

European Guideline Robin Sequence An Initiative From the European Reference Network for Rare Craniofacial Anomalies and Ear, Nose and Throat Disorders (ERN-CRANIO)

By the Working Group on Writing a European Guideline on Robin Sequence

Abstract: A European guideline on Robin Sequence was developed within the European Reference Network for rare and/or complex craniofacial anomalies and ear, nose, and throat disorders. The guideline provides an overview of optimal care provisions for patients with Robin Sequence and recommendations for the improvement of care.

Key Words: Cleft palate, glossoptosis, guideline, neonatal airway obstruction, neonatal mandibular distraction, Robin sequence

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EUROPEAN REFERENCE NETWORK (ERN) CRANIO

A multidisciplinary steering group was appointed to develop the guideline in January 2021. The members of the steering group are primarily members of the subgroup Cleft lip/palate and orodental anomalies, including Robin Sequence, within ERN-CRANIO. The guideline steering group consisted initially of representatives of 11 ERN-CRANIO centers and individual experts from GOSH, London. Per January 2022 some new centres reached ERN CRANIO specific criteria for endorsement of new ERN members and therefore the steering group was extended with 7 representatives from these newly endorsed centers. All representing professionals were specialized in pediatrics, orthodontics, maxillofacial surgery, or plastic surgery. Professionals represented the following countries: the Netherlands, Italy,

France, Spain, Portugal, Sweden, Finland, Norway, Germany, Belgium, Austria, and Ireland. Professionals from the United Kingdom are not ERN members, but have great expertise on this topic and were involved as affiliated partners. The guideline steering group was chaired by a maxillofacial surgeon. The overall literature search strategy was carried out by a professional medical information specialist and selection was done by 2 steering group members with the supervision of Qualicura. The literature review, the grading and its conclusions were written by the group of research fellows. The review of literature and discussion with the steering group through the evidence to decision framework led to the final considerations and recommendations.

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Address correspondence and reprint requests to Khalid El Ghouli, MD, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands; E-mail: k.elghoul@erasmusmc.nl

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Steering Group

Prof. Dr. V. Abadie, pediatrician, Hôpital Universitaire Necker, Paris, France

Dr. Bohórquez, maxillofacial surgeon, Vall d'Hebron, Barcelona, Spain

Dr. N.W. Bulstrode, MBBS, BSc (Hons), MD, FRCS (Plast), plastic surgeon, Great Ormond Street Hospital, London, United Kingdom

Mr. Gareth Davies, patient representative ERN, ePAG member, France

Dr. M. Hakelius, plastic surgeon, Uppsala University Hospital, Uppsala, Sweden

Dr. J. Ong, MBBS, MRCS, FRCS (Plast), plastic surgeon, Great Ormond Street Hospital, London, United Kingdom

Prof. I.M.J. Mathijssen, MD, PhD, MBA-H, plastic surgeon, Erasmus Medical Center, Rotterdam, the Netherlands

Dr. E. Matos, Santa Maria Hospital, Lisbon, Portugal

Dr. F. Mazzoleni, San Gerardo Hospital, Monza, Italy

Prof. dr A. Mink van der Molen, MD, PhD, plastic surgeon, Utrecht Medical Center, Utrecht, the Netherlands

Dr. M. Muradin, maxillofacial surgeon, Utrecht Medical Center, Utrecht, the Netherlands

Dr. E. Neovius, plastic surgeon, Karolinska Hospital, Stockholm, Sweden

Dr. K. Piacentile, maxillofacial surgeon, San Bortolo Hospital Vicenza, Italy

Dr. M. Redondo, maxillofacial surgeon, Hospital 12 de Octubre, Madrid, Spain

Dr. P. Vuola, orthodontist, Helsinki University Hospital, Helsinki, Finland

Prof. E.B. Wolvius, MD, DMD, PhD, maxillofacial surgeon, Erasmus Medical Center, Rotterdam, the Netherlands

Prof. Dr. Med. Dr. Med. Dent. Siegmund Reinert, Ärztlicher Direktor der Klinik und Poliklinik für Mund-, Kiefer und Gesichtschirurgie, Plastische Operationen, Tübingen, Germany

Dr. Dylan Murray, FDS, FFD, FRCSI, FRCSI (Plast), plastic surgeon, the Children's University Hospital, Temple Street, where he has joined the Craniofacial Team, Dublin, Ireland

Dr. Petra Peterson, MD, specialist in Plastic surgery and ENT, Karolinska, Stockholm, Sweden

Dr. Greet Hens, Departement Neurowetenschappen, KU Leuven, Belgium

Dr. P. Schachner, maxillofacial surgeon, Salzburg, Austria

Dr. A Sivertsen, plastic surgeon, Bergen, Norway

Supported by

Drs. W.F.E Irvine, MSc, guideline methodologist, Qualicura, Breda, the Netherlands

Dr. L.F.J. Welling-van Overveld, MSc, PhD, guideline methodologist, Qualicura, Breda, the Netherlands

Group of research fellows:

M. van Breugel, Utrecht Medical Center, Utrecht, the Netherlands

K. van Schalkwijk, Utrecht Medical Center, Utrecht, the Netherlands

E. Verhey, Utrecht Medical Center, Utrecht, the Netherlands

A. Khan, BSc (Hons), Great Ormond Street Hospital, London, United Kingdom

L. Baillie, Great Ormond Street Hospital, London, United Kingdom

N. Bishop, Great Ormond Street Hospital, London, United Kingdom

C.R.T. Hillyar, MBBS, BSc (Hons), MSc, DPhil, Craniofacial Research Fellow, Great Ormond Street Hospital, London, United Kingdom

Dr. M.J. Koudstaal, MD, DMD, PhD, maxillofacial surgeon, Erasmus Medical Center, Rotterdam, the Netherlands

L. van de Lande, PhD student, MD, Great Ormond Street Hospital, London, United Kingdom

A. Nibber, BMBCh, BSc (Hons), DPhil, Craniofacial Research Fellow, Great Ormond Street Hospital, London, United Kingdom

N. Panciewicz, Great Ormond Street Hospital, London, United Kingdom

A. Ramjeeawan, Great Ormond Street Hospital, London, United Kingdom

A. Bouter, MD, Erasmus Medical Center, Rotterdam, the Netherlands

K. El Ghoul, MD, Erasmus Medical Center, Rotterdam, the Netherlands

B. Logjes, MD, PhD, Erasmus Medical Center, Rotterdam, the Netherlands

P. van der Plas, PhD student, Erasmus Medical Center, Rotterdam, the Netherlands

J. Kats, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands

E. Weissbach, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands

M. van Veen—van der Hoek, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands

Experts on each topic of the guideline were consulted to review the chapters and write recommendations:

Dr. A.J.N. Bittermann, MD, PhD, ENT specialist, Utrecht Medical Center, Utrecht, the Netherlands

Dr. M.-J.H. van den Boogaard, MD, PhD, geneticist, Utrecht Medical Center, Utrecht, the Netherlands

Dr. S. Coenraad, MD, PhD, ENT specialist, Utrecht Medical Center, Utrecht, the Netherlands

Dr. K. Dulfer, Ms, PhD, psychologist, Erasmus Medical Center, Rotterdam, the Netherlands

Dr. K. Joosten, MD, PhD, pediatrician, Erasmus Medical Center, Rotterdam, the Netherlands

Dr. A.M.A. Lachmeijer, MD, PhD, geneticist, Utrecht Medical Center, Utrecht, the Netherlands

Dr. M.S.M. Muradin, MD, DMD, PhD, maxillofacial surgeon, Utrecht Medical Center, Utrecht, the Netherlands

Dr. N.C.J. Peters, prenatal physician, Erasmus Medical Center, Rotterdam, the Netherlands

Drs. M. Pleumeekers, MD, plastic surgeon, Erasmus Medical Center, Rotterdam, the Netherlands

Dr. H. Swanenburg de Veye, MD, PhD, psychologist, Utrecht Medical Center, Utrecht, the Netherlands

Per chapter the following research fellows and experts were involved:

- Chapter 1: Eppo Wolvius, Irene Mathijssen
- Chapter 2: Willemijn Irvine
- Chapter 3: Marie-José van den Boogaard, Guus Lachmeijer
- Chapter 4: Anisha Bouter, Nina Peters, Maarten Koudstaal
- Chapter 5: Emmy Verheij, Khalid El Ghoul, Nina Peters, Joost Bitterman, Saskia Coenraad
- Chapter 6: Anoopama Ramjeeawan, Lara van de Lande, Neil Bulstrode, Juling Ong, Christian Poets
- Chapter 7: Ahad Khan, Anjan Nibber, Neil Bulstrode
- Chapter 8: Natalie Panciewicz, Lauren Baillie, Juling Ong
- Chapter 9: Kim van Schalkwijk, Marvick Muradin
- Chapter 10: Henriette de Vey
- Chapter 11: Natalie Bishop, Christopher Hillyar, Neil Bulstrode, Juling Ong, Christian Poets
- Chapter 12: Aebele Mink van der Molen, Marvick Muradin, Irene Mathijssen, Eppo Wolvius
- Chapter 13: Bob Logjes, Mieke Pleumeekers
- Chapter 14: Jacoba Kats, Karolijn Dulfer, Irene Mathijssen
- Chapter 15: Elin Weissbach, Jacoba Kats, Mariska van Veen, Maarten Koudstaal, Eppo Wolvius

SUMMARY

This guideline provides the following chapters:

Chapter 1 Introduction

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- Purpose of the guideline
- Scope of the guideline
- Relationship to other congenital facial malformations
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- About Robin Sequence
- European Reference Networks

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- 2.2 Support
- 2.3 Aim and target audience guideline
 - 2.3.1 Target audience
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- 2.8.8 Formulating recommendations
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Chapter 4 Diagnostic criteria for Robin Sequence

Chapter 5 Prenatal diagnosis, counselling, preventive measures at birth, and management of patients with Robin Sequence during delivery

Chapter 6 Breathing problems and airway

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Chapter 8 Speech problems

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Chapter 10 Psychosocial problems in patients and/or parents of patients with Robin Sequence

Chapter 11 Nonsurgical treatment in Robin Sequence

Chapter 12 Surgical treatment of mandibular-related problems in Robin Sequence

Chapter 13 Surgical treatment of palate-related problems in Robin Sequence

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Appendix A Literature searches

Appendix B Delphi round evaluation

Appendix C1 Bottleneck analysis survey

Appendix C2 Analysis of patient and public involvement

SUMMARY

The following recommendations were agreed on:

Chapter 3. Genetics: Genetic Work-up of Patients With Robin Sequence

- What is the best genetic work-up strategy in patients with (isolated and nonisolated) Robin Sequence?

Recommendations

- Offer genetic counselling antenatally to all parents when ultrasound, performed and scored in a standardized way and with experience of dedicated physicians, shows signs of retrognathia.
- Refer all neonates/infants with Robin Sequence (RS) as soon as possible to a clinical geneticist within a center of expertise. If early referral is not feasible referral at the age of 6 months is recommended.
- Refer all children with RS after 2 to 3 years to a clinical geneticist for clinical and genetic re-evaluation, if initial screening yielded no underlying diagnosis.
- Perform genetic testing minimally comprising CNV-analysis and (trio)-WES based gene panel analysis targeting RS-associated genes. If this not feasible perform at least CNV-analysis and a limited targeted gene panel for Stickler syndrome

Chapter 4. Diagnostic Criteria for Robin sequence

- Based on which criteria should Robin Sequence be diagnosed?

Recommendations

- Use the original 3 criteria for the diagnosis of RS: micrognathia, glossoptosis, and airway obstruction, whereas the RS is primarily based on the criterium obstructive sleep apnea (OSA) confirmed with polysomnography.
- What diagnostic criteria and tools should be used for the diagnosis of micrognathia and glossoptosis?

Recommendations

- As further described in Chapter 6 on breathing and airway, it is recommended to screen for breathing problems with continuous oximetry and clinical assessment. A baseline PSG should be performed in each RS patient to determine the severity of upper airway obstruction (UAO) and should be repeated for monitoring treatment effectiveness.

Chapter 5. Prenatal Diagnosis, Counselling, and Preventive Measures at Birth and Management of RS During Delivery

- Which findings on the prenatal ultrasound will raise the suspicion of a diagnosis of RS?
- What is the policy for counselling parents expecting a child with RS?
- What is the policy for a safe delivery of a child with RS?

Recommendations

- Consider the diagnosis RS if a routine ultrasonographic scan shows an abnormal facial profile.
- Refer patients to a center of expertise for additional ultrasonography screening (and/or MRI) when there is a suspicion or family history of micrognathia or when an abnormal facial profile was seen on an ultrasonographic scan.
- The sonographer in the center of expertise should consider the diagnosis of RS based on an inferior facial angle < 45.5 degrees or a lower jaw length measurement of ≥ 2 SD below the mean on prenatal ultrasound from 18 weeks of gestation onwards.
- In the availability of an MRI, the health care provider in the center of expertise should consider the diagnosis RS in case of the presence of an isolated cleft palate (CP), a tongue shape index of > 80% and an inferior facial angle of < 48 degrees.
- Offer genetic counseling to parents when a prenatal diagnosis of RS is suspected (see chapter Genetics).
- Inform parents about possible postnatal difficulties with breathing and feeding and the treatment options. This should be done by care providers from a center of expertise.
- Schedule the delivery of a child with a prenatal suspicion of RS with the presence of a physician who has expertise with difficult airways in neonates.

Chapter 6. Breathing Problems and Airway

- What is the policy for screening and monitoring of breathing problems (OSA) in patients with RS?
- What are the indications and policy for treatment of breathing problems (OSA) in patients with RS?

Recommendations

- If the diagnosis of RS is suspected on prenatal assessment (see Chapter 5) consider preparing a team for a risk birth; consider inclusion of specialists from ENT, pediatric anesthetics, and neonatology. This should ideally take place within or in consultation with a unit with specialist expertise with RS.
- Stabilize infants presenting (acutely) in severe respiratory distress following standard resuscitation algorithms (ALS, APLS, EPLS).
- If RS is suspected (persisting airway and/or breathing problems) patients should be managed in consultation with an expert centre regarding assessment and management.
- Screen for breathing problems with regular clinical assessment and continuous oximetry.
- Perform a baseline sleep study in every new-born with suspected RS to determine the severity at initial presentation.
- Monitor breathing problems by repeated sleep studies to assess outcomes following treatment or clinical deterioration.
- Perform a flexible nasoendoscopy for every RS patient to identify all levels of obstruction.
- Management for each patient with RS should be decided by MDT following the recommended investigations (continuous oximetry, clinical assessment, PSG, FNE).

Chapter 7. Feeding Problems and Growth

- What is the policy for screening and monitoring of feeding problems in patients with RS?

Recommendations

- Standardize assessment protocols for feeding problems at initial presentation and monitor frequently throughout early life.
- Utilize standardized growth charts to assess and monitor growth.
- Dietician advice should be requested for all babies with isolated or nonisolated RS at the initial assessment and throughout early life.
- Request SLT assessment in all patients with isolated or nonisolated RS.
- Consider investigations of swallow and esophageal function (EMG, fiberoptic endoscopic evaluation, esophageal monitoring) to inform decision-making by the MDT.
- Record and monitor changes to intake and growth (weight, length, and head circumference) to evaluate the efficacy of interventions.
- Monitor feeding and growth more frequently throughout any surgical interventions.
- Consider investigations of swallow and oesophageal function (EMG, fiberoptic endoscopic evaluation, esophageal monitoring) to inform decision making by the MDT in patients with severe feeding problems (elaborate in professional perspective, tone down PH).

- What are the indications and policy for treatment of feeding problems in patients with RS?

Recommendations

- MDT to determine which patients may benefit from nonsurgical and surgical interventions to improve feeding.
- Consider using hypercaloric feeds as first line to support growth.
- Use an NGT when oral intake remains insufficient with modified feeds.
- Always consider breathing interventions as part of a complete treatment strategy to optimize growth and feeding.
- Consider gastrostomy tube placement in children with UAO who fail to respond to surgical and nonsurgical interventions aiming to improve breathing.
- Be aware of the potential growth and feeding risks associated with surgical interventions to improve breathing after surgical interventions are conducted (TLA/MDO) and intervene early to support (see Chapter 12).

Chapter 8. Speech Problems

- What is the prognostic value of certain patient and treatment characteristics in the prognosis of speech and language development in patients with RS?
 - Diagnosis of RS versus isolated CP
 - Width of cleft
 - Extent of cleft
 - Timing of primary palatoplasty
 - Type of primary palatoplasty
 - Airway and/or feeding management
- What is the policy for screening and monitoring of speech problems in patients with RS?
- What are the indications and policy for treatment of speech problems in patients with RS?

Recommendations

- Advice on early language stimulation, babbling and modelling early sounds (with particular emphasis on oral pressure consonants) to be provided to parents preprimary palatoplasty and in the first few weeks postprimary palatoplasty.
- At the age of 2 and 3 years, a formal 1:1 assessment of speech and language skills should be carried out by a speech and language pathologist (SLP) specializing in CLP and VPD. Clinicians should be alert to the fact that there may be a higher incidence of articulation errors in this population.
- Regular screening of speech from the age of 5 years until growth is complete (at least every 5 years).
- On suspicion of significant VPD or mild VPD, a referral should be made to a specialist in velopharyngeal investigations. An SLP and surgeon specializing in CLP and VPD and RS should be present in the expert team.
- Treatment for CSCs to be delivered directly by specialist SLP or by community SLP with support of the specialist SLP.

Chapter 9. Dentofacial Deformities

- What is the prognosis for facial development of children with isolated RS?
- What is the policy for screening and monitoring of dentofacial anomalies in patients with RS?
- What are the indications and policy for treatment of dentofacial anomalies in patients with RS?

Recommendations

- Schedule dental visit at age 5 to 6 years to screen for the presence of hypodontia using panoramic radiographs in patients with RS with bi-annual review until skeletal maturity.
- Centralize the care of dental screening and surgical treatment in patients with RS in centers of expertise and recommend shared-care for orthodontic treatment.
- Inform parents early that functional (breathing, occlusion) and esthetic issues can occur at skeletal maturity and can be treated with mandibular and maxillary advancement surgery.

Chapter 10. Psychosocial Problems in Patients and/or Parents of Patients With RS

- What is the policy for screening and monitoring of psychosocial problems in patients with RS?
- What are the indications and policy for treatment of psychosocial problems in patients with RS?

Recommendations

- Parents of newly (prenatally) diagnosed children with RS should have access to a clinical psychology and social service with appropriate professional expertise and knowledge of RS, preferably connected to a cleft team.
- In addition to consultations, it is advised to the cleft team to screen parents of children with RS (with and without CP) for the presence of psychosocial and emotional problems at 1, 6, and 12 months after birth with the example: Distress Thermometer for Parents. With the results of the Thermometer it can be decided if/which support for parents is needed.
- In addition to consultations, it is advised to the cleft team to screen children with RS (with and without CP) at age 2, 5, 8, 12, 15, and 22 years to measure psychosocial problems using validated tools. Based on results of the screening, offer parents and/or child further diagnostic tests or treatment if necessary.
- The MDT should be alert to the complex social problems sometimes experienced by families of patients with RS and provide additional specialist support.
- Inform parents at an early stage about the existing patient organizations and the options that they offer for online and offline contact with other parents and children.

Chapter 11. Nonsurgical Treatment in RS

- What is the indication for nonsurgical treatment of the mandibular-related breathing problems in RS?
- What are the most optimal nonsurgical treatment modalities for mandibular-related breathing problems in RS?

Recommendations

- Include nonsurgical interventions, that is prone positioning, NPA, TPP and/or CPAP, in the treatment algorithm of mandibular-related breathing difficulties in infants with RS.
- Consider ET intubation as a life-saving measure in patients who do not respond to above-described nonsurgical interventions, acting as a bridge for teams to consider definitive options for further escalation of care.
- In case a nonsurgical intervention fails to adequately control OSA, care should be escalated to adequately support respiration.
- In case a nonsurgical intervention is still necessary after 6 to 9 months, MDT should re-evaluate treatment to discuss with parents to continue nonsurgical treatment or change to surgical intervention.
- Clinicians should consider both nonsurgical and surgical interventions (as per the recommendations set out in Chapter 12) described in this guideline.

Consensus statements

Supine positioning of RS patients can cause breathing disturbances during sleep	Agreement 90%
Clinicians need to balance the risk associated with prone positioning with regard to SIDS against the potential benefits of prone positioning to improve upper airway obstruction in RS infants	Agreement 100%
Prone or lateral positioning with continuous (home) oximetry is appropriate as a first-line treatment for patients with RS and OSA	Agreement 85%
There is inconclusive evidence to prove superiority of one breathing intervention for RS patients over another, therefore the selection of a nonsurgical treatment strategy for breathing should be guided by consideration of the effectiveness of each intervention as well as local expertise	Agreement 75%

Chapter 12. Surgical Treatment of Mandibular-related Problems in RS

- What is the most optimal surgical treatment modality, MDO versus TLA, for the mandibular-related breathing problems in RS patients?

Recommendations

- Start with nonsurgical treatment for the management of mild-moderate OSA in patients with RS, see Chapter 11—*Nonsurgical treatment*.
- For cases of OSA which do not respond to nonsurgical treatment consider MDO or tracheostomy. First, exclude obstructions of the airway below the level of the tongue base prior to surgery.
- In centers with local expertise, TLA can be discussed as an alternative for cases of OSA which do not respond to nonsurgical treatment. However, breathing and feeding outcomes are better with MDO than with TLA; this should be discussed with the parents by shared decision-making.
- If using an internal device for MDO, virtual 3D planning is recommended.
- Consider tracheostomy over MDO in patients with syndromic status, low-birth weight and neurologic impairment.
- If breathing problems persist or reoccur, MDT should review all treatment options. Consider mandibular distraction osteogenesis to end nonsurgical treatment (eg, CPAP) for severe OSA or to decannulate (see Chapter 11).
- Overcorrect in mandibular distraction osteogenesis because of intrinsic mandibular growth disturbances in RS and disturbed growth resulting from surgery.

Chapter 13. Surgical Treatment of Palate-related Problems in RS

- Which screening is required to allow surgical repair of CP in RS, related to breathing problems?
- Which surgical treatment options can be considered?
- What is the best timing for surgical treatment of palate-related problems in RS, related to speech and breathing problems regarding the best timing and short/long-term effects?

Recommendations

- Consider avoiding a pharyngoplasty in patients with RS as it might induce or recur OSA.

Consensus statements:

PSG (with or without palatal plate) before palatoplasty is appropriate to demonstrate the likelihood of breathing disturbances being induced or worsened by palatoplasty in RS patients	Agreement 70.5%
Using PSG results to guide treatment decisions on type and timing for palatoplasty may prevent (a worsening of) breathing disturbances after palatoplasty in RS patients	Agreement 70.5%
Using PSG results to guide treatment decisions on type and timing of speech improving surgery is appropriate in Robin patients with (suspicion of) breathing disturbances	Agreement 82%
A PSG in RS patients following palate or speech improving surgery (taken at least 3 mo afterwards) is appropriate to monitor the effect of the surgery on breathing.	Agreement 82%

Chapter 14. Quality of Life

- What is the physical health-related quality of life (HRQoL) of children with RS?
- What is the psychosocial HRQoL of children with RS?
- What is the HRQoL of parents of children with RS?

Recommendations

- Parents should have a key role in the management of their child with RS.
- Screen parents' assessment of their child's HRQoL using validated, multidimensional, generic as well as disease specific instruments.
- Consider screening the impact of parenting a child with RS on parents' own HRQoL (see Chapter 10).
- Consider the use of patient-reported outcome measures (PROMS) to improve evaluation of all patients care in relation to their QoL.

Chapter 15. Organization of Care

- What are the minimal standards of care to treat patients with RS and how should it be monitored?

Recommendations

- Provide information about RS and instructions on care to parents, including the various difficulties that can occur and the different options in treatment. This information is preferably uniform and online available in their own language.
- All health care professionals, in particular those in first line care, and lay persons should have access to this guideline in their own language.
- The ERN and designated centers of expertise should ensure online search engine optimization to direct patients seeking information on RS.
- Provide peer contact to parents.
- Ensure good communication between care givers within the center of expertise, between the team and external care givers, and between the team and the parents.
- A center of expertise should be consulted anytime there is a suspicion of RS, prenatally or postnatally.
- Offer care to patients with RS in a center of expertise, that is cleft and craniofacial centers, defined by:
 - *Good accessibility of care.*
 - *Providing 24/7 clinical services.*
 - *Protocol for transition of care for patients who reach adulthood.*
 - *Systematic evaluation of outcomes and implementing changes in treatment protocol that are the result of these evaluations.*
 - *Innovation and scientific research (educational workshops, research meetings, congresses, courses, publications).*
 - *Additional and continuing training of all team members.*
 - *Centres of expertise responsible for the management of RS should make long-term provisions to ensure continuity of care.*
 - *Updated information for patients and caregivers (informative meetings for parents, if available provide information on patients' associations, parents' experts).*
 - *Collaboration with patient representatives.*
- Offer care to patients with RS by a multidisciplinary team, which encompasses:
 - *Core team members:*
 - *Perinatal neonatologist*
 - *Team coordinator*
 - *Prenatal physician*
 - *(IC-) pediatrician*
 - *Nutritionists/feeding specialists*
 - *Pediatric anesthesiologist*
 - *Otorhinolaryngology/audiologist*
 - *Speech therapist*
 - *Nurse specialist*

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- Surgeon with expertise in cleft and craniofacial care
- Psychologist
- Respiratory specialist
- Orthodontist

• With availability of:

- Pediatric surgeon
- Cardiologist
- Neurologist
- Ophthalmologist
- Ventilation team
- Clinical geneticist
- Social worker
- Prosthodontic dentist

• Essential facilities:

- Pediatric ICU
- Sleep study facility
- Audiological evaluation
- Supportive facilities:
- 3D-photography
- Radiographical imaging, CT/CBCT, MRI
- 3D virtual computer planning facility
- Dental lab
- Strive for national centralization of care for RS

CHAPTER 1. INTRODUCTION

Background for Making the Guideline

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a CP is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided into confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided into syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing).

Incidence figures for isolated and nonisolated RS are scant, ranging from 1:8500 to 1:14,000, but the reliability of the estimates is believed to be low as different definitions for the diagnosis RS have been used.¹ At present, there is no internationally accepted consensus about either diagnosis or treatment, and the type and timing of procedures applied seem to be highly heterogeneous. As a result, treatment options vary within and among different European countries and are often based on expert opinion. So far, no national and/or international guideline for RS has been developed. Since practice and expert opinions vary, it is relevant to discuss the available literature, current practice and current experiences with different health care professionals in Europe. An international guideline will result in a more aligned and uniform organization of care for patients with RS in the European member states.

Purpose of the Guideline

There is a need to establish an international guideline regarding patients with RS in collaboration with several European countries due to the wide phenotypic spectrum, the variety of diagnostic criteria, and therapeutic options for RS. The

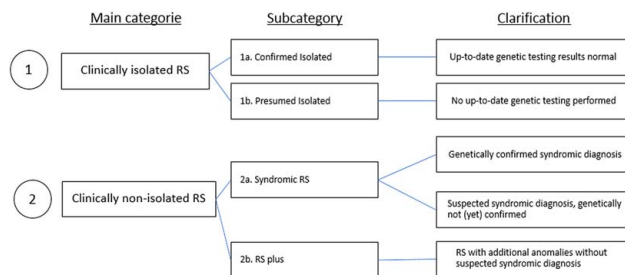


FIGURE 1. Categories for patients with Robin sequence (RS).

guideline should fit the current practice in the countries involved and will give health care professionals tools to align and standardize health care throughout Europe.

The guideline can support health care professionals in discussing the use of certain techniques or instruments with other health care professionals or their national council. In addition, this guideline will provide RS patients (and their parents) and health care professionals with an overview of the optimal care concerning the various and multidisciplinary aspects of RS.

Scope of the Guideline

The guideline concentrates on all patients with RS without a genetically confirmed or strongly suspected underlying syndrome—or chromosomal diagnosis. Thus, RS cases with a clinical syndrome diagnosis like, for example, Stickler syndrome, craniofacial microsomia, Nager syndrome, Treacher Collins syndrome, 22q11 syndrome (category 2a—Syndromic RS, Figure 1) are excluded from this guideline.

In Chapter 3 on Genetics, the RS categories are explained in more detail. With up-to-date next-generation genetic testing implemented in routine diagnostic workup of RS patients, we use in this guideline the following RS categories:

- clinically isolated RS, which is subdivided in (1a) confirmed isolated RS (after up-to-date genetic testing) and (1b) presumed isolated RS (no up-to-date genetic testing performed);
- clinically nonisolated RS, which is subdivided in category (2a) syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis after up-to-date genetic testing) and category (2b) RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing) (Fig. 1).

Recommendations on the following questions are provided in this guideline:

Chapter 3. Genetics: genetic work-up of patients with RS
Question

- What is the indication and policy for genetic work-up of patients with isolated and nonisolated RS?

Chapter 4. Diagnostic criteria for RS
Question

- Based on which criteria should RS be diagnosed?

Chapter 5. Prenatal diagnosis, counselling, and preventive measures at birth and management of patients with RS during delivery

Questions

- Which screening options (type and frequency) are necessary to prenatally diagnose RS?

- What is the policy for counselling for parents expecting a child with RS?
- What preventive measures are necessary at birth for patients with RS?
- What policy is necessary for the management of patients with RS during delivery?

Chapter 6. Breathing problems and airway

Questions

- What is the policy for screening and monitoring of breathing problems (OSA) in patients with RS?
- What are the indications and policy for treatment of breathing problems (OSA) in patients with RS?

Chapter 7. Feeding problems and growth

Questions

- What is the policy for screening and monitoring of feeding problems in patients with RS?
- What are the indications and policy for treatment of feeding problems in patients with RS?

Chapter 8. Speech problems

Questions

- What is the prognostic value of certain patient and treatment characteristics in the prognosis of speech and language development in patients with RS?
 - Diagnosis of RS versus isolated CP.
 - Width of cleft.
 - Extent of cleft.
 - Timing of primary palatoplasty.
 - Type of primary palatoplasty.
 - Airway and/or feeding management.
 - Language development.
- What is the policy for screening and monitoring of speech problems in patients with RS?
- What are the indications for treatment of speech problems in patients with RS?

Chapter 9. Dentofacial anomalies

Questions

- What is the prognosis for facial development of patients with RS?
- What is the policy for screening and monitoring of dentofacial deformities in patients with RS?
- What are the indications and policy for treatment of dentofacial deformities in patients with RS?

Chapter 10. Psychosocial problems in patients and/or parents of patients with RS

Questions

- What is the policy for screening and monitoring of psychosocial problems patients with RS?
- What are the indications and policy for treatment of psychosocial problems in patients with RS?

Chapter 11. Nonsurgical treatment in RS

Questions

- What is the indication for nonsurgical treatment of the mandibular-related breathing problems in RS?
- What are the most optimal nonsurgical treatment modalities for mandibular-related breathing problems in RS?

Chapter 12. Surgical treatment of mandibular-related problems in RS

Questions

- What is the indication for surgical treatment of the mandibular-related breathing problems in RS?
- What is the most optimal treatment modality for the mandibular-related breathing problems in RS?

Chapter 13. Surgical treatment of palate-related problems in RS

Questions

- What is the indication for surgical treatment of the palate related problems in RS, related to speech and breathing problems?
- What is the most optimal treatment modality for the palate related problems in RS, related to speech and breathing problems?

Chapter 14. Quality of life

Question

- What are recommendations to optimize quality of life for patients with RS?

Chapter 15. Organization of care for RS patients

Question

- What are the minimal care standards to treat patients with RS and how should it be monitored?

Relationship to Other Congenital Facial Malformations

The facial characteristics of patients with other craniofacial anomalies, such as Stickler syndrome, Nager syndrome, Treacher Collins (mandibulofacial dysostosis), and 22q11 syndrome, can show an overlap with patients with RS. These patients experience similar difficulties due to the underdevelopment of the mandible and CP resulting in similar functional problems as patients with RS encounter. This may include difficulties with breathing, feeding, speech, and dentofacial growth. Therefore, potential screening, treatment, and the multidisciplinary approach needed for these patients has overlap with the policy for patients with RS. This guideline might be helpful to organize and optimize care for patients with similar craniofacial characteristics. However, further studies are needed to reveal possible differences in outcome for the different treatment strategies in specific underlying syndromal diagnoses.

Intended Users of the Guideline

This guideline is primarily written for all health care professionals involved in the care for patients with RS, including paediatricians, maxillofacial surgeons, plastic surgeons, otorhinolaryngologists, anesthesiologists, orthodontists, geneticists, psychologists, speech therapists, and nurse specialists. Secondly, this guideline is made to provide patients and their parents or other persons who are involved in the medical care of patients with RS with more information about the care process.

About RS

In 1923, Pierre Robin, a Parisian stomatologist, described a range of findings consisting of breathing problems in patients with glossoptosis and related micrognathia. In 1934, he stated that in these patients also CP could be seen. Hanson and Smith (1975) noted that the anomalies described by Robin (1923, 1934) occur as a developmental sequence, but initially, they used the term Robin anomalad.² Only in 1982 the term RS was

proposed.³ RS is not considered a syndrome, but rather as a sequence, a series of specific developmental malformations which can be attributed to a single cause. The micrognathia results in glossoptosis leading to UAO.

The severity of the respiratory problems varies widely among RS patients for which several management strategies can be used including nonsurgical and surgical measures. Due to the wide heterogeneity of the condition, lack of consensus on the definition of the diagnosis, the wide choice of treatments, there is, unfortunately, no consensus on which strategy should be followed, and which relevant factors should be considered for decision-making.

European Reference Networks

ERNs are virtual networks of health care providers from across Europe. The networks aim to pool expertise on complex and rare diseases and concentrate knowledge and resources. There are 24 ERNs, each focusing on a particular disease area. ERN-CRANIO focuses on rare and/or complex craniofacial anomalies and ear, nose, and throat disorders. More information and updates can be found on the website of the ERNCRANIO <https://ern-cranio.eu/>.

ERN-CRANIO seeks to facilitate cooperation between multidisciplinary experts across Europe to support the provision of high-quality care. It is a multidisciplinary network of highly specialized health care professionals.

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CHAPTER 2. METHODOLOGY

Validity of the Guideline

In general, every guideline needs to be updated every 5 years. Consequently, the board of the ERN-CRANIO will install a new workgroup no later than 2027 to review the currency guideline or some of its chapters. Advancement of the review process is advised only if there are strong indications that new evidence will alter the guideline recommendations. ERN-CRANIO is primarily responsible for the validity of the guideline. The cooperating associations share the responsibility and inform the ERN-CRANIO when new developments are of influence on the guideline.

Support

The development of this guideline was supported by Qualicura, an independent health care support agency that guides the development of medical guidelines.

Aim and Target Audience of the Guideline

The aim of this guideline is to provide health care professionals and patients (and parents of patients) with RS with an overview of the optimal care concerning the various and multidisciplinary aspects of RS and offer with recommendations to improve health outcomes and organization of care.

Target Audience

- Health care professionals dealing with RS.
- Patients with RS and parents of patients with RS.

Patient Population

Patients with isolated RS or nonisolated RS.

According to the Orphanet, Snomed, and ICD10 coding systems, this considers:

Orphanet: ORPHA: 436003; ORPHA: 363294; ORPHA: 718; ORPHA: 364577
 ; ORPHA: 1388; ORPHA: 3104; ORPHA: 1388; ORPHA: 2888; ORPHA: 138055; ORPHA: 138041
 ; ORPHA: 138047; ORPHA: 138050; ORPHA: 3102; ORPHA: 3450; ORPHA: 2886
 ; ORPHA: :138059; ORPHA: 138044; ORPHA: 138069
 Snomed: 723461007; 4602007
 ICD10: Q87.0

Steering Group

A multidisciplinary steering group was appointed to develop the guideline in January 2021. The members of the steering group are primarily members of the subgroup Cleft lip/palate and orodental anomalies, including RS, within ERN-CRANIO. The guideline steering group consisted initially of representatives of 11 ERN-CRANIO centers and individual experts from GOSH, London. Per January 2022 some new centres reached ERN-CRANIO specific criteria for endorsement of new ERN members and therefore the steering group was extended with 7 representatives from these newly endorsed centers. All representing professionals were specialized in pediatrics, orthodontics, maxillofacial surgery, or plastic surgery. Professionals represented the following countries: the Netherlands, Italy, France, Spain, Portugal, Sweden, Finland, Norway, Germany, Belgium, Austria, and Ireland. Professionals from the United Kingdom are not ERN members, but have great expertise on this topic and were involved as affiliated partners. The guideline steering group was chaired by a maxillofacial surgeon. The overall literature search strategy was carried out by a professional medical information specialist and selection was done by 2 steering group members with the supervision of Qualicura. The literature review, the grading and its conclusions were written by the group of research fellows. The review of literature and discussion with the steering group through the evidence to decision framework led to the final considerations and recommendations.

Steering Group

Prof. Dr. V. Abadie, pediatrician, Hôpital Universitaire Necker, Paris, France

D. Bohórquez, maxillofacial surgeon, Vall d'Hebron, Barcelona, Spain

Dr. N.W. Bulstrode, MBBS, BSc (Hons), MD, FRCS (Plast), plastic surgeon, Great Ormond Street Hospital, London, United Kingdom

Mr. Gareth Davies, patient representative ERN, ePAG member, France

Dr. M. Hakelius, plastic surgeon, Uppsala University Hospital, Uppsala, Sweden

Dr. J. Ong, MBBS, MRCS, FRCS (Plast), plastic surgeon, Great Ormond Street Hospital, London, United Kingdom

Prof. I.M.J. Mathijssen, MD, PhD, MBA-H, plastic surgeon, Erasmus Medical Center, Rotterdam, the Netherlands

Dr. E. Matos, Santa Maria Hospital, Lisbon, Portugal

Dr. F. Mazzoleni, San Gerardo Hospital, Monza, Italy
 Prof. Dr A. Mink van der Molen, MD, PhD, plastic surgeon, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. M. Muradin, maxillofacial surgeon, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. E. Neovius, plastic surgeon, Karolinska Hospital, Stockholm, Sweden
 Dr. K. Piacentile, maxillofacial surgeon, San Bortolo Hospital Vicenza, Italy
 Dr. M. Redondo, maxillofacial surgeon, Hospital 12 de Octubre, Madrid, Spain
 Dr. P. Vuola, orthodontist, Helsinki University Hospital, Helsinki, Finland
 Prof. E.B. Wolvius, MD, DMD, PhD, maxillofacial surgeon, Erasmus Medical Center, Rotterdam, the Netherlands
 Prof. Dr. Med. Dr. Med. Dent. Siegmund Reinert, Ärztlicher Direktor der Klinik und Poliklinik für Mund-, Kiefer und Gesichtschirurgie, Plastische Operationen, Tübingen, Germany
 Dr. Dylan Murray, FDS, FFD, FRCSI, FRCSI (Plast), plastic surgeon, the Children's University Hospital, Temple Street, where he has joined the Craniofacial Team, Dublin, Ireland
 Dr. Petra Peterson, MD, specialist in Plastic surgery and ENT, Karolinska, Stockholm, Sweden
 Dr. Greet Hens, Departement Neurowetenschappen, KU Leuven, Belgium
 Dr. P. Schachner, maxillofacial surgeon, Salzburg, Austria
 Dr. A Sivertsen, plastic surgeon, Bergen, Norway

Supported by

Drs. W.F.E Irvine, MSc, guideline methodologist, Qualicura, Breda, the Netherlands
 Dr. L.F.J. Welling—van Overveld, MSc, PhD, guideline methodologist, Qualicura, Breda, the Netherlands

Group of research fellows:

M. van Breugel, Utrecht Medical Center, Utrecht, the Netherlands
 K. van Schalkwijk, Utrecht Medical Center, Utrecht, the Netherlands
 E. Verhey, Utrecht Medical Center, Utrecht, the Netherlands
 A. Khan, BSc (Hons), Great Ormond Street Hospital, London, United Kingdom
 L. Baillie, Great Ormond Street Hospital, London, United Kingdom
 N. Bishop, Great Ormond Street Hospital, London, United Kingdom
 C.R.T. Hillyar, MBBS, BSc (Hons), MSc, DPhil, Craniofacial Research Fellow, Great Ormond Street Hospital, London, United Kingdom
 Dr. M.J. Koudstaal, MD, DMD, PhD, maxillofacial surgeon, Erasmus Medical Center, Rotterdam, the Netherlands
 L. van de Lande, PhD student, MD, Great Ormond Street Hospital, London, United Kingdom
 A. Nibber, BMBCh, BSc (Hons), DPhil, Craniofacial Research Fellow, Great Ormond Street Hospital, London, United Kingdom
 N. Panciewicz, Great Ormond Street Hospital, London, United Kingdom
 A. Ramjeeawan, Great Ormond Street Hospital, London, United Kingdom
 A. Bouter, MD, Erasmus Medical Center, Rotterdam, the Netherlands

K. El Ghoul, MD, Erasmus Medical Center, Rotterdam, the Netherlands
 B. Logjes, MD, PhD, Erasmus Medical Center, Rotterdam, the Netherlands
 P. van der Plas, PhD student, Erasmus Medical Center, Rotterdam, the Netherlands
 J. Kats, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands
 E. Weissbach, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands
 M. van Veen—van der Hoek, nurse specialist, Erasmus Medical Center, Rotterdam, the Netherlands

Experts on each topic of the guideline were consulted to review the chapters and write recommendations:

Dr. A.J.N. Bittermann, MD, PhD, ENT specialist, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. M-J.H. van den Boogaard, MD, PhD, geneticist, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. S. Coenraad, MD, PhD, ENT specialist, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. K. Dulfer, Ms, PhD, psychologist, Erasmus Medical Center, Rotterdam, the Netherlands
 Dr. K. Joosten, MD, PhD, pediatrician, Erasmus Medical Center, Rotterdam, the Netherlands
 Dr. A.M.A. Lachmeijer, MD, PhD, geneticist, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. M.S.M. Muradin, MD, DMD, PhD, maxillofacial surgeon, Utrecht Medical Center, Utrecht, the Netherlands
 Dr. N.C.J. Peters, prenatal physician, Erasmus Medical Center, Rotterdam, the Netherlands
 Drs. M. Pleumeekers, MD, plastic surgeon, Erasmus Medical Center, Rotterdam, the Netherlands
 Dr. H. Swanenburg de Veye, MD, PhD, psychologist, Utrecht Medical Center, Utrecht, the Netherlands

Per chapter the following research fellows and experts were involved:

- Chapter 1: Eppo Wolvius, Irene Mathijssen
- Chapter 2: Willemijn Irvine
- Chapter 3: Marie-José van den Boogaard, Guus Lachmeijer
- Chapter 4: Anisha Bouter, Nina Peters, Maarten Koudstaal
- Chapter 5: Emmy Verheij, Khalid El Ghoul, Nina Peters, Joost Bitterman, Saskia Coenraad
- Chapter 6: Anoopama Ramjeeawan, Lara van de Lande, Neil Bulstrode, Juling Ong, Christian Poets
- Chapter 7: Ahad Khan, Anjan Nibber, Neil Bulstrode
- Chapter 8: Natalie Panciewicz, Lauren Baillie, Juling Ong
- Chapter 9: Kim van Schalkwijk, Marvick Muradin
- Chapter 10: Henriette de Vey
- Chapter 11: Natalie Bishop, Christopher Hillyar, Neil Bulstrode, Juling Ong, Christian Poets
- Chapter 12: Aebele Mink van der Molen, Marvick Muradin, Irene Mathijssen, Eppo Wolvius
- Chapter 13: Bob Logjes, Mieke Pleumeekers
- Chapter 14: Jacoba Kats, Karolijn Dulfer, Irene Mathijssen
- Chapter 15: Elin Weissbach, Jacoba Kats, Mariska van Veen, Maarten Koudstaal, Eppo Wolvius

Conflicts of Interest

All members of the steering group declared their conflicts of interest. No measures had to be implemented to prevent conflicting interests in the evidence to decision phase.

Patient Perspectives

Since the guideline will be developed for patients and parents of patients, the patient perspective will be of major importance in this guideline. The perspective of patients was included by analysing relevant bottlenecks from the online survey, see Chapter 15. Furthermore, the ERN-CRANIO ePAG lead was engaged in defining considerations and recommendations and during the authorization phase of this guideline.

Implementation

The implementation of the guideline and the practical feasibility of the recommendations were taken into account during the different phases of guideline development. In doing so, explicit consideration was given to factors that could promote or hinder the implementation of the guideline in practice.

Methods

Bottleneck Analysis

A draft list of bottlenecks from a professional perspective was written by the chair, vice chair and nurse specialist. Members of the steering group were asked to give feedback on the draft bottleneck analysis. The first set of bottlenecks were discussed during the first conference of the steering group in January 2021. No additional chapters were added regarding the bottlenecks of the professionals.

All health care professionals included in the ERN-CRANIO steering group were asked to approach their RS patients. A digital survey was sent to the parents of the patients presented in their national language. This led to the identification of a group of interviewees. An online survey was set up with open and closed questions. All patients and parents of patients were asked what difficulties they (had) experienced in the health care process and in their lives. The questionnaire was built up according to the proposed guideline chapters and the health care process, namely diagnosis and referral, organization of care, communication and information, breathing difficulties, feeding difficulties, speech difficulties, surgical treatments, orthodontic treatment, psychosocial aspects of care, and follow-up. In addition, all patients were asked to name the top 3 best practices a top 3 difficulties they experienced in the care process. Results were analyzed by nurse specialist (E.L. Weissbach). Most frequently mentioned difficulties included difficulties in receiving adequate information on the diagnosis and the treatment, difficulties in getting referred to an experienced medical center, and absence of psychological care. Other relevant bottlenecks were included in the chapter on organization of care (Chapter 15).

Questions and Outcomes

The bottleneck analysis formed the basis for the questions for the guideline. To maintain a clear and readable chapter, questions in the guideline were formulated in a broad and clinically relevant way. The terms for specified questions to facilitate the literature search were mentioned in the summary of literature and search strategy.

This guideline comprises chapters on diagnostics, genetics, functional problems, nonsurgical and surgical treatment, psychology, quality of life, and organization of care. Questions for the nonsurgical chapters (Chapter 3–11, 14, and 15) are formulated in a structured way. Likewise, questions for the surgical chapters (Chapter 12 and 13) are also formulated in a similar

and structured way. All questions were circulated among experts in participating centers before becoming definitive.

