orphanaesthesia

Anesthesia recommendations for

Costello syndrome

Disease name: Costello syndrome

ICD 10: Q87.8

ORPHAcode: 3071

Synonyms: HRAS-related Costello syndrome; Significant phenotypic overlap with cardiofaciocutaneous syndrome and Noonan syndrome

Disease summary: Costello syndrome (CS) is a rare multisystem RASopathy caused by activating germline variants in HRAS. It is characterized by prenatal overgrowth and polyhydramnios, postnatal failure to thrive, severe feeding difficulties, short stature, developmental delay, hypotonia, distinctive craniofacial features, loose skin, musculoskeletal abnormalities, cardiac disease and tumor predisposition [1-3]. Phenotypic overlap with other RASopathies is common, particularly in infancy; molecular confirmation is important whenever the diagnosis is uncertain [2,3].

The main perioperative risks are cardiac, airway/respiratory, neurologic/spinal and metabolic-nutritional. Cardiovascular involvement is frequent and may include hypertrophic cardiomyopathy (HCM), congenital heart disease, pulmonary valve stenosis and atrial tachyarrhythmias; disease may be progressive or recur after apparently reassuring earlier assessment [1,2,4]. Airway and respiratory problems may include macrocephaly, short neck, relative macroglossia, redundant upper-airway tissue, papillomata, tonsillar/adenoidal hypertrophy, laryngomalacia, tracheobronchomalacia, increased secretions, aspiration and obstructive or central sleep apnea [2,5,6]. Neurologic and spinal problems may include posterior fossa crowding, Chiari I malformation, syringomyelia, tethered cord, scoliosis and kyphosis. Severe feeding problems, gastro-esophageal reflux, dysphagia, tube feeding and hypoglycemia are also clinically relevant for anesthesia planning [2,3,7-10].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.

Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.

Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANESTHETIC TECHNIQUE**	Treat the airway as potentially difficult and potentially obstructive. Anticipate difficult mask ventilation and/or intubation. Nasal intubation should be approached cautiously because choanal narrowing or atresia may be present.
B	**BLOOD PRODUCTS (COAGULATION)**	No syndrome-specific bleeding tendency is known.
C	**CIRCULATION**	Assume relevant cardiac risk until recently excluded. Important problems include HCM, pulmonary valve stenosis or other congenital heart disease, atrial tachyarrhythmias and possible progression after earlier normal studies.
D	**DRUGS**	Use non-depolarizing neuromuscular blockers and avoid succinylcholine. Sedative premedication must be titrated carefully in obstructive sleep apnea.
E	**EQUIPMENT**	Difficult-airway equipment.

Typical surgery and procedures

Typical procedures include excision of papillomata, adenotonsillectomy, airway endoscopy/bronchoscopy, dental procedures, gastroscopy, feeding-tube placement or revision, recto-sigmoidoscopy, herniotomy, orchidopexy, bladder tumor resection or surveillance, Achilles tendon lengthening, foot or hip surgery, spinal fusion/scoliosis surgery and MRI or other imaging requiring sedation or anesthesia [2,9,10].

Type of anesthesia

General anesthesia is the most frequently reported technique in CS. Published cases describe both inhalational and intravenous induction, use of sevoflurane or total intravenous anesthesia, non-depolarizing neuromuscular blockers and selected peripheral nerve blocks [11-15]. There is no proven syndrome-specific advantage of either inhalational or intravenous induction; the choice should be guided by cardiac status, aspiration risk, anticipated airway difficulty and procedure type.

A supraglottic airway may be reasonable for short, low-risk procedures in carefully selected patients. Endotracheal intubation is usually preferable when reflux, dysphagia, aspiration risk, airway surgery, longer surgery, major surgery or uncertain ventilation is present. Regional

anesthesia is not contraindicated per se but is limited by anatomy, cooperation, cardiac physiology and the need for reliable perioperative monitoring [11-15].

Necessary additional preoperative testing (beside standard care)

Cardiac assessment: A recent 12-lead ECG and echocardiography should be available before anesthesia. Holter monitoring, telemetry or formal cardiology review is advised if there is known HCM, congenital heart disease, arrhythmia, palpitations, syncope, poor exercise tolerance, abnormal examination or no recent cardiac assessment. Apparently resolved HCM or arrhythmia does not eliminate the need for later surveillance [2-4].

