



HAUTE AUTORITÉ DE SANTÉ

GUIDE - LONG-TERM CONDITIONS

XERODERMA PIGMENTOSUM

NATIONAL DIAGNOSIS AND TREATMENT PROTOCOL FOR A RARE DISEASE

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The French National Diagnosis and Treatment Protocol (PNDS) for Xeroderma Pigmentosum was drafted by the designated reference centre, with methodological support from the French National Authority for Health (HAS), pursuant to the provisions of the 2005–2008 French National Rare Diseases Plan.

HAS validates this PNDS as part of its remit in dealing with long-term conditions. This protocol as well as the resulting list of surgical procedures and services (LAP) is revised every three years.

In the interim, the LAP is revised, at minimum, on a yearly basis. This list is available on the HAS website.

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1. Introduction

The purpose of this national diagnosis and treatment protocol (PNDS) is to outline to health providers the optimum management and integrated care pathway for patients with long-term conditions (ALD), particularly with status ALD 11: xeroderma pigmentosum (XP).

This is a practical resource which the general practitioner (GP)¹, in consultation with the specialist, may refer to when managing the disease in question, in particular when drawing up the care plan in collaboration with the specialist and patient.

A PNDS guide cannot be comprehensive, i.e. cover all comorbidities, hospital care protocols, etc. It does not claim to cover all the ways in which stroke may be managed, nor does it a discharge doctors from their responsibility to their patients. This guide nevertheless describes the main organisation of management of patients with XP, which is mainly applied in the dermatology departments of hospitals.

XP is a rare disorder transmitted in an autosomal recessive manner, characterised by hypersensitivity to the sun and ultraviolet rays. Around 80% of patients have a deficiency in their DNA nucleotide excision repair system (NER, DNA). These patients are affected by the conventional form of XP. Around 20% of sufferers are variant patients (XP-V), which means that the NER works, but the defect is in the post-replication process, which allows a cell to synthesise DNA in spite of a lesion on the template strand (translesional synthesis). The typical XP symptoms appear later among XPV patients.

The incidence of Xeroderma pigmentosum is around 1/1,000,000 births in Europe.

Xeroderma pigmentosum is a rare disease for which there is no curative treatment at present. Only prevention (protection against sunlight) can minimise the development of complications in patients.

Furthermore, the significance of this disease's impact in social, psychological and affective terms, justifies personalised management (involvement of social/educational welfare assistant, psychologist visit at home, if necessary). Regular therapeutic education consultations (involving patients and their close family), along with consultations screening for complications are essential throughout the follow-up period.

¹ The doctor specified by the patient to the health insurance fund.

2. Diagnosis and initial assessment

2.1 Objectives

- Detect the disease early on.
- Confirm the diagnosis for XP.
- Identify comorbidities.
- Obtain and provide genetic information.
- Provide therapeutic education to patients and/or their close relatives.
- Plan treatment management.
- Provide information to patients and/or their close relatives.
- Give the patient a document certifying the diagnosis and providing a list of useful links and emergency procedures.

2.2 Professionals involved

- The specialist is tasked with detecting the disease (dermatologist, paediatric dermatologist, neurologist, paediatrician) or it may become evident as a result of a family survey or prenatal test.
- Diagnosis, initial evaluation and total patient management are based on multidisciplinary cooperation, coordinated by the specialist at the centre of expertise, and will involve:
 - Doctors in several disciplines: biologists, cancer specialists and any other relevant specialist, if necessary (geneticist, plastic surgeon or dermatology surgeon, etc.)
 - Ancillary medical staff: nurses, physiotherapists, psychologists, psychomotricians, occupational therapists, social workers
 - These health professionals work together with the GP or paediatrician, offering total management of the patient's care.