For questions in the nonsurgical and surgical chapters specific patient outcomes were chosen and rated according to importance. The patient outcomes were described in the summary of literature per chapter. The “weight” of outcomes was taken into account when formulating the recommendations.

Literature Search and Selection of Literature

A systematic search of the literature was performed to identify all available literature on RS and synonyms. The search was conducted in Embase, Pubmed/Medline Ovid. The full search strategy is reported in the supplementary material.

Inclusion and exclusion criteria:	
Type of studies	Original articles
	Systematic review of sufficient quality:
	The question in the systematic review matches the question of the guideline.
	The search of the systematic review was conducted in at least 2 relevant databases, such as the Cochrane Library, Medline/Pubmed.
	The full search strategy was reported.
	No relevant items were missing in the search strategy.
Type of patients	Patients with Robin Sequence
Subject	Specified per chapter
Exclusion criteria	Patients with syndromic Robin Sequence
	Original studies with <10 included patients with Robin Sequence
	Articles published before 2000
	Case reports
	Expert opinion
	Letters
	Editorials
	Narrative reviews

The initial search was performed in February 2021. A total of 3,438 publications were screened by title and abstract and assigned per topic (Chapters 3–15) by 2 persons, the chair and vice-chair. In case of doubt, the article was included. After screening by title and abstract 3,065 were excluded and for 373 publications full text was reviewed. The selected studies were categorized according to topic (diagnosis, nonsurgical therapy, surgical therapy, etc.), covering the different chapters of the guideline.

To ensure inclusion of all relevant articles, the search strategy was repeated in November 2021 to identify new publications. This resulted in 195 articles, of which after screening by title and abstract, 162 were excluded. An additional 33 publications were reviewed based on full text. After full text assessment a total of 168 studies were included in the literature analysis for this guideline.

Summary of Literature

The most important findings from the literature were described in the summary of literature per chapter (Chapters 3–15). Literature with a high risk of bias was found for several chapters and hardly any evidence was found for a couple of chapters. Percentages were rounded in the conclusions. The steering group decided to include expert opinions for the chapters with hardly any evidence. Therefore, specific experts on each topic of the guideline were consulted to review the chapter. In addition, experts were asked to write considerations and recommendations to initiate the discussion during the meeting in November 2021. In the end, all written text was discussed during the meeting in November 2021.

Quality of Evidence

Based on the “Grading Recommendations Assessment, Development and Evaluation (GRADE)” methodology, all of the evidence on one outcome of interest, was collectively assessed as a “body of knowledge” to determine the quality of evidence on that outcome. This approach was used in 2 different ways, according to the question and type of evidence. The different approaches can be categorized as follows:

(A) Quality assessment for interventional or diagnostic questions (comparison of interventions or screening methods)

The quality of the body of knowledge was assessed following the GRADE methodology. GRADE results in the categorization of evidence into 4 levels: high, moderate, low, and very low. These levels correspond with the confidence we should have about the conclusion the evidence provides us with.¹

GRADE	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

(B) For evidence from single arm-studies (observational and noncomparative).

RS is considered a rare disease. Therefore, on many subjects in the guideline there is a lack of evidence from comparative studies. In this case, the writing committee worked with the best available evidence. Most of the times this evidence is from observational, single arm studies. A body of knowledge consisting of this type of evidence, cannot be properly assessed by using the GRADE methodology. In assessing this type of evidence, the writers did act from a similar perspective. In judging the quality of evidence, methodological quality of single studies and overall, of the body of knowledge, heterogeneity (inconsistency), and effect size (imprecision) were considered. In addition, it was investigated in what degree the reviewed data was matching with the reviewed intervention and the desired population (directness of the evidence). Last, the body of knowledge is screened for signs of publication bias.

These articles do not have a GRADE, because the quality of evidence is so low it cannot be quantified as such. The conclusions from this type of evidence could not get a GRADE level so they are denoted as “Quality of Evidence without GRADE,” which can be interpreted as less than a very low GRADE score. Instead of a GRADE level, an impression of the quality of evidence based on study type, risk of bias, inconsistency, imprecision, directness of the evidence and publication bias, has been added to the conclusion to give some insight into the strengths and weaknesses of the evidence for these observational studies. For example: “Conclusion based on evidence from (n=6) single arm observational studies with a low risk of bias, no important issues with imprecision, directness of evidence or publication bias, but with substantial heterogeneity.”

Formulating Conclusions

For each chapter a conclusion was given when literature was available. Conclusions are drawn based on a body of knowledge for each assessed outcome. If no literature was available, no conclusions were drawn.

Considerations

To determine the strength and direction of a recommendation, the following aspects were examined in addition to the quality of evidence:

- Balance of benefits and harms
- Professional perspective
- Costs and resources
- Inequity of the recommendation
- Feasibility of the recommendation
- Acceptability of the recommendation

Conclusions were written by the group of research fellows based on the available literature. When no evidence was available, experts were consulted to write draft considerations. The draft considerations were discussed in the meeting in November 2021.

Formulating Recommendations

The recommendations provide an answer to the basic question and are based on the best available scientific evidence and the most important considerations. The strength of the scientific evidence and the weight that the working group assigns to the considerations together determine the strength of the recommendation. In accordance with the GRADE method, a low probative value of conclusions in the systematic literature analysis does not exclude a strong recommendation in advance, and weak recommendations are also possible with a high probative value.

The strength and content of the recommendation was always determined by weighing all relevant arguments using the evidence to decision framework (gdt.grade.pro.org). When no evidence was available, experts were consulted to write draft recommendations. The draft recommendations were discussed in the RS Guideline meeting in November 2021.

Conditions (Organization of Care)

The bottleneck analysis and the development of the guideline explicitly consider the aspects related to organization of care. This contains all aspects that are preconditions for providing care, such as coordination, communication, (financial) resources, manpower, and infrastructure. More general, overarching, and additional aspects of the organization of care are discussed in Chapter 15.

Knowledge Gaps

During the development of this guideline a systematic literature search was performed to answer the questions. For each question the steering group investigated whether (additional) scientific research was necessary. If relevant, recommendations for further research can be found in a separate paragraph at the end of each chapter.

Evaluation and Authorization Phase

The draft guideline was submitted to all expert centres involved in the care for patients with RS and endorsed by the ERN-CRANIO as expert center for RS. On top of that, the complete draft was reviewed by the ERN-CRANIO ePAG lead. The comments were collected and discussed with the steering

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group. All reviewers received extensive and personalized rebuttals explaining per comment why it was accepted, amended, or rejected. As a result of the comments, the draft guideline was adapted and extensive conversation with all involved parties through online meetings were held between January and December 2022 to come to a consensus on the final version.

Delphi Process

By following the protocol as described under 11 several suggested recommendations in chapters 11 and 13 did not find approval of all stakeholders. Multiple adaptations did not lead to overall agreement and suitable recommendations. To identify and document areas of agreement and disagreement for these important topics, a Delphi process was started.

The Delphi method is a systematic, iterative approach to identify consensus without face-to-face interaction. The aim is to identify consensus on statements of fact, rather than to create recommendations. It is the preferable methodology for reaching formal consensus in case of large groups (> 12 participants) and geographical disparity of the panel members according to the ERN Methodological handbooks.

First the panel created statements of fact out of the suggested recommendations that did not reach consensus. These statements were included in a digital survey with a 9-point Likert-scale to measure agreement. The steering group agreed up front to identify consensus if least 70% of group members voted 7 (agree) or above and to include a maximum of 3 voting rounds. Because of the multidisciplinary nature of the topics, group members were instructed to decide on their vote together with the multidisciplinary team at their center. An option of “not voting” was given for all questions in case group members felt neither they or their team members had enough expertise to answer the question.

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CHAPTER 3. GENETICS

Introduction

Definition and Classification

RS, defined as the triad of micrognathia, glossoptosis, and a varying grade of airway obstruction, can be categorized into 3 subgroups; (1) isolated RS; children showing merely the core components, (2) syndromic, nonisolated, RS; children present-

ing with RS symptoms as part of a syndrome, and (3) a RS-plus group; children with additional malformations that seem not be related to a syndrome.¹

Considering the fact that up-to-date next-generation genetic testing is increasingly implemented in routine diagnostic work-up of RS patients, the above-mentioned categories can be further refined and a slight modification is proposed. We consider 2 main categories; (1) clinically isolated RS and (2) clinically nonisolated RS. After thorough clinical evaluation and follow up by an experienced clinical geneticist and pediatrician these categories can be subdivided in: (1a) Isolated RS, (2a) syndromic RS (clinically strongly suspected for a syndromic diagnosis), and (2b) RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis) (Figure 1). Based on performed genetic testing these categories can be further refined. Syndromic RS can subsequently be subdivided in (2a.1) RS syndrome diagnosis (confirmed by genetic analysis) and (2a.2) clinically syndromic RS (syndrome diagnosis genetically not yet confirmed). In addition, isolated RS and RS plus can be subdivided based on genetic testing. When up to date genetic testing is *not* performed, an underlying genetic disorder should still be considered.

Several retrospective cohort studies thoroughly evaluated the etiology and diagnostic categories in the RS population (1–4). Although varying in study characteristics, definitions and designs, these studies demonstrate that RS is most frequently nonisolated. The percentage of cases with syndromic RS and RS plus differed between these studies. The minimum and maximum reported percentages of categories were as follows: Syndromic RS: 19.0% to 38.4%; and RS plus: 19% to 33.3%. Thus, less than half of RS patients were categorized as isolated RS (range 37.7%–47.7%).

Etiology

RS can be the result of multiple etiologic factors, resulting in isolated reduced outgrowth of the mandible and glossoptosis. RS can also be associated with an underlying neuromuscular, collagen/bone or metabolic disorder. Finally, RS can be part of many underlying syndromes which can be caused by genetic disorders; chromosomal or single gene defects.^{5,6} To date, searching the OMIM-database (www.OMIM.org) on “Robin” results in more than 170 different genetic disease entries, and searching Face2Gene (<https://app.face2gene.com/>) on HPO-terms “Pierre-Robin sequence” or “Robin mandible” yields an association with 100 different syndromes.

A diagnosis and better understanding of the etiopathogenesis could result in better treatment for individual RS-patients. The association between the underlying etiological diagnosis and mandibular morphology and eventual mandibular growth, might influence the surgical airway management.⁵ Basart et al earlier on already endorsed this view.² They stated that, for instance, a patient with RS due to a deformation is likely to demonstrate a significant spontaneous amelioration of the RS manifestations, while a patient with a dysplasia who has developed RS prenatally due to the abnormal tissue formation in the mandible, larynx and pharynx, will continue having abnormal tissue development postnatally. In order to reach a higher level of personalized treatment implementing up-to-date genetic testing in daily diagnostics is useful.

Finding the underlying diagnosis is not only crucial for tailored management for the RS related problems, but also heavily influences the way management and follow-up of RS patients should be organized. For example, RS patients with a 22q11.2 deletion will comprise an additional clinical workup that focusses

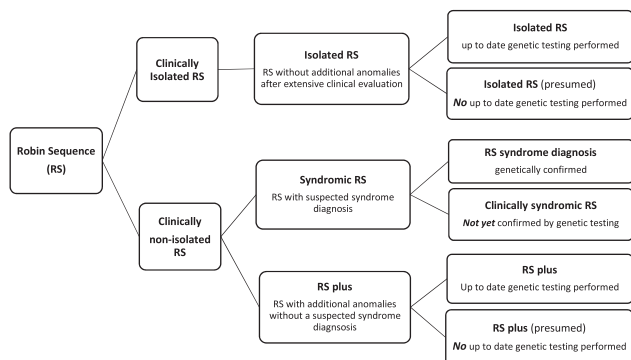


FIGURE 1. RS categories.

on identification of an array of possibly associated anomalies (eg, cardiac, urogenital, skeletal, gastrointestinal, ophthalmic), and require ongoing support in cognitive and psychological domains.⁷ And RS patients with Stickler syndrome will benefit from regular ophthalmic and skeletal follow-up.⁸

Finally, knowing the underlying genetic diagnosis of patients with RS yields accurate recurrence risks for future pregnancies of parents or their families. This makes prenatal testing or preimplantation genetic testing possible for a pregnancy at increased risk.

Genetic Diagnostics

Genetic testing is a crucial component in the diagnostic work-up in RS cases (isolated and nonisolated). Especially, the introduction of copy number variant (CNV) analysis (array-CGH and SNP-array) and next-generation sequencing (whole exome sequencing, WES, or WES-based gene panel analysis), considerably improves the diagnostic yield in children with congenital anomalies.^{9,10} The implementation of next generation genetic testing also led and will lead to the identification of new genes involved in RS related syndromes. For example, trio-WES analyses recently revealed SLC10A7-gene as a novel RS gene.¹¹

For many RS patients with a clinical suspicion of an underlying syndromic diagnosis, the causative genetic defect could only until recently be identified.² This number is only expected to increase since the yield and scope of DNA-diagnostics is continuously expanding, the quality of DNA-testing is continuously improving and costs are falling. Studies of cost-effectiveness recently have shown that WES is most cost-effective when applied at initial presentation to tertiary care compared with first clinical genetics assessment and the standard diagnostic pathway.^{10,12}

Novel Genetic Mechanisms

With the advancement of DNA-technology novel underlying etiologic mechanisms have been discovered that will escape detection by WES. For example, disruption of noncoding elements (CNEs) with regulatory activity upstream of the *SOX9* gene, identified as an underlying cause of isolated RS, will be missed.^{13,14} This also applies to noncoding repeat expansions in the *EIF4A3* gene that cause RS associated Richieri-Costa-Pereira syndrome.¹⁵ Finally, the organization of DNA in 3-dimensional units—called Topologically Associating Domains (TADs), cannot be investigated through WES. Loss, inversions, and repositioning of boundaries of TADs can lead to congenital anomalies, including RS.¹⁶ With a novel DNA-technique called “long-read sequencing” these DNA rearrangements can be identified. Finally, WES cannot detect epigenetic aberrations. Recent insights in epigenetic regulation of gene expression have led to the recognition of syndrome-related epigenetic signatures that can pinpoint specific syndromes.

It is only a question of time when whole genome sequencing (WGS) will be implemented in routine diagnostics as an “all-in-one” genetic test, combining the detection of CNVs, structural chromosomal rearrangements and single base pair changes, including the assessment of regulatory intronic and epigenetic regions.⁹

Follow-up

Clinical genetic re-evaluation, including up-to-date genetic testing, of RS patients who do not have an etiologic diagnosis, is found to be valuable. Izumi et al reported a change in diagnosis

from the prenatal setting to re-evaluation at more than 1 year follow up.⁴ A change from isolated to syndromic RS was made in 18% of patients and a change in diagnosis from syndromic to isolated RS was made in 4% of patients.⁴ The most frequent diagnosed syndrome was Stickler syndrome ~22% (27/125).

Basart et al demonstrated that re-evaluation of 191 RS patients changed the initial diagnosis in 48 cases (25.1%). There seemed to be a slight increase in the number of newly diagnosed RS patients from 2001 on. The spectrum of final diagnoses was broad, including 22 different Mendelian disorders, of which Stickler syndrome was most common (14,1%). The most frequent change (in 13 of the 49 patients) was a change from isolated RS to a nonisolated RS, often because patients had been found to have additional abnormalities at a later age that usually were not or only with great difficulty detectable in infancy.²

Prenatal Diagnostics

Parallel to the above discussed postnatal setting, next generation genetic testing is making a rapid entrance in prenatal diagnostics. Until recently only conventional genetic testing (eg, karyotyping, QF-PCR, CNV-analyses, FISH studies) and targeted single gene testing was prenatally performed. Aneuploidy and copy number variation are detected in up to 40% of pregnancies with malformations.¹⁷ In approximately 60% of malformations the underlying etiology is unresolved with a proportion of cases being the result of monogenic disorders.¹⁸ The PAGE study¹⁹ (n=160 trios prenatal WES) reported a 8,5% additional diagnostic yield to conventional genetic testing and the Columbia study²⁰ (n=234 trios prenatal WES) reported an added diagnostic yield of 10.3%.⁹ The knowledge gained from prenatal WES will improve prognostic counselling, leading to informed parental decision making.

In various European countries rapid WES is already implemented in routine prenatal care. Dedens et. al reported a diagnostic yield of 33% in 18/54 cases with fetal congenital anomalies. WES results impacted prenatal and peripartum parental and clinical decision making in 68% of cases.¹⁸

Although WGS is not part of routine prenatal genetic diagnostics yet, it certainly will in the coming years. Recently, Zhou et al published a study in which prenatal WGS not only detected all pathogenic genetic variants in 22 diagnosed cases identified by chromosomal microarray analysis, chromosomal microarray analysis (CMA) plus WES, yielding a diagnostic rate of 19.8% (22/110), but also provided additional and clinically significant information, including a case of balanced translocation and a case of intrauterine infection (CMV), which might not be detectable by CMA or WES.¹⁹

Pre and Post-test Genetic Counseling

Pre and post-test counseling by a dedicated clinical geneticist/ genetic counselor is necessary, especially in view of finding variants of unknown significance and their interpretation. Additionally, a clinical geneticist will know best what types of underlying genetic causes could be missed by each test and decide which should be first tier choice and whether tailored additional testing is of added value.

Conclusion

In conclusion, for isolated and nonisolated RS cases identification of the correct diagnosis by up-to-date genetic testing is important for tailored personalized care and long-term management, and crucial for accurate genetic counselling in a pre and postnatal setting.

For this chapter the following question was, therefore, addressed:

- **What is the best genetic work-up strategy in patients with (isolated and nonisolated) Robin sequence?**

To answer this question, we have looked into the yield and accurateness of (up to date) diagnostic DNA tests, as outcomes of interest, in cohorts with isolated and nonisolated RS.

Literature Search

For this guideline, a systematic literature search was conducted. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Genetic testing is performed Outcome measures
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

After rough selection and labeling a full text assessment of 18 studies was performed for this chapter. Two studies were excluded because they were not original articles but consist of a review/education chapter.^{20,21} One study, a qualitative, semi-structured interview study, is excluded on incorrect outcome.²² After reading the full text of the remaining 14 papers we concluded none of the studies provide insight into the total yield and diagnostic accurateness of the different genetic tests for RS.

Summary of literature Study

Our literature search did not yield appropriate papers to summarize.

Conclusions of Literature Study

Based on the literature, no conclusion regarding the optimal genetic work-up in RS could be drawn.

Considerations

Professional Perspective

Clinical Genetic diagnostic work-up of clinically isolated and nonisolated RS involves clinical evaluation, pre and posttest counseling and tailored DNA-diagnostics.

Diagnostic work-up and counseling by a clinical geneticist

Antenatal

Since phenotyping based on prenatal ultrasound is hampered as compared to postnatal physical examination; for example, ultrasonic detection of a CP can be challenging, antenatal counseling by a clinical geneticist is of benefit to all parents when ultrasound before 21 weeks' gestation shows signs of retrogathia, whether or not in combination with a CP. This is even more relevant for fetuses with additional anomalies and/ or

growth retardation. In this way parents have an opportunity to seek for an underlying genetic cause that might influence their choice regarding continuation of the pregnancy. If RS with or without additional anomalies is suspected after 24 weeks gestation, genetic counselling and testing can be of importance for peripartum parental and clinical decision making. To ensure optimal care, it is pivotal that close collaboration between all prenatally involved clinicians and clinical geneticists in a multidisciplinary setting is provided for.

Postpartum

Early referral off all RS cases (clinically isolated RS and clinically nonisolated) to a dedicated clinical geneticist with expertise in the field of clefting is increasingly important in the prevention of a Diagnostic Odyssey. The earlier a genetic underlying diagnosis is made or rejected, the sooner tailored management and follow-up can be arranged.

If it is not possible to organize clinical genetic counselling neonatally, in our experience evaluation by a clinical geneticist at the age of 6 months is important. At that time additional features might become more apparent and there is more information available on the early developmental milestones. For a child with remaining suspicion of a genetic diagnosis re-evaluation is recommended at least after 2 to 3 years. Earlier even if there are remarkable new findings. Re-evaluation is not only important in view of the broadening of the array and quality of DNA-diagnostics but for considerations of management workup as well.

DNA-diagnostics

In up-to-date clinical genetics care a standard genetic workup in cases with isolated and nonisolated RS comprises CNV-analysis (SNP-array, high resolution microarray) and (trio) WES-based gene panel analysis targeting all known RS-associated genes. Based on the family history, physical examination and developmental characteristics, a clinical geneticist can specifically choose for more tailored testing, for example, single gene analysis (Sanger-sequencing), karyotyping, FISH-analysis, or even broader testing, for example, open exome analysis, epigenetic tests (Episign), long-read sequencing, or WGS in research setting.

If accessibility to and quality of genetic diagnostics, including clinical genetic workup and genetic testing, is limited, we recommend to test RS patients at least for CNVs and perform a limited targeted gene panel for Stickler syndrome. When there is a strong suspicion of a specific syndrome, targeted single gene analysis can be ordered. If feasible, WES based gene panel analysis for all known clefting/ RS-related genes, as a next step, would be highly recommended.

Expert Forum Meeting

Regular online (inter)national expert forum meetings will be beneficial in order to discuss and (re-) evaluate complex patients in a multidisciplinary setting.

Balance of benefits and harms

Thorough clinical evaluation and follow-up by a clinical geneticist and genetic testing can lead to the identification of rare diagnosis in an early stage, which is of significant added value.

Foremost, early diagnosis prevents a long Diagnostic Odyssey and provides the opportunity of timely monitoring of possible associated anomalies. Prognostic outcome and future perspectives of a molecular diagnosis can give direction to the choice of treatment. Also, when severe diagnoses are excluded by genetic testing, parents and patients often experience relief.

Finally, it allows accurate genetic counseling with a personalized recurrence risk and possibility of prenatal diagnostics in next pregnancies.

Broad genetic testing can introduce anxiety in the parents of a child with RS, in prenatal and postnatal settings. When a diagnosis is confirmed, the clinical spectrum can be very broad and the severity might differ between cases. Some features can appear later in life. These uncertainties can be a burden for (future) parents and patients. Genetic testing can also reveal variants of unknown significance, requiring further segregation analysis in the family and additional clinical work-up. Finally, broad genetic testing (eg, WES, and in the near future WGS) can detect unsolicited findings (UF). UF are detected variants that are unrelated to the initial clinical question the DNA test was initiated for (23). However, UF might be medically relevant. The chance that an UF is detected is, however, low; less than 1%.²³

The above-mentioned issues, illustrate the complexity of broad genetic testing, requiring accurate genetic counseling. When genetic testing is performed (future) parents and/or patient have to be aware of the pros and cons of genetic testing. It is of great importance that genetic testing is based on shared decision making and that patients and caregivers understand the information they received. In this process clinicians and (future) parents and/or patients together define which genetic test would be most suitable in the given situation. The selected test is based on clinical evidence and expected outcomes with inclusion of patients and/or parents' preferences and values.

Costs and Resources

Although next-generation sequencing is proven a cost-effective test to detect rare and/or Mendelian disorders in children, more specific when applied at initial presentation to tertiary care centers.^{12,24} The impact on costs and resources of genetic testing will vary per member state, depending on the available national budget, care providers and laboratory facilities. The recommendations constitute the optimal genetic workup, which will not be accessible for each member state. Therefore, we formulate a minimal required genetic workup strategy, in which many rare diagnoses will be missed. Costs are lowest and resources are most efficiently used when care and genetic tests for congenital disorders are centralized in a limited number of expert centres and laboratories per member state.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe regarding accessibility to up-to-date genetic testing (eg, next-generation sequencing, long-read sequencing and WGS). At present, not every member state offers the laboratory facilities well equipped for genetic testing of rare disorders, as RS. By defining a minimal required genetic workup strategy for RS as well as the optimal genetic workup strategy, this guideline will help all member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal genetic testing and are discussed with members from participating European countries. Accessibility to and quality of genetic diagnostics, including clinical genetic workup and genetic testing, was paramount in the discussions. Qualified

clinical geneticists and high-quality laboratories and centralization of care are proposed as core values. However, in some countries the national organization of healthcare might impede high-level specialized care in expert centres. National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert centre might not be feasible, and collaboration with an expert centre in the surrounding countries should be considered.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale of the Recommendation

The essential principle of the recommendations is to offer the most optimal genetic evaluation and counseling to patients with RS and their parents. The diagnosis, treatment and follow-up of isolated and nonisolated RS and associated recurrence risk is complex and has a lifelong impact on the patients.

Recommendations

- Offer genetic counselling antenatally to all parents when ultrasound, performed and scored in a standardized way and with experience of dedicated physicians shows signs of retrognathia.
- Refer all neonates/ infants with RS as soon as possible to a clinical geneticist within a center of expertise. If early referral is not feasible referral at the age of 6 months is recommended.
- Refer all children with RS after 2 to 3 years to a clinical geneticist for clinical and genetic re-evaluation, if initial screening yielded no underlying diagnosis.
- Perform genetic testing minimally comprising CNV-analysis and (trio)-WES based gene panel analysis targeting RS-associated genes. If this not feasible perform at least CNV-analysis and a limited targeted gene panel for Stickler syndrome.

Research Gap

There are hardly any studies evaluating a thoroughly characterized and well classified RS cohort (isolated and nonisolated), in which all patients received up-to-date genetic testing, and the specifically used diagnostic platforms and analysing tools are reported.

Therefore, prospective and follow-up studies, in pre and postnatal settings, taken into account the above-mentioned issues, are necessary to assess the exact yield of the different genetic tests and to gain more insight in which RS patients will benefit most from genetic testing. It is also important that the psychosocial and clinical impact and the effect on treatment outcomes of genetic testing will be further studied. In such a study, the quality of life of people with RS and their parents should be a major issue to be addressed.

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CHAPTER 4. DIAGNOSTIC CRITERIA FOR ROBIN SEQUENCE

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a CP is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing excluding known syndromes and good clinical outcome except those linked to RS at 18/24 months of age) and presumed isolated RS (no up-to-date genetic testing performed or child below 18/24 mo of age). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing). It is thought that the anomalies in RS are secondarily caused by one another, starting with micrognathia causing abnormal upward and posterior displacement of the tongue, which would lead to airway obstruction.¹ Therefore, it should be seen as a sequence.² However, the exact pathophysiology remains unclear.^{3,4} There are studies that suggest lingual and pharyngeal motor dysfunction in patients with RS. Micrognathia may have an osseous origin or a neuromuscular origin reducing outgrowth of the mandible and increasing airway obstruction.^{5,6}

CP is seen in 80% to 90% of patients with RS.^{7,8} It is suggested that due to the abnormal position of the tongue the palatal shelves cannot fuse before the 10th week of gestation resulting into a wide U-shaped CP.⁹ CP is a clinical diagnosis but can be classified in various ways. A U-shaped cleft is thought to be typical for RS.¹⁰ Despite this being part of the sequence, it is generally not included as one of the mandatory features for the diagnosis of RS. Breugem et al (2016) reached consensus on micrognathia being the primary characteristic of RS.¹¹ Other mandatory diagnostic characteristics included glossoptosis and airway obstruction, but CP was considered a common and additional feature.

A study by Basart et al shows that in the Netherlands and Belgium alone, more than 6 different criteria are used for the diagnosis of RS and that sometimes even within one center there is no uniformity.¹² Internationally, the same trend is seen.^{13,14}

Uniformity in the criteria for RS is much needed for clinical practice, multidisciplinary treatment and optimal patient care.

Also, an international shared definition contributes to research, allowing identification of optimal management strategies and treatment protocols.

In order to achieve uniformity, consensus on how to diagnose the different entities on which the diagnosis RS is based is also needed. Therefore, the following research questions were addressed.

- Based on which criteria should RS be diagnosed?
- What diagnostic criteria and tools should be used for the diagnosis of micrognathia and glossoptosis?

The diagnosis RS is based on 3 entities: micrognathia, glossoptosis and UAO. The diagnostic criteria and tools to measure UAO are reported in a separate chapter on breathing issues (Chapter 6). Therefore, only the first 2 entities are addressed in this chapter.

To answer the first question, we investigated the diagnostic criteria that are being used in different countries and centers as the outcomes of interest. For the second research question, sensitivity and specificity of diagnostic tools, jaw index and cephalometric measurements were the outcomes of interest.

Literature Search

For this guideline, a systematic literature search was conducted. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria for the additional literature search	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Criteria and tools to diagnose micrognathia Criteria for the diagnosis of glossoptosis Cephalometric measurements Jaw index Endoscopy outcomes
Exclusion criteria	Patients with syndromic Robin sequence Sample size < 10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion.

After rough selection and labeling a full text assessment of (n = 40) studies was performed to answer the first research question of this chapter. Several studies were excluded due to incorrect outcome (n = 35). Eventually 5 articles that discussed the criteria for the diagnosis of RS were included: a cross-sectional study by van Lieshout et al (2015), a cross-sectional study by Basart et al (2015), 2 cross-sectional studies with a literature review by Breugem et al (2008 and 2009) and 1 retrospective review by van Nunen et al (2018).^{3,4,12,13,14} With the above-mentioned search, no papers were found that discussed the diagnostics of glossoptosis and micrognathia as separate entities. To properly address our second research question, it was therefore decided to perform an additional literature search. Patients with RS as well as healthy patients were included, since we were interested in how to diagnose the entities separately.

The details are mentioned in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>. A total of 205 articles was found of which 37 were included based on

abstract screening. After further assessment 7 articles were included to answer the second research question of this chapter. Of these, 4 studies addressed micrognathia: a retrospective cohort study by Gao et al (2019), a pilot study by Basart et al (2018) and 2 prospective cohort studies by Mermans et al (2020) and Mimouni et al (2020).¹⁵⁻¹⁸ Glossoptosis was discussed in 3 studies: a retrospective study by Lee et al. (2018) and 2 prospective cohort studies by Manica et al. (2016 and 2018).^{19,20,21}

Summary of Literature Study Based on Which Criteria Should Robin Sequence be Diagnosed?

An overview of current patterns of practice in Europe was given by van Lieshout et al in a cross-sectional study.¹³ An online survey was set out among European clinicians to assess the definitions for RS that are being used. A total of 101 surveys were returned with a response rate of 21%. Most clinicians were from the UK, Germany, the Netherlands, Sweden, and France. Overall, 56 different combinations of features were mentioned. Besides micrognathia/retrognathia/mandibular hypoplasia, glossoptosis and UAO, CP was mentioned as a mandatory feature in 55-96% of the responses, varying between the countries. The top 3 most often-mentioned combinations all included CP. Also, 19% included feeding difficulties as mandatory for the diagnosis. These results show a large variety in features considered necessary for the diagnosis RS. The authors encourage the establishment of international guidelines, but do not make any recommendations for a consensus on the diagnostic criteria for RS.

In a cross-sectional study by Basart et al a questionnaire was sent to the members of cleft teams in the Netherlands and Belgium.¹² 35 questionnaires from 14 cleft teams were returned, consisting of 6 different definitions for RS. Also, within one cleft team multiple definitions were used. CP was considered an obligated feature in 93% of the responses. Surprisingly, glossoptosis was considered obligated in only 52% and UAO in 46% of the responses. The high number of responses that consider CP as a mandatory feature could be influenced by the fact that this questionnaire was set out among clinicians in cleft teams. No proposal is made by the authors for a uniform set of diagnostic criteria.

In the study by Breugem et al (2008) a questionnaire was held among all members of CP teams attending at a meeting of the Dutch Cleft Palate and Craniofacial Association.³ There were 66 responses containing of 29 different descriptions. CP was included in 9 out of 10 most mentioned definitions, whereas UAO was only included in 2 out of these 10 definitions. The authors recommend using original definition stated by Pierre Robin.³ In 2009, the research group of Breugem et al also sent out a questionnaire to all participating cleft teams of the American Cleft Palate—Craniofacial Association.¹⁴ They received 73 responses with a response rate of 35% containing 14 different definitions. With 44% the combination of micrognathia, glossoptosis and CP was most mentioned. Micrognathia, glossoptosis and airway problems followed with 18%. An additional literature search by the authors of 50 consecutive manuscripts, from 2007 counting backwards, revealed 15 different definitions. Micrognathia, glossoptosis and breathing problems +/- CP was the most common definition (34%), together with micrognathia, glossoptosis and CP (34%).

To assess the discussion on nomenclature and definitions, a literature review was performed by van Nunen et al (2018).⁴ Of the 440 included studies, 62% used the eponym Pierre Robin sequence and 23% used Robin Sequence. With 29%, micrognathia, glossoptosis, UAO +/- CP was the most prevalent

definition. In 46% of the articles, CP was stated a necessary feature for the diagnosis. There was a significant shift toward the use of the definition micrognathia, glossoptosis, obstructive upper airway distress with or without CP between 2009 and 2016.

What Diagnostic Criteria and Tools Should be Used for the Diagnosis of Micrognathia and Glossoptosis?

Diagnosing micrognathia

The reproducibility of the jaw index as a measurement tool for diagnosing micrognathia in newborns was investigated by Merman et al (2020).¹⁷ This study was performed in healthy newborns and the jaw-index was defined as the alveolar overjet × (maxillary arch / mandibular arch). The interclass correlation coefficient was 0.74 (CI 0.49–0.86) and the intraclass correlation coefficient 0.81 (CI 0.66–0.89).

The use of 3 dimensional (3D) photogrammetric analysis is studied by Basart et al (2018).¹⁶ 4 isolated RS patients and 8 nonisolated RS patients were included. The age of the patients ranged from 0 to 135 months. Mandibular size was measured on both CT-scan as 3D scanning using landmarks for antero-posterior and cranial-caudal position. Correlation of the mandibular volume using 3D photography and CT-scan was 0.8799.

In the study by Gao et al (2019) a method was proposed to classify mandibular morphology.¹⁵ For this purpose, 150 infants with isolated RS were included in a retrospective study. Evaluation of the mandibular was performed based on 11 anatomic landmarks and 19 semi-landmarks on computed tomography. Distribution in the scatter plots and the canonical variate analysis showed a 3-group pattern. This resulted in the classification of 3 subtypes, being (1) a shorter mandibular body, (2) a shorter mandibular body with an obtuse mandibular angle, and (3) a shorter mandibular body and ramus. The authors state that different causes of UAO can be related to the subtypes and that different osteotomy lines could be used during the sagittal split osteotomy depending on the type of mandibular morphology.

To define the position of the chin and to purpose normal values a prospective observational study was performed by Mimouni et al (2020).¹⁸ Two hundred four healthy newborn infants were included. The goniomandibular length, the goniomaxillary lengths and the goniomandibular / goniomaxillary ratio were measured using sliding calipers at the age 2 days. The mean goniomandibular length was 5.1 cm ± 0.3 SD and the mean goniomaxillary length was 5.4 cm ± 0.3 SD. The mean goniomaxillary/goniomandibular ratio was 1.06 ± 0.05 SD. The normal ratio was defined as being within ± 2 SD of the mean, being between 0.96 and 1.16.

Diagnosing glossoptosis

In the retrospective study by Lee et al (2018) the reliability of bedside awake endoscopy (AE) and drug-induced sleep endoscopy (DISE) was investigated.¹⁹ Thirty-five children with PRS underwent both AE and DISE. The AE was performed at a median age of 5.5 days (range 0–61 d) and the DISE at a median age of 21 days (range 0–216 d). Base-of-tongue airway obstruction was seen on both AE and DISE in 10 patients (28.6%) and on DISE but not on AE in 10 patients (28.6). This resulted in a sensitivity of 50.0% (95% CI 27.2%–72.8%) and a specificity of 86.7% (95% CI 59.5%–98.3%) for awake endoscopy. Significantly more cases of tongue-based obstruction were demonstrated using DISE, compared to AE ($P=0.039$) In the PRS patients in which DISE showed no abnormalities, is un-

known whether tongue-based airway obstruction was not present or whether this is underestimated with DISE.

Manica et al (2016) evaluated 2 classification systems for glossoptosis.²⁰ In this prospective cohort study 58 RS patients were included, of which 24 had isolated RS. Clinical severity was rated using the Cole classification and the grade of obstruction was determined during DISE, using Yellon (Y) and de Sousa (S) criteria. Patients with severe clinical symptoms were rated as Cole 3. The probability of developing severe symptoms was higher in patients graded as Yellon 3 (68.4%, $P=0.0012$) and in patients classified as moderate and severe de Sousa (respectively, 61.5% and 62.5%, $P=0.015$). This shows that patients with a high degree of obstruction were more likely to develop severe clinical manifestations.

In the cross-sectional cohort study by Manica et al (2018) 80 patients were included.²¹ The Yellon criteria had a sensitivity of 56.2% and a specificity of 85.4% for detecting Cole 3 patients with severe clinical symptoms. Use of the de Sousa criteria showed a sensitivity of 28.1% and a specificity of 93.8%. Sensitivity was significantly higher for the Yellon criteria ($P<0.001$) whereas the de Sousa criteria had a higher specificity ($P=0.038$). The overall correlation for Y and S was low (respectively, $\rho=0.372$, $P<0.001$ and $\rho=0.439$, $P<0.001$).

Conclusions

Quality of evidence without GRADE:–	Diagnostic criteria RS Studies indicate there is a large variety in definitions used for the diagnosis of Robin Sequence. There is agreement that Robin sequence consists of at least micrognathia, glossoptosis and airway obstruction. A lack in consensus exists on the inclusion of cleft palate as a mandatory feature. References: (3, 4, 12, 13, 14) <i>Conclusion based on evidence from n = 5 single arm-observational studies with a high risk of bias and significant inconsistency but no issues with imprecision, indirectness or publication bias</i>
Quality of evidence without GRADE:–	Micrognathia Studies indicate that micrognathia can be diagnosed using the jaw-index, computed tomography and 3 dimensional (3D) photogrammetric analysis. References: (15, 16, 17, 18) <i>Conclusion based on evidence from (n = 4) single arm-observational studies with a high risk of bias and significant inconsistency but no issues with imprecision, indirectness or publication bias</i>
Quality of evidence without GRADE:–	Glossoptosis One study indicates that awake sleep endoscopy seems to be less sensitive for diagnosing tongue-based airway obstruction when compared to drug-induced endoscopy. Two studies indicate that the use of a classification method to predict the severity of obstruction had a low sensitivity. References: (15, 16, 19) <i>Conclusion based on evidence from (n = 3) single arm-observational studies with a high risk of bias and significant inconsistency but no issues with imprecision, indirectness or publication bias</i>

Considerations

Quality of Evidence

The variety of definitions used for the diagnosis RS was demonstrated in 4 studies that held a questionnaire among clinicians. All studies have no grade level as these were all noncomparable cohort studies.^{3,12,13,14} The additional papers obtained through the additional literature search addressing micrognathia and glossoptosis were all single arm cohort studies and retrospective studies and therefore had no grade level as well.^{15–21}

Professional Perspective

Based on the current literature search, the guideline development group agrees to the consensus published by van Breughem et al (2016) that the diagnosis RS should be based on the presence of micrognathia, glossoptosis and UAO, with a CP as a common additional feature.¹¹ Other than the previous mentioned consensus, the guideline development group advocates for confirming the diagnosis with a sleep study, taking into account that airway obstruction can develop over time.

Since there are no tools to accurately objectify micrognathia and glossoptosis, in clinical practice the diagnosis RS depends mostly on the presence of UAO, diagnosed with sleep study, the gold standard being the polysomnography (PSG) after screening with clinical assessment.

Balance of Benefits and Harms

Some harm could be done to patients with RS by applying different diagnostic criteria. The lack of consensus on a definition could cause confusion for patients and their parents. Implementation of a clear definition for the diagnosis RS could lead to less heterogeneity within the patient population and will contribute to research purposes. This can contribute to more insight into outcomes and clinical course of patients with RS, which can help patients and parents in their expectations.

Micrognathia can be a clinical diagnosis. However, diagnostic tools may include radiographic imaging. It is important to consider whether the added diagnostic value outweighs the radiation load, especially when taken in account of the young age of patients.

To diagnose glossoptosis, awake endoscopy (AE) and drug-induced endoscopy (DISE) can be used. DISE might be more effective in detecting glossoptosis. It is challenging to determine the position of the tongue an awake baby due to muscle contraction and upright position. On the other hand, after DISE, risks and side effects inherent to the use of anesthesia can occur. Therefore, it is important to take in account the risks of the endoscopy in general anesthesia.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available national budget, care providers, and facilities. The recommendations constitute the essential requirements for appropriate treatment of patients with RS and accordingly these requirements should be implemented. Costs are lowest and resources are most efficiently used when care for congenital disorders is centralized in a limited number of expert centers per member state.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe about care for patients with rare diseases. At present, not every member state offers an expert center for RS, or the level of provided care does not (yet) meet all the requirements outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the

appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal health care and are discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as one of the core values. However, in some countries the national organization of health care might impede centralization.

National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and collaboration with an expert center in the surrounding countries should be considered.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory

Rationale of the Recommendations

To establish an agreement on nomenclature and a clear definition, it is advised to use the criteria for RS as initially described by Dr Pierre Robin, meaning a patient can be diagnosed with RS when the following 3 entities are present: micrognathia, glossoptosis and airway obstruction. Although a CP is present in the vast majority of the RS patients, the CP is not mandatory for the diagnosis of RS. As long as no objective tools are available to quantify micrognathia and glossoptosis in the newborn, the diagnosis of RS depends on the criterium OSA, confirmed with polysomnography (PSG) as the golden standard.

Recommendations

- Use the original 3 criteria for the diagnosis of RS: micrognathia, glossoptosis and airway obstruction, whereas the RS is primarily based on the criterium OSA confirmed with sleep study.
- As further described in Chapter 6 on breathing and airway, it is recommended to screen for breathing problems with continuous oximetry and clinical assessment. A baseline PSG should be performed in each RS patient to determine the severity and can be repeated for monitoring after treatment.

Research Gap

From the 3 diagnostic features of RS, UAO is the only objectifiable one. So far, classification and quantification of glossoptosis and micrognathia is lacking. This knowledge gap needs filling through further research. Future studies with facial 3D stereophotography could be beneficial in quantifying the micrognathia and subsequently identifying patients with micrognathia at risk for OSA leading to the diagnosis of RS.

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CHAPTER 5. PRENATAL DIAGNOSIS AND COUNSELING

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a CP is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

A fetal ultrasound is commonly performed for diagnostic, screening, and monitoring purposes during pregnancy. This imaging technique is widely available in most countries and institutions. Prenatal sonographic findings can be suggestive of a RS diagnosis. However, a definite diagnosis of RS can only be made postnatally when the child is born revealing a neonatal airway obstruction. When looking for a potential diagnosis of RS, the fetal ultrasound typically aims at identifying findings predictive of RS such as micrognathia, glossoptosis and polyhydramnios. A small inferior facial angle (IFA) measured on ultrasound seems to be associated with a postnatal diagnosis of RS.^{1–3} The prediction of the severity of a postnatal airway obstruction should alert the medical team to prepare for a safe delivery of the RS patient. In addition, a prenatal diagnosis of RS allows the parents to be informed about what to expect at a much earlier stage compared to when the child is diagnosed with RS directly postnatally revealing unexcepted breathing and/or feeding difficulties. Sandow et al studied the parents' experience in having a child with RS. They described an emotional time where the information was confusing and was not suited to the parents needs and understanding.⁴

When available, prenatal magnetic resonance imaging (MRI) could be used as an additional prenatal diagnostic tool to screen for intrauterine abnormalities. However, its use is largely limited to cases of multiple sonographic fetal abnormalities, that is, suggestive of an underlying syndrome, or inconclusive ultrasounds.

Besides imaging modalities, prenatal genetic testing, by means of a chorion villus biopsy or amniocentesis, can aid in identifying genetic abnormalities associated with RS. This is discussed in Chapter 4 on genetic testing and will therefore not be highlighted any further here.

In prenatal diagnostics, the aim is to identify objective measurements predictive of RS which are easy to measure and widely available. While a number of prenatal sonographic features are associated with RS, specific guidelines for a reliable prenatal diagnostic workup is lacking. In order to be able to counsel future parents and prepare for a safe delivery,

it is necessary to consolidate reliable prenatal diagnostic measures from literature and infer specific recommendations. Subsequently, this chapter aims to answer the following questions:

- Which findings on the prenatal ultrasound will raise the suspicion of a diagnosis of RS?
- What is the policy for counselling parents expecting a child with RS?
- What is the policy for a safe delivery of a child with RS?

The outcomes of interest for the first question are diagnostic accuracy of inferior face angle, lower jaw length and abnormal amniotic fluid levels as seen on prenatal ultrasound or MRI. To obtain information on the policy for counselling parents expecting a child with RS we looked into the predictive value of prenatal ultrasound findings for the functional phenotype after birth. As a child born with RS is likely to suffer breathing abnormalities, for the third question we looked into the necessary measurements that are needed to assure an adequate airway directly after birth.

Literature Study

For this guideline, a systematic literature search was conducted. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin Sequence and their parents/caregivers
Subject	Prenatal diagnostics for Robin sequence
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

After rough selection and labelling, a full text assessment of 24 studies was performed for this chapter. Six studies were excluded due to a wrong study population, 5 studies were excluded due to a limited number of patients, 2 studies were excluded due to the study design, and 2 studies were excluded due to a wrong outcome.

We included 9 studies regarding prenatal diagnostics,^{1,2,5-12} 3 of which also focused on the relation between prenatal suspicion of RS and functional phenotype of RS, including airway obstruction.⁵⁻⁷

Summary of Literature Study

Which Findings on the Prenatal Ultrasound and MRI Will Raise the Suspicion of a Diagnosis of Robin Sequence?

