together with pneumococcus, it is one of the leading microorganisms responsible for bacterial sinusitis in adults and children (Conrad et al. 2002, Gehanno^a 2003, Sokol 2001). *H. influenzae* is a species that is naturally susceptible to antibi-

otics active against Gram-negative bacteria with intermediate sensitivity to 14- and 15-carbon macrolides and natural resistance to lincosamides and 16-carbon macrolides. *H. influenzae* has acquired a number of resistance mechanisms to antibiotics because of its frequent exposure to the commensal flora of treated patients. The frequency of resistant strains of *H. influenzae* varies from one country to another (Hoban et al. 2002). As with pneumococcus, while there is a large amount of data on the resistance of *H. influenzae* to antibiotics, few studies distinguish the strains isolated from sinusitis. A number of studies report the susceptibility to antibiotics of strains isolated from acute otitis media discharge or from the flora of the oropharynx (Drugeon et al. 2002, Boulesteix et al. 1995, Dellamonica et al. 2002, Gehanno et al. 2001, Offredo et al. 2003, Talon et al. 2000).

7.2.1 Resistance to β -lactams

Different mechanisms of resistance to β -lactams have been described in *H. influenzae* (Jorgensen 1992). The resistance to β -lactams is related above all to the production of β -lactamases or a modification of the penicillin-binding proteins (PBP), the target of the β -lactams. Depending on the resistance mechanism, the in vitro activity of the different β -lactams (penicillins and cephalosporins) is modified to a greater or lesser extent (Dabernat^a et al. 2002, Dabernat et al. 2004).

7.2.1.1 β -lactamase production

The production of β -lactamases, usually of the TEM type, is the most common mechanism. The minimum inhibitory concentrations (MIC) of amoxicillin range from 0.25 mg/L for susceptible strains to 8 mg/L for β -lactamase-producing strains (Dabernat et al. 2004, Table 4). The activity of aminopenicillins of the amoxicillin type is restored by a β -lactamase inhibitor such as clavulanic acid, with the MIC of the combination amoxicillin-clavulanic acid being 0.25-0.5 mg/L. The 2nd and 3rd generation cephalosporins, resistant to β -lactamases, retain comparable activity to that of susceptible strains (Dabernat et al. 2004, Table 4). The MIC of the 3rd generation cephalosporins remain very low (MIC cefotaxime 0.015 mg/L) (Dabernat et al. 2004, Table 4). The study by Drugeon et al. (2002) involving 751 strains of

H. influenzae isolated in adult respiratory tract infections reports for 245 β -lactamase-producing strains MIC₉₀ of 2 mg/L for the combination amoxicillin-clavulanic acid, 0.25 mg/L for cefpodoxime and 8 mg/l for cefuroxime. In this study, cefuroxime is the least active compound with only 64.5% of the β -lactamase-producing strains susceptible, whereas 100% of these strains are susceptible to amoxicillin-clavulanic acid and cefpodoxime.

The percentage of β -lactamase-producing strains in France is increasing regularly with the incidence practically doubling over the last 10 years, from 15% in 1990 to 40% in 1999 (Dabernata et al. 2002). In 2001, the rate was 33.8% with a relative plateau for a few years (Dabernat et al, 2004). On the basis of the results of some clinical studies, the percentages of β -lactamase-producing strains of *H. influenzae* from sinusitis discharge varies from 16.1% (Gehanno et al. 2002) to 54% (Goldstein et al. 2003).

7.2.1.2 Strains of reduced susceptibility to β -lactams by modification of the target, known as "low BLNAR"

Reduced susceptibility by modification of the β -lactam target or "low BLNAR" (" β -lactam negative ampicillin-resistant strains") phenotype is more rare, found in 8 to 10% of usually unencapsulated strains and responsible for chronic bronchopulmonary and ENT infections (Dabernat^a et al. 2002, Dabernat et al. 2004). This mechanism causes a moderate reduction in the activity of the β -lactams, affecting more particularly 1st and 2nd generation cephalosporins (Dabernat et al. 2004, Table 4).

In France in 2001, of 752 strains of *H. influenzae* studied, 142 (18.9%) were of reduced susceptibility to β -lactams (low level resistance or "low BLNAR") with a moderate increase of the MIC of amoxicillin, the combination amoxicillin-clavulanic acid and cefotaxime. Cefpodoxime remains the most active oral β -lactam (Dabernat et al. 2004, Table 4).

This type of resistance is difficult to detect in vitro and it is not possible to predict its clinical impact. Up until now, the observed moderate reduction in β -lactam activity does not appear to cause clinical failures. However, as *H. influenzae* is a transformable bacterium like pneumococcus, the development of the incidence of resistant strains due to impairment of PBP should be monitored.

Table 4. In vitro activity of β -lactams against with *H. influenzae* according to the mechanism of resistance to these antibiotics (adapted from Dabernat et al. 2004).

β -lactams (Number of strains)	All strains	Sensitive strains	MIC ₅₀ /MIC ₉₀ ^a		
			Bla(+) ^b strains	"Low BLNAR" ^c strains	
Units	mg/l	mg/l	mg/l	mg/l	mg/l
				Bla(-) ^b	Bla(+)
amoxicillin (n=737)	0.5/16	0.25/0.5	16/32	1/2	16/32
amoxicillin-clavulanic acid (n=737)	0.25/1	0.25/0.5	0.25/0.5	1/2	1/1
cefaclor (n=391)	4/16	4/8	4/8	8/32	16/32
cefuroxime (n=391)	1/2	0.5/1	0.5/1	2/4	2/4
cefpodoxime (n=391)	0.06/0.25	0.06/0.12	0.06/0.12	0.12/0.25	0.12/0.25
cefotaxime (n=737)	0.015/0.03	0.015/0.03	0.015/0.03	0.03/0.06	0.03/0.06

^a MIC₅₀, MIC inhibiting 50% of strains; MIC₉₀, MIC inhibiting 90% of strains tested.