2.3 Content of initial assessment

- The assessment is adapted to the patient's age, the nature of the deficiency, the circumstances of diagnosis and the clinical signs. It comprises:
 - a specialist consultation for the patient
 - tests carried out in a specialised laboratory (UDS)
 - a specialist consultation for the members of the patient's family
 - genetic counselling with information about the options available for prenatal diagnosis.

► Clinical diagnosis

- On average, the first cutaneous signs appear between the ages of 1 and 2 (75%), with the child's skin being normal at birth. The first sign is

most often an abnormally severe reaction after even minimal exposure to the sun: erythema on exposed areas, unusual due to its intensity and duration. The appearance of blisters is possible.

- The clinical aspect of the disease is characterised by pseudo-poikiloderma, which develops gradually, being predominant on areas exposed to sunlight or poorly protected (inadequate protection from clothing). This pseudo-poikiloderma includes dyschromic disorders (mottled hypopigmentation, freckles), skin atrophy, dryness and fragility, as well as sclerosis which may be responsible for synechia around the corners of the mouth, eyelids and nostrils. These cutaneous signs are accompanied by ocular symptoms, in particular photophobia, which may be displayed.
- The later the stage the patient is seen, the easier it is to make a clinical diagnosis, all the more so when the symptoms occur in the context of a family history.
- Apart from these situations, diagnosis will be evident in a young child who is highly photosensitive and must be confirmed by complementary investigations in order to rule out other photosensitive conditions, especially other genophotodermatoses (Cockayne Syndrome, trichothiodystrophy, etc.).
- A neurological examination is absolutely necessary for any patient with XP. If any abnormality comes to light during the examination, a neurological consultation must be made automatically. In the event of delayed growth or signs of early ageing (possible link with Cockayne Syndrome), an initial neurological consultation will also be requested.
- The benefit of diagnosing XP early on comes mainly from the importance of early education about photoprotection and early screening for tumours.

► **Quantifying DNA repair synthesis (Unscheduled DNA synthesis (UDS))**

This is the biological reference method used to confirm a clinical diagnosis. This examination is carried out on a culture of dermal fibroblasts taken from a cutaneous biopsy taken from covered skin. If necessary, the complementation group (search for the mutated change and mutation) may be established in the laboratory if the clinic can justify it.

► **Genetic counselling**

A genetic counselling consultation will be able to provide answers to questions from parents, the child affected and close relatives about the risk of recurrence (see also section 2.4 Family screening).

XP is transmitted in an autosomal recessive manner. In the case of a couple who have a child affected by this disorder, the risk of recurrence is 25%.

The considerable genetic heterogeneity which is typical of the different forms of XP is reflected in the diversity of its clinical manifestations: 7 genetic

groups or complementation groups (A to G) for the classic form and 1 complementation group for the XP variant (XP-V). In France, 60% of XP patients belong to complementation group C.

Given the severity of the disease and the fact that it is incurable, it is possible, as part of the genetic counselling consultation, to suggest a prenatal diagnosis is made for couples at risk (parents who have already had a child for whom the diagnosis of XP has been confirmed in the laboratory, XP in the family, etc.).

2.4 Family screening

When a patient has been diagnosed as having XP, the immediate family must be examined by a dermatologist in order to find the symptoms indicating the condition. This systematic screening must include at least brothers and sisters, but may be extended to other members, depending on family relationships and the possibility of several consanguinity loops. Drawing up a family tree is an absolutely necessary aspect of this process.

2.5 Disclosure of diagnosis

- The diagnosis must be disclosed during a specific consultation at the centre of expertise. This should comprise: an explanation of the diagnosis, along with a follow-up and treatment plan. Other members of the multidisciplinary team, in particular a nurse and psychologist, may also be present.
- A card or form certifying the diagnosis (treatment diary where applicable) must be given to patients and/or their families.
- Information about patient associations is given during this visit.

3. Treatment management

Given that there is no curative treatment for this condition, its management basically relies on preventive measures, which mainly involves photoprotection, as well as on early detection and treatment of cutaneous and ocular tumours.