Ultrasound

There are a number of studies which looked into prenatal sonographic findings predictive of RS. Nguyen et al reported on the inferior facial angle (IFA) as a marker for micrognathia predictive of RS, measured on prenatal ultrasound and MRI.² An IFA <45.5 degrees measured on prenatal ultrasound was defined

as the optimal cut-off value for a postnatal RS diagnosis with a sensitivity of 84% and a specificity of 81%. For MRI, an IFA < 48° was defined as micrognathia from previous studies and showed a sensitivity and specificity of 76% and 83%, respectively.² Furthermore, an IFA <45.5 degrees is discussed to differentiate between those with micrognathia and airway obstruction and those with micrognathia without airway obstruction compared to an IFA <49.2 degrees reported earlier by Rotten et al.³ The RS patient population in these studies also included those with a syndromic diagnosis and was not limited to isolated RS. Kruse et al previously reported on a normative index of lower jaw length (LJL) by gestational age (GA) or femur length (FL) to diagnose micrognathia.⁶ They concluded that foetuses with an LJL measurement ≥ 2 SD below the mean are suspect of RS.⁶ The sensitivity of this index to detect micrognathia was reported to be 93.8% and 87.5% when conditional to GA or FL, respectively. This was assessed retrospectively on prenatal ultrasound for 16 neonates with subjective micrognathia, that is, based on assessment of the fetal profile on ultrasound. Fourteen received a postnatal diagnosis of isolated RS and 2 were diagnosed with a syndromic associated with micrognathia. Di Pasquo et al, defining RS as a triad of micrognathia, glossoptosis and a CP, used prenatal ultrasound recordings of the IFA and glossoptosis to assess their predictive value for a prenatal RS diagnosis.⁵ Glossoptosis was defined as an inability of the tongue to reach the mandibular alveolar ridge during sonographic examination. Based on an IFA < 50 degrees and sonographic observation of glossoptosis, 47 foetuses were suspected of RS of which 28 were suspected of isolated RS and 19 of nonisolated RS. Of those with a suspicion of isolated RS, a postnatal confirmation was noted in 22 cases (78.6%) and 6 were postnatally diagnosed with nonisolated RS. For all included foetuses with a prenatal suspicion of RS the diagnosis was confirmed after birth. However, the study does not differentiate between those with or without airway obstruction and included cases in which the pregnancy was terminated in the group with a postnatal diagnosis of RS.⁵ Lind et al, maintaining the same definition for RS and overlapping with DiPasquo et al, reported an RS diagnosis in 33 cases with prenatal 2D and 3D sonographic findings of micrognathia, without providing a definition, and/or CP.⁷ The combination of micrognathia and a P showed a 100% sensitivity for a postnatal RS diagnosis.⁷ Kluivers et al evaluated the amount of amniotic fluid on ultrasound and/or MRI as a measure to differentiate between isolated RS or associated syndromic diagnoses.¹² Abnormal amniotic fluid levels, that is, polyhydramnios and oligohydramnios without specification of associated amniotic fluid index values, were associated with a 2.3 (95% CI: 1.3–6.3, *P* = 0.007) times higher likelihood of a syndromic diagnosis compared to those with normal amniotic fluid levels. In particular, polyhydramnios was associated with increased odds of a syndromic diagnosis (OR = 4.18, 95% CI: 1.6–10.9, *P* = 0.003) in those with RS.¹²

Prenatal MRI

All the included studies reporting on the use of prenatal MRI to aid the diagnosis of RS were conducted at the Boston Children’s Hospital. As such, a considerable overlap in study populations can be expected. Rogers et al (2016) examined micrognathia (graded as “minor,” “moderate,” or “severe”), glossoptosis and CP as prenatal MRI features predictive of RS. Of 49 cases with micrognathia observed on fetal MRI, 23 (44.2%) were diagnosed with RS of which included 9 isolated cases.¹⁰ All of those with “severe” micrognathia, 13/15 (86.7%) of those with “moderate” micrognathia, and 3/27 (11.1%) with “minor” micrognathia on fetal MRI were diagnosed with RS

postnatally. For the included population, that is, referred for a fetal MRI, the odds of an RS diagnosis were 2.83 (95% CI: 0.85–9.4472) for those with micrognathia observed on prenatal ultrasound compared to those without a suspicion of micrognathia. A diagnosis of RS was noted in 14 of 15 (93.3%) infants with a CP on prenatal MRI. Glossoptosis was noted in 4 viable fetuses on prenatal MRI, all of whom were diagnosed with RS severe enough to require surgical management. The study does not provide definitions for micrognathia or glossoptosis, but all cases of RS had polysomnographic findings of airway obstruction.¹⁰ Kooiman et al found the IFA, jaw index and a measure of oropharyngeal space (OPS) on fetal MRI to be significantly smaller in those with RS compared to a normal control group and a group with micrognathia but not RS.⁸ Resnick et al showed measures of the tongue on fetal MRI to be significantly different in RS compared to a normal control group. In particular, the tongue shape index (TSI) and tongue length were significantly higher and the tongue was noted to touch the posterior pharyngeal wall in 19% of RS cases and in none of the control group ($P < 0.001$).¹¹ In a subsequent study of the same population, Resnick et al (2017) described an algorithm to predict RS from fetal MRI measures. Significant predictor variables included the presence of an isolated CP (OR = 38.8, 95% CI: 4.8–312.8, $P < 0.001$), a tongue shape index (TSI) > 80% (OR = 8.7, 95% CI: 1.5–51.2, $P = 0.014$) and an IFA < 48 degrees (OR = 14.5, 95% CI: 2.0–110.6, $P = 0.007$).¹

What is the Policy for Counselling Parents Expecting a Child With RS?

In a survey where the parents of RS of 8 different European countries filled in a questionnaire about the organization of care regarding RS, over 70% of parents indicated to have received proper and understandable information on RS since the child was diagnosed, over 20% of parents indicated not to have received this proper and understandable information. In this last group there was a lack of basic information and instructions on feeding and respiratory issues given by nonexpert centers.¹³

Prediction of the postnatal phenotype of RS prenatally appears to be difficult; DiPasquo et al and Lind et al found that a prenatal suspicion of RS was associated with a more severe phenotype postnatally, compared to patients with RS diagnosed postnatally.^{5,7} Kruse et al found no relation between the prenatal ultrasound indices, that is lower jaw length corrected for femur length (fetal growth) or gestational age, and the severity of airway obstruction.⁶ In the study by Rogers et al (2017), 13 of 15 (86.7%) with a cleft palate and all 4 viable infants with glossoptosis on prenatal MR required surgical management of airway obstruction. Sandow et al studied the parents' experience in having a child with RS. They described an emotional time where the information was confusing and was not suited to the parents needs and understanding.⁴ Prenatal diagnosis offers the possibility of preparing the parents and informing them at a much earlier stage compared to when the child is diagnosed with RS postnatally. Especially when immediate intervention is needed after birth, prenatal counselling could be very helpful.

Counselling of parents expecting a child with RS should include information about associated syndromes, potential breathing and feeding difficulties and treatment options offered by an multidisciplinary team at expert centers.

What is the Policy for a Safe Delivery of a Child With RS?

In a survey study the parents of children where the diagnosis RS was suspected prenatally indicated that in 55.6% there were any

precautions or measures taken with regard to the delivery and in 38.9% of the cases there were no precautions of measures taken.¹³ As mentioned above, a prenatal diagnosis of RS could be associated with a more severe phenotype postnatally.^{5,7} However, Kruse et al found no relation between the severity of airway obstruction and the index values between the lower jaw length stratified by femur length or gestational age.⁶ DiPasquo et al and Lind et al used the classification revised by Cole et al defining 3 grades of severity of phenotype.^{5,7,14} A grade 3, the most severe phenotype, was defined as severe feeding difficulties and respiratory obstruction with arterial oxygen saturation (SaO₂) < 90% for more than 5% of the time and partial pressure of carbon dioxide (pCO₂) > 50 mm Hg, and/or apnea and hypopnea index > 10/hour on polysomnography or cyanotic attacks requiring intervention for the UAO.¹⁴ Even though the available literature is not consistent in finding a relation between a prenatal suspicion of RS and respiratory insufficiency, when there is a prenatal suspicion precautionary measures should be taken. When a child is born with a respiratory obstruction, immediate intervention securing the airway (ie, placement of nasopharyngeal tube, laryngeal mask, orotracheal intubation) could be required. According to DiPasquo et al and Lind et al around 30% of patients with a prenatal suspicion of RS had a grade 3 phenotype,^{5,7} and would need an airway intervention after birth. Due to the glossoptosis and retrognathia, airway management in RS can be difficult.^{15,16} In addition, when there is a suspicion of an accompanying syndrome, airway management can be even more challenging. Therefore, care providers experienced in difficult airway management, should be informed and be part of the health care team managing the delivery of a child with RS. Since RS is a rare condition, we would recommend a delivery in a tertiary referral center in order to provide the appropriate clinical setting with experienced health care providers, preferably a tertiary referral center, is important.

Conclusions

Quality of evidence without GRADE:	Ultrasound There are cautious indications that an inferior facial angle (IFA) < 45.5 degrees on prenatal ultrasound is the optimal cut-off value on prenatal ultrasound for a postnatal RS diagnosis. Reference: [2] <i>Conclusion based on a single cross-sectional study with a heterogenic group of patients and possible risk of bias.</i>
Quality of evidence without GRADE:	There are cautious indications that foetuses with a lower jaw length (LJL) measurement of ≥ 2 standard deviations (SD) below the mean are suspect of having RS. Reference: [6] <i>Conclusion based on a single cross-sectional study with a heterogenic group of patients and possible risk of bias.</i>
Quality of evidence without GRADE:	There are cautious indications that abnormal amniotic fluid levels measured on ultrasound, i.e., polyhydramnios and oligohydramnios, can differentiate between isolated RS or associated syndromic diagnoses. Reference: [12] <i>Conclusion based on indirect evidence from a single cross-sectional study with a heterogenic group of patients and possible risk of bias.</i>
Quality of evidence without GRADE:	MRI There are cautious indications that an IFA < 48° on MRI is related to a postnatal RS diagnosis.

Quality of evidence without GRADE:	<p>Reference: [2] <i>Conclusion based on a single cross-sectional study with a heterogenic group of patients and possible risk of bias.</i> There are cautious indications that an isolated cleft palate noted on prenatal MRI is associated with a postnatal diagnosis of RS with a sensitivity of 93.3%.</p>
Quality of evidence without GRADE:	<p>Reference: [10] <i>Conclusion based on a single cross-sectional study with a heterogenic group of patients and possible risk of bias.</i> There are cautious indications that an isolated cleft palate, a tongue shape index and an IFA <48 degrees on prenatal MRI are associated with a postnatal diagnosis of RS.</p>
Quality of evidence without GRADE:	<p>Reference: [1] <i>Conclusion based on a single cross-sectional study</i> There are indications that a prenatal suspicion of RS is related to more severe phenotype. Parents expecting a child with RS should be informed on the syndrome and associated difficulties. Reference: [5, 6, 7] Conclusions based on evidence from (n = 2) case control studies and (n = 1) single arm study, with an intermediate risk of bias and inconsistency but no imprecision and indirectness.</p>
Quality of evidence without GRADE:	<p>There are indications that a prenatal suspicion of RS could be related to a severe respiratory obstruction, which raises the need to scheduling the delivery with the presence of a physician experienced in difficult airway management. Reference: [5, 6, 7] Conclusions based on evidence from (n = 2) case control studies and (n = 1) single arm study, with an intermediate risk of bias and inconsistency but no imprecision and indirectness.</p>

**Considerations
 Quality of Evidence**

The overall quality of evidence was low. There are some notes to be made regarding the quality assessment of the selected studies. First, the studies from DiPasquo et al and Lind et al are both (partly) conducted at the Necker hospital in Paris^{5,7}; overlap in population is likely. Also, in the studies by DiPasquo et al the difference was made between isolated and nonisolated RS.⁵ However nonisolated RS also included patients with different syndromes. No distinction is made between patients with isolated RS and those with additional syndromic diagnoses in the main results of all studies conducted at the Boston Children’s Hospital.^{1,2,8,10–12}. In the study by Kruse et al 3 patients with a syndrome were included.⁶ For the comparison between prenatal diagnosis and postnatal phenotype (including respiratory insufficiency) it was not possible to extract the data

only from patients with isolated RS.^{5,6} As a result, patients with a syndrome could be included in the outcome “respiratory insufficiency.” For the outcome of “respiratory insufficiency,” methodological quality was scored as intermediate risk of bias because DiPasquo et al and Lind et al received 4 stars using the Newcastle-Ottawa scale.¹⁷ In addition, for this outcome the studies were also scored as indirect evidence since all 3 studies answered the question whether a more severe phenotype could be predicted from prenatal diagnostics, rather than the actual questions; *what is the policy for counselling of parents expecting a child with Robin sequence?* and *what is needed for a safe delivery of a child with Robin sequence?*

Professional Perspectives

With support, counseling and careful perinatal management, neonates with RS and their parents benefit from a prenatal diagnosis. Prenatal diagnosis of RS starts with recognition of the micrognathia by ultrasound screening programs (eg, 20 wk anomaly scan) by assessment of the fetal profile in a sagittal view and the mandibula in an axial plane. When there is a suspicion of micrognathia, we recommend referral to a tertiary center with an expertise in RS for an extended (2D and 3D) ultrasound examination with the purpose of estimating the extent of the micrognathia, assessment of the fetal palate, screening for other (associated) congenital anomalies and genetic testing (see Chapter 3 Genetics). When the micrognathia is confirmed, future parents should be counseled by (1) a prenatal physician and obstetrician about the course of their pregnancy and delivery, (2) a prenatal clinical geneticist about the possibilities and limitations of prenatal invasive testing, and (3) postnatal physicians about what to expect after birth and thereafter if the RS suspicion is confirmed after birth. For prenatal counselling and perinatal management, a fetal MRI could be of added value, if available.

For perinatal management the assessment of the risk of a threatened airway after birth is essential and although the literature is scarce, when there is a severe micrognathia (IFA < 49), presence of glossoptosis [eg, by assessment of the tongue shaped index (TSI) > 80%], polyhydramnios, CP and/or suspicion or confirmed syndromal RS, there is a high risk of a threatened airway after birth. A (daytime) delivery (or planned caesarian section) in a clinical setting with presence of different medical specialists (eg, obstetrician, anesthesiologist, neonatologist and ENT doctor) and the presence of a neonatal intensive care unit is then to be considered. This is, of course, dependent on the logistics within the referral center.

Balance of Benefits and Harms

Prenatal screening and expressing the possible diagnosis of RS could result in an emotional and difficult time for parents. However, allowing the parents and the medical team to prepare them emotionally and to arrange a safe delivery respectively will be much more beneficial compared to an unexpected postnatal diagnosis.

Costs and Resources

A prenatal ultrasound should already be available in every European member state. However, prenatal screening for RS may require additional costs and time for training specialized personal. This already will differ among individual centers and

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should be organized nationally. In addition, an MRI is a costly diagnostic tool, and not available in every center.

Inequity of the Recommendation

We expect inequity regarding a prenatal MRI. It is most likely that this is not available in every individual center. Prenatal ultrasound is expected to be available in public healthcare across Europe, however the costs may not always be covered by healthcare insurance.

Feasibility of the Recommendation

It may be difficult to organize deliveries in a center of expertise for all pregnancies in which RS is suspected. This could result in an overload for the center, especially when the threshold for suspicion of RS is low. The availability and capacity of such specialized centers will differ among member states.

Acceptability of the Recommendation

The rationale of the counseling of parents expecting a child with RS is to provide them with high quality information on what they can expect for their child and to ensure a safe delivery. A prenatal ultrasound should include assessment for signs of RS.

Rationale of the Recommendation

Considering ultrasound is widely available we aimed to recommend practical and clear-cut measurements which have minimal interperson variability. Regarding parent counselling we feel it is essential to offer complete information to the parents. To avoid confusing information and since expertise centers have more experience and more different medical specialties involved in RS care, this should be done in an expertise center in our opinion. For the same reason we feel it is important that if a delivery can be planned, it should be done in an expertise center.

Recommendations

- Consider the diagnosis RS if a routine ultrasonographic scan shows an abnormal facial profile.
- Refer patients to a center of expertise for additional ultrasonography screening (and/or MRI) when there is a suspicion or family history of micrognathia or when an abnormal facial profile was seen on an ultrasonographic scan.
- The sonographer in the center of expertise should consider the diagnosis of RS based on an inferior facial angle < 45.5 degrees or a lower jaw length measurement of ≥ 2 SD below the mean on prenatal ultrasound from 18 weeks of gestation onwards.
- In the availability of an MRI, the health care provider in the center of expertise should consider the diagnosis RS in case of the presence of an isolated CP, a tongue shape index of > 80% and an inferior facial angle of <48 degrees.
- Offer genetic counselling to parents when a prenatal diagnosis of RS is suspected (see chapter Genetics).
- Inform parents about possible postnatal difficulties with breathing and feeding and the treatment options. This should be done by care providers from a center of expertise.
- Schedule the delivery of a child with a prenatal suspicion of RS with the presence of a physician who has expertise with difficult airways in neonates.

Research Gap

There is insufficient literature available focusing on discriminating prenatally isolated from nonisolated RS and direct postnatal airway management in RS.

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CHAPTER 6. BREATHING AND AIRWAY

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a CP is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing).

Obstructive airway events are rare with fewer than 1 event per hour in the normal infant population.^{1,2} OSA syndrome in children aged 1 to 23 months usually presents with both objective and subjective findings. Breathing issues are expected to occur in RS as obstruction and is one of the diagnostic criteria of RS. Airway obstruction may occur at the tongue base or in the laryngopharyngeal area or both. These breathing difficulties can be intermittent and have a broad range of severity. Symptoms are often exacerbated when the child is asleep in the supine position due to the retro-positioned tongue falling backwards to occlude the residual airway, or during bottle feeding. Upper airway dysfunction occurring during sleep (sleep disordered breathing) encompasses a range of sleep-related breathing disorders including OSA, central apneas, hypoventilation, and hypoxia. Symptoms include snoring and/or increased respiratory effort due to higher airway resistance and collapse of the pharyngeal walls. This compromises normal oxygenation, ventilation, and the child’s sleep pattern.³⁻⁵ Obstruction may also occur when the child is awake, responsible for discomfort, stertor, respiratory distress, cyanotic attack or can be a sign of brief resolved unexplained events (BRUE), or formerly apparent life-threatening events (ALTE).³⁶⁻³⁸ UAO is reported in 18% to 100% of RS patients, depending on the study cited.⁶⁻¹¹ Untreated UAO can result in significant long-term metabolic, cardiovascular, neurocognitive and behavioral morbidity, and death.¹² It is closely related to feeding problems and growth failure, which is further compromised by an increased incidence of oro-oesophageal motor disorders in these patients. This is addressed in more detail in Chapter 7 Feeding and Growth.

Timely diagnosis of UAO is essential and starts with expert clinical evaluation with selected investigations. Methods to screen and monitor breathing problems include clinical assessment by observing the tracheal tug (suprasternal, intercostal, and subcostal recessions), audible stridor or stertor, or objective investigations such as oximetry in supine and/or prone position, feeding difficulties in the various positions and its effect on oxygen desaturation and CO2 transcutaneous pressure, capillary blood gas, polysomnography (PSG), and flexible nasoendoscopy (FNE). PSG is a sleep study and is considered the gold standard for the detection of OSA, which can be performed in a standard format or using a split-night PSG. The split night PSG initiates with room air followed by an alternative intervention midway through the sleep study time for the remaining part of the PSG. FNE can be used to

confirm the level of airway obstruction at the tongue base and to identify additional airway anomalies (including laryngomalacia) which may contribute to identifying the type and severity of OSA.¹³⁻¹⁵ FNE can be performed with or without sedation.¹⁶

This chapter aims to identify clear information about screening and monitoring of breathing problems occurring in RS and provide policy guidance for clinicians treating these breathing problems.

To address the policy for breathing difficulties in patients with RS the following questions were included in this chapter:

- **What is the policy for screening and monitoring of breathing problems (OSA) in patients with RS?**
- **What are the indications and policy for treatment of breathing problems (OSA) in patients with RS?**

To answer the above questions, we investigated the literature on clinical assessments for UAO, oximetry, polygraphy, polysomnography, and FNE for screening and monitoring of OSA as outcomes of interest. Factors important to the timing and choice of treatment will also be discussed. Finally, an algorithm on treatment of acute respiratory distress is presented. The algorithm is based on plenary discussions and final agreement of the expert centres participating in this European guideline on RS.

Definitions

The definitions of apnea, hypopnea and OSA severity are described in the AASM scoring manual (Berry et al). The clinical grading by Cole et al consists of: Grade 1: no respiratory distress when nursed supine; Grade 2: intermittent evidence of mild respiratory obstruction when nursed supine and feeding precipitates some respiratory distress, Grade 3: moderate to severe respiratory distress when nursed supine, unable to feed orally.¹⁷

Literature search

A systematic search of the literature search was performed to identify all available literature on RS. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria

Type of studies	Original studies
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Breathing, airway, and sleep Screening and monitoring of OSA OR Indications for treatment of OSA
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence. Articles published prior to 2000. Research amongst populations in developing countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion.

After rough selection and labelling a full text assessment of (n = 134) studies was performed for this chapter. Several studies were excluded due to small (< 10 cases) sample size (n = 11) or incorrect outcome (n = 107). In this chapter (n = 16) studies are described.

Summary of Literature Study

What is the Policy for Screening and Monitoring of Breathing Problems (OSA) in Patients With RS?

Clinical assessment of UAO

No studies are available that analysed or validated the most accurate method for clinical assessment of breathing issues in RS.

A case series study by Wilson et al 2000 described that late-onset breathing issues can occur and respiratory difficulties may not always be present at the initial assessment based on respiratory signs. Ten out of their 11 cases (type of RS not specified) had upper airway issues, of which 7 had “late onset” (ie, onset between day 24 and day 51). This suggests that RS patients can have late-onset breathing issues or that clinical evaluation alone is not sufficient for the identification of airway problems.⁹

Manica et al in 2018 found a relationship between the clinical grading by Cole et al and PSG outcomes (n = 55, of which 26 isolated, 14 RS-plus, 15 syndromic) in their prospective study, this might suggest that clinical evaluation is useful in the workup of RS.¹⁸

Oximetry and blood gas

Abadie et al 2002 recorded central apneas or hypopneas by repeated systematic respiratory and cardiac monitoring. Each child (n = 66, isolated RS) had recurrent measures of pulse oximetry (SaO₂) and PCO₂. The timing and duration of these measurements were not reported in this retrospective study and PSG was indicated when clinical data were insufficient to evaluate respiratory disorders. It is unclear from this paper what the definition was for “insufficient clinical data.”

Glynn et al 2011 performed a retrospective review including 62 isolated RS patients. They recorded and monitored continuous oxygen saturation over a 24 to 36-hour period. In their analysis they consider oxygen saturation of less than 90% for more than 5% of the time as significant and unsatisfactory. Justification of this threshold or outcomes related to this were not mentioned in their study.

Kwan et al 2021 performed a 2-center retrospective study to assess whether the capillary blood gas sampling (PCO₂ and HCO₃) values are associated with the need for airway intervention.¹⁹ A total of 274 RS patients were reviewed (71% isolated), of these, 111 cases had information available on capillary blood gas sampling (86% isolated). The remainder were patients with severe airway obstructions or multiple comorbidities, such as prematurity, metabolic disorders, and/or synchronous cardiac pathologies. Others were referred for surgical intervention or had already been intubated. They used a cut-off value for PCO₂ at 55 mm Hg and HCO₃ at 30 mEq/L. Patients who ultimately required airway intervention demonstrated significant higher mean capillary PCO₂/HCO₃ values at every measured time domain (day-of-life 0–6 and 7–30). Significant airway obstruction was demonstrated by capillary blood gas values as early as the first weeks of life. This study suggested that a single, normal capillary blood gas value prior to day-of-life 9 may provide false reassurance, as a sufficient period of time has not elapsed to detect mild to moderate CO₂ retention. It also suggested that RS patients with chronic airway obstruction tend to demonstrate abnormal capillary blood gas values by day-of-life 9. Thus, a normal capillary blood gas values obtained after day-of-life 9 may indicate that airway intervention is less likely to be necessary. The authors suggest that patients who have normal capillary blood gas values may benefit from continued monitoring for CO₂ retention over the first 30 days of life.

Polysomnography

Daniel et al 2013 reported the use of PSG with transcutaneous O₂/CO₂ monitoring for a period of at least 4 hours of sleep time. Sleep staging for infants <6 months of age was completed using the Anders, Emde & Parmelee criteria and those >6 months with the AASM. Respiratory events were considered significant if they lasted >2 respiratory cycles and were terminated by an arousal and/or desaturation of >3%. Information was collected on AHI, OAH1, OAH1 during rapid eye movements, OAH1 during slow wave or quiet sleep, mean duration apneas and hypopneas, and O₂ and CO₂ levels. All included patients (n = 39, of which 15 with isolated RS) were shown to have OSA. There were no significant differences between severe OSA in isolated RS versus those with additional abnormalities. There were no significant differences with respect to the proportion requiring airway interventions other than prone positioning in hospital (53.3 for isolated versus 79.2% for nonisolated) or on discharge (46.7 for isolated versus 66.7% for nonisolated). Airway intervention other than prone positioning was required in 27 patients (type of RS not specified) in hospital and 23 on discharge. The authors of this study implemented PSG as a standard part of their diagnostic workup for RS following this retrospective review.

Van Lieshout et al 2014 used the Guilleminault criteria to score the severity of OSA from PSG results in 42/59 children, of these 26 took place before the age of 1 year (median age of the total group, 47 days, range 5–348 d) and before upper airway related surgical interventions. No significant differences were seen in the outcomes of isolated RS (PSG results, n = 21) versus nonisolated RS (PSG results, n = 16) in their retrospective cohort study. These outcomes included the percentage of patients who had a PSG, patients under 1 year old having PSG, the proportion diagnosed with OSA, and the numbers found to have each mild, moderate or severe OSA.

Hong et al 2020 indicated a PSG when respiratory symptoms including gasping, choking, colour change during sleep, failure to thrive, hospitalisation for any respiratory symptoms were apparent. This prospective study included 14 patients, 11 isolated and the remaining 3 with associated malformations (nonisolated RS). PSG was performed starting with the patient in its usual sleep position (nonprone or prone) and then approximately midway in the study once clinically useful information had been obtained (after typically 1.5–2 h of sleep time) the participant was switched to the other body position. Staging and scoring were completed according to AASM guideline. PSG was performed successfully for 12 participants in both body positions, nonprone to prone in 9 patients. In 9 patients OAH1 and CAI decreased in 9 infants from nonprone to prone position, sleep efficiency increased in 8 patients and AHI decreased in 9. However, this study was not able to demonstrate statistically significant differences between non-prone and prone body positions for obstructive AHI, central apnea index, arousal index (signed-rank test $P = 0.065$) and sleep efficiency ($P = 0.227$).²⁰

Manica et al 2018, reported that all RS patients (n = 55, 26 isolated RS, 14 RS-plus, 15 syndromic except those needing immediate respiratory support, are indicated for PSG. Although a relationship was seen for clinical grading by Cole et al and PSG outcome severity, for some patients in whom no clinical signs were seen in supine position (Cole 1) the PSG outcomes demonstrated OSA. This indicated that a PSG is needed, even when there are no clinical signs suggestive of breathing issues.¹⁸ Moreover, they reported that oxyhemoglobin saturation during PSG examination showed higher determination coefficients, even when compared to AHI. For example, an oxygen saturation

<90% was strongly associated with clinical manifestations and influenced more than one third of severity grading variation.

Hicks et al 2018 performed a retrospective study on infants (n = 31, 13 syndromic, 18 isolated RS) treated in NICU. PSG was performed in 64.5% pre-intervention, of which a subgroup underwent a split-night PSG.²¹ From the paper it is unclear when split-night PSG was indicated, yet in the discussion the authors mention that split-night PSG is of particular use in assessing the clinical effect of surgical advancement of the mandible.

Duarte et al 2021 performed a retrospective cohort study (n = 71 RS patient under 90 days of age, 19 syndromic).²² At their center, all patients who did not receive respiratory support (n = 49), such as tracheostomy, intubation, of continuous positive airway pressure (CPAP), underwent a PSG. With the PSG respiratory dysfunction could be diagnosed in all patients without respiratory interventions. Sleep studies were performed according to the AASM. 15 patients had AHI < 10, 15 AHI 10.1–20 and 19 AHI > 20.

Wiechers et al 2021 performed a retrospective study on isolated RS patients (n = 307).²³ Following admission, they performed a PSG on all patients before and after the appliance of a Tuebingen Palatal Plate (an orthodontic appliance) which was placed in all infants with a mixed obstructive apnoea index (MOAI) of > 3 as part of their standardized protocol. Sleep studies were performed in a supine position according to AASM. The MOAI decreased from a median (IQR) of 9.0 (3.4–22.8) to 0.9 (0.3–1.9) at discharge ($P < 0.001$).

Buchenau et al (2017) tested all infants with an 8-channel polygraphy to set a baseline for their study on the preepiglottic baton plate (PEBP).²⁴ From their baseline data in 122 infants with isolated RS, it becomes clear that oximetry measurements (DI80, defined as the number of desaturation events to $\leq 80\%$ pulse oximeter saturation (SpO₂) per hour of recording) can show normal results, while PSG shows moderate or severe OSA.

Flexible nasoendoscopy

Bravo et al 2005, found in their prospective study that FNE is useful for the evaluation of OSA in RS patients (n = 52, type not specified) who had not had previous surgical treatment and reported an 87% sensitivity and 100% specificity for its diagnosis as confirmed by PSG. The FNE findings were said to be significantly correlated (although a P -value was not provided in this paper) with AHI, arousal index, snoring time, percentage of sleep time spent at saturation of oxygen <90% and to have a significant inverse correlation with total sleep time, sleep efficiency and the mean saturation of oxygen during sleep. They did not state whether patients included underwent FNE awake or with sedation, however, they commented that FNE can be performed routinely in children using topical anaesthesia, and that complications were rare and only occur when the endoscope is placed beyond the glottis or in the lower respiratory tract.⁶

Abadie et al 2002 performed FNE without sedation in 60 isolated RS patients and found an unusual aspect in 45 cases (sensitivity 75%), which was not further specified. FNE was performed when upper airway difficulties were suspected. From their retrospective work it is unclear which criteria they used for suspicion of airway difficulties.¹⁶

De Sousa et al 2003 performed a prospective study in 56 RS patients, all underwent a first FNE without sedation within the first month of life, a second FNE during the following 6 months, and the third during the 12th month of life to assess respiratory obstruction and severity of glossoptosis. Types of obstruction were described according to the Sher et al classification. There

was no significant difference between severity outcome on FNE and clinical severity (Spearman coefficient = 0.26, $P = 0.09$). All 42 patients with type 1 respiratory obstruction showed mild or no clinical manifestation at 6 months of age, but all children presented with some degree of tongue retro-positioning, mainly mild (52.4%) and moderate (40.5%). At 12 months of age, the latter group of children did not show any clinical manifestations. The 10 children with type 2 respiratory obstruction evolved to type 1 with mild tongue retro-positioning on FNE at 12 months of age, and all cases of 3 or 4 respiratory obstruction showed the same type up to the end of their 1st year of life.²⁵

Van Lieshout et al 2014 retrospectively studied 59 RS cases (36 isolated, 8 syndromic, 15 with associated anomalies) and reported FNE results under sedation for 12 patients (4 isolated, 8 nonisolated) at a median age of 24 days. Main indications for FNE were intubation (n = 4), removal of endotracheal tube (n = 1) and evaluation of clinical airway obstruction (n = 8).²⁶

Manica et al 2016 studied FNE with sedation prospectively (n = 58, 24 isolated, 15 syndromic, 19 RS-plus) and correlated the clinical grading of symptoms according to Cole et al with endoscopy outcomes using the Yellon and de Sousa classifications. They found airway anomalies in 17.4% of isolated RS and 55.6% of RS-plus. However, it was unclear from this study what type of anomalies were specifically seen in RS as other types of disorders were included in their study population. Especially in severely affected patients (Cole grade 3) airway abnormalities were seen, which were confirmed by both Yellon and de Sousa endoscopic classification. Moreover, the worse the anatomical findings, the larger technical difficulties for performing endoscopy were noted, with major difficulty in laryngeal exposure in 15.5% of their study population (n = 58, of which 24 isolated RS and 19 RS-plus).²⁷

Duarte et al 2021 performed a retrospective cohort study (n = 71) in RS patient under 90 days of age, 19 were syndromic. All patients underwent an otolaryngology evaluation for flexible and rigid airway endoscopy to assess the degree of glossoptosis.²² The Yellon scale was used for grading severity: 8 patients had Grade 1, 37 Grade 2, and 26 Grade 3. In their univariate analysis they found that Grade 3 glossoptosis raised the risk for needing respiratory support (OR 12.75, 1.03–157.14). This association was not detected in multi-variate analysis.

Radiographic measurements

Duarte et al 2021, performed a retrospective cohort study (n = 71 RS patient under 90 days of age, 19 syndromic).²² They measured the mandibular length on CT-scans at a mean age of 39 days and found that mandibular length was independently associated with the need for airway support. A reduction by approximately 27% was seen in risk for each additional mm in mandibular length at diagnosis, OR = 0.73 (0.56–0.96). The need for respiratory support was associated with a protective effect of the mandible length, where they used AHI < 10 as a reference group.

What are the Indications and Policy for Treatment of Breathing Problems (OSA) in Patients With RS?

Polysomnography

Children under 2 years of age present as a unique population with a predisposition to UAO for a variety of reasons. As a result, age-appropriate evaluation for airway obstruction and breathing difficulties is necessary for the assessment of babies and young children with RS. Scoring parameters and levels of severity for children differs from that of adults and clinicians should refer to AASM scoring guidelines and the appropriate ERS statements for the relevant age group. As all patients with

RS will present within the first 2 years of life, the European Respiratory Society (ERS) guidelines for children aged 1 to 23 months can be used to grade severity of OSA on PSG (AHI of <1 episode hour⁻¹ is healthy, mild OSAS frequently seen with AHI 1-5, moderate with AHI > 5-10, and severe with AHI > 10 (28). The ERS has recommended treatment for children with an AHI > 5 (without symptoms), or for those with an AHI 1 to 5 (with symptoms or risk factors). Mild central sleep apnoeas are common in otherwise healthy infants without clear evidence of associated long-term morbidity. As the frequency of central apnea varies according to age and definition, the OAHl rather than the AHI may be more relevant in stratifying the severity of OSAS in children and guiding treatment. Some groups prefer the MOAI instead of the MOAHI for RS infants, because the latter has a lower interobserver agreement.³⁵

Oximetry and Blood Gases

In a study by De Buys Roessingh et al 2007 (n = 8/48, of which 32 isolated RS) intervention (nasopharyngeal tube) was indicated in cases with persistent desaturation at less than 90% with clinical evidence of respiratory distress or chronic carbon dioxide retention as evidenced by a base excess of more than 6.5.²⁹

Conclusions

Quality of evidence without GRADE	<p>Diagnostic value of evaluation based on respiratory signs for breathing problems</p> <p>There are cautious indications that clinical assessment after birth is not sufficient as late-onset breathing issues can occur or are not captured by clinical evaluation at initial assessment.</p> <p>Reference: (9)</p> <p>It is likely that clinical evaluation contributes to the RS workup as a relationship was found with the severity of PSG outcomes.</p> <p>Reference: (16).</p> <p><i>Conclusion based on evidence from (n=2) single-arm studies with a high risk of bias and important heterogeneity important imprecision and partially indirect evidence.</i></p>
Quality of evidence without GRADE	<p>Diagnostic value of evaluation based on oximetry for breathing problems</p> <p>There are cautious indications that recurrent measures of oxygen desaturation of less than 90% for more than 5% of the measured time, over a period of 24-36h, can be considered unsatisfactory</p> <p>Reference: (17).</p> <p><i>Conclusion based on evidence from (n=1) single-arm retrospective study with high risk of bias and imprecision but no important heterogeneity or indirect evidence.</i></p> <p>There are indications to suggest that the sensitivity of oximetry (DI80) for obstructive breathing problems is lower than the sensitivity of PSG in children with RS.</p> <p>Reference: (24)</p> <p><i>Conclusion based on indirect evidence from (n=1) study, with a high risk of bias and heterogeneity but no important imprecision.</i></p>
Quality of evidence without GRADE: -	<p>Value of evaluation based on blood gas for breathing problems.</p> <p>There are cautious indications that patients with significant airway obstruction may present with raised capillary blood gas results (pCO₂ > 55 mmHg or</p>

Quality of evidence without GRADE	<p>HCO₃ mEq/L. However, those who present with normal values up to DOL 9 should continue to be monitored over the first 30 DOLs. Elevated blood gas parameters may support the need for airway intervention.</p> <p>Reference: (19).</p> <p><i>Conclusion based on evidence from (n=1) single-arm retrospective study with high risk of bias and no important heterogeneity, imprecision or indirect evidence.</i></p> <p>Diagnostic Value of PSG for breathing issues in PRS</p> <p>Studies indicate a routine PSG is useful in the screening for breathing abnormalities for all RS patients also when clinical signs for respiratory distress are absent.</p> <p>References: (10, 16).</p> <p>PSG is a modality of assessment that can diagnose OSA, and has been used to assess severity of OSA.</p> <p>References: (10, 18, 26)</p> <p><i>Conclusion based on evidence from (n=5) single-armed retrospective studies with high risk of bias, important heterogeneity and indirectness of evidence but no significant imprecision.</i></p>
Quality of evidence without GRADE	<p>Value of PSG for monitoring breathing issues</p> <p>Studies indicate PSG is useful for monitoring RS patients even for those with improvement but not completely resolved airway obstruction. PSG is also useful to monitor effect on OSA following interventions.</p> <p>References: (20, 23)</p> <p><i>Conclusion based on indirect evidence from (n=2) single armed studies with high risk of bias but no important heterogeneity or imprecision.</i></p>
Quality of evidence without GRADE	<p>Diagnostic value of FN for breathing problems</p> <p>Studies indicate FN is useful for evaluating the level of obstruction leading to OSA and airway abnormalities in RS patients. The degree of glossoptosis detected on FN may be associated with need for respiratory support.</p> <p>References: (6, 16, 22, 27, 27)</p> <p><i>Conclusion based on evidence (n=5) single armed retrospective studies with high risk of bias, significant heterogeneity and indirectness of evidence but no important imprecision.</i></p>
Quality of evidence without GRADE	<p>PSG as an indicator for treatment</p> <p>No studies identified from the literature review evaluated the PSG scores at which to begin treatment of breathing. However, as per the ERS statement on OSA in children 1-23 mo old, those with an AHI of > 5 or 1-5 with respiratory symptoms should receive treatment.</p> <p>References: (3)</p> <p><i>Conclusion based on ERS Statement on sleep disordered breathing. This statement is based on a systematic literature review, but the quality of included evidence is not made explicit.</i></p>
Quality of evidence without GRADE	<p>Oximetry and blood gases as an indicator for treatment</p> <p>Persistent desaturation of less than 90% with clinical evidence of respiratory distress or chronic carbon dioxide retention, evidenced by a base excess of more than 6.5, have been used as parameters to</p>

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indicate airway or breathing management. Reference: (29).

Conclusion based on indirect evidence from (n=1) single-arm retrospective study with high risk of bias, significant heterogeneity and possible imprecision.

Considerations Quality of Evidence

Data used for policy for screening and monitoring and policy for intervention were sourced from 10 studies. Five of these were retrospective observational studies and 5 were prospective studies. Of the prospective studies, 2 compared outcomes for RS patients grouped by severity (observational), 2 evaluated the use of a single intervention for the whole group of patients (different interventions), and 1 compared the use of 2 classification systems used following FNE. 3 studies did not separate results for isolated RS from nonisolated RS, 3 included only isolated RS, 2 separated some results but not all, and 2 separated results, with one study finding no differences between isolated RS and syndromic RS, but the other finding there were differences between the management needed in isolated RS and syndromic RS. Since no studies compared the same interventions, a grade assessment could not be performed. Given that there were no interventional studies addressing the same outcome, and half the studies used were purely observational, the evidence base of these recommendations may not be considered comprehensive and are likely to be liable to the biases of the individual authors.

Patient's Perspective

Seeing your infant struggle to breathe can cause acute distress for parents, whether in a hospital environment or at home. Therefore, it is important for healthcare practitioners to be aware of this distress and offer timely counseling and education around warning signs and what do or not to do given the circumstances. Where PR is diagnosed antenatally, counseling and education around breathing need to begin in preparation for birth.

Professional Perspective

Infants presenting acutely in severe respiratory distress should be stabilised by clinicians following standard resuscitation algorithms (ALS, APLS, EPLS). If RS is suspected on the primary clinical assessment, then further advice on management should be requested from a team with experience in the management of this condition. When patients with RS present with acute severe respiratory distress, appropriate assessment of the upper airway and use of a NPA or a laryngeal mask might suitably stabilize the airway. If diagnosis of RS is suspected on prenatal assessment, for example US (see Chapter 5), consideration should be given to prepare a team for a risk birth, and consideration should be given for including specialists from ENT, paediatric anaesthetics and neonatology. This should ideally take place within or in consultation with a unit with specialist expertise with RS.

As breathing problems may not be initially apparent in babies with RS, clinicians should maintain a high index of suspicion in infants with micrognathia with or without a CP. Furthermore, the clinical severity can vary significantly between children and over time. Typically, these breathing difficulties tend to occur while sleeping (particularly in the supine position), while feeding and when distressed. As breathing function typically varies with these events of normal activity, a 24 to

48-hour period of continuous assessment can be particularly informative to screen for these characteristic features.¹⁶ Clinical assessment of respiratory distress in a child with suspicion for PR at first presentation after birth may be normal but late onset respiratory distress may occur within 2 months after birth. With education, close communication with families and repeated clinical assessments a balance of inpatient and community care can be achieved with appropriately timed interventions to support breathing and growth.¹⁰ A decrease in weight or growth trajectory is a sign of clinical deterioration which should prompt further investigation and intervention.

PSG is the gold standard for the objective assessment of respiratory function and should be considered not only in the event of clinical deterioration in a child with features of isolated and nonisolated RS but should be performed for all children suspected of having RS. Inclusion of PSG cardiorespiratory parameters only will suffice; inclusion of the EEG (electroencephalogram) component may provide further information but is not necessary.

During the first year of life, PSG may be unavailable or difficult to interpret. A recent publication by Kaditis and Gozal³⁷ points out that the interpretation difficulties have to do with a lack of studies on reference parameters in healthy infants. Reference values for PSG, polygraphy or nocturnal oximetry have been reported only in very few studies and only with small sample sizes. Median and maximum AHI values vary widely amongst studies, making it difficult to define what normal outcome is in neonatal PSGs. Additionally, respiratory parameters are affected by the specific state of sleep and wakefulness. Until today, it is unknown whether sleep duration and patterns of infants undergoing PSG in clinical practice can be directly compared to that of healthy infants on whom reference parameters are based.

In infants where PSG is unavailable or difficult to interpret, transcutaneous pCO₂ and oxygen saturation recording may be useful, but cut-off criteria are not universally agreed upon yet.

In addition, cardiorespiratory polysomnograms, are a less time-consuming diagnostic tool, and more appropriate particularly in settings with limited resources and accessibility to a full PSG set up. Although OAH scores from the PSG are useful in stratifying severity according to AASM definitions other measures (oxygen desaturation index, mean oxygen saturation, absolute oxygen saturation, %total sleep time <90% oxygen saturation, sleep efficiency, arousal index) should also be considered in the interpretation of the study relative to the overall clinical presentation. PSG in newborns should be carried out (or repeated) at 2 or 3 weeks or later, because prior to this age the outcome may be unclear because it may be influenced by the immature breathing and brain development of the newborn.

As the availability of comprehensive cardiorespiratory polysomnograms may be limited, due to location, an individual measure such as oximetry may be utilised. Although oximetry alone provides less comprehensive information on respiratory function it is able to detect significant desaturations in an emergency situation. Oximetry readings fluctuate even in healthy children who generally maintain oxygen saturations above 95% in room air. In 5- to 11-year-olds, oximetry readings of <94% for up to 5% of total sleep time can still be regarded as normal and up to 5% of infants can have oximetry readings down to 90% for more than 4% of the time.³¹

Oximetry can be utilized to detect night-to-night variation as well as alerting carers to significant desaturations³¹ in the community. The information gained from oximetry should be considered in addition to a full PSG³² when screening or

monitoring breathing problems in RS, but cannot be used to diagnose OSA or sleep disordered breathing.

Flexible nasoendoscopy (FNE) is a qualitative method of assessment which can be useful in confirming obstruction of the airway at the tongue base in the supine position as well as determining additional anatomical levels of obstruction,^{27,33} however, it should not be used for diagnosis of OSA alone. Clinicians should be aware that scoring systems correlate poorly with the severity of clinical breathing problems in RS but may help guide clinicians on the suitability of different options for intervention. FNE may be safely performed with sedation in theatre, or without sedation in the outpatient setting, depending on the patient, therefore use of sedation or not when performing FNE should be decided on a case-by-case basis. Additionally, during FNE in sedation, the difficulty intubating should be determined, as this data is important for future airway management

Proposed Protocol

No papers reviewed in the literature search for this guideline included a validated algorithm for the management of airway and breathing problems in RS, however Hicks et al included an algorithm based on their experience over 8 years. Following several discussions, the group of writers and members of the Steering Group agreed on the algorithm for the management of RS patients.

Balance of Benefits and Harms

Due to the high prevalence of breathing disorders and potential mortality of breathing problems in RS, all patients with RS should be appropriately assessed as per our recommendations to facilitate appropriate management for airway and or breathing problems. Patients with RS with acute respiratory compromise should undergo immediate resuscitation as per ALS, due to the adverse outcome of respiratory failure.

Stable patients should undergo assessment for OSA/airway or breathing problems as detailed in the first part of this chapter, and Multidisciplinary Team (MDT) evaluation, due to the adverse risk of breathing problems, benefits of which outweigh harms. While FNE is useful for detecting airway abnormalities in RS patients,^{6,16,26,27} it may be challenging in severely affected patients.²⁶ Additionally, results from FNE should be interpreted cautiously given that there is a lack of a validated scale for FNE outcomes.^{6,27} However, it is important to understand the anatomical nature of the obstruction to ensure appropriate treatment is given, therefore use of FNE should be discussed and decided on a case-by-case approach.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available care providers and facilities. Some elements of screening and monitoring would be available in all settings for example, clinical assessment and oximetry. However, in some centres the availability of polysomnography, flexible nasoendoscopy and MDT to review may be limited, therefore patients are likely to require referral to a tertiary centre.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe with regards to care for patients with rare diseases. At present, not every member state offers an expert centre for RS or the level of provided care does not (yet) meet all requirements that are outlined in this guideline. By defining the baseline of

required care for RS, this guideline will help these members stated to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu), and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal health care and are discussed with a member from participating European countries. Quality of care was paramount in the discussions. Centralisation is proposed as one of the core values. However, in some countries the national organization of health care might impede centralisation. National implementation of the ERNCs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and the collaboration with an expert centre in the surrounding countries can be an option.