Airway and respiratory assessment: Actively ask about snoring, witnessed apnea, stridor, airway obstruction during sleep or sedation, recurrent infections, secretion problems, aspiration, previous difficult mask ventilation or intubation, tracheo-/laryngomalacia and prior bronchoscopy or polysomnography. Polysomnography should be considered when symptoms suggest clinically relevant sleep-disordered breathing or when postoperative airway compromise would alter perioperative planning. Lung function testing is useful in older children or adults with significant kyphoscoliosis, chronic lung disease or planned spinal surgery [2,5,6,9,10].

Neurologic and spinal assessment: Routine MRI before every anesthetic is not evidence-based. However, CS is progressive, and a low threshold for updated brain/spine imaging and neurology or neurosurgery review is appropriate with central apnea, bulbar symptoms, dysphagia out of proportion, new vomiting or headaches, gait change, new weakness, rapidly progressive scoliosis, bladder dysfunction or concern for Chiari malformation, syringomyelia, tethered cord or cervicomedullary compression [2,3,7,9,10].

Feeding, reflux and aspiration risk: Dysphagia, gastro-esophageal reflux, impaired gastric motility, aspiration history and feeding-tube dependence should be documented. Previous swallow study, aspiration pneumonia, fundoplication, gastrostomy or gastrojejunal/jejunal feeding may materially change the induction plan and postoperative feeding strategy [2,3,8].

Endocrine and glucose risk: Check point-of-care glucose on the day of surgery in infants and young children and in any patient with previous hypoglycemia, hyperinsulinism, growth-hormone deficiency, adrenal insufficiency, diazoxide treatment, poor intake, tube feeding or prolonged fasting. The exact timing of repeated glucose measurements should be individualized according to age, fasting duration, previous metabolic instability, procedure length and postoperative feeding delay. Endocrinology advice is prudent in recent or unstable hypoglycemia, known adrenal insufficiency or complex glucose management [2,3,8,16-18].

Fasting: Avoid unnecessarily prolonged fasting. In children, current European fasting recommendations support clear fluids until 1 hour, breast milk until 3 hours, formula until 4 hours and solid food until 6 hours before anesthesia, unless individual aspiration risk requires modification. Severe reflux, impaired gastric emptying or special enteral regimens require an individual plan [19,20].

Particular preparation for airway management

Prepare for both difficult intubation and dynamic airway obstruction. A pediatric or adult difficult-airway trolley, according to age, should include videolaryngoscopy, flexible bronchoscopy, different sizes of supraglottic airway devices, oral/nasal airways, bougies or stylets, suction,

equipment for optimal positioning/ramping and a clear rescue plan for failed oxygenation. Experienced personnel should be present for induction if difficulty is expected [5,6,11-15].

When difficult intubation is likely and aspiration risk is not prohibitive, maintaining spontaneous breathing until ventilation or intubation is secured is often advisable. If aspiration risk is high, a modified rapid sequence induction may be appropriate, but only with an immediately available difficult-airway plan and rescue options. Nasal intubation should be performed only after careful assessment because choanal narrowing or atresia has been described [5,6,11-15].

Particular preparation for transfusion or administration of blood products

There is no known CS-specific bleeding tendency. Blood product preparation should follow the surgical indication, expected blood loss, patient size, cardiac reserve and institutional standards.

Particular preparation for anticoagulation

No syndrome-specific anticoagulation issue is known. Apply standard perioperative anticoagulation and thromboprophylaxis principles, taking into account mobility, orthopedic deformity, cardiac disease and the planned procedure [9,10].

Particular precautions for positioning, transportation and mobilization

Scoliosis, kyphosis, hip dysplasia, club foot, tight Achilles tendons, ulnar deviation, joint contractures, osteopenia/osteoporosis, hypotonia and ligamentous laxity may make positioning difficult and increase the risk of pressure injury, nerve stretch or painful postoperative mobilization. Document pre-existing deformities, pad pressure points carefully, avoid forced joint positions and plan postoperative mobilization with nursing, physiotherapy and pain services when needed [9,10].

For patients with known or suspected Chiari malformation, posterior fossa crowding, syringomyelia or cervicomedullary compression, avoid excessive neck extension, abrupt head movement and positions that could worsen craniospinal compression. Reassess the need for neuroimaging or neurosurgical advice if new neurologic or bulbar symptoms are present [2,3,7].

