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Review

French practical guidelines for the diagnosis and management of relapsing polychondritis

Protocole national de diagnostic et de soins pour la polychondrite chronique atrophiante

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Abbreviations: Ab, antibodies
AFPCA, *Association francophone contre la polychondrite chronique atrophiante*
ANCA, anti-neutrophil cytoplasmic antibody
CBC, complete blood count
CCP, citrullinated cyclic peptides
COPD, chronic obstructive pulmonary disease
CRI, Club Rhumatismes et Inflammation
CRP, C-reactive protein
CT, computed tomography
ENA, soluble nuclear antigens
ENT, ear, nose and throat
FPGDM, French Practical Guidelines for the Diagnosis and Management
GPA, granulomatosis with polyangiitis
GRIO, Osteoporosis Research and Information Group
HAS, French National Authority for Health
IBD, chronic inflammatory bowel diseases
IPSS-R, Revised International Prognostic Scoring System
IV, intravenous
LTC, long-term condition
MA, Marketing Authorisation
MAGIC, mouth and genital ulcers with inflamed cartilages
MPO, myeloperoxidase
MRI, magnetic resonance imaging
NSAID, non-steroidal anti-inflammatory drug
PET, positron emission tomography
PFT, pulmonary function testing
PR3, Proteinase 3
SAVI, STING associated vasculopathy with onset in infancy
TPE, therapeutic patient education
VEXAS, vacuoles, E1 enzyme, X linked, autoinflammatory, somatic
WHO, World Health Organization.

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ABSTRACT

Relapsing polychondritis is a rare systemic disease. It usually begins in middle-aged individuals. This diagnosis is mainly suggested in the presence of chondritis, i.e. inflammatory flares on the cartilage, in particular of the ears, nose or respiratory tract, and more rarely in the presence of other manifestations. The formal diagnosis of relapsing polychondritis cannot be established with certainty before the onset of chondritis, which can sometimes occur several years after the first signs. No laboratory test is specific of relapsing polychondritis, the diagnosis is usually based on clinical evidence and the elimination of differential diagnoses. Relapsing polychondritis is a long-lasting and often unpredictable disease, evolving in the form of relapses interspersed with periods of remission that can be very prolonged. Its management is not codified and depends on the nature of the patient's symptoms and association or not with myelodysplasia/vacuoles, E1 enzyme, X linked, autoinflammatory, somatic (VEXAS). Some minor forms can be treated with non-steroidal anti-inflammatory drugs, or a short course of corticosteroids with possibly a background treatment of colchicine. However, the treatment strategy is often based on the lowest possible dosage of corticosteroids combined with background treatment with conventional immunosuppressants (e.g. methotrexate, azathioprine, mycophenolate mofetil, rarely cyclophosphamide) or targeted therapies. Specific strategies are required if relapsing polychondritis is associated with myelodysplasia/VEXAS. Forms limited to the cartilage of the nose or ears have a good prognosis. Involvement of the cartilage of the respiratory tract, cardiovascular involvement, and association with myelodysplasia/VEXAS (more frequent in men over 50 years of age) are detrimental to the prognosis of the disease.

RÉSUMÉ

La polychondrite chronique atrophiante (PCA) est une maladie systémique rare. Elle survient généralement chez des individus d'âge moyen. Ce diagnostic est principalement suggéré en présence de chondrite, c'est-à-dire de poussées inflammatoires du cartilage, en particulier des oreilles, du nez ou des voies respiratoires, et plus rarement en présence d'autres manifestations. Le diagnostic formel de PCA ne peut être établi avec certitude avant l'apparition de la chondrite, qui peut parfois survenir plusieurs années après les premiers signes. Aucun test de laboratoire n'est spécifique de la PCA, le diagnostic est généralement basé sur des éléments cliniques et l'élimination des diagnostics différentiels. La PCA est une maladie de longue durée et souvent imprévisible, évoluant sous forme de rechutes entrecoupées de périodes de rémission pouvant être très prolongées. Sa prise en charge n'est pas codifiée et dépend de la nature des symptômes du patient et de l'association ou non avec une myélodysplasie/*vacuoles, E1 enzyme, X linked, autoinflammatory, somatic* (VEXAS). Certaines formes mineures peuvent être traitées avec des anti-inflammatoires non stéroïdiens ou une courte corticothérapie

avec éventuellement un traitement de fond à la colchicine. Cependant, la stratégie de traitement repose souvent sur la dose la plus faible possible de corticostéroïdes combinée à un traitement de fond avec des immunosuppresseurs conventionnels (par exemple, le méthotrexate, l'azathioprine, le mycophénolate mofétil, rarement le cyclophosphamide) ou des thérapies ciblées. Des stratégies spécifiques sont nécessaires si la PCA est associée à une myélodysplasie/VEXAS. Les formes limitées au cartilage du nez ou des oreilles ont un bon pronostic. L'atteinte du cartilage des voies respiratoires, l'atteinte cardiovasculaire et l'association avec une myélodysplasie/VEXAS (plus fréquente chez les hommes de plus de 50 ans) sont défavorables au pronostic de la maladie.

1. Summary for the family doctor

Relapsing polychondritis is a rare systemic disease, primarily affecting the cartilage of the ears, nose and respiratory tract. It may also affect other organs or tissues, particularly the joints, eyes, cochleovestibular system, skin and cardiovascular system. It can sometimes be associated with myelodysplastic syndrome. Relapsing polychondritis usually begins in middle-aged individuals (typically 40–55 years), but can occur at any age. Paediatric forms are however exceptional. There is a discrete female predominance, less marked than in other autoimmune diseases. Given the rarity of this disease and its potentially poor prognosis, which justifies medical follow-up adapted to its severity, the management of patients suffering from relapsing polychondritis is preferably carried out within the framework of a national centre of reference or competence for rare autoimmune systemic diseases, alongside the attending physician and organ specialists (depending on the patient's symptoms).

The diagnosis of relapsing polychondritis is mainly suggested in the presence of chondrites, i.e. inflammatory episodes of the cartilage, in particular of the ears, nose or respiratory tract, and more rarely by other manifestations (deterioration of general status unexplained prolonged fever, and involvement of other organs). Although not pathognomonic, chondritis of the ears is one of the main manifestations of the disease and consists of inflammatory changes to the cartilage of the ears (most often the helix); the inflammation thus avoids the lobule, which has no cartilage. The formal diagnosis of relapsing polychondritis cannot be established with certainty before the onset of chondritis, which can sometimes occur several years after the first signs. The diagnosis of relapsing polychondritis cannot be made with any laboratory test (including autoantibodies) and is usually based on clinical evidence and the elimination of differential diagnoses (mainly granulomatosis with polyangiitis [GPA]). The initial work-up usually includes laboratory tests to document an inflammatory syndrome (absent in 40% of cases of flares), eliminate the main differential diagnoses, look for associated disease (present in 20–30% of cases), look for organ involvement and identify any contraindications to treatment. This initial work-up usually includes standard laboratory tests, with careful analysis of the complete blood count (CBC) (looking for abnormalities that might suggest myelodysplasia), testing for inflammatory syndrome, an immunological work-up (antinuclear antibodies and rheumatoid factors that may be weakly present, anti-neutrophil cytoplasmic antibodies [ANCA] that are absent), imaging tests with sinus scans, cervico-thoracic scans with sequences in inspiration and expiration, functional respiratory exploration, and cardiac ultrasound. This assessment may be completed according to the suspected organ involvement. Cartilage biopsy is not usually recommended.

