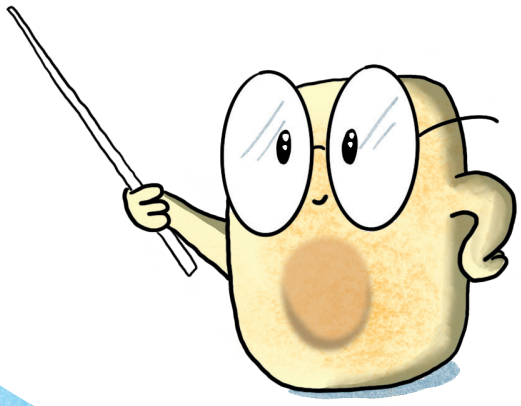
A GUIDE FOR PARENTS

UNDERSTANDING ADRENOCORTICAL CARCINOMA IN CHILDHOOD



Adrenocortical carcinoma (ACC) in one's own child is a shock – diagnosis, treatment, and follow-up care present families with enormous challenges.

This guide explains the essential medical basics in an accessible way, explores key topics in greater depth, supports parents in making informed decisions together with the treatment team.

In addition, it offers experiences and practical advice on how families can cope with the demanding everyday life with ACC. Its aim is to provide not only knowledge, but also reassurance and hope.

Important Contacts

Here you will find support, up-to-date information, and opportunities to connect with other families affected by ACC:

ENS@T-PACT – International network for research and exchange on adrenal diseases
Internet: ensat.wildapricot.org, E-mail: ensatkids@ensat.org

Let's Cure ACC – Patient organization for families affected by ACC
Internet: www.letscureacc.com, E-mail: contact@letscureacc.com

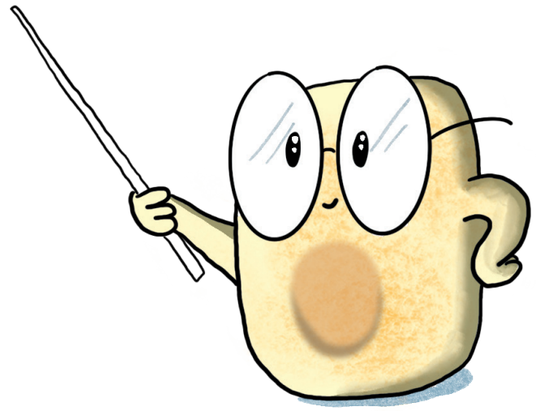
Your Personal Contacts
Please note here the most important contact persons from your child's medical team:

About this Guide

The contents of this guide are based on publicly available information and scientific studies. The recommendations are aligned with the currently applicable treatment guidelines for adrenocortical carcinoma (ACC) in children.

This guide is intended to provide parents with background information and to help them feel better prepared for conversations with their child's medical team. However, it does not in any way replace the expertise of the treating professionals. Please always consult your doctors, especially when it comes to questions about diagnosis and treatment. Prescription medicines shall be used under medical supervision. Trademarks used in this guide cannot be used by third parties without the express authorization of their owners.

This guide was written by Prof. Dr. Verena Wiegering, University Hospital Würzburg and University Medicine Frankfurt a.M., member of the international working group ENS@T-PACT, in collaboration with Dr. Marc Büdenbender, Let's Cure ACC. We thank all patients and their families who shared their experiences with us and thus made a significant contribution to this brochure.



Together, one step at a time

Dear Parents, Patients, and Relatives,

Adrenocortical carcinoma (ACC) is a very rare form of cancer that can occur in both adults and children. Treating this disease is complex and requires a high level of expertise as well as close interdisciplinary and international collaboration. Specialists around the world work together to provide affected children with the best possible care. Although the course of the disease varies greatly from child to child and is often difficult to predict, we know that the chances of recovery in childhood are generally better than in adults. We cannot undo the diagnosis – and can only begin to imagine what it means for you as a family. But we are committed to supporting you with reliable medical information and compassionate guidance.

Adrenocortical carcinoma, also known as adrenal cortex carcinoma, arises in the adrenal glands, which sit atop each kidney in the abdominal cavity and play a vital role in the body's hormone system. There are less aggressive forms, known as adenomas, and highly aggressive forms that tend to spread (metastasise) early, forming new tumours in other parts of the body (known as metastases or distant metastases). Because ACC is such a rare tumour, this brochure is intended to serve as a guide. It is divided into a medical section and a section specifically for patients and families. Our aim is to significantly improve the prognosis of this disease—and we can only achieve that together.

As physicians and researchers, we need your support to ensure good communication, provide the best possible treatment, and collect clinical data and tumour-specific information. Only then can we gain new insights and develop better therapies. This brochure is therefore not only a source of information, but also an invitation to reach out to us with your questions. At the same time, we encourage you to contact specialists and other affected families to help ensure the best possible support for you and your child during this challenging time.

A Cancer Diagnosis Changes Everything

A cancer diagnosis of your beloved child turns life upside down in an instant. Suddenly, everything is different. You may feel paralyzed, angry, sad, desperate, or stunned—or all of these at once. The familiar routine of school, training, or work is suddenly replaced by hospital stays and cancer treatments. Your family find yourself surrounded by unfamiliar people, constant beeping, IV poles, and bald heads.

Countless questions arise

- What happens now?
- What will we have to face?
- Why us?
- Will my child die?

Some of these questions have no answers—but many others do. This brochure aims to address some of them. What matters most: despite the cancer diagnosis, your child remains who they are—unique and loved. And you are not alone.

What Matters to Us

Before we delve deeper into the topic, we would like to share some important messages that may help you find moments of calm and clarity in the coming weeks and months:

Childhood and adolescent cancer is curable.
Thanks to tremendous progress in medicine, the chances of recovery have significantly improved in recent years. Most children and adolescents can now be treated successfully.

It is not your fault.
Cancer is many things—unfair, unpredictable, devastating—but it is never your fault. Childhood cancer simply happens, however unjust that may feel.

You are not alone.
There are many other children, teenagers, and families who are going through similar experiences. Ask your care team about ways to connect with other affected families. You can also connect with others through the patient organization Let's Cure ACC (see dedicated section).

Your feelings are valid.
Whatever you are feeling—anger, fear, sadness, confusion, hope—it's okay. There is no "right" or "wrong" way to feel, especially after a cancer diagnosis.

Never give up.
Your child will have both good days and bad, and you will feel exhausted too. But hope will carry you forward and help you keep going.

Let others support you.
Even though no one can take the illness away from your child—or from you—there are many people—family, friends, doctors, nurses—who will walk this difficult path with you. Accept help and support wherever possible.

Your life goes on.
Even when cancer seems to take over everything, your life continues. Holding on to familiar routines—no matter how small—can bring comfort and a sense of control. And remember to care for your own well-being. You'll need strength for the road ahead.

There are no stupid questions.
Cancer and everything related to it can be overwhelming. It's perfectly normal not to understand everything right away. Don't hesitate to ask questions, and prepare for medical consultations by writing down what you want to ask.

Get informed—wisely.
Knowledge can ease fears and provide a sense of security. But too much information can also become overwhelming. Make sure to rely on trustworthy sources such as websites from professional medical societies or your treatment team. Be cautious with information from unverified sources like "Dr. Google" or YouTube.

Only you decide for your child.
There are often different treatment options. Which doctors or centres will be your primary care team? When is the right time to seek a second opinion? There may be differing treatment recommendations. You will be called upon to make decisions for your child. Be proactive, put together the best possible medical network, and don't hesitate to seek multiple expert opinions when important treatment decisions arise.

ACC – Understanding a Rare Disease Better

What is Cancer?

Cancer is a general term for many different malignant diseases, which can vary greatly in their characteristics, treatment options, and chances of recovery. The disease arises when cells begin to grow uncontrollably due to changes in their genetic material. These cancerous cells displace or severely impair the function of healthy cells. Cancer may appear as leukemia, which affects the blood and bone marrow, or as solid tumours, which can develop in nearly any part of the body.

Despite intensive research, the exact causes of cancer in children remain largely unknown. Various theories exist, but many remain hypothetical and cannot be confirmed in each case. What is important to know: cancers in children and adolescents are fundamentally different from those in adults, even if they share similar names. Their causes are currently unexplained, and parents cannot be held responsible for their child's illness. Some cancers, such as certain forms of adrenocortical carcinoma (ACC), may have a hereditary component and occur more frequently in certain families. For this reason, genetic counseling may sometimes be recommended.

Cancer is not contagious—it cannot be transmitted from person to person or from animals to humans. There is no scientific evidence that food, unknown sources of radiation, or other environmental factors cause cancer in children.

Adrenal Tumours in Childhood

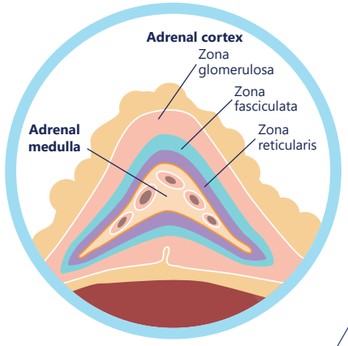
Humans have two adrenal glands, one located on top of each kidney. These small, triangular glands play a crucial role in the body's hormonal and stress response system.