Interactions of chronic disease and anesthesia medications

Beta-blockers, antiarrhythmics and other cardiac medication should usually be continued perioperatively unless cardiology recommends otherwise. Drugs that prolong QT interval or provoke tachycardia should be used thoughtfully in patients with arrhythmia history [2-4,21].

Growth hormone treatment may be used in some patients but requires cardiac surveillance because of concern for development or worsening of HCM. Diazoxide may be used for hyperinsulinism and requires a perioperative glucose and fluid plan. Etomidate should be avoided or used only after endocrine consideration in patients with known or suspected adrenal insufficiency [2,3,16-18].

Some patients may receive off-label MEK inhibition, such as trametinib, for severe cardiomyopathy or refractory atrial arrhythmia. These data remain emerging and are not a basis for routine anesthesia management; perioperative planning should be individualized in consultation with cardiology, genetics and, where relevant, oncology or pharmacology [22,23].

Anesthetic procedure

Sedative premedication should not be routine. If anxiolysis is necessary, use small titrated doses under appropriate monitoring, particularly in patients with obstructive sleep apnea (OSA), airway obstruction, HCM or arrhythmia [2,5,6].

Induction should be atraumatic and well planned. Optimize positioning, preoxygenation and suction. Avoid tachycardia, hypovolemia, hypotension, marked sympathetic stimulation and large decreases in systemic vascular resistance. In HCM, especially with dynamic left ventricular outflow tract obstruction, anesthetic goals are extrapolated from general HCM practice and include sinus rhythm, adequate preload, maintained or increased afterload, avoidance of tachycardia and avoidance of unnecessary increases in contractility; vasopressors that support systemic vascular resistance without increasing contractility may be preferable for hypotension in this setting [2,4,21].

Use non-depolarizing neuromuscular blocking agents if muscle relaxation is required. Concern regarding succinylcholine is based on one published bradycardia/asystole event during induction; this supports avoidance when an effective alternative is available but does not establish a syndrome-wide absolute contraindication. Objective neuromuscular monitoring is recommended [11-15].

The available literature does not demonstrate increased CS-specific susceptibility to malignant hyperthermia. Routine avoidance of volatile agents solely because of CS is therefore not supported. Volatile anesthesia, including sevoflurane, and total intravenous anesthesia have both been used; standard vigilance for hypermetabolism, rhabdomyolysis and temperature changes remains appropriate [11-15].

Ventilation should avoid hypoxemia, hypercapnia and acidosis. In HCM, avoid unnecessarily high intrathoracic pressures that reduce venous return. In patients with airway malacia or dynamic obstruction, adjust positive pressure, spontaneous ventilation, airway device choice and extubation timing to the individual pathophysiology [2,4-6,21].

Analgesia should be multimodal and opioid-sparing where possible because OSA and airway malacia increase the consequences of opioid-induced respiratory depression. Peripheral regional techniques may be useful and should usually be ultrasound guided. Neuraxial techniques are not absolutely contraindicated, but in significant HCM or hemodynamic fragility they require careful titration to avoid abrupt reductions in systemic vascular resistance [11-15,21].

Glucose should be checked pre-induction in at-risk patients and then repeated according to age, fasting duration, previous hypoglycemia/hyperinsulinism, infusion strategy, procedure length and expected delay to feeding. Glucose-containing maintenance fluid should be considered in infants, patients with hyperinsulinism or previous hypoglycemia and patients in whom postoperative feeding will be delayed [16-20].

Particular or additional monitoring

Standard monitoring is required for all patients. Consider invasive arterial pressure monitoring for major surgery, significant HCM, pulmonary hypertension, important congenital heart disease, relevant arrhythmia history, expected hemodynamic instability or difficult access. Continuous ECG monitoring and postoperative telemetry should be considered in patients with known arrhythmia or significant cardiac disease. Use objective neuromuscular monitoring whenever neuromuscular blockers are administered. Repeat glucose measurement perioperatively in infants, patients with previous hypoglycemia or hyperinsulinism, prolonged fasting, major surgery, glucose infusion or delayed postoperative feeding [1-21].

Possible complications

Relevant complications include difficult mask ventilation, difficult intubation, airway obstruction during induction or emergence, laryngospasm, stridor, secretion retention, aspiration, postoperative desaturation, prolonged oxygen requirement, bradycardia, atrial tachyarrhythmia, HCM-related hypotension or worsening left ventricular outflow tract obstruction, hypoglycemia, delayed feeding, difficult positioning, pressure injury and delayed mobilization [1-21].