3.1 Objectives

- Prevent and/or bring under control early dermatologic complications and their consequences.
- Treat complications.
- Ensure therapeutic education for patients and/or their families.
- Ensure total management of patients and their families.

3.2 Professionals involved

- Total management of XP is based on multidisciplinary cooperation, coordinated by a specialist at the centre of expertise.
- Total patient management involves numerous health professionals at the hospital and in the community: GP, ophthalmologist, paediatrician, geneticist, neurologist, biologist, cancer specialist, haematologist, surgeon (neurosurgeon, maxillo-facial surgeon, plastic surgeon), anaesthetist, radiotherapist, ENT specialist, stomatologist, psychiatrist, psychologist, psychomotrician, physiotherapist, occupational therapist, nurse, social worker, speech therapist, etc.
- Coordination with other healthcare structures: long-term care and rehabilitation service (SSR), home-based care (HAD), medical residential care for children (MECS), healthcare network with service providers.

3.3 Therapeutic patient education and lifestyle adjustment

► Therapeutic education

- Therapeutic education must be initiated during the first visit and reinforced during each subsequent visit. It involves training and evaluating patients' knowledge and, where necessary, that of their families in terms of understanding the disease, information on the development of treatments, understanding prevention and treatment at home.

► Lifestyle adjustments

- Lifestyle adjustments must remain conducive to the child's development (see section 4.5 Consultations with ancillary medical staff - social/educational welfare assistant).
- Integration in the community: attendance at day nursery or school must be facilitated, and the host institution (head teacher, teachers, school doctor, occupational doctor) must be kept informed about the child's specific situation by drafting an individual childcare protocol (PAI).
- In a work environment, patients should inform the company doctor about their illness.
- Patient associations may help with therapeutic education and lifestyle adjustments.

Healthcare professionals and patients must be informed about the existence of patient associations by centres of expertise, institutional websites and Orphanet.

3.4 Photoprotection

- Photoprotection is the first measure to be adopted as a means of preventing pre-cancerous and cancerous lesions.
- **Time-based photoprotection** means that patients must be particularly careful when out in the sun between 8 AM and 6PM, especially during the summer period.
- Maximum photoprotection must be provided through clothing and protecting the patients' daily surroundings (home, car, school, work, etc.) and through treatment, supplemented by topical sunscreen products.
- Removal of artificial light sources emitting UV rays, such as ordinary neon and halogen light sources. These emissions must be monitored using a dosimeter (recalibrated once a year).
- Anti-UV screens must be fitted on the windows of vehicles, homes and classrooms in schools (to be replaced every 10 years). These screens must feature in every consultation and hospital room where patients are treated.
- **Photoprotection through clothing:** Long clothes must be worn which cover every part of the body, as well as gloves, closed shoes, wide-brimmed hats and sun glasses with lenses large enough to block the UV rays, with the frames being broad at the sides.
- Children in particular may be advised to take vitamin D.
- **Photoprotection using topical sunscreen products:** The choice of products will include those with a sun protection factor of 50 or more (classified as 50+, i.e. offering an extremely high level of protection in keeping with Recommendation 2006/247/EC of the Commission of the European Communities of 22 September 2006 on the efficacy of sunscreen products and the claims made relating thereto). The product

must be reapplied every two hours. It must also be applied at the recommended dose (2 mg / cm²), equivalent to around 50 ml, to cover exposed areas (face and hands) for a day.

- While waiting to have windows in the surrounding environment fitted with anti-UV filters, whose effectiveness can be controlled, or if in doubt about the adequacy of the protection provided, an external sunscreen must be used.

3.5 Other preventive treatments

- Oral retinoids are no longer prescribed in France (opinion of working group) due to the poor toleration of the high dosages required (2 mg/kg/day) and to the incidence of recurrence when this treatment is discontinued with the development of a tumour.