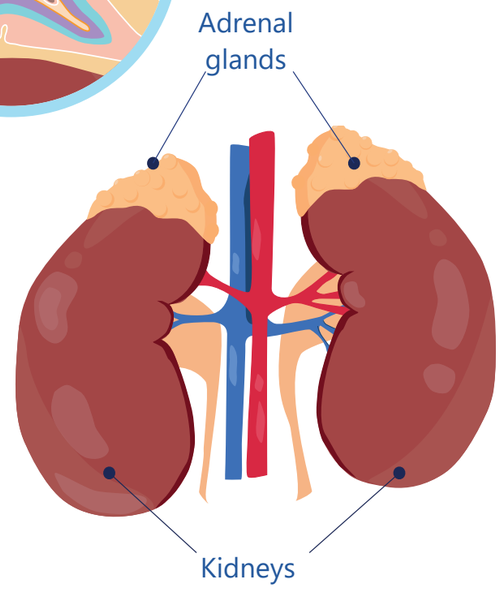
The adrenal gland consists of a medulla (inner part), a cortex (outer layer), and a surrounding capsule.

The adrenal cortex is divided into three zones:

Zona glomerulosa	Zona fasciculata	Zona reticularis
produces mineralocorticoids, such as aldosterone, which help regulate blood pressure and electrolyte balance.	produces glucocorticoids, such as cortisol, which play a role in metabolism, stress response, and immune regulation.	produces androgens (male sex hormones), which contribute to the development of secondary sexual characteristics and can affect growth and puberty.

The adrenal medulla primarily produces catecholamines, hormones that play a key role in increasing heart rate and blood pressure.

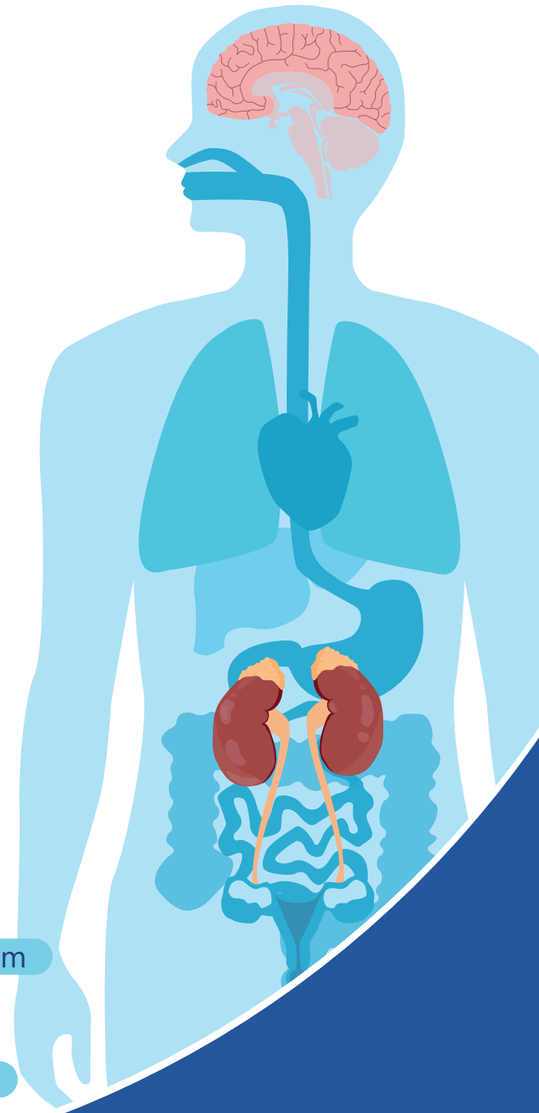




Adrenal glands play an **important role in the body by producing**

hormones that help regulate:

- The immune system
- The metabolism
- The blood pressure
- The stress response



In children and adolescents, several types of tumours can arise in the adrenal gland. The most common is neuroblastoma, which, like pheochromocytoma, originates from the adrenal medulla. From the adrenal cortex, both adenomas (benign tumours) and carcinomas (malignant tumours) may develop. Rarely, distant metastases from other tumours may also spread to the adrenal gland.

When an adrenal tumour is suspected, it is crucial to determine whether the tumour is benign or malignant, whether it is hormonally active, and whether there is evidence of a hereditary cancer predisposition syndrome (e.g., Li-Fraumeni syndrome). These factors are essential for planning further treatment.

ACC in Childhood

Adrenocortical carcinomas (ACC) are highly malignant (very aggressive) tumours that originate in the adrenal cortex. This type of tumour is rare in both adults and children. The incidence among individuals under 20 years of age is about 0.2–0.3 per million per year, corresponding to approximately 100 new cases annually in Germany. Paediatric ACC can occur sporadically or in association with hereditary syndromes such as:

- Li-Fraumeni syndrome
- Beckwith-Wiedemann syndrome
- Multiple endocrine neoplasia type 1 (MEN 1)

Genetic factors can play a significant role in the development of ACC. For example, in southern Brazil, paediatric ACC is about 15 times more common than elsewhere due to a specific inherited mutation (p.R337H) in the TP53 gene that is frequently found in this region.

The exact cause of ACC is still largely unknown. The disease occurs more frequently in early childhood and after puberty (around 30% of cases).

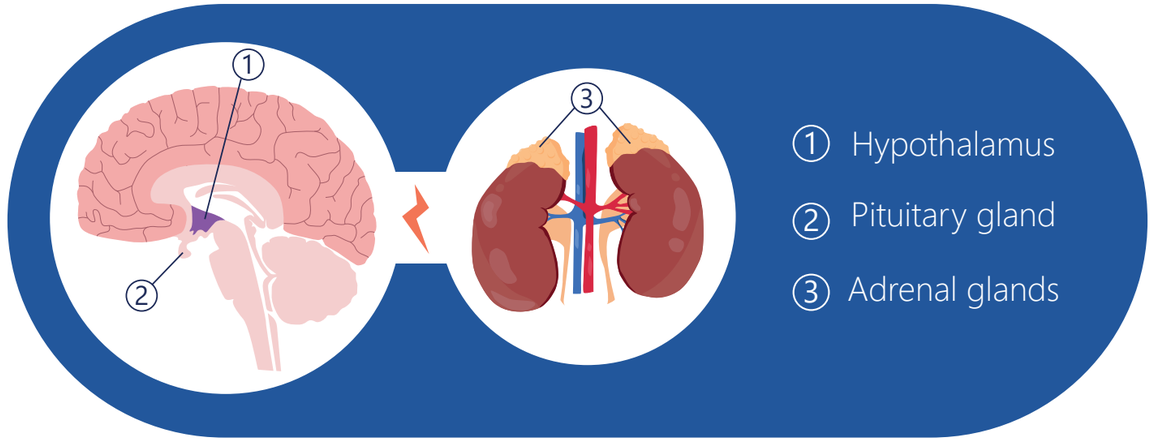
Unlike in adult patients, the majority of paediatric adrenocortical carcinomas (around 80–90%) are hormone-active, and the resulting excess hormone production is often the first and most important warning signal that leads to the diagnosis. The symptoms depend on which hormones are overproduced and may include signs of virilization (such as pubic hair, acne, or deepening of the voice), rapid growth or early puberty, or features of Cushing's syndrome, such as weight gain, round face, and high blood pressure.

In some children, the tumour is recognised because of symptoms related to its size or local growth, such as abdominal or back pain, a visible or palpable mass, or a feeling of fullness or pressure in the abdomen. In a smaller number of cases, ACC is discovered coincidentally during imaging performed for another reason — for example, during an ultrasound or CT scan — a finding referred to as an "adrenal incidentaloma."
Thus, paediatric ACC can be detected in three main ways: through hormone-related symptoms, through local tumour effects, or as an incidental finding, with hormone overproduction being by far the most frequent presentation in children.

Hormones out of Balance

The adrenal glands make important hormones such as cortisol, aldosterone, and androgens. These hormones help your body deal with stress, control metabolism and blood pressure, and support normal growth and sexual development.

The brain helps control this process through a system called the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus and the pituitary gland send signals (called ACTH) to the adrenal glands, telling them to make cortisol. When enough cortisol is in the blood, the brain slows down these signals to keep everything in balance.



The hormone aldosterone, however, is controlled in a different way — mainly by the kidneys and the blood pressure system (renin-angiotensin-aldosterone system, RAAS).
Androgens, the "male-type" hormones also made in small amounts by the adrenal glands, are partly influenced by the same brain signals that control cortisol.

In hormone-active ACC tumours, however, these feedback loops are overridden. The tumour produces hormones independently of ACTH, leading to persistently high hormone levels and clear clinical symptoms.

One of the most common hormone effects is Cushing's syndrome, caused by excess cortisol. Affected children may gain weight rapidly, especially around the abdomen, develop a rounded face, a buffalo hump, purple stretch marks, and show signs of slowed growth. Skin may bruise easily, and mood swings or fatigue can appear. Girls may have irregular or absent periods.

Another common finding is the development of male physical characteristics (virilization), especially in girls, with signs like increased body or facial hair, acne, clitoromegaly, and a deepening of the voice. In boys, signs may include early pubic hair growth or genital changes. Some tumours trigger precocious puberty, leading to early development of secondary sex characteristics.

