

# A&I

## ANÄSTHESIOLOGIE & INTENSIVMEDIZIN

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**Cornelia de Lange syndrome**

**Costello syndrome**

orphan**a**nesthesia

a project of the German Society  
of Anaesthesiology and Intensive Care Medicine

**SUPPLEMENT NR. 4 | 2021**

## OrphanAnesthesia –

### ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter [www.ai-online.info](http://www.ai-online.info) veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

## OrphanAnesthesia –

### a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommendations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via [www.ai-online.info](http://www.ai-online.info). As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

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# orphananesthesia

## Anaesthesia recommendations for **Costello syndrome**

**Disease name:** Costello syndrome

**ICD 10:** Q87.8

**Synonyms:** FCS syndrome, Fasciocutaneoskeletal syndrome. Significant phenotypical overlap with CFC (cardiofaciocutaneous syndrome) and Noonan syndrome.

**Disease summary:** Costello syndrome (CS) is a rare disorder (so-called RAS-opathy, see below), affecting up to 300 people worldwide. First described by Dr Jack Costello in 1977, the syndrome is characterised by failure to thrive (FTT), poor feeding, short stature, developmental delay, distinctive facial features, excessive loose skin, cardiac abnormalities, and an increased risk of tumour development.

RAS is a family of genes coding for small GTPases and includes amongst others HRAS. The HRAS gene is a proto-oncogene, which forms part of the MAPK (mitogen activated protein kinase) signalling pathway. Up-regulation of this signalling pathway causes unopposed cell growth, causing tumour predisposition. The MAPK pathway is also the site of mutations causing both CFC and Noonan syndrome.

CS can be caused by a number of mutations in the HRAS gene. Most mutations do occur de novo, but there is some evidence that a minority are inherited in an autosomal dominant manner.

Patients with CS are born large for gestational age, and there is a strong association with polyhydramnios and preterm labour. Growth later slows due to feeding difficulties. Head circumference is affected to a lesser degree than height and weight, which gives rise to relative macrocephaly. Growth Hormone (GH) deficiency can cause neonatal hypoglycaemia, and contributes to growth retardation.

The disease is characterised by distinctive facial features including downslanting palpebral fissures, epicanthic folds, ptosis, flattened nasal bridge (hypertelorism), low set ears, thick lips, macroglossia and short neck. Facial features become increasingly coarse with age, hair thins and patients begin to look older than their biological age. They are often hypotonic, adopting a hyperextended arched posture. They have increased ligamentous laxity, and deep palmar and plantar creases. They also have excessive loose soft tissue particularly around the hands but this feature, despite being one of the most classical features of CS, doesn't manifest until after infancy, making the diagnosis difficult in the first year of life. Scoliosis, hip dysplasia and club foot are present frequently.

Cardiac involvement is a common feature of CS and may comprise congenital pulmonary stenosis, hypertrophic obstructive cardiomyopathy (HOCM) and supraventricular arrhythmias. Latter are typically multifocal, may occur independently of cardiomyopathy and may cause sudden cardiac death in patients with CS.

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Neurologic deficits may include nystagmus, hypotonia, epilepsy and cognitive delays. Expressive language is particularly affected. Structural brain abnormalities may include relative ventriculomegaly, macrocephaly, syrinx, cerebellar tonsillar herniation and posterior fossa crowding which may require ventriculostomy or a ventriculoperitoneal shunt.

Dysphagia and gastro-oesophageal reflux may be present. Excessive tissue may result in abnormalities of the glottis aperture. Laryngeal papillomas have been reported. Obstructive sleep apnoea is a common feature.

The papillomata that are typical of CS occur at bodily openings, but develop only in later childhood making the distinction between CS, CFC and Noonan syndrome difficult in infancy.

As a result of the unopposed activation of the MAPK pathway, patients with CS have an increased risk of tumour formation. Typical are rhabdomyosarcomas, while neuroblastomas and bladder transitional cell carcinomas also may occur.

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Medicine is in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)

### Typical surgery

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Typical surgeries undertaken in patients with CS include excision of papillomata, adenotonsillectomy, bladder tumour resection, herniotomy, Achilles tendon lengthening and tenotomy, hip reconstructive surgery, foot surgery and spinal fusion/scoliosis correction. Common diagnostic procedures will include magnetic resonance imaging (MRI), oesophago-gastroduodenoscopy (e.g. for a feeding tube), recto-sigmoidoscopy and bronchoscopy.