Postoperative care

All patients should receive careful and usually prolonged post-anesthesia care unit (PACU) monitoring. Overnight ward, high-dependency (HDU) or intensive care (ICU) observation should be considered according to age, cardiac status, airway/OSA burden, airway difficulty, procedure type, opioid exposure and metabolic stability. No validated CS-specific disposition thresholds are available [1-21].

HDU/ICU admission should be considered for infants and young children; significant HCM, pulmonary hypertension or arrhythmia; known obstructive or central sleep apnea; airway malacia or previous difficult-airway management; airway, ENT, major orthopedic or spinal surgery; relevant opioid administration; prolonged fasting; feeding-tube dependence; or ongoing hypoglycemia risk [1-21].

Monitor for stridor, obstruction, secretion retention, aspiration, desaturation and rhythm disturbance. Suction should be readily available, and the threshold for non-invasive ventilation or escalation of care should be low in patients with sleep-disordered breathing or airway malacia. Re-establish the patient's usual oral or enteral feeding as early as safely possible and continue glucose monitoring until intake and glucose values are stable [2,5,6,16-20].

Disease-related acute problems and effect on anesthesia and recovery

Acute perioperative deterioration should prompt focused consideration of four CS-relevant diagnoses: airway obstruction or secretion retention; atrial tachyarrhythmia or HCM-related hemodynamic compromise; aspiration or sleep-disordered breathing; and hypoglycemia. New vomiting, headache, bulbar symptoms, central apnea, gait change or unexplained respiratory deterioration may indicate progression of Chiari malformation, posterior fossa crowding, syringomyelia or tethered cord and should trigger neurologic reassessment [2-7,16-21].

Ambulatory anesthesia

Office-based or low-resource ambulatory anesthesia is not recommended. Same-day discharge, if considered at all, should be restricted to carefully selected patients in hospital-capable centers with full airway rescue, recent stable cardiac assessment, no clinically relevant sleep apnea or aspiration risk, an uncomplicated low-risk procedure and a defined postoperative observation and escalation plan. Conservative selection is appropriate because no safe ambulatory subgroup has been defined in the available evidence [2,5,6,11-15].

Obstetrical anesthesia

Robust maternal obstetric anesthesia data for women with CS are lacking. If an affected adult becomes pregnant, management should be individualized and should include updated cardiac assessment, airway assessment and consideration of spinal/neuraxial anatomy before delivery planning. Neuraxial analgesia or anesthesia may be feasible but should be titrated carefully in significant HCM or hemodynamic fragility. General anesthesia should be planned as a potentially difficult airway with aspiration risk [1-7,9-15,21].

Pregnancy with a fetus affected by CS is often associated with polyhydramnios, large-for-gestational-age fetal growth, fetal tachyarrhythmia, preterm labor and neonatal hypoglycemia or feeding difficulty. Neonatal teams should be prepared for respiratory, cardiac, feeding and glucose problems after delivery [2,3,16-20].

