



## Review

## Tracheobronchial involvement of relapsing polychondritis

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## ARTICLE INFO

## Keywords:

Relapsing polychondritis  
Respiratory infections  
Tracheal stenosis  
Tracheo-bronchomalacy  
Endoscopy

## ABSTRACT

Recent studies show that relapsing polychondritis patients with tracheobronchial involvement are distinct from others in terms of clinical characteristics, therapeutic management, and disease evolution. Tracheobronchial involvement affects 20 to 50% of patients and may reveal the disease. It should be sought at the time of diagnosis and at each follow-up visit. Respiratory impairment is confirmed by computed tomography (CT) of the chest, including the cervical portion of the trachea, with end-inspiratory and dynamic expiratory scans, and pulmonary function tests. These investigations should be performed, even in asymptomatic patients, at the time of diagnosis, and repeated as necessary during follow-up. Bronchoscopy and a fortiori endoscopic intervention should be considered with caution and performed only by expert endoscopists after careful evaluation of the risks and benefits of such procedures, which can lead to damage or perforation of the airways and bronchospasm. Early detection and management of tracheobronchial involvement in relapsing polychondritis has significantly improved the prognosis of patients, especially with the development of interventional fiberoptic bronchoscopy. However, relapsing polychondritis-related morbidity and mortality are still elevated, particularly in tracheobronchial disease.

## 1. Introduction

Relapsing polychondritis (RP) is a rare systemic disease which can be disabling and life-threatening. It is characterized by recurrent bouts of inflammation followed, in some cases, by degeneration and deformation involving the cartilage of the ears, nose, larynx, and tracheobronchial tree [1–3]. Other structures that consist of proteoglycans can also be involved, such as the eyes, heart, and inner ear. There may also be manifestations of vasculitis.

A recent cluster analysis identified three separate phenotypes: a hematological form (in 10% of cases), a respiratory form (in 25% of cases), and a mild form with a good prognosis (approximately 65% of cases) [4]. Tracheobronchial involvement is the hallmark of the respiratory phenotype of RP, which was classically considered to carry a poor prognosis. In this large series, patients with such a phenotype received more intensive treatment and suffered from more infections but no patient died of airway collapse or obstruction due to RP, which has been a significant cause of mortality in older series. Another study

confirmed that patients with lower respiratory tract involvement have different characteristics [5]. These results show that patients with associated tracheobronchial involvement are distinct from others in terms of clinical characteristics, therapeutic management, and disease evolution [4].

Here, we review the current knowledge of respiratory tract involvement and its management in RP, with special emphasis on the most recent data.

## 2. Epidemiology

RP chiefly affects middle-aged adults, with a slight female predominance, but cases have been reported in the very young and very elderly [6]. All ethnic groups are affected. In the US, the estimated incidence of RP is 3.5 per million inhabitants per year [7] and the prevalence among Department of Defense beneficiaries is 4.5 per million inhabitants [8]. A more recent population-based cohort study found an incidence of 0.71 per million inhabitants per year [9]. The

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<https://doi.org/10.1016/j.autrev.2019.102353>

Received 7 March 2019; Accepted 11 March 2019

Available online 16 July 2019

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prevalence of respiratory impairment is 20–50% [1,4,10,11] during RP. Respiratory symptoms often lead to diagnosis (50% of cases). In the study of Dion et al., involving 142 patients, the tracheobronchial cluster represented one quarter of patients, was characterized by a younger age, and could be isolated [4]. A negative correlation was found in two studies between tracheobronchial and auricular involvement [12,13].

### 3. Clinical manifestations of tracheobronchial involvement

Respiratory involvement is inaugural in 10% of cases [14,15]. Airway involvement occurs early during the course of the disease, at a mean of 2.5 years after diagnosis [4].

Laryngeal involvement is manifested by pain and soreness of the larynx, above the thyroid gland. Dysphonia, aphonia, or hoarseness of the voice are possible. Laryngeal involvement may result in laryngomalacia or laryngeal stenosis, responsible for inspiratory dyspnea [14,16].

Tracheobronchial involvement leads to inflammation or even destruction of the cartilage, which can result in tracheo- and bronchomalacia. These are responsible for tracheobronchial obstruction, manifested by progressively increasing inspiratory dyspnea, cough, stridor, tracheal pain, and even respiratory distress. There may also be edema and soreness of the tracheal cartilage.

