RETT SYNDROME:

Comprehensive Care Guidelines

International Rett Syndrome Foundation
Accelerating Research. Empowering Families.

International Rett Syndrome Foundation is pleased to provide this resource to the Rett syndrome community. Developed in collaboration with Rett syndrome experts throughout the US, these Care Guidelines are intended to be used to support a meaningful partnership between caregivers and the physicians, nurses, and therapists that are involved in the care of their loved one with Rett syndrome. This is a medical resource, intended for families to share with their providers, to ensure their loved one is receiving care that is recommended by leading Rett syndrome experts.

IRSF would like to express gratitude to the 18 Rett syndrome Centers of Excellence and experts that volunteered time and effort to develop this list of recommendations.

Boston Children's Hospital, Children's of Alabama, Children's Hospital Colorado, Children's Health Dallas, Children's Hospital Los Angeles, Children's Hospital of Philadelphia, Cincinnati Children's Hospital and Medical Center, Gillette Children's Specialty Healthcare, Greenwood Genetic Center, Kennedy Krieger Institute, Montefiore Medical Center, Nationwide Children's Hospital, Rush University Medical Center, St. Louis Children's Hospital, Texas Children's Hospital, UCSF Benioff Children's Hospital, UNC Children's, Vanderbilt University Medical Center, Theresa Bartolotta, Ph.D., CCC-SLP, Judy Lariviere, M.Ed., OTR/L

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UPDATE CURRENT MEDICATIONS AND ALLERGIES

WEIGHT

HEIGHT

BMI

TANNER STAGE

Genetics/MECP2 Testing Results

- Counsel family on genetic test results.
- Refer to Genetics if necessary for additional counseling or genetic evaluation.
- Family and PCP should keep a copy of genetic results.

- **MECP2 mutations:** Pathogenic mutations in the MECP2 gene located on the X chromosome cause Rett Syndrome[1]. Mutations are de novo over 99% of the time and so not expected to recur in the family[2]. Rare inherited cases of Rett Syndrome from maternal carriers with skewed X-inactivation have been reported. Genetics referral indicated if family is interested in pursuing carrier testing. Most mutations in MECP2 can be identified by gene sequencing analysis[3]. If no abnormalities are identified by sequencing, but there is high clinical suspicion for Rett Syndrome, then additional deletion/duplication analysis of MECP2 is necessary to detect intragenic deletions or duplications that are frequently missed by sequencing.
- **Rett Syndrome and Overlapping Disorders:** Identifying an accurate genetic diagnosis is crucial to determining appropriate treatment and management of an individual's symptoms. Over 90 genes have been identified as causing syndromes with features overlapping those observed in Rett Syndrome. Given this genetic heterogeneity, it is becoming increasingly common to pursue broader genetic testing for patients suspected of having Rett Syndrome. This can include whole exome sequencing (WES) or genetic testing using a multigene panel including MECP2 as well as multiple other related genes. Over 90 genetic panels evaluating for Rett Syndrome and overlapping disorders are available from CLIA-certified laboratories in the United States. Of note, many gene panels include both sequencing and deletion/duplication analysis of genes on the panel. It is uncommon for WES analysis to include identification of deletions or duplications, although new options may soon become available given ongoing advancements in genetic testing technologies[4,5].
- **Genetic Counseling:** Referral to Genetics is recommended to review recurrence risks and answer related questions. Genetic testing results are often essential for enrollment in clinical trials. However, not every patient with a clinical diagnosis of Rett Syndrome will have an identifiable genetic cause.

Growth, Development and Nutrition

- Document weight, height, BMI.
- Assess for adequate intake of calories, fluids, calcium and vitamin D.

- **Poor weight gain[6,7]:** Unexplained fatigue and irritability may be additional signs that dietary requirements are not being met. Consider introduction of calorie-dense foods (oils, syrups, avocado) and GI/Nutrition consults. May need gastrostomy to supplement caloric intake and maintain growth. Counsel families that use of a gastrostomy does not preclude oral feeding provided oral route is determined safe. Use CDC/WHO growth charts to track growth and try to keep BMI at a healthy percentile on growth curve.
- **Calcium/Vitamin D[8]:** Ensure recommended Vitamin D intake: 400-1000 IU daily. Target serum levels of 25-OH-Vitamin D 30-40 ng/ml. Ensure age-related recommended calcium intake: two to four servings daily of milk and dairy products. Calcium is absorbed best from food sources.