If the tumour produces aldosterone, symptoms may include high blood pressure, muscle cramps, fatigue, and abdominal pain — often linked to low potassium levels. Typical signs of hormone-active ACC in children include:

- Obesity
- Flushed, rounded face with pudgy cheeks *(moon face)*
- Fatty, rounded hump high on the back just below the neck *(buffalo hump)*
- Purple stretch marks *(especially on the abdomen, thighs, breasts, and arms)*
- Thinning, fragile skin that bruises easily
- Irregular or absent menstrual periods for those who have a menstrual cycle
- Accelerated growth followed by delayed growth due to hormonal arrest *(in children and teens)*
- Virilization: development of male traits *(body and pubic hair, acne, deeper voice, enlarged clitoris in females)*
- Mood swings
- High blood pressure
- Osteoporosis
- Diabetes

Because young children may not be able to express what they feel, changes in appearance, growth, or behaviour are often the first clues. Blood and urine tests can confirm hormone excess. A combination of high cortisol with low ACTH levels points clearly to the adrenal gland as the source. Early recognition of these hormonal signs is critical — they are the body's way of signaling that something is wrong.

Prognostic Factors in Childhood ACC

With limited statistical data and the unique nature of each case, it's impossible to predict the exact outcome. It largely depends on the stage of the disease, the child's age, and biological characteristics of the tumour. The prognosis is often more favorable in children under three years of age and in cases where the tumour is well-defined and can be completely removed by surgery. In contrast, older children with metastatic disease (stage IV) often face a poorer and more variable prognosis, even with intensive treatment. The extent of the disease is classified using international staging systems such as COG or ENS@T.

Children's Oncology Group (COG) tumour staging system for ACC in children

Stages	Description
I	• Tumour completely resected (removed) with a margin of healthy tissue. • Tumour weight <100 grams and size <200 cm^3. • No evidence of spread to lymph nodes or other organs.
II	• Tumour completely resected, but either weight ≥100 grams or size ≥200 cm^3. • No lymph node involvement or metastasis.
III	• Tumour not completely resected and/or regional lymph nodes involved. • No distant metastases. • May include local invasion into surrounding tissues.
IV	Distant metastases present at diagnosis (e.g., lungs, liver, bones, or distant lymph nodes), regardless of tumour size or lymph node involvement.

ENS@T Staging System for ACC

(European Network for the Study of Adrenal Tumours)

Stages	Description
I	Tumour ≤5 cm in greatest dimension, confined to the adrenal gland, no local invasion or metastases.
II	Tumour >5 cm, still confined to the adrenal gland, no local invasion or metastases.
III	Tumour with any of the following: • Invasion into surrounding tissue or adjacent organs • Involvement of regional lymph nodes • Tumour thrombus in vena cava or renal vein (No distant metastases)
IV	Distant metastases present (e.g., lungs, liver, bones, distant lymph nodes).

In addition, there are biological features such as a high proliferation index, hormonal activity, or specific genetic characteristics that are associated with a poorer prognosis. These factors are increasingly being taken into account in studies and treatment guidelines to allow for more targeted therapy. Molecular genetic alterations in the tumour can provide starting points for targeted treatments, especially in the event of a recurrence. Therefore, it is advisable to analyse the tumour molecularly as early as possible. In the case of disease progression or relapse, this may open up additional treatment options.

Currently, treatment recommendations are primarily based on staging. However, more and more additional factors are being considered to identify patients at higher or lower risk at an early stage and to enable a more individualised treatment approach.

Medical Examinations for Diagnosis and Ongoing Care

Early Detection – Timely Action

Throughout the course of the disease – from the initial diagnosis through treatment and into long-term follow-up – a range of diagnostic procedures is used to monitor how the disease is progressing, evaluate how well the treatment is working, and detect possible relapses or side effects at an early stage.

The most important types of examinations are outlined below. The medical team will always aim to explain each step in a way that is age-appropriate and easy to understand. If anything is unclear, please don't hesitate to ask questions.

At diagnosis, a variety of tests are performed to determine the stage of the disease. These same tests are often repeated during treatment to assess how the tumour is responding and to identify any complications caused by surgery, chemotherapy, or, where applicable, radiation therapy. The findings help the medical team tailor the treatment plan **to each patient's individual needs, with the goal of achieving the best possible outcome while minimizing side effects.** The type and timing of examinations depend on the clinical situation and are carefully chosen by the treating physicians.

After treatment has ended, structured follow-up care plays a key role in detecting any recurrence of the disease as early as possible. In most cases, follow-up visits are scheduled every three months during the first two years, as this is when the risk of relapse is highest. Over time, these intervals are gradually extended to every six to twelve months. Follow-up typically continues for up to ten years, although the intensity of monitoring is reduced over time as the risk decreases.

For children with a genetic predisposition to cancer, lifelong and close monitoring is recommended, even after the standard follow-up period has ended. This ongoing care ensures that any new developments can be detected and addressed without delay.

A MULTIDISCIPLINARY TEAM

ACC involves a rare endocrine tumour, so you should be treated by an expert centre that provides a team of doctors, including mainly an endocrinologist, a pediatric oncologist, a radiologist, a surgeon, a nurse, a pathologist, a nutritionist, a radiotherapist, a nuclear radiologist who will be able to communicate with each other as a multidisciplinary team and as one unanimous voice about your medical results.

Blood Tests

Blood tests play a very versatile role in cancer treatment. They provide doctors with important information for diagnosis, treatment planning, monitoring the course of the disease, and follow-up care. Blood tests analyse various components of the blood through a series of laboratory analyses. Blood samples are typically collected either by a needle from a vein, through a central venous line, or via a small finger prick (also called a fingerstick). A complete blood count (CBC) evaluates parameters such as white blood cells (leukocytes), haemoglobin levels, and platelets (thrombocytes).

Patients undergoing chemotherapy often show reduced levels of these blood components, which can lead to an increased risk of infection. In such cases, a transfusion may become necessary. Blood counts are also crucial in determining the appropriate timing for the next cycle of chemotherapy. In addition, various organ functions can be assessed through blood tests. In ACC, hormone testing plays an important role, as it provides information on tumour activity as well as on treatment effects and potential side effects.

Hormones in blood and urine as ACC tumour markers

ACC tumours, especially in children, are hormonally active in about 80% of cases and produce excessive amounts of steroid hormones such as cortisol or androgens. These so-called tumour markers are important both for diagnosis and for monitoring the course of the disease.

Methods

Steroid levels can be measured in blood plasma or urine. The most informative method is the analysis of 24-hour urine collection, as it reflects the total amount of steroids produced over one day. For this reason, it remains the gold standard, even though the procedure is somewhat demanding. Once the individual steroid profile of a tumour is known, monitoring can sometimes be simplified using spot urine samples or blood tests.

Diagnosis

Steroid measurement is particularly important at the time of initial diagnosis to detect possible hormone overproduction. The symptoms caused by this (e.g., Cushing's syndrome or virilization—meaning masculinization in girls or early onset of puberty in boys) are not always obvious at first glance. Steroid analysis also helps distinguish between benign and malignant tumours, since malignant tumours often show an abnormal steroid profile with increased production of precursors or unusual metabolites.

Monitoring and follow-up

After treatment, regular measurement of steroid levels is an important part of follow-up care. Rising or newly abnormal steroid profiles can indicate recurrence (relapse) or progression of the disease—often even before imaging methods show changes. In this way, both the effectiveness of therapy and tumour activity can be monitored reliably.

Tumour Tissue Analysis (Histopathology)

Even if diagnostic tests—particularly hormone profiles and imaging—strongly suggest an ACC, the definitive diagnosis can only be confirmed by examining the tumour tissue removed during surgery.

Experienced pathologists can identify characteristic features of the tumour under a microscope (histological examination). In addition, a molecular genetic analysis is performed, which may play a role in therapeutic decision-making. Today, part of the tumour tissue is also frozen after the necessary diagnostic procedures—either for research purposes or to investigate personalised treatment options. This is, of course, only done with the consent of the parents and the child.

Biopsy

A biopsy involves removing a tissue sample from the body to determine whether a tumour is benign or malignant and to identify the specific tissue type. In the case of ACC, a biopsy is usually not required, as diagnosis and treatment planning can often be based on hormone production levels.

However, in certain cases—such as inoperable tumours or when molecular pathology is needed—a biopsy may be necessary. Every biopsy carries a risk of tumour cell dissemination, so the potential benefits and risks must be carefully weighed. This decision is made jointly with the treating physicians and experts, enabling individualised treatment planning.

Computed Tomography (CT)

Computed tomography (CT) is a specialized imaging technique using X-rays to detect abnormal tissue structures. During the scan, the patient lies still while a computer-controlled X-ray beam creates detailed cross-sectional images of the body, which are later reviewed by radiologists.

Because CT involves radiation exposure, its use is generally conservative. However, for certain organs such as the lungs, CT is particularly effective. In children, low-dose techniques are often used to minimize radiation exposure.

Positron Emission Tomography (PET)

PET/CT is an imaging method based on the principles of scintigraphy. A radioactively labeled substance, often glucose (FDG), is injected into the body. A scanner then detects metabolic activity in different tissues. Since tumour tissue typically shows elevated metabolic activity, tumours and metastases can be clearly distinguished from healthy tissue. On PET images, these areas appear as bright spots.