In addition, costosternal chondritis can also affect breathing, occasionally even resulting in complete cartilaginous destruction. Costosternal chondritis is present in 35% of patients [14].

RP can lead to sudden death (due to laryngeal or tracheal spasm) or acute edema during an inflammatory attack. However, this is now very rare since the improvement of treatment and interventional endoscopic procedures [10]. There is also an elevated frequency of lower respiratory tract infections, which are often associated with bronchiectasis.

RP is associated with autoimmune diseases in 22% to 30% of cases, which may also have their own respiratory component [2–4].

### 4. Diagnostic and classification criteria

There are no validated classification or diagnostic criteria for RP. The diagnosis of RP is based on clinical evidence and physician experience [1,14,17]. The most commonly used criteria are the Michet criteria [2], but they are for classification. Patients are classified as having RP if they fulfill two major criteria or one major and two minor criteria. Laryngo-tracheal involvement is a major criterion of this classification. It is now commonly accepted that the exclusion of differential diagnoses, particularly granulomatosis with polyangiitis (Wegener's), which can mimic RP, is crucial. Thus, positive anti-neutrophil cytoplasm antibodies (ANCA) with anti-PR3 specificity, involvement of the lung parenchyma, posterior non-cartilaginous tracheal wall, kidney, or destructive ear nose throat (ENT) lesions classify the patient as having granulomatosis with polyangiitis and not RP, with therapeutic consequences. A delay in the diagnosis is common, with a median time from first symptoms to diagnosis ranging from 1.9 to 3.2 years [1,8,9].

Classification criteria of relapsing polychondritis according to Michet *et al* [2].

#### Major Criteria

- Auricular chondritis
- Nasal chondritis
- Laryngotracheal chondritis

#### Minor Criteria

- Ocular inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
- Hearing loss, vestibular dysfunction
- Seronegative inflammatory arthritis



Fig. 1. Unenhanced CT scan, showing thickening of the anterior and lateral wall of the upper trachea, with sparing of the posterior membrane, in a 48-year-old man with relapsing polychondritis. Focal calcification is seen on the left-hand side (arrows).

classification or even diagnostic criteria and improving its categorization into subsets, a prerequisite for future therapeutic trials [18,19].

### 5. Imaging

The main imaging method used to diagnose RP is computed tomography (CT), with end-inspiratory and dynamic expiratory scans. A chest CT scan, including an expiratory acquisition, should be routinely performed at diagnosis, even in the absence of respiratory symptoms. It should be repeated as necessary during the evolution of the disease. The cervical portion of the trachea should be included. Thus, the acquisition should start below the vocal cords. Expiratory CT scan images can be acquired at a very low dose of X-rays to minimize the radiation dose. This is made possible by newer image reconstruction modes (iterative reconstruction), allowing the suppression of background noise in the images. Several typical CT scan patterns may be encountered [11,20]:

- 1) A thickening of the tracheal or tracheobronchial wall, defined by a wall thickness > 2 mm, with or without calcifications, is observed in 40% of cases. Sparing of the posterior membranous part of the tracheal wall, which does not contain cartilage, is highly typical (Figs. 1–3) [21]. The administration of iodinated contrast medium is not required for the demonstration of tracheal or bronchial wall thickening.
- 2) Fixed lumen narrowing and/or tracheobronchial obstruction, including subglottic stenosis. Stenosis is defined as at least a 25% reduction in the diameter of the lumen (Figs. 4, 5).
- 3) Tracheobronchomalacia detected on dynamic expiratory CT, which should be systematically performed. It is characterized by excessive



Fig. 2. Another example of anterior and lateral wall thickening of the trachea at a lower level, in a 77-year-old woman with relapsing polychondritis.

The next steps, currently ongoing, consist of developing RP



**Fig. 3.** Extensively calcified anterior and lateral wall thickening of the trachea at the level of the aortic arch in a 51-year-old man. At this stage, the lesions are irreversible.

collapse of the tracheal or bronchial lumen during expiration (Fig. 6B). Such excessive collapse may only affect the trachea, the main bronchi, or both.