Gastroenterology[9]

- Document feeding methods and length of feeding time.
- Screen for chewing/swallowing problems, GE reflux/vomiting, and constipation. Refer to Gastroenterology for management if needed.

- **Prolonged feeding times:** Long feeding times (>30 min) increase risk for aspiration and exacerbate daytime fatigue significantly detracting from quality of life for patient and family; prolonged feeding times in conjunction with poor weight gain may be an indication that a gastrostomy tube is needed.
- **Chewing/swallowing difficulties:** Referral to Speech or Occupational Therapist or GI consult to assess, especially if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). Swallow study is necessary to assess safety if there is history of choking/gagging during meals. In some cases, thickeners for liquids may be helpful to prevent aspiration and reduce the need for a gastrostomy tube.
- **Constipation:** This is a very common problem that may contribute to irritability; osmotic laxatives (Miralax, Lactulose, Milk of Magnesia, glycerin) and stimulant laxatives (senna, bisacodyl) are often a part of long-term treatment with a goal of one soft BM per day or every other day.
- **Reflux:** This is a very common problem, especially in the younger child. It presents with irritability following meals, neck arching, wet burping and overt regurgitation/emesis. Reflux is often made worse by concomitant delayed stomach emptying and air-swallowing; PPI or H2 –acid blocker therapies are used empirically. Referral to GI may be necessary to formally diagnosis and exclude complications such as ulcers and strictures.
- **Dysmotility:** In addition to constipation and reflux, GI dysmotility in Rett Syndrome can also result in gallbladder dysfunction and volvulus. These are uncommon but very important causes of abdominal pain and discomfort that should not be overlooked. In adolescents and young adults, when severe abdominal pain is suspected and associated with meals then gallbladder dysfunction needs to considered. This is best assessed by abdominal ultrasound and/or HIDA scan. Liver function panel is relatively insensitive for detecting gallbladder dysfunction in Rett Syndrome[10]. The need for cholecystectomy is relatively uncommon. Sudden onset of severe abdominal pain accompanied by increased abdominal distention may be caused by twisting of the gastrointestinal tract (volvulus) which requires immediate medical attention.

Respiratory

- Screen for awake disordered breathing (hyperventilating or breath-holding), color change, or air swallowing.
- Screen for sleep disorder breathing (snoring, breathing pauses while asleep)

- Screen for awake disordered breathing which most often manifests as frequent hyperventilation and breath-holding (sometimes associated with cyanosis). These behaviors are episodic and may be worse with anxiety. Irregular breathing may disrupt feeding and result in air swallowing which can exacerbate GI symptoms but is otherwise not considered harmful. There is limited data on optimal management of the irregular breathing with anecdotal reports indicating inconsistent response to medications.
- Screen for snoring and pauses in breathing while asleep and if present, consider ordering a comprehensive sleep study or referral to Sleep medicine for further evaluation.
- Consider referring to Pulmonology for evaluation if any of the following circumstances are present11:
  - History of frequent respiratory infections
  - Observation of persistent hypoxemia (spO2 <95%), nocturnal hypoventilation (CO2 > 50mm for > 25% of total sleep time), or sleep-disordered breathing on sleep study
  - Prior to consideration for scoliosis surgery

Neurology

DEVELOPMENT
- Documentation of baseline, gains and losses of milestones.
- Fine motor (hand use): reaching, raking grasp, pincer grasp, holding objects, using cup.
- Gross motor: sitting, standing, walking.
- Language: coo, babble, words, phrases

NEUROLOGY
- Screen for presence of seizures and spells suspicious for seizures. Encourage caregivers to maintain a seizure log with detailed description, frequency and duration of seizures/spells. Refer to Neurology if a new type of spell occurs repeatedly.
- Document weight. If weight changes by more than 10-20%, encourage family to contact Neurology and inquire whether antiseizure medication dose changes are needed
- Screen for abnormal movements (e.g. tremor, myoclonus, chorea and dystonia) and document level of impact on daily activities. Refer to Neurology for management if abnormal movement is impeding activities.
- Document whether patient is receiving any FDA approved treatments for Rett Syndrome.