Relapsing polychondritis is a long-lasting and often unpredictable disease, evolving in the form of relapses interspersed with periods of remission that can be very prolonged. A majority of patients experience relapses, justifying the use of the term "chronic" in the name of the disease. The main objectives of the management of relapsing polychondritis are to control disease activity and inflammatory flare-ups, to prevent relapses and sequelae, to maintain quality of life, and in some cases to manage associated diseases such as myelodysplasia.

The therapeutic management of relapsing polychondritis is not codified and depends on the nature of the patient's symptoms. Some minor forms can be treated with non-steroidal anti-inflammatory drugs (NSAIDs), or a short course of corticosteroids, potentially with a background treatment with colchicine or even dapsone. However, the treatment strategy is often based on the lowest possible dosage of corticosteroids combined with background treatment with conventional immunosuppressants (e.g. methotrexate, azathioprine, mycophenolate mofetil, rarely cyclophosphamide) or targeted therapies. Due to the rarity of the disease, there are no randomised trials to identify the optimal management strategy, currently based on a few case series.

The prognosis of the disease is related to the nature of organ involvement. Forms limited to inflammatory involvement of the cartilage of the nose or ears have a good prognosis. Involvement of the cartilage of the respiratory tract, cardiovascular involvement and association with myelodysplasia (more frequent in men developing the disease after the age of 50) are detrimental to the prognosis of the disease.

The family doctor plays an important role in the management of patients with relapsing polychondritis, facilitating interaction between the various organ specialists and ensuring the close follow-up that is essential for the early detection of relapses, complications and the management of the sequelae of the disease.

2. Introduction

Relapsing polychondritis is a rare disease characterised by the occurrence of repeated episodes of inflammation in certain cartilage structures associated with various systemic manifestations. The prevalence of diagnosed relapsing polychondritis is estimated to be between 4.5 and 20 per million inhabitants in adults. Relapsing polychondritis is very rare in children.

Data on pathophysiology are scarce and suggest an autoimmune mechanism.

Compared to historical series, the prognosis has improved significantly. The main factors of poor prognosis are male gender, presence of associated haematological disease, tracheobronchial involvement and cardiovascular involvement.

Treatment is usually based on corticosteroid therapy sometimes combined with immunosuppressants in an empirical manner as there are no randomised therapeutic trials in relapsing polychondritis. The use of targeted therapies has recently been reported in clinical cases and short series with varying results. Some minor

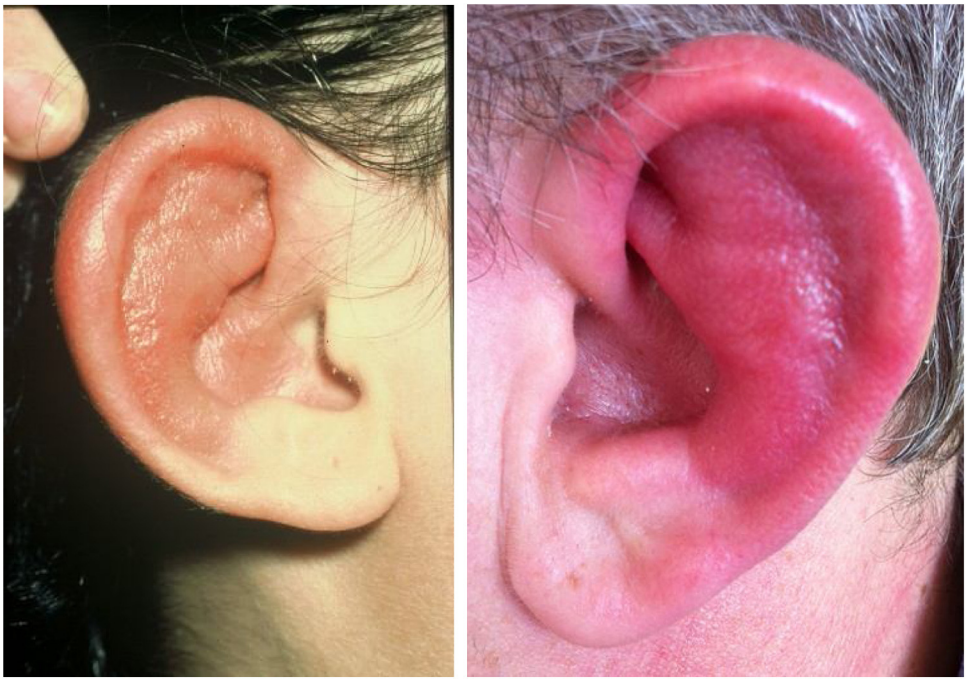

Fig. 1. Chondritis of the ear, acute phase.

forms may warrant abstention from treatment, with brief anti-inflammatory treatment for occasional peripheral chondritis.

3. Diagnosis and initial assessment [1–9]

3.1. Objectives of the initial assessment

It refers to the assessment of a patient presenting with, or reporting, manifestations that may suggest a diagnosis of relapsing polychondritis.

The main objectives are:

- to eliminate differential diagnoses;
- to establish the diagnosis of relapsing polychondritis;
- to assess the severity of the disease;
- to search for an associated disease (in particular a myelodysplastic syndrome which worsens the prognosis).

3.2. Professionals involved

The professionals involved are:

- the family doctor;
- the specialist doctor with expertise in the management of patients with relapsing polychondritis, usually a rheumatologist or internist (sometimes ophthalmologists, ear, nose throat [ENT] specialists, dermatologists, pulmonologists, cardiologists, haematologists, and paediatricians);
- nurses who provide care, therapeutic education and potentially coordination of care between the hospital and the community;
- physiotherapists and occupational therapists who have a central role in the management of chronic joint involvement and vestibular rehabilitation;
- the hearing aid acoustician (in case of need for hearing aids);
- the psychologist in chronic forms of the disease;
- social workers who have an important role in dealing with the social consequences of the chronic forms of the disease.

3.3. Discovery circumstances

In 60% of cases, relapsing polychondritis presents in the "classic" way with typical chondritis of the pinna and nasal root, which is usually relatively easy to diagnose.

Nevertheless, the presentation is atypical in 40% of cases and may begin with isolated joint symptoms (non-erosive polyarthritis, sternocostal involvement), respiratory symptoms (pseudo-asthma, bronchial stenosis, bronchiectasis, respiratory insufficiency), ENT symptoms (dysphonia with hoarse voice, laryngeal dyspnoea, sudden deafness or vertigo), ocular symptoms (mainly episcleritis or scleritis), cutaneous symptoms (nodular eruption, neutrophilic dermatosis, purpura) or even long-term fever, a change in general condition or unexplained inflammatory syndrome.

In these clinical situations, the diagnosis should be made and a history of undetected chondritis should be carefully investigated on retrospective questioning of the patient and his/her family. However, chondritis may only occur later, after several months or years of evolution.