### Type of anaesthesia

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Because CS is such a rare condition, there is a scarcity of literature regarding the anaesthetic management of these children. In the few case reports that exist, all procedures necessitated general anaesthesia with endotracheal intubation. In one, gastro-oesophageal reflux required a rapid sequence induction, while in the others anaesthesia was achieved by gas induction with sevoflurane. There is one case report in the literature of a cardiac arrest on induction of a child with CS in whom suxamethonium precipitated bradycardia progressing to asystole. Even though data are scarce, we recommend the use of a non-depolarising muscle relaxant where possible.

The few case reports which discuss anaesthetic technique in children with CS describe both IV and inhalational induction without incident. Anaesthesia was maintained in all cases with sevoflurane, and nitrous oxide was also used in the majority of cases. Both classes of non-depolarising muscle relaxants were used successfully, and where appropriate a nerve block was performed (ilio-inguinal/ilio-hypogastric block in a child having orchidopexy).

### Necessary additional pre-operative testing (beside standard care)

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Due to the predisposition to obstructive sleep apnoea, these patients should ideally have a sleep study, as well as facilities put in place for safe peri-operative care. In addition, there is a tendency to difficult intubation, both due to laxity of laryngopharyngeal structures and to the combination of macrocephaly, macroglossia and short neck. A comprehensive airway assessment should be undertaken where possible.

Older children with progressive kyphoscoliosis may undergo spinal fusion and therefore should routinely have pre-operative lung function tests to assess the degree of restrictive lung disease.

Cardiac involvement is common. Possible pulmonary stenosis, HOCM or supraventricular tachycardias must be investigated. All patients should have a pre-operative ECG and Echocardiography, and cardiology input where necessary to optimise medical management.

If the sleep study or history suggests central apnoea, or if there are other findings by history of exam to suggest posterior fossa crowding, additional evaluations may be needed prior to anaesthesia given the risk for cerebellar tonsillar herniation. A history of poor feeding, bulbar weakness, cranial nerve palsies or headaches suggests compression of the brainstem. In these patients, MRI of the brain and spinal cord (to evaluate for syrinx) should be obtained. Neurosurgical consultation may be required for posterior fossa decompression, ventriculostomy or shunt placement.

Notably, Costello syndrome is a progressive disorder. Therefore, if a patient has previously had normal neuro-imaging or cardio-imaging, this does not preclude development of new

structural abnormalities, and repeated MRI or echocardiography should be considered if the patient's exam or interim history are concerned.

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#### **Particular preparation for airway management**

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As previously described, the physical features of CS increase the risk of a difficult intubation. This includes macrocephaly, macroglossia, short neck, airway papilloma and tonsillar hypertrophy. Mouth opening is usually unaffected.

An increased incidence of obstructive sleep apnoea in children with CS combined with tracheomalacia is likely to cause some degree of airway obstruction on induction.

Children with CS have a tendency towards an excess of tracheobronchial secretions, and premedication with an antisialagogue must be weighed against cardiac side effects.

It is also of note that there is an increased incidence of choanal atresia in patients with CS, and therefore nasal intubation should be undertaken judiciously.

Equipment for the management of a difficult airway is obligatory and fibre-optic intubation has to be considered routinely. Video-laryngoscopy may be beneficial in some cases.

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#### **Particular preparation for transfusion or administration of blood products**

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There is no known link between CS and bleeding tendencies.

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#### **Particular preparation for anticoagulation**

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None reported.

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#### **Particular precautions for positioning, transportation and mobilisation**

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There are several orthopaedic manifestations of CS which are relevant for both peri-operative patient positioning, and post-operative mobilisation. These are scoliosis, kyphosis, ulnar deviation of the wrist, elbow and shoulder contractures, hip dysplasia, tight Achilles tendons, foot deformities, and osteoporosis/osteopaenia. All these can make patient positioning technically difficult, and painful. They also increase the risk of pressure sore development, unless meticulous attention to detail is adhered to when positioning the anaesthetised patient. This is complicated by hypotonia and ligamentous laxity, which can make malpositioning more likely.