^b Bla(+) β -lactamase-producing strains; Bla(-), non- β -lactamase-producing strains.

^c Low β -lactam resistance strains.

7.2.1.3 Strains with both mechanisms of resistance (β -lactamases and "low BLNAR")

β -lactamase-producing strains resistant to the combination amoxicillin-clavulanic acid have been described (Doern et al. 1997). Clavulanic acid no longer restores the activity of amoxicillin in vitro. In 2001 out of 752 strains of *H. influenzae* studied, 50 were both β -lactamase-producing and "low BLNAR", i.e. 6.6% of the total strains studied (Dabernat et al. 2004).

7.2.2 Resistance to macrolides, lincosamides, streptogramins, ketolides (MLSK)

H. influenzae strains possess natural resistance to lincosamides and 16-carbon macrolides according to the rules of the Antibiotic Sensitivity Test Committee of the French Microbiology Society (CA-SFM) (Comité de l'Antibiogramme 2003); they naturally exhibit intermediate susceptibility to 14- and 15-carbon macrolides, pristinamycin and telithromycin, the species being classified in the moderately susceptible category. In the absence of any resistance mechanism, the use of these compounds against *H. influenzae* will be determined by their tissue diffusion (antibiotic level obtained in the sinus).

A recent French study of 142 strains shows modal MICs of erythromycin of 2-4 mg/L, clarithromycin of 4 mg/L, azithromycin of 1 mg/L and telithromycin of 1-2 mg/L, without revealing any acquired resistance to macrolides (Dabernat^b et al. 2002). Telithromycin, a new representative of the class of ketolides, has similar activity to azithromycin (a 15-carbon macrolide) and exhibits significantly superior activity to the 14-carbon macrolides represented by erythromycin and clarithromycin (Dabernat^b et al. 2002, Drugeon^a et al. 2003).

Several in vitro studies show that all of the strains of *H. influenzae* behave homogeneously towards pristinamycin (streptogramin family) with a modal MIC of 2 mg/L, without revealing any acquired resistance to this antibiotic (Dabernat 2000, Leclercq 1999). It is important to stress that pristinamycin exerts bactericidal activity against *H. influenzae* with minimal bactericidal concentrations (MBC) close to the MIC at about 2 mg /L (Dabernat 2000, Drugeon^c 2003).

7.2.3 Resistance to fluoroquinolones

The appearance of fluoroquinolone-resistant strains of *H. influenzae* has been documented for some ten years, but remains very rare (Biedenbach et al. 2003, Decousser et al. 2002, Hoban et al. 2002, Jones et al. 2002, Jones et al. 2003, Karlowsky^b et al. 2003, Sahm et al. 2000, Sokol 2001, Boswell et al. 2002).

7.3 State of resistance to antibiotics in *Moraxella catarrhalis*

This Gram-negative bacterium is the 3rd most common cause of bacterial sinusitis in adults and children (Conrad et al. 2002, Gehanno^a 2003, Sokol 2001).

Acquired resistance to antibiotics in this bacterium essentially involves the penicillins, with the production of β -lactamases

currently affecting more than 90% of strains. This production of β -lactamases (of the BRO type) causes resistance to aminopenicillins (ampicillin) and penicillin G. Activity in aminopenicillins of the amoxicillin type is restored by a β -lactamase inhibitor of the type of clavulanic acid; that of the cephalosporins is not affected (Chaibi et al. 1995). A recent study of 385 clinical strains of β -lactamase-producing *M. catarrhalis* describes MIC values inhibiting 90% of these strains (MIC₉₀) of 8 mg/L for amoxicillin, 0.5 mg/L for cefixime and 2 mg/L for cefepime (Schmitz et al. 2002). Taking the results from some clinical studies, the percentages of strains of β -lactamase-producing *M. catarrhalis* from sinusitis discharge varies from 91.5% (Sokol 2001) to 100% (Gehanno et al. 2002).

All these studies report very good activity for the other classes of antibiotics, particularly MLSK and fluoroquinolones, used in the treatment of respiratory tract and ENT infections in which *M. catarrhalis* may be involved (Decousser et al. 2002, Drugeon^a et al. 2003, Goldstein et al. 2003, Hoban et al. 2002, Jones^c et al. 2002, Jones et al. 2003, Sahm et al. 2000, Schmitz et al. 2002).

7.4 State of resistance to antibiotics in staphylococci, streptococci

The possible implication of *S. pyogenes* in 5 to 10% of cases of maxillary sinusitis and of *S. aureus* in less than 5% of cases (Gehanno^a 2003) requires a brief consideration of the state of resistance to β -lactams and macrolides in these two bacterial species. Here again, very few studies on strains isolated from sinusitis are available.

S. pyogenes remains susceptible to β -lactams, pristinamycin and telithromycin; conversely, its percentage resistance to macrolides has been on the increase for several years. In France, in 2003, this figure exceeded 20% of all invasive and non-invasive strains (Bouvet et al. 2004).