3.4. Suspicion of diagnosis/confirmation of diagnosis/differential diagnosis

3.4.1. Chondritis during relapsing polychondritis

The diagnosis of relapsing polychondritis is essentially clinical and should be made in the presence of an episode of chondritis. Ear chondritis may regress spontaneously within a few days. In the majority of cases, patients do not have active chondritis at the time the diagnosis of relapsing polychondritis is made. The diagnosis of relapsing polychondritis is therefore based on questioning, sometimes on photographic evidence of typical ear chondritis (inflammation of the cartilaginous part of the ear, not involving the lobule [Fig. 1]) or clinical signs of consequences of cartilage flare-ups in the form of deformities (thickening of the helix, change in the texture of the cartilage [softened or calcified appearance], saddle-shaped nasal deformity or deformity of the chondro-sternal cartilages [Figs. 2 and 3]). Nasal chondritis is usually characterised by pain, sometimes intense, at the root of the nose (junction

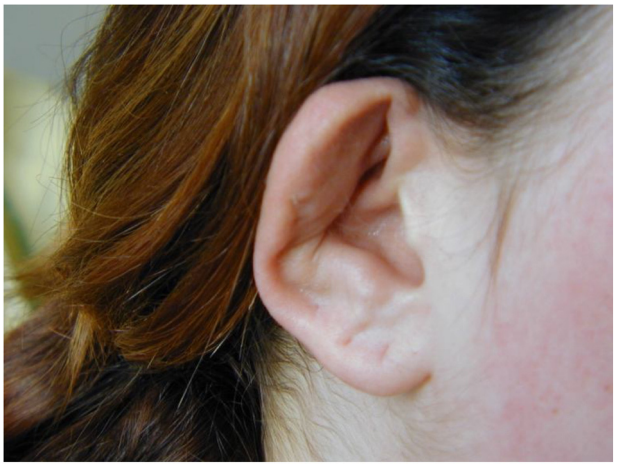

Fig. 2. Sequelae of chondritis of the ear.

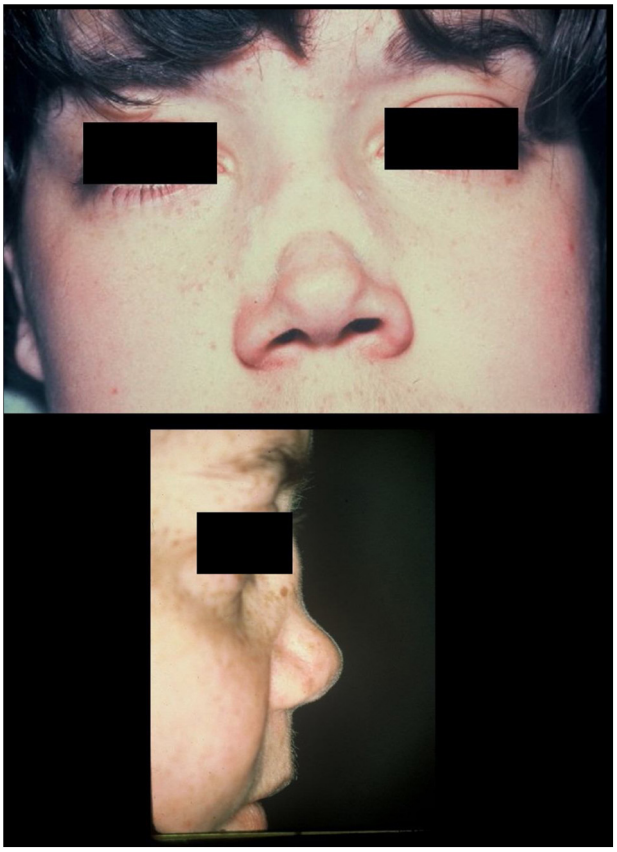

Fig. 3. Nasal deformity, front and side view.

between the nasal bone and the nasal cartilage). Local inflammatory signs (inflammatory oedema of the nasal root) are inconstant. Involvement of the sternocostal cartilages is common and is manifested mainly by increased chest pain on palpation.

Respiratory tract involvement may manifest itself in a variety of ways: anterior neck pain which may initially suggest De Quervain's thyroiditis, dysphonia, stridor or inspiratory dyspnoea in case of laryngeal involvement, dry cough and retrosternal pain, wheezing or dyspnoea in case of tracheal involvement.

The occurrence of chondritis is of course suggestive of a diagnosis of relapsing polychondritis, but physiological or pathological conditions that may mimic chondritis should be ruled out (Table 1).

Clinical examination can distinguish these conditions from typical chondritis. The clinical context (absence of puncture, piercing, infectious entry point), the absence of ear lobule involvement, the fact that the inflammatory flare is painful and lasts more than one day are all suggestive of chondritis. Another element is contralateral recurrence (ear chondritis is typically tilted).

Chondritis is an emblematic manifestation of the disease, but is not pathognomonic of relapsing polychondritis and can occasionally be found in the course of various inflammatory diseases. Given the rarity of these situations, it is therefore sometimes difficult to establish formally whether chondritis is a non-specific manifestation of another inflammatory disease or part of an overlapping syndrome with relapsing polychondritis.

Among immuno-inflammatory diseases, the main differential diagnosis is GPA. In contrast to GPA, in relapsing polychondritis there is a negativity of anti-PR3 and -MPO ANCA, no pulmonary nodules on chest computed tomography (CT), and no renal involvement. Perforation of the nasal septum, crusty rhinitis, sinusitis, especially destructive sinusitis, and epistaxis are suggestive of GPA.

A true chondritis may be the consequence of a localized infection (usually a single episode). Other aetiologies are listed in Table 1.

3.4.2. Extra-chondritic manifestations of relapsing polychondritis

3.4.2.1. Articular manifestations. Joint involvement is very frequent (52 to 85%). It is often the first manifestation of the disease, and when it is isolated, many differential diagnoses are discussed. It most often presents as poly- or oligoarthritis or acute or sub-acute arthralgia which may be migratory. It is usually asymmetrical, affecting both large and small joints. The involvement is typically neither erosive nor deforming. The presence of axial symptoms should suggest the presence of associated spondyloarthritis.

3.4.2.2. Audio-vestibular involvement. Hearing loss occurs in 19–46% of cases. Sensorineural deafness is the most common form of hearing loss, usually presenting as sudden uni- or bilateral deafness, and is a therapeutic emergency. It is related to cochlear involvement and usually predominates in the high frequencies. A vestibular syndrome may be associated with cochlear involvement or occur alone. Conductive hearing loss is also possible with various mechanisms: stenosis of the external auditory canal secondary to chondritis of the pinna, serous otitis possibly secondary to Eustachian tube involvement.

3.4.2.3. Dermatological manifestations. The reported frequency of dermatological manifestations varies between 17 and 46%. The most frequent lesions are lower limb nodules and vascular purpura. Various other elementary lesions are possible. Skin histology usually shows leukocytoclastic vasculitis, more rarely neutrophilic infiltrate or septal panniculitis. Recurrent oral aphthosis is possible and rarer forms involving bipolar aphthosis are sometimes reported in the literature as "MAGIC syndrome" (mouth and genital ulcers with inflamed cartilages). In patients with relapsing polychondritis associated with myelodysplastic syndrome, skin involvement is extremely frequent (90% of patients) with a high proportion of neutrophilic dermatoses. This association should lead to the consideration of a VEXAS syndrome (see paragraph Section 4.4.3).