- 4) Air trapping during dynamic expiration, which can be due to malacia [21] or fixed tracheobronchial stenoses (Fig. 5). Air trapping is defined by the presence of lung areas that fail to increase in attenuation after full expiration relative to full inspiration. It can exhibit a lobular, segmental, lobar, or even pulmonary distribution. On inspiratory CT images, the corresponding areas may show mosaic perfusion. Mosaic perfusion consists of heterogeneity of the lung parenchyma attenuation, with hypodense (abnormal) areas of vascular rarefaction, and hyperdense (normal) lung areas, where more vessels are visible. Mosaic perfusion can be detected without administration of a contrast agent and is due to hypoxic vasoconstriction in poorly ventilated areas (Fig. 5).
- 5) Bronchiectasis, frequently observed in our experience, may be due to either direct cartilaginous injury, the consequence of recurrent infections, or both (Fig. 7).

Apart from bronchial abnormalities, there is no lung parenchymal involvement during RP [10]. In summary, some abnormalities on dynamic expiratory CT images (malacia and air trapping) may not be visible on inspiratory CT images [20]. Malacia and air trapping are the result of cartilage inflammation and are the unique CT abnormalities detectable at early stages of RP [10,20,21]. Early detection is important, because treatment may change the prognosis.

Post-processing of CT images with 3D rendering (virtual bronchoscopy) may facilitate the visualization of stenosis and size reductions for interventional endoscopists, but their added value for the detection of bronchial abnormalities has not been demonstrated [10].

Magnetic resonance imaging (MRI) is considered to be more sensitive than CT for the distinction between fibrosis and inflammation. Fibrosis is characterized by low signal intensity on T1- and T2-weighted images, whereas inflammation is characterized by high signal intensity on T2-weighted images and enhancement following gadolinium injection [22]. However, MRI is limited for the evaluation of the airway wall by its low spatial resolution compared to CT.

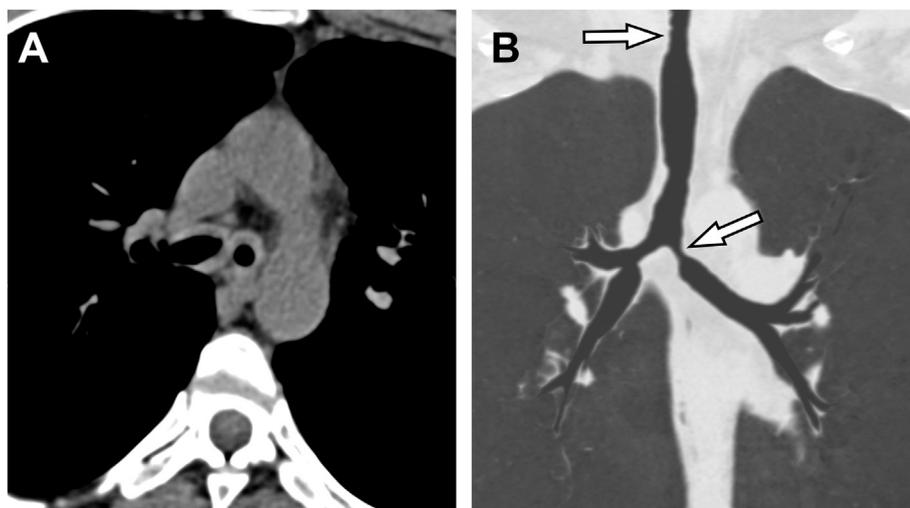
Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan may reveal active cartilaginous lesions at any stage of the disease [23–25], with the limitation of very low spatial resolution. PET/CT may also reveal unsuspected cartilaginous involvement (Fig. 6). Although its performance has not been fully evaluated, follow-up of standard uptake value (SUV) can be useful to distinguish between active and fibrotic lesions, especially for patients with isolated tracheobronchial involvement.

### 6. Pulmonary function testing

Pulmonary function testing must be performed at diagnosis and repeated annually to detect airway impairment and estimate its progression. It should not be performed during a superimposed infection. Spirometry, volume-flow curves, and the measurement of upper airway resistance may show early involvement in asymptomatic patients [10,26]. Obstructive disease (FEV1/FVC < 70%) and reduced exercise capacity (walk test desaturation and decreased distance walked) should be sought.