Acceptability of the Recommendation

It is expected that all stakeholders want to apply and will be applying the recommendations, because they are employed in ERN acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as this guideline on RS is obligatory.

Rationale of the Recommendations

Airway and breathing problems in RS are important, with serious consequences if not appropriately managed. The investigations for screening and monitoring facilitate an appropriate in-depth investigation of these patients who may have presentations that improve or worsen with time. Given that this is a rare condition, nontertiary centres may have limited experience in screening and managing these patients.

Recommendations

- If the diagnosis of RS is suspected on prenatal assessment (see Chapter 5) consider preparing a team for a risk birth; consider inclusion of specialists from ENT, paediatric anaesthetics and neonatology. This should ideally take place within or in consultation with a unit with specialist expertise with RS.
- Stabilise infants presenting (acutely) in severe respiratory distress following standard resuscitation algorithms (APLS, EPLS).
- If RS is suspected (persisting airway and/or breathing problems), patients should be managed in consultation with an expert center regarding assessment and management.
- Screen for breathing problems with regular clinical assessment and continuous oximetry.
- Perform a baseline sleep study in every newborn with suspected RS to determine the severity at initial presentation.
- Monitor breathing problems by repeated sleep studies to assess outcomes following treatment or clinical deterioration.
- Perform a flexible nasoendoscopy for every RS patient to identify all levels of obstruction.

- Management for each patient with RS should be decided by MDT following the recommended investigations (continuous oximetry, clinical assessment, PSG, FNE).
- A recommendation for the algorithm for the management of RS patient is provided (see PPT).

Research Gap

The literature on airway and breathing problems in RS is limited; most studies were retrospective review of management by one center, or prospective without comparing interventions; few comparative studies have been performed, which has therefore led to difficulty in making evidence-based recommendations on which modalities of screening and monitoring to include, and algorithms for management of airway and/or breathing problems in RS. A European registry currently being established to compare diagnostic and treatment modalities for RS.

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may result in prolonged feeding times. Some children are completely unable to feed orally.

In addition to these difficulties, reflux,²⁻⁴ vomiting,⁵ or regurgitation⁶ are commonly reported and may be associated with the generation of negative intrathoracic pressure due to airway obstruction at the tongue base. However, upper and lower oesophageal sphincter anomalies⁶⁻⁸ ranging from 30% to 70% have also been identified in these children. Aspiration is also a significant risk affecting 5% to 65% of these infants.^{5,9}

A question frequently posed is whether or not infants with RS require screening and monitoring of feeding problems. Numerous studies have shown that feeding problems are often associated with poor growth and increased number and length of hospital admissions. However, it is unclear whether all infants with RS require screening and monitoring, or just those that meet specific criteria. Currently, there is not a specific policy in place for the screening and monitoring of feeding problems.

Methods to screen and monitor for feeding problems include clinical assessment (identifying the type of feeding problem), and the utilisation of objective investigations such as EMG, fiberoptic endoscopic evaluation, oesophageal pH monitoring, growth parameters (head circumference, z-scores for weight, weight for height, height for age, weight gain, length gain, percentiles), and volume intake.

It is important to note that feeding problems are closely associated with airway problems, and airway problems may indeed be the most significant risk factor for the development of feeding problems. Therefore, identifying and monitoring airway problems in any infants with RS should be considered. However, specific parameters to monitor and screen for airway problems are beyond the remit of this chapter and can be found in Chapter 6.

The clinical assessment involves the recognition of the various types of feeding problems but can broadly be split into: (1) poor sucking and/or swallowing, which may manifest as prolonged feeding, reduced intake, aspiration, or an absence of oral feeds, (2) esophageal motility disorders and pharyngo-laryngeal disorders such as: aspiration (sometimes silent), gastroesophageal reflux, vomiting, oesophageal sphincter abnormalities, or (3) failure to thrive as indicated by impaired weight or length gain. Often feeding difficulties are defined as the requirement of enteral feeding including nasogastric tube (NGT) requirement or gastrostomy tube placement. The prevalence of these feeding problems varies significantly, and often these feeding difficulties manifest in combination. Careful recognition is required to initiate early intervention.

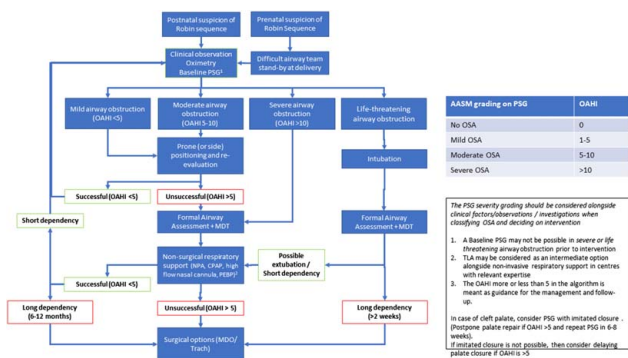
Once patients with feeding problems are recognized the dilemma of how to effectively treat these patients arises. There are a number of direct feeding methodologies such as NGT placement and gastrostomy that may be utilized. Additional interventions, both nonsurgical and surgical aimed at treating airway obstruction and indirectly feeding problems are also described in the literature but discussed further in Chapter 11 and 12.

In order to describe and develop a policy for diagnosing and treating feeding problems in patients with RS, the following questions were included in this chapter:

- What is the policy for screening and monitoring of feeding problems in patients with RS?
- What are the indications and policy for treatment of feeding problems in patients with RS?

To answer these questions, we have investigated the following outcomes of interest: feeding, suckling, feeding times, dysphagia, gastroesophageal reflux, aspiration, and the indications for nasogastric tubes, gastrostomy and the PEBP.

Appendix 6.1 Algorithm Flowchart



CHAPTER 7. FEEDING AND GROWTH

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of RS patients a CP is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

Whilst feeding problems are a well-known functional difficulty in patients with RS, these problems are heterogenous. The characteristic features of RS which include micrognathia, glossoptosis, and airway obstruction with or without CP, may play contributory roles in feeding problems either directly through anatomical impairment of deglutination or suction, or indirectly due to airway obstruction.¹ Airway obstruction may lead to exhaustion making it difficult for the infant to feed, and also increase the metabolic demands thereby affecting growth. Both

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Literature search

For this guideline, a systematic literature search was conducted to identify studies that reported type, prevalence and severity of feeding problems in isolated and nonisolated RS. Treatment options and policy for monitoring feeding problems were also investigated. Studies that reported outcomes for syndromic RS patients were excluded. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria

Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Feeding, suckling, feeding times, dysphagia, gastroesophageal reflux, aspiration, nasogastric tubes, gastrostomy, pre-epiglottic baton plate
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

For this guideline, a systematic literature search was conducted, and articles were screened based on relevance of title and abstract to the questions posed in this chapter. A total of 78 articles were assessed for relevance based on the content of the full text, of which 23 articles satisfied the inclusion criteria. 55 articles were excluded because of wrong population ($n=33$), wrong outcome ($n=19$), too small cohort ($n=3$). A full summary table of the 23 studies included in this chapter can be found in the Appendix, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Summary of Literature Study

What is the Policy for Screening and Monitoring of Feeding Problems in Patients With RS?

Anatomical grading

The correlation between anatomical variations and feeding disorders has been assessed by few studies in the literature.^{6,10} Abadie et al 2002 retrospectively reviewed 66 isolated RS patients and found that there was poor correlation between anatomical features and severity of feeding disorders (ranging from none or minor, to dangerous bottle feeding and UAO), except for major grades of micrognathia and glossoptosis.⁶

In their retrospective cohort study Morice et al 2018 studied 24 isolated RS patients of which 79% of patients required enteral feeding were categorised into very mild ($N=3$; < 3 wk of enteral feeding), mild ($N=2$; 3 wk to 3 mo), moderate ($N=4$; 3–6 mo), severe ($N=9$; 6–12 mo), very severe ($N=1$; > 12 mo) based on the duration of enteral feeding requirement. Using multivariate analysis, the authors found that severe micrognathia, severe glossoptosis, laryngomalacia and syndromal RS status were not predictive of long-lasting enteral feeding.¹⁰

Intake

Only 2 studies measured intake as a parameter to monitor for feeding disorders.

Nassar et al 2006 investigated the benefits of prone positioning and NPA usage in 26 patients with isolated and nonisolated RS. The volume of milk intake was increased following

treatment and was associated with a shorter duration of oral feeding. Only 33% of patients required additional nutritional supplementation through NGT feeding at discharge, compared to 69.2% at admission.¹¹

Marques et al 2010 evaluated total volume of milk ingested at week 1, 2, and 3 of hospitalization in 11 isolated RS patients that required a NPA and feeding facility techniques (eg, prone position, nipple modification). The authors noted that the mean volume ingested significantly increased in weeks 2 and 3 versus week 1 ($P=0.001$) and the need for feeding tubes to supplement nutrition decreased from 63% at week 1 to 18% at weeks 2 and 3 (9).

Electromyography

Oesophageal sphincter abnormalities (eg, hypertonia or failure to relax) were described in 3 studies using electromyography (EMG).^{6–8} Prevalence ranged from 30% to 54% and additional complications such as gastroesophageal reflux disease (GERD) were reported. Abadie et al 2002 performed oesophageal manometry in 43 isolated RS patients and found that lower oesophageal hypertonia and lower oesophageal sphincter failure to relax increased in incidence according to severity of feeding difficulty, but that this was not statistically significant.⁶ Baujat et al 2002 investigated oesophageal disorders in 27 isolated RS patients and noted oesophageal abnormalities in 50% of the cohort. Reflux in these patients was resistant to classic GERD treatment. However, clinical and manometric abnormalities showed a trend to spontaneous resolution after 12 months.⁸

Baudon et al 2002, used electromyography to assess incoordination of sucking and swallowing in 24 patients with isolated ($N=21$) and nonisolated ($N=3$) RS and compared these results to 16 infants with GERD who were otherwise healthy. The authors found that the frequency of oesophageal disturbances was much higher in the RS group than GERD patients.⁷

In their retrospective cohort study of 25 patients with isolated PRS, Renault et al 2000, using EMG identified that the majority of RS patients (52%) have moderate abnormalities, often suffering from dysphagia, and require NGT insertion. EMG results showed that abnormalities of the tongue and inability to perform rhythmic sucking as a major source of feeding problems severity.¹² In a later study by Renault et al 2011 the authors used EMG to assess motor function in a cohort of infants including 57 isolated PRS patients. The following severity categories were noted: normal coordination or mild suck-swallow disorder ($n=27$), moderate suck-swallow disorder ($n=14$), severe disorders ($n=16$). Length of enteral feeding was more common in increased severity grades.¹³

Fiberoptic endoscopic evaluation

Marques et al 2010 used fiberoptic endoscopic evaluation to assess the efficacy of NPA and feeding facility techniques in 11 isolated RS patients in hospital over 3 weeks. The authors reported that 7 patients were at risk of aspiration at week one, and this was decreased to 4 patients in weeks 2 and 3.⁹

Oesophageal pH monitoring

Dudkiewicz et al 2000 highlighted the importance of diagnosing RS patients with GERD using techniques such as 24-hour oesophageal pH monitoring.¹⁴ Marques et al 2009 used 24-hour oesophageal pH monitoring to assess the efficacy of NPA in 20 isolated RS patients. The prevalence of abnormal GERD (>95th percentile of the Vandenplas reference for normal children) at 2 months of age was 30%, and this significantly decreased at assessment at 4 and 6 months, highlighting the efficacy of NPA treatment and also the usefulness of oesophageal pH monitoring for detecting GERD.²

Growth

Six studies reported changes in growth in isolated and non-isolated RS patients either in the context of the improvement in feeding difficulties following intervention, or as a way to characterise the natural progression of RS.^{4,5,15–18} Four studies aimed to characterise growth changes in patients with RS, but did not assess the effects of a specific treatment modality on growth.^{4,5,16,18} Only Dorise et al 2019 specifically reported referral to a dietician for feeding and growth problems in a cohort of 49 infants with isolated and nonisolated RS. The authors noted that malnutrition, defined as weight for age Z-score of ≤ -1 , was present in 57% of the cohort at discharge and that over 30% of patients were not assessed by a dietician. The authors called for the development of a uniform guideline with recommendations for referral to a dietician.⁵ In their retrospective cohort study, Evans et al 2006 characterized failure to thrive and developmental delay in 63 isolated RS patients. Failure to thrive was noted in 27% of the cohort and developmental delay reported in 10%, but no other definition was provided for successful treatment other than “adequate nourishment.”¹⁶ Stubenitsky et al 2010 noted the length of hospital stay and airway obstruction delayed weight gain in 46 isolated RS patients during 4 weeks of admission, and growth improvements were noted when airway treatment was available.⁴ Finally, in a cohort of 34 isolated RS patients, growth (weight and height, related to age) was assessed at 2 and 12 months, with authors noting growth catch up during these months. By a year, the majority of patients were noted with be within a standard deviation of the mean for healthy children of the same sex category.¹⁸

The specific effects of treatments on growth are discussed in the section below. The main methods to characterize growth were by daily weight gain, or use of standardized growth charts published by the National Center for Health Statistics.^{15,17}

What are the Indications and Policy for Treatment of Feeding Problems in Patients With RS?

In total 10 studies from our literature search reported the effects of specific feeding interventions including NGT, hypercaloric feed, and gastrostomy.

The majority of interventions were aimed at the treatment of airway problems; however, the effects of feeding were often assessed as secondary outcomes. The efficacy of these interventions is discussed in Chapters 11 and 12.

Nasogastric tube insertion

A review of the literature identified 4 studies that specifically reported on the effectiveness of NGT feeding in isolated RS patients. In a retrospective cohort study by Anderson et al 2007, 12 isolated RS patients were treated with NGT feeding. After NGT insertion, the feeding difficulties that contributed to failure to thrive improved. As such, the median daily weight gain was 28 g per day while in hospital, and after discharge the median daily weight gain was 31 g per day. After parents had undertaken training to care for an NGT at home, 8 patients achieved a greater rate of weight gain at home compared to in hospital. No complications were associated with the use of NGT feeding and no patients were readmitted with failure to thrive.¹⁵

A retrospective cohort study by Smith and Senders 2006 included 36 isolated RS patients, of which 19 patients received NGT feeding for feeding difficulties due to UAO. Of these 19 isolated RS patients, 10 (52.6%) patients were successfully treated with NGT feeding, while 9 (47.4%) patients ultimately required surgical management with gastrostomy. Of the 33 isolated RS patients who had 3-year follow-up data, a successful oral diet was present in 30/33 (90.9%) patients. Of the 12 non-

isolated RS patients in this study, 10 patients received NGT feeding for feeding difficulties due to UAO. Of these 10 non-isolated RS patients, no (0.0%) patients were successfully treated with NGT feeding, with all 10 (100.0%) patients requiring surgical management with gastrostomy.¹⁹

In a prospective cohort study by Gozu et al 2010, 15 isolated patients were included of which 9 patients received NGT feeding, NGT feeding alone was successful in 3/3 (100.0%) patients with isolated RS; while prolonged intubation with NGT feeding was successful in 5/6 (83.3%) patients with isolated RS.²⁰

In a retrospective mixed cohort study by de Buys Roessingh et al 2007 with 32 isolated and nonisolated RS patients, 11 patients received NGT feeding. The utilization of NGT feeding enabled all (100.0%) patients to avoid gastrostomy.²¹

Hypercaloric feed

Only one study, Marques et al 2004, investigated the efficacy of a hypercaloric diet (milk formula supplemented with 5% to 7% glucose polymers and 3% to 5% medium chain triglycerides) on feeding problems and growth in 23 isolated RS infants. Overall, 9 patients received the hypercaloric diet compared to 14 receiving a normal milk formula. The authors concluded that a hypercaloric diet was associated with earlier clinical improvement, and a shorter duration of NPA requirement. Infants in both groups remained below the 50th percentile for weight of the National Center for Health Statistics in the study period but weight gains were significantly higher in the group with the hypercaloric diet.¹⁷

Gastrostomy

No studies were found that reported on the effects of gastrostomy.

Tuebingen Palate Plate (TPP)

Two studies by Wiechers and colleagues have investigated the efficacy of TPP on growth. Wiechers et al 2019 noted that following TPP, the requirement for a NGT decreased from 73% at admission to 14% at discharge in a cohort of 22 isolated RS patients. Weight gain was noted between admission and discharge in all patients. The authors hypothesized that the promotion of mandibular growth may alleviate UAO, thereby alleviating feeding difficulties.²²

In a larger retrospective single center study by Wiechers et al 2021 in 307 isolated RS patients TPP and specialised feeding techniques reduced the number of children requiring NGF between admission and discharge after a mean of 3 weeks from 55.1% to 13.7%. In addition, at one-year follow-up, weight gain had improved from discharge (Z scores -1.17 versus -0.44). None of the patients required surgical treatment for their airway.²³

Overall, these studies highlight that weight recovery after initial growth failure is possible in RS infants even without nasogastric tube feeding with the adoption of TPP for upper airway management.^{22,23}

Conclusions

Quality of evidence without GRADE

Anatomical grading

There is limited evidence that anatomical features are not an effective way to screen for feeding problems. There was poor correlation between anatomical features and severity of feeding problems, except for major micrognathia and glossoptosis. References: Abadie et al, 2002, Morice et al, 2018 (6, 10).

Conclusion based on evidence from 2 single arm-observational studies with a high risk

of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Intake
 There is limited evidence that monitoring intake is an effective way to screen for feeding problems. There are cautious indications that intake is an effective method for monitoring the utility of treatments such as NPAs and feeding facility techniques.
 References: Marques et al 2010, Nassar et al 2006 (9, 11).
Conclusion based on evidence from 2 single arm-observational studies with a high risk of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Electromyography
 There are indications that oesophageal manometry and EMG are effective ways to detect oesophageal sphincter abnormalities and swallowing difficulties, respectively.
 References: Abadie et al 2001, Baudon et al 2002, Baujat et al 2002, Renault et al 2000, Renault et al 2011 (6-8, 12, 13).
Conclusion based on evidence from 5 single arm-observational studies with a high risk of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Fiberoptic endoscopic evaluation
 There are cautious indications that fiberoptic endoscopic evaluation is an effective way to detect aspiration and monitor feeding problems and the efficacy of treatment in patients with RS. (e.g. NPA).
 References: Marques et al 2010 (9).
Conclusion based on evidence from one single arm-observational study with a high risk of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Oesophageal pH monitoring
 There are cautious indications that oesophageal pH monitoring is an effective way to detect feeding problems, particularly GERD, in patients with RS, and also be used to assess the efficacy of treatments for RS (e.g. NPA).
 References: Marques et al 2009, Dudkiewicz et al 2000 (2, 14).
Conclusion based on evidence from 2 single arm-observational studies with a high risk of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Growth
 There are indications that suggest weight and height gain for age, and the use of standardized growth charts are reliable methods to screen and monitor for feeding problems and to assess the efficacy of treatment.
 References : Stubenitsky et al 2010, Dorise et al, 2019, Anderson et al 2007, Evans et al 2006, Marques et al 2004, Wan et al 2014 (4, 5, 15-18).
Conclusion based on evidence from 6 single arm-observational studies with a high risk of bias, but no important issues with indirectness, inconsistency, or imprecision.

Quality of evidence without GRADE

Nasogastric tube (NGT)
 There are indications that NGT treatment may lead to an improvement in weight gain in 53-100% of isolated RS patients

and in 0-83% in nonisolated RS patients.
 References: Anderson et al 2007, Smith and Senders 2006, Gozu et al 2010, de Buys Roessingh et al 2007 (15,19-21).
Conclusion based on evidence from 4 single arm-observational studies with a high risk of bias and inconsistency but no important issues with indirectness, or imprecision.

Quality of evidence with GRADE: LOW

Hypercaloric diet
 There are indications that hypercaloric formula diets are associated with earlier clinical improvement but and more weight gain in RS patients with feeding problems compared to normal formula.
 References: Marques et al, 2004 (17).
Tubingen palatal plate
 There are indications that the Tubingen palatal plate combined with specialized feeding techniques helps about 85% of patients to get off their NGT during their initial hospital stay
 References: Wiechers et al 2019, Wiechers et al 2021 (22, 23).
Conclusion based on evidence from 2 single arm-observational studies, both with a high risk of bias, but no important issues with indirectness, inconsistency or imprecision.

Considerations
Quality of Evidence

Data on screening, monitoring, and treatment modalities were all based on a single-arm retrospective or prospective cohort studies without any comparison between differing screening, monitoring or treatment modalities. As such, GRADE assessment could not be completed. The majority of studies were of poor methodological quality as assessed using the Newcastle-Ottawa Scale and were at high risk of bias. Only Smith and Senders 2006 reported outcomes for isolated and nonisolated patients separately, whereas Wiechers et al 2019 included only infants with isolated RS. In the former study, no significant differences between the isolated and nonisolated patients were observed.¹⁹

Professional Perspective

Almost all children with RS will be affected by a combination of feeding problems resulting in reduced growth and failure to thrive. Throughout early life, cleft and craniofacial teams should recognise the importance of family bonding and breast feeding. Early review by a lactation consultant is invaluable to support nutrition by breast milk if at all possible.

These needs should be balanced with well-judged and timed medical intervention to support optimal growth and development. As RS is a rare condition, care will need to be tailored to the individual medical as well as social needs of the patient.

There is a complex interplay between feeding disorders and breathing difficulties which impact growth in RS. Clinical teams caring for patients with RS should be aware of these relationships and combine their expertise to assess, monitor and treat all facets of the clinical presentation.

Early recognition of feeding problems and subsequent monitoring of these problems is particularly important in infancy due to low nutritional stores which are rapidly exhausted by the combination of respiratory compromise and feeding difficulties.

As there is no clear methodology for screening for feeding problems, the majority of studies focus on clinical assessment of feeding and growth. These clinical assessments by specialised

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Speech and Language therapists, Nutritionists and Paediatricians are necessary to identify feeding disorders early and support growth by timely intervention.

Swallowing and oesophageal disorders leading to gastro oesophageal reflux, poor sucking and swallowing are well recognized in RS and clinicians should have a low threshold for treatment. Diagnosis is usually made on clinical grounds. An NGT can be used to provide nutrition and when there is concern about a safe swallow or inadequate oral intake.

A minority of cases may benefit from investigation by oesophageal pH monitoring, or investigations to assess anomalies of swallow and oesophageal mobility. Although rarely required, they may help identify and define feeding dysfunction in patients with complex presentations who fail to respond to feeding interventions.

Medical treatment, dietician input, the use of special feeding bottles with variable milk flow, supportive enteral feeding by NGT and hypercaloric feeding should be considered early. As feeding and growth problems may also reflect airway compromise, teams should consider nonsurgical and surgical airway interventions to support feeding and growth, particularly as there is evidence of catch-up growth once airway problems are sufficiently addressed.

Although there is little evidence for gastrostomy use in RS, this can be considered when feeding support is likely to be permanent or for extended periods. As a result, more severe presentations of RS and failure of interventions are often reflected in an increased requirement for gastrostomy placement. Particular care should be taken when NGT are used concurrently with CPAP to reduce the risk of secondary morbidities such as pressure injuries.

Clinicians will be aware that normal development of feeding in the infant can be significantly compromised over the longer term by the development of orally aversive behaviours. These can develop following short-term feeding intervention (eg, NGT) or airway interventions (eg, NPA, MDO). Dietician input and feeding support should be available for all patients with RS and particularly in anticipation of the temporary weight loss that is often seen with surgical interventions such as MDO and TLA in the peri-operative period. As feeding and weight gain can recover with intervention (e.g. more in MDO than TLA), teams should aim to achieve normal growth trajectories for their patients and be aware of faltering growth as a strong marker of inappropriate treatment.

RS patients experience significant problems inherent to the condition as well as secondary to medical intervention. These patients and their families require regular, close support by teams with expertise and experience in the critical early years of life.

Importance of Outcomes

Feeding problems primarily impact growth during the first year of life. A number of studies have shown that treatment of feeding problems such as NGT and gastrostomy placement are associated with improved growth (weight and length gain), and reduced feeding problems. It is of the utmost importance to focus on treatment of feeding problems to improve growth in infants with RS.

Balance of Benefits and Harms

In RS, the majority of feeding problems manifest within the first few weeks of life and persist during the first year of life. This is a period of life when growth and development are particularly sensitive to feeding problems and therefore warrant particular

assessment and support. NG feeding facilitates enteral feeding of babies without impacting breathing and can be administered throughout the day. In addition, NGT can facilitate feeding when there is a concern about a safe or effective swallow. There are known risks associated with NGT feeding such as the potential for pressure injuries around the nose as well as the potential misplacement of the tube. Concurrent noninvasive ventilation with CPAP masks together with NG tube feeding can be associated with air leakage, distension of the stomach as well as an increased risk of pressure injuries. Although care of the NGT will be within the scope of healthcare teams, education will be required if patients are to be managed by families in the community.

Similarly, high caloric infant feeds can provide significant benefit to infants with RS who have increased calorific demands from work of breathing. These should be under the advice of the paediatric dietician and paediatrician who will be able to monitor growth parameters as well as for potential complications such as osmotic diarrhea, microelement and electrolyte imbalances.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available care providers and facilities. The recommendations concern the essential requirements for adequate treatment of infants with isolated and nonisolated RS and should thus be implemented. Costs are lowest and resources are most efficiently used when care for craniofacial disorders is centralised in a limited number of expert centers per member state. A general rule that can be applied is one expert center per 10 million inhabitants.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe with regard to care for patients with rare diseases. At present, not every member state offers an expert centre for RS, or the level of provided care does not (yet) meet all the requirements that are outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

It is expected that all stakeholders want to apply and will be applying the recommendations, because they are employed in ERN acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance and implementation of ERN guidelines such as this guideline on RS is obligatory.

Acceptability of the Recommendation

It is expected that all stakeholders want to apply and will be applying the recommendations, because they are employed in ERN acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries partic-

icipating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance and implementation of ERN guidelines such as this guideline on RS is obligatory.

Rationale for Recommendation

The essential principle of the recommendations is to offer the most optimal methods for screening, monitoring, and treating feeding problems to patients with RS and their parents. Early screening of feeding problems alongside treatment and monitoring of feeding problems in isolated and nonisolated RS may be associated with improved growth and reduced long-term feeding complications.

Recommendations Screening and Monitoring of Feeding Problems

- Standardize assessment protocols for feeding problems at initial presentation and monitor frequently throughout early life.
- Counselling of parents expecting a child with Robin sequence should highlight the potential difficulties of (breast) feeding and reassure them of the MDT strategy for monitoring and intervention.
- Utilize standardized growth charts to assess and monitor growth.
- Dietician advice should be requested for all babies with isolated or nonisolated RS at the initial assessment and throughout early life.
- Request SLT assessment in all patients with isolated or nonisolated RS.
- Record and monitor changes to intake (weight, length, and head circumference) to evaluate the efficacy of interventions.
- Monitor feeding and growth more frequently throughout any surgical interventions.
- Investigations of swallow and oesophageal function (EMG, fibreoptic endoscopic evaluation, oesophageal monitoring) may be considered by the MDT to define feeding dysfunction in complex patients who fail to respond to feeding support.

Treatment of Feeding Problems

- MDT to determine which patients may benefit from nonsurgical and surgical interventions to improve feeding.
- Use an NGT when oral intake is unsafe or insufficient to support growth.
- Consider using hypercaloric feeds if growth remains insufficient with standard feeds.
- Always consider breathing interventions as part of a complete treatment strategy to optimise growth and feeding.
- Consider gastrostomy tube placement in children with UAO who fail to respond to surgical and nonsurgical interventions aiming to improve breathing.
- Be aware of the potential growth and feeding risks associated with surgical interventions to improve breathing are conducted (TLA/MDO) and intervene early to support (see Chapter 12).

Research Gap

Feeding and growth disorders are one of the most significant causes of morbidity in babies with RS. There is a lack of prospective studies examining the role of surgical and nonsurgical intervention on feeding and growth outcomes in isolated and nonisolated RS.

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CHAPTER 8. SPEECH AND LANGUAGE

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

CP is reported to occur in up to 90% of RS cases.¹ Current studies reporting speech outcomes in RS therefore all involve children presenting with CP alongside RS. There are no papers reporting speech outcomes in children presenting with a RS diagnosis without CP.

It is well-known that being born with a CP can affect a child's communication skills. A meta-analysis has shown that young children with nonsyndromic cleft lip and/or palate (CL/P) experience delays relative to their peers across multiple speech and language constructs during early childhood and that compared to their typically developing peers, children with nonsyndromic CL/P present with a reduced consonant inventory, reduced speech accuracy and increased speech errors as well as impairments in their receptive and expressive language skills.² Research in the general population has shown that when speech and language difficulties persist into primary school, they can lead to long-term problems with literacy, relationships, behaviour and school attainment.³

The most common speech difficulties experienced by children with a CP include velopharyngeal dysfunction (VPD) and atypical articulatory patterns known as cleft speech characteristics (CSCs). Features of VPD include hypernasality (increased nasal resonance), nasal emission (audible or inaudible airflow from the nose during speech) and nasal turbulence (turbulent airflow from the nose during speech). CSCs can be categorised

according to where in the vocal tract the errors occur: anterior (eg, palatalization, lateralization) posterior (eg, backing to velar), nonoral (eg, active nasal fricatives, pharyngeal fricatives, glottal articulation) and passive (eg, nasal realisations of plosives and/or fricatives).

Individuals presenting with significant features of VPD will typically be offered further instrumental investigations in a specialist clinic. These investigations will help to inform future management decisions. If secondary surgery is indicated, the types of surgery carried out will vary between centers and according to anatomical presentation.

The overall reported prevalence of VPD in patients with RS ranges from 14.3%⁴ to 60%⁵ with the rate of secondary speech surgery ranging from 13.4%⁶ to 47.6%.⁷ Baker et al found that only 32% of their RS cohort had good articulation skills, with no evidence of CSCs, at the age of 5 years.⁸

Comprehensive care pathways already exist for children born with a CP. However, it has been suggested that children born with CP as part of RS may be at greater risk of speech difficulties than those born with an isolated cleft palate without RS (ICP). For example, studies looking at the CP population as a whole and not specifically RS have reported correlations between an increased width of CP and increased frequency of hypernasality.⁹

In order to determine the right care pathway for RS patients with CP, more information on prognostic factors, screening, monitoring and treatment indications in this population is needed. Based on recent studies, clinical experience and reports from families of children born with RS and CP, this guideline aims to address the following questions:

- **What is the prognostic value of certain patient and treatment characteristics in the prognosis of speech and language development in patients with RS and CP?**
 - Diagnosis of RS versus ICP
 - Width of cleft
 - Extent of clefting in the palate
 - Timing of primary palatoplasty
 - Type of primary palatoplasty
 - Airway and/or feeding management
- **What is the policy for screening and monitoring of speech problems in patients with RS and cleft palate?**
- **What are the indications for treatment of speech problems in patients with RS and cleft palate?**

To answer these questions, the following outcomes of interest were examined: velopharyngeal dysfunction, need for secondary speech surgery, cleft speech characteristics, and language development.

Speech and language outcomes in syndromic RS (ie, where RS occurs as part of a syndrome such as Stickler Syndrome or 22q11.2 Deletion Syndrome) will not be reported in this guideline as it is not possible to determine with any certainty whether outcomes reported in these studies are due purely to the diagnosis of RS or to the underlying syndrome. Communication profiles vary across syndromes.

Speech and language outcomes in RS children without a cleft palate will also not be reported in this guideline. Speech and language difficulties would not be expected in this particular cohort given that without a history of cleft palate, they would not be at any increased risk of velopharyngeal dysfunction or hearing impairment.

Literature Study

A systematic search of the literature was performed to identify all available literature on RS and appropriate synonyms. The

search was conducted in Embase, Pubmed/Medline Ovid, Web of Science, and the Cochrane Central Register of Trials. The full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin Sequence
Subject	Velopharyngeal dysfunction, need for secondary speech surgery, cleft speech characteristics, language development
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

After rough selection and labelling, a full text assessment of 25 studies was performed for this chapter. Ten studies were excluded due to incorrect outcomes (n=5), wrong population (n=2), nonseparation of nonisolated and isolated RS (n=2) and lack of statistical analysis (n=1). Four articles were included by the authors aside from the search results. Three of these articles fit the inclusion and search criteria but were not identified in the original search because the publication dates were after the search date.^{8,10,11} A further study by Baillie and Sell,¹² has also been referenced but was not detected in the original literature search as RS is not referred to within the abstract. In this chapter therefore, the outcomes of 15 studies are described.

Summary of Literature Study

What is the Prognostic Value of Certain Patient and Treatment Characteristics in the Prognosis of Speech and Language Development in Patients With RS and CP?

Diagnosis of RS versus ICP

Nine studies compared speech outcomes in patients with RS versus ICP, as it has been hypothesized that patients with RS have poorer speech outcomes. Table 2 summarizes if a significant difference was reported between the 2 groups with regard to outcomes for VPD, secondary surgery for VPD and articulation.

The evidence regarding incidence of VPD and secondary speech surgery in the RS population is clearly conflicting, with

some studies reporting significantly higher rates of VPD and secondary speech surgery in RS children compared with ICP children and others finding no difference between the 2 groups. However, 4 of the 6 studies that looked at articulation outcomes (7, 8, 10, 12) found that there was a difference in articulation outcome, with the RS children presenting with more frequent and severe articulation errors.

Width of cleft

Only 2 studies looked at width of the cleft palate as a possible influencing factor on the rate of VPD and need for secondary speech surgery. Logjes et al¹¹ concluded that a wider cleft is associated with a higher risk of developing VPD and/or needing secondary speech surgery but it should be acknowledged that their analysis included 47 ICP patients alongside the 44 RS patients and only 19/44 RS patients had isolated RS. They argued that cleft width could be independently responsible for VPD in both RS and ICP patients. In contrast, Morice et al¹⁶ found that there was no difference in the rate of VPD according to cleft width.

Although Gustafsson et al¹⁷ did not look specifically at whether there was an association between cleft width and the subsequent need for secondary speech surgery, they did note that children presenting with wider clefts had a higher trend toward developing a palatal fistula.

Extent of cleft

It is important to note that within the literature reviewed for this guideline, 6 different classification systems were used to describe the extent of clefting in the palate. For example, one paper compares patients with a cleft of the soft palate only with those who had a cleft of the hard and soft palate⁸, another categorised patients into “complete” or “partial” cleft palates,¹⁶ another divided the palate into sixths as described by Sommerlad et al¹² and others used previously published classification systems, for example, the Veau¹⁸ classification system,^{6,10} the Jensen et al¹⁹ classification system^{11,17} and the Andersson et al²⁰ classification system.¹⁴

Four studies found no significant association between the extent of the cleft palate in RS and speech outcomes and/or need for secondary speech surgery.^{6,14,16,17} Baker et al⁸ conducted a case control study among RS patients with cleft palate (n=37) and ICP patients (n=37). In all, 97% of their RS patients presented with a cleft that extended into the hard palate, compared with only 54% of the ICP patients. They reported that the extent of the cleft significantly influenced the speech outcomes but ultimately, as the 2 groups were not matched by extent of the cleft, they were unable to conclude whether it was the diagnosis of RS that contributed to the poorer speech outcomes or whether the extent of the cleft had a greater influence.

Two other studies^{11,12} also concluded that a more severe cleft was associated with a higher risk of VPD but neither study split their

TABLE 2. Summary of Studies Comparing Speech Outcomes in Patients With RS Versus ICP

	No. patients (RS/ICP)	Significant difference in features of VPD	Significant difference in secondary surgery for VPD	Significant difference in articulation (CSCs)
Goudy et al (2011) ⁴	21/42	No	No	Not reported
Stransky et al (2013) ¹³	55/129	Yes	No	No
Filip et al (2015) ¹⁴	93/351	—	Yes	Not reported
Hardwicke et al (2016) ⁷	21/24	Yes	Yes	Yes
Baillie and Sell (2020) ¹²	72/112	Yes	—	Yes
Taku et al (2020) ¹⁵	15/40	No	No	Not reported
Logjes et al (2021) ¹¹	19/47	No	No	RS and non-RS reported together
Baker et al (2021) ⁸	37/37	No	No	Yes
Schwaiger et al (2021) ¹⁰	43/128	No	iRS and niRS reported together	Yes

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findings into separate results for RS and ICP. This makes it difficult to conclude whether it was the diagnosis of RS or the extent of the cleft that had the greatest influence on velopharyngeal function.

Despite including cleft width as a variable, another study¹⁰ did not, in the end, compare Veau type I with Veau type II as only 4 patients in their RS group presented with Veau type I (compared with 83 of the ICP group).

Timing of primary palatoplasty

Of the papers reviewed for this chapter, 5 looked at whether the age at primary palatoplasty affected speech outcomes.^{7,8,11,15,17} All these studies found that the age at primary palatoplasty did not significantly contribute to their speech outcomes and/or the need for secondary speech surgery.

Type of palatoplasty

Only 4 of the studies looked specifically at type of primary palatoplasty as a variable that could affect speech outcomes.^{14,16,17,21} The primary palatoplasty techniques described in these studies are: Veau-Wardill-Kilner, the Bardach 2-flap, von Langenbeck, minimal incision, Sommerlad intravelar veloplasty (IVVP), and Furlow techniques. Morice et al¹⁶ also described palatoplasties being undertaken in 1 or 2 stages depending on the width of the cleft.

In 3 of the studies,^{14,16,17} the type of primary palatoplasty did not have an impact on rate of VPD or the need for secondary speech surgery. However, Prado-Oliveira et al²¹ reported a significant difference in nasality, with significantly better nasality outcomes on their live 4-point scale ($P=0.012$) and the live *cul-de-sac* test ($P<0.001$) following the Furlow procedure than the von Langenbeck procedure. In the study by Morice et al,¹⁶ single versus 2-stage repairs did not significantly impact VPD.

Airway and/or feeding management

The impact of early airway management and feeding difficulties on speech outcomes has been discussed in several papers.^{5,7,10,13,15,16,17} The majority of studies found that the various airway and/or feeding management strategies did not lead to a significant difference in speech outcomes.^{5,10,13,16,17} However, Schwaiger et al¹⁰ did find differences in speech outcomes relating to airway management, with those RS patients requiring airway management having a better VP outcome but poorer articulation outcome than the group who did not require airway management.

Hardwicke et al⁷ found that the speech outcomes for RS children who required airway intervention as neonates were significantly worse than those for ICP children. However, it should be acknowledged that this study did not include the group of RS children who did *not* require early airway intervention. It is therefore not possible to conclude whether it is the airway intervention that is the contributing factor or something more intrinsic to the diagnosis of RS itself.

Although there are weaknesses to each of the studies, in the 3 studies that used the same classification system for early airway obstruction and intervention,^{5,16,17} no significant association was found between the different categories and either velopharyngeal function or need for secondary speech surgery.

Language development

There is very little information in the literature regarding the language profiles of children with RS. However, it is well documented that children born with ICP often perform poorly on language assessments compared with their noncleft peers.

Only 2 papers included in this literature search looked at language development in children with RS and both compared outcomes with an ICP control group. Using data from language assessments, Baker et al⁸ found no significant difference between

the RS and ICP groups in terms of the number of children presenting with language delay at the age of 3 years. Similarly, although their study used parental responses to a developmental questionnaire instead, Van Eeden et al²² found that there was no statistically significant difference in communication behaviors between the 2 groups. However, the latter study did note that there was a significant negative correlation between the extent of the cleft and expressive language and social communication skills, regardless of whether the child had a diagnosis of RS.

What is the Policy for Screening and Monitoring of Speech Problems in Patients With RS?

The literature was examined for existing screening and monitoring policies for children with RS. No literature was available on this. However, on analysis of the current literature comparing RS with ICP there is no conclusive evidence to suggest that RS children, who may present with a wider or more extensive CP, who may require neonatal airway intervention or who may undergo primary palatoplasty at a later age than usual, require closer monitoring of their velopharyngeal function or language skills than their ICP peers. However, there is some tentative evidence to suggest that children with RS are more likely to present with articulation errors/CSCs, and therefore careful attention should be paid to these children's developing speech sound systems in the early years.^{7,8,10,11,12}

What are the Indications of Policy for Treatment of Speech Problems in Patients With RS?

The literature was specifically examined for evidence of treatment options in children with RS. No literature was available on the indications of policy for treatment of speech problems in this population.

Conclusions

Quality of evidence without GRADE	It is unclear if the diagnosis of RS in itself is associated with a higher risk of developing VPD and needing secondary speech surgery, compared to a diagnosis of ICP.
	Studies indicate that a diagnosis of RS is prognostic for worse articulation (CSCs) compared to a diagnosis of ICP.
	Ref: (4,8,7,10,11,12,13,14,15)
	<i>Conclusion based on (n=9) case-control studies with a possible risk of bias and some issues around heterogeneity and imprecision. No important issues with indirectness or publication bias were detected.</i>
Quality of evidence without GRADE	These studies indicate that the variables of cleft width, extent of cleft, timing of palatoplasty, type of palatoplasty, airway or feeding problems at birth are not predictive of the risk of developing VPD and/or CSCs or the need for secondary surgery for speech.
	Ref: (5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 21)
	<i>Conclusion based on (n=13) observational studies with a low overall risk of bias but issues around heterogeneity and imprecision. Issues with indirectness were detected in 2 studies. Publication bias was not detected in any of these studies.</i>
	Studies indicate there is no difference in language development between patients

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Quality of evidence without GRADE	with RS compared with ICP Ref: (8, 12) <i>Conclusion based on (n=2) case control studies with low risk of bias and no important issues around indirectness or publication bias. Issues with heterogeneity and imprecision were detected.</i>
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Considerations

Quality of Evidence

Overall, the quality of evidence in these studies is low due to methodological weaknesses. This impacts on what conclusions can be drawn for this population and makes intercenter comparison difficult.

The main methodological weaknesses are described below:

- Despite the publication date allowing inclusion into the literature search, the birth dates of some patient cohorts date back considerably further, for example, one study¹⁷ reports on patients born between 1990 and 2009, while another¹⁴ reports on patients born between 1980 and 2010. Protocols are likely to have changed over this time frame which may lead to issues around the influence of confounding factors, for example, type of palatoplasty and surgeon.
- The use of different primary palatoplasty techniques and protocols.
- The use of different speech assessments.
- Varying age at time of speech assessment.
- Few studies include information on hearing status and hearing background.
- Thresholds for performing secondary speech surgery specific to individual cleft centers.
- Different classification systems describing extent of cleft.
- The use of different airway managements in RS patients [eg, positioning versus NPA, positioning versus tongue-lip adhesion or tracheostomy, positioning versus NPA or endotracheal intubation (ET) or tracheostomy].
- Some studies reported only the need for secondary speech surgery as a speech outcome relating to VPD, meaning that there is likely to have been a group of patients with features of VPD who did not meet the threshold for surgical intervention but should have been counted as a poor outcome.

Professional Perspective

All children born with RS and cleft palate should attend a speech and language assessment early on in their speech and language development, as detailed in universal guidelines for cleft lip and palate management. General advice on speech and language stimulation can be provided to parents and carers preprimary and/or postprimary palatoplasty. However, it is recommended that at the ages of ~2 and 3 years, each child should attend for a more detailed 1:1 assessment with a SLP specializing in CL/P and VPD. Alongside their developing language skills, this appointment should include an assessment of the child's sound repertoire and velopharyngeal function, with advice tailored as appropriate.

As with all children presenting with CLP, it is recommended that those born with RS and cleft palate attend regular screening of their speech and language skills with a follow-up pattern that is in accordance with the national cleft guidelines of their country. Given the changes in velopharyngeal function that can occur later on in childhood and in the teenage years

due to growth and adenoid involution, it is important that children are not discharged in early childhood.

In order for outcomes to be meaningfully compared across centres, speech screening should follow guidelines such as those set out in the Universal Parameters for Reporting Speech Outcomes in Individuals with Cleft Palate.²³

If there are concerns about velopharyngeal function, a referral should be made to a specialist clinic where a detailed perceptual assessment of speech can be carried out alongside instrumental investigations such as lateral videofluoroscopy and nasendoscopy. These clinics should include a SLP and surgeon specializing in CLP and VPD. The instrumental investigations will help to inform future management decisions. Where secondary speech surgery is recommended, the procedure to be carried out will be decided by the surgical team and will differ according to the individual surgeon and center in which it is to be performed, as well as the medical history and presentation of the individual patient.

Since 4 out of 6 studies reported poorer articulation outcomes in RS children, with more frequent and severe CSCs being noted, these aspects need close monitoring in RS children. For a child who presents with CSCs, it should be determined whether speech therapy is the primary course of action or whether secondary speech surgery is indicated before therapy can be successful, for example, as would be the case for passive CSCs or those posterior and nonoral CSCs suspected to have arisen due to VPD. The specialist SLP can deliver therapy directly or support the community SLP in providing this. Dosage and type of intervention will be determined on an individual basis.

Most of the papers analyzed for this guideline used experienced cleft specialist SLPs to assess and monitor speech and velopharyngeal function. This is considered essential for good quality patient care and has therefore been made a recommendation in this guideline.

Finally, close monitoring of hearing status is essential in children born with a cleft palate, as studies have shown that they frequently experience middle ear problems and associated hearing loss, which can, in turn, impact on speech and language development.²⁴

Patient's Perspective

As stated earlier, poor speech can have a significant impact on educational attainment, social integration, and psychosocial well-being. The burden of treatment, which can include long periods of speech and language therapy, time off school for appointments, and possible further surgeries can take its toll on the child and their family. Throughout a child's journey with the cleft team, therefore, it is helpful for families to be given information on what they might do at home to facilitate speech and language development and promote general well-being. Parents and carers can help to identify early warning signs that challenges are becoming problematic for the child and promote effective coping strategies. On indication, children must have access to a clinical psychologist (see Chapter 10).

Balance of Benefits and Harms

It is recommended that RS patients follow the ICP care pathways embedded in the workflow of the cleft team because the necessary multidisciplinary expertise for the management of cleft palate is already in place. A prerequisite should be that the cleft team has links with a center specialising in the management of RS. In other words, it is possible that not every cleft team can cover the full scope of care of the RS patient.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available national budget, care providers, and facilities. The recommendations constitute the essential requirements for appropriate treatment of patients with RS and accordingly these requirements should be implemented. As RS patients can follow the ICP care pathways and their management is embedded in the workflow of the cleft team, being part of the RS expertise center, a reduction of costs and efficient use of resources might be expected. In general, costs are lowest and resources are most efficiently used when care for congenital disorders including RS is centralized in a limited number of expert centers per member state.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe around care for patients with rare diseases. At present, not every member state offers an expert centre for RS, or the level of provided care does not (yet) meet all the requirements outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal health care and are discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as one of the core values. However, in some countries the national organization of health care might impede centralization. National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and collaboration with an expert center in the surrounding countries should be considered.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale of the Recommendation

There is no conclusive evidence in the literature to suggest that children born with RS are more at risk of developing VPD and/or requiring secondary speech surgery than their ICP peers. However, based on the literature reviewed for this guideline, there is evidence to suggest that they may be more at risk of developing poor articulation.