3.4.2.4. Eye involvement. The occurrence of ocular inflammation is common (44–65%). The most common conditions are episcleritis and scleritis. Recurrent conjunctivitis, uveitis and keratitis are also observed. Scleritis is most often anterior and may be complicated by scleromalacia, or even perforation in rare necrotising forms.

3.4.2.5. Cardiovascular involvement. Cardiac anomalies are dominated by valvulopathy. These are reported in 6 to 27% of patients

Table 1
Conditions that may be confused with chondritis or that lead to deformity of the nose and ears.

Damage to the ear	Localised dermatological conditions of the ears including ear erysipelas, shingles, frostbite
	Chronic lupus
	Sarcoidosis
	Sweet's syndrome
	Leishmaniasis
	Haematoderma
	Sequelae of otohaematoma (contact sports)
	Insect bite
	Vasomotor redness
	Erythermalgia of the ears
	Sunburn
	Necrotising external otitis
	Painful nodules of the ear (Winkler's disease or chondrodermatitis nodularis chronica helicis)
	Catastrophic antiphospholipid syndrome
	Malignant tumour (lymphoma) of the ear
	Pain in the ears sine materia
	Pathomimicry/self-manipulation
Nose damage	Post-traumatic (nasal bone fracture and especially contact sports such as rugby, boxing)
	Sarcoidosis
	Granulomatosis with polyangiitis
	Cocaine use (perforation of the nasal septum)
	Chronic infections (syphilis, leprosy, rhinoscleroma)
	Post-septoplasty deformity or perforation
	Antiphospholipid syndrome (perforation of the nasal septum)
	Constitutional deformation
	Congenital syphilis
	Single gene diseases in children (including SAVI)
	Nasal T/NK lymphoma
Trachea and/or bronchial tubes	Post-intubation or post-traumatic tracheal stenosis
	Granulomatosis with polyangiitis
	Saber-sheath deformation (COPD)
	Chronic or intracellular infections
	Crohn's disease
	Sarcoidosis
	Amyloidosis
	IgG4 disease
	Osteochondroplastic tracheobronchopathy
	Mounier-Kuhn syndrome (tracheobronchomegaly)
	Keutel syndrome
	Constitutional stenosis
	Other tracheobronchial tree calcifications
	Intricacy with asthma

SAVI: STING associated vasculopathy with onset in infancy; COPD: Chronic obstructive pulmonary disease

depending on the series. Valvular involvement typically appears after several years of evolution, including in asymptomatic patients. The most frequent anomaly is aortic insufficiency, generally related to annular dilation accompanying ectasia of the initial portion of the ascending aorta. Other less common conditions are mitral insufficiency or double mitral and aortic localisation. Conductive abnormalities are also described, mainly atrioventricular conduction disorders. Pericarditis is found with a frequency ranging from 3 to 6%. It is sometimes difficult to distinguish a cardiac involvement of relapsing polychondritis from a non-specific anomaly discovered incidentally, particularly in an elderly subject.

Although rare, large vessel involvement is described in relapsing polychondritis and is dominated by aortic aneurysms with a reported frequency of 4–6%. They are frequently located in the ascending thoracic aorta and might be responsible for aortic insufficiency. They have also been described in the descending thoracic and abdominal segments of the aorta as well as in other large arterial trunks. Stenoses and/or dilated lesions may be associated with large vessels involvement, resulting in a picture similar to Takayasu's disease.

Deep vein thrombosis (4–10% of cases) sometimes complicates the disease, especially in VEXAS.

3.4.2.6. Neurological manifestations. Rare, very diverse and exceptionally revealing central neurological manifestations have been described. The most frequent are meningitis and meningoencephalitis, most often lymphocytic, optic neuritis, involvement of other cranial nerves as well as limbic encephalitis. Ruling out differential diagnosis, in particular an infection, is fundamental.

Because of their exceptional nature, peripheral neurological manifestations should always be considered as a differential diagnosis.

3.4.2.7. Relapsing polychondritis and haematological diseases. The most frequently reported association is that of a myelodysplastic syndrome. This condition is found in 6 to 11% of patients. It mainly affects men, mainly over 50 years old, and very frequently involves the skin. The disease is difficult to treat, its course is marked by numerous infectious complications and survival is diminished.

It should be noted that there are patients with relapsing polychondritis associated with myelodysplastic syndrome without UBA1 mutation.

3.4.2.8. Other events. In case of proliferative glomerulonephritis, a differential diagnosis such as GPA must absolutely be considered, as renal involvement is not a manifestation of relapsing polychondritis.

3.4.3. VEXAS syndrome

At the end of 2020, a new entity was described: the VEXAS syndrome (Vacuoles, E1 enzyme, X linked, Auto-inflammatory, Somatic). This is an auto-inflammatory syndrome associated with a somatic (i.e. acquired) mutation of the *UBA1* gene, which is

located on the X chromosome and therefore affects mostly men. This syndrome should be considered mainly in men over 50 years old with treatment-resistant atypical polychondritis, fever, skin involvement (mainly neutrophilic dermatosis), pulmonary infiltrates (very suggestive), macrocytic anaemia, myelodysplastic syndrome, chronic myelomonocytic leukaemia or monoclonal gammapathy. Diagnosis is made by identification of vacuoles in bone marrow precursors, and confirmed by a test for the UBA1 mutation in the bone marrow or, failing that, in the blood.

The description of this syndrome will probably open up new therapeutic perspectives.

3.4.4. Diagnostic confirmation

As relapsing polychondritis is a systemic disease, it should be considered as a matter of principle in the presence of various extra-cartilaginous manifestations, but obviously the diagnosis of relapsing polychondritis can only be made with certainty in the presence of chondritis (Table 2).

The initial work-up should include a family tree, a standard laboratory work-up, a search for an inflammatory syndrome (absent in 40% of cases of articular manifestations), and an immunological work-up (anti-nuclear and anti-ENA antibodies, rheumatoid and anti-CCP antibodies, anti-MPO and anti-PR3 ANCAs, and if necessary HLA B27 typing) which aims to rule out the main differential diagnoses (in particular ANCA-associated vasculitis, especially GPA) and to search for another associated inflammatory disease. Testing for anti-cartilage Ab, anti-collagen type 2 Ab and/or anti-matrillin 1 Ab is unnecessary as they are neither sensitive nor specific.

Table 2
Frequency of the main clinical manifestations of relapsing polychondritis.

Clinical manifestations	Cumulative frequency during follow-up
Chondritis of the ear	70 to 95%
Chondritis of the nose	35 to 63%
Sternocostal chondritis	44 to 65%
Laryngotracheobronchial chondritis	21 to 56%
Inflammatory joint disease	52 to 85%
Eye involvement	44 to 65%
Audio-vestibular involvement	19 to 46%
Skin involvement	17 to 46%
Valvular involvement	6 to 27%
Central neurological manifestations	5 to 9%
Myelodysplasia	6 to 9%

Particular attention should be paid to the blood count, because of the possibility of associated myelodysplasia, and consideration should be given to a myelogram with cytogenetic studies if there is a persistent abnormality of the blood lines, including isolated macrocytosis.

Finally, any other appropriate tests should be carried out according to the clinical context and any suspicion of organ involvement (Table 3).