3.6 Treatments for complications

► Management of cutaneous tumours

Surgical intervention must always be considered as the first-line treatment in the case of a cutaneous tumour. The prescription of other treatments must be considered and/or discussed on a case by case basis, according to the clinical situation.

– **Surgery**

Surgical intervention is the main treatment for malignant cutaneous tumours. It must be carried out as early as possible to limit as much as possible the damage associated with scarring. It is the specialist's responsibility to indicate this treatment.

– **Radiotherapy**

Radiotherapy is rarely indicated, most often when surgery is impossible. It is the responsibility of the specialist to indicate this treatment, who will discuss with the radiotherapist the dose to be used.

– **General chemotherapy**

- Chemotherapy is mainly proposed for advanced squamous cell carcinomas which are impossible to treat via surgery or radiotherapy, or which are inoperable and metastatic. Lastly, it is proposed in exceptional cases for reducing tumour volume prior to surgery.
- Most XP cells are hypersensitive to antitumour drugs. The dose to be administered will be determined jointly by the cancer specialists and dermatologists.

– **Local topical treatments**

- Topical treatment with 5-fluorouracil is used in addition to surgery for precancerous lesions (keratoses).

- Cryotherapy is used in the treatment of pre-epitheliomatous lesions (keratoses).
- Imiquimod 5% cream is used as a supplement to contribute to the regression of basal cell carcinomas on surface areas of the trunk and those less than 1 cm².

– **Other local treatments**

Other local treatments may be used in a specialised context, such as dynamic phototherapy.

▶ **Management of neurological complications**

There is no preventive treatment for neurological complications with XP. Treatments will be symptomatic of the various neurological complications.

▶ **Management of ocular complications**

- **Prevention of ocular phototoxicity:** sunglasses offering maximum possible protection, corrective glasses adapted for ocular complications if necessary.
- **Treatment for non-tumour ocular complications:** treatment of trophic and irritant disorders of the conjunctivae and cornea using healing and/or vitamin topical substances, artificial tears and gels.
- **Treatment for ocular tumours:** surgical excision, keratoplasties, grafts, curietherapy or radiotherapy will be carried out depending on the type and site of the tumour.

▶ **Management of skin dryness**

This is a major problem for a large number of patients and requires the application of skin emollients.

4. Follow-up

This is carried out by the centre of expertise at a frequency that depends on the nature and severity of the disorder and the therapy being provided.

4.1 Objectives

- Inform patients about the current state of knowledge and recent advancements (investigations, disease and treatments).
- Monitor for the onset of complications.
- Monitor the efficacy, tolerance (screen for side-effects) and compliance with the prescribed treatment(s).
- Continue therapeutic education for patients and/or their families.
- Support any pregnancy-related project: genetic counselling, prenatal diagnosis.
- These objectives will be achieved through good cooperation between the specialists and treating doctor.

4.2 Professionals involved

- The specialist at the centre of expertise is responsible for follow-up, taking into account the opinions of the different specialists in the multidisciplinary team and in collaboration with community health professionals.
- Social medical follow-up is also provided involving: doctors in small and medium sized companies, school doctors, social workers. Social workers are involved, in particular, to assist with administrative procedures, link-up with administrative authorities and social departments in the sector, follow-up integration at school, and give occupational guidance and information about disability legislation.

4.3 Frequency of visits to the centre of expertise

- Once the diagnosis of XP has been confirmed during the first visit, a stringent dermatological follow-up must be initiated, with visits three times a year. This frequency may be higher depending on the progression of the disease or in the event of complications.

4.4 Content of the medical consultations

► Dermatological examination

- A dermatological examination is recommended for every patient at least three times a year, if there are no complications.
- One visit every year will be devoted to educating patients and their families about photoprotection in all its forms and about screening for cutaneous tumours and other complications.
- The aim of these consultations is to screen, as early as possible, for the appearance of precancerous or cancerous lesions in order to be able to

propose treatment for them as quickly as possible. Monitoring via dermatoscopy may be envisaged.