Existing care pathways for children born with CL/P already ensure that speech and language skills are monitored from an early age in order to ensure that early intervention can be offered when needed. The outcomes of the literature included in this study suggest that children born with cleft palate as part of RS should follow the same care pathway as no substantial as-

pects suggesting different care were found. The existing care pathways and guidelines for children with CL/P have arisen following recommendations from national audits such as that by the UK Clinical Standards Advisory Group (CSAG) in 1998.²⁵ These proposed recommendations are also in accordance with the Dutch Guideline for Cleft Lip and Palate.²⁶

Recommendations

- Advice on early language stimulation, babbling, and modelling early sounds (with particular emphasis on oral pressure consonants) should be provided to parents before primary palatoplasty and in the first few weeks after primary palatoplasty.
- Between the age of 18 months and 3 years, at least one formal 1:1 assessment of speech and language skills should be carried out by a SLP specializing in CLP and VPD. Clinicians should be alert to the fact that there may be a higher incidence of articulation errors in this population.
- Regular reviews of speech and language should be carried out from the age of 5 years until facial growth is complete. These reviews should take place no less frequently than every 5 years for children where there are no cleft-related speech concerns. For children who do present with cleft-related speech concerns, these reviews should take place on a more frequent 6 to 12 monthly basis.
- On suspicion of VPD, a referral should be made for specialist velopharyngeal investigations. A SLP and surgeon specializing in CLP and VPD and RS should be present in the expert team.
- Treatment for CSCs should be delivered directly by specialist SLP or by community SLP with support of the specialist SLP.
- For RS children whose airways difficulties are being managed with a tracheostomy, it is recommended that the cleft specialist SLP work closely with the SLP specializing in ENT/tracheostomies in order to ensure advice and intervention for speech and language difficulties is appropriate.

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CHAPTER 9. DENTOFACIAL DEFORMITIES

Introduction

RS is defined as the triad of micrognathia, glossoptosis, and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided into syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing).

As RS is characterized by underdevelopment of the mandible, awareness of dentofacial deformities in patients with RS is essential to identify problems in an early phase and start treatment if needed. There is a lack of clear information about the screening options (type and frequency) that are necessary to diagnose and monitor dentofacial anomalies. In addition, there is a lack of clear treatment options of dentofacial anomalies in RS.

There are different dentofacial deformities that can occur in patients with RS one of which is tooth agenesis. The prevalence of tooth agenesis in the general population is around 6.9% excluding third molar agenesis but was reported to be just over 40% in children with RS.¹ In descriptive and observational studies among RS patients with tooth agenesis two thirds had bilateral tooth agenesis. Among the RS children with tooth agenesis, almost half had agenesis patterns involving both mandibular premolars.² A second dentofacial deformity more frequently seen in RS patients is taurodontism, which is found in 92.73% of patients with RS.³

Last, children with RS are known to have convex facial morphology mostly due to a retrognathic mandible. Stimulation of normal growth by orthodontic treatment might not compensate the micrognathia. To inform patients about the prognosis and treatment of facial/mandibular growth, clear information is needed. To structure the result, the following research questions were formulated:

- **What is the prognosis for facial development of children with isolated RS?**
- **What is the policy for screening and monitoring of dentofacial anomalies in patients with RS?**
- **What are the indications and policy for treatment of dentofacial anomalies in patients with RS?**

To answer these questions, we have looked into dentofacial anomalies as outcomes of interest.

Literature Study

For this guideline, a systematic literature search was conducted. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria

Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Dentofacial anomalies
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion.

After rough selection and labeling a full text assessment of 51 studies was performed for this chapter. Several studies were excluded due to sample size ($n=5$), incorrect outcome ($n=25$), incorrect population ($n=12$) or incorrect study design ($n=1$). In this chapter, 8 studies are described.

Summary of Literature Study

What is the Prognosis for Facial Development of Children With Isolated RS?

Daskalogiannakis et al (2000) published a retrospective cohort study to investigate the difference in craniofacial and mandibular morphology between patients with isolated RS and isolated cleft palate.⁴ The study compared cephalograms of 96 isolated RS patients compared with an isolated cleft palate group (iCP) of 50 patients before and after the second stage of tooth development. Significant differences were identified between the 2 groups, particularly in the size and sagittal position of the mandible, which was consistently shorter in the isolated RS group at all 3 ages. Less difference was noted in the inclination of the palatal plane, the facial height proportions and midface depth. They concluded that patients with isolated RS had a significantly smaller mandible as compared with patients with isolated cleft palate and the difference does not change after the age of 5 years.

Krimmel et al (2009) performed a prospective, cross sectional cohort study to analyse facial development in RS compared with the normal population.⁵ Thirty-seven children with RS (including cleft palate) and 344 healthy children younger than 8 years were scanned 3-dimensionally. Twenty-one standard anthropometric landmarks were identified, and the images were superimposed. The facial growth of children with RS in the transversal and vertical direction was normal. In the sagittal direction, the mandibular deficit was confirmed. All landmarks of the midface and lower face demonstrated a significant sagittal deficit. This difference remained constant for all ages compared with healthy children.

Ozawa et al (2012) published a retrospective cohort study.⁶ The objective was to evaluate the facial profile of children with isolated RS and to compare these to a control group that had no pathologies and exhibited regular and balanced facial growth with no skeletal alterations. Angular and ratio analyses of the facial profiles in both groups were captured through digital photographs. The isolated RS group was divided into 2 groups; complete and incomplete cleft palate to investigate the possible influence of the degree of cleft palate on the facial profile. The facial convexity angle and the facial inferior third angle were considerably higher in the isolated RS group than in the control group and there were no significant differences between the

isolated RS with or without cleft palate. The facial profile was more convex in individuals with isolated RS than in those with regular facial growth. The mandible was responsible for the convexity of the profile in isolated RS because of lack of anterior projection.

In 2010, jaw size, jaw relationship, and facial proportions of children with isolated RS (iRS) were compared with isolated cleft palate (iCP) by Shen et al.⁷ A retrospective cohort study compared radiographic findings in children with iRS an iCP patient at 2-time intervals [ages 4–7 y (T1) and ages 10–13 y (T2)]. Linear and angular measurements were obtained and compared using cephalograms. The sample included 13 children with RS and 14 children with iCP. Mandibular length, maxillary length, and sagittal jaw relationship were measured.

During childhood (T1), mandibular length, and maxillary length were similar in both RS and iCP group. In older children (T2) mandibular length was significantly shorter in iRS compared with the iCP group ($P=0.009$). Maxillary length in RS and iCP was similar in T2 but significantly shorter in comparison to age-matched norms with a difference of 14.5 mm ($P=0.037$) in RS and 12.4 mm ($P=0.045$) for iCP. In iRS there was no sagittal jaw discrepancy due to a proportionate deficiency in maxillary and mandibular length; whereas, children with isolated cleft palate showed a greater sagittal jaw discrepancy due to normal mandibular length and deficiency in maxillary length. In conclusion, children with iRS have a proportionate retrusion of the maxilla and mandible, resulting in a convex facial profile by early adolescence.

Suri et al in (2006) studied prevalence of hypodontia comparing morphology of mandible of subject with RS with and without mandibular hypodontia.⁸ The study compared 16 Caucasian children with isolated PS with mandibular hypodontia and 18 isolated RS patients without hypodontia. Lateral cephalographs were compared before and after orthodontic treatment (T1 mean age 11.7, T2 mean age 16.6 y). They concluded children with isolated RS with mandibular hypodontia had smaller mandibles than children with isolated RS without hypodontia. This pattern of growth did not change during adolescence, and magnitude of differences increased.

Suri et al (2010) studied craniofacial morphology and adolescent facial growth in subjects with RS.⁹ They compared 34 cephalometric tracings of isolated RS patients compared to a normal population before and after orthodontic treatment. Significant differences were noted, with the isolated RS group showing smaller cranial base length, shorter maxillary and mandibular length, increased palatal and mandibular plane inclinations and more open mandibular flexure. In summary, subjects with RS had reduced cranial base and maxillary and mandibular lengths. The deficiency was most pronounced in the body of the mandible. A vertical growth worsened the profile. There was no evidence of catch-up growth.

Yang et al (2021) investigated the phenotypes and predominant skeletodental patterns in Pierre-Robin patients.¹⁰ They compared cephalographic and orthomographic measurement of a group of 26 Korean preadolescent RS patients to the standardized normal values of the Korean preadolescents. They found one third of Korean preadolescent patients with RS showed congenital missing teeth. The predominant skeletodental patterns included Class II relationship, posteriorly positioned maxilla and mandible, hyper-divergent pattern, high gonial angle, small mandibular body length to anterior cranial base ratio and linguoversion of the maxillary and mandibular incisors.

What is the Policy for Screening and Monitoring of Dentofacial Anomalies in Patients With RS?

No literature was found to answer this question. Based on expert opinions, screening methods used for other craniofacial anomalies (like cleft palate or craniofacial microsomia) could be considered.

What are the Indications and Policy for Treatment of Dentofacial Anomalies in Patients With RS?

In 2019, Pfaff et al¹¹ published a retrospective study about the requirement of orthognathic surgery for RS patients at skeletal maturity. Orthognathic requirement of conservatively managed RS and CP patients (aged > 13 y) were reviewed and analyzed. Sixty-four patients with RS were included (n = 22 iRS, n = 42 syndromic RS). In all, 96.6% had a cleft palate and 39.3% required orthognathic surgery at skeletal maturity. iRS and sRS demonstrated no difference in occlusal relationships or mandibular surgery frequency. The majority of RS patients requiring mandibular advancement had a class II occlusion. Comparison of RS to iCP patients (n=17) revealed a comparable frequency of orthognathic surgery between the 2. However; RS patients did require mandibular advancement surgery at a greater frequency than cleft palate patients (P=0.006). These data suggest that mandibular micrognathia in conservatively managed RS may not resolve over time and may require surgical intervention.

Conclusions

Quality of evidence without GRADE	It is likely that children with nonsyndromic RS have a proportionate underdevelopment of the maxilla and mandible, resulting in a convex profile after growth. References: [6,7,9,10] <i>Conclusion based on evidence from (n=4) single arm-observational studies with a low risk of bias and no important indirectness, inconsistency and imprecision</i>
Quality of evidence without GRADE	Studies indicate that in patients with isolated Robin Sequence, mandibular catch-up growth may not be present and therefore patients may require surgical intervention after cessation of growth. References: [9], [11] <i>Conclusion based on evidence from (n=2) single arm-observational studies with a low risk of bias and no important indirectness, inconsistency, and imprecision</i>

Considerations

Quality of Evidence

The conclusions are based on a low quality of evidence but none of the included studies has a high risk of bias. Because of the low incidence of RS, groups are small and inclusions were made over a longer period of time resulting in only retrospective studies.

Professional Perspective

Depending on the experience of professionals in the different settings of the national health care within the EU different approaches exist in treatment of dentofacial disorders of the growing child with RS. Although mandibular growth could resolve the initial breathing problem, complete catch-up growth is not to be expected. It should, therefore, be stressed that

children with RS, need follow up at specialized centres during their childhood.

Close cooperation between dentist and orthodontist of the child with the center is key. Expert centers have several treatment options, either prosthetic, orthodontic and orthognathic surgical, depending on the different dentofacial conditions in children with RS. Orthodontic treatment as a final solution for disorders in occlusion should be outweighed against combined orthodontic-orthognathic and prosthetic treatment, including dental implantology. The aim of the treatment should be to create facial harmony after cessation of growth and to reduce the risk of recurrence of breathing problems (OSA) at adult age. This should be discussed with parents and patients to find the ideal individual course of treatment.

Balance of Benefits and Harms

Included studies cannot support the theory of mandibular catch-up growth. Although evidence is of low quality, all growth-related articles report a convex profile with underdevelopment of the mandible after pubertal growth. This indicates that children with RS have a persisting underdevelopment of the midface and mandible. Orthodontic treatment should be started with the knowledge that catch-up growth is not expected in RS.

After cessation of growth, the persisting underdevelopment of the midface and mandible can be corrected using a combined orthodontic/surgical treatment. Aim of the surgical intervention is to create a facial harmony after cessation of growth in patients with RS. Because of a high prevalence of tooth agenesis, a solely class I occlusion should not be the aim of the treatment.

There is no specific dentofacial screening method for RS patients. Tooth agenesis can be assessed on panoramic radiographs around the age of 5 years. With a high prevalence of hypodontia, early screening might be advised to start early orthodontic treatment if necessary. We advise similar timing of the dental screening as usually is performed in other craniofacial anomalies (like cleft palate or craniofacial microsomia).

Cost and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available national budget, care providers and facilities. The recommendations constitute the essential requirements for appropriate treatment of patients with RS and accordingly these requirements should be implemented. Costs are lowest and resources are most efficiently used when care for congenital disorders is centralized in a limited number of expert centres per member state. The costs for screening for dentofacial anomalies in RS patients are considered low. The screening can be incorporated in routine dental visits.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe about care for patients with rare diseases. At present, not every member state offers an expert center for RS, or the level of provided care does not (yet) meet all the requirements outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice. Screening tools using panoramic

radiographs and cephalographic radiographs are widely available across Europe.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal health care and are discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as one of the core values. However, in some countries the national organization of health care might impede centralization. National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and collaboration with an expert center in the surrounding countries should be considered. Because of the low incidence of RS, centralized care is advised. Orthodontic treatment and surgical treatment might be more extensive.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale of the Recommendation

The micrognathia, as one of the 3 entities that define RS, may imply convex facial morphology and comes often with tooth agenesis. As a result, close monitoring and screening of facial growth and dental development for the RS patient is mandatory. Often a combined orthodontic and surgical management after cessation of facial growth is necessary to create a functional and esthetical good outcome.

Recommendations

- Schedule dental visit at age 5 to 6 years to screen for presence of hypodontia using panoramic radiographs in patients with RS with bi-annual review until skeletal maturity.
- Centralize the care of dental screening and surgical treatment in patients with RS in centers of expertise and recommend shared-care for orthodontic treatment.
- Inform parents early that functional (breathing, occlusion) and esthetic issues can occur at skeletal maturity and can be treated with mandibular and maxillary advancement surgery.

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CHAPTER 10. PSYCHOSOCIAL PROBLEMS IN ROBIN SEQUENCE

Introduction

RS is defined as the triad of micrognathia, glossoptosis, and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided into syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

Parents of a child with a congenital anomaly, such as RS, have various reasons to be concerned about their child's future. Experience has taught us that these concerns usually develop immediately after the congenital anomaly is diagnosed (during the prenatal stage or later) and may be present at various moments in the child's development. Sandow et al¹ studied parental experiences of having a child diagnosed with RS as well as the role of genetic counseling in RS. Those participants who did recall experiences with genetic services reported that they were minimal and uninformative. The authors conclude that genetic counselling would be a valuable source of information and support for parents both at the time of antenatal diagnosis, and potentially 6 to 12 months later in the outpatient environment when these children are all routinely reviewed by their clinical care team. Clinical practice reveals that parents can experience acceptance problems, grief, and concerns about issues such as their child's social acceptance in the future. The course of the guidance offered to parents (and child) regarding the psychosocial well-being (such as cognitive and neuro-

psychomotor development and psychological functioning) and raising the child is sometimes complex and covers various phases in the development of the child from baby to (young) adult. Studies as well as clinical practice reveal that parents always have many questions about the anomaly and can experience feelings like disappointment, grief, and probably acceptance problems.^{1,2}

Questionnaires filled out for the bottleneck analysis for this guideline (see Chapter 15) revealed that 47 out of 94 parents (50%) described that they received psychological or psychosocial counseling and 31 of them found it useful. Twenty-six out of the 35 parents (74%) who did not receive counseling or support would have liked to receive it. Reasons why they thought it might be helpful were the possibility to share feelings, pain, and thoughts, to receive support on coping strategies and support during the prenatal phase. Counselling was sometimes not perceived as supportive when the psychologist was not familiar with the disease or when it was felt that counselling was proposed too early or too late in the care process. Other parents described that their own social network replaced professional help and some felt they did not need support.

Although much of the primary treatment is medical/surgical in nature, the ultimate goal of the entire treatment by the team in a center of expertise is to achieve psychosocial well-being of the child with RS and his or her family. RS is more complex in its clinical phenotype and demands on greater complexity of care in comparison to other diagnosis like for example cleft types,³ especially in the first year of life. Prolonged hypoxia, secondary to airway obstruction in the neonatal period and the first months of life, may possibly led to delayed neuro-psychomotor development.⁴ It is therefore desirable to create a special inventory about whether and when parents and child could benefit from psychosocial support and—if so—at which moments in the development of the child this can best take place. Although some craniofacial or cleft syndromes are associated with neurodevelopmental delay or other psychosocial problems, this is less clear for patients with RS.

Little research is done with a focus on cognitive and/or psychosocial development in children with RS.³⁻⁸ However, they conclude that there are no significant differences in cognitive and/or psychosocial development between children with or without isolated RS. A recent study among 72 adolescents with RS (12–18 y old) concluded that adolescents with RS have favorable rates of depression compared with a norm population. On an individual level, mild and moderate depression was observed in the RS group. In the subpopulation that scored above the threshold for mild depression, “anxiety” was the most frequent symptom (26.7%) followed by “self-esteem” (25.7%) and “instrumental helplessness” (25.3%). Multivariate regression analysis considering all factors that may affect depression symptoms showed that only the COHIP score (vocal quality of life) was a significant determinant for depression.⁹

To offer potential recommendations on screening, monitoring and treatment, the following questions were addressed:

- **What is the policy for screening and monitoring of psychosocial problems in patients with RS?**
- **What are the indications and policy for treatment of psychosocial problems in patients with RS?**

To answer these questions, we have looked into cognitive development, psychosocial well-being of child and parents, and recommendations on screening, monitoring, and treatment as outcomes of interest.

Literature Search

For this guideline, a systematic literature search was performed. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria

Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Cognitive development, psychosocial functioning, and difficulties
Exclusion criteria	Patients with syndromic Robin Sequence Sample size <10 Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

After rough selection and labeling a full text assessment of (n = 15) studies was performed for this chapter. All studies were excluded due to incorrect outcome (n = 6), wrong population (2), sample size (6), and other (1). As a result, no literature was included from the search on RS. Therefore, alongside the search, the Dutch cleft guideline and ERN craniofacial microsomia guideline were included as a supplement to the professional opinion. The guidelines were thoroughly checked with the AGREE II guideline assessment and found to be of good quality, with an average score over all items of 6 and 7 out of 7, respectively. Complete AGREEII score sheets are available.

Summary of Literature Study

What is the Policy for Screening and Monitoring of Psychosocial Problems in Patients With RS?

Clinical experience from different psychologists, social workers, and other specialists working in cleft centers in the Netherlands has taught us those parents of a child with a congenital anomaly such as RS, have various reasons to be concerned about their child's future, right after hearing the diagnosis and at various moments in the child's development.

As recommended in the Dutch guideline on treatment of patients with clefts¹⁰ and the European guideline craniofacial microsomia¹¹ psychosocial screening should form a standard part of good quality care for children with RS and it is useful to screen parents and children for possible psychosocial problems. Screening moments should take place at birth and at different moments in the life of a child with RS both for child factors and family/parent factors by means of consultations and standardized instruments. In a consultation with parents and/or child, particular attention could be paid to problems associated with RS and its medical treatment, especially in the first few months after birth of the child when decisions about feeding, breathing and surgical treatment must be made. Based on the literature, no defined ages were found at which this screening should take place.

The ICHOM (International Consortium of Health Outcomes Measurement) Standard Set for Clefts¹² advises to see patients and their family at age 8, 12, and 22 to measure psychosocial well-being and quality of life using the Cleft Q. The ICHOM standard set is the result of work of leading physicians, measurement experts, and patients from different countries and

sets are available for many diseases and congenital malformations. In addition, to screen psychosocial wellbeing of the parents it is advised to screen parents soon after diagnosis (prenatal and/or postnatal) of their child by consultation and further to use the Distress Thermometer for Parents¹³ to measure family stress, in the first year of life at 1, 6, and 12 months after the birth of their child. Although this tool is not especially validated in parents of RS children, it is an (international) tool validated for parents of children with chronic illness and the best-known specific tool for screening psychosocial and emotional problems of parents at the first year of the life of their child.

What Are the Indications and Policy for Treatment of Psychosocial Problems in Patients With RS?

Unfortunately, no literature is available on the policy for treatment of psychosocial difficulties with PRS.

Conclusions

Quality of evidence without GRADE

Guidelines as well as expert opinion indicate that psychosocial screening at different moments in the life of a child with RS should form a standard part of good quality care for children with RS and their parents. References: (10, 11)
Overall AGREE score Dutch Cleft guideline = 6
Overall AGREE score CFM guideline = 7
AGREE assessments of both guidelines available in Appendix, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>

Considerations

Quality of Evidence

Because there is no literature available the conclusions are based on expert opinion with a low quality of evidence.

Professional Perspective

Having a psychologist and a medical social worker present enables psychosocial difficulties to be identified, with the aim being early intervention if necessary for children as well as for parents. Referrals to cleft specialists would provide (prospective) parents with further information, emotional support, and realistic accounts of what life is like with a child who is born with RS.

Health social work is recommended to work with the family, not just on the way to accompany by socioemotional support the family on the diagnosis acceptance, but also to inform about different rights and accesses they have with the diagnosis.

A social worker after social evaluation detects risk indicators in social familiar context, defining the social healthy diagnosis, for the whole development and well-being of the kid. After that the professional can orientate and assessorate the family about the services and resources (social, educational, psychological, and communitarian) there are in the family living area to increase or maintains the quality of life and autonomy of the child and respective family.

It should be highlighted the health social worker competence in the hospital context, as a part of the assistance health team, the professional works with the interdisciplinary hospital team

determining and collaborating to define the working way goals, to accompany the families in the distress acceptance and treatment adhesion.

Outdoors the hospital is important the external social work coordination and teamwork with the family origin context, especially in complex social cases which the social determinants of health affect directly the development of the child, because difficulties influence the access to the hospital and treatment and medical follow-ups adhesion. The main goal is planned in order to create a strong network and coordination with the municipality social worker assigned in the living area of the patient. This network permits the possibility to create with the family a work plan to support the basis need covering, if its need, and supporting the family on the way to take adhesion treatment and medical follow-ups adhesion.

The quality of the information received at the time of diagnosis (prenatal and/or postnatal) can considerably influence parents' long-term well-being, as well as their attitudes toward the diagnosis.¹⁴ So, if the diagnosis is made prenatally, this might improve the parents' knowledge of infants with RS and the required postnatal therapy. The desire to terminate the pregnancy could play a role, so adequate psychosocial counselling and support appears to be extremely important and must start at that moment.

If the screening (as advised above) of the child and/or parents indicates that psychosocial problems that may be related to isolated RS or medical treatment are present, further psychosocial examination and or intervention within the cleft team is indicated for children as well as their parents.

Contact with people who have experienced similar situations can be helpful. Therefore, it is desirable to inform parents and patients at an early stage about the existing patient organizations and the options that they offer for online and offline contact with other parents and children.

Balance of Benefits and Harms

Clinical experience shows that parents of children with RS need psychosocial support, especially during the first year of life when decisions must be made about problems with breathing, feeding, surgical treatment and so on. In addition, feelings of disappointment about the anomaly are often present and can be hard to handle for the parents. Parents are supposed to be happy about their baby. It's difficult to reject your child without feeling guilty or be angry with it (eg., because you feel aggrieved). In addition, the way family, friends, and others react to the anomaly can vary greatly and can sometimes also be confusing. Having access to a psychologist, medical social worker and a cleft team specializing in RS will have obvious biopsychosocial benefits for patients and their families including providing a high standard of care, improving patient quality of life and potentially reducing hospital stays and visits.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available care providers and facilities. The recommendations concern essential requirements for adequate treatment of patients with RS and should thus be implemented on a routine basis in specialized centers. Costs are lowest and resources are most efficiently used when care for RS is centralized in dedicated expert centers.

Inequity of the Recommendation

The goal of the ERN's is to eliminate inequality within Europe with regard to care for patients with rare diseases. At present, not every member state offers an expert center for RS, or the level of provided care does not meet all the requirements that are outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies can guide a patient in Europe to the available centers of expertise (www.ern-cranio.eu) and can support care for providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal health care and care discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as a solution.

Acceptability of the Recommendation

It is expected that all stakeholders want to apply and will be applying the recommendations, because they are employed in ERN-acknowledged institution. National implementation plans are necessary to ensure that recommendations fit the situation in each country.

Rationale of the Recommendations

The rationale for having psychological input in a specialist team for RS is to pre-empt any psychological issues experienced by the child and family that could have an impact on the patient journey, and to ensure that the team approach is holistic.

The scientific literature does not provide enough information to make any statements regarding effectiveness of psychosocial screening and guidance on the psychosocial development and well-being of children with RS as there is evidence for supporting parents.

Based on our own experience from clinical practice, we can conclude that it is good practice to screen parents and children routinely from birth (or even prenatally) on for psychosocial problems to give them support or treatment when necessary. In order to offer this a cleft team must have access to a psychologist and a medical social worker.

Contact with people who have experienced similar situations can be helpful. Therefore, it is desirable to inform parents and patients at an early stage about the existing patient organizations and the option that they offer for online and offline contact. Support groups may provide parents with a sense of community and support. They play an invaluable role by allowing families to meet, provide advice, and share experiences; however, checks and balances are needed to ensure information provided is helpful. Some support groups provide training for their one-to-one contact which covers basic befriending and listening skills. Adequately trained parents who provide positive support and information can become a valuable asset for patients and indeed the care team.

Recommendations

- Parents of newly (prenatally) diagnosed children with RS should have access to a clinical psychology and social service with appropriate professional expertise and knowledge of RS, preferably connected to a cleft team.
- In addition to consultations, it is advised to the cleft team to screen parents of children with RS (with and without cleft palate) for the presence of psychosocial and emotional problems at 1, 6, and 12 months after birth with the example: Distress Thermometer for Parents. With the

results of the Thermometer, it can be decided if and which support for parents is needed.

- In addition to consultations, it is advised to the cleft team to screen children with RS (with and without cleft palate) at age 2, 5, 8, 12, 15, and 22 to measure psychosocial problems using validated tools. Based on results of the screening, offer the parents and/or child further diagnostic tests or treatment if necessary.
- The MDT should be alert to the complex social problems sometimes experienced by families of patients with RS and provide additional specialist support.
- Inform parents at an early stage about the existing patient organizations and the options that they offer for online and offline contact with other parents and children.

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CHAPTER 11. NONSURGICAL MANAGEMENT OF MANDIBULAR-RELATED BREATHING PROBLEMS IN RS PATIENTS

Introduction

RS is defined as the triad of micrognathia, glossoptosis, and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided into syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing).

The indications for the nonsurgical treatment of the mandibular-related breathing problems in infants with RS can be divided into 2 main areas. The first includes breathing difficulties that occur during wakefulness and sleep (eg, UAO, respiratory distress, and OSA); the second includes feeding difficulties which arise from difficulty coordinating breathing and feeding, for example, desaturations during feeding and aspiration (feeding difficulties are discussed in more detail in Chapter 7).

In infants with RS, breathing difficulties are primarily caused by a retro-displaced tongue-base due to micrognathia, which partially and/or intermittently occludes the upper airway. Other mechanisms include a lack of voluntary control over the tongue musculature, a negative pressure pull which displaces the tongue into the hypopharynx, and midface hypoplasia.

Positioning therapy is often used as first-line in the management of respiratory problems in infants with RS. Positioning therapy consists of placing the infant prone or laterally, rather than supine, during wakefulness and sleep. This aims to relieve obstruction at the level of the tongue-base by allowing the mandible and tongue to fall forward. Thus, positioning may be more successful in RS patients with mild UAO. Further, after 4 to 6 months of age positioning therapy may be less effective because infants are able to move themselves into other positions. Also, any recommendation on this intervention has to be weighed against the increased risk of sudden infant death syndrome (SIDS) associated with the prone sleeping position and the fact that a literature review¹ concluded that there is no high-level evidence that home monitoring may be of use in preventing SIDS. It is relevant to note no patients with RS were included in this review.¹ However, parents may be reassured by having home monitoring for patients with RS.

If breathing difficulties are not relieved by positional therapy, a nasopharyngeal airway (NPA) or CPAP may be trialed. The use of an NPA or CPAP aims to support gas exchange, minimize airway obstruction, prevent hypoxia, and promote normal neurologic development. In addition, an ET can also be

considered when severe airway obstruction persists as immediate and temporary measure.

A PEBP (also known as the Tübingen Palatal Plate, TPP), which lifts the tongue-base from the posterior pharyngeal wall, may also be used in centres with orthodontic expertise. PEBP is an evolution of an obturator plate which includes a baton that sits behind the tongue-base. The baton helps to move the tongue-base forward, for example, away from the oropharyngeal wall, thereby opening the upper airway.

The glossoptosis found in RS jeopardizes the normal physiological functions of the upper aerodigestive tract. This results in an increased work of breathing due to UAO as well as a discoordination of respiratory and swallowing efforts. Patients may present with aspiration of secretions, gastroesophageal reflux, dehydration, and failure to thrive. Feeding difficulties and interventions are an important aspect of care and will be addressed in Chapter 7.

The nonsurgical management of breathing difficulties aims to improve respiration and weight gain through improved ventilation which mitigates the risk of infants with RS succumbing from the effects of respiratory failure, hypoxia, cor pulmonale, and failure to thrive.

This chapter describes the indications for nonsurgical interventions to support breathing as well as providing recommendations for treatment.

- **What are the indications for nonsurgical treatment of the mandibular-related breathing problems in RS?**
- **What are the most optimal nonsurgical treatment modalities for mandibular-related breathing problems in RS?**

To answer these questions, the following outcomes of interest were studied: indications for the nonsurgical management of isolated and nonisolated RS, and effectiveness of the different nonsurgical interventions for isolated and nonisolated RS.

Literature Search

A systematic literature search was performed to identify studies that reported the use of nonsurgical management options to treat infants with RS. Studies that reported outcomes for cohorts of isolated or nonisolated RS patients (or mixed cohorts comprised of isolated and nonisolated RS patients) were included. Studies that reported outcomes for syndromic RS patients were excluded. The full search strategy is reported in supplementary material.

Inclusion and exclusion criteria	
Type of studies	Original articles Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Indications for the nonsurgical management of isolated and nonisolated Robin sequence Effectiveness of the different nonsurgical interventions for isolated and nonisolated Robin sequence
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

Seventy-four articles were assessed for relevance based on the full text. Thirty-two articles that reported the use of

nonsurgical treatments in isolated and/or nonisolated RS patients were included. Five prospective cohort studies²⁻⁶ and 26 retrospective cohort studies.⁷⁻³³ At last, one cross-over RCT on PEBP was included.³⁴

Summary of Literature Study

What Are the Indications for Nonsurgical Treatment of Mandibular-related Breathing Problems in RS?

The priority of nonsurgical treatment is to address the airway, which may become occluded either spontaneously or predominantly with sleep or feeding. Progressive airway obstruction often occurs from the first week after birth, but can also persist beyond this. The main indications for nonsurgical treatment are signs of breathing difficulties, for which an approach to detection and screening is discussed in Chapter 6.

Due to a lack of quantified indications for the separate nonsurgical treatment entities, literature was reviewed to see when and for what type and severity of problems the respective treatment was suggested in the various study populations.

Prone positioning

A review of the literature identified 7 studies that reported on the use of prone positioning in isolated RS patients. In the majority of these (n = 6), prone positioning was offered first-line to all infants with RS, irrespective of the severity of UAO or OSA.^{2,5,17,20,24,26,27} In Marques et al,² positioning therapy was required for <30 days in patients that were not offered any other nonsurgical treatments, while in Van Lieshout et al²⁰ 30/32 (93.8%) isolated RS patients received positioning therapy for <28 days and 2/32 (6.3%) received positioning therapy for more than 28 days. In van Lieshout et al,²⁰ prone positioning was offered to 32/36 (88.9%) isolated RS patients, with the remaining 4 (11.1%) receiving either NPA or ET intubation (followed by tracheostomy) in the neonatal period, illustrating that in some cases it may be necessary to prioritize life-saving interventions over less invasive options such as positioning therapy.

A single retrospective cohort study by Blanc et al⁹ reported the use of prone positioning in nonisolated RS patients. Forty-five of 128 (35.2%) of nonisolated RS patients required prone or lateral positioning therapy, while a large proportion were not offered any intervention for their breathing problems (47.7%). All of these patients had a U-shaped cleft palate.

A review of the literature also identified 7 retrospective cohort studies that reported on prone positioning in mixed cohorts of nonisolated/syndromic and isolated RS patients. In 2 of these, prone positioning was offered first-line to all (100.0%) infants with RS, irrespective of the severity of UAO or OSA.^{14,17} However, in a retrospective cohort study by Schaefer et al,¹⁶ patients were offered prone or lateral positioning if: (1) desaturations occurred that were caused by supraglottic/tongue base obstruction as identified on nasoendoscopy and bronchoscopy; or (2) no desaturations occurred but sleep disturbance was identified by polysomnography and supraglottic and/or tongue-base obstruction was subsequently identified by nasoendoscopy and/or bronchoscopy; or (3) no sleep disturbance occurred on polysomnography but desaturations occurred during feeding. Ultimately, however, 21/21 (100.0%) patients met these criteria, although if they had not then these infants would have been observed only.

Al-Samkari et al⁸ report on 11/18 (61.1%) RS patients in whom prone and lateral positioning alone was considered sufficient, including 2 syndromic patients, while 7 needed oral or nasal airway or intubation.

The study by Abel et al⁷ with 86 isolated and 18 syndromic RS patients started with positioning first if the sleep study indicated mild UAO.

One study evaluated sleep studies and sleep quality in 21 RS patients (12 isolated cases) during supine and prone positioning.¹² For 13 patients prone positioning was the best position for breathing and sleeping. For 4 the supine positioning was best and the results were equal for 1. Overall, infants did not have significantly less obstructive sleep apneas while placed prone, but a significantly higher sleep efficiency.

Kukkola et al³¹ evaluated 10 years of treating RS patients. Nine patients required immediate airway intervention before PSG. Sixty-seven were evaluated with polysomnography in the supine, side, and prone position. OSA was shown to be sleep position dependent, with the highest OAHl and OAI in supine position and the lowest in side or prone position. Although there was an association found between prone sleeping position and significant improvement in OSA, OAI, WOB and ODI, over 75% of patients continued to have moderate or severe OSA. Positioning alone was used in 73% of patients with the remainder requiring escalation to active or invasive treatment (HFNC, CPAP, NPA, or tracheostomy). Infants with isolated and nonisolated RS had similar degrees of OSA.

Nasopharyngeal airway

A review of the literature identified 4 retrospective cohort studies that reported the number of isolated RS patients that received an NPA. In van Lieshout et al,²⁰ only 3 infants with isolated RS received an NPA for UAO after positioning therapy failed, 1 within and 1 after the first 28 days of life. In Butow et al,⁴ 16 infants with isolated RS received an NPA for their compromised airways for a period of up to 3 months. In Anderson et al,³³ all patients (12/12) received an NPA for moderate to severe UAO. Two infants with severe UAO were transferred with an NPA in place, while assessment and insertion of an NPA in the remaining 10 infants with moderate UAO occurred early after admission. The median time to insert an NPA was 1 day and the median time that an NPA remained in situ was 68 days (range, 24–127 d). In Schmidt et al,²⁸ 77/111 isolated RS patients received an NPA after desaturations and pre-sternal retractions occurred despite positioning therapy. The NPA was meant to bridge the time to placement of the PEBP.

A review of the literature also identified 8 studies that reported on the use of an NPA in mixed cohorts of nonisolated and isolated RS patients. In Li et al,²⁴ 2/28 infants with isolated RS received an NPA for UAO after positioning therapy failed. In De Buys Roessingh,¹⁸ 8 infants with isolated/nonisolated RS received an NPA after CPAP failed to control severe UAO. In Kam et al (2015), 23 infants with isolated RS received an NPA for UAO.

Al Samkari et al⁸ report on 7/18 RS patients in whom prone and lateral positioning alone was not sufficient, of whom 5 required a nasal cannula or oral airway and intubation was required in 2 (including 2 syndromic patients). Twelve other patients (5 syndromic RS) failed nonsurgical, including NPA, interventions, and received surgical treatment.

The study by Abel et al⁷ with 86 isolated and 18 syndromic RS patients trialed NPA for moderate and severe UAO, based on a PSG.

Drago Marquezini Salmen and Marques¹³ report on 107 RS patients (12 nonisolated and 17 syndromic cases) with severe breathing difficulties. Initial assessment was done with awake nasopharyngoscopy in horizontal position. If the obstruction was type 1 (the tongue is retropositioned and touches the pos-

terior pharynx wall) or type 2 (the tongue presses the palate against the pharynx wall) a NPA was performed.

Wagener et al²⁹ reviewed 22 neonates with RS (17 isolated), of whom 2 did not require any airway intervention, based on clinical assessment and continuous oxygen saturation monitoring. Those who needed support, were all treated with NPA.

Kukkola et al³¹ evaluated 10 years of treating 67 RS patients. Two had NPA, nasal cannula in 4 and CPAP in 7.

Continuous positive airway pressure

A review of the literature identified 2 retrospective cohort studies that reported the percentage of infants with isolated and nonisolated RS patients that received CPAP.^{23,28} Criteria for initiating CPAP in RS patients have been reported by one study. A retrospective cohort study by Ameddeo et al²³, included 31 isolated and 13 nonisolated (3 with a defined syndromes) RS patients, of which 9 (6 isolated and 3 nonisolated) received CPAP. In these 9 patients, CPAP was initiated at birth in 7 patients and at 7 and 10 days in the remaining 2 patients. In all 7 patients who had CPAP initiated at birth, this happened after admission to the NICU for severe UAO. The remaining 2 patients received CPAP after having moderate UAO assessed on polysomnography. For the patients with moderate UAO, non-invasive CPAP was started during sleep periods only if the OAH1 was > 10 events per hour and/or ODI was > 15 events per hour and/or SpO₂ min was <90% and/or PtcCO₂ was > 50 mm Hg.²³ Median CPAP duration in isolated RS patients was 1.6 months (range, 1–5.5 mo) (23). In Schmidt et al,²⁸ 15 infants with isolated RS had initially been offered ventilatory assistance in the form of CPAP prior to the NPA when desaturation and presternal retractions occurred despite the practice of prone positioning, but were then switched to a PEBP, that is the NPA was meant to bridge the time to placement of the PEBP.

In De Buys Roessingh et al.¹⁸ 11 infants with isolated/non-isolated RS received CPAP for severe UAO that was not controlled by positioning therapy. This study concluded that CPAP is a relatively safe treatment modality until the patients “grow out of their breathing difficulties.” In Kam et al,²¹ 14 infants with isolated/nonisolated RS received CPAP for UAO.

Endotracheal intubation

In Hamdi et al,¹⁵ ET intubation was required for severe UAO in 2 isolated RS patients. In van Lieshout et al,²⁰ 3 infants with isolated RS also received ET intubation as a bridge to tracheostomy for less than 28 days. In Schmidt et al,²⁸ 3 infants with isolated RS were immediately intubated after birth. In the remaining retrospective cohort study, all infants were due to undergo surgical treatment of RS. However, only 17/40 (42.5%) patients were successfully intubated with an ET tube. The remaining 23 (57.5%) received a lar-yngal mask airway.²⁵

A review of the literature also identified one retrospective cohort study that reported the use of ET intubation in non-isolated RS patients and 2 retrospective cohort studies that reported ET intubation in infants from mixed cohorts of isolated and nonisolated RS patients. In Hamdi et al,¹⁵ ET intubation was required for severe UAO in 3 nonisolated RS patients. In all of these, ET intubation acted as a temporary bridge to a surgical airway. In Li et al,¹⁴ of the 28 infants that received ET intubation, 26 received ET intubation after failure of prone positioning to relieve airway obstruction, while only 2 received ET intubation after NPA insertion failed to relieve airway obstruction. The maximum duration of ET intubation was 3 weeks.¹⁴

Pre-epiglottic baton plate

The majority of papers on the PEBP come from one center in Tubingen, and thus overlap between the presented cohorts is likely. In 5 analyzed studies, the PEBP was applied to provide relief of UAO and/or OSA. In Buchenau et al,³⁴ the PEBP was compared against a sham procedure, that is a plate without a pharyngeal extension, in 11 infants with isolated RS (mean age, 3 d). After 48 hours of wearing the PEBP, mean mixed-obstructive apnea index had fallen from 13.8 to 3.9 ($P < 0.001$), while it remained largely unchanged at 14.8 ($P = 0.84$) after the sham procedure. In Bacher et al (2011), the PEBP was indicated for patients ($n = 15$) with OSA and a MOAI of > 3, treated between November 2002 and January 2005. The PEBP was used in all patients in whom positional therapy in the referring centers failed. The plate remained *in situ* for 3 months, day and night and infants usually required a larger plate during this period. Overnight sleep studies were performed in supine position.

In Buchenau et al,¹⁰ 122 isolated RS were treated with the PEBP between January 2003 and January 2013. The authors report the PEBP as first line treatment for mild, moderate and severe UAO, after failure of positional therapy in the referring centers in 122 isolated cases. 18 patients without OSA were still treated, with the aim to stimulate mandibular growth.

In a study from South-Africa by Butow et al,⁴ PEBP therapy was offered to treat UAO to 189 isolated RS patients and reported as successful in 159 (84%). No details on the indication or PSG are given. In a Berlin study, Schmidt et al,²⁸ offered all patients ($n = 111$) PEBP therapy for UAO, which were either stable with prone positioning or showed signs of distressed breathing such as desaturation and sternal retractions. The described indication for PEBP in patients that had been stable with positioning was their experience of respiratory and feeding issues in 12 out of 21 patients within a few weeks of their initial discharge.

Poets et al⁶ enrolled 49 RS patients between February 2013 and September 2015 in a bicentric study, with the majority of patients coming from Tubingen; 43 patients had isolated RS. Prior to referral, these patients were trialed for prone positioning and/or NPA. Endoscopic evaluation was performed to decide on the type of plate (with a pharyngeal spur or with a perforated tube attached to the spur). Sleep study data were available for 41 infants and showed a decrease in MOAI from 15.9 at admission (IQR 6.3–31.5) to 2.3 (1.2–5.4) at discharge. During follow-up, 5 patients were lost to follow-up, one discontinued the use of the plate, and in 8 no sleep study was available. Three months later, data were available for 32 infants and showed a MOAI of 0.7 (0.1–2.4). Mean SDS for weight between admission and 3-month follow-up remained unchanged (–0.84 versus –0.87). No infant needed mechanical ventilation or tracheostomy.

In Wiechers et al,³² 303/307 (98.7%) isolated RS patients treated between 1998 and 2019 were offered PEBP treatment, based on MOAI on sleep study of ≥ 3 . This study focused on weight gain, thus no sleep study data were reported.

What are the Best Nonsurgical Treatment Modalities for Mandible-related Breathing Problems in Patients with RS?

Prone positioning

A review of the literature identified 5 studies that reported on the success rate of positioning therapy in isolated RS patients. In the 3 retrospective cohort studies, the success rate of positioning therapy was 48.5% (16/33 patients), 72.2% (26/36 pa-

tients), and 27.9% (31/111 patients) (2,17,28). In a prospective cohort study by Gozu et al⁵ and a pre-post intervention study by Hong et al,²⁶ the success rate of positioning therapy was 60.0% (9/15 patients) and 66.7% (6/9 patients), respectively. In the latter, positioning therapy resulted in improvement in OAH, CAI, AI, and SE values on polysomnography.

A review of the literature also identified 2 studies that reported the success rate of positioning therapy in nonisolated RS patients, while a further 4 studies reported on the effectiveness of positioning therapy in mixed cohorts of isolated and nonisolated RS patients. In 2 studies, the success rate of positioning therapy in nonisolated RS patients was 41.7% (5/12 patients) and 100.0% (3/3 patients),^{17,26} while in the remaining 4 studies the success rate of positioning therapy was 74.5% (82/110 patients), 47.6% (10/21 patients), 64.6% (31/48 patients), and 75.0% (9/12 patients) in RS patients from mixed cohorts.^{14,16,17,26}

Al-Samkari et al⁸ report on 11/18 (61.1%) RS patients in whom prone and lateral positioning alone was sufficient, including 2 syndromic patients, while 7 needed oral or nasal airway or intubation. Twelve other patients (5 syndromic RS) failed nonsurgical interventions, including prone positioning, and received surgical treatment.

The study by Abel et al⁷ with 86 isolated and 18 syndromic RS patients started with positioning first if the sleep study indicated mild UAO. This was successful in all 27 patients, as confirmed with follow-up sleep studies.

Kukkola et al³¹ evaluated 10 years of treating 67 RS patients. They considered 15/67 were not sufficiently treated with positional treatment only, although 75% continued to have a MOAHI > 5/h.

Sixty-seven were evaluated with polysomnography, taken the position into account. Infants with isolated and nonisolated RS had similar degrees of OSA. 52/67 (77.6%) were considered sufficiently treated with positional treatment only. Infants that were treated with prone positioning were offered a pulse oximeter. Although the sleeping position was associated with improvement of OSA, this did not completely normalize the OAH, OAI, WOB, and ODI values with over 75% of patients continuing to have moderate or severe OSA (OAH > 5).