FDG-PET is commonly used at the time of diagnosis to detect metastases and is also helpful in assessing treatment response during follow-up. For optimal accuracy, the patient must lie still and be fasting, as high digestive activity can reduce image clarity.

Ultrasound (Sonography)

Ultrasound imaging uses high-frequency sound waves, which are inaudible to the human ear, to visualize internal structures. The returning echoes are converted into real-time images on a monitor. Tumour tissue produces different echo patterns than healthy tissue.

Ultrasound is completely safe and painless. It is frequently used both at the time of diagnosis and during treatment, as it is quick, easy to perform, and provides important information about the tumour and abdominal organs.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) uses a strong magnetic field to measure the movement of hydrogen atoms in the body and generate highly detailed images. Patients and their companions must not wear or carry any metal objects, and the patient must remain still during the procedure.

MRI is especially well suited for visualizing soft tissues and is a routine examination in the diagnosis and follow-up of ACC. Since the scan can take a considerable amount of time, sedation is often used for younger children. From the age of about 5–6 years, an attempt without sedation can often be made, especially with a parent present. This procedure is non-invasive and not associated with any known side effects.

Ensuring Best Care for Your Child

Expertise and Experience Are Essential

If a malignant disease is suspected—such as adrenocortical carcinoma (ACC)—the child should be referred immediately to a paediatric oncology and haematology centre, also known as a childhood cancer centre. These specialized departments primarily treat malignant diseases. Their physicians and nursing staff are specially trained and experienced with all available treatment options and possible complications. This provides the best possible conditions for addressing the disease as effectively as possible. Since paediatric ACC is extremely rare, it is advisable that treatment is carried out in collaboration with a centre that specializes in ACC.

This may mean longer travel times for you as parents, but it is a necessary step to ensure the best possible treatment for your child. The therapy is based on well-established medical knowledge gathered through the treatment and observation of many young cancer patients. For almost all types of cancer, standardized treatment protocols exist—defined treatment plans tailored to the specific disease to enable the most successful therapy possible. Nevertheless, research in this field is ongoing to further improve outcomes. For this reason, your child's treatment will likely follow a dedicated protocol.

Such a protocol is developed to define the optimal dosage and duration of therapy for the specific condition. At the same time, it is used to evaluate whether improvements compared to the current standard of care are possible. Because every child responds differently to treatment, it may be necessary to adapt the protocol to individual needs. Before therapy begins, the treating physician will discuss the planned protocol with you, explaining both the benefits and potential risks. You will be asked to give your informed consent. Your child will also be informed about the treatment in an age-appropriate manner and, if applicable, asked for their consent.
Each treatment protocol is complex—especially for those without a medical background. However, every step will be explained to you in detail, so that you are always informed about the next stages of therapy.

International Collaboration and Second Opinions

In the case of very rare diseases like ACC, even specialized centres with high patient volumes may encounter ambiguity regarding the best treatment options. That is why international collaboration and, if necessary, obtaining a second expert opinion is both sensible and important.

Several international networks focus on paediatric ACC, including ENS@T Kids/PACT, EXPeRT, and IC-PACT. These networks work closely together and offer you and your doctors the opportunity to obtain a second opinion through a shared tumour board. Don't hesitate to seek expert advice if you have questions or uncertainties. In most cases, it is easiest if your treating physicians initiate the contact. However, we are also happy to provide personal consultation for patients and their families.

Advancing Research – Improving Care

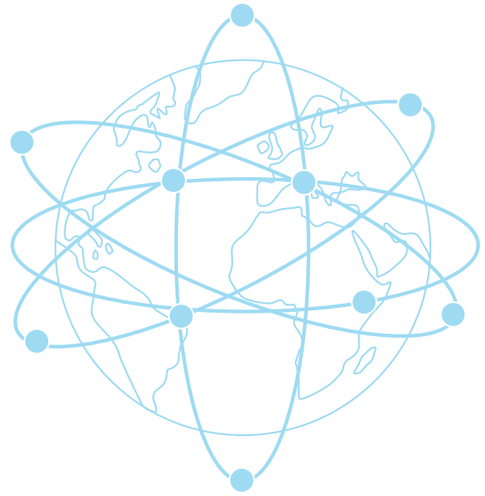
Your child is at the centre of everything we do – and everything we know about childhood ACC is aimed at ensuring the best possible care. Thanks to scientific research, treatments can now be better tailored to each individual child, side effects can be reduced, and long-term chances of cure can be improved. In particular, molecular genetic analyses help to better assess individual risks and enable the development of targeted, personalised treatment approaches.

Because ACC in children is extremely rare, knowledge about the disease remains limited compared to other types of cancer. This makes it all the more important to use every available piece of information to improve diagnostics and therapy. International collaboration allows findings to be pooled and applied more quickly around the world – a crucial advantage for every affected child.

A key element in this effort is the documentation of each child's disease course in a registry. All children with ACC should, in principle, be included. This registry collects data such as laboratory values, MRI scans, and observed side effects – essential information that helps researchers better understand ACC and improve future treatment strategies. Participation does not require any additional examinations or procedures and has no impact on your child's medical care.

In addition, your child may be eligible to participate in a clinical trial. In some cases, such a study may offer access to a promising new medication. These therapies are only considered after careful evaluation and based on encouraging results from similar conditions. If such a treatment might be suitable for your child, the medical team will explain all potential benefits, risks, and alternatives in detail. Your child will also be informed in an age-appropriate way and, if applicable, involved in the decision-making process.

Participation in registries, clinical trials, or the sharing of tissue samples is always voluntary. No matter what you decide, your child will receive the best possible care. However, by supporting this research effort, you are making a vital contribution to expanding knowledge about ACC – not only for your own child but for all children affected by this rare disease.



https://ensat.wildapricot.org/

Understanding Treatment – What to Expect

Individually Planned – Safely Delivered

The treatment of adrenocortical carcinoma (ACC) in children follows a structured and scientifically based approach. Treatment recommendations are guided by international guidelines developed from the latest research findings and many years of clinical experience. These guidelines provide coordinated treatment plans tailored to different disease courses and risk profiles.

The so-called first-line therapy – the initial treatment phase after diagnosis – typically involves surgery. In case of an advanced disease, chemotherapy and the drug mitotane are usually necessary. The goal is to remove the tumour as completely as possible, prevent recurrence, and eliminate any remaining cancer cells in the body. In some cases, it may also be necessary to supplement the treatment with radiation therapy or investigational therapies (e.g. immunotherapy).

The specific treatment measures used in each case depend on the individual disease situation and are carefully discussed within the interdisciplinary care team.
In the following section, you will find an overview of the treatment options, their role in the overall therapy process, and their potential benefits and side effects.

Treatment According to Disease Stage

In current treatment recommendations, the management of ACC is primarily based on the tumour stage at diagnosis. The most important prognostic factors are how far the tumour has spread and whether it can be completely removed.

Early Stages (Stage I and II)

If the tumour is still confined to the adrenal gland (Stage I: tumour ≤ 5 cm, Stage II: tumour > 5 cm), treatment usually consists of surgery. The affected adrenal gland is completely removed.

- Open surgery is generally recommended to ensure complete tumour removal with a "safety margin" (R0 resection).
- Laparoscopic (keyhole) surgery is only possible for small, well-circumscribed tumours, but is generally not recommended if malignancy is suspected.

After surgery, in certain risk situations (e.g. large tumour size, invasion of adjacent tissue, or incomplete resection), additional treatment with mitotane may be considered. This drug specifically targets adrenal cells and is intended to reduce the risk of recurrence.* If no risk factors are present—especially if the Ki-67 proliferation index is below 10%—close follow-up is usually sufficient.

*Mitotane is approved for the treatment of advanced or metastatic adrenocortical carcinoma. Its use in adjuvant setting is endorsed by guidelines, with individualised implementation.

Locally Advanced Stage (Stage III)

In this stage, the tumour has already invaded surrounding structures, such as fat tissue, lymph nodes, or large blood vessels.

- The goal remains complete tumour removal whenever possible. Surgery is technically demanding and may require resection of adjacent organs or vessel segments.
- As a rule, adjuvant treatment with mitotane is recommended after surgery to reduce the risk of recurrence.*
- In cases of high recurrence risk, mitotane may, in selected situations, be combined with chemotherapy (e.g. the EDP regimen: etoposide, doxorubicin, cisplatin). Risk factors include incomplete resection (R1/R2), lymph node involvement, vascular or organ infiltration, a high Ki-67 index (>10–20%), and large tumours.*

If the tumour cannot be completely removed at first, chemotherapy may sometimes be given along with mitotane before surgery (called neoadjuvant therapy) to shrink the tumour and make it removable.

*Mitotane is approved for the treatment of advanced or metastatic adrenocortical carcinoma. Its use in adjuvant setting is endorsed by guidelines, with individualised implementation.

Metastatic Stage (Stage IV)

If the tumour has already spread to distant organs (e.g. lungs, liver, or bones), a comprehensive multimodal treatment approach is required.

- Treatment usually begins with systemic therapy, consisting of mitotane and chemotherapy (EDP regimen: etoposide, doxorubicin, cisplatin).
- If, during systemic therapy, the primary tumour and metastases appear fully resectable, surgery may subsequently be performed.
- If the tumours do not respond adequately or continue to progress, other systemic therapies can be considered (e.g. chemotherapy, immunotherapies, targeted therapies, or a combination of these).