- **Developmental Milestones[12]:** Developmental regression (reduced hand use, gross motor skills and language) typically stops between 2-3 years of age. Skills can be maintained and possibly regained with vigorous therapies.
- **Seizures and Spells:** Refer to Neurology for seizures and spells suspicious for seizures. Neurology follow-up at least every 6 months if treated with an anticonvulsant. For those with difficult to control seizures, neurology follow-up more often than 6 months may be needed. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Patients can have multiple types of seizures although some, such as infantile spasms and absence seizures are rare[13,14]. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order video EEG monitoring to accurately characterize whether a type of event is a seizure or not. Video EEG monitoring is typically only helpful if the frequency of the spells would reasonably predict that they would be captured during the planned recording interval. There are no specific treatments for seizures that have greater efficacy in Rett Syndrome compared to other etiologies of epilepsy. Selection of anti-seizure medications should focus on the

potential side effect profile within the overall Rett symptom burden. For example, some anti-seizure medications may worsen common existing comorbidities in Rett Syndrome (e.g. clobazam might worsen drooling, urinary retention, constipation, and muscle tone) while others may have added benefits such as lamotrigine for improving mood and the use of carbonic anhydrase inhibitors such as topiramate and zonisamide to reduce breath holding.

- **Abnormal movements**: Stereotyped, repetitive hand movements (hand-wringing, mouthing, tapping, etc) are seen in all people with Rett Syndrome[15]. These often disrupt purposeful hand use. No medication treatments are available for hand stereotypies, but use of elbow splints or hand guards can help constrain repetitive movements and may improve purposeful hand use. Ataxic gait and impaired spatial awareness (proprioception) are very common. Regular occupational and physical therapy are important for maintaining range of motion and preventing further loss of function. Initially, most patients have low muscle tone that progresses over many years to high muscle tone, rigidity, and dystonia. Neurology or Physiatry may manage high muscle tone using botox injections or other medications to help maintain function and prevent contractures. Additional types of abnormal, involuntary movements that may occur are tremors, chorea, myoclonus and ocular dystonia. When frequent, these involuntary movements can further limit function and may require symptomatic management by Neurology.
- **Rett specific treatments:** Based on the results of a Phase 3 randomized controlled trial16, trofinetide was FDA approved in March 2023 for global symptom management in patients with Rett Syndrome over the age of 2 years. Patients with Rett Syndrome demonstrated statistically significant improvement on the Rett Syndrome Behavior Questionnaire (RSBQ) and the Clinical Global Impression – Improvement (CGI-I) score. Patients starting on trofinetide should be made aware of the very common gastrointestinal side effects and a management plan preemptively instituted.

Cardiovascular

- Check QTc interval with EKG; if abnormal, refer to Cardiology.

- **Abnormal EKG:** Yearly EKG to check for prolonged QTc interval which can develop at any time and may be more likely in patients with severe breathing irregularity[17]. Referral to Cardiology for further evaluation if the EKG is abnormal. Medications that can prolong QTc interval (e.g. certain antidepressants and mood stabilizers) should be used with caution in patients with documented QTc prolongation following input from Cardiology. A current EKG is recommended before anesthesia.

Skin

- Screen for skin breakdown from hand-mouthing or ill-fitting braces.
- Screen for pressure ulcers.

- Breakdown from mouthing or equipment or lack of re-positioning: Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe elbow splints or protective gloves to prevent skin breakdown from mouthing. Decubitus ulcers in non-ambulatory patients need referral to Plastic surgery/wound specialist for management and Physiatry to facilitate equipment modifications that prevent recurrence.