Obstructive disorders during the course of RP may be inspiratory and/or expiratory and reversible or incomplete. The residual volume (RV) can also increase without distension (normal total lung capacity (TLC) and RV/TLC) [27]. Reduced inspiratory flow (the plateau of the inspiratory curve on the volume-flow curve), however, indicates extra-thoracic involvement but the correlation is not always good. Reduced expiratory flow indicates intra-thoracic obstruction [15,27] (Fig. 8). There is no ventilation-perfusion disorder associated with RP nor diffusion or gas exchange abnormality, and the alveolar-capillary gradient and dead space are normal. Elasticity is also not decreased (no decrease in TLC).

The initial reduction in the size of the respiratory tract is due to inflammatory edema, but later results from collapse related to malacia and, finally, fibrous stenosis. There are therefore three presentations of obstruction: fixed obstruction with a double plateau volume flow curve (expiratory and inspiratory involvement), variable or extra-thoracic



**Fig. 4.** A) Unenhanced CT scan showing thickening of the main bronchi wall in a 36-year-old woman with relapsing polycondritis. B) Coronal reformation, demonstrating 50% stenosis at the origin of the left main bronchus (arrow). There is also narrowing of the lumen of the subglottic trachea (arrow heads), highlighting the need to include the cervical portion of the trachea during CT acquisition.



Fig. 5. A) Unenhanced CT scan, showing wall thickening of the entire trachea and both main bronchi, with stenosis of the left main bronchus, in a 47-year-old man with relapsing polychondritis. B) Axial transverse view, showing major stenosis of the left main bronchus lumen (arrow). There is mosaic perfusion of the left lung parenchyma, with slightly decreased attenuation and fewer vessels than in the right lung. C) Expiratory CT scan image demonstrating diffuse air trapping of the left lung.

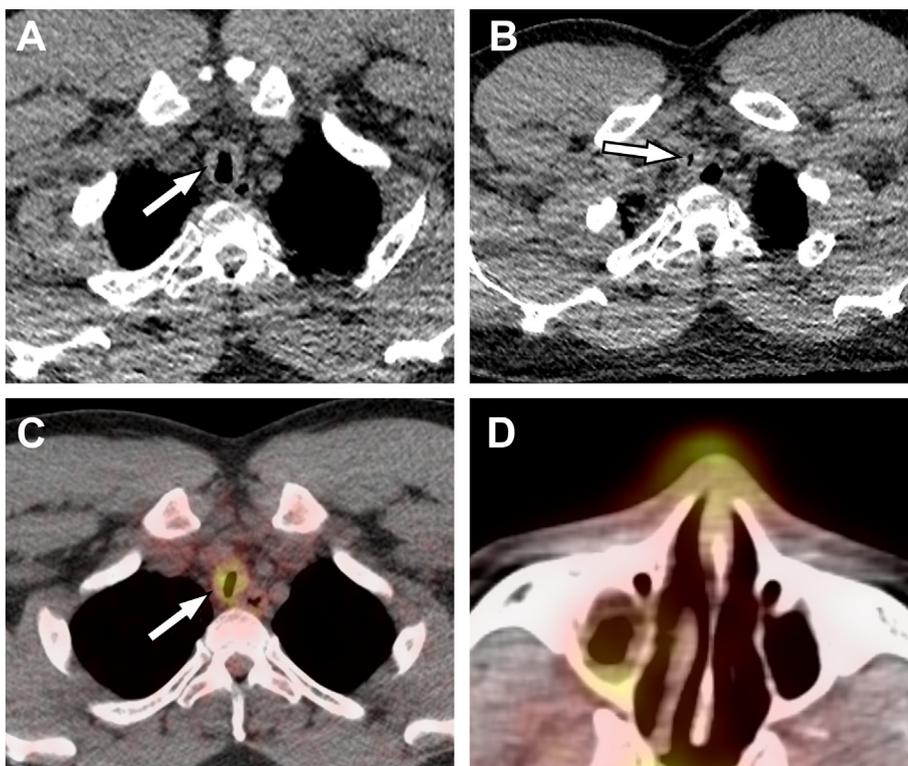


Fig. 6. CT scans of a patient with relapsing polychondritis and respiratory involvement. A) Inspiratory CT scan, showing thickening of the tracheal anterior wall (arrow). B) Dynamic expiratory CT scan, showing narrowing of the trachea, indicating tracheomalacia (arrow). C) Positron emission tomography, showing FDG uptake of the tracheal cartilage, demonstrating an inflammatory process (arrow). D) FDG uptake of the nasal cartilage, without clinical symptoms, in the same patient.