In Table A (see the Appendix) data are summarized from 12 studies, which included a total of 766 RS patients, that reported treatment success rates for positioning therapy. The definitions of treatment success varied for each study, but included relief of airway obstruction, absence of respiratory distress, good pulmonary ventilation, stabilization of desaturations and parasternal recession, and improvement in sleep study values. Two retrospective cohort studies, 2 prospective cohort studies, and one pre-post intervention study, which included a total of 204 isolated RS patients that received positioning therapy, revealed a success rate ranging from 27.9% to 72.2%.^{2,5,17,26,28} Another retrospective cohort study and one pre-post intervention study, which included a total of 15 nonisolated RS patients that received positioning therapy, reported a success rate ranging from 41.7% to 100%.^{17,26} A further 5 retrospective cohort studies and one pre-post intervention study, which included a total of 303 patients that received positioning therapy, revealed a success rate ranging from 47.6% to 100% for mixed cohorts of isolated and nonisolated/syndromic RS patients.^{7,8,14,16,17,26}

Nasopharyngeal airway

A review of the literature identified 4 studies that reported success rates for NPA insertion in isolated RS patients. These studies revealed that the success rate of NPA insertion was

highly heterogeneous: 60.0% (9/15 patients), 100.0% (12/12 patients), 87.5% (14/16 patients), and 80.5% (62/77 patients).^{2,6,28,33} To determine the appropriate duration of use of an NPA, Marques et al² follow-up every 15 days to reassess whether the NPA could be removed or not, up to a maximum follow-up period of 6 months.

A review of the literature also identified one study that reported on the success rate of NPA insertion in a mixed cohort of isolated and nonisolated RS patients. In a retrospective cohort study by Li et al,¹⁴ only 2/110 (1.8%) infants received an NPA. One of these 2 patients initially obtained relief of UAO, but subsequently suffered an episode of aspiration pneumonia and later required ET. The other received ET due to a poor response to an NPA.

In the study by Abel et al⁷ with 86 isolated and 18 syndromic RS patients NPA was effective to treat moderate and severe UAO, based on a PSG, in 63/77. After a median duration of 8 months and repeated sleep studies every 2 months, the NPA could be removed. Follow-up sleep studies confirmed the resolutions of UAO. No complications of the NPA treatment were observed. It is not mentioned how the sleep study results differed between the isolated and syndromic patients. The 14 patients with persistent severe UAO required a tracheostomy. Nine of out these 14 patients could be decannulated without further treatment at a mean age of 3 years (range 2–5 y).

Drago Marquezini Salmen and Marques¹³ report on 107 RS patients (12 nonisolated and 17 syndromic cases) with severe breathing difficulties. Initial assessment was done with awake nasopharyngoscopy in horizontal position. If the obstruction was type 1 (n = 95) or type 2 (= 2) a NPA was performed. The effect was monitored with continuous pulse oximetry and clinical observation. The NPA was used for a mean time of 57 days + 38 days. No complications of the use of NPA occurred and no patients required other measurements besides the NPA.

Wagener et al²⁹ review 20 neonates with RS (17 isolated), who were all treated with NPA. The NPA was required for a mean duration of 44 days (range 16–104 d). All babies had improvement of weight gain. None of the babies required surgical intervention.

Kukkola et al³¹ evaluated 10-years of treating 67 RS patients. They considered 15/67 not sufficiently treated with positional treatment only, although 75% continued to have a MOAHI > 5/h. Two had NPA, nasal cannula in 4 and CPAP in 7. One patient with a nasal cannula and one with CPAP needed a change to NPA, while one patient with NPA required a tracheostomy. Infants that were treated with prone positioning were offered a pulse oximeter.

In Table B (see the Appendix), data are summarized from 10 studies, which included a total of 538 RS patients that reported treatment success rates for NPA insertion. The definitions of treatment success varied for each study, but included relief of airway obstruction, avoidance of readmission and failure to thrive, avoidance of additional ventilatory support with CPAP, good pulmonary ventilation and stabilization of desaturations. Three retrospective cohort studies and one prospective study, which included a total of 138 isolated RS patients that received an NPA, reported a success rate ranging from 60.0% to 100%.^{2,5,28,33} Another 5 retrospective cohort studies, which included a total of 200 patients that received an NPA, reported a success rate ranging from 50.0% to 100% for a mixed cohort of isolated and nonisolated/syndromic RS patients.^{7,13,14,29,31}

Continuous positive airway pressure

A review of the literature identified one study that reported the success rate of CPAP in isolated RS patients. In retro-

spective cohort study by Ameddeo et al,²³ 9/31 (29.0%) isolated and nonisolated RS patients were treated with CPAP. Of these 9 patients, 4 isolated and 1 nonisolated patients were successfully treated with CPAP in the NICU and avoided tracheostomy, unlike the other 3 isolated and 1 nonisolated patients. The criteria for CPAP withdrawal were normal gas exchange in 2 patients and normal polysomnography and gas exchange in 1 patient. The remaining patient had not been weaned off CPAP by the end of the study. In 2 isolated and 2 nonisolated RS patients, CPAP was started outside of the NICU to treat moderate OSA identified on polysomnography. All 4 patients were managed successfully, and the 2 isolated patients were weaned off CPAP after achieving spontaneous gas exchange within 1.2 months. The other 2 patients were CPAP dependent 4 months after initiation. CPAP was therefore successful in 9/13 (66.9%) of isolated and nonisolated RS patients (6/9 and 3/4, respectively).

In a retrospective cohort study by de Buys Roessingh et al,¹⁸ a mixed cohort of 11 isolated and nonisolated RS patients were treated with CPAP. Of these 11 patients, CPAP successfully resolved airway obstruction in only 3 (27.3%) patients, while in 8 (72.7%) patients CPAP was replaced by an NPA because CPAP alone was not sufficient at resolving airway obstruction.

In Table C (see the Appendix), data are summarized from 2 studies, which included a total of 63 RS patients, that reported treatment success rates for CPAP. The definitions of treatment success varied for each study but included improvement of airway obstruction and avoidance of tracheostomy. One retrospective cohort study, which included a total of 9 isolated RS patients that received CPAP, reported a success rate of 66.7% (23). Another retrospective cohort study, which included a total of 11 patients that received CPAP, reported a success rate of 27.3% for a mixed cohort of isolated and nonisolated RS patients.¹⁸

Endotracheal intubation

A review of the literature identified 2 studies that reported the success rate of ET intubation in isolated RS patients. In a retrospective cohort study by Yin et al,²⁵ 17 isolated RS patients were intubated, with 12/17 (70.6%) successfully decannulated. In another retrospective cohort study by Hamdi et al (2004), 2 patients with isolated RS received ET intubation for 1 to 4 days, and both (100.0%) of these patients avoided the need for surgical airway management.

A review of the literature also identified one study that reported success rates of ET intubation in nonisolated RS patients and 2 studies reported success rates in mixed cohorts of isolated and nonisolated RS patients. In Hamdi et al,¹⁵ 3/9 (33.3%) patients with nonisolated RS received ET intubation. However, all 3 patients ultimately required surgical airway management. In the studies of mixed cohorts, the success rate of ET intubation was 40.0% (2/5 patients) and 60.7% (17/28 patients).^{14,15}

Pre-epiglottic baton plate

A review of the literature identified 4 studies that reported the effectiveness of PEBP insertion in isolated RS patients. A cohort study by Bacher et al³ included 15 isolated RS patients that were treated with a PEBP. The plate remained *in situ* for 3 months, day and night and usually required a larger plate during this period. Overnight sleep studies were performed in supine position. Intervention with PEBP was associated with significant improvement in sleep study parameters, including a

significant decrease in MOAI from baseline to discharge and from baseline to 3 months follow-up, a significant decrease in ODI from baseline to discharge, a significant decrease in capillary blood CO₂ pressure from baseline to 3 months follow-up, and a significant increase in weight gain between baseline and discharge and baseline and 3 months follow-up. At 3 months after treatment, 1 child out of 15 (6.7%) had a MOAI > 3.

In Buchenau et al,¹⁰ 122 isolated RS were treated with the PEBP. The authors reported improvement of the MOAI. Eighteen patients without OSA were still treated, with the aim to stimulate mandibular growth. All patients with either mild (n = 30), moderate (n = 19) or severe MOAI (n = 55) improved to a MOAI below 3, after 3 months follow-up. Two further studies reported success rates for PEBP in isolated RS patients of 84.1% (159/189 patients) and 100.0% (111/111 patients).^{6,28} In Schmidt et al²⁸ it was reported that in 111/111 (100%) the breathing problems diminished in all patients with isolated RS without showing PSG data.

In Poets et al,⁶ sleep study data were available for 41 infants and showed a decrease in MOAI from 15.9 at admission (IQR 6.3–31.5) to 2.3 (1.2–5.4) at discharge. During follow-up one discontinued the use of the plate, and in 8 no sleep study was available. Three months later, data were available for 32 infants and showed a MOAI of 0.7 (0.1–2.4). Mean SDS for weight between admission and 3-month follow-up remained unchanged (–0.84 versus –0.87). No infant needed mechanical ventilation or tracheostomy. Success rate for PEBP in this study is at least 32/41 (78.0%) and at best 40/41 (97.6%).

Finally, a retrospective cohort study by Wiechers et al³² reported that PEBP therapy was successful in 300/303 (99.0%) patients with isolated RS. In the 3 infants where PEBP was unsuccessful, PEBP was discontinued due to recurrent pressure marks. Sleep study (taken in supine position) results were available in 246 infants and demonstrated a significant 10-fold reduction in MOAI from 9.0 (3.4–22.8) to 0.9 (0.3–1.9) 3 months afterwards (with the plate *in situ*). Four did not have actual OSAS. While good results were reported for the sleep studies, the Z-score for weight changed from –0.28 at birth (n = 296); –1.11 at admission (n = 307); –1.17 at discharge (n = 307); –1.09 after 3 months (n = 240); to –0.44 at 1-year follow-up (n = 183), all were fully orally fed at the time.

One additional cross-over RCT in 11 RS patients with isolated RS was analyzed.³⁴ Sleep studies were taken at baseline and again 48 hours after inserting a PEBP (with velar extension) or a conventional palatal plate without velar extension (CPP) as control intervention; infants were assigned to the alternative treatment (CPP or PEBP) after another 48 hours. This study showed a mean decrease in MOAI of 71% with the PEBP *in situ*, with a mean MOAI of 3.9 (95% CI: 1.6–9.5) but hardly any effect or even a worsening of the MOAI with the CPP. These data indicate a large decrease in airway obstruction already 48 hours after application of the PEBP and a clear difference to the CPP.

In Table D (the Appendix) data are summarized from 6 studies, which included a total of 814 RS patients that reported a success rate for PEBP therapy. The definition of treatment success was consistent across studies and included resolution of upper airway obstruction. In these (largely retrospective) cohort studies, 814 RS patients were treated with a PEBP with a high success rate ranging from 78.0%–100%.^{3,4,6,10,28,32}

Conclusions

Positioning Therapy
Overall conclusion
 Studies indicate that prone positioning is indicated as a first-choice treatment for upper airway obstruction in almost all cases of the breathing problems, except in acute respiratory failure.
 References: 2, 5, 9, 12, 14, 16, 17, 20, 26–28, 31
Conclusion based on evidence from 12 (n=12) single arm-observational studies with a low risk of bias, significant heterogeneity and indirect evidence but no issues with imprecision or publication bias.

Success rate Isolated RS only
 There are indications that the success rate of prone positioning therapy in isolated RS varies from 28% to 72%.
 References: 5, 7, 8, 17, 20, 31
Conclusion based on evidence from 7 (n=6) single arm-observational studies with a high risk of bias and significant inconsistency, but no issues with imprecision, indirectness, or publication bias.

Success rate all RS patients
 There are cautious indications that the success rate of positioning therapy in RS patients varies from 28% to 100%.
 References: 2, 5, 7, 8, 14, 16, 17, 26, 28, 31
Conclusion based on evidence from 5 (n=10) single arm-observational studies with a high risk of bias, significant heterogeneity, but no issues with indirectness, imprecision or publication bias.

Nasopharyngeal airway
Overall conclusion
 There are indications that NPA insertion is a second-choice treatment in RS cases after positioning therapy fails to control obstructive sleep apnea and upper airway obstruction.
 References: 7, 8, 13, 14, 18, 20, 21, 29, 31, 33
Conclusion based on evidence from 12 (n=10) single arm-observational studies with a low risk of bias, significant heterogeneity and imprecision, but no issues with indirectness or publication bias.

Success rate isolated RS only
 There are indications that the success rate of NPA insertion in isolated RS varies from 60 – 87.5%.
 References: 2, 4, 17
Conclusion based on evidence from 8 (n=3) single arm-observational studies with a risk of bias, significant heterogeneity and imprecision, but no issues with indirectness or publication bias.

Success rate all RS patients
 There are indications that the success rate of NPA insertion in isolated RS varies from 50% to 100%.
 References: 2, 4, 7, 8, 13, 28, 31, 33
Conclusion based on evidence from 9 (n=8) single arm-observational studies with a risk of bias, significant heterogeneity and

imprecision, but no issues with indirectness or publication bias.

Indication for continuous positive airway pressure (CPAP)
 Studies indicate that CPAP is a second-choice treatment for isolated and nonisolated RS cases after positioning therapy fails to control obstructive sleep apnea and upper airway obstruction.
 References: 18, 23, 31
Conclusion based on evidence from 3 (n=3) single arm-observational studies with low risk of bias, significant heterogeneity, but no issues with imprecision, indirectness, or publication bias.

Success rate of CPAP for patients with RS.
 There are cautious indications that the success rate of CPAP RS patients varies from 27% to 67%.
 References: 18, 23
Conclusion based on evidence from 2 (n=2) single arm-observational studies with a high risk of bias, significant heterogeneity and imprecision but no issues with indirectness, or publication bias.

Endotracheal intubation
 Studies indicate that ET intubation is first the choice of treatment in an acute situation in patients with the most severe obstruction.
 References: 14, 15, 20, 25
Conclusion based on evidence from 5 (n=4) single arm-observational studies with a high risk of bias and significant heterogeneity, but no issues with imprecision, indirectness, or publication bias.

Indication for Pre-epiglottic baton plate
 Studies indicate that PEBP insertion is a second-choice treatment in isolated and nonisolated RS patients after positioning therapy fails to control obstructive sleep apnea and upper airway obstruction.
 References: 3, 4, 6, 10, 28, 32, 34
Conclusion based on evidence from 6 (n=6) single arm-observational studies with a high risk of bias and significant heterogeneity, but no issues with imprecision, indirectness, or publication bias, and one crossover-RCT

Success rate of Pre-epiglottic baton plate
 There are indications that the success rate of PEBP therapy in isolated and nonisolated RS varies from 84% to 100%.
 References: 4, 6, 10, 28, 32
Conclusion based on evidence from 6 (n=5) single arm-observational studies with a high risk of bias and significant heterogeneity but no issues with imprecision, indirectness, or publication bias.

Effect of Pre-epiglottic baton plate (with velar extension) on sleep apnea index
 There are indications that PEBP application with velar extension results in a significant decrease in the number of obstructive events per hour (MOAI) in children with Robin Sequence compared to a conventional plate without velar extension.
 Reference: 34

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Considerations Quality of Evidence

Despite the fact that most of the included studies were not suitable for GRADE assessment, a judgment of the quality of the evidence for the effectiveness of nonsurgical interventions to treat the mandibular-related breathing problems of RS was made. The evidence on indications for treatment options is heterogeneous and most probably biased by local preferences. However, it is obvious positioning therapy is most often used as the first treatment option. Looking at the evidence body, the evidence mainly suffered from a lack of comparability to no intervention. However, studies on the nonsurgical management of RS will always suffer from lack of comparability to no intervention since it would be unethical not to provide nonsurgical treatment to RS infants with breathing problems in order to collect data for a control arm.

Heterogeneity between studies was significant and downgrades the confidence in conclusions drawn over all included studies, therefore conclusions should be interpreted with caution. Overall study results for positioning therapy may suggest lower success rates but looking at the best quality of evidence, where the results were confirmed with PSG³¹ it is likely that the success rate of prone positioning lies much higher than the overall results of included studies.

It is also not possible from the data reported in some studies⁴ to quantify the confounding influence of the use of multiple nonsurgical approaches to airway management on the efficacy of each individual treatment.

The 6 articles on the application of PEBP originate from 5 experienced centers. Possibly, in 2 papers^{3,10} from one center some cases may have been reported twice. Five papers demonstrated outcome data from sleep studies.^{4,6,10,28,32} The RCT from Buchenau et al³⁴ is well conducted in this field, but GRADE assessment and Cochrane risk of bias assessment for crossover studies still revealed some concerns for methodological bias and indirectness of evidence. Besides that, the sample size was small, which raises concerns for imprecision. This resulted in the necessity of rating down the level of evidence from high to low. However, the paper from Buchenau et al³⁴ is still of better quality than the main part of included literature for this guideline. Despite the low grade, due to its comparative design it gives better indications of the estimated effect than the other, observational, studies.

One paper on the PEBP in 111 infants with isolated RS reported that breathing problems diminished in all patients and that feeding tubes could be removed in all but 4 infants prior to hospital discharge, but no details on polysomnography results or sleep position are provided.²⁸

Professional Perspective

Although there are many studies looking at the RS population, the general body of evidence for the effectiveness of nonsurgical management is subject to limitations. Nevertheless, there is limited evidence for individual nonsurgical interventions, as well as inclusion with surgical interventions, in an overall algorithm of care for babies at all levels of severity of mandible-related breathing problems in RS.

In the nonemergent presentation, clinicians should implement a trial of positioning and assess the effectiveness of lateral first and then prone positioning on the clinical features of RS such as breathing, feeding and growth. Given the risk of sudden infant death syndrome (SIDS) associated with prone positioning in healthy newborns and the risk of unwanted changes in positioning during sleep from side or prone to the back, the use of oximetry is strongly recom-

mended. Teams caring for RS patients will need to reassess this at frequent intervals and escalate care if symptoms persist.

The choice of the use of nonsurgical interventions such as NPA, CPAP, high flow nasal cannula, and PEBP will depend on local expertise and experience, and this will influence the ability for care to be provided in the community. If NPA is effective, this can enable patients to be discharged home with the relevant support and represents a simple, widely available solution for patients who require more support than positioning alone can achieve.

For the minority of patients who cannot be managed in the community with simple measures such as positioning or NPA then all other options including CPAP, ET intubation, PEBP and/or surgical management need to be considered.

If available, then teams could consider PEBP which appears effective and safe for many patients with RS. So far, the breathing outcomes in the studies assessing the use of the PEBP show promising results and warrants further evaluation. However, in these studies, the PEBP has been inserted after positional treatment for mild, moderate, and severe airway obstruction. Further, in some studies, the PEBP was utilized in all patients including those who were stable with positioning treatment, whereas other interventions were mainly researched in a population for whom positioning treatment had really failed. This may lead to an overestimation of the efficacy of the PEBP. Future studies with clear consensus on the indication for this treatment and patient inclusion, with adequate PSG data should therefore verify the accuracy of the PEBP results compared to other non/mildly-invasive treatments like positioning or NPA. At present, the effect estimates should be interpreted with caution.

ET intubation is a life-saving measure which is able to provide a definitive nonsurgical airway in patients who do not respond to prone positioning, NPA, and/or CPAP. Although intubation should be considered as a marker of severity there are some children in which it can provide support and recovery from a temporary clinical deterioration. In the majority of babies, however, it will act as a bridge for teams to consider definitive options for further escalation of care.

Patient Perspective

Ensuring that their child is safe at home is one of the most important considerations for parents of infants with RS. Parents are looking for an expert team with the resources to provide accurate assessment, timely support and care which is personalized to their child's requirements. This team should strive to facilitate and normalize life to the extent that is possible without compromising patient care. Home oximetry is an example which can help provide this feeling of assurance for parents of children undergoing interventions such as prone positioning treatment which enhances the sense of safety. However, as stated above, evidence for the effectiveness of home monitoring is lacking.

Importance of Outcomes

The indications for, and effectiveness of nonsurgical interventions is of highest importance for determining and harmonizing the treatment algorithms for the nonsurgical management of mandibular-related breathing problems in RS.

Balance of Benefits and Harms

Nonsurgical interventions offer a relatively safe, first-line approach to the management of mandibular-related breathing

difficulties in infants with RS. The effectiveness of nonsurgical interventions ranges from 43.9% for CPAP to 94.1% for PEBP insertion, the latter reported by a limited number of centers with specific orthodontic expertise. Due to the relatively high effectiveness, low invasiveness and availability of a range of different nonsurgical approaches to the management of breathing difficulties in RS, the majority of infants will receive benefit from nonsurgical approaches to care.

Clinicians and many families will be aware of the general recommendation for infants is to be nursed in the supine position to reduce the risk of sudden death infant syndrome (SIDS), however, prone positioning is widely accepted, but may not completely relieve obstruction in many patients. As many infants respond to lateral positioning, this may be a trialed initially with true prone positioning trialed in those who do not respond. Positioning treatment is easily taught, although escalation of care must occur in nonresponders. Oximetry may be reassuring in monitoring infants who are being managed with true prone positioning, but whether it provides a sufficiently early warning in case of impending life-threatening hypoxaemia in a home setting remains an unproven assumption. Clinicians should always balance the possible benefits of prone positioning against the concerns regarding SIDS.

The pressure generated by CPAP effectively “stents” the airway to support respiration in up to 3-quarter of children. It is often considered second line management as there may be some difficulties in achieving an adequate seal without excessive pressure on the face. Constant pressure on the immature craniofacial skeleton may be a cause of long-term mechanical deformity/ growth restriction. This is a particular concern in patients with RS who are already at risk of maxillary and mandibular retrusion. An alternative to the use of CPAP may be the use of high flow nasal cannula (also known as Optiflow).

The use of the NPA is variable and success is highly dependent on the experience of the team and education of parents. In babies with RS, the appropriately sized endotracheal tube is small and easily narrowed or blocked with secretions. It needs constant monitoring and management to provide a clear airway and the ability to change the tube in the event of complete obstruction. As with all airway compromise this represents a potential airway emergency. Effective sizing of the tube also requires that the length is optimized. If the tube is too short, it will not provide a clear airway past the occluding tongue base, and if it is too long, then there will be stimulation of the epiglottis and vomiting or coughing. Correct positioning is achieved when air is perceived to outflow from the tube during expiration, with little or no outflow of saliva or milk during feeding.²

The PEBP appears to be effective but with availability limited to centers with orthodontic experience in this technique. Potential harms include limited effectiveness without accurate sizing, risk of pressure injuries to adjacent soft tissues and mechanical device failure. Specialist sizing, placement, manufacture and monitoring to enable timely adjustments of these devices is essential. Parents should be aware they have to visit the clinic after approximately 3 months (and sometimes even more often) as the plate needs to be adapted to the fast-growing maxilla.¹⁰

ET may be required to provide a safe airway in the emergent situation in infants with RS in a hospital setting. This should be regarded as a temporary measure, as long-term intubation is associated with significant risks such as subglottic stenosis. Although some patients may avoid surgical management with a period of short-term intubation, for the majority, intubation is a feature of more severe disease requiring escalation of care.

Costs and Resources

The costs associated with the utilization of positioning therapy is minimal; however, significant training and monitoring by clinicians and families is important to ensure that escalation of care can be implemented in a timely manner. Similarly, the use of NPA requires experience with the placement and appropriate sizing of the tube and training of families in the management of the NPA if the child is to be cared for in the community. CPAP utilization and ET intubation should be available in every pediatric center in every European member state and the requirement for inpatient management is a significant cost and resource consideration. CPAP may be considered for use in the community with selected patients and families with appropriate training and clinical monitoring.

Expertise in the use of a PEBP currently appears to be geographically limited to specialist centres in which there is expertise at treating infants with RS with this device.

Inequity of the Recommendation

There is inequity in availability and experience in nonsurgical modalities, home care and screening/ monitoring. Also, there is inequity in the availability for long-term monitoring in the hospital between different hospitals/ member states. This can influence the team’s choice for a nonsurgical or a surgical approach. In practice, this could cause children to receive surgery while they could very well be managed in a nonsurgical manner if they were allowed more time in the hospital.

Feasibility of the Recommendation

The majority of the nonsurgical interventions recommended in this Chapter are available in all pediatric centres, however, implementation of some nonsurgical interventions (eg, PEBP) will be dependent on local expertise.

Acceptability of the Recommendation

It is expected that all stakeholders should strive to adhere to the recommendations set out in this Chapter. National implementation plans are necessary to ensure that recommendations are adapted to the situation in each country. In addition, not all countries participating in ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale of the Recommendations

The rationale of the recommendations presented in this Chapter was to assess the indications for, and effectiveness of the full range of nonsurgical therapies to establish a harmonized treatment algorithm for the nonsurgical management of mandibular-related breathing difficulties in infants with RS. These recommendations should be interpreted with consideration to the recommendations set out in Chapter 12 on the surgical management of RS patients.

Recommendations

- Include nonsurgical interventions, that is, prone positioning, NPA, TPP and/or CPAP, in the treatment algorithm of mandibular-related breathing difficulties in infants with RS.
- Parents and caregivers should be provided training in the management of interventions (eg, NPA, NGT) to facilitate care in the community.

- Consider ET intubation as a life-saving measure in patients who do not respond to above-described nonsurgical interventions, acting as a bridge for teams to consider definitive options for further escalation of care.
- In the case that a nonsurgical intervention fails to adequately control OSA care should be escalated to adequately support respiration.
- In the case that nonsurgical intervention is still necessary after 6 to 9 months MDT should re-evaluate treatment to discuss with parents to continue nonsurgical treatment or change to surgical intervention.
- Clinicians should consider both nonsurgical and surgical interventions (as per the recommendations set out in Chapter 12) described in this guideline.

Consensus

Initially, the following recommendations were also proposed by the guideline development group:

- Consider positioning therapy (either prone or lateral positioning with a saturation monitor) as first-line to relieve mandibular-related OSA. Monitor the child during the first year of life for difficulties with breathing and feeding and measure length and weight growth.
- If positioning therapy fails to relieve UAO, other nonsurgical interventions should be considered: CPAP, NPA, high flow nasal cannula and PEBP. The selection of each intervention should be guided by consideration of the effectiveness of each intervention as well as local expertise in the utilization of each intervention.

However, during the comment and authorization phase these recommendations did not receive approval from all stakeholders and consensus could not be reached by following the initial methods for creating recommendations. Therefore, formal consensus was sought by using a Delphi process for these specific topics. After 2 Delphi rounds, consensus (minimum of 70% agreement) was identified on the following statements:

1. Supine positioning of RS patients can cause breathing disturbances during sleep—**Agreement 90%**
2. Clinicians need to balance the risk associated with prone positioning with regard to SIDS against the potential benefits of prone positioning to improve upper airway obstruction in RS infants—**Agreement 100%**
3. Prone or lateral positioning with continuous (home) oximetry is as first line an appropriate treatment for patients with RS and OSA—**Agreement 85%**
4. There is inconclusive evidence to prove superiority of one breathing intervention for RS patients over another, therefore the selection of a nonsurgical treatment strategy for breathing should be guided by consideration of the effectiveness of each intervention as well as local expertise—**Agreement 75%**

Details of the Delphi procedure are described in the methodology chapter and a report of the evaluation between round 1 and 2 is available in the supplementary materials.

Research Gap

The overall evidence in this chapter is weak due to the lack of good comparative studies. It is noteworthy the literature and evidence for nonsurgical treatment seems to be under-represented compared to literature and evidence for the surgical treatment whereas the nonsurgical therapies, especially prone positioning, are used much more often than the surgical thera-

pies. To solve the issue of advantages and disadvantages of various nonsurgical treatment modalities, well designed prospective cohort studies are required. In view of the limited number of patients a multicenter approach is recommended. The ERN network could play a prominent and leading role here. Currently, the treatment algorithm presented in chapter 6 is meant as guidance and with outcomes of these future multicenter studies the algorithm will be further refined. Prospective studies might yield better criteria for choosing one or the other treatment modality, either surgical (MDO, TLA) or nonsurgical (positioning therapy, CPAP, NPA, PEBP, HFNC).

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CHAPTER 12. SURGICAL TREATMENT OF MANDIBULAR-RELATED BREATHING PROBLEMS IN ROBIN SEQUENCE

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

If nonsurgical treatment of mandibular-related breathing problems in RS is unsuccessful, surgical therapy is called for. The most successful surgical intervention to treat severe OSA, to date, is a tracheostomy. However, long-term cannulation comes with certain drawbacks and side effects (eg, interference with speech and language development, suprastomal, laryngeal or tracheal granulations, suprastomal and tracheal collapse, subglottic stenosis, hemorrhage, tracheocutaneous and tracheo-oesophageal fistulae, swallowing problems and bronchopulmonary infections and therefore alternatives such as mandibular distraction osteogenesis (MDO) and tongue-lip adhesion (TLA) should be considered.¹ Mandible traction by wires (MTW) has been described to be effective as well, but is not commonly used and therefore not part of this guideline.^{2,3}

It should be stressed that prior to a surgical treatment of breathing problems the diagnostic work up includes endoscopy of the entire upper airway tract to exclude additional lower airway obstructions and other problems. Andrews et al (2013) reviewed 133 cases of micrognathia and upper airway obstruction that needed admission into the ICU, including 194 RS patients and 29 with a specific syndrome.⁴ In 83 patients laryngo/bronchoscopy was done to identify concomitant airway anomalies. They found that in 23/83 (28%), endoscopy revealed tracheal/laryngeal problems making mandibular distraction osteogenesis not a feasible treatment option. Out of these 23 patients, 16 were diagnosed with RS and 6 with micrognathia associated with a specific syndrome and one with craniofacial microsomia. The breathing issues in these 16 were treated with a tracheostomy (n=11) or home monitoring/positioning/nasopharyngeal tube. However, finding of tracheal/laryngeal problems do not exclude MDO or TLA as additional treatment options for UAO to laryngeal and tracheal plasties.⁵

MDO is an operative procedure to gradually lengthen the mandible with an internal or external device creating airway space at the tongue base. MDO for severe cases of RS should be

evaluated primarily with regards to normalization of breathing and feeding and secondarily to avoidance of additional interventions like tracheostomies, complications like damage to the developing teeth, mechanical failure, nerve injuries, excessive scarring, all compared to the effect of other surgical options like TLA. It appears as the MDO has gained popularity over the TLA since the introduction of the MDO technique during the 1990s.

TLA is an operative procedure designed to temporarily fixate the posteriorly displaced tongue forward to the lower lip. The operation can be done as early as within the first weeks after birth. The fixation is loosened when the lower incisors have formed and begin to cause problems, usually scheduled between 6 and 8 months of age, or at time of closure of a Cleft palate, if present. In some centers it is considered as an alternative for MDO in nonsevere OSA cases and problems which sometimes are seen in nonsurgical measures, like recurrent loss of NPA or inability of parents to deal with these nonsurgical treatment options.

Choice of Surgical Technique

The last decades several surgical options have been used in the treatment of breathing problems in isolated and nonisolated RS. All come, of course, with their own merits, successes, and drawbacks. Of these currently TLA and MDO are widely used. However, it remains unclear which of the 2 procedures is considered as primary choice of treatment in RS children. In addition, the subperiosteal release of the floor of the mouth (SRFM) as a third surgical option has been mentioned but only few papers report outcomes and only limited number of centers currently seem to apply this technique.

The next chapter will evaluate aspects of the different surgical options to find common ground for recommendations when to use which technique for treatment of RS to improve breathing problems with impact on feeding problems and growth, complications, and effect on long-term growth.

For this chapter the following question were addressed.

- **What is the most optimal surgical treatment modality, MDO versus TLA, for the mandibular-related breathing problems in RS patients?**

To achieve an integral overview, we have investigated the implications of the surgical options MDO and TLA for breathing, feeding and growth, timing of the surgery, as well as the short- and long-term complications and need for a secondary intervention.

To answer these questions, we have investigated the following parameters as outcomes of interest:

- Successful airway management expressed in breathing parameters, such as apnea hypopnea index, oxygen saturation, decannulation
- Successful recovery of feeding issues expressed in parameters, such as the need for a nasogastric tube, gastrostomy, ability to drink (oral feeds) and weight percentiles
- prevention of tracheostomy
- Timing of the surgery
- Complications of the surgical treatment:
 - The need of secondary interventions to treat remaining/recurring breathing problems: tracheostomy or MDO after TLA or tracheotomy after MDO.
 - Infections
 - Device failure
 - Tooth injuries
 - Nerve injuries

- Long-term effects of MDO and TLA on mandibular growth.

Literature Search

For this guideline, a systematic literature search was conducted. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin Sequence
Subject	Breathing, feeding and growth, complications of surgery at short and long term after TLA, MDO, subperiosteal release floor of the mouth
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion.

After rough selection and labeling a full text assessment of (n = 172) studies was performed for this chapter. Several studies were excluded (n = 134) due to sample size (n = 19), incorrect outcome (n = 34), study design (n = 41) or for other reasons. In this chapter (n = 34) studies are described.

Summary of Literature Study Mandibular Distraction Osteogenesis

Effect of MDO on breathing problems

Burstein et al (2005) analyzed the short-term outcome of MDO in a case series of 20 RS cases (15 isolated RS and 5 syndromic RS), aged between 7 days and 5.5 years.⁶ In 14 patients a tracheostomy was avoided but not in 2, whereas 4 of 6 patients who had previous tracheostomy were decannulated after mandibular distraction. Preoperative polysomnography (PSG) (n = 9) showed a respiratory disturbance index ranging from 6.9 to 26, with a mean of 15.3; postoperative index ranged from 0 to 1.9, with a mean of 1.1.

Genecov et al (2009) studied the short-term success of MDO in patients with mandibular airway obstruction syndrome, defined as OSA, swallowing abnormalities, and failure to thrive in the presence of micrognathia, glossoptosis, gastroesophageal or laryngeal reflux, and micro-aspiration in a group of 81 patients (n = 78 isolated RS, n = 3 syndromic RS).⁷ The age ranged from 5 days to 6 years, with a mean of 1.2 years. Tracheostomy was prevented in 25 (96%) of 26 patients, and decannulation after distraction was possible in 38 (92%) of 41 patients. Success, defined as decannulation within 1 year of the start of distraction or prevention of tracheostomy in a patient otherwise deemed as a candidate, was found in 63 (94%) of 67 patients. Preoperative PSG (n = 67) had a respiratory disturbance index ranging from 35 to 50; postoperative PSG showed an index of 5 to 15 in 65 patients, while it remained above 35 in 2 patients.

Goldstein et al (2015) did a retrospective study on 28 patients, 18 with isolated RS, to evaluate the short-term success of MDO at a mean age of 58 days (range 11–312) in the treatment of upper airway obstruction (UAO) in RS.⁸ In 20 patients, preoperative PSG was done, resulting in an average apnea-hypopnea index (AHI) of 39.3 ± 22.0/h. In 14 patients the post-

operative AHI was significantly reduced (mean $3.0 \pm 1.5/h$; $P < 0.0001$). Distraction was successful in all ($n = 14$) but 4 patients. These patients required a tracheostomy ($n = 3$) or TLA ($n = 1$). The failure was explained because of low muscular tone and syndromic diagnoses such as Antley-Bixler and Mobius in 3 and due to device failure in one.

Hunter et al (2021) studied the feasibility of the GILLS score to predict outcome in MDO for treatment of PRS in 21 patients as measured by the obviation of the need for tracheotomy.⁹ A GILLS score of ≤ 3 had a 100% success in avoiding tracheotomy, had a positive predictive value of 100%, a negative predictive value of 50%, 83% sensitivity, and 100% specificity. These data imply that the GILLS scoring algorithm is applicable to aiding in the selection of patients with RS for MDO, including patients with known syndromes.

Meyer et al (2008) did a retrospective study of 74 cases of RS, 53 iRS. Outcome was measured by means of capillary blood gas and oximetry.¹⁰ Twenty-seven of the iRS group did not need any other therapy than prone positioning, 10 were managed successfully by nonsurgical intervention by means of NPA, 16 acquired surgical intervention. Primary complaint at first presentation was airway (16), airway/feeding (9), feeding (8) and none (11). Surgical intervention in iRS consisted of MDO only (14), tracheotomy only (1) and tracheotomy after MDO (1). The child with tracheotomy only was managed by this technique in a period (before 2000) that MDO was thought to be unsuitable for infants < 2 kg. In the sRS group ($n = 21$) 9 were successfully managed by prone positioning, 4 by NPA, 4 by MDO and 4 finally needed tracheostomy after MDO.

Resnick (2018) did a study on virtual planning for MDO treatment in RS. Seventeen infants were operated on because nonsurgical treatment failed, of which 7 had a syndromic diagnosis including Nager and Stickler.¹¹ Mean age at operation was 87 ± 96 days. At pre-MDO PSG registration ($n = 13$) 84.6% had severe OSA, 7.7% moderate and 7.7% mild-moderate OSA. Early post-treatment evaluation ($n = 15$) showed no OSA in 80% of the cases and minor residual OSA in 20%. Two of the 3 patients with residual OSA had a syndromic diagnosis.

Runyan et al (2018) did a retrospective study on 177 infants with RS, where they compared the management (prone positioning versus tracheostomy versus MDO) to get an insight in prediction of the need for surgical management of UAO.¹² The nonsurgical group (prone positioning) consisted of 49 cases (51% syndromic), MDO 68 (44.1% syndromic), tracheostomy 54 (66.7% syndromic). Mean AHI was measured for all groups before and after intervention: nonsurgical 12.9 versus 3.1, MDO 43.3 versus 7.0 and tracheostomy 39.2 versus 6.0. Patients treated with surgery had a statistically significant higher incidence of requiring a surgical feeding, a significant delay in the time required to feed exclusively by mouth and an objectively worse sleep study. The greatest predictor for the need of surgical intervention was $AHI > 20$. Over two thirds of those treated surgically (67.5%) had an obstructive $AHI > 20$, compared to only 11.5% of those treated with prone positioning. Of the 69 MDOs, 6 required subsequent tracheostomy (8.8%); low birth weight and neurologic impairment were found to be risk factors for the outcome that MDO failed to prevent tracheostomy, taking intervariable interactions into consideration. Syndromic status was not an independent risk factor but including it next to low birth weight and neurologic impairment raised pretest sensitivity and specificity from 77.6% and 60.0% to 64.3% and 100%.

Of the 54 patients treated primarily with tracheostomy, 33 received MDO and 19 (57.5%) were successfully decannulated.

Risk factors for failure of decannulation were low birth weight, syndromic status, and absence of cleft palate.

Soto et al (2021) reviewed retrospectively outcome after MDO in 29 RS cases, 16 iPRS, and 13 sPRS, based on genetic evaluation.¹³ AHI changed from $22.27 \pm 12/27$ pre-MDO treatment to 5.24 ± 4.50 post-MDO with no statistic difference between the 2 groups iPRS or sPRS ($P = 0.4369$). Postop decannulation was 93% for iPRS versus 77% for sPRS. There is a potential role for MDO in reducing the need for traditional surgical interventions for respiratory and feeding problems in both iPRS and sPRS patients.

Tahiri et al (2015) did a retrospective study on a group of 121 children with RS, treated with MDO, of which 81 had a weight < 4 kg and 40 a weight > 4 kg to look at the efficacy, safety, and complication profile of MDO in infants < 4 kg with RS.¹⁴ The indication for MDO was failed conservative treatment, no central apnea, no $AHI > 20$ or significant carbon dioxide retention. Follow-up time was nearly 3 years. There was no significant difference in success of MDO to treat airway obstruction in the < 4 kg group versus the control group (92.6% versus 88.9%, $P = 0.45$), defined as decannulation, avoidance of tracheotomy, or significant improvement of OSA that allows discharge to home.

Wittenborn et al (2004) studied retrospectively a cohort of 17 RS (14 isolated RS, 2 Stickler and 1 Treacher Collins syndrome) to evaluate the outcome of MDO with a mean follow-up time of 16.5 months (range 8–48 mo).¹⁵ The indication for MDO was failed conservative therapy. Age at surgery varied from 5 to 120 days. Ten cases who underwent preoperative and postoperative polygraphic studies showed improvement in obstructive apnea. Three patients had postoperative polysomnographic studies only; the results were comparable to those of patients with preoperative and postoperative studies. Fourteen out of 17 had a successful outcome after extubation: 3 required tracheostomy (1 because of previously undiagnosed tracheal stenosis). The diagnoses of these 3 are not mentioned.

Effect of MDO on feeding, growth, and gastro-esophageal reflux

Adhikari et al (2016) designed a retrospective cohort study including 73 children who underwent MDO for upper airway obstruction at a mean age of 2 months [interquartile range (IQR), 1.7–4.2] for nonsyndromic infants ($n = 31$) and 3.3 months (IQR, 2.1–7.4) for those with syndromes ($n = 42$).¹⁶ Most children (83%) required supplemental feeding preoperatively with 55 (75%) needing nasogastric tube feeds and 6 (8%) a percutaneous gastrostomy tube, but 12 months postoperatively, 97% of the nonsyndromic infants fed orally. At the end of the first postoperative year, 56 patients (77%) were feeding orally, 5 (7%) had NGTs, and 12 (16%) had PEGs (including 7 who had NGTs before distraction but who then went on to have PEGs due to prolonged feeding difficulties). The average growth of the patients followed within 1 centile line of their birth-predicted trajectories. Complete data were available for 52 patients, and in this group, failure to thrive was observed in 5 (23%) of the nonsyndromic cohort and 8 (27%) of the syndromic cohort, before distraction. At 1-year post-MDO, growth had improved with 19 (86%) of the nonsyndromic cohort and 25 (83%) of the syndromic cohort growing within 2 centile lines of their weights at MDO. There was no statistical difference between the nonsyndromic and syndromic cohorts ($P > 0.05$), but the difference in growth velocities at distraction and 1-year post-MDO was statistically significant ($P = 0.006$), showing overall positive growth.

Breik et al (2016) published a systematic review on the effects of MDO on feeding and gastro-esophageal reflux disease

(GERD).¹⁷ Twenty-one studies relevant to feeding and 4 studies relevant to GERD outcomes were included. Selection criteria for the patients were micrognathia with clinical evidence of upper airway obstruction and failed conservative treatments, syndromic and nonsyndromic children and bilateral MDO. Patients with unilateral MDO, central apnea or lower airway abnormalities, TMJ ankylosis, craniofacial microsomia or other mandibular condition leading to airway obstruction were excluded. All studies were case series (16) and case reports (5), including 300 patients in total. After MDO 82% of children was feeding exclusively orally within 12 months after surgery over a mean period of 3 years (range 1–7 y). The percentage of feeding adjuncts before MDO is not presented, other than the phrase “most of the children who were able to feed orally were weaned off gastrostomy tubes or NG tubes preoperatively.” The overall percentage of children with iPRS who were feeding orally was 93.7% compared with only 72.9% in the syndromic group ($P < 0.004$). A growth decline within the first 6 weeks after surgery was observed in multiple studies. Overall, out of 70 patients with preoperative GERD, only 4 had evidence of GERD after surgery.

Gary et al (2018) retrospectively analyzed quantitatively weight gain following MDO at a mean age of 215 days in 22 RS cases (17 isolated RS, 5 syndromic RS) with at least 6 months follow-up.¹⁸ Patient weight data, feeding methods preoperatively and postoperatively, and PSG data preoperatively and postoperatively were collected. Each patient’s weight plotted over time was then compared with his or her closest standardized growth curve, and linear regression analysis was utilized to quantify patient growth by calculating actual and expected average daily weight gain (g/d). Percentile changes were analyzed as well. 19 of the 22 children gained significantly less weight than expected from birth to time of MDO and significantly more weight than expected from MDO to device removal, MDO to 6 months postoperatively, and MDO to 12 months postoperatively. The average growth percentile for the cohort was 37.3 at birth, declined to 22.7 by MDO, and increased to 28.5 and 33.5 at device removal and 6 months postoperatively, respectively. More than 70% of children were exclusively orally fed within 6 months of MDO. Children with isolated RS had superior weight gain than children with syndromic RS following surgery.

Goldstein (2015) reported on 20 patients (74%) who transitioned from nasogastric or gastrostomy tubes to complete oral feeding after 4 or 11 months postdistractor, respectively.⁸ Three of the ones that did not improve in feeding, had a failed MDO with respect to breathing.

Harris et al (2021) presents a retrospective cohort study of patients with RS treated at Boston Children’s Hospital from 1995 to 2016.¹⁹ The primary predictor variable was type of intervention (no operation, tongue-lip adhesion, MDO). The primary outcome measure was weight-for-age Z-score. A control group of patients with isolated cleft palate without RS was also included. Individuals with tracheostomy or insufficient growth data were excluded. Descriptive statistics were calculated, and statistical significance was set at $P < .05$. A total of 222 subjects were included: no operation, $n = 61$ (27.5%); tongue-lip adhesion, $n = 78$ (35.1%); MDO, $n = 22$ (9.9%); and control, $n = 61$ (27.5%). Mean age at tongue-lip adhesion was 37 ± 99 days compared with 247 ± 312 days for MDO ($P < 0.05$). At 6 months of age, the MDO group had the lowest mean weight ($Z = -2.34 \pm 1.88$, $P < 0.05$) and both surgical groups were underweight compared with controls ($P < 0.05$). By 24 months of age, there were no weight differences between any study group. Individuals that had MDO at < 3 months of age

had significantly faster weight gain than those that had later operations ($P < 0.05$).

Luo et al (2018) retrospectively analyzed preoperative and postoperative body weight in 41 children with RS who underwent MDO treatment for breathing difficulties between the ages of 16 days and 7 months.²⁰ All suffered from eating difficulties as well. The body weight of the infants at the time of birth, first visit, MDO surgery, distractor removal, and palatoplasty surgery was recorded. The body weight percentile significantly fell from 34.4 at birth to 13.1 at the time of MDO ($P < 0.001$), and increased to 28.3 at distractor removal ($P < 0.05$) following MDO, finally reaching 42.4 at palatoplasty surgery ($P < 0.001$). The infants who accepted MDO treatment at < 1 month of age maintained a significantly higher body weight percentile than those who accepted MDO surgery at 1 to 3 months or 4 to 7 months of age, at the time of both MDO and palatoplasty surgeries ($P < 0.05$). After the MDO procedure, the body weight percentiles of the RS infants with a cleft palate were comparable to those without a cleft palate at the time of palatoplasty surgery. The body weight percentile quickly climbed to 74.03 at the time of distractor removal, from 46.71 at the time of MDO. In conclusion, early MDO was beneficial in severe cases of RS for patients to recover body weight and to allow for earlier palatoplasty surgery.

Runyan et al 2018 did a retrospective study on 177 infants with RS, where they compared the management (prone positioning versus tracheostomy versus MDO) to get an insight in prediction of the need for surgical management of UAO.¹² The nonsurgical group (prone positioning) consisted of 49 cases (51 % syndromic), MDO 68 (44.1% syndromic), tracheostomy 54 (66.7% syndromic). Those treated with prone positioning or with MDO had a significantly lower requirement for surgical feeding assistance (23.7%, 22.1%, and 80%, respectively) and earlier onset of feeding exclusively by mouth (53.2 d, 167.3 d, and 763 d, respectively) compared with the tracheostomy group.