The diagnosis of relapsing polychondritis can be facilitated by the use of different sets of published criteria. The Michet criteria are the most suitable for clinical practice (Table 4). To meet these criteria, two major criteria or one major and two minor criteria are required. In practice, these criteria are neither necessary nor sufficient to make a diagnosis of relapsing polychondritis and have no individual diagnostic value.

Table 3
List of additional tests to be carried out, discussed, and avoided in case of suspicion of relapsing polychondritis.

Examinations carried out systematically	
Baseline electrocardiogram	Testing for rhythmic or conduction disorders
Pulmonary function testing	With flow-volume curves (inspiratory and expiratory) and a reversibility test in case of obstructive syndrome ± 6-minute walk test
Dynamic inspiratory and expiratory CT of the neck and chest, possibly with two- or three-dimensional reconstruction	Testing for: (a) thickening and/or calcifications of the tracheobronchial rings initially avoiding the posterior (membranous, non-cartilaginous) portion of the trachea; (b) tracheobronchomalacia (expiratory collapse); (c) permanent tracheobronchial stenosis; (d) respiratory trapping; (e) pulmonary infiltrates (infection but also VEXAS); (f) dilation of the ascending aorta and signs of aortitis (injected CT); (g) arguments in favour of certain differential diagnoses (e.g. pulmonary nodules in GPA)
Trans-thoracic echocardiography	Detect or confirm dilation of the ascending aorta, valvulopathy
Examinations to be carried out according to the context	
ENT consultation with audiogram	Testing conductive and/or sensorineural hearing loss, assessment of vestibular function
Brain MRI exploring the auditory nerve and inner ear	In case of cochlea-vestibular manifestations
CT of the facial sinuses	Search for arguments in favour of a GPA in particular
Biopsy of the ENT mucosa	Search for differential diagnoses (GPA, sarcoidosis, amyloidosis. . .)
Ophthalmology consultation	In case of inflammatory eye disease
X-ray of painful joints and joint ultrasound	In case of peripheral inflammatory joint disease
Spine and sacroiliac MRI	In case of suspected spondyloarthritis
PET-scanner	The role of PET-CT in relapsing polychondritis is not well defined, but it can sometimes reveal sub-clinical damage (indication to be discussed with a specialist team)
Tests not recommended	
Biopsy of the pinna cartilage	Not useful for diagnosis
Tracheobronchial cartilage biopsy	Dangerous and not recommended
"RP-specific" autoantibodies (collagen-II; Matrillin-I, etc.)	Not useful for diagnosis

VEXAS: Vacuoles, E1 enzyme, X linked, Auto-inflammatory, Somatic; GPA: granulomatosis with polyangiitis; CT: computed tomography.

Table 4
Classification criteria for polychondritis according to Michet.

Major criteria	Minor criteria
Auricular chondritis Nasal chondritis Laryngotracheal chondritis	Ocular inflammation (conjunctivitis, episcleritis, uveitis, keratitis) Hypoacusis Vestibular dysfunction Seronegative polyarthritis

Table 5
Main comorbidities associated with relapsing polychondritis.

Sjögren's syndrome
Hashimoto's thyroiditis
Haemopathies: myelodysplasias and lymphomas
Type 1 diabetes
Systemic lupus
Antiphospholipid syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Spondyloarthritis
Behçet's disease
MAGIC syndrome
Crohn's disease and ulcerative colitis
Primary biliary cholangitis
Myasthenia

MAGIC: mouth and genital ulcers with inflamed cartilages.

3.5. Assessment of severity and prognosis

The evaluation of severity is based on the identification of involvement associated with a poor prognosis. Purely chondritic, auricular or nasal forms have a favourable prognosis but may lead to functional discomfort and/or aesthetic sequelae due to progressive cartilage deformation. The respiratory tract involvement can lead to infections, acute respiratory failure and be life-threatening, or result in significant respiratory functional sequelae. In the absence of appropriate management, episodes of scleritis can lead to scleromalacia, which is perforating in rare cases. The cochleovestibular apparatus involvement may lead to deafness or, rarely, to permanent postural instability. If haematologic disorders (myelodysplasia) are associated, the prognosis is unfavourable, frequently leading to significant transfusion dependence. Quality of life is often significantly impaired.

The assessment of the extent of the disease is based primarily on clinical examination data, supplemented by paraclinical tests and specialised consultations when necessary.

Relapsing polychondritis is associated with another disease in 20–30% of cases, which should be investigated at least clinically (see Table 5). In the majority of cases it is an autoimmune or inflammatory disease, or myelodysplasia.

3.6. Diagnosis disclosure and patient information

The diagnosis should, if possible, be disclosed in a dedicated consultation during which the diagnosis, its consequences and the outlines of therapeutic management, as well as any major adverse events, are explained. This information should be presented according to the patient's level of understanding. It is essential to emphasise that relapsing polychondritis is not a contagious or hereditary disease, and is therefore not transmissible to family members or offspring. The main signs of relapse and what to do in the event of a relapse should be explained to patients. The contact details of patient organisations must be made available. Psychological support may be offered, if necessary.

3.7. Paediatric specificities

Relapsing polychondritis is even rarer in children and few observations or series of observations have been reported. The mean age of onset of paediatric relapsing polychondritis is 9 years old with a balanced sex ratio (close to 1). Relapsing polychondritis does not involve the growth plates. The early onset may reflect likely underlying genetic factors although no Mendelian cause of relapsing polychondritis is known to date. In this respect, two monogenic diseases have been clearly associated with inflammatory chondritis, namely cryopyrinopathies (*NLRP3* gene mutation, dominant form with relapsing fever) and protein Kinase C delta deficiency (associated with lupus, recessive form linked to *PRKCD* gene mutations). Other genetic diseases that affect cartilage represent differential diagnoses such as Keutel syndrome with diffuse cartilage calcifications, autosomal recessive transmission by mutation of the *MGP* gene. Williams-Campbell syndrome, on the other hand, corresponds to a respiratory malformation with a complete defect of the bronchial cartilage and the potential gene involved is not known. Other differential diagnoses more specific to paediatrics are self-manipulation, maltreatment (Silverman syndrome with induced chondral lesions), congenital syphilis and immune causes: HLA class I molecule deficiency and destruction of the nasal septum, interferonopathies (SAVI, TREX 1…), hypomorphic deficiencies in RAG1 and RAG2.

Corticosteroid therapy is offered in the majority of cases and almost half of the patients are on immunosuppressants. It should be noted that corticosteroid therapy may be combined with specific measures in this paediatric context, in particular the administration of growth hormone in the event of significant impact on growth.

4. Therapeutic management [10–13]

4.1. General principles

In the majority of cases, relapsing polychondritis evolves in flares, occurring more or less close to each other, whose severity and duration are very variable and unpredictable. Approximately 15% of patients have a continuously evolving form. The management of the disease therefore includes:

- treatment of flares: this depends on the type of disease and its prognosis. Depending on the case, it may be purely symptomatic (NSAIDs and analgesics) or involve corticosteroid therapy potentially combined with immunosuppressants;
- background treatment is indicated in certain patients in order to reduce the frequency and severity of flares, to prevent sequelae, and/or to reduce the need for corticosteroids (corticosteroid-sparing). It is discussed on a case-by-case basis according to the clinical phenotype, the course, the comorbidities, the sequelae and the prognosis of the disease.