Orthopedics/Rehabilitation

- Assess spinal curve/back asymmetry on physical exam. Obtain spine x-ray if curve seen on exam. If Cobb angle >20 degrees, consider Orthopedic surgery referral.
- Starting at age 4 years screen for abnormal hip range of motion (limited abduction) and leg length discrepancy. Hip X-ray or referral to Orthopedic surgery if found.
- Screen for contractures and use or need of devices to prevent them (AFOs and splints)
- Discuss risk of fractures due to osteopenia and factors that increase risk
- Screen for mobility needs and use of mobility aids

- **Scoliosis:** Increased risk of neuromuscular scoliosis after age 6 years[18]; The greatest risk is in non-ambulatory patients. If asymmetry is seen on exam, an X-ray of the spine should be ordered to determine Cobb angle. If Cobb angle is greater than 20 degrees, consider Orthopedic referral. Surgical correction may be indicated when the Cobb angle is greater than 40 degrees[19,20].
- **Increased risk of hip subluxation[21]:** Examine hip range of motion due to the high risk for hip subluxation and contractures, especially in non-ambulatory patients. Either may be a source of pain and cause irritability. AP X-Rays of the pelvis may be needed to evaluate femoral head position. Consider Orthopedic referral if femoral head dislocation or migration is seen.
- **Prevent contractures:** Encourage families and caregivers to inspect all joints and practice daily range of motion exercises, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT[22] and Physiatry consults for bracing and splinting. Consider Neurology or Physiatry consult for Botox or other medications to alleviate hypertonia.
- **Osteopenia and fractures[23]:** Higher risk of fracture due to immobility and use of medications that increase osteopenia risk including certain anticonvulsants, proton pump inhibitors, and menses management medications. The greatest risk for fractures is in the long bones, especially the femur. In addition to routine screening of calcium, vitamin D intake, and 25-OH-vitamin D levels, consider Dexascan for immobile patients and referral to Endocrine for osteopenia management. Inquire about and institute appropriate safeguards for preventable causes of fracture beyond osteopenia such as falls from bed, bed rail entrapment, tripping over physical obstructions at home, or non-accidental trauma.
- **Equipment:** Risks of injury due to outgrown equipment (See SKIN above). Caregivers may need lifts, shower accommodations, bed-side toilets, etc. Consider Physiatry referral for formal assessment of equipment needs.

Endocrinology/Gynecology

- **Menarche:** Menarche occurs at usual time. Periods may be irregular due to low body weight or stress though thyroid dysfunction needs to be excluded as a cause. Menses suppression can be considered[24,25], especially if it disrupts the interactions with family or if menses is associated with increased seizure activity. The full impact of menses suppression on bone and circulatory health should be reviewed with family; an IUD is a consideration. Well-woman examination should include breast exam. In patients with epilepsy, counsel family to document increases in seizure frequency corresponding to menses (catamenial seizures) and discuss with Neurology. Carbonic anhydrase inhibitors are sometimes prescribed to treat catamenial seizures.
- **Premature adrenarche:** Despite normal timing of menarche, breast buds and pubic hair may begin earlier than in typically developing children[26].

Urology

- **Urine retention/Urinary tract infections:** Autonomic dysfunction and constipation can both cause incomplete bladder emptying and urine retention increasing the risk for urinary tract infections. Consider urinalysis/urine culture when there is unexplained agitation or fever unrelated to a respiratory illness. Recurrent urinary tract infections or persistent bladder distention (not voiding for > 8-10 h/day for > 1 day/week) require referral to Urology for further evaluation and management to prevent kidney damage. Screen for use of the antiseizure medication clobazam which can cause urine retention as a side effect.

- **Kidney stones:** Suboptimal hydration and use of carbonic anhydrase inhibitors (including acetazolamide, topiramate and zonisamide) are potential risk factors for kidney stones. Kidney stones are an important source of pain that should be considered when determining causes of pain/increased agitation. Referral to Urology is indicated if a kidney stone is identified.

Psychiatric/Behavioral

- Screen for symptoms of anxiety and depression such as social withdrawal, screaming and irritability.
- Screen for sensory processing difficulties.

- **Mood Disorders:** Anxiety may manifest as increased nervousness/irritability or tremor in social settings, social withdrawal, or difficulty with parental separation[27]. Consider anxiolytic medication if these symptoms are excessive (>30 minutes) and chronically (>15 days per months) interfering with activities. Frequent periods of unprovoked inconsolable crying are common and could be a sign of an underlying depression. Consider treatment with SSRI medications such as escitalopram, sertraline or fluoxetine. Benzodiazepines such as clonazepam or diazepam can be used as needed for acute periods of anxiety related to procedures, travel or outings.

- **Irritability from non-psychiatric causes:** Screen for non-