In addition, supportive treatments play an important role, for example in managing hormone-related symptoms (such as Cushing's syndrome) or alleviating other complaints. Especially in Stage IV, the disease course can vary greatly, so treatment is best managed by an experienced team of specialists who can regularly adapt therapy to the individual situation.

Surgery

The Central Role of Surgery in the Treatment of ACC

Surgery is a cornerstone of treatment for ACC and plays a decisive role in determining the patient's long-term outcome. The primary goal is complete tumour removal with a clear margin—referred to as an R0 resection. Only with such a complete resection, where no microscopic tumour cells remain, can the risk of recurrence be minimized and the chance of long-term survival be significantly improved. If microscopic tumour cells remain (R1 resection) or if the resection margin cannot be clearly assessed (RX), the prognosis worsens considerably.

In well-defined, non-metastatic tumours, a primary R0 resection is often feasible. However, if complete removal is not possible at diagnosis—due to tumour size, location, or local invasion—surgery is initially deferred. In these cases, neoadjuvant chemotherapy is usually administered over two to four cycles to shrink the tumour and improve the likelihood of a successful later operation. A biopsy is typically avoided in this context, as the diagnosis can often be reliably established through imaging and hormone analysis, and a biopsy carries the risk of tumour cell dissemination.

The importance of surgery within the overall treatment plan is well supported by evidence: studies show that when surgery is performed in a specialized centre, the risk of relapse is significantly reduced, and survival outcomes improve. For this reason, international guidelines—such as those from the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumours (ENS@T)—strongly recommend that surgery be carried out in high-volume centres with expertise in ACC. In paediatric cases, collaboration between an experienced adrenal surgeon from adult medicine and a paediatric surgeon may be beneficial to ensure the best possible surgical outcome. Careful planning and close interdisciplinary coordination among experienced specialists are essential for long-term treatment success.

SURGICAL PROCEDURES

An ACC tumour must be removed as completely as possible through surgery. There are different surgical methods for this. In most cases, an open operation is performed. In this procedure, the surgeon makes a larger incision in the abdomen to access and remove the tumour as safely and completely as possible. This approach is especially important when the tumour is large or has already grown into surrounding tissues.

In certain, rare cases—such as when the tumour is small and clearly defined—minimally invasive (so-called "keyhole") surgery may be possible. This laparoscopic technique involves only small incisions. However, it is only suitable in very experienced centres, as there is a risk that tumour cells may be left behind or spread within the body. Some hospitals also use robot-assisted techniques, which can allow for even more precise surgery. However, there is currently limited experience with these methods in the treatment of ACC.

Possible Complications

As with any major surgery, the removal of an ACC tumour carries certain risks. The specific complications that may occur depend, among other things, on the size of the tumour and whether it has grown into surrounding tissue.

General surgical risks include:

Bleeding	Injury	Infections
during or after the procedure	to nearby organs or structures, such as blood vessels, intestines, or the stomach	for example at the surgical site or within the abdominal cavity

In specialized centres, the risk of such complications is kept as low as possible through careful planning and the experience of the surgical team. Before the operation, a thorough consultation is held in which the treatment team explains the individual risks and the procedure in detail and answers all questions.

Chemotherapies

Chemotherapy is a treatment using medications that inhibit cell growth. These drugs, known as cytotoxic agents, interfere with the cell cycle in various ways. However, they affect not only cancer cells, as intended, but also other rapidly dividing cells in the body—such as blood cells, mucous membranes, and hair follicles.

Chemotherapy is usually given as a combination of different cytotoxic agents over several days, most often by infusion. To flush the drugs from the body and protect organs—particularly the kidneys—large volumes of fluids are typically administered alongside.

Depending on the child's age and the anticipated duration of treatment, a central venous catheter is usually required. This involves a minor surgical procedure to insert a catheter into a large vein. The external end may be accessed via a chamber under the skin (port system) or via an external line (Hickman or Broviac catheter). This catheter can also be used for blood draws, reducing the need for frequent needle sticks.

Between chemotherapy cycles, children can usually return home—unless complications such as infections make hospitalisation necessary. The number of chemotherapy cycles generally depends on the stage of the disease and the treatment response.

Standard Regimen: EDP

The most commonly used chemotherapy for ACC is called the EDP regimen, which combines three drugs:

Etoposide	Doxorubicin	Platin (Cisplatin or Carboplatin)
blocks cell division so that cancer cells cannot keep multiplying	damages the DNA of cancer cells, preventing them from growing	interferes with the DNA structure of cancer cells, which leads to their destruction

These three medications are usually given together in cycles, with rest periods in between to allow the body to recover. In addition to EDP, other drugs may be used in children with ACC, sometimes in combination or as alternatives depending on the situation.

Side Effects of Chemotherapy

Because chemotherapy inhibits cell growth, it affects not only cancer cells but also healthy cells. This leads to various side effects. Hair growth may stop, and hair may fall out. One of the most significant side effects is changes in the blood count. All blood components—red and white blood cells as well as platelets—can be reduced.

Red blood cells (erythrocytes)

These transport oxygen. If levels are too low, the child may feel weak, tired, have headaches or dizziness, or appear pale. If the haemoglobin (Hb) drops below a certain level or symptoms are severe, a red blood cell transfusion may be necessary.

White blood cells (leukocytes)

These protect the body from infections. During chemotherapy, the child is particularly vulnerable, especially when leukocyte counts are very low. Precautionary measures include:

- Avoiding contact with people showing signs of infection (e.g., flu, cough, fever)
- Avoiding large gatherings
- Informing your doctor immediately if the child has been exposed to contagious illnesses like chickenpox

Preventive measures often include antifungal mouthwashes to reduce the risk of fungal infections in the digestive tract and weekend antibiotics to prevent *Pneumocystis jirovecii* infections, which can lead to severe pneumonia. Despite precautions, infections can still occur and may require hospitalisation. Fever is often a warning sign and should be evaluated immediately.

Platelets (thrombocytes)

These help with blood clotting. Low platelet counts can lead to symptoms such as pinpoint skin bleeding (petechiae), frequent bruising, or nosebleeds. In such cases, consult your doctor. Platelet transfusions (thrombocyte concentrates) may be needed.

Many children experience nausea and loss of appetite during chemotherapy. These symptoms can often be reduced with preventive medication, but nausea may still persist for several days after treatment. Taste preferences may also change—previously preferred foods may become unappealing.

If the mucous membranes are affected (mucositis), the child may feel pain while eating or swallowing. If the intestinal lining is inflamed, diarrhea may occur.

Almost any organ system—especially the liver, kidneys, inner ear, and heart—can be affected by specific chemotherapy agents. As every child reacts differently, it is important to report any observations to the care team. Depending on the severity of side effects, the treatment plan may be adjusted.

Specific Side Effects of Individual Chemotherapy Agents

Etoposide (VP-16)

Common side effects include allergic reactions during infusion. The child is therefore monitored during administration (usually using a pulse oximeter). At high doses, skin irritation may occur—ranging from redness and peeling to blistering in severe cases.

Doxorubicin (and other anthracyclines)

These drugs can damage the heart muscle, especially at high doses. However, at the doses currently used, significant damage is rare. Heart function is monitored regularly using echocardiography—before, during, and after treatment ends. Urine may appear red during and shortly after the infusion due to the medication's color. This is harmless.

Platin (Carboplatin/Cisplatin)

These agents can impair kidney function. Cisplatin may also damage the inner ear and cause permanent hearing loss. Hearing is therefore checked regularly during treatment. Children should avoid loud noise (e.g., music with headphones) during and after cisplatin infusions. Nausea is also a common side effect.

Therapy with Mitotane

A unique aspect of treating adrenocortical carcinoma (ACC) is the use of mitotane. It is the only approved drug specifically for carcinomas of the adrenal cortex. Discovered in 1949, it has been used in patients with ACC since 1959. Mitotane is considered a standard systemic therapy for patients with adrenocortical carcinoma who require medical treatment. In recent years, it has also increasingly been used in patients whose tumours were completely removed but who have a risk of recurrence.*

Mitotane works in two main ways

- It destroys adrenal cancer cells (this is called the adrenolytic effect).
- It reduces the excess production of hormones such as cortisol, which occurs frequently with ACC tumours

This dual action can help control the tumour and its symptoms.

Significance of Mitotane in ACC Therapy

Mitotane is a key drug in the treatment of ACC and the only medicine specifically approved for this disease. It has been shown to provide significant clinical benefit in patients with advanced ACC that cannot be completely removed or has spread to other parts of the body (unresectable/ metastatic).

In the adjuvant setting—after complete tumour removal and with the aim of reducing or delaying the risk of the cancer coming back—numerous studies show that mitotane can significantly improve recurrence-free survival in patients with a high risk of relapse. Retrospective studies indicate a reduction in relapse risk of up to 30–40% and benefits in overall survival.
In patients with a low risk of relape, research has shown that adjuvant treatment with mitotane can be safely omitted without negatively affecting prognosis.*
Please speak with your doctor if you're unsure, and always follow their advice and treatment plan.