The main treatment goals are to control symptoms, prevent cartilage destruction (especially of the tracheobronchial tract) and respiratory and cardiovascular complications, maintain hearing and vision, quality of life, and prevent adverse drug reactions.

Evaluating the efficacy of these drugs is difficult because the natural history of relapsing polychondritis is highly variable from patient to patient. Thus, in the absence of randomised therapeutic trials and prospective cohorts of sufficient size, treatment recommendations are based primarily on the cumulative experience of experts, retrospective case series of often limited size and case reports.

4.2. Treatments

The drugs used are:

- NSAIDs and colchicine;
- corticosteroids (prednisone, intravenous methylprednisolone, infiltrations, etc.): they are very often necessary. Corticosteroid therapy, in its various forms of administration and dosage, remains a major medication for this disease due to its rapid efficacy and manageability. Corticosteroid dependence is however frequent, justifying the use of other drugs;
- dapsone: it is a historical disease-modifying drug approved in France for the treatment of relapsing polychondritis. However, the experts do not recommend its introduction before having led additional investigations. Notably, it is contraindicated in cases of glucose-6-phosphate dehydrogenase (G6-PD) deficiency, which should be investigated before starting treatment (major risk of haemolysis); agranulocytosis, marrow failure as well as drug reaction with eosinophilia and systemic symptoms (DRESS) can occur.
- typical immunosuppressive drugs: methotrexate (taken weekly), azathioprine, mycophenolate mofetil (or mycophenolic acid), intravenous cyclophosphamide, leflunomide, more rarely ciclosporin;
- targeted therapies: several targeted therapies with a marketing authorisation for inflammatory rheumatism have been tried with inconsistent and sometimes transient efficacy: in particular, anti-TNF-α or anti-IL-6 (notably tocilizumab), or even anakinra or abatacept; a short open-label study on rituximab proved disappointing;
- the potential of Janus kinase inhibitors and other targeted therapies (anti-IL-17, anti-IL-12/23) remains to be evaluated.

4.3. Indications

The indications for the various drugs are empirical. They take into account clinical common sense, pathophysiological and pharmacological considerations, experience and expert opinion.

4.3.1. Joint manifestations

The aim of the treatment of joint involvement is to control pain, restore joint function and maintain ambulation.

Relapses are treated with NSAIDs and painkillers, or more commonly with systemic corticosteroids. This can be initiated or increased to the lowest possible effective dose, e.g. 15–20 mg/day prednisone-equivalent in adults not exceeding 0.5 mg/kg/day prednisone over a few days followed by a gradual decrease to the minimum effective dose.

Local infiltrations (knee, shoulder, ankle, etc.) may be useful.

Colchicine (1 mg/d, or even 2 mg/d initially over two or three days in the absence of renal insufficiency, advanced age or risky polymedication) can be tried, stopping it in the event of ineffectiveness after one month of treatment or adverse events. This treatment contraindicates the use of macrolides and pristinamycin because of the risk of severe toxicity by overdose.

Prolonged corticosteroid therapy, which is often necessary, should not be prescribed on a long-term basis at more than 5–7.5 mg/day of prednisone without considering corticosteroid-sparing therapy. Prevention of corticosteroid-induced osteoporosis should be carried out in accordance with international guidelines.

Background immunosuppressive therapy (preferably methotrexate) is warranted in cases of frequent use of corticosteroids, corticosteroid dependence or significant adverse events of NSAIDs and/or corticosteroids. If methotrexate fails, a second-line immunosuppressant (including azathioprine, mycophenolate mofetil and leflunomide) and/or targeted therapy (preferably anti-TNF or IL-6 receptor inhibitor) may be used. The use of cyclophosphamide, a potent immunosuppressant, is not indicated in joint disease due to a poor benefit–risk ratio.

4.3.2. Chondritis of the nose and ears

The treatment goal is primarily to control disease activity and prevent deformity.

Relapses are treated with NSAIDs and painkillers, or more frequently with systemic corticosteroids in short courses. For example, in adults, this will be initiated at 0.5 to 1 mg/kg/day of prednisone, without exceeding 60 to 70 mg/day, for a few days until improvement, followed by a gradual decrease over ten days. In case of corticosteroid resistance or corticosteroid dependence, the introduction of a background treatment will be discussed (for example, colchicine or methotrexate).

In case of severe aesthetic sequelae, nasal plastic surgery can be performed, after medical/surgical consultation. This procedure must be performed at a distance from any inflammatory episode and under low-dose corticosteroids as much as possible.

4.3.3. Laryngeal and tracheobronchial chondritis

The management of patients with laryngeal or tracheobronchial relapsing polychondritis should be done in close collaboration with the pulmonologist and/or ENT physician.

The aim of the treatment is to rapidly obtain as complete and lasting control of the cartilage inflammation as possible, in the hope of avoiding the development of tracheobronchomalacia and respiratory insufficiency, while avoiding an excessive iatrogenic risk, particularly the risk of infection.

Initial corticosteroid therapy is 0.5 to 1 mg/kg/day of prednisone-equivalent, not exceeding 60 to 70 mg/day for at least 3 weeks depending on severity and clinical course, followed by a tapering dose with the aim of reaching a dosage of less than or equal to 15 mg/day at 3 months and less than or equal to 10 mg/day at 6 months. Infusions of methylprednisolone (250–1000 mg/d for 1–3 days) may be used depending on severity. Inhaled corticosteroid therapy may be used in combination.

In the event of a severe relapse causing acute respiratory failure, induction treatment combines high-dose corticosteroid therapy initiated by boluses of methylprednisolone and intravenous bolus cyclophosphamide (0.5 to 0.7 g/m^2, taking into account age and renal function by analogy with the treatment of necrotising vasculitis – see Appendix 2). Advice from an expert centre is recommended. Once remission has been achieved, maintenance treatment is based on a conventional immunosuppressant (mycophenolate mofetil or azathioprine) administered for several years, in combination with minimum effective corticosteroid therapy.

Antibiotic treatment should be instituted if there is any doubt, as infections often accompany disease flare-ups.

The prevention of the risk of pulmonary infection must be optimised in parallel with the initiation of these drugs (prevention of pneumocystis, vaccinations, physiotherapy in particular).

4.3.3.1. Local therapy. In an emergency, a tracheostomy, often transient, may be necessary in case of symptomatic glottic or subglottic stenosis. In non-emergency cases of bronchial stenosis, interventional endoscopy can be used to perform balloon dilation, bronchoscopic dilation and the insertion of endo-bronchial or endo-tracheal prostheses depending on the situation.

When considered, fibroscopy should be carefully discussed because of the specific risks associated with this procedure in patients with tracheobronchial involvement: risk of bronchospasm, acute inflammatory flare, laryngeal oedema, perforation, potentially fatal. The benefit–risk ratio of this procedure must be discussed in consultation with a highly specialised team. When necessary, fibroscopy should be performed by a cautious and trained operator

with tracheostomy, resuscitation and thoracic surgery facilities nearby, possibly preceded by a bolus of methylprednisolone.

4.3.4. Other impairments

The treatment of other disorders (inner ear, eye, central nervous system, cardiovascular system) is not codified.