Effect of timing of MDO on outcome

Breik et al (2016) published a review on the outcome of UAO management by MDO, including a subanalysis on age at MDO.¹⁷ Forty-one studies were included with a total of 408 patients ($377 < 6$ mo of age at surgery; $12 \geq 6$ to < 18 ; $19 \geq 18$). All 16 failures (failure to reach the planned advancement in upper airway obstruction) were operated on below the age of 6 months (16/377) and no failures between 6 to 18 and above 18 months. There was no significant difference between these 3 age groups. A further analysis was done within the first group, dividing the patients into those < 2 months and those between 2 to 6 months. 7/176 in the youngest group failed and 2/57 in the 2 to 6 months-group, which also was not a significant difference. Regarding the influence of syndromic state on success rate they found that primary MDO successful in 97.6% iPRS cases versus 90.7% in sRS.

Decannulation of presurgical tracheostomy cases was successful in 26/31 cases (83.9%) in iRS and 44/55 (80%) in syndromic anomalies. Decannulation was significantly more successful with an age < 24 months at which MDO was done than > 24 months, 87% versus 70.7%, OR 1 versus 2.76.

Carlson et al (2021) looked at the rate of adverse events after MDO treatment in PRS patients using the American College of Surgeons (ACS) National Surgical Quality Improvement Program Pediatric (NSQIP-Pediatric) database.²¹ This database has been used extensively to analyze 30-day surgical outcomes and is of particular use for less commonly performed surgical procedures. Of the 208 cases 7.3% ($n = 36$) experienced an adverse event, reoperation ($n = 14$), and read-mission ($n = 11$) be-

ing most common. Patients < 365 days old at the time of operation were more likely to experience an adverse event (26.1% versus 10.8%; $P=0.005$). However, among patients less than 1 year of age, differences in the complication rates between patients ≤ 28 days and >28 days (30.2% versus 22.2%; $P=0.47$) and those weighing ≤ 4 kg and >4 kg (31.7% versus 11.5%; $P=0.063$) did not reach statistical significance.

Lee et al (2020) looked whether performing MDO during the neonatal period increased complications as measured through health-care burden.²² The data were collected from a publicly available pediatric inpatient care database in the USA. It is unclear how reliable the data within this database are. RS patients receiving MDO prior to 12 months of age were included over a period of 12 years. The study sample contained 102 RS patients, of whom 50 (49.0%) were distracted in the neonatal period (28 days of age). Non-neonatal children (between 28 d and 1 y of age) were seen at a mean age of 12 weeks and operated on at an age of 14 weeks, whereas neonates were seen at a mean age of 0.8 weeks and operated on with a mean of one week later. Multiple regression models confirmed neonatal MDO was not associated with increased complications. It seemed that nearly half of the patients per group had non-isolated RS, including syndromic cases.

Luo et al (2018) retrospectively analyzed preoperative and postoperative body weight in 41 children with RS who underwent MDO treatment for breathing difficulties.²⁰ Patients were divided based on age at surgery: < 1 months ($n=8$), 1 to 3 months ($n=21$), and 4 to 7 months ($n=12$). The mean body weight percentile at first visit for the 3 age groups were 24.7, 14.2, and 5.0, respectively ($P<0.05$), while it was similar at birth. At the time of palatoplasty, there was still a significant difference between the <1 month of age at surgery versus the other 2 groups ($P<0.05$). The infants who accepted MDO treatment at <1 month of age maintained a significantly higher body weight percentile than those who accepted MDO surgery at 1 to 3 months or 4 to 7 months of age, at the time of both MDO and palatoplasty surgeries ($P<0.05$).

Taufique et al (2021) did a retrospective chart review of distraction in 69 RS cases, 51 isolated-isolated-RS and 18 nonisolated cases.²³ They looked at outcomes in children <3, 3.0 to 3.5, 3.5 to 4, and >4 kg. The mean age at MDO was 25 ± 20 days and mean weight was 3.32 ± 0.44 kg. There was no statistically significant correlation between weight ($P=0.699$) or age ($P=0.422$) and unfavorable postoperative outcomes. No patients (0%) underwent tracheostomy pre-MDO. Two patients (2.9%) required tracheostomy postsurgery; neither was <3 kg. Eight patients (11.6%) required a G-tube postoperatively. They concluded that MDO as treatment is a safe procedure in RS-cases. It should be noted that severe syndromic cases like Treacher-Collins were excluded for this study.

Complications of MDO

Paes et al (2016) retrospectively analyzed complications in a cohort of 10 RS cases following MDO and compared the outcomes with a RS cohort that did not undergo a MDO.²⁴ In one MDO case a skin infection and another MDO case a mechanical problem with the device were noted. Overall, in the MDO group more agenesia ($P:0.17$), shape anomalies ($P=0.007$), positional changes ($P=0.009$) and root malformations ($P=0.043$) were seen.

Flores et al (2014) reported a series of isolated RS patients, comparing TLA ($n=24$) with MDO ($n=15$).²⁵ The MDO complications included equipment failure ($n=1$) and infection ($n=3$). TLA complications were wound dehiscence ($n=3$) and scar contracture revision ($n=3$).

Steinberg et al 2016 analyzed complications following MDO in a cross-sectional study in 85 RS cases (71 isolated and 14 nonisolated RS).²⁶ In 48 % of the cases a permanent first molar injury, and in 14% a primary second molar injury as recorded on radiographs. Twenty-three of the 85 cases underwent in the out-patient clinic testing of the nerve function. Six cases of lower lip depressor weakness in 40 half mouths (20 patients) with a median follow up of 8.7 years, range 5.5 to 13.2 years were seen following MDO.

Adhikari et al (2016) designed a retrospective cohort study including 73 children (30 nonsyndromic, 1 temporomandibular joint ankylosis after sepsis, 33 specific syndromes and 22 other syndromes) who underwent MDO for upper airway obstruction.¹⁶ Two syndromic infants died at home after MDO: one aspirated during sleep and the other died after a failed tracheostomy tube change. Complications were respiratory infection (1), infection of distractor activation arm (1), early distractor removal for infection (4), device failure (3). Developmental defects of the molars were commonly encountered (76%). By invitation, they explored sensitivity deficits and encountered 5 cases out of 12 that showed mental nerve hypoesthesia with testing.

Tahiri et al 2014 grouped together 711 cases of MDO from 18 articles including 53 % isolated RS and 7 % syndromic RS patients.²⁷ The rest of the patients had other craniofacial anomalies associated with mandibular hypoplasia. They found 7.7% of complications in 376 isolated RS cases. The most common reported complications were infection (6.3%) with or without abscess formation, apertognathia (3.0%), nerve injury (2.5%), and hypertrophic scarring (2.3%).

Tahiri et al (2015) did a retrospective study on a group of 121 children of which 81 had a weight < 4 kg and 40 a weight > 4 kg to look at the efficacy, safety, and complication profile of MDO in infants < 4 kg with RS.¹⁴ The most common complication in each group was surgical site infection (9.9% and 20.0%; $P=0.15$). Overall complication rates were similar between the 2 groups (17.3% versus 25.0%; $P=0.34$). In the < 4 kg group, 2 patients had a major complication, namely fibrous nonunion and severe trismus. In the > 4 kg no major complications occurred. The rates of repeat distraction were similar between the 2 groups (6.3% and 13.5%; $P=0.28$).

Greathouse et al (2016) reported a retrospective review of all neonates with RS treated with TLA ($n=15$) or MDO ($n=74$; 23% isolated RS).²⁸ Overall, in the MDO complications were seen in 20.3%. A mandibular fracture from erosion of the adhesion occurred in 1 patient (6.7%). MDO bony nonunion $n=1$; infection $n=11$; mechanical failure $n=1$.

Resnick et al (2019) presented a retrospective cohort study of RS infants treated with TLA or MDO ($n=24$).²⁹ Eighteen patients (41%) were syndromic. In the MDO group, in 10 (42%) cases complications were scored: skin infections occurred in 9 cases and in one case mechanical failure.

Long-term effect of MDO on mandibular growth

Paes et al 2016 showed their long-term results after MDO. Ten patients underwent MDO at a mean age of 3.7 months (range 11 d to 27 mo).²⁴ At a mean age of 6.8 years (range 5.0–7.9 y) radiographic analysis was done and matched with 10 healthy unoperated controls with no need for orthodontic or orthognathic treatment because of any facial disharmony.

Mandibular length was shorter ($P=0.030$), but mandibular ramus height was comparable ($P=0.838$) with that of the nonmandibular distraction osteogenesis group. Compared with healthy controls, all RS infants had a significantly shorter mandible.

Tongue Lip Adhesion (TLA)

Effect of TLA on breathing problems

Broucsault et al (2018) did a retrospective study in 37 cases (31 isolated RS, 6 syndromic RS).³⁰ All patients were treated by means of TLA with a mean age of operation of 45 days, range 8 to 210 days. All patients had confirmed severe obstructive sleep apnoea. All patients required respiratory support prior to surgery: 8 intubated patients, 15 patients with noninvasive ventilation and 14 patients with NPAs. All parameters were improved on postoperative PSG: oxygen saturation, hypercapnia, apnoea-hypopnoea index, bradycardia ($P < 0.005$). Mean oxygen saturation was improved postoperatively in all patients with a value greater than or equal to 95% in 27 patients (72.9%). The median value for mean postoperative oxygen saturation was 96% (95–97.5; $P = 0.0007$). The AHI decreased in all patients. TLA improved airway obstruction in all infants with PRS and resolved OSA in 29 patients. However, 8 patients (22%) required tracheostomy ($n = 5$) or noninvasive ventilation ($n = 3$) due to chronic respiratory failure. These last results explain the relatively high postoperative median AHI of 27 per hour (range: 5–65) ($P < 0.0001$) for the group as a whole.

Cozzi et al (2008) studied retrospectively the charts of 48 infants with RS undergoing glossopexy after unsuccessful non-operative treatment.³¹ Weight measurements were analyzed at 4 time-points: at birth, on admission for glossopexy, on admission for lysis of lip-tongue adhesion (TLA), and at follow-up. Weight velocity was assessed using Tanner's tables. TLA resolved airway compromise in 36 infants (75%). Release of TLA was accomplished in 34 patients.

Kirchner et al (2003) studied retrospectively 107 RS patients, managed with prone positioning ($n = 74$, 69%) or with TLA ($n = 29$, 31%).³³ In this TLA sub-cohort of 29 cases, there were 14 isolated RS and 15 syndromic RS. The data about the effect on breathing are not very specific. Mean age at TLA surgery was 26.3 days. Average time to extubation 4.8 days. In the 24 uneventfully healed TLA cases the airway obstruction was successfully relieved in 20 (83%), with 4 cases finally requiring tracheostomy, adding up to a total of 6 tracheostomy cases in the TLA group (of whom 5 were syndromic RS), which can be considered a failure of treatment. Overall, the group was successful with prone positioning with only 29/107 requiring surgery, and TLA successful in 23/29 cases. Failures were mainly in the syndromic RS group. Six patients who underwent TLA (21%) required a tracheostomy (5 syndromic RS).

Mermans et al (2018) retrospectively evaluated 41 RS patients ($n = 14$ isolated RS, 27 syndromic RS) who underwent TLA.³³ All had TLA at an average age of 26 days. In 16 cases a preoperative and postoperative PSG was performed. In 13 of these cases (81.3%) improvement was observed, in 2 (12.5%) the results were inconclusive, and in 1 (6.3%) no improvement was seen. From 16 cases a preop and postop PSG was available, showing a drop of AHI (data from 8 cases) from median 15.5 to postop 9.5 and drop of ODI (data of 12 cases) from median 23.0 to postop 10.5. Patients were extubated after a mean of 2.2 days. Reintervention was needed in 7 patients because of a wound dehiscence. The mean age of TLA release was 9.7 months.

Viezel-Mathieu et al (2016) presented a systematic review on TLA including a 81.3% ($n = 218$ out of 268) success rate in relieving airway obstruction caused by RS.³⁴ Isolated RS cases had a higher success (91.5%) compared to syndromic RS (79.8%), which was statistically significant ($P = 0.0361$). Eight cases who were initially successfully managed with TLA required a repeat procedure due to dehiscence, and ultimately

were considered in the successful treatment group. In 50 cases additional airway interventions were necessary following the TLA: tracheostomy 27, MDO 5, nonspecified surgery 1. Seventeen cases did not receive additional therapy.

Effect of TLA on feeding problems and growth

Broucsault et al (2018) performed a retrospective single centre study on the effect of TLA for RS.³⁰ A total of 37 patients with RS were included, 6 nonisolated and 31 isolated. A positive effect is reported on feeding (22/37) and weight gain (20/37) without further specification.

Cozzi et al (2008) studied retrospectively the charts of 48 infants with RS undergoing glossopexy after unsuccessful non-operative treatment.³¹ Weight measurements were analyzed at 4 time-points: at birth, on admission for glossopexy, on admission for lysis of lip-tongue adhesion (TLA), and at follow-up. Weight velocity was assessed using Tanner's tables. Release of TLA was accomplished in 34 patients. The mean body weight fell from the 39.9 ± 5.1th percentile at birth into the 9.7 ± 2.6th percentile before glossopexy ($P < 0.0001$). The mean body weight increased to the 17.5 ± 4.6th percentile on admission for lysis of TLA (glossopexy versus lysis, $P > 0.05$). After a mean period of 4 years from TLA lysis, the mean body weight increased to the 34.6 ± 5.6th percentile at follow-up (lysis vs. follow-up, $P < 0.01$). The difference between mean body weight percentile at follow-up and at birth was not significant ($P > 0.05$).

Khansa et al (2017) reported the outcome of a prospective study of 28 RS patients (of which $n = 9$, 32% syndromic) of which 8 underwent TLA, 10 MDO and 10 conservative treatments (prone positioning).³⁶ One patient in the MDO group and one patient in the TLA group could not be weaned off nonoral feeds postoperatively and required gastrostomy tube placement (10% and 12.5%, respectively; $P = 1$). Both of those newborns had a syndrome. Overall, patients with a syndrome had a greater likelihood of requiring a gastrostomy tube compared with patients without a syndrome (22.2 percent versus 0 percent; $P = 0.03$). For patients who were successfully weaned off nonoral feeds, there was no difference in days to full oral feeds between the MDO and TLA groups (67 d for MDO and 45 d for TLA; $P = 0.7$). Patients in all 3 groups improved their weight percentiles significantly and moved to a higher weight curve. There were no differences in the improvement in weight percentile at any period among the 3 groups. There was also no difference in the duration of failure to thrive after surgery between the MDO and TLA.

Kirchner et al (2003) retrospectively analysed a group of 107 RS cases over 28 years of which 29 eventually underwent TLA and 4 cases a tracheostomy.³² Of those 29 a total of 14 (48.3%) were syndromic. No MDO done in this study. No patient demonstrated an exacerbation of feeding difficulties postoperatively, and most demonstrated improved feeding associated with relief of upper airway obstruction. NGT feedings were required in 93.1% of patients preoperatively and in 72.4% postoperatively. Sixty-two percent of these infants were successfully weaned off nasogastric feedings within 6 months of surgery.

Papoff et al (2013) retrospectively compared 9 RS patients with TLA with 9 RS patients with MDO.³⁶ Feeding was clearly not the focus of this study, but it is noted that weaning off from NG tube feeding was faster in the MDO group compared to the TLA group ($P < 0.003$). Mean days after surgery to full oral feeds 44 ± 24 for MDO versus 217 ± 134 days for TLA.

Susarla et al (2017) compared in a cohort of 61 RS (43 isolated RS, 18 syndromic RS) retrospectively TLA (31 RS) and MDO (30 RS) in retrospect.³⁷ The groups were statistically comparable with regard to demographic and clinical factors (P

> 0.18). Gastrostomy rates were higher in patients who underwent TLA (48%) versus those who underwent MDO (16.7%; $P=0.008$). In an adjusted model, subjects undergoing TLA were more likely to require gastrostomy tube for nutritional support (OR, 6.5; 95% CI, 1.7–25.2; $P=0.007$). Among the secondary predictor variables, an additional syndromic diagnosis aside from RS conferred an increased risk for gastrostomy tube placement (OR, 4.1; 95% CI, 1.3–13.3; $P=0.02$).

Effect of timing of the TLA on outcome

The reported range of day of intervention for TLA varies considerably with a minimum of 1 day (day after birth) in Bijnen et al (2009) up to 210 days.^{30,33,37,38} The average age of intervention is about 4 to 7 weeks of age. Studies describe that until the TLA initially conservative treatment (prone positioning) is performed. In the literature no data is available on a possible relation between the age at which the TLA is performed and the rate of complications.

Complications of TLA

Bijnen et al (2009) reports postoperative complications related to the operation occurred in 12 neonates (55%), all without lasting effect: in 5 patients (23%), a (partial) dehiscence of the mucosal flaps appeared within a few days, and 4 of these had to be reoperated on, in 1 patient even 3 times.³⁸ Six patients developed a small abscess on the chin around the suture, for which drainage was performed and which disappeared completely after removal of the supporting mandibular suture with button. On the long-term, none of these patients developed significant scarring. One patient had to be reintubated for 2 days owing to postoperative bronchospasm, but none of the patients required a tracheostomy.

Broucqsaault et al (2018) did a retrospective study in 48 cases (35 isolated RS, 13 syndromic RS).³⁰ All were treated by means of TLA with a mean age of operation of 45 days, range 8 to 210 days. No intraoperative complications and the immediate post-operative course was uneventful in 37 patients (out of 48). Four patients (10.8%) presented with suture dehiscence, requiring re-operation. One case developed a chin abscess requiring drainage and local haemostasis had to be performed in one case.

Flores et al (2014) reported a series of isolated RS patients, comparing TLA ($n=24$) with MDO ($n=15$). The TLA complications included wound dehiscence ($n=3$) and scar contracture of the cutaneous aspect of the lower lip requiring surgical revision ($n=3$).²⁵

Greathouse et al (2016) reported a retrospective review of all neonates with RS treated with TLA or MDO.²⁸ The numbers for isolated RS and syndromic RS are not given, only percentages (40% isolated RS in TLA and 23% in MDO group, $P=0.20$). Overall, in the MDO complications were seen in 20.3% and in the TLA group 53.3%. The complications in the TLA group were typically partial wound separation (26.7%) or complete wound dehiscence (20%). Although required in 33.3%, scar requiring separate revision was not included as a complication. A mandibular fracture from erosion of the adhesion occurred in 1 patient (6.7%). No death in the TLA group was recorded. MDO bony nonunion $n=1$; infection $n=11$; mechanical failure $n=1$.

Khansa et al (2017) reported the outcome of a prospective study of 28 RS patients (of which 32% syndromic) of which 8 underwent TLA, 10 MDO, and 10 conservative treatments.³⁵ Two TLA patients had a complication, consisting of reintubation. Both patients were extubated successfully 3 to

5 days later. No other complications of TLA are mentioned in this study.

Kirschner et al (2003) studied retrospectively 107 RS patients, managed with prone positioning ($n=74$) or with TLA ($n=29$) of whom 14 isolated RS.³² Dehiscence of the TLA occurred in 5 patients (17.2%), 2 of whom subsequently required tracheostomy, 2 of whom were thereafter successfully managed by prone positioning alone, and 1 of whom underwent repeat TLA. Within the group of patients who underwent mucosal adhesion alone, the dehiscence rate was 41.6%. When the adhesion included muscular sutures, however, dehiscence was not observed in any patient. Of the 24 patients in whom primary TLA healed uneventfully, airway obstruction was successfully relieved in 20 (83.3%). Failure of a healed TLA to relieve the airway obstruction resulted in conversion to a tracheostomy in 4 patients. Thus, 6 patients who underwent TLA (20.7%) ultimately required a tracheostomy; 5 of these patients (83.3%) were syndromic RS.

Papoff et al (2013) retrospectively compared 9 RS patients with TLA with 9 RS patients with MDO. TLA led to surgical complications in 2 infants (out of 9), both of whom had wound dehiscence and underwent repeat TLA.³⁶

Resnick et al (2019) presented a retrospective cohort study of RS infants treated with TLA or MDO.²⁹ Forty-three patients were included (TLA, $n=19$ [44%]; MDO, $n=24$ [56%]). Eighteen patients (41%) were syndromic. There were 5 (26%) minor complications (skin infections) and no major complications in the TLA group. In the MDO group, in 37% of the cases complications were scored: skin infections occurred in 9 cases and in one case mechanical failure.

Viezel-Mathieu et al (2016) did a review study that included 268 RS cases (174 isolated and 94 syndromic RS) in which they found the following complications associated with TLA: Dehiscence 22(8.2%), Abscess/infection 7 (2.6%), Edema/stridor 4 (1.5%), adhesion 2 (0.7%), death 1 (0.4%), granuloma 1 (0.4%) with a total of 37 (13.8%) in 268 cases.³⁴ Additional surgery was required in 12.3% (33/268) of treated surgery. This includes 27 cases of tracheostomy, 5 cases of MDO and 1 nonspecified. Although not specified complications were seen less in isolated RS compared to syndromic RS.

TLA and long-term effect on mandibular growth

No studies in the literature were found which evaluated the relation between mandibular growth and TLA.

Comparison of MDO Versus TLA

Comparison effect MDO Versus TLA on breathing problems

Almajed et al (2017) did a systematic review of the literature to evaluate outcome after surgical interventions in Infants with RS.³⁹ Forty-nine studies reported 94% success after MDO. Age at surgery ranged from 1 to 11 months. Surgical procedure was done from 1 month onwards. In this group of studies, the only children needing tracheotomy after MDO were nonisolated cases (AHI > 15 events/h).

Greathouse et al (2016) reports a retrospective review of all neonates with RS treated with TLA or MDO.²⁸ The numbers for isolated RS and syndromic RS are not given, only percentages (40% isolated RS in TLA and 23% in MDO group, $P=0.20$). The success rate was significantly higher in the MDO group compared with TLA (90.5% versus 60.0%; $P < 0.008$). Postoperative tracheostomies occurred in 8.1% of the MDO group and 33.3% of the TLA group ($P < 0.02$). Preoperative AHI was similar between the 2 groups (38.3 versus 38.1). The apnea-hypopnea index was significantly improved in the MDO

group at 1 month (7.0 versus 21.7; $P < 0.002$) and 1 year (5.7 versus 20.5; $P < 0.005$). Surgical complications were statistically less in the MDO group (20.3 versus 53.3%; $P < 0.02$). The repeat MDO or conversion to MDO was 5.4 % for the MDO group and 20.0 % for the TLA group, $P = 0.09$.

Flores et al (2014) reports series of isolated RS patients, comparing TLA ($n = 24$) with MDO ($n = 15$).²⁵ Breathing result are reported 1 month and 1 year postintervention. There were no post-procedure tracheostomies in the MDO group and 4 tracheostomies in the TLA group. The preoperative oxygen saturations were significantly lower in MDO group compared with tongue-lip adhesion (76.5% versus 82%; $P < 0.05$). Preoperative apnea-hypopnea index was significantly higher in the MDO group compared with the TLA group (47 versus 37.6; $P < 0.05$). Despite these preoperative differences, patients undergoing MDO demonstrated significantly higher oxygen saturation levels at 1 month (98.3% versus 87.5%; $P < 0.05$) and 1 year postoperatively (98.5 percent versus 89.2 percent; $P < 0.05$) and lower AHI at 1 month (10.9 versus 21.6; $P < 0.05$) and 1 year postoperatively (2.5 versus 22.1; $P < 0.05$) compared with TLA. Surgical complications were comparable between the 2 groups.

Khansa et al (2017) studied 22 patients with RS (13 isolated RS, 9 syndromic RS) prospectively.³⁵ Initial treatment was prone positioning and if this failed either MDO or TLA was performed, based on the preference of the surgeon and parents. Ten patients underwent MDO, and 8 TLA. No differences were found in the frequency of syndrome diagnosis, gestational age, or Apgar scores among the 3 groups. Initial PSG was performed at a mean age of 21 days for children who received MDO and 28 days for children who received TLA. Average age at TLA was 43 days (range, 13–55 d), and average age at MDO was 42 days (range, 21–67 d). Patients treated with MDO had the highest baseline AHI (27.7), followed by those treated with TLA (15.2). Postoperatively, there were no differences in days to extubation, rate of reintubation, days to discharge, and readmission rates between the MDO and TLA groups. Clinically, all patients in the study had resolution of their airway obstruction symptoms. Follow-up PSG was performed at a mean age of 83 day for children who received MDO and 67 days for children who received TLA. On analysis of the follow-up polysomnographic recordings, the degree of OSA improved in all 3 groups, with patients in the MDO group exhibiting the greatest reduction in AHI (94.6% reduction from 27.7 to 1.5), followed by patients in the TLA group [81.6 percent reduction from 15.2 to 2.8, $P = 0.014$, compared with MDO. Residual moderate OSA was detected in 12.5% of the TLA group and 0% in the MDO group. Weight gain was similar for both groups. The authors state it is impossible to determine how the outcome of TLA would be if performed in children with a higher AHI and advise to select the best suited therapy per individual patient.

Papoff et al (2013) retrospectively compared MDO versus TLA in 18 RS cases (5 isolated RS).³⁶ The primary outcome measures were successful weaning from respiratory support and resumption of full oral feeding. Nine underwent TLA and 9 MDO. After discharge, residual respiratory distress was diagnosed more commonly after TLA than after MDO (6/9 versus 1/9, $P = 0.050$).

Resnick et al (2019) presented a retrospective cohort study of RS infants treated with TLA or MDO.²⁹ Forty-three patients were included (TLA, $n = 19$ [44%]; MDO, $n = 24$ [56%]). Eighteen patients (41%) were syndromic. Patients in the TLA group were significantly younger at operation (28.2 d) compared with those in the MDO group (87.1 d; $P = 0.002$). The mean AHI score was 19.2 for the entire sample and was

significantly worse for the MDO group than for the TLA group ($P = 0.041$). The MDO group had more severe preoperative OA (AHI score, 20.5; OA severity score, 4.7) than the TLA group (AHI score, 17.6; OA severity score, 3.6; $P < 0.041$). Postoperative AHI score and OA severity score for the TLA group were 11.7 (33.5% decrease; $P = 0.496$) and 2.3 (improvement by 1.3 levels; $P = 0.051$), respectively. Postoperative AHI score and OA severity score for the MDO group were 1.1 (94.6% decrease; $P < 0.001$) and 0.2 (improvement by 4.60.8 levels; $P < 0.0001$), respectively. Successful resolution of OA occurred in 9 patients (47%) in the TLA group and 22 patients (92%) in the MDO group.

Comparison effect MDO versus TLA on weight gain

Harris et al (2021) report on the weight gain over first 3 years of life in patients with RS from a retrospective cohort study of patients with RS treated at Boston Children's Hospital from 1995 to 2016.¹⁹ The primary predictor variable was type of intervention (no operation, TLA, MDO). The primary outcome measure was weight-for-age Z-score. A control group of patients with isolated cleft palate without RS was also included. Individuals with tracheostomy or insufficient growth data were excluded.

A total of 222 subjects were included: no operation, $n = 61$ (27.5%); TLA, $n = 78$ (35.1%); MDO, $n = 22$ (9.9%); and control, $n = 61$ (27.5%). Mean age at TLA was 37 ± 99 days compared with 247 ± 312 days for MDO ($P < 0.05$). At 6 months of age, the MDO group had the lowest mean weight ($Z = -2.34 \pm 1.88$, $P < 0.05$) and both surgical groups were underweight compared with controls ($P < 0.05$). By 24 months of age, there were no weight differences between any study group. Individuals that had MDO at < 3 months of age had significantly faster weight gain than those that had later operations ($P < 0.05$).

It was concluded patients with RS who had an airway operation in the first year of life demonstrated poorer early weight gain but caught up to controls by 2 years of age. Patients that had MDO before 3 months of age had faster weight gain than those that had later operations. Neither age at operation nor type of intervention affected growth outcomes by 3 years of age, which were comparable with controls.

Nunen et al (2021) performed a retrospective medical chart review included a total of 42 patients, 17 of which had undergone MDO and 25 TLA.⁴⁰ This study aimed to improve procedural selection by examining weight gain following MDO and TLA. The mean body weight in both groups was below the 50th population percentile at birth and fell further in the period before surgery. A mixed model analysis demonstrated that postoperative weight gain depended on the progression of time and preoperative weight. Conversely, biological sex, congenital comorbidities, method of feeding, the respective cleft team, and the type of surgery did not significantly influence the evolution of postoperative body weight. In conclusion, both MDO and TLA were able to restore weight growth in infants affected by RS, though a clear superiority of either technique could not be established.

Papoff et al (2013) retrospectively compared MDO versus TLA in 18 RS cases (5 isolated RS).³⁶ The primary outcome measures were successful weaning from respiratory support and resumption of full oral feeding. Nine underwent TLA and 9 MDO. Weaning from nasogastric feeding was faster after MDO than after TLA (mean days after surgery to full oral feeds 44 ± 24 versus 217 ± 134 , $P < 0.003$).

Susarla et al (2017) compared in a cohort of 61 RS (43 isolated RS, 18 syndromic RS) retrospectively TLA (31 RS) and MDO (30 RS).³⁷ The groups were statistically comparable with regard to demographic and clinical factors ($P > 0.18$).

Gastrostomy rates were higher in patients who underwent TLA (48%) versus those who underwent distraction osteogenesis (17%; $P=0.008$). In an adjusted model, subjects undergoing tongue-lip adhesion were more likely to require gastrostomy tube for nutritional support (OR, 6.5; 95% CI, 1.7–25.2; $P=0.007$). Among the secondary predictor variables, an additional syndromic diagnosis aside from RS conferred an increased risk for gastrostomy tube placement (OR, 4.1; 95% CI, 1.3–13.3; $P=0.02$).

Conclusions

Quality of evidence without GRADE: –	<p>Effect of MDO on breathing</p> <p>There are cautious indications that MDO is associated with clinical improvement for RS patients with upper airway obstruction in various outcome measures (avoidance of tracheostomy/decannulation, OSA, AHI and respiratory disturbance index). References: [6, 7, 8, 10, 12, 29, 27, 15].</p> <p><i>Conclusion based on evidence from 6 single arm-observational studies and 1 systematic review with a high risk of bias, detected heterogeneity and imprecision but no important issues with indirectness.</i></p>
Quality of evidence without GRADE: –	<p>Effect of MDO on feeding and growth</p> <p>Studies indicate that MDO is associated with a major clinically relevant improvement of feeding, weight gain and growth to expected levels for their peer group (isolated RS and nonisolated RS having a better outcome compared to syndromic RS), improvement in symptoms of GERD and dependance on nasogastric tube feeds (measured 6 to 12 mo) post-MDO. References: [16, 17, 18, 20].</p> <p><i>Conclusion based on evidence from 5 single arm-observational studies with a high risk of bias and heterogeneity, but no important issues with indirectness and imprecision.</i></p>
Quality of evidence with GRADE: +	<p>Effect of timing of the MDO on outcome</p> <p>There are cautious indications that MDO is not associated with a lower succesrate to be performed at neonatal age (before the age of 28 d) compared to older age (≤ 365 d). References: [21, 22, 20].</p>
Quality of evidence without GRADE	<p>Effect of timing of the MDO on outcome</p> <p>There are cautious that MDO is a safe procedure with similar success and complication rates to be performed at neonatal age, before the age of 1-2 months compared to older age. References: [17, 22, 20, 23].</p> <p><i>Conclusion based on evidence from 4 single arm-observational studies with a high risk of bias and heterogeneity but no important issues with indirectness and imprecision.</i></p>
Quality of evidence without GRADE	<p>Effect of MDO on mandibular growth</p> <p>Studies indicate that following MDO on the long run the mandible in the RS cohort remains relatively short compared with healthy subjects necessitating secondary procedures. Reference: [24].</p> <p><i>Conclusion based on evidence from 1 single arm-observational studies with a possible</i></p>

Quality of evidence without GRADE

risk of bias, but no important issues with indirectness, inconsistency, and imprecision.

Complications of MDO
 Studies report the following complications in MDO (ranging from 6.7% to 48%); skin infection around the pins with or without abscess formation, nerve injury (inferior alveolar nerve and marginal mandibular branch of the facial nerve), hypertrophic scarring and open bite. With preoperative virtual planning for MDO the risk of damaging permanent teeth might be diminished. Complications of external devices (mechanical failure) seem to occur more frequently than with internal devices. References: [16, 28, 25, 24, 29, 26, 27, 14]

Conclusion based on evidence from 7 single arm-observational studies and 1 systematic review with a high risk of bias and heterogeneity but no important issues with indirectness and imprecision.

Quality of evidence without GRADE

Effect of TLA on breathing
 Studies indicate that TLA is associated with improve the breathing problems in the great majority of children with RS, with AHI drop from median 15.5 to postop 9.5 and drop of ODI from median 23.0 to postop 10.5, showing higher success rates in isolated RS (91.5%) compared to syndromic RS (79.8%), and post-TLA respiratory failure varies from 21%–29%. References: [30, 31, 33, 34].

Conclusion based on evidence from 6 single arm-observational studies with a high risk of bias and heterogeneity but no important issues with indirectness and imprecision.

Quality of evidence without GRADE

Effect of TLA on feeding, growth and weight gain

There are cautious indications that TLA has a positive effect on:
 Naso-gastric tube feedings, with 93.1% preoperatively to 72.4% postoperatively dependance, and 62% of pts were weaned off NG tube feeding <6 month after TLA. Mean body weight, with increase from 9.7 ± 2.6 before to 17.5 ± 4.6th after TLA. After a mean period of 4 y from TLA lysis, the mean body weight increased to the 34.6 ± 5.6th percentile at follow-up (lysis vs follow-up, $P < 0.01$). References : [35, 31, 32, 36, 37].

Conclusion based on evidence from 5 single arm-observational studies with a high risk of bias, inconsistency and imprecision but no important issues with indirectness.

Quality of evidence without GRADE

Effect of timing of TLA on outcome
 Studies indicate that TLA can be performed at any age after birth reported to be performed at 1 day after birth to 210 d and no data is available on effect of timing of TLA on outcome. References: [38, 33, 30, 37].

Conclusion based on evidence from 4 single arm-observational studies with a high risk of bias and heterogeneity but no important issues with indirectness and imprecision.

Quality of evidence without GRADE

Complications of TLA
 Studies indicate that despite TLA is generally considered as a safe procedure; several complications may occur, listed here in

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decreasing frequency: wound dehiscence (30%–55%), abscess/infection formation, edema/stridor, adhesion, death (very rare), granuloma (very rare).
References: [38, 30, 25, 28, 32, 35, 36, 29, 34].
Conclusion based on evidence from 9 single arm-observational studies with a high risk of bias, heterogeneity but no important issues with indirectness and imprecision.

Quality of evidence with GRADE: ++

Comparison of MDO vs TLA on breathing in RS

Studies indicate that successful resolution of OSA is higher with MDO (96%) than with TLA (45%) and residual respiratory distress is more reported after TLA than after MDO. Studies indicate that MDO leads to lower AHI and higher oxygen saturation levels than after TLA.

After MDO significantly higher O2 saturation levels at 1 year postoperatively (98.5% versus 89.2%; $P < 0.05$) and lower AHI at 1 month (10.9–38.3 versus 21.6–38.1; $P < 0.05$) and 1 year postoperatively (2.5–5.7 versus 20.5–22.1) compared with TLA.

Studies indicate that the need for secondary treatment, (MDO or tracheotomy after TLA, or tracheotomy after MDO) is significantly lower for MDO (2%–6%) than for TLA (22%–45%).

Studies indicate that tracheotomy is successfully avoided in 97% for MDO vs 89% for TLA.

References: [39, 25, 28, 35, 36, 29]

Quality of evidence with GRADE: +

Comparison of MDO vs TLA on feeding, growth and weight gain

There are cautious indications that there was no significant difference in weight gain between MDO groups and TLA groups (follow-up 20–36 mo). No clear superiority of either technique could be established regarding weight gain in mixed group (iRS and syndromic RS cases).

References: [35, 40, 19]

Quality of evidence with GRADE: +

There are cautious indications weaning from nasogastric feeding was significantly faster after MDO than after TLA. and
References: [36].

Quality of evidence with GRADE: ++

There are indications that gastrostomy rates were significantly higher (OR 6.5) in patients who underwent TLA versus those who underwent MDO.
References: [37].

comes. Most studies were of poor methodological quality as assessed using the Newcastle-Ottawa Scale and were at high risk of bias. In 11 studies treatment options were compared with retrospectively or prospectively collected data. Those are assessed with GRADE but none of the outcomes exceeded the quality level of Low, mainly due to inconsistency in patient groups or outcomes, the absence of measures to regulate bias such as randomization and the small sample sizes.

Professional Perspective

Depending on the experience and tradition of the expertise centres with both nonsurgical and surgical options, it seems to vary per centre when the decision is taken to change from nonsurgical to a surgical strategy. In addition, the treatment strategy is determined depending on the severity of the OSA and additional comorbidity in the RS patient, whereas isolated RS respond to therapies better than nonisolated RS, obviously starting with the nonsurgical ones. In general, in severe OSA the tracheostomy should be avoided whenever possible and therefore, centres chose to perform the MDO even in the first weeks after birth showing successful outcomes. In any case, high expectations with parents about decannulation must be managed to avoid disappointment following a MDO procedure. For a relatively small group of mainly nonisolated RS with severe OSA the tracheostomy is unavoidable and despite single or multiple MDO's the patient cannot be decannulated. Overall, the complications seen in MDO, either with internal or external devices, are manageable. The drawback of external devices compared to internal devices is the burden of care during the consolidation period (3–4 mo), before removal of the device. Virtual computer planning based on CT-scans could help avoiding damage to teeth and with planning the desired vector for the distraction with an internal device. A wrong vector might result in an open bite deformity and/or a vertical facial growth pattern. The latter might result in recurrence of UAO/OSA.

During childhood the lack of growth of the mandible might result in recurrence of OSA, sometimes requiring revisional MDO during early and later childhood. Despite mandibular lengthening by means of MDO, the mandible could remain hypoplastic. This might lead to occlusal problems, that call for combined orthodontic/orthognathic surgical treatment after cessation of growth.

TLA seems to improve the breathing problems in most children with isolated RS, but frequently does not solve the problems completely as the micrognathia remains unchanged compared to MDO. The outcomes of breathing following MDO are better compared to TLA for isolated RS. The question arises whether cases of mild or moderate OSA that will benefit from a TLA procedure alone are the same patients who can be managed successfully with a less invasive NPA as a temporarily measure. The 2 techniques probably have different indications and outcomes (eg. feeding, weight, mandibular growth) and are incommensurable. The complications of TLA are mostly minor and manageable.

Finally, it should be noticed that the literature on subperiosteal release floor of mouth is extremely sparse with just 2 studies published in the last 20 years, making it impossible to make any sound recommendations on this technique.

Balance of Benefits and Harms

The advantage of MDO is more predictable to solve the breathing problems which is also beneficial for both feeding and growth compared to TLA. Considering the complications of MDO the possible injuries to teeth are manageable or even avoidable with the pre-operative virtual computer planning. Virtual planning

Considerations

Quality of Evidence

The overall quality of evidence of the literature on surgery of mandibular-related breathing problems in patients with RS was low. Heterogeneity of the patient population within and between studies had a negative influence on the quality of evidence. In a great part of the analyzed literature, no clear distinction was made between isolated and nonisolated RS, including patients with additional syndromic diagnoses. Data on outcomes of surgical treatment options were mainly based on single-arm retrospective or prospective cohort studies and, therefore, subject to uncontrolled confounding. As such, GRADE assessment could not be completed for most out-

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might add to the predictability of 3-dimensional movement of the distracted segment to its desired goal, too. Other MDO complications are overall minor, for example local infections and transient nerve palsies of the mandibular ramus of the facial nerve. TLA is a relatively simple procedure, which can be performed from the day after birth onwards. TLA complications occur more frequently than the MDO complications but are also minor and manageable. In general, TLA might work in isolated RS but there are no reliable preoperative parameters to predict its effectiveness. A second drawback is its dependence on enough physiological growth of the mandible until the take down of the adhesion around (on average) 8 months of age. If the mandibular growth in this period is insufficient, the breathing problems may recur after taking down. Growth of the mandible is usually better in isolated RS compared to nonisolated RS, but the genetic diagnosis is often not yet available at the time the decision about surgical intervention needs to be made. Quality of life should be considered in the surgical treatment of RS. Logjes et al (2017) describes improvement in QoL after both MDO and TLA, but no significant difference between both techniques in a mixed group of RS cases.⁴¹

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available national budget, care providers and facilities. The recommendations constitute the essential requirements for appropriate treatment of patients with RS and accordingly these requirements should be implemented. Costs are lowest and resources are most efficiently used when care for congenital disorders is centralized in a limited number of expert centers per member state. Regarding costs of the different treatment options including surgical requirements (for example distraction devices, specific software) and hospital stay, it should be recognized that it is extremely difficult to calculate these precisely, per member state. Although it seems obvious that on the short term the costs for a MDO are higher than for a TLA but on the long-term different clinical outcomes from these 2 procedures might have major impact on the total cost calculation.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe about care for patients with rare diseases. At present, not every member state offers an expert center for RS, or the level of provided care does not (yet) meet all the requirements outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centres of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal healthcare and are discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as one of the core values. However, in some countries the national organization of health care might impede centralization. National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and collaboration with an expert center in the surrounding countries should be considered.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale for Recommendations

To choose the most optimal surgical treatment of the breathing problems in RS patients, other nonsurgical options have been tried or at least discussed in the team. The pros and cons of TLA versus MDO should be weighed against the background what is best for the patient on the short and long-term.

Recommendations

- Start with nonsurgical treatment for the management of mild-moderate OSA in patients with Robin sequence, see *Chapter 11—Nonsurgical treatment*.
- For cases of OSA which do not respond to nonsurgical treatment consider MDO or tracheostomy. First, exclude obstructions of the airway below the level of the tongue base prior to surgery.
- In centers with local expertise, TLA can be discussed as an alternative for cases of OSA which do not respond to nonsurgical treatment. However, the breathing and feeding outcomes are better with MDO than with TLA to be discussed with the parents by shared-decision making.
- If using an internal device for MDO, virtual 3D planning is recommended.
- Consider tracheostomy over MDO in patients with syndromic status, low birth weight and neurologic impairment.
- If as breathing problems persist or reoccur, MDT should review all treatment options. Consider mandibular distraction osteogenesis to end nonsurgical treatment (eg, CPAP) for severe OSA or to decannulate (see Chapter 11).
- Overcorrect in mandibular distraction osteogenesis because of intrinsic mandibular growth disturbances in RS and disturbed growth resulting from surgery.

Research Gaps

The overall evidence in this chapter is weak due to the lack of good comparative studies.

To solve the issue of advantages and disadvantages of tracheostomy versus MDO versus TLA versus SRFM one or more well designed prospective trial(s) are required. In view of the limited number of patients a multicenter approach is recommended. We realize that RCT's will difficult to design for RS. The algorithm in chapter 6 may serve as a baseline for future studies. The same applies, regarding the lack of evidence, for a conservative approach versus operative interventions. Prospective studies might also yield better criteria for choosing one or the other treatment modality, either surgical or nonsurgical.

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pharyngeal flap or sphincter pharyngoplasty—might have a higher chance of developing breathing difficulties.⁶

Regarding optimal treatment for palate surgery in children with RS, there is a conflict between minimizing the chance of airway-related problems and facilitating normal feeding and speech development. This chapter focuses on the implications that surgical closure of the CP has on breathing and speech in a child with RS. It also reviews the same issues following speech-improving surgical procedures.

To study indication for palate surgery in patients with RS and offer recommendations for treatment, the following questions were posed:

- Which screening is required to allow surgical repair of cleft palate in RS, related to breathing problems?
- Which surgical treatment options can be considered?
- What is the best timing for surgical treatment of palate-related problems in RS, related to speech and breathing problems regarding the best timing and short/long term effects?

Outcomes that are investigated in this chapter included:

- Indication and timing for CP repair.
- Airway compromise or OSA after primary CP repair.
- Airway compromise or OSA after speech-improving surgery.

Literature Search

For this guideline, a systematic literature search was conducted. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria

Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Indication for surgical repair of cleft palate (CP) or speech-improving surgery Speech / VPI outcomes Airway compromise / obstructive sleep apnea (OSA) outcomes
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion.

After rough selection and labeling, a full text assessment of 34 studies was performed for this chapter. Several studies were excluded due to *sample size* (n=2), *wrong population* (n=3), *incorrect outcome* (n=22) or *other* (n=1). In this chapter, 6 studies are described that investigated airway compromise (acute respiratory distress or OSA) after palate related surgery in patients with RS.

Summary of Literature Study

Which Screening is Required to Allow Surgical Repair of Cleft Palate in RS, Related to Breathing Problems?

The indication for palate surgery related to speech is thoroughly described in chapter 8. So far, 3 studies have described

CHAPTER 13. SURGICAL TREATMENT OF PALATE-RELATED PROBLEMS IN RS

Introduction

A CP is present in about 80% to 90% of children with RS, although it is not considered a prerequisite for the diagnosis.^{1,2} Often, a wide U-shaped cleft of the secondary palate is present (Chapter 4 “Diagnostic criteria”). Patients with CP have an open communication between the nasal cavity and oral cavity. This primarily results in difficulty feeding and speaking (further discussed in Chapters 7 and 8). Primary closure of the CP aims to improve these complaints.