The duration of mitotane is determined individually—depending on risk profile, tumour stage, and tolerability. Because mitotane affects the hormonal system, close medical monitoring is essential. Cortisone replacement therapy is almost always required; in many cases, mineralocorticoid substitution is also necessary.

*Mitotane is approved for the treatment of advanced or metastatic adrenocortical carcinoma. Its use in adjuvant setting is endorsed by guidelines, with individualised implementation.

Administration and Monitoring of Blood Levels

Mitotane is taken in tablet form, preferably with high-fat food such as milk, chocolate, oil. Since side effects may be dose- and level-dependent, a slow dose escalation is often necessary. Target blood levels are 14–20 mg/L, which typically takes several weeks to achieve.

Your child may find the tablets hard to swallow. Talk to your doctor, they can guide you on the best approach. If your doctor gives you specific instructions, always follow their advice.

Blood levels are first checked after 2–3 weeks of treatment until the maintenance levels of mitotane, and then about every 4 weeks. Testing is done in specialized laboratories. Your treating physician will explain this procedure to you.

Important Safety Information for Parents Handling Mitotane

Mitotane is an effective medication used to treat adrenocortical carcinoma, but it is also classified as a toxic substance. As a parent or caregiver, it is crucial to take special precautions when handling this medicine. Always wash your hands thoroughly before and after giving the tablets to your child. If your child cannot swallow the whole tablet, speak to your medical team for advice. Always follow their instructions carefully and minimize direct contact with the medication.

Make sure that siblings or other children do not touch the medication, and always store it securely out of reach. Mitotane should be administered exactly as prescribed, and any missed or extra doses must be discussed with your healthcare provider. Safe handling is essential to protect both your child and everyone else in your home.

Side Effects and Management

Most side effects depend on the blood concentration of the drug but often improve over the course of treatment and usually disappear after discontinuation. One of the most significant effects involves the healthy adrenal gland: mitotane suppresses its hormone production—particularly the essential stress hormone cortisol—leading to adrenal insufficiency during the treatment phase. After treatment, adrenal function must be assessed before discontinuing hormone replacement therapy.

Hydrocortisone Replacement Therapy

During treatment with mitotane, the body's own cortisol production is suppressed and must be replaced with oral hydrocortisone tablets.

Hormone replacement usually begins within the first few weeks of mitotane therapy.

A typical daily dose is approximately 50 mg, as mitotane accelerates cortisol breakdown in the liver.

Important: Hydrocortisone must never be stopped abruptly, as this can lead to a life-threatening Addison (adrenal) crisis (see below).

Fludrocortisone Replacement Therapy

Due to impaired production of mineralocorticoids, electrolyte imbalances can occur. Blood sodium and potassium levels may fall or rise to life-threatening levels.

Regular blood tests help determine the need for fludrocortisone substitution (daily oral tablet therapy).

Other Common Side Effects

Gastrointestinal symptoms: loss of appetite, nausea, diarrhea

Treatment options include:

- Metoclopramide or Dimenhydrinate for nausea
- Loperamide for diarrhea

If symptoms persist, contact your doctor immediately. An urgent adjustment of the hydrocortisone dose or a temporary pause in mitotane therapy may be necessary.

Skin reactions

Occasional rashes, which usually resolve during the course of treatment.

Neurological side effects (less common, usually with high blood levels)

Dizziness, balance disturbances, speech issues, difficulty concentrating.

Caution: May impair the ability to drive or operate machinery.

Laboratory changes

Increased cholesterol and liver enzymes (e.g., GGT).

Mild leukopenia (reduced white blood cells).

Lower levels of sex hormones (may result in breast development or precocious puberty).

Possible thyroid hormones impairment.

In most cases, no interruption of therapy is required.

In cases of significantly elevated liver enzymes (e.g., bilirubin, AST, ALT exceeding three times the baseline), immediate medical consultation is necessary.

Important Notes

- Mitotane induces the liver enzyme CYP3A4, which accelerates the metabolism of many medications (e.g., antibiotics). Therefore, consult your doctor before taking any additional medications.
- If getting pregnant may be relevant for your adolescent daughter, please be aware that mitotane can seriously harm an unborn child. It is therefore essential to avoid any risk of pregnancy during treatment and for a period afterwards by using effective contraception. As mitotane may also affect fertility, it's important to discuss the possibility of preserving eggs with the medical team before starting therapy. For male adolescents, mitotane may also impair temporarily or permanently sperm production. It is also strongly recommended to discuss sperm preservation (cryopreservation) with the medical team before starting treatment.

Duration of Therapy

- The duration of mitotane treatment depends on the clinical response and tolerability.
- In an adjuvant setting mitotane is usually administered for at least two years. If well tolerated, treatment can be extended.
- Measures will be implemented to ensure safe drug use and prevent early discontinuation.

Long-Term Effects

Long-term effects—especially on neurocognitive development in children—are not yet sufficiently researched and are currently being studied. Initial clinical observations suggest that most acute side effects disappear after discontinuation or when mitotane levels decrease. However, lasting side effects may occur. In some cases, the remaining adrenal gland may not recover. Persistent reductions in physical resilience and neurological impairments have also been reported.

If you experience any of these effects or have any questions or concerns, please contact your treating physician promptly.

Mitotane and Addison Crisis – What You Need to Know

If your child is receiving treatment with mitotane, it's important to be aware of a serious side effect: adrenal insufficiency. This condition occurs when the body can no longer produce enough cortisol, a hormone that plays a vital role in regulating stress responses, blood pressure, blood sugar, and metabolism.

Mitotane specifically targets the adrenal cortex – the part of the adrenal gland that produces cortisol – and over time, it suppresses natural cortisol production. This effect is expected and often long-term. Therefore, patients on mitotane need a cortisol replacement therapy, and careful adjustments during times of illness or physical stress.

What Is an Addison Crisis?

An Addison crisis (also called adrenal crisis) is a life-threatening emergency caused by a sudden and severe lack of cortisol. Without enough cortisol, the body cannot respond to physical stress, and blood pressure can drop dangerously low, potentially leading to shock, unconsciousness, or even death if not treated quickly. Typical signs of a crisis include:

- Sudden and severe fatigue or weakness
- Dizziness or fainting
- Nausea, vomiting, or abdominal pain
- Fever
- Rapid heartbeat and low blood pressure
- Low blood sugar
- Confusion or drowsiness

What to Do in an Emergency

If you suspect an Addison crisis:

1. Immediately give the emergency injection of hydrocortisone or administer a rectal suppository if available and appropriate.
2. Call emergency services (112 in Europe or 911 in the US) and state clearly:
   "My child has adrenal insufficiency and is in adrenal crisis. Immediate intravenous hydrocortisone is required."
3. Present the medical emergency card and any medication list, if available.
4. Keep the person lying down, warm, and calm while waiting for professional help.

Emergency medication is essential to bridge the time until safe hospital treatment with intravenous hydrocortisone and fluid replacement can begin.

Preventing a Crisis – Stress Dosing with Hydrocortisone

Since mitotane suppresses cortisol production, your child will be on daily hydrocortisone tablets to replace what the body can no longer make. But in certain situations – like illness, fever, or injury – this dose must be temporarily increased to mimic the body's natural stress response. This is called stress dosing, and it is a key part of preventing adrenal crisis.

Your medical team will give you a personalised plan for your child, but general guidance includes:

- Double or triple the usual daily hydrocortisone dose at the first sign of:
  - Fever above 38°C (100.4°F)
  - Infections (including colds or flu-like symptoms)
  - Vomiting or diarrhea
  - Accidents or injuries
  - Surgical, dental, or other medical procedures
- If vomiting or inability to swallow tablets occurs, use the emergency injection or suppository immediately, and seek medical attention.

Return to the regular dose only once recovery is complete.

Be Prepared – Every Day

Adrenal insufficiency caused by mitotane is long-term, but with preparation, it can be safely managed. Make sure to:

- Carry an emergency hydrocortisone injection (or rectal suppository) at all times.
- Ensure you or other family members are trained in how and when to administer emergency medication for your child.
- Your child wears a medical ID bracelet or necklace indicating adrenal insufficiency.
- All family members carry your child's steroid emergency card at all times – this helps paramedics and doctors act quickly in case of an emergency.
- Make sure friends, school staff, and caregivers know about the condition and understand what to do in an emergency.

Adrenal insufficiency doesn't have to limit your life – but it does require attention and readiness. With the right replacement therapy, stress dosing, and emergency planning, you or your child can stay safe and well protected. If you ever have questions or concerns, don't hesitate to reach out to your care team.

Other Therapies

Other oral drugs, called steroidogenesis inhibitors (e.g., ketoconazole, metyrapone, and osilodrostat), are used to reduce the overproduction of cortisol.

Lastly, there are certain new drugs or different drug combinations that are not approved for use but being studied in clinical trials (e.g. immunotherapy and targeted therapies).

Targeted therapies aim directly at specific weak points or growth signals of the tumour cells, while immunotherapies work by activating the body's own immune system to attack the cancer. While surgery and chemotherapy are established standard treatments for ACC, these newer approaches are not yet part of standard care. They may be considered if chemotherapy is not sufficiently effective or in cases of relapse.