Post-operatively, both pain and pre-existing deformities (predominantly lower limb) as well as hypotonia, make mobilisation a multidisciplinary problem. Poor or delayed mobilisation predisposes the patient to complications such as atelectasis and lower respiratory tract infection, and thromboembolism.

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### Interactions of chronic disease and anaesthesia medications

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Patients may receive antiepileptics and stimulants or antidepressants for behavioural disorders. Induction of or competition in metabolic pathways has to be taken into consideration with drug dosing in CS.

Growth hormone replacement has been used in some children with CS. It may improve bone density in cases of osteopaenia/osteoporosis, however, it may lead to cardiac (left-ventricular) hypertrophy and worsen pre-existing HOCM.

There is an association between CS and hypothalamic-pituitary-adrenal (HPA) axis dysfunction (hypothyroidism, hypopituitarism, hypoadrenalism), however, the small numbers of children with CS mean that it has not been fully elucidated. The use of anaesthetic drugs that interfere with the HPA axis, such as etomidate, has to be questioned.

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### Anaesthetic procedure

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General anaesthesia (GA) over regional blocks has been most commonly described. Both intravenous and inhalational inductions have been undertaken successfully in patients with CS. An antisialagogue to minimise secretions must be weighed against its cardiac side effects. Sedatives for premedication must be avoided. Airway obstruction on induction is common and may be relieved with placement of an oropharyngeal airway. Facilities should be made available for difficult intubation. A non-depolarising muscle relaxant should be used in preference to a depolarising muscle relaxant where possible. (Bradycardia and asystole have been reported with the use of suxamethonium.) Acceleromyometry is strongly recommended. Maintenance of anaesthesia may include TIVA or volatiles such as sevoflurane, with or without the addition of nitrous oxide. There are no data to suggest limitations to opioid analgesia other than OSA considerations. Anti-emetics should be used carefully with respect to cardiac anomalies.

The feasibility of peripheral nerve blocks has to be evaluated individually, given the anatomic deformities. Ultrasound guidance is recommended.

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### Particular or additional monitoring

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Non-invasive monitoring is the mainstay for anaesthesia in patients with CS. It is prudent to consider invasive pressure monitoring in cases of cardiac anomalies. Monitoring should continue into the post-operative phase for a period of at least 24 hours.

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### Possible complications

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Respiratory compromise must be anticipated and avoided. Prepare for a difficult airway scenario to avoid a "cannot intubate, cannot ventilate" situation.

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### Post-operative care

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Routine post-operative care should include monitoring for a period of at least 24 hours under high-dependency conditions as respiratory distress may occur. Patients with CS are likely to develop stridor in the post-operative phase, due to choanal atresia, laryngotracheomalacia and copious secretions. They require frequent suctioning to clear secretions and maintain adequate oxygen saturations and normal respiratory rates and patterns. Meticulous care should be taken when positioning patients to avoid development of pressure sores.

In cases of GH deficiency, patients are prone to hypoglycaemia due to hyperinsulinaemia or increased insulin-like effects. Blood glucose levels should be checked and frequently in the peri-operative period.

Feeding difficulties are a classic feature of CS and many patients will be fed enterally, or by a combination of oral and enteral feeds. It is important to re-establish feeding early in the post-operative course.

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#### **Disease-related acute problems and effect on anaesthesia and recovery**

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As a last resort in a “cannot intubate, cannot ventilate” situation, an emergency airway puncture-set must be at hand.

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#### **Ambulatory anaesthesia**

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Because of the expectably difficult airway in patients with CS, the needed additional devices and necessary prolonged post-operative supervision, it cannot be recommended to perform general anaesthesia under ambulatory conditions or outside a major anaesthesiological department.

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#### **Obstetrical anaesthesia**

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There are no obstetric case reports of patients with CS.

Pregnancy with a foetus with CS is often complicated by a polyhydramnios, and LGA birth-weight (large for gestational age). Literature suggests an increased incidence of pre-term labour. Hypoglycaemia is a significant concern in the early neonatal period, as is poor feeding and FTT.



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## Further information:

The Costello Syndrome Family Network (USA); URL: [www.costellosyndromeusa.org](http://www.costellosyndromeusa.org)  
Costello Syndrome Support Group (UK); URL: [www.costellokids.com](http://www.costellokids.com)

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