References

1. Kirkwood A, Prottengeier J. Anaesthesia recommendations for patients suffering from Costello syndrome. OrphanAnaesthesia. Last modified 2016; A&I version 2021.
2. Gripp KW, Morse LA, Axelrad M, et al. Costello syndrome: clinical phenotype, genotype, and management guidelines. Am J Med Genet A. 2019;179(9):1725-1744.
3. Gripp KW, Rauen KA. HRAS-Related Costello Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®. Seattle: University of Washington; updated NCBI Bookshelf version.
4. Lin AE, Alexander ME, Colan SD, et al. Clinical, pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: a Ras/MAPK pathway syndrome. Am J Med Genet A. 2011;155A(3):486-507.
5. Gomez-Ospina N, Kuo JS, et al. Respiratory system involvement in Costello syndrome. Am J Med Genet A. 2016;170A:1849-1857.
6. Della Marca G, Vasta I, Scarano E, et al. Obstructive sleep apnea in Costello syndrome. Am J Med Genet A. 2006;140A(3):257-262.
7. Gripp KW, Hopkins E, Doyle D, Dobyns WB. High incidence of progressive postnatal cerebellar enlargement in Costello syndrome: brain overgrowth associated with HRAS mutations as the likely cause of structural brain and spinal cord abnormalities. Am J Med Genet A. 2010;152A(5):1161-1168.
8. Leoni C, Viscogliosi G, Tartaglia M, Aoki Y, Zampino G. Multidisciplinary management of Costello syndrome: current perspectives. J Multidiscip Healthc. 2022;15:1277-1296.
9. Detweiler S, Thacker MM, Hopkins E, Conway L, Gripp KW. Orthopedic manifestations and implications for individuals with Costello syndrome. Am J Med Genet A. 2013;161A(8):1940-1949.
10. Machida M, Rocos B, Taira K, et al. Costello syndrome-associated orthopaedic manifestations focussed on kyphoscoliosis. J Pediatr Orthop B. 2023;32(4):357-362.
11. Katcher K, Bothwell M, Tobias JD. Anaesthetic implications of Costello syndrome. Paediatr Anaesth. 2003;13(3):257-262.
12. Shukry M, Boucher J, Madduri D, de Armendi AJ. Anesthetic considerations in the child with Costello syndrome: risks of cardiac arrest upon induction of anesthesia. Paediatr Anaesth. 2008;18(6):567-568.
13. Tsutsui M, Sugahara S, Motosuneya T, Wada H, Fukuda I, Umeda E, et al. Anesthetic management of a child with Costello syndrome complicated by congenital absence of the portal vein: a case report. Paediatr Anaesth. 2009;19(7):714-715.
14. Akcil EF, Dilmen OK, Tunali Y. Anaesthetic management in Costello syndrome. Turk J Anaesthesiol Reanim. 2015;43(6):427-430.
15. Ugata K, Imamachi N, Hashimoto A, Saito Y. Anesthetic management in an adult patient with Costello syndrome: a case report. A A Pract. 2019;13(2):41-43.
16. Alexander S, Ramadan D, Alkhayyat H, et al. Costello syndrome and hyperinsulinemic hypoglycemia. Am J Med Genet A. 2005;139A(3):227-230.
17. Vuralli D, et al. Hyperinsulinemic hypoglycemia in a patient with Costello syndrome. Mol Syndromol. 2020;11(4):1-10.
18. Onesimo R, et al. Management of nutritional and gastrointestinal issues in RASopathies: a narrative review. 2022.

19. Frykholm P, Disma N, Andersson H, et al. Pre-operative fasting in children: a guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol. 2022;39(1):4-25.
20. Sümpelmann R, et al. Perioperative Nüchternzeiten bei Kindern und Jugendlichen. Anästh Intensivmed. 2022;63:320-328.
21. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2024;83(23):2324-2405.
22. Geddes GC, Parent JJ, Lander J, et al. MEK inhibition improves cardiomyopathy in Costello syndrome. J Am Coll Cardiol. 2023;81(14):1439-1441.
23. Kato AS, Shwaish NS, Hwang EY, Mandapati R, Lee JW. Novel use of trametinib for treatment of atrial arrhythmia in absence of cardiomyopathy in a patient with Costello syndrome. Cardiol Young. 2024;34(12):2703-2705.

Date last modified: **May 2026**

This recommendation was prepared in 2014 by:

Author(s)

Alana Kirkwood, Anesthesiologist, Great Ormond Street Hospital, London, United Kingdom

Johannes Prottengeier, Anesthesiologist, Klinikum Klagenfurt, Austria
johannes.prottengeier@kabeg.at

Disclosure: The author(s) has no financial or other competing interest to disclose. This recommendation was unfunded.

This recommendation was reviewed by:

Reviewer(s)

Stanlies D'Souza, Anesthesiologist, Tufts University School of Medicine, Springfield, MA, USA
stanlies.d'souza@baystatehealth.org

Mark Wainwright, Division of Neurology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Illinois
m-wainwright@northwestern.edu

Disclosure: The reviewer(s) have no financial or other competing interest to disclose.

Update and revision (2026)
Johannes Prottengeier, Anesthesiologist, Klinikum Klagenfurt, Austria
johannes.prottengeier@kabeg.at

Reviewer
Martin Jöhr, Former head of the Division of Pediatric Anesthesia, Lucerne Hospital (LUKS) Adligenswil, Switzerland
joehrmartin@bluewin.ch

Editorial Review
Christine Gaik, Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, University Hospital Giessen and Marburg, Campus Marburg and Philipps University of Marburg, Germany
gaikc@med.uni-marburg.de