It is difficult to give representative figures of the resistance of *S. aureus* in sinusitis discharge in view of the lack of available data. Staphylococci are generally susceptible to the combination amoxicillin-clavulanic acid, to oral cephalosporins, apart from cefpodoxime and cefixime, and to pristinamycin and telithromycin.

A recent study involving 485 patients suffering from acute maxillary sinusitis in France, Tunisia, Poland and Argentina reports the isolation of *S. aureus* as a pathogenic bacterium in 15% of cases (Gehanno^a et al. 2004). The 32 strains studied all remained susceptible to pristinamycin (MIC₉₀ of 0.25 mg/L) and cefuroxime (MIC₉₀ of 1 mg/L).

Studies suggest increased carriage in the community of methicillin-resistant *S. aureus* (MRSA) (Salgado et al, 2003), with a global rate of MRSA colonisation estimated as about 1%.

7.5 Antibiotic therapy of acute rhinosinusitis: current situation

The analysis of the studies published since the initial work by the SGIS (Klossek et al. 2001) is presented below.

7.5.1 Results

Ten articles were selected, corresponding to nine multicentre, comparative, prospective and randomised studies, and one non-comparative open-label study involving a specific population either at particular risk or following treatment failure.

The results are given in tables 5 to 8. Where no information was available (missing or unclear response), this is indicated by "NS" for not specified.

7.5.1.1 Critical analysis of diagnostic methods (table 5)

Clinical signs:

The clinical signs whose presence is required for the diagnosis of acute rhinosinusitis are indicated by "+". For the majority of authors, the diagnosis is based on a combination of signs, without the presence of any being obligatory; these are indicated by "±". Nevertheless, certain authors mention the frequency of these signs, which are then reported in the table. All the authors clearly indicate the clinical criteria required for the diagnosis of acute rhinosinusitis.

Radiological signs:

Nine of the ten trials reported required a radiological diagnosis, based on plain film examinations (Gehanno^a et al 2000, Dubreuil et al 2001, Gehanno et al. 2002, Roos et al. 2002, Gehanno^c et al. 2003, Klossek et al. 2003, Luterman et al. 2003, Henry et al. 2003, Gehanno^a et al. 2004), and in two trials a CT scan (Gehanno et al. 2002, Roos et al. 2002, Gehanno^c et al. 2003). Only one author did not employ these examinations (Rakkar et al. 2001).

Bacteriological samples:

Taken during 7 of the trials (Gehanno^a et al. 2000, Dubreuil et al. 2001, Gehanno et al. 2002, Roos et al. 2002, Gehanno^c et al. 2003, Klossek et al. 2003, Luterman et al. 2003, Gehanno^a et al. 2004), the samples came from the middle meatus in 6 trials, by puncture (Roos et al. 2002), or by both techniques without distinction (Klossek et al. 2003, Luterman et al. 2003).

It seems that, from the point of view of diagnostic criteria, these recent studies are of better quality than the older studies.

7.5.1.2 Critical analysis of the methodology of the trials

(table 6)

- Nine of the ten trials analysed were randomised, but the method of randomisation (by centre, centralised, by server, computerised, by block, etc.) is described for only 2/9 trials (Dubreuil et al. 2001, Rakkar et al. 2001).
- The "a priori" calculation of population size is clearly justified in 7/9 randomised trials.
- Concomitant medications in the form of nasal decongestants were permitted in all trials.
- The treatment durations are always specified; several trials include a short treatment arm: 5 days (Dubreuil et al. 2001, Gehanno et al. 2002, Roos et al. 2002, Luterman et al. 2003), 4 days (Gehanno^a et al. 2004) and even 3 days (Henry et al. 2003).
- The procedures for analysis of the results vary from one

study to another:

Thus, the time to evaluation of the principal criterion is usually within a variable period in relation to the end of treatment (EOT) (Gehanno^a et al. 2000, Dubreuil et al. 2001, Gehanno et al. 2002, Rakkar et al. 2001, Roos et al. 2002, Klossek et al. 2003, Luterman et al. 2003, Gehanno^a et al. 2004), the period varying from 3 days to 24 days, or at the end of the study (Henry et al. 2003).

- The results are only available by intention to treat (ITT) in 8/10 trials.
- As this involved the demonstration of efficacy of a theoretically "potent" anti-infective agent in an acute disease without a reputation for severity, the criterion of "clinical cure" should have been the only one used, that of clinical improvement not being satisfactory. However, for the majority of the studies reported, the reader is given the percentage of satisfactory clinical responses, not the percentage of patients actually cured (6/10).
- The possibility of correlating the clinical results with the microbial aetiology remains very difficult. The percentage cures according to microbial aetiology are only available for 3 studies (Gehanno^a et al. 2000, Gehanno et al. 2002, Gehanno^a et al. 2004), and the results of microbial eradication by organism are available for only 5 studies (Dubreuil et al. 2001, Gehanno et al. 2002, Roos et al. 2002, Klossek et al. 2003, Luterman et al. 2003). These data represent small populations and for this reason have a very limited impact (tables 7 and 8).

7.5.1.3 Analysis of results (table 9)

Antibiotics tested:

In the case of the β -lactams, a new dosage of amoxicillin-clavulanic acid, Augmentin[®] 1 g/125 mg, was evaluated in 2 daily doses, but this was compared with the old dosage in 3 divided daily doses (0.5 g/125 mg). The other β -lactams either served as comparators or were evaluated with treatment durations reduced to 5 days.