- Furthermore, in the case of patients who have been treated for a malignant cutaneous tumour, regular monitoring involves early screening for any relapse locally or in the lymph node region, which must be given appropriate treatment.

► **Neurological examination**

- If any abnormality comes to light during the initial neurological examination, a neurological follow-up consultation will be made automatically and a search must be carried out for the complementation group. Patients with neurological disorders basically belong to the groups A, B, D and G.
- Any indication for carrying out additional examinations (EEG, evoked potentials, brain scan, electromyogram, neuromuscular biopsy) will be discussed based on the clinical neurological symptoms.
- Only the audiogram must be discussed outside any clinical symptoms for patients in the groups at risk of neurological complications (A, D and B or G in the event of association with Cockayne Syndrome).

► **Ophthalmologic examination**

- In the case of asymptomatic patients, an ophthalmologic examination of the eye's anterior segment must be carried out every 3-6 months.
- In the case of ocular complications, the frequency of visits will be adapted to the type of functional or tumoral ocular condition.
- Imaging examinations (MRI, scanner) will be useful in evaluating the spread of tumoral lesions and in detecting any recurrence.
- The examination may sometimes be carried out under general anaesthetic, allowing intraoperative ablation of suspect lesions.

4.5 Consultations with ancillary medical staff

► **Psychologist**

- Systematic psychological management of patients with XP and their families (parents, siblings) must be encouraged. When XP is confirmed as the diagnosis, this limits considerably the activities that can be done outdoors during sunshine hours and means a major adjustment in terms of activities carried out indoors. Due to these specific clinical features, along with the multiple surgical interventions required and their scars, regular evaluation must be suggested to patients, including their close relatives, in order to screen for any depressive disorders as early as possible.
- The manifestation of neurological and/or ophthalmologic complications may also increase the sense of isolation felt by patients and their close relatives.

- Similarly, certain stages in life, such as adolescence, may require more frequent psychological follow-up.
- Follow-up will be tailored to each patient's requirements, based on the psychological impact and may require, if necessary, the opinion of a psychiatrist.
- It must be possible to carry out this psychological follow-up close to where patients live (local consultation).

► **Physiotherapist / occupational therapist / psychomotrician / speech therapist**

Personalised management must be suggested in the event of neurological or ophthalmologic complications, or in the case of functional sequelae following treatment for tumour lesions.

4.6 Social medical management

- The characteristics of the disease and the preventive and treatment measures involved cause the youngest patients great problems in terms of integration at school, as well as professional problems for adults due to being unable to carry out a large number of shared activities with the rest of their company. This also involves major changes in the family structure.
- Families must be monitored by a social/education welfare assistant to provide them with the best support in dealing with social and administrative matters. This person's role will be to evaluate the living conditions of patients and their families, to improve the provision of social welfare and help them adapt to their family, school and professional environment.
- It is also desirable to visit patients in their everyday surroundings (home, school, workplace) to verify that the essential preventive measures have been implemented properly in the environment (quality of sun screens, ergonomic adaptation of living environment for disabled patients).
- If necessary, the patient may be referred to Regional homes for the disabled (MDPH) created by the law of 11 February 1995, including CDES (Regional Commission for Special Education) and Cotorep (Commission for Vocational Guidance and Reintegration of Disabled Workers). MDPH provides a single office with the aim of informing people, welcoming and advising them, evaluating their needs and proposing a personalised plan for compensation, support and monitoring via a commission of rights and autonomy.
- In this situation, it is helpful to inform patients and their parents about the benefit of patient associations.

► **Useful information**

- National Diagnosis and Treatment Protocol available at: www.has-sante.fr (long-term condition (ALD) section)
- General Information: <http://www.orphanet.net/>
- Patient associations: <http://www.enfantsdelalune.org/>

Appendix 1 - Participants

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