Current research includes experimental strategies such as:

- PD-1/PD-L1 inhibitors (e.g., Nivolumab, Pembrolizumab) that stimulate the immune system
- Multi-tyrosine kinase inhibitors (e.g., Cabozantinib) that block tumour growth signals
- Specific antibodies targeting genetic mutations
- Cell-based therapies such as CAR-T cell therapy

Whether such a treatment is suitable for your child must be evaluated carefully. Your care team will explain possible benefits and side effects based on the latest research.

Side effects of these drugs under investigation vary depending on the specific drug and may include fever, low blood pressure, fluid retention, autoimmune reactions, or nerve pain. These effects can result from immune system activation or interference with growth pathways. The exact side effect profile depends on the specific drug and will be discussed with you in detail beforehand.

Radiation Therapy

Radiation therapy is primarily used in high-risk situations and is not considered a standard treatment for ACC in paediatric care. However, it can be very effective—especially when the tumour cannot be completely removed or when individual metastases need to be treated. In such cases, radiation may be an important additional treatment option.

The radiation field is precisely calculated based on the extent of the tumour. Modern radiation techniques aim to minimize exposure to surrounding healthy tissue. Planning often includes marking specific spots on the skin.

During radiation sessions, the child must remain completely still for a short time. School-aged children can usually manage this without assistance; younger children may require daily sedation. Radiation is typically given once daily over a period of three to four weeks.

Depending on the location and dosage of the radiation, acute side effects may include:

- Skin redness
- Nausea
- Diarrhea
- Changes in blood counts

Because the type and severity of side effects depend heavily on the treatment area and radiation dose, they should be discussed in detail with the radiation oncologist in advance. Preventive measures may also be considered where appropriate.

Local Therapies

Local therapies are not part of the standard treatment for ACC. They may be considered in special situations, for example if surgery is not possible or to treat individual tumour sites in a targeted way. Whether such a treatment is suitable will be carefully evaluated by the medical team and discussed in detail with the parents. The goal of these procedures is to relieve symptoms and to influence the course of the disease.

Local chemotherapies include Transarterial Chemoembolization (TACE), which delivers medications directly to tumours and blocks their blood supply; local ablation techniques like Radiofrequency Ablation (RFA) or Microwave Ablation (MWA), which destroy tumours with heat; and nuclear medicine approaches using targeted radioactive substances, which are still experimental.

YOUR NOTES

General Recommendations

Sports and Leisure

The illness and its necessary treatments will place a considerable burden on both your child and your family, especially at the beginning. Time and energy will be consumed. For both you and your child, it is best to maintain as much normalcy as possible and to continue everyday activities whenever feasible.

Talk to your doctor about any special precautions that may need to be taken. If your child feels well, they can be active according to their needs and abilities. There is no need to insist on fixed rest periods unless medically advised. Naturally, there will be days—especially following chemotherapy—when your child feels very tired and needs rest. That is a normal response to the treatment. On other days, your child may feel more energetic, and it is important to encourage participation in normal activities such as school, hobbies, and physical exercise. This helps them reconnect with daily life and better cope with the treatment.

Physical activity, in particular, has been shown to improve treatment tolerance and reduce side effects. For this reason, many paediatric oncology units now offer sports medicine programmes alongside therapy.

Nutrition

A balanced diet is important throughout the course of treatment. Please consult your medical team to find out whether there are any specific dietary restrictions. Special diets are only necessary in exceptional cases. In some instances, medication side effects require certain precautions—particularly avoiding grapefruit juice (due to drug interactions) and raw meat products (because of infection risk).

Vaccinations

If your child is scheduled to receive vaccinations, consult your doctor to clarify whether and when these can be administered during the course of treatment. In some cases, the spleen must be surgically removed (splenectomy), which initially compromises the immune system. In such situations, your doctor will ensure that your child receives comprehensive vaccination coverage (e.g., against pneumococci).

Other Medications

Children undergoing cancer treatment should not take any additional medication without prior approval from the oncology team. Some drugs that are generally considered safe—such as aspirin—should be avoided during treatment due to an increased risk of bleeding. In the event of fever or pain, always inform your medical team so that the appropriate course of action can be discussed.

When to Contact Your Medical Team Immediately

Please contact your doctor or treatment team right away if your child experiences any of the following:

- Fever or other signs of infection, or if they simply appear unwell
- Contact with measles or chickenpox, or symptoms of any contagious illness
- Persistent headaches or other unexplained pain
- Difficulty walking or other motor impairments
- Painful urination or bowel movements
- Red or swollen areas on the body
- Vomiting not clearly linked to chemotherapy
- Vision problems, such as double vision or blurriness
- Signs of bleeding, such as nosebleeds, blood in the urine, stool, or vomit, or frequent bruising
- Deep sadness, depression, or other noticeable behavioural changes
- Treatment-related side effects such as mouth inflammation, constipation (no bowel movement for more than two days), diarrhea, or numbness in fingertips

You should also inform your doctor if your child is scheduled for any vaccinations or dental procedures to allow for proper coordination.

Explaining the Diagnosis – Honest, Sensitive, and Age-Appropriate

Perhaps the most difficult task for you as parents is to explain the serious diagnosis and the upcoming, burdensome treatment to your child in a way that helps them understand the significance of the new situation and cope with it – especially when you are struggling with your own emotions. You are not alone in this process. You can turn to the treatment team at any time if you need support.

Often, the first instinct is to protect the child from one's own fearful perspective – to avoid talking about the illness and the implications of the diagnosis altogether. But you likely sense it already: your child – regardless of their age – has long realized that something is wrong. Conversations with doctors, encounters with hospital staff, and their own discomfort speak for themselves.

That's why it is important to be honest with children and to include them in conversations. As their main source of trust and emotional security, you carry the responsibility of explaining the illness to your child – in an age-appropriate way – answering their questions sincerely, and supporting them in their fears and worries. Mutual trust and openness help the entire family navigate this difficult path and offer a sense of stability and safety.

Talking to your child about such a serious topic is easier said than done – especially when the diagnosis is still difficult for you to accept. There is no "perfect" way to talk about cancer. As a family, you must find what feels right for you. Paediatric oncology wards usually have picture books and materials that can help open the topic in a playful and gentle way.

Younger children can feel the symptoms of the illness, but may not yet understand what "cancer" means. A simple explanation is often enough. For example, you could say:
"The pain in your belly is coming from a tumour that the doctor found during the tests. A tumour is like a little ball that can grow if you don't do anything. You'll now get medicine to help make the tumour go away. We hope it works – and then your belly will feel better again."

Brochure to Talk with Your Child About ACC

This brochure is designed to help you talk to your child about their ACC diagnosis. Using a comic-style format, it explains complex medical facts in a simple and child-friendly way.

The brochure was developed by ESTEVE in collaboration with ENS@T and Let's Cure ACC. It is available through this QR code

Children of primary school age have often heard the word "cancer." They may know that cells can spread in the body, and they might even be aware of someone who died from cancer in their circle of family or friends. You cannot prevent your child from being confronted with the word. On the ward, they will see other children who look different, overhear conversations, and might even be directly asked about their illness.

It is therefore neither possible nor advisable to hide the truth from your child. It's better if they are given information about the situation early on, in a way they can understand. Your child should know that they have a type of cancer, that cancer in children is often very different from cancer in adults, and that the doctors are using very strong medicine to try to cure the disease.

Teenagers can often grasp the full implications of a diagnosis just as adults do. That can make it even harder for parents to speak openly about the illness and their own fears. But the more openly you deal with the situation, the more trust and reassurance you can give your child. It is often helpful not to try to protect adolescents by keeping things from them, but instead to involve them in medical conversations. Secrecy or the sense of not being told something often causes more insecurity than the actual information would.

Not everything has to be said in the first conversation. Take time, in a private and calm setting, to talk with your child about your concerns and theirs. Regardless of your child's age, it is important to prepare them well for upcoming procedures and examinations: describe painful procedures as painful, and be honest when something will not hurt. Assuring them that you will be there, and that it's okay to complain or be upset if something hurts, helps many children cope better with the situation.

The Diagnosis Affects the Whole Family

The diagnosis was certainly a shocking experience for you. Since the causes of tumour development are generally unknown, it is natural to look for someone or something to blame – sometimes even oneself. Many parents believe they should have acted more quickly when their child first began feeling unwell.

Even though you may be thinking a lot about possible causes of the illness, current scientific understanding suggests that nothing you did or failed to do as parents caused this disease. While some types of cancer in adults are partially linked to external factors such as smoking, no such connection is known for childhood adrenocortical carcinoma. There is also no evidence that events during pregnancy caused the condition.

However, it is known that in very rare cases, adrenocortical carcinomas or other types of cancer can occur more frequently within families. Researchers are working to identify genetic changes that may be linked to this. Some genes or genetic defects have already been associated with an increased risk of cancer. For this reason, you may be advised to undergo genetic counselling. This can help better assess the potential risk within your family. In addition, targeted preventive check-ups for affected patients or family members can help detect tumours at an early stage – with the goal of avoiding or shortening burdensome treatments.

Everyone copes with such a diagnosis in their own individual way. It may help to accept, at least to some degree, your partner's thoughts or reactions – even if they seem hard to understand at first. In such moments, a silent gesture of support may be enough for some parents; sometimes, reaching out, talking, and consciously making time for one another – despite the many hospital visits – can also help. Sharing your worries with one another can ease the emotional burden – and after the tears, new hope often begins to emerge. Crying can be a great relief and deserves its space.