For quinolones with antipneumococcal activity, moxifloxacin was evaluated versus amoxicillin-clavulanic acid or trovafloxacin.

The therapeutic innovation came with telithromycin, the first ketolide to have obtained its MA.

In July 2003, pristinamycin obtained a MA for 4 days at a dosage of 2 g/day in 2 divided doses.

The macrolides tested were principally clarithromycin and azithromycin.

Overall, and apart from telithromycin, the innovative nature of the studies is clearly based on the evaluation of treatment durations limited to 5 days, and even 4 days with pristinamycin and 3 days with azithromycin.

Evaluation of the efficacy of antibiotics (table 9):

The justification for the use of antibiotics in acute bacterial maxillary sinusitis cannot be questioned.

In view of all the criticisms and reservations and the impossibility of comparing the studies with one another, this new analysis, while admittedly confined to the small number of relevant studies available, does not yield the conclusion of the superiority of one family of antibiotics over another.

The comparative studies analysed are non-inferiority studies; a high percentage of clinical successes was observed for each of them and it was concluded that there was no difference between the treatments compared.

The study by Gehanno with moxifloxacin (Gehanno^c et al. 2003), although non-comparative, deserves to be mentioned as it confirms the place assigned to the antipneumococcal quinolones by the health authorities in France; 175 patients following treatment failure and 41 with sinusitis at risk of complications were evaluable per protocol. From a bacteriological viewpoint, 15/23 *S. pneumoniae* I/R were responsible in the patients with treatment failure. The cure rates were 166/175 (94.9%) for patients with treatment failure, and 34/41 (82.9%) in patients with sinusitis at risk of complications. The bacteriological eradication rates were 97.2% and 95.2%, respectively.

Certain conclusions can be drawn from the analysis of recent clinical studies between 2001 and 2004

- The equivalence of 5 and 10 days of treatment has been demonstrated for two β -lactams, cefuroxime axetil (Dubreuil et al. 2001) and cefpodoxime proxetil (Gehanno et al. 2002).
- Pristinamycin for 4 days is as effective and as well tolerated as cefuroxime axetil for 5 days (Gehanno^a et al. 2004).
- Telithromycin exhibits clinical efficacy comparable to that of amoxicillin-clavulanic acid (Luterman et al. 2003), and also comparable efficacy for respective treatment durations of 5 and 10 days (Roos et al. 2002).
- Azithromycin administered for 3 days is as effective as when administered for 6 days, or as 10 days of amoxicillin-clavulanic acid (Henry et al. 2003), and significantly better tolerated from the digestive point of view, but the MA has not been granted in France in this indication.
- Moxifloxacin represents second-line treatment in patients with treatment failure or at risk of complications (Gehanno^c et al. 2003).

Practical consequences:

In the absence of proven superiority of one compound over the others, and taking into account the marketing authorisations (MA), the choices proposed in the AFSSAPS recommendations supplemented in 2003 by the addition of telithromycin, do not require modification (table 10).

In particular, in respect of the antipneumococcal quinolones, it should be pointed out that they were granted a MA in acute rhinosinusitis (Official Gazette of 8 September 2000, page 1467): as first-line treatment in frontal, ethmoidal and sphenoidal rhinosinusitis (outside our scope) and following the failure of initial antibiotic therapy in the other forms of acute rhi-

nosinusitis after bacteriological and/or radiological documentation. In this respect, Gehanno's study clearly confirms the value of moxifloxacin in patients at particular risk or with treatment failure (Gehanno^c et al. 2003).

The benefit of antibiotics with a validated treatment regimen shortened to 4 days (which is the case with pristinamycin), or 5 days (as is the case with cefuroxime axetil, cefpodoxime proxetil and telithromycin) should also be stressed.

7.5.2 Shortened course of treatment

The ecological impact of the prescription of antibiotics arouses concerns as a result of the constant increase in bacterial resistance in community-acquired infections. To combat this development, the WHO in 2000 drew up recommendations to encourage the use of the most active antibiotics in association with shorter courses of treatment than conventional ones (World Health Organization, 2000). The conventional course of treatment was established empirically on the basis of criteria derived from the clinical and bacteriological analysis of failures and relapses. The appearance of new compounds and the improvement of the pharmacodynamic qualities of some (long half-life, intracellular accumulation, tissue diffusion) enabled this conventional course of treatment to be re-assessed with the aid of experimental models and comparative clinical trials.

The potential advantages of shortened courses of antibiotic treatment are numerous: optimisation of acceptability and compliance, reduction of the risk of adverse effects, less impact on flora. All of these advantages combine to reduce the global costs of the management of this disease, even if the antibiotic prescribed in a shortened course of treatment costs more than that prescribed for the conventional period (Pichiero et al. 1997).

The duration of conventional treatment in adult maxillary rhinosinusitis is 10 to 14 days. Trials in acute maxillary rhinosinusitis have validated a shortened course of treatment of 5 days or fewer with different antibiotics (Cefuroxime Axetil, Cefpodoxime Proxetil, Cotrimoxazole, Azithromycin, Pristinamycin, Telithromycin) (Guay 2003).

In summary, resistance concerns *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in particular. The published percentages are increasing regularly. This phenomenon requires appropriate use of antibiotic therapy and compliance with prescriptions that are appropriate to the local epidemiology. Identification of the causative bacterium, particularly following treatment failure, is desirable both to understand the mechanism of the failure and to follow the development of the resistance mechanisms concerned. Sampling from the middle meatus, which is less uncomfortable than sinus puncture, has satisfactory reliability when performed in accordance with the rules of the art. This technique should be encouraged among specialists and the awareness of general practitioners about its possibilities should be heightened. Finally, collaboration between clinician and microbiologist is always to be recommended for the optimal use of antibiotics.