In severe forms, treatment is based on boluses of methylprednisolone (250 to 1000 mg/day for 1 to 3 days) combined with an immunosuppressant and/or a targeted therapy followed by high-dose corticosteroid therapy (prednisone 1 mg/kg/day without exceeding 60 to 70 mg/day).

In case of ocular involvement, treatment should be discussed with an ophthalmologist experienced in systemic diseases.

The management of the active phase of inflammatory manifestations is based on local treatment, combined with systemic treatment during the following manifestations: scleritis, ulcerated keratitis, posterior uveitis with or without retinal vasculitis. In the specific case of scleritis without signs of severity and episcleritis, systemic treatment with NSAIDs may be effective. Severe scleritis requires treatment with high-dose systemic corticosteroids and immunosuppressants. In case of severe or recurrent ophthalmic involvement, background therapy should be reassessed in consultation with a referral/competence centre.

Local herpetic or bacterial superinfection should be investigated and treated if there is any doubt.

The development of an ascending aortic aneurysm or aortic or mitral valve disease may require surgical intervention. If a surgical decision is made, efforts should be made to intervene in a planned manner, in a patient with controlled systemic inflammation (to limit the risk of suture loosening), with corticosteroid therapy at the minimum effective dose. In this case, a complete exploration of the large efferent vessels of the aorta should be performed as well as a careful anaesthetic evaluation. In case of aortic ectasia, a preventive beta-blocker treatment may be discussed, by analogy with Marfan's disease.

Infective endocarditis testing should be systematically conducted in case of ascending aorta involvement or the onset or worsening of aortic or mitral insufficiency.

Some patients can benefit from ENT implants that are now compatible with magnetic resonance imaging (MRI).

4.3.5. Treatment of paediatric forms

As these situations are very rare, they require getting in contact with an expert centre.

4.3.6. In the presence of myelodysplastic syndrome

The treatment approach for patients with relapsing polychondritis associated with myelodysplastic syndrome as well as for VEXAS syndrome requires specialised management in collaboration with a team specialised in myelodysplastic syndrome.

Systemic corticosteroid therapy is used as the first line of treatment for the manifestations of relapsing polychondritis in this setting. As corticosteroid dependence is common and immunosuppressants are poorly tolerated, targeted therapies are often used with very inconsistent efficacy. Early treatment with a hypomethylating agent (azacitidine) is therefore an option to consider in order to control relapsing polychondritis in difficult cases. Transfusion support and prevention of haemochromatosis may be necessary. Allogeneic stem cell transplantation should be discussed in a multidisciplinary consultation meeting taking into account age and IPSS-R.

4.3.7. Additional measures

Support measures are the same as those for any systemic corticosteroid therapy.

Patients should be vaccinated as soon as possible against pneumococcus, influenza and emerging diseases according to current recommendations (Covid-19). Some treatments decrease the antibody response to vaccinations, especially anti-Covid. It is also recommended that vaccinations be updated in accordance with the vaccination schedule.

Respiratory physiotherapy is important for bronchial congestion.

It is important to ensure that there is no gastroesophageal reflux or sleep apnoea syndrome, which may be aggravating factors.

The complications of corticosteroid therapy, immunosuppressants and targeted therapies must be systematically prevented and the patient educated to this end (see Section 4.4 and refer to the sheets drawn up by the rheumatism and inflammation club: http://www.cri-net.com/fiches-pratiques-et-eSessions/dernieres-mises-a-jour).

Particular attention should be paid to the control of cardiovascular risk.

The patient and his or her attending physician must be informed of the risks of progression of the disease, of the potential risk related to tracheobronchial intubation in the event of elective surgery, and of the situations which should lead to an emergency consultation. We refer the reader to the document "Fiche urgence" (emergency form) drawn up under the aegis of the FAI^{2}R network (Appendix 1).

The patient can obtain a personal emergency card from his or her specialist doctor in the reference and competence centres of the FAI^{2}R health network.

4.4. Therapeutic patient education and lifestyle modification

Therapeutic patient education (TPE) is an integral part of chronic disease management. TPE is a key element in the overall management of the patient. This approach, which must be multidisciplinary, has been defined by the World Health Organization (WHO):

> "TPE aims to help patients acquire or maintain the skills they need to manage their living with a chronic disease as well as possible."

It is an integral and ongoing part of patient care and involves organised activities, including psychosocial support, designed to make patients aware and informed about their illness, hospital care, organisation and procedures, and health- and illness-related behaviours. This aims to help them (and their families) understand their illness and treatment, work together and take responsibility for their own care in order to help them maintain and improve their quality of life.

Oral or written information and preventive advice can be given by a health professional on various occasions, but they do not amount to therapeutic patient education. The educational approach is participatory and person-centred, not simply the transmission of knowledge or skills. It is a partnership between the patient, possibly a caregiver and the health care team, with the aim of helping the sick person to take care of him or herself.

Thus, TPE gives patients the opportunity to be at the centre of an individualised and controlled health care pathway between a therapeutic standard offered by the health care team and the patient's own standard based on his or her representations and projects.

4.4.1. TPE for patients with relapsing polychondritis

For patients with relapsing polychondritis, therapeutic education will focus on the topics presented in Table 6.

Patients who have already completed TPE sessions can participate in reinforcement sessions, a form of continuous TPE, which consolidate and update the patient's skills, or in repeat sessions,

Table 6
Therapeutic patient education?.

Topics to be addressed	Educational objectives (non-exhaustive list)
What is relapsing polychondritis?	To be able to define its clinical manifestations To understand the meaning of laboratory-based monitoring, to know how to obtain the information necessary for monitoring from routine lab tests To be able to explain in your own words the mechanism of the disease (chronic disease, autoimmunity, cartilage inflammation) Introduction to the importance of regular monitoring
The treatments	To understand your treatment, to be able to define the kinetics of action of your treatments, to understand adverse events To know how to use your treatment on a daily basis, to understand the need to take your treatment regularly Adaptation of hygiene and dietary rules to the use of corticosteroid and/or immunosuppressive treatment
Relapse of the disease	To recognise the onset of clinical and biological signs of disease activity and take appropriate action To identify triggers and learn how to prevent them (including the importance of good adherence to treatment)
Hygiene and dietary measures	To know and to adapt your diet while on corticosteroid therapy (individualised salt and slow and fast sugar intake), to adopt a balanced diet To raise awareness of the risk of infection (reminder of vaccinations, hygiene rules to reduce the risk of infection, etc.); To be aware of the importance of smoking cessation
Living with it	To expressing your representations and feelings about the disease; To normalise the experience of fatigue and make better use of energy To adopt measures that focus on your well-being To develop self-esteem damaged by the disease (self-esteem, self-image, self-confidence) To discover and mobilise resources that can be used to deal with the challenges encountered on a daily basis (psychologist, social workers, disability status, etc.) To express the impact of the disease on daily life and develop coping strategies

when the patient needs further follow-up in case of difficulties in learning, non-achievement of the chosen skills, changes in the patient's health status, context and living conditions.

4.4.2. TPE for family members or caregivers who accompany patients with particularly severe relapsing polychondritis

The role of carers is essential in supporting patients with particularly severe relapsing polychondritis (a rare situation). It is therefore necessary to prevent, identify, guide and manage the needs and difficulties related to this support. Caregivers can be offered individual and/or group TPE to prevent the exhaustion and also accompaniment and participation with the patients in TPE sessions.