Fig. 7. Unenhanced CT scan, demonstrating bronchiectasis of both lower lobes. The bronchial diameter is enlarged relative to the accompanying artery.

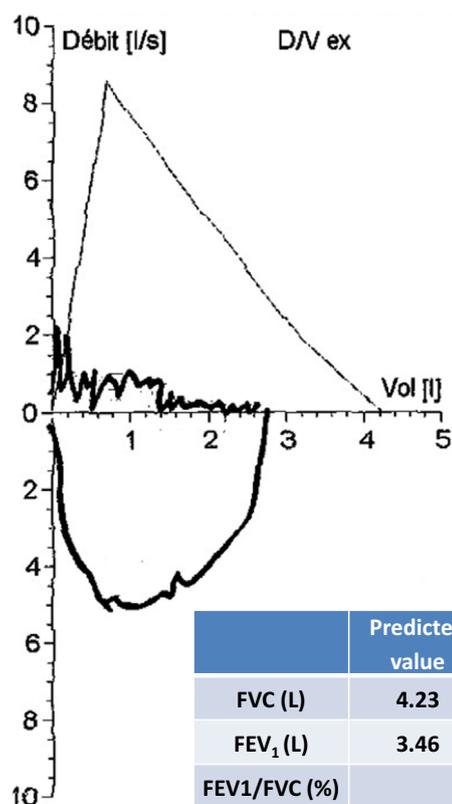
dynamic obstruction, corresponding to the upper airways (extra-thoracic trachea or larynx, inspiratory involvement), and variable or dynamic intra-thoracic obstruction (expiratory involvement). The most common presentation is fixed obstruction due to stenosis.

The decrease in maximum ventilation is mainly due to a reduction

in forced expiratory flow. When severe, it can lead to hypercapnia; hypoxemia is much rarer and associated with alveolar hypoventilation [10].

### 7. Fibroscopy

Fibroscopy should be performed in patients with respiratory symptoms, especially when interventional endoscopy is necessary. It can evaluate mucositis, define the severity (narrowing or stenosis), and allow the dynamic assessment of possible collapse (expiratory maneuver or coughing). However, it should be performed with care because of increased morbidity and mortality associated with the procedure: risk of acute flare-up of the disease, leading to edema of the respiratory or supraglottic airways, bronchospasm, bleeding, respiratory distress, or even death. It should only be performed by an experienced interventional endoscopist with trained personnel and an emergency airway and tracheostomy kit nearby [10]. The correlation with dynamic CT for stenosis or malacia is good. For example, in one study [10], 22 patients had both examinations, of which 17 had lesions by fibroscopy comparable to those detected by CT. Fibroscopy may not detect thickening



**Fig. 8.** Limitation of expiratory flow (upper part of the curve), corresponding to an intra-thoracic obstruction of the large airways, with a flat curve. During expiration, intra-thoracic pressure compresses the airway wall due to the destruction of cartilage induced by relapsing polychondritis. In contrast, the tracing appears to be normal during inspiration (lower part of the curve). Inspiratory flow induces a positive intraluminal pressure in the large airways, which becomes greater than the intra thoracic pressure, allowing re-expansion of the lumen of the airways damaged by relapsing polychondritis.

but is more sensitive for the detection of edema or stenosis in a narrow area.

**8. Pathophysiology of respiratory impairment**

An immune origin, involving humoral and cellular immunity, is suspected [14,17,28], as:

1) there is an associated autoimmune disease in up to 30% of cases, 2) chondritis lesions contain a CD4<sup>+</sup> T-cell lymphocyte infiltrate and plasmocytes, as well as immune deposits, 3) autoantibodies directed against type II collagen are detected in approximately 30% of cases, or against other types of minor collagen (IX and XI) or cartilage proteins, such as oligomeric proteins of the cartilaginous matrix (COMP) and matrilin-1, 4) a specific T-cell response against collagen II peptides, which represents 95% of cartilage collagen, or specific to matrilin-1 is sometimes observed, 5) there is an association with Class-II MHC, 6) high-dose glucocorticoids (GCs) are generally effective, and especially 7) RP-like symptoms are reproduced in animal models after immunization against type II collagen or matrilin-1. Hansson et al. demonstrated that antibodies against matrilin-1 were associated with tracheobronchial involvement in 69% of cases and were able to bind cartilage structures *in vivo* [29]. They developed a mouse model in which tracheobronchial and nasal chondritis, (without ear or articular involvement), dependent on the complement system, B cells, and class-II MHC, were induced after immunization against matrilin-1 [30,31].