8. Non-antibiotic treatment

8.1 Corticosteroid therapy

Inflammation is a physiological response (non-specific immunity) of the rhinosinus mucosa to infection (Stoll 2001). Nevertheless, this response is the source of sometimes uncomfortable symptomatic disorders (pain, congestion). Local and systemic proprietary corticosteroid products are prescribed to reduce the oedema and relieve the pain.

Two recent French studies (Ferrand et al. 2000, Pessey et al. 2001) report a prescribing frequency of almost 40% for primarily systemic or local corticosteroid therapy combined with vasoconstrictors in adults in general practice.

8.1.1 Local corticosteroids

Local specialities combining a corticosteroid with one (or more) antibiotics have been withdrawn from the market (because of the presence of the antibiotic). Proprietary products for nasal use containing a corticosteroid should still be avoided in the case of infection according to the current Marketing Authorisations (MA).

Three studies (Nayak et al. 2002, Meltzer et al. 2000, Dolor et al. 2001) evaluated the clinical efficacy and safety of nasally administered corticosteroids combined with oral antibiotic therapy. However, these studies were not performed during episodes of bacteriologically documented acute sinusitis and the antibiotic therapy used, although consistent with the recommendations of the choice of compounds, was prescribed in two studies over an unusual length of time (3 weeks).

In the study by Dolor (2001), a local vasoconstrictor was combined during the first three days and a positive result in the group combining administration of cefuroxime and the vasoconstrictor was achieved in 73%, which is astonishing compared to the results usually observed with this antibiotic prescribed alone (Buchanan et al. 2003, Scott et al. 2001).

It is therefore premature, on the basis of these studies involving major methodological biases, to draw any objective conclusions about the value of local corticosteroids combined with an oral antibiotic in community-acquired sinus diseases. New and methodologically appropriate studies are advisable.

8.1.2 Systemic corticosteroids

Two studies combining systemic corticosteroids in short courses with antibiotic treatment are available in this indication.

The first study (Gehanno^b et al. 2000) involved 417 patients randomised versus placebo, receiving either 5 days or 10 days of the same antibiotic (amoxicillin-clavulanic acid 500 mg x 3/day). These adult subjects suffering from acute maxillary sinusitis were randomised to receive during the first 5 days either methylprednisolone (8 mg x 3/day) or placebo. A very significant improvement in pain ($p=0.016$) in the group treated with methylprednisolone was observed on D4.

The second placebo-controlled double-blind study (Klossek et al. 2004) involved 289 patients with hyperalgetic maxillary rhinosinusitis. The aim of this study was to evaluate the efficacy and safety of prednisolone administered systemically for 3 days in single doses of 0.8 to 1 mg/kg/day. The antibiotic administered in combination was cefpodoxime (200 mg x 2/day) and paracetamol was permitted (<3 g/day). A significant reduction in pain, nasal obstruction and the consumption of paracetamol in favour of the prednisolone-treated group was observed at the end of the three days. The safety associated with the antibiotic was also good.

Finally, these data indicate the possible use of systemic corticosteroid therapy in the event of a major (painful) inflammatory reaction combined with antibiotic therapy in accordance with the recommendations of the AFSSAPS. Similarly, it seems that local treatment can be pursued in this situation, subject to antibiotic treatment consistent with the recommendations.

8.2 Systemic non-steroidal anti-inflammatory drugs (NSAID)

The role of NSAIDs at anti-inflammatory doses remains to be evaluated.

8.3 Vasoconstrictors

These may be used both orally and locally (nasally). Although they have not been evaluated in controlled studies, vasoconstrictors are widely used in the first few days of treatment of acute rhinosinusitis (Kaliner 1998). They are also frequently used in combination in studies evaluating antibiotics. In acute rhinitis, their use is well tolerated, particularly when they are not combined with certain excipients (Dorn et al. 2003). Their use in the short term, in accordance with their contra-indications and dosages, poses no problems (Lundberg et al. 1999). They significantly reduce nasal obstruction and improve nasal discharge and comfort for the patient, particularly during sleep. Oral ingestion of vasoconstrictors is less popular, even if their efficacy is well documented (Bertrand et al. 1996, Malm 1994, Roth et al. 1997).

The oral forms as well as almost all the local forms are not indicated in children under 12 years.

The indications for phenylpropanolamine-based proprietary products have been limited because of the exceptional risk of cerebrovascular accidents.

Combinations of local antibiotics and vasoconstrictors have been withdrawn from the market (because of the presence of the local antibiotics).

Only the combination ibuprofen (200 mg) and pseudoephedrine (30 mg) systemically has been the subject of a

MA variation for its proposed use in acute maxillary rhinosinusitis of viral origin.

8.4 Mucolytics

Although these treatments are fairly widely used in current practice, there has been no study to confirm their value in this clinical situation.

8.5 Other treatments

- Analgesics are often used, but have not been assessed in this disease. Antipyretics are also widely used. It seems preferable to use paracetamol rather than aspirin so as not to interfere with haemostasis in the eventuality of a surgical procedure.
- Aerosol treatments have a mechanical action, have not been evaluated in this indication, are often very burdensome, but nevertheless remain widely prescribed in this situation.