In the absence of a proven surgical approach for palate repair, various treatment modalities are available to treat a primary CP or velopharyngeal insufficiency (VPI). In patients with RS however, there is always a chance to potentially induce or worsen breathing. Bergeron et al (2019) investigated airway compromise after primary CP repair in 43 RS-patients.³ Before surgery the obstructive apnea-hypopnea index (AHI) was 3.4 + 3.9 and after surgery 5.9 + 14.5 (P=0.30). Basically, these children have a restricted upper airway at baseline and are more likely to develop respiratory distress due to palatal and lingual swelling post-operatively.⁴ They are also at risk to develop more severe airway-related problems, such as stridor, reintubation or tracheostomy with prolonged hospital stay and unplanned admission to an intensive care unit.^{4,5} Selection of an optimal palatal treatment modality seems warranted, as certain repair techniques—like the

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the indication for cleft palate surgery in patients with RS, regarding speech and breathing outcome. RS was defined by a triad of micrognathia, glossoptosis and airway obstruction. However, airway compromise was not uniformly defined, and only clinically assessed in 1 study⁷ while the others used preoperative polysomnographies (PGSs) in all RS-patients.^{4,5}

Costa et al (2014) included 74 isolated RS-patients and 39 isolated cleft palate (ICP) patients, treated between January 2000 and December 2012.⁵ Airway obstruction was defined by one that necessitated nonsurgical or surgical intervention. Before CP repair, a PSG was routinely performed in all patients; before 2005 were only evaluated clinically. If the AHI was ≤ 5 and there was no significant carbon dioxide retention, the palate was repaired. Surgical treatment compromised a von Langenbeck technique for reconstruction of the hard palate and Furlow or intravelar veloplasty for soft palate repair. Postoperative PSG was not performed unless there was a concern for OSA as determined by a pulmonologist. The total airway complication rate (ie, reintubation, hospital admission, emergency room visit) was 6.8% (5/74) for RS versus 7.7% (3/39) for ICP-patients ($P=1.00$). Three out of 5 RS-patients with airway complications had previously been treated for OSA.

Van Lieshout et al (2016) assessed airway compromise following CP repair in 30 RS-patients versus 45 ICP-patients using several straight-line repair techniques.⁴ Airway obstruction was defined by one that necessitated intervention. Prior to CP repair, a PSG with removable custom-made palatal plate was routinely performed in all RS-patients. CP repair in RS-patients was only undertaken once the PSG was normal. In 30% (9/30) of RS-patients, varying degrees of airway compromise developed which were not observed in ICP-patients at all. In all patients, airway compromise resolved quickly and was most likely explained by lingual and palatal swelling postoperatively. In 1 RS-patients, airway compromise resolved after 7 days.

Logies et al (2021) investigated CP repair outcomes in 74 RS-patients versus 83 ICP-patients. Preoperative airway compromise was clinically assessed, which makes the diagnosis of RS less reliable.⁷ In case of a clinical suspected compromised airway, a supplemental PSG was performed ($n=26$). Repair of CP was undertaken if the patient was cleared regarding breathing based on PSG ($n=26$), home oximetry findings ($n=1$), or based on clinical judgment. Surgical protocol involved straight-line repair with intravelar veloplasty (SLIV) or primary Furlow palatoplasty. None of the RS-patients seemed to develop acute airway compromise following primary CP repair. During follow-up, OSA, confirmed by PSG, was detected in 5 RS-patients without other surgery. However, the number of patients that were formally tested with PSG was not mentioned.

Prescher et al (2021) investigated the impact of CP repair in 21 isolated RS-patients who previously underwent mandibular distraction osteogenesis (MDO).⁸ Before and after surgery (MDO and CP repair) a PSG was performed. CP repair was done by a 2-stage repair. Five patients (24%) experienced a relapse of previously resolved airway compromise following CP repair. One patient had a prolonged postoperative intubation and 3 patients had recurrence of OSA after CP repair, of which 2 required repeat MDO.

Naros et al (2021) investigated Tuebingen PEBP therapy in 143 isolated and nonisolated RS-patients (121 isolated RS-patients) with a cleft palate.⁹ Therefore, a retrospective analysis was performed between 2000 and 2020. All patients underwent PSG soon after birth, before and after surgery. Surgical protocol involved an one-stage radical intravelar veloplasty with or without lateral incisions (Sommerlad). PSG soon after birth—at 0.9 (± 2.3) months—demonstrated a mixed-obstructive apnea

index (MOAI) of 9.4/hour. After PEBP therapy, MOAI dropped to 0.9/hour at 1.1 month and 0.1/hour before surgery (8.6 ± 4.8 mo). In 7% of patients (10/143) airway compromise was experienced, including desaturations ($n=4$), swelling of the tongue ($n=4$), and laryngospasm ($n=2$). However, 11.2% of patients (16/143) underwent prophylactic temporary NPA treatment to prevent airway compromise. All NPAs were removed after some hours of monitoring without any complications.

Which Surgical Treatment Options Can be Considered?

Primary cleft palate repair

In patients with RS, various surgical treatment options have been used to primary repair a CP, and include straight line repair techniques for the hard palate^{4,5,7} and various intravelar veloplasties for soft palate muscle realignment^{5,7,9} that are similar to the surgical treatment options available in non-RS CP-patients. However, with a lack of comparative studies or prospective design, there is no literature on the optimal surgical treatment for primary CP repair in patients with RS, regarding to speech and breathing. Therefore, no conclusions were written. that are similar to the surgical treatment options available in non-RS CP-patients. However, with a lack of comparative studies or prospective design, there is no literature on the optimal surgical treatment for primary CP repair in patients with RS, regarding to speech and breathing. Therefore, no conclusions were written.

Speech-improving surgery

The same applies to the surgical approach to treat VPI. The use of a pharyngeoplasty in patients related to the airway in RS was debated in 3 articles, in a total of 21 isolated RS-patients.^{10,11,12} Postoperative airway compromise was only clinically assessed. OSA was not observed in patients with isolated RS, except for one RS patient. However, all studies lack objective measurements, such as a PSG or oximetry, and thus no conclusions can be drawn.

What is the Best Timing for Surgical Treatment of Palate-related Problems in RS, Related to Speech and Breathing Problems Regarding the Best Timing and Short/Long-term Effects?

Timing cleft palate repair

Costa et al (2014) included 74 isolated RS-patients and 39 isolated CP-patients. Airway obstruction was defined by one that necessitated nonsurgical or surgical intervention.⁵ Before CP repair, a PSG was routinely performed in all patients. If the AHI was ≤ 5 and there was no significant carbon dioxide retention, the palate was repaired. Primary CP repair was performed at 18 (± 10.5) months in patients with isolated RS versus 13.3 (± 2.8) months in patients with ICP ($P=0.006$).

Timing of primary CP repair in patients with RS was also evaluated by Van Lieshout et al (2016).⁴ CP surgery was performed in 30 RS-patients versus 45 ICP-patients. Airway obstruction was defined by one that necessitated intervention. Prior to CP repair, a PSG with removable custom-made palatal plate was routinely performed in all RS-patients. CP repair in RS-patients was only undertaken once the PSG was normal. Based on preoperative PSG data with palatal plate, CP repair was postponed in 2/30 (7%) of RS-patients. The mean age at the time of repair was 12.4 months in RS versus 10.9 months in patients with ICP ($P=0.05$).

Logies et al (2021) investigated CP repair outcomes in 75 isolated RS-patients versus 83 isolated cleft palate (ICP) patients.⁷ Airway compromise pre-operatively was clinically assessed and in case of a clinical suspected compromised airway, a supplemental PSG was performed. Repair of CP was undertaken if the patient was cleared regarding breathing based on PSG (n=26), home oximetry findings (n=1), or based on clinical judgment. Based on their preoperative protocol, CP was closed at 13.7 (± 5.3) months in RS-patients and at 11.3 (± 5.1) months in patients with ICP (P=0.004). CP repair beyond 12 months of age occurred in 32/75 (43%) RS-patients, including both isolated and nonisolated cases.

Prescher et al (2021) investigated the impact of CP repair in 21 isolated RS-patients who previously underwent MDO.⁸ CP repair was done by a 2-stage repair. Before and after surgery (MDO and CP repair) a PSG was performed. Mean age at first stage CP repair was 12.9 (± 6.0) months with an average of 319.4 (± 166.4) days between surgeries.

Naros et al (2021) investigated Tuebingen PEBP therapy in 143 isolated and nonisolated RS-patients (121 isolated RS-patients) with a cleft palate.⁹ Therefore, a retrospective analysis was performed between 2000 and 2020. All patients underwent PSG soon after birth, before and after surgery. Surgical protocol involved an one-stage radical intravelar veloplasty with or without lateral incisions (Sommerlad). The mean age at the time of CP repair was 12.0 (± 7.0) months in RS-patients. However, in patients with syndromic RS, CP repair was performed significantly later than in isolated RS-patients (17 versus 10 mo, P=0.0001).

Conclusions

<p>Quality of evidence Without GRADE</p>	<p>There are cautious indications that primary repair of the cleft palate in RS-patients is safe with regard to breathing if the AHI is < 5 and there is no significant carbon dioxide retention and/or a normal PSG with or without a custom-made palatal plate. References: (4,5,7) <i>Conclusions based on evidence from 3 retrospective studies, with an intermediate risk of bias and heterogeneity, but no important inconsistency and imprecisions.</i></p>
<p>Quality of evidence Without GRADE</p>	<p>There are cautious indications that primary repair of the cleft palate in RS-patients is delayed with an average of 2-5 mo, due to a compromised airway assessed by a preoperative PSG. References: (4,5,7) <i>Conclusions based on evidence from 3 retrospective studies, with an intermediate risk of bias and heterogeneity but no important inconsistency and imprecisions.</i></p>

**Considerations
Quality of Evidence**

The overall quality of evidence on the indication of palate surgery in patients with RS was low. All studies were retrospective cohort studies with relatively small sample sizes. There are some notes to be made regarding the quality assessment of the selected studies. First, in 2 studies no distinction in outcomes (timing, OSA outcomes or sleep parameters) was made between

isolated RS and those with nonisolated RS, including patients with additional syndromic diagnoses.^{5,7}

Second, the variety of definition used for the diagnosis of RS as well as for objectively determining airway obstruction. In 2 studies not all RS patients underwent a PSG before primary CP-repair.^{5,7} In addition, none of the 3 studies on pharyngoplasties objectively assessed the airway in RS (eg, PSG or oximetry) related to speech improving surgeries, but only reported clinical assessments.^{10,11,12}

Professional Perspective

Safe closure of a cleft palate in a RS patient can only be performed if a PSG demonstrates that OSA has resolved or is very mild. The use of a palatal plate that mimics a closed palate helps in deciding on the safety of palate surgery, particularly if the plate is able to cover most of the cleft. A minimal cleft of the posterior part of the soft palate is usually not suited for a plate and the PSG can be done without it. During follow-up after surgery, a PSG is indicated in patients with a clinical suspicion of airway compromise to exclude OSA.

Even though no evidence could be found, the guideline development group advocates for a PSG before undertaking speech improving surgery. A PSG at this stage should then demonstrate no OSA. The use of a pharyngeal flap has the potential risk of inducing OSA, and therefore an intervelar plasty or the use of a buccal flap for lengthening of the soft palate might be safer. Following speech improving surgery, a PSG should be performed in a low threshold manner to exclude OSA.

Some centers advocate early palatal closure (7–9 mo), as it might improve tongue position and improve obstructive breathing.¹³ Irrespective of the timing of the palate repair, close PSG monitoring is mandatory.

Balance of Benefits and Harms

Speech development benefits from early closure of a cleft palate but should not be done at the expense of breathing. Due to the high prevalence of breathing disorders and potential severity of breathing problems in RS following palate or speech-improving surgery, all patients with RS should be appropriately assessed and managed for airway and breathing problems before and after palate or speech improving surgery.

Performing PSGs imposes a burden on the patients to visit the hospital but can prevent airway obstruction and this clearly outweighs the harm. To lessen the burden of hospital visits one could consider home-based sleep studies as an initial screening tool.

Rationale of the Recommendation

There is no conclusive evidence in the literature that gives guidance to the most optimal surgical technique, the best timing and perioperative airway and breathing monitoring for the management of the palate-related problems in RS patients.

Recommendations

- Consider avoiding a pharyngoplasty in patients with RS as it might induce or recur OSA. If pharyngoplasty is considered for VPI, always inform parents on other surgical solutions for VPI as well.

Consensus

Initially, the following recommendations were also proposed by the guideline development group:

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- Perform a PSG (with or without palatal plate) in patients with RS that are being considered for palatal surgery and only perform a palatoplasty if the PSG is uneventful.
- Perform a PSG in patients with RS that are being considered for speech improving surgery and only perform the surgery if the PSG is uneventful.
- Perform a PSG in patients with RS following palate or speech improving surgery (at least 3 mo afterwards) to monitor breathing.

However, during the comment and authorization phase these recommendations did not receive approval from all stakeholders and consensus could not be reached by following the initial methods for creating recommendations. Therefore, formal consensus was sought by using a Delphi process for these specific topics. After 2 Delphi rounds, consensus (minimum of 70% agreement) was identified on the following statements:

- PSG (with or without palatal plate) before palatoplasty is appropriate to demonstrate the likelihood of breathing disturbances being induced or worsened by palatoplasty in RS patients—**Agreement 70.5%**.
- Using PSG results to guide treatment decisions on type and timing for palatoplasty may prevent (a worsening of) breathing disturbances after palatoplasty in RS patients—**Agreement 70.5%**
- Using PSG results to guide treatment decisions on type and timing of speech improving surgery is appropriate in Robin patients with (suspicion of) breathing disturbances—**Agreement 82%**
- A PSG in RS patients following palate or speech improving surgery (taken at least 3 mo afterwards) is appropriate to monitor the effect of the surgery on breathing—**Agreement 82%**

Details of the Delphi procedure are described in the Chapter 1 and 2 and a report of the evaluation between round 1 and 2 is available in the supplementary materials.

Research Gap

The overall evidence in this chapter is weak due to the lack of good comparative studies. To solve the issue of ideal timing of palate repair in RS patients and impact on breathing, appropriately designed prospective studies with PSG monitoring are needed.

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CHAPTER 14. HEALTH-RELATED QUALITY OF LIFE

Introduction

RS is defined as the triad of micrognathia, glossoptosis, and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed). Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to date genetic testing).

Over the last decades, pediatric health care has improved, resulting in better survival rates for children. Whereas mortality has long been the main outcome of care, focus has shifted to long-term morbidity outcomes relevant to daily life. In children, important outcomes in daily life are physical, mental, and social development outcomes as well as family and parent outcomes*. This is in line with the evolution of value-based health care as the standard of care in which patient-reported outcomes

(PROs), such as HRQoL, play an important role. Although there is no consensus regarding the definition of HRQoL, it is generally agreed to be a multidimensional concept which considers the subjective evaluation of the influence of disease on physical, mental, and social aspects in daily life. HRQoL is also an important outcome for children with RS. Depending on the severity of their breathing and feeding problems, growth and important functions like eating may be impaired. The complexity and severity of these problems can have an impact on a child's HRQoL. HRQoL is assessed through PROM. In younger children (< 8 y old) PROs such as HRQoL are proxy-reported by their parents. From the age of 8 years and older, children generally have the cognitive and socioemotional skills to self-report on PROs when willing and able to provide their perspective. In addition, both parent-reported and self-reported HRQoL in the child provides a complete picture of the impact of the disease or treatment.

Undergoing treatment for RS can also impact the HRQoL of children with RS and their parents. Treatment for RS starts directly after birth when the child is admitted to a neonatal or pediatric intensive care unit (NICU or PICU). Admission to an intensive care unit in itself often is a very stressful experience for infants and their parents. After discharge, most children with RS still have breathing and feeding problems which can impact their daily life and the daily life of their parents. For example, if a child is discharged home with a tracheostomy, their parents become responsible for the care 24 hours a day. This might be an enormous burden for parents. In addition, the definitive diagnosis of RS can be very stressful for parents. They may also have questions such as “will my child have an associated syndrome?”

To support children with RS and their parents optimally, it is important to address the HRQoL prognosis to parents of newly diagnosed patients. During outpatient care, assessing and discussing HRQoL outcomes can be done to inform individual patients and/or their parents after treatment for RS. HRQoL outcomes can also be used for research purposes or to evaluate the impact of different treatments on children's HRQoL within centers or between different centers.

For this chapter the following questions were addressed:

- What is the physical HRQoL of children with RS?
- What is the psychosocial HRQoL of children with RS?
- What is the HRQoL of parents of children with RS?

To answer these questions, we performed a literature search into physical and psychosocial HRQoL domains. We also searched for papers on HRQoL in parents as outcomes of interest.

**for readability, the term “parents” includes both parents and other significant caregivers.*

Literature Search

For this guideline, a systematic literature search was performed. The search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

The inclusion and exclusion criteria are reported in further detail in Chapter 2: Methodology. After rough selection and labeling, a full text assessment of n=15 studies was performed. Several studies were excluded due to wrong population (n=4), sample size too small (n = 1), or for covering a different outcome (n=4). In this chapter, 6 studies were included. Five of these studies are cross-sectional studies assessing physical and psychosocial HRQoL in children with RS.¹⁻⁵ Two of the studies reported on experienced changes in HRQoL after

Inclusion and exclusion criteria

Type of study	Original studies Systematic reviews
Type of patients included	Patients with isolated and nonisolated Robin sequence Parents of patients with isolated and nonisolated Robin sequence
Subject	Physical Health-related Quality of Life Psychosocial Health-related Quality of life Parental Health-related Quality of life
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 participants Publication date before 2000 Case reports Expert opinions Research amongst populations in developmental countries Editorials Conference abstracts Publications exclusively based on expert opinion

treatment^{3,4} and 3 reported on physical and psychosocial HRQoL outcomes in the longer term.^{1,2,5} One qualitative study about family experience with RS was also included.⁶

Summary of Literature Study

What is the Physical HRQoL of Children With RS?

Hong et al (2012) studied the benefits of Mandibular Distraction Osteogenesis (MDO) on HRQoL at 4-year follow-up.³ Twenty-one children with severe upper airway obstruction were included: 16 with isolated RS and 5 with nonisolated RS. After MDO, children improved on the physical QoL scale of the Glasgow Children's Benefit Inventory (GCBI). No significant differences between isolated and nonisolated RS were found, with the exception of the vitality domain (of the scale). In this domain the isolated group improved more after MDO.

Loges et al (2019) studied 12 RS children treated with MDO and 10 RS children treated with tongue lip adhesion (TLA) with a follow-up range of 1.3 to 10.5 years.⁴ Of the total 22 children included, 9 had isolated RS and 13 had nonisolated RS. Both groups improved on the physical QoL scale of the GCBI. No significant differences between the 2 treatments and between nonisolated versus isolated RS children were found.

Dulfer et al (2016) studied the association between the current respiratory status of RS children (median age 8.9 y) and OSA-related QoL. Parents of children with RS (n = 53; 32 isolated RS, 21 nonisolated RS) reported more problems with sleep and physical functioning compared with the norm.² The sleep disturbance scores were significantly higher in those children with RS who were previously treated with respiratory support and who had persistent respiratory problems, compared with children with RS who were previously treated with prone position or who previously received respiratory support but had no OSA at that time.

Basart et al (2017) studied 102 children (mean age 8.8 y) with RS: 46 isolated and 56 nonisolated.¹ Depending on the age of the child, different HRQoL questionnaires were used. Parents of 28 children with RS between 0 and 5 years reported significantly more lung and sleep problems, more problems with motor functioning and communication compared with the Dutch norm group. In the 6 to 7 years age group, parents of children with RS reported significantly higher levels of physical functioning for their child with RS compared with the Dutch norm group.

Thouvenin et al (2021) studied 72 (mean 14.4 y) children with RS: 59 isolated, 13 nonisolated.⁵ They assessed self-reported oral-specific, vocal-specific, and generic QoL. Compared with norm data, RS children had comparable oral-specific QoL. Their voice-related physical QoL was better than norm data from children with comparable pathologies. Those with isolated RS had better scores than those with nonisolated RS.

Psychosocial HRQoL in children with RS

Hong et al (2012) found that after MDO, children improved on the psychosocial HRQoL scale of the GCBI. No significant differences between isolated and nonisolated RS were found.³

Logjes et al (2019) aimed to compare the HRQoL of children with RS between 2 treatments; MDO and TLA.⁴ A total of 22 children with RS, N=9 isolated N=13 nonisolated, are included in the study. Children with RS in both treatment groups improved on the psychosocial HRQoL scale. No differences between isolated and nonisolated RS children were found.

Dulfer et al (2016) found no differences in parent-reported psychosocial HRQoL in 53 children with RS (32 isolated RS and 21 nonisolated RS) compared with norm data.²

Basart et al (2017) found no differences in psychosocial HRQoL in younger RS children (<7 y old) in comparison to the Dutch norm group.¹ RS children older than 13 years old reported higher levels of emotional functioning compared with the norm. Parents of children with nonisolated RS reported that their child had a higher dissatisfaction with their nose than parents of children with isolated RS. No other differences between isolated and nonisolated psychosocial HRQoL domains were found.

Thouvenin et al (2021) found a better psychosocial HRQoL (moods and emotions) in children with RS compared with norm data.⁵ On the other hand, RS children scores worse on autonomy compared with the norm. As to their voice-related psychosocial HRQoL, RS children scored comparable to the norm. Overall, children with isolated RS obtained better psychosocial HRQoL scores than those with nonisolated RS.

HRQoL of parents of children with RS

Compared with the norm population, Dulfer et al (2016) found more caregiver concerns in parents of children with RS.² Basart et al (2017) found that > 30% of parents of children with RS reported distress regarding or in the form of: leisure activities/relaxing (32.7%), depression (34.7%), feeling tense or nervous (37.8%), and fatigue (46.9%). Clinical distress was indicated by 34.7% of the parents.¹ Parents of children with nonisolated RS reported more distress, less satisfaction with treatment, less support and more of a negative influence on family compared with parents of children with isolated RS. In the group of children who had received MDO treatment, parental distress was seemingly elevated as, although the percentage of parents who scored in the clinical range of the thermometer mean score was similar to the NPA group, they answered more questions above the cut-off level of > 30%. Parental distress was indicated as higher in the NPA, MDO, and tracheotomy group.

Skirko et al (2020) published a qualitative study about family experience with RS. Parents of 13 children with RS were interviewed about their experiences.⁶ Parents reported extreme stress surrounding some of their children’s early physical symptoms, such as difficulties with breathing and feeding.

Conclusions

Quality of evidence without GRADE	Studies indicate that there is an improvement in physical and psychosocial HRQoL after both mandibular distraction osteogenesis and tongue-lip adhesion. After MDO, children with isolated RS improved more in the vitality domain compared to children with nonisolated RS. References: (3,4) <i>Conclusion based on single arm observational studies (n = 2) with a high risk of bias, some important imprecision, no indirectness, and no inconsistency.</i>
Quality of evidence without GRADE	Studies indicate that physical HRQoL in children with RS was worse compared to norm data, but oral-specific HRQoL was comparable with norm data. There are cautious indications that the physical HRQoL is worse in younger RS children (≤ 5 y old) with more functional and communication problems. There are cautious indications that children with isolated RS obtained better physical HRQoL compared to children with nonisolated RS References : (1,2,5) <i>Conclusion based on single arm observational studies (n = 2) with a high risk of bias, imprecision, no indirectness, and no inconsistency.</i>
Quality of evidence without GRADE	There are cautious indications psychosocial HRQoL in RS was comparable or better compared to norm data. References: (2, 3, 4, 5) <i>Based on a single arm observational study (n = 1) with a high risk of bias, some important imprecision, no indirectness, and no inconsistency</i>
Quality of evidence without GRADE	Studies indicated that parents of children with RS reported more stress and caregiver concerns than the norm. References: (1,2,6) <i>Based on single arm observational studies (n = 3) with a high risk of bias, significant heterogeneity but no indirectness, and no inconsistency.</i>

Considerations

Quality of Evidence

Two retrospective studies regarding HRQoL changes before and after found an improved HRQoL in children with RS after MDO and/or TLA assessed with the Glasgow Children’s Benefit Inventory.^{3,4} Both studies included a small number of participants; respectively n=21 (of which 13 were isolated) and n=22 (of which 9 were isolated). The follow-up periods included in the studies varied from 1.3 years to 10.5 years after treatment. In the study of Logjes et al (2019), the mean follow-up age differed significantly between treatments (MDO 7.4 y versus TLA 4.1 y, P<0.001). Both studies did not focus on parental HRQoL.

Three cross-sectional studies had a follow-up period between 9 and 14 years and had larger sample sizes.^{1,2,5} Dulfer et al (2016) is the only study that assessed disease-specific HRQoL related to obstructive sleep apnea in 53 children with RS treated with prone positioning, nonsurgical, or surgical respiratory treatment.² They found more parent-reported sleep disturbance and physical distress compared with norm data. No differences regarding psy-

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chosocial HRQoL were found. This is in contrast with Basart et al (2017) who found higher scores of physical and emotional functioning in older RS children compared with the norm on a generic HRQoL instrument.¹ Thouvenin et al (2020) also found comparable generic HRQoL in 72 RS children.⁵ Moreover, they had the only study that assessed disease-specific oral and voice related HRQoL. As for parents, Basart et al (2017), Dulfer et al (2016), and Skirko et al (2020) reported distress and caregiver concerns, for example regarding their child's early physical symptoms such as difficulties with breathing and feeding.^{1,2,6}

The previously reported studies used different questionnaires to assess HRQoL. This makes it hard to draw a firm conclusion regarding the impact of RS treatment on HRQoL in daily life of children and their parents. There is a need for international consensus how and when to measure HRQoL in RS children as part of a core outcome set of important PROs in the RS population.

Overall, the quality of evidence in these studies is compromised due to high risk of bias, differences in populations (isolated RS versus nonisolated RS) and treatments, small sample sizes, and differences in questionnaires (PROMs). This has a negative influence on the reliability of the conclusions and therefore impacts applicability of the conclusions in practice.

Professional Perspective

As from professional perspective, discussing PROs such as HRQoL with parents and their (older) children, will empower them in daily life. Screening for worse HRQoL and, if necessary, provide appropriate care or referral will improve long-term outcomes in both children and their parents.

Balance of Benefits and Harms

Assessment of HRQoL in children with RS and discussing these outcomes with RS children and/or their parents, as part of value-based health care, will have obvious benefits for patients and their families. It will provide a high standard of care, improving patient quality of life and parental quality of life. Parents and children fill in HRQoL outcomes at home, this might better prepare them for the outpatient consult with the clinician. The clinician benefits since he/she can monitor the HRQoL outcomes beforehand, resulting in a more efficient consult with the patient and its parent.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available care providers, facilities, and infrastructure and technical support from the organization. The recommendations concern essential requirements for the HRQoL of children with RS and should thus be implemented on a routine basis in specialized centers.

Inequity of the Recommendations

The goal of the ERNs is to eliminate inequality within Europe with regards to care for patients with rare diseases. Measuring HRQoL with validated, age-appropriate, freely available instruments can be helpful in improving care across the participating countries.

Feasibility of the Recommendations

Recommendations refer to the general requirements for delivering optimal health care and care, discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as a solution.

Acceptability of the Recommendation

It is expected that all stakeholders want to apply and will apply the recommendations, because they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country.

Rationale of the Recommendations

More prospective, longer-term follow-up studies are needed to examine the influence of different treatments on the HRQoL of children with RS and their parents. Based on our own experience from clinical practice, we can conclude that it is good practice to screen parents and children from birth throughout adolescence since every life phase represents different challenges impacting HRQoL.

Recommendations

- Parents should have a key role in the management of their child with RS.
- Screen parents' assessment of their child's HRQoL using validated, multidimensional, generic as well as disease specific instruments.
- Consider screening the impact of parenting a child with RS on parents' own HRQoL (see Chapter 10).
- Consider the use of PROMS to improve evaluation of all patients care in relation to their QoL.

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CHAPTER 15. ORGANIZATION OF CARE

Introduction

RS is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction. In the majority of the RS patients a cleft palate is present. RS can be categorized in 2 main categories: clinically isolated RS and clinically nonisolated RS. Clinically isolated RS is subsequently subdivided in confirmed isolated RS (after up-to-date genetic testing) and presumed isolated RS (no up-to-date genetic testing performed).

Clinically nonisolated RS is subdivided in syndromic RS (genetically confirmed or clinically still strongly suspected syndromic diagnosis, after up-to-date genetic testing) and RS plus (RS with additional anomalies without suspected recognizable syndromic diagnosis, after up-to-date genetic testing).

The presentation of RS is highly variable with multiple systems involved with obviously airway problems at the forefront. Because of this wide presentation, many specialties are involved: perinatology, neonatology, (Intensive Care-) pediatrics, otorhinolaryngology, clinical genetics, speech pathology, nutritionists, feeding specialists, plastic surgery, maxillofacial surgery, orthodontics, ophthalmology, genetics, general surgery, cardiology, neurology, dentistry, audiology, psychology, nurse specialists and social work. The multidisciplinary management of patients with RS is much more complex than the airway management only, and therefore, optimal coordination and communication among health care professionals, and with parents of patients and patients themselves are mandatory. The tasks and responsibilities of all healthcare providers should be clear for all involved.

Care Coordinator

Nowadays, the care coordinator within the center of expertise plays an essential role in optimizing the process of coordination and communication. A care coordinator is a trained professional, often a specialized nurse, and essential in the optimal organization of care overall. The coordinator is responsible for ensuring that a care plan is in place and carried out. The coordinator can greatly assist in ensuring coordination, and continuity of care. Often, parents and patients find their first way to the care coordinators, and with that, the care is provided as smoothly as possible. Care coordinators are also available to support the practical and emotional needs of parents and patients throughout the progression of the condition. They may also provide vital education to other professionals, to enable appropriate care and support to be provided. The care coordinator plays an essential role in optimizing the communication between parents and health care professionals, among the health care professionals, being either within one center or between different centers.

Minimal Care Standards

Due to the rarity of RS the diagnosis of this condition is often delayed. This is associated with significant hardship for patients and families, unnecessary appointments, referrals, and tests, and causes delay in starting appropriate treatment. The rarity of the condition necessitates the formation of multidisciplinary centers of expertise to provide high quality and up-to-date information on the condition, to accommodate accurate and timely diagnosis, to guide parents and patient throughout the patient journey, and to give access to appropriate multidisciplinary care. Therefore, to make recommendations on the minimal care standards for this multidisciplinary treatment of patients with RS, the following question was addressed:

- **What are the minimal care standards to treat patients with RS and how should it be monitored?**

To guarantee good quality of care for the patients with RS, it is important to explore parents' and patients' experience in their care process, so called patient and public involvement (PPI) (1). To identify these aspects, a survey was shared with the parents of RS patients of the participating hospitals of ERN-CRANIO with an expertise in RS. Aim of this survey was to gain insight in parents' experiences on the organization of care and

information management in their child with RS, either good or bad, within the various member states. Via a digital survey (Appendix C1, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>) in their own language the parents of patients of the participating hospitals were requested to identify their needs, values, preferences and experiences in the care process. Outcomes of the PPI's analysis are displayed in the Appendix C2, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

The considerations and recommendations in this chapter were based on the outcomes of the PPI's analysis, the literature and expert opinions.

Literature Search

The literature search for this chapter was directed toward care aspects mentioned by patients regarding the topics communication, information, referral, timing of provided care, and collaboration. The review of literature and conclusions were based on the article of Sandow et al (2). The systematic literature search was conducted in Embase, Pubmed/Medline Ovid. Full search details are available in Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>.

Inclusion and exclusion criteria	
Type of studies	Original studies Systematic reviews
Type of patients	Patients with isolated and nonisolated Robin sequence
Subject	Organization of care PPI's reported in the care process Outcome measures
Exclusion criteria	Patients with syndromic Robin sequence Sample size <10 patients with Robin sequence Publication date before 2000 Research among populations in developmental countries Case reports Editorials Conference abstracts Publications exclusively based on expert opinion

After rough selection and labeling a full text assessment of (n = 9) studies was performed for this chapter. Several studies were excluded due to incorrect outcome (n=4) and for other reasons, like being a narrative review (n=4). In this chapter only one study from Sandow et al (2020) is included (2). Here, parents' lived experience of their child's diagnosis of RS is described. This study explores the period at and after the time of diagnosis, the subsequent care and management required, and the supports accessed by parents.

Summary of Literature Study PPI Analysis

The PPI analysis (see Appendix C1 and C2, Supplemental Digital Content 1, <http://links.lww.com/SCS/F471>) revealed responses from 94 parents from 8 different countries. 58,9% of the parents mentioned important obstacles regarding the first weeks after birth of their child with the absence of information on practical aspects regarding feeding techniques and sleeping positions. Parents experienced a lack of practical instruction by care professionals in local care facilities after birth and support with fitting material for feeding. They reported that these instructions were given as soon as referral to specialized care took place. It was also perceived as helpful when in case of prenatal suspicion of RS, a referral was made to a center of expertise.

Information

When asked specifically about obstacles regarding information about RS, 22% of the parents replied that they missed information on RS after receiving the diagnosis. Apparently, basic information on RS and instructions were missing in nonexpert centers and it was helpful to receive information and instructions by specific members of specialized teams such as pediatricians, surgeons, speech therapists, geneticists, and specialized nurses. It was also appreciated when specialists explained the various scenarios about the possible difficulties and various treatment paths as this was felt as honest and complete information. Several parents stated that peer contact helped them to understand the variety of manifestations in RS and treatment options. The parents suggested that peer contact might be beneficial for other parents as well.

Nearly 80% of parents described that they looked for information on the internet. It was specified that they searched for pictures of RS to understand the appearance, information on medical websites and patient associations. In one case information was retrieved from scientific publications. Some parents described that they liked to read forums and experiences by peers, for example, via social media channels. In some countries it was mentioned that they couldn't easily find information in their own language or that information that was found was inconsistent, unclear, or useless and that it didn't help to understand the specific situation of their child. It was also mentioned that some information was causing anxiety in parents.

Communication

The communication with care givers caused obstacles in 15% of the parents. These were specified by different views of specialists within expertise centers regarding the best treatment strategies, but also by problems that parents perceived in sharing data between hospitals and care settings and unnecessary duplication of care when a child's growth or dental health was followed, and measurements were performed simultaneously by different institutions. A low number of parents reported problems during the follow-up appointments (5%) and this was mostly specified by the problems regarding the exchange of data between care settings.

Referral

The referral to a specialized center was an obstacle, especially when parents felt that care givers didn't recognize RS or when the referral took long. Important problems that caused delay in the referral process were the recognition of the diagnosis RS and the differentiation with the treatment for cleft palate. Parents described that their children were treated for cleft palate while the breathing and feeding problems were not addressed. Once referral took place parents stated that they received adequate information, instruction, and guidance.

In all, 19% of the parents described that RS was suspected prenatally. In the majority of these cases (55%), the suspicion led to measures such as prenatal counseling, additional controls of the child before and after labor and information and guidance by specialist teams. These measures were perceived as helpful and supportive.

Psychological Counseling

A total of 47 out of 94 parents (50%) described that they received psychological or psychosocial counseling and 31 of them found it useful. Twenty-six out of the 35 parents (74%) who did not receive counseling or support would have liked to

receive it. Reasons why they thought it might be helpful were the possibility to share feelings, pain, and thoughts, to receive support on coping strategies and support during the prenatal phase. Counselling was sometimes not perceived as supportive when the psychologist was not familiar with the disease or when it was felt that counselling was proposed too early or too late in the care process. Other parents described that their own social network replaced professional help and some felt they did not need support.

Literature

In the cross-sectional study of Sandow et al (2020), parents of patients with RS were interviewed face-to-face or by phone to examine the parents' experience of their child's diagnosis of RS (2). They looked at (1) perceptions of antenatal detection and diagnosis; (2) timing and delivery of genetic test results; and (3) participants' re-call of genetic service involvement and support offered. In total, the parents of 10 isolated RS cases, all with cleft palate, were interviewed, of which 4 antenatally and 6 postnatally.

To 1: Participants, regardless of the timing of their child's diagnosis, could appreciate that an antenatal detection might make the neonatal period for a child with RS less confronting by allowing time to process information and prepare emotionally and practically by meeting with hospital staff. Antenatal detection of micrognathia came with anxiety during the pregnancy and uncertainty about what it would mean for the newborn.

To 2: When genetic information was given to participants, sometimes the way it was done is what they remembered most strongly. In general, genetic services at age of 6 to 12 months of their child (after the initial period) would be useful. The parents particularly want to learn about recurrence risks for themselves as well as for their child in the future.

To 3: Most participants did not remember seeing any genetic counsellors or geneticists, or at the very least it did not stand out to them as an important part of their child's diagnosis and management.

The authors concluded that the information given at the time of diagnosis was not suitable to the immediate needs and understanding of the parents and adjusting this could make a significant difference to the overall experience. Antenatal detection of RS is considered as a critical point where parents could benefit most from genetic counselling. Whereas later in the child's first year of life, the role of the genetic counsellor would then be to ensure parents are aware of the services available.

**Conclusions
For Outcomes Assessed Without GRADE**

Quality of evidence without GRADE	From the PPI analysis conducted in expert centers:
	<i>Information</i>
	There are cautious indications that roughly one-quarter of the parents of patients with RS experienced a lack of basic information and instructions in nonexpert centers. The parents appreciated practical instruction and when specialists explained honestly the various scenarios about the possible difficulties and various treatment paths. The parents suggested peer contact and uniform (online) information in their language.

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Communication

There are cautious indications that in a minority of the parents the communication with care givers caused obstacles, particularly regarding the different views on best treatment strategy within the center of expertise, sharing data between hospitals and care settings and unnecessary duplication of measurements and care.

Referral

There are cautious indications that referral to a center of expertise formed obstacles, especially when parents felt that care givers did not recognize RS in their patient or when the referral took a long time. In case of postnatal diagnosis, quick referral to a center of expertise is necessary.

Psychological counseling

There are cautious indications that parents of patients with RS would appreciate psychological counseling to share feelings, pain, and thoughts, and to receive support on coping strategies and support during the prenatal phase and after birth.

Quality of evidence without GRADE

From the literature:

There are cautious indications that antenatal detection of RS is considered as a critical point where parents could benefit most from genetic counselling. Later in the child's first year of life, the role of the genetic counsellor would be to ensure parents are aware of the services available.

Reference: (2)

Conclusion based on evidence from one article (n = 1) cross-sectional study (10 isolated RS patients all with CP) with a high risk of bias, with detected imprecision (small sample) and no important indirectness, inconsistency and impression.

Considerations

Quality of Evidence

The study of Sandow et al (2000) has no grade level as this is a cross-sectional noncomparative study (2). The risk of bias was assessed with AXIS which revealed that the study was well designed but has a large bias risk due to the small sample size and possible ascertainment bias. No efforts to find a justified sample size were reported and parents in the sample were either on the high satisfaction end or the very low satisfaction end of the spectrum. Including more, but also parents with a “not satisfied, not unsatisfied” view on their care experiences could have decreased the bias risk.

Professional Perspective

In the last 2 decades, the care coordinator has become indispensable in the multidisciplinary care of RS patients. The coordinator plays an essential role in the coordination and communication between parents and health care professionals, among the health care professionals.

Multidisciplinary care requires optimal coordination and communication within the team, toward health care professionals outside the team and last but not least the patient and their parents. As the management of the RS patient is mainly nonsurgical directed to safeguarding the airway, it seems obvious the overall responsibility of the patient is in the hands of nonsurgical disciplines like pediatrics (ICU), anesthesiology or peri/neonatologists depending on the local organization.

Treating patients with RS requires a multidisciplinary team that should meet the following requirements:

1. Presence of and collaboration within a multidisciplinary team.
2. Experience with treatment of RS .
3. Access to the necessary facilities:
 - Pediatric ICU
 - Sleep study facility
 - Audiological evaluation
 - Good accessibility of care
 - Prompt management of child with respiratory distress
 - Timely referral
 - Providing 24/7 clinical services
4. Core team working in center of expertise:
 - Peri/neonatologist
 - Team coordinator
 - Prenatal physician
 - (IC-) pediatrician
 - Nutritionists/feeding specialists
 - Pediatric anesthesiologist
 - Otorhinolaryngology/audiologist
 - Speech therapist
 - Nurse specialist
 - Surgeon with expertise in cleft and craniofacial care
 - Psychologist
 - Genetic specialist

Access to a wider team:

- Orthodontist
- General surgeon
- Cardiologist
- Neurologist
- Ventilation team

5. Protocol for transition of care for patients when they reach adulthood
6. Systematic evaluation of outcomes and implementing changes in treatment protocol that are the result of these evaluations
7. Innovation and scientific research (educational workshops, research meetings, congresses, courses, publications)
8. Additional and continuing training of all team members
9. Updated information for patients and caregivers (informative meetings for parents)
10. Collaboration with patient representatives

While not necessary in all cases, access to the following is desirable:

- 3D-photography, radiographical imaging, CT/CBCT, MRI, 3D virtual computer planning facility
- Dental lab
- Clinical geneticist
- Psychologist
- Social worker
- Prosthodontic dentist

Centralization

Health care for patients with RS requires a multidisciplinary approach, given the complex care these patients need. Centralization results in more expertise, higher quality of care and more opportunities for scientific research to improve care.

Health care for patients with RS is centralised in expertise centres in different countries in Europe. However, patients are not always aware of this. In addition, not every European

country will have a specialist centre for RS. Centralization might result in less expertise being present in other institutions and a longer travel distance for patients.

Professionals treating RS are already connected in European Reference Network (ERNs) with a focus on complex craniofacial anomalies and ear, nose and throat (ENT) disorders (ERN-CRANIO). ERNs are virtual networks of health care providers from across Europe. The networks aim to pool together expertise on complex and rare diseases and concentrate knowledge and resources. There are 24 ERNs, each focusing on a particular disease area. A general rule of thumb is that one expertise center is required for a specific group of diagnoses for every 10 million inhabitants.

Monitoring

Current practice varies in different European countries. In addition to developing a guideline with standards of care, it is relevant to monitor the outcome of these standards of care in the future with the participating institutions. Monitoring standards of care should encourage institutions to change their current practice if results of treatment are insufficient. In addition, institutions can learn from each other and can help each other by implementing optimal organization of care. It is important to mention that monitoring standards of care is not intended to criticize each other but to improve the quality of health care together. Monitoring standards of care might require some effort from the team but can result in many valuable (international) results that will improve quality of care.

Balance of Benefits and Harms

Benefits of good and timely provision of information, communication, referral, psychological support, prenatal detection, and genetic counselling will help the parents to prepare themselves to cope with their child's diagnosis of RS. It will assist in early provision of the required care for the child during delivery and in the postnatal phase. On the other hand, hearing that your unborn child may have RS, will cause anxiety with the parents, which could be a significant burden to them especially if the diagnosis is not confirmed after birth.

Costs and Resources

The impact on costs and resources of the given recommendations will vary per member state, depending on the available national budget, care providers and facilities. The recommendations constitute the essential requirements for appropriate treatment of patients with RS and accordingly these requirements should be implemented. Costs are lowest and resources are most efficiently used when care for congenital disorders is centralized in a limited number of expert centres per member state.

Inequity of the Recommendation

The goal of the ERNs is to eliminate inequality within Europe about care for patients with rare diseases. At present, not every member state offers an expert center for RS, or the level of provided care does not (yet) meet all the requirements outlined in this guideline. By defining the baseline of required care for RS, this guideline will help these member states to reach the appropriate level. The ERN on craniofacial anomalies and ENT disorders (ERN-CRANIO) can guide a patient in Europe to the available centers of expertise (www.ern-cranio.eu) and can support care providers with diagnosis and treatment advice.

Feasibility of the Recommendation

Recommendations refer to the general requirements for delivering optimal healthcare and are discussed with members from participating European countries. Quality of care was paramount in the discussions. Centralization is proposed as one of the core values. However, in some countries the national organization of health care might impede centralization. National implementation of the ERNs that fits the situation of each country is necessary. For the member states with the lowest number of inhabitants, the establishment of an expert center might not be feasible, and collaboration with an expert center in the surrounding countries should be considered.

Acceptability of the Recommendation

It is expected that all stakeholders strive to adhere to the recommendations, since they are employed in ERN-acknowledged institutions. National implementation plans are necessary to ensure that recommendations fit the situation in each country. In addition, not all countries participating in the ERN-CRANIO are represented in the guideline development group, and new members will join within the coming years. For these countries, acceptance, and implementation of ERN guidelines such as the current guideline on RS is mandatory.

Rationale of the Recommendation

The essential principle of the recommendations is to offer the most optimal care to patients with RS and their parents. The diagnosis, treatment, and follow-up of this condition is complex and has a lifelong impact on the patients. This necessitates a dedication from healthcare providers to continue training in all aspects of this care.

Recommendations

- Provide information about RS and instructions on care to parents, including the various difficulties that can occur and the different options in treatment. This information is preferably uniform and online available in their own language.
- All health care professionals, in particular those in first line care, and lay persons should have access to this guideline in their own language.
- The ERN and designated centers of expertise should ensure online search engine optimisation to direct patients seeking information on RS.
- Provide peer contact to parents.
- Ensure good communication between care givers within the center of expertise, between the team and external care givers, and between the team and the parents.
- A center of expertise should be consulted anytime there is a suspicion of RS, prenatally or postnatally.
- Offer care to patients with RS in a center of expertise, i.e. cleft and craniofacial centers, defined by: Good accessibility of care Providing 24/7 clinical services Protocol for transition of care for patients who reach adulthood Systematic evaluation of outcomes and implementing changes in treatment protocol that are the result of these evaluations Innovation and scientific research (educational workshops, research meetings, congresses, courses, publications) Additional and continuing training of all team members Centers of expertise responsible for the management of RS should make long-term provisions to ensure continuity of care Updated information for patients and caregivers (informative meetings for parents, (if available provide information on patients' associations, parents' experts) Collaboration with patient representatives

- Offer care to patients with RS by a multidisciplinary team, which encompasses:

Core team members:

- Peri/neonatologist
- Team coordinator
- Prenatal physician
- (IC-) pediatrician
- Nutritionists/feeding specialists
- Paediatric anaesthesiologist
- Otorhinolaryngology/audiologist
- Speech therapist
- Nurse specialist
- Surgeon with expertise in cleft and craniofacial care
- Psychologist
- Respiratory specialist
- Orthodontist

Availability of:

- Pediatric surgeon
- Cardiologist
- Neurologist
- Ophthalmologist
- Ventilation team
- Clinical geneticist
- Social worker
- Prosthodontic dentist

Essential facilities:

- Pediatric ICU
- Sleep study facility
- Audiological evaluation

Supportive facilities:

- 3D-photography
- radiographical imaging, CT/CBCT, MRI
- 3D virtual computer planning facility
- Dental lab
- Strive for national centralization of care for RS.

Research Gap

The research on RS should be directed toward the following gaps: distribution of information on RS for patients, parents, and professionals; optimizing referral to specialized care centers: optimizing coordination and communication between specialist within and between different hospitals; and optimizing psychosocial counseling. All PROMs should be studied for patients with RS and be translated and validated in all ERN-CRANIO languages.

An initiative to instate an international registry on RS care for prospective data collection and studies would increase the knowledge on the diagnosis and management of the RS patients. Therefore, outcome measures between centers (clinical and patient outcomes) should be aligned to compare different management regimes and learn from best practices.

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