Talk to other affected parents, to doctors, nurses, or the hospital's psychosocial support team about your thoughts and feelings. Don't hesitate to ask for support – whether professional or from your personal circle of family and friends. You don't have to carry the burden alone.

Especially during a time when you are still trying to process the devastating news, it can be overwhelming to repeatedly explain everything to concerned relatives. Be honest with yourself and clearly say if you're not ready to talk about it. The more openly you communicate your needs, the easier it will be for others to support you and be there when you need them.

If your child already attends a daycare facility, kindergarten, or school, it's a good idea to inform them about the situation and involve them. Support from childcare centres, schools, or even a sports club can be emotionally important and empowering for your child. Returning to everyday life later on will be easier if those around you have already walked part of the journey with you.

Staying Strong as a Family

Siblings often imagine frightening scenarios about what might be happening to the sick child. It can be very helpful to maintain close contact with them and, if possible, allow them to visit the hospital. This gives them a chance to keep their strong bond with their sick sibling and see for themselves what is really going on. They will often discover that, despite the treatments, there are cheerful children there – and that other families are also facing similar challenges. This can make it easier for you as parents to explain the situation to the siblings in an empathetic and understandable way.

Age-appropriate information is also important so that siblings do not live in fear of catching the disease themselves or developing it too. It is not uncommon for siblings to feel guilty, imagining that the illness might somehow be their fault. These thoughts should be addressed openly and proactively.

Another important point: as parents, you cannot be in two places at once. Naturally, the sick child receives special attention – both in the hospital and at home. If your child receives small gifts or extra care from you or visitors, it's important not to forget the siblings. Make a conscious effort to also give your other children dedicated time and undivided attention.

Try to stay involved in your healthy children's lives, even from the hospital. Include them in everyday family life whenever possible. Especially when you are at home, strive to keep things as normal as possible. Stick to your usual family rules – they provide structure and a sense of security, which will make it easier for everyone to return to everyday life later on.

Accept help – and don't hesitate to ask for it. Try to simplify your family's daily routine as much as possible. If someone offers to pick up your child from school, drive you to the hospital, or run errands, don't be afraid to say yes. This will give you time and energy for the things that matter most right now.

Also, consider reaching out to local support services for help. All of this will benefit your children and ease the burden on you. The psychosocial support team at your hospital will also be there to advise and assist you.

And above all: take a little time each day that is not devoted to worrying about the illness. It will do you and your child good to create small moments of calm and joy – opportunities to regain strength and simply be carefree for a while.

Connect with Other Families

Sharing experiences with others in similar situations can provide new strength and valuable support—because no one understands the impact of the diagnosis and therapies on your family better than other affected families. Paediatric adrenocortical carcinoma (ACC) is extremely rare, which can make it difficult to find other parents of young patients.

You may meet other families in specialized clinics and start a conversation there. You can also inform your medical team of your interest in connecting—they may be able to help establish contact with others.

The international patient organization Let's Cure ACC also offers support. Let's Cure ACC was founded in 2021 by patients for patients and is happy to assist you with your concerns.

You can find helpful information about the disease at www.letscureacc.com.

Glossary

Adenoma: A benign tumour of the adrenal cortex.

Adjuvant (adjuvant therapy): Additional treatment after complete tumour removal, when the patient is initially considered tumour-free. The goal is to destroy any remaining, invisible cancer cells and thereby reduce the risk of recurrence.

Adrenal insufficiency: Inadequate hormone production by the adrenal cortex, often as a result of treatment, requiring hormone replacement therapy.

Adrenocortical carcinoma (ACC): A rare malignant tumour of the adrenal cortex that can occur in both children and adults.

Beckwith-Wiedemann syndrome (BWS): A rare genetic condition associated with overgrowth in childhood. Typical features include an enlarged body or body parts, an unusually large tongue, and an increased risk of certain tumours, including paediatric ACC.

Biopsy: Removal of tissue for microscopic examination to determine the type of tumour.

COG (Children's Oncology Group): An organization that develops treatment protocols for paediatric tumours, including ACC.

Computed tomography (CT): Imaging technique using X-rays to visualize tumours and metastases.

Cushing's syndrome: A condition caused by excessive cortisol production, leading to symptoms such as weight gain and high blood pressure.

Cytostatics: Drugs that inhibit cell growth and are used in chemotherapy.

ENS@T: European Network for the Study of Adrenal Tumours.

ENS@T-PACT: PACT means Paediatric Adrenocortical Tumour Registry and is a special registry within ENS@T that focuses on adrenocortical tumours in children and adolescents. The aim is to collect data internationally, improve treatment, and develop new therapies.

Fludrocortisone: A synthetic mineralocorticoid used to treat disorders of salt balance.

Histopathology: Examination of tissue samples under the microscope to detect disease-related changes. It is based on histology, the study of the normal structure and organization of tissues. In cancer diagnosis, histopathology is used to determine whether a tumour is benign or malignant and to describe its specific characteristics.

Hormone activity: The ability of a tumour to produce hormones that can lead to specific clinical symptoms.

Hydrocortisone: A synthetic cortisol used as replacement therapy in adrenal insufficiency.

Hypothyroidism: Underactive thyroid function; a possible consequence of therapy.

IC-PACT: Stands for International Paediatric Adrenocortical Tumour Registry. It is a global registry for paediatric adrenocortical tumours. The purpose is to combine data from many countries, improve understanding of the disease, optimize treatment, and enable international research studies.

Immunotherapy: Treatment that activates the immune system to fight cancer (e.g. PD-1/PD-L1 inhibitors).

Let's Cure ACC: An international patient organization for people with ACC and their families. The initiative provides information, support, networking, and advocacy, and collaborates closely with doctors and researchers to improve care and advance ACC research worldwide.

Li-Fraumeni syndrome: A genetic condition that increases the risk of certain cancers, including ACC.

Local Ablation Techniques: In these methods, the tumour is destroyed directly using special probes. Heat is often applied, for example with radiofrequency ablation (RFA) or microwave ablation (MWA). These techniques are mainly used for single metastases in the liver or lungs.

Local Chemotherapies: In a procedure called Transarterial Chemoembolization (TACE), medications are delivered directly into the tumour through a blood vessel. At the same time, the tumour's blood supply is blocked so that the cancer cells receive fewer nutrients. This procedure is mainly used for metastases in the liver. In some specialized centres, other regional methods are also available, where a high dose of chemotherapy is delivered specifically into the liver.

Magnetic resonance imaging (MRI): Imaging technique using magnetic fields to provide detailed images of soft tissues.

Metastasis: The spread of cancer cells from a primary tumour to other parts of the body.

Mitotane (Lysodren): A drug used to treat ACC that inhibits hormone production and targets tumour cells.

Molecular genetic analysis: Examination of tumour tissue for genetic alterations to better assess prognosis and ideally personalize treatment.

Neoadjuvant (neoadjuvant therapy): Treatment that is given before surgery, while one or more tumours are still present. The aim is to shrink the tumour(s), make surgery easier or more successful, and to treat possible microscopic spread of cancer cells at an early stage.

Neoplasm: An abnormal and uncontrolled growth of tissue in the body caused by changes in cells. Neoplasms can be benign (non-cancerous) or malignant (cancerous).

Nuclear Medicine Approaches: Research centres are also studying radioactive substances that can be delivered directly into the tumour or linked to antibodies. However, these treatments are still experimental.

Positron emission tomography (PET): Imaging technique for visualizing metabolic activity, often combined with CT (PET/CT).

Proliferation index Ki-67: A measure of tumour cell growth activity; often relevant for prognosis.

Psychosocial service: Support services for patients and families to help manage emotional distress and provide guidance on social and legal matters.

Pubertas praecox: Premature onset of puberty.

Radiotherapy: Use of ionizing radiation to destroy cancer cells.

Recurrence: Return of a tumour after treatment.

Resection status: Describes whether a tumour has been completely removed during surgery and whether the surgical margins are free of cancer cells. The categories are: R0 (tumour completely removed, margins tumour-free), R1 (microscopic cancer cells remain at the margins), R2 (visible tumour tissue left behind), and RX (it cannot be assessed whether tumour remains are present).

Staging: Classification system for describing the extent of tumour spread (e.g. localized or metastatic).

Steroids (steroid hormones): Steroids are a specific group of hormones that are made from cholesterol. They include cortisol, aldosterone, and the sex hormones (androgens, oestrogens, progesterone). Steroids regulate many vital body functions, such as metabolism, blood pressure, and sexual development.

TP53 gene: A tumour suppressor gene; mutations are associated with cancer development.

Virilization: Masculinization in girls or early puberty in boys due to excess androgen production.

Zona glomerulosa: The outermost layer of the adrenal cortex, primarily responsible for the production of aldosterone, a mineralocorticoid hormone.

Zona reticularis: The innermost layer of the adrenal cortex, primarily responsible for producing adrenal androgens and, to a lesser extent, oestrogens.

Zona fasciculata: The middle layer of the adrenal cortex. It is primarily responsible for the production of glucocorticoids, such as cortisol.

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