- Among the other treatments proposed, the following may be mentioned: acupuncture (Pothman et al. 1982), homeopathy (Wiesenaueer et al. 1989) and Myrtol (Federspil et al. 1997). None of these treatments can be adopted because of the numerous methodological biases and the absence of bacteriological confirmation of the cases of rhinosinusitis included in these studies.
- In a study involving 1325 patients, a fusafungine dose-metered aerosol was used alone for the treatment of upper respiratory tract infections (Samolinski et al. 1996). It has, however, never been evaluated in acute maxillary rhinosinusitis.

In summary, as with oral corticosteroids, studies are required to evaluate all these treatments.

9. Conclusion

Many episodes of rhinosinusitis are viral: the suggestion of a bacterial infection results in the institution of antibiotic treatment which is designed to relieve the symptoms more rapidly and reduce the risk of orbital and encephalomeningeal complications.

No evaluation has revealed any predisposing or exacerbating role for allergy, asthma, immunodepression, smoking and pollution.

The diagnostic procedure is currently based on previous history and clinical examination. The use of an "otoscope" to perform "rhinoscopy" is the most accessible and relevant examination for the general practitioner: it is easy to learn (conduct and interpretation) and should be encouraged.

Because of their lack of specificity and sensitivity, Sinus X-rays are not indicated routinely.

In the context of an epidemic, viral rhinosinusitis without purulent nasal discharge or localised pain requires only symptomatic treatment.

When the infection is doubtful, it is preferable to prescribe symptomatic treatment and to inform and monitor the patient. This decision does not jeopardise the prognosis.

When there is a probable bacterial origin (clearly localised, stereotyped pain and homolateral purulent rhinorrhoea) antibiotic therapy is instituted in accordance with the prescribing

rules (MA) to obtain maximum efficacy.

It is empirical and must be effective against pneumococci and *H. influenzae* whose resistance profiles in France are changing.

In view of recent data, the choice should be between:

- the combination amoxicillin - clavulanic acid (7 to 10 days),
- cefpodoxime proxetil (5 days),
- cefotiam hexetil (5 days),
- cefuroxime axetil (5 days),
- pristinamycin (4 days),
- telithromycin (5 days).

Short courses of treatment validated by the MA should be given precedence as they improve compliance, reduce adverse effects, improve the ecological impact and decrease treatment costs.

Symptomatic treatments involve analgesics, antipyretics and vasoconstrictors (in adults and children over 12 years of age). Subject to appropriate antibiotic therapy, systemic corticosteroids are justified in the case of severe sinus pain (inflammation). The benefit of local corticosteroids remains to be established.

The incidence of complications, even if low, encourages vigilance over the potential risk of a complication, even if the patient is receiving antibiotic therapy.

10. Tables and figures

Medical monitoring procedures in cases of rhinosinusitis

- I. Expected outcome of treatment of rhinosinusitis:
- The pains recedes very rapidly and disappears within a few days (3 to 5 days),
 - Nasal discharge becomes clearer and disappears gradually,
 - Any nasal obstruction regresses,
 - The mean duration of this process is about 7 days.
- II. Signs which should alert the patient and cause him to visit the doctor again:
- Occurrence of obnubilation, somnolence,
 - Occurrence of vomiting,
 - Occurrence, persistence or recurrence of high fever,
 - Meningeal signs,
 - Neurological signs:
 - Headaches
 - Speech difficulty(aphasia, ...)
 - Motor deficit
 - Occurrence of unilateral or bilateral palpebral oedema:
 - Diplopia
 - Impairment of visual acuity

Table 5. Acute rhinosinusitis: critical analysis of diagnostic methods.

	Headache	Facial pain	Sinus, peri-orbital pain	Purulent nasal discharge	Nasal congestion	Cough	Fever	Imaging Standard: ST CT scan: CTS	Meatus: M Puncture: P
Gehanno ^a et al. 2000	+	+	+	+	NS	NS	NS	ST	M
Dubreuil et al. 2001	± 81-84%	NS	NS	± 95%	± 94-97%	NS	± 25-26%	ST	M
Gehanno et al. 2002	±	NS 100%	NS	+	NS	NS	± 24%	ST/CTS	M
Rakkar et al. 2001	±	NS	NS	±	±	±	NS	No	No
Roos et al. 2002	±	NS	NS	±	±	NS	NS	ST/CTS	P
Gehanno ^c et al. 2003	NS	+	NS	+	NS	NS	NS 24%	ST/CTS	M
Klossek et al. 2003	± 80-83%	NS	NS	± 89%	± 93-95%	± 67,8-71%	± 4,4-6,7%	ST	M/P
Luterman et al. 2003	+	NS	NS	+	NS	NS	NS 1,75%	ST	M/P
Henry et al. 2003	± 86%	NS 93%	NS	± 96%	± 98%	NS	NS	ST	0
Gehanno ^a et al. 2004	NS	NS	+	+	NS	NS	30-34%	ST	M

Table 6. Antibiotic therapy of acute rhinosinusitis: critical analysis material and methods (1).

Design (numbers included)	Duration (d)	Double blind	A priori calculation of numbers	Method of randomisation described	Analysis by ITT	Decongestant permitted	Evaluation: principal criterion/other	Study of bacteriological eradication
Gehanno ^a et al. 2000 Multicentre (372) ACA: 1g/125 bid ACA: 500mg/125mg tid	8 d	yes	yes	no	yes	Yes	3-5 j EOT/ 18-25 d EOT	no
Dubreuil et al. 2001 Multicentre (401) CUR: 250 mg bid x 5 d CUR: 250 mg bid x 10 d	5 10	yes	yes	yes	yes	Yes	EOT	yes
Gehanno et al. 2002 Multicentre (491) CPD: 200 mg bid x 5 d CPD: 200 mg bid x 10 d	5 10	yes	yes	no	yes	Yes	EOT, PP	yes
Rakkar et al. 2001 Multicentre (475 pts) MXF: 0.4 g od x 10 d ACA: 0.875 g bid x 10 d	10 10	no	no	yes	yes	Yes	D14-21 EOT/ D26-45 EOT	No
Gehanno ^a et al. 2004 Multicentre PRIST 2g bid x 4d CUR 250 mg bid x 5d	4 5	yes	yes	yes	yes	Yes	7-14d/ EOT/21-26d EOT	Yes

Table 6. Antibiotic therapy of acute rhinosinusitis: critical analysis material and methods (2).

Design (numbers included)	Duration (d)	Double blind	A priori calculation of numbers	Method of randomisation described	Analysis by ITT	Decongestant permitted	Evaluation: principal criterion/other	Study of bacteriological eradication
Roos et al. 2002 Multicentre (343) TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d	5 10	yes	yes	no	yes	yes	D17-17-21 EOT, PP/ 3-4 weeks	yes
Gehanno ^c et al. 2003 Multicentre, (258) open, non- comparative MXF: 400 mg od x 7 d	7	no	no	-	yes	yes		
Klossek et al. 2003 Multicentre (503) MXF: 0.4 g od x 7 d TRO: 0.2 g od x 10 d	7 10	yes	yes	no	NS	yes	D7-10 EOT	yes
Luterman et al. 2003 Multicentre (754) TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d ACA: 0.5g/125 tid x 10 d	5 10 10	yes	yes	no	no	yes	D17-24 EOT	yes
Henry et al. 2003 Multicentre (941) AZM: 500 mg od x 3d AZM: 500 mg od x 6 d ACA: 500mg/125 tid x 10 d	3 d 6 d 10 d	yes	yes	no	yes	yes	End of study(d28)/ D10 EOT	no

EOT: end of treatment
 ACA: amoxicillin-clavulanic acid
 AZM: azithromycin
 CUR: cefuroxime axetil
 CPD: cefpodoxime proxetil
 MXF: moxifloxacin
 TEL: telithromycin
 TRO: trovafloxacin
 PRIST: pristinamycin

Table 7. Acute rhinosinusitis. Bacteriological eradication.

	Dubreuil et al. 2001 CUR		Gehanno et al. 2002 CPD		Luterman et al. 2003 TEL ACA			Ross et al. 2002 TEL		Klossek et al. 2003 MXF TRO	
	5 d	10 d	5 d	10 d	5 d	10 d	10 d	5 d	10 d	7 d	10 d
<i>S. pneumoniae</i>	59/60		38/38	35/36	2/2	2/2	2/4	28/30	25/28	35/35	37/40
<i>S. pyogenes</i>								1/1	1/1		
<i>S. aureus</i>			13/17	15/17				7/7	4/4	13/14	17/18
<i>Haemophilus spp</i>	55/56	55/56	25/26	34/36	3/3	3/3	1/1	14/14	11/13	20/20	25/25
<i>M. catarrhalis</i>			6/7	10/10			1/1	6/7	3/4	9/9	4/4
Other Gram negative bacilli								4/4		44/45	48/51

ACA: amoxicillin-clavulanic acid

MXF: moxifloxacin

CUR: cefuroxime axetil

TEL: telithromycin

CPD: cefpodoxime proxetil

TRO: trovafloxacin

Table 8. Acute rhinosinusitis: clinical outcome according to bacteriological aetiology (favourable outcome).

	Gehanno et al. 2002		Gehanno ^a et al. 2000		Gehanno ^a et al. 2004	
	CPD 5 D	CPD 10 D	ACA 1 g bid	ACA 0,5 g tid	PRIST 4 D	CUR 5 D
n patients	194	215	47	46	220	214
<i>S. pneumoniae</i>	36/38	34/36	17/18	15/16	41/47	27/31
<i>H. influenzae</i>	25/26	33/36	19/20	18/19	19/21	23/28
<i>M. catarrhalis</i>	7/7	10/10	5/5	6/6	8/8	8/10
<i>S. aureus</i>	16/17	13/17	1/2	4/5	15/16	17/19
<i>Streptococcus spp</i>			7/7	6/6		
<i>Enterobacteriaceae</i>			6/7	7/8		

Table 9. Antibiotic therapy of acute rhinosinusitis: critical analysis of clinical results by ITT/PP.