4.4.3. Connection with patient organisations

Patient organisations have a key role in supporting patients with rare diseases. Patient organisations provide support for patients and their relatives in therapeutic education, in collaboration with healthcare professionals, and in the realisation of a certain number of requests aimed at improving the patient's daily life. Patient organisations also provide a place for listening and sharing where patients and their carers can meet.

In France, there is one patient association dedicated to the support of those with RP: the Association Francophone contre la Polychondrite Chronique Atrophiante (AFPCA): http://www.afpca.fr/.

5. Follow-up

5.1. Objectives

The objectives are:

- to specify the activity and severity of the disease;
- to screen for sub-clinical visceral involvement related to relapsing polychondritis;
- to assess the acceptability, efficacy and tolerability of treatments;
- to test for potential comorbidities, to assess the vascular risk and the risk of infection.

5.2. Professionals involved

Professionals involved are as follows:

- relapsing polychondritis requires specialist management in collaboration with the treating physician.
- monitoring involves, depending on the initial assessment and the evolution:
- involvement of centres of reference or competence;
- specialist consultations (internists, ENT specialists, rheumatologists, ophthalmologists, dermatologists, haematologists, pneumologists, paediatric rheumatologists, cardiologists);
- consultations with the family physician;
- potential support from physiotherapists, dieticians, psychologists and social workers.

Other specialists may be involved, usually at the request of the above-mentioned doctors.

5.3. Frequency and content of consultations

Exclusive outpatient care is not always possible, and hospitalisation must be possible at any time if necessary. In other situations, the frequency of consultations and tests must be adapted:

- to the patient's clinical condition;
- to the severity and progression of the disease, the type of visceral involvement and/or the occurrence of intercurrent events;
- to the treatments used (monitoring, tolerability, adverse events);
- to any special situations (e.g. pregnancy, difficulties in adhering to treatment).

A clinical examination may be suggested:

- initially monthly, in case of severe and progressive relapsing polychondritis;
- every 3 months in intermediate situations;
- every 6 months during quiescence or for mild relapsing polychondritis;
- even once a year after several years of quiescence.

Disease monitoring can be aided by the Relapsing Polychondritis Disease Activity Index (RPDAI) [14] and Relapsing Polychondritis Damage Index (RPDAM) scores [15].

5.3.1. Interview and clinical examination

The follow-up medical interview and clinical examination are identical to those carried out during the initial assessment. Particular attention should be paid to checking the patient's understanding of their disease and treatment, as well as their adherence to the treatment. Adverse events, particularly related to corticosteroid therapy, should be assessed.

In children, particular attention should be paid to regular assessment of weight, height, pubertal stage and psychosocial development.

5.3.2. Paraclinical testing

Similarly, the frequency of complementary testing is adapted:

- to the patient's clinical condition;
- to the activity and severity of the disease;
- to comorbidities;
- to treatments.

These tests aim to:

- monitor relapsing polychondritis and detect specific, sometimes asymptomatic, disorders (especially cardiac, aortic, tracheal and haematological);
- screen for treatment complications.

This should be done clinically during consultations and with morphological tests such as, depending on the case, chest X-ray, cardiac ultrasound, thoracic CT scan and pulmonary function testing. The frequency with which these tests are repeated depends on the severity and progression of the disease. Less severe and less progressive forms of relapsing polychondritis do not require routine annual morphological monitoring.

Laboratory-based monitoring includes:

- monitoring of any inflammatory syndrome, although the absence of an inflammatory syndrome does not exclude the development of relapsing polychondritis;
- blood count to look for myelodysplasia;
- depending on the treatments prescribed: blood count, creatinine level, transaminases, gamma-GT and alkaline phosphatases;
- monitoring of carbohydrate and lipid levels: once a year if corticosteroids and/or tocilizumab.

Bone densitometry should be performed at initiation and then every 2 years for prolonged corticosteroid therapy, as recommended.

In case of ophthalmological or audio-vestibular impairment, joint follow-up with an ophthalmologist and ENT doctor will be applied.

6. Pregnancy

There is usually no particular interaction of pregnancy on relapsing polychondritis or of relapsing polychondritis on pregnancy. Pregnancy should be planned and anticipated, especially with regard to prior treatments and vaccinations [16].

Disclosure of interest

LA reports no conflict of interest. NCC reports no conflict of interest. AM reports consulting fees from GSK. LS reports research funding from AbbVie and consulting fees/meeting fees from GSK, LFB and Janssen-Cilag. AB reports consulting fees/speaking fees from Roche Chugai and Grifolds. JD reports no conflicts of interest. NM reports no conflicts of interest. GM reports no conflicts of interest.

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The French version is available free of charge on the following link: Haute Autorité de Santé–Polychondrite Chronique Atrophiante (http://has-sante.fr).

Appendix A. Appendix 1 - Emergency form

To be found on the Orphanet website:
https://www.orpha.net/data/patho/Emg/Int/fr/Polychondrite-Atrophiante_FR_fr_EMG_ORPHA728.pdf

Appendix B. Appendix 2 - Terms of use of cyclophosphamide (Adapted from PNDS Systemic necrotising vasculitis - June 2019)

Pre-administration precautions

Fertility preservation should be ensured, or at least offered to patients, both in women of childbearing age and in men.

Hydration before and during the infusion is essential. It is supplemented by the administration of Mesna (off-label and with no certainty over its value for doses of cyclophosphamide <600 mg/m^2 by bolus), administered during and after the cyclophosphamide infusion:

- 1/3 of the equivalent dose of cyclophosphamide (in mg) by IV at H0;
- then 2/3 of the dose by IV at the end of the infusion (90th mins);
- and 2/3 of the dose at H4, by mouth.

When cyclophosphamide is given orally, Mesna can also be given orally (equivalent daily dose in mg - possible off-label for oral route).

Monitoring of cyclophosphamide therapy is based on complete blood count and platelet count, creatinine levels and testing for haematuria, at least:

- before each infusion;
- every 2 weeks for the first 3 months;
- then monthly if oral treatment is continued.

If the neutrophils are $< 1.5 \times 10^9$/L at the scheduled bolus date, the dose should be reduced by 25% or even postponed (trying not to

delay treatment for more than 2 weeks, in which case an alternative therapy should be discussed).

Cyclophosphamide administration schedule

- In patients with normal renal function and under 65 years of age, the recommended regimen is bolus cyclophosphamide IV at a dose of 0.6 g/m^2 on D1, D15 and D29, followed by 0.7 g/m^2 every 21 days (total of 6 infusions).
- In patients with a GFR < 30 ml/min and under 65 years of age, the recommended regimen is bolus cyclophosphamide IV at a dose of 0.5 g/m^2 on D1, D15 and D29 and then every 21 days (total of 6 boluses).
- In patients over 65 years of age, regardless of renal function, the recommended regimen is: cyclophosphamide bolus IV prescribed at a dose of 0.5 g fixed dose at D1, D15 and D29, and then every 21 days (total of 6 boluses).
- In case of incomplete remission, 3 additional boluses can be performed.
- The maximum dose of each bolus is limited to 1200 mg.

Following induction therapy with cyclophosphamide, maintenance therapy should be started between 2 and 4 weeks after the last bolus of cyclophosphamide, regardless of the maintenance therapy chosen.

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