Thus, according to current data, RP is a probable autoimmune disease, with specific immunization against cartilage structures and matrilin-1 shown to be responsible for the tracheobronchial phenotype.

The mechanism of respiratory involvement, including tracheal or bronchial obstruction, depends on the stage of the disease: inflammatory edema occurs during the active phase, followed by malacia, resulting from cartilage destruction, and then stenosis due to fibrous replacement of the impaired cartilage [10]. Bronchial cartilage inflammation may also impair mucociliary function [1]. The mechanism of bronchial dilation has been the subject of debate, but probably

involves several causes. It may be due to inflammatory destruction of the cartilage of the tracheobronchial axis of the proximal bronchi but also recurrent bronchial infections resulting from the inefficiency of bronchial drainage, when coughing, because of bronchial collapse.

**9. Histology**

Histological specimens of the anterior tracheal cartilage are sometimes obtained during fibroscopy but there is no histological specificity. If performed, there is perichondral lympho-plasmocytic cellular infiltration of the cartilage, with the loss of basophilic staining of the cartilaginous matrix, corresponding to the loss of proteoglycans. The cartilage is gradually replaced by fibrous tissue. These abnormalities evolve from the periphery to the center and predominate at the junction between the cartilage and connective tissue.

**10. Treatment of relapsing polychondritis respiratory disease**

Therapeutic management is empirical. It is not based on therapeutic trial data but mainly the physician's experience and the data from a few case series and involves a collaboration between the pulmonologist and the rheumatologist or internist. The goal of treatment is to control symptoms and maintain airway stability [10].

**10.1. General treatment**

General treatment is the same as for other forms of the disease. GCs are an important component of RP treatment and show good efficacy but often high-dose steroid dependence. Doses of up to 1 mg/kg/day are sometimes prescribed, depending on the severity of the disease. High doses of intravenous methylprednisolone may be necessary if the oral route is not sufficient or if there is acute respiratory distress. GCs are used to control acute airway flare-ups and reduce their severity, duration, and frequency [32]. They are sometimes associated with antibiotics because coexistence with an infection is sometimes difficult to

rule out. Most patients require long-term treatment with GCs for months or even years [1,10].

Oral GCs are very often associated with immunosuppressive agents for their steroid-sparing effect. Immunosuppressants (methotrexate, cyclophosphamide, azathioprine, or mycophenolate mofetil) should be considered if there is involvement of a vital organ, insufficient response to GCs, high-dose steroid dependence, or as a first line agent to reduce GC doses. The choice of the agent is empirical. Methotrexate is widely used and appears to be effective [1].

Biologics have been tried in this often-steroid dependent disease [33–35]. Some authors have advocated that current data from case reports support the use of infliximab for RP with pulmonary involvement, with early therapy being associated with improved outcomes [35]. However, their use is not based on any therapeutic prospective trial and comparison of the effectiveness of the various agents is difficult between the different series. Adalimumab and infliximab have been the most commonly used. During the first six months, the rates of response and complete response were less than two-thirds and approximately one-third, respectively, with only a modest reduction in median daily GC dose [34]. Although adalimumab appeared to have the highest rate of persistence, almost all patients had to discontinue the TNF inhibitor due to insufficient efficacy (24–35%), loss of efficacy (28–30%), or adverse drug reactions, the most frequent being infections (20–15%).

### 10.2. Local treatment

Techniques for local treatment should only be performed in highly specialized centers with a thoracic surgery service nearby. They consist of interventional endoscopic treatment most often using rigid bronchoscopy and include thermocoagulation, laser, balloon dilation or bronchoscopes of increasing size, and tracheobronchial prosthesis.

For focal bronchial stenosis, the proposed treatment is balloon dilatation or bronchoscopes of increasing size, high frequency thermocoagulation, or laser. In case of recurrence, a prosthesis may be proposed.

For more diffuse stenosis with a malacia component, a tracheobronchial prosthesis may be proposed, consisting of a Montgomery tube for high glottic stenosis, a bifurcated prosthesis for tracheobronchial involvement, or a straight prosthesis for bronchial involvement. These stents also make it possible to evaluate the improvement of symptoms upon resolution of the obstruction and thus select patients who could benefit from extensive surgery, such as tracheobronchoplasty [10].

Silicone prostheses are most often used because they are more durable and can be removed if necessary but their insertion is sometimes limited by technical difficulties. In case of failure of silicone prosthesis, a covered metal prosthesis can be discussed [36]. Tracheostomy may be necessary for severe subglottic involvement.

The complications of interventional endoscopy include the risk of acute flare-up, perforation, prosthesis migration, increased mucous secretion, with risk of obstruction of the prosthesis, bronchospasm, and increased cough [10,37].

The use of these local therapeutic interventions must be considered when medical treatments fail or for patients awaiting the effect of the medical treatment who have major bronchial involvement associated with a high risk of morbidity and mortality. Local management reduces respiratory symptoms in most patients [11].

The decision of local or general treatment or a combination is made on a case by case basis after a multidisciplinary evaluation involving the pulmonologist, the operator, the radiologist, and the rheumatologist or internist. In a study by Dion et al., 15% of patients with tracheobronchial involvement required local endoscopic treatment [4].

### 10.3. Other treatments

Respiratory physiotherapy plays an important role in bronchial drainage, which improves ventilation and prevents secondary

infections.

There are few studies on inhaled treatments, which are not recommended. One clinical case, however, reported the efficacy of high doses of inhaled fluticasone in a patient with tracheal inflammatory exacerbations, which reduced the oral GC dose [38].

For patients with moderate to severe tracheobronchial involvement, particularly those with malacia, screening for obstructive sleep apnea or hypercapnia can be performed, as they may benefit from noninvasive positive-pressure ventilation, which can be an alternative to interventional endoscopy in some cases [39,40].

The prevention of infectious complications, associated or not with bronchiectasis, also needs to be emphasized. Such measures can include pneumococcal and influenza vaccination, antibiotics, surveillance of the nature of bacterial colonization and treatment of bronchial superinfections, and low-dose azithromycin prophylaxis for symptomatic and superinfected bronchiectasis.

One of the most challenging issues is the differential diagnosis between flare-ups and respiratory tract infections in those patients with a chronic obstructive respiratory disease. Furthermore, infections and flare-ups can coexist or succeed one another by a few days [18].

## 11. Evolution and prognosis

The evolution of the disease is progressive, consisting of flare-ups, leading to possible permanent destruction of the cartilage [1]. Some symptoms may persist between flare-ups.

Overall RP survival has improved considerably. It was 55% at 10 years in 1986 [2], 94% at 8 years in 1998 [1], and 83% at 10 years in the most recent study [4]. The improved prognosis is partially due to the availability of interventional treatments, but RP-related morbidity and mortality are still high, particularly in tracheobronchial disease. In the most recent study, these patients received more intensive treatment, were prone to infections, and were frequently admitted to the intensive care unit [4]. However, their survival (although impaired) was not significantly less than that of patients with the mildest phenotype and tracheobronchial involvement no longer appears to be a factor of excess mortality in multivariate analysis [4].

An activity score, the relapsing polychondritis disease activity index (RPDAI), has been developed based on clinical and biological data [41]. It consists of 27 weighted items, including respiratory chondritis, with or without respiratory failure.

Damage is defined as irreversible manifestations of the disease that are unlikely to benefit from treatment escalation, ascertained by clinical assessment, and present for at least three months. A damage score has also recently been finalized and includes three respiratory items: permanent chest wall deformities, dysphonia, and obstructive syndrome (laryngeal, tracheal, or bronchial) [42].

## 12. Conclusions

Over the past few years, it has become clear that there are distinct forms of RP in terms of clinical characteristics, therapeutic management, and disease evolution. Overall, RP survival has improved considerably. However, more complete characterization of the different subsets and their pathophysiological features are needed to establish more appropriate therapeutic strategies based on the patients' disease characteristics and prognosis.

### Contributors

N.d.M. and X.P. wrote the initial draft. D.D., C.L., J.D., N.C.C., L.M., G.C., and M.P.R. reviewed the manuscript and made substantial contributions to the discussion of the content. All authors reviewed and/or edited the manuscript before submission and agreed to its publication.

## Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

## Patient consent

Not required.

## Provenance and peer review

Not commissioned; externally peer reviewed.

## Declaration of Competing Interest

None declared.

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