	Description of study	End of treatment (EOT) ITT/PP	End of study / follow-up ITT/PP
Gehanno ^a et al. 2000	ACA 1g/125 bid versus 0.5g/125 tid	Cure ITT at EOT: 155/179 (86.6%) Versus 336/360 (93.3%)	Cure ITT at end of follow-up: 147/179 (82.1%) Versus 302/360 (83.9%)
Dubreuil et al. 2001	CUR 0.25 g bid x 5 d CUR 0.25 g bid x 10 d	Cure + improvement ITT: 176/206 (85%) 169/195 (87%)	Cure + improvement ITT: 148/206 (72%) 141/195 (72%)
Gehanno et al. 2002	CPD: 0.2 g bid x 5 d CPD: 0.2 g bid x 10 d CPD: 0.2 g bid x 5 d CPD: 0.2 g bid x 10 d	Cure + improvement at EOT PP: 185/194 (95.4%) 196/215 (91.2%) ITT: 221/236 (93.6%) 228/250 (91.5%)	Cure + improvement ITT: 221/236 (93.6%) 228/250 (91.2%)
Rakkar et al. 2001	MXF: 0.4 g od x 10 d ACA: 0.875 x bid x 10 d		Cure + improvement TOC ITT 85% 82%
Roos et al. 2002	TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d		Cure + improvement ITT: 135/167 (80.8%) 145/168 (86.3%) PP: 112/123 (91.1%) 121/123 (91%)
Gehanno ^a et al. 2004	PRIST: 2g bid x 4d CUR: 250mg bid x5d	Improvement and cure at EOT PP: PRIST 201/220 (91.4%) CUR 195/214 (91.1%) ITT PRIST: 208/234 (88.9%) CUR:199/224 (88.8%)	Cure and improvement ITT PRIST 85.04% CUR 83.04% PP PRIST 88.57% CUR 85.83%
Gehanno ^c et al. 2003	MXF: 0.4 g od	Cure + improvement ITT. 7-10D EOT: 230/255 (90.2%)	Cure + improvement 7-10 d EOT ITT 226/230 (98.3%)
Klossek et al. 2003	MXF: 0.4 g od x 7 d TRO: 0.2 g od x 10 d	Cure + improvement EOT 216/223 (96.9%) 211/229 (92.1%)	Cure + improvement late follow-up 205/216 (94.9%) 206/211 (97.6%)
Luterman et al. 2003	TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d ACA: 0.5g /125 tid x 10 d TEL: 0.8 g od x 5 d TEL: 0.8 g od x 10 d ACA: 0.5g /125 tid x 10		Cure PP 17-24d EOT: 110/146 (75.3%) 102/140(72.9%) 102/137(74.5%) Late follow-up(d31-45): 95/136 (69.9%) 90/133 (67.7%) 92/130 (70.8%)
Henry et al. 2003	AZM 0.5 g od x 3 d Versus 0.5 g od x 6 d Versus ACA 0.5/125 tid x 10 d	Success + improvement ITT at EOT: 268/703 (88.8%) 265/298 (88.9%) 248/291 (85.2%)	Cure ITT at end of study: 213/298 (71.5%) 218/294 (74.1%) 206/288 (71.5%)

EOT: end of treatment
 ACA: amoxicillin-clavulanic acid
 AZM: azithromycin
 CUR: cefuroxime axetil
 CPD: cefpodoxime proxetil
 MXF: moxifloxacin
 TEL: telithromycin
 TRO: trovafloxacin
 PRIST: pristinamycin

Table 10. Localisation and 1st-line treatment of acute sinusitis.
Modified from AFSSAPS October 2005.

Localisation	Symptoms	1st line antibiotic therapy
Maxillary	Unilateral or bilateral suborbital pain with exacerbation when the head is leaning forward; sometimes pulsatile and maximal at end of afternoon and at night	amoxicillin-clavulanate 2nd and 3rd generation cephalosporins (except cefixime): cefuroxime axetil, cefpodoxime proxetil, cefotiam-hexetil pristinamycin telithromycin
Frontal	Supra-orbital headache	Ditto or fluoroquinolone active against pneumococcus (levofloxacin, moxifloxacin)
Ethmoidal	Filling of medial angle of eye, palpebral oedema. Retro-orbital headache	Ditto or fluoroquinolone active against pneumococcus (levofloxacin, moxifloxacin)
Sphenoidal	Permanent retro-orbital headache radiating to the vertex, may simulate intracranial hypertensive pain in its location, intensity and persistence. Purulent discharge on posterior pharyngeal wall (very posterior localisation of sinus ostium for drainage) visible with tongue depressor	Ditto or fluoroquinolone active against pneumococcus (levofloxacin, moxifloxacin)

Clinical signs suggestive of complicated sinusitis: meningeal syndrome, exophthalmia, palpebral oedema, ocular mobility disorders, insomnia-inducing pain

11. Abbreviations

AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (French Health Products Safety Agency)	HIV	Human immunodeficiency virus
AMRS	Acute maxillary rhinosinusitis	ITT	Intention to treat
AOM	Acute otitis media	MA	Marketing Authorisation
BLNAR	β -lactam negative ampicillin-resistant strains	MBC	Minimum bactericidal concentration
CA-SFM	Comité de l'Antibiogramme de la Société Française de Microbiologie (Antibiotic Sensitivity Test Committee of the French Microbiology Society)	MIC	Minimum inhibitory concentration
CSF	Cerebrospinal fluid	MIC90	MIC inhibiting 90% of the strains tested
CT	Computerised tomography	MLSK	Macrolides, lincosamides, streptogramins, ketolides
DNA	Deoxyribonucleic acid	MRI	Magnetic resonance imaging
ENT	Ear, nose and throat	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
EOT	End of treatment	NSAID	Non-steroidal anti-inflammatory drug
FQAP	Fluoroquinolone with antipneumococcal activity	PBP	Penicillin-binding proteins
GP	General practitioner	PP	Per protocol
		PRSP	<i>Pneumococcus</i> with reduced susceptibility to penicillin
		SGIS	Study Group of Infectious Rhinosinusitis
		WHO	World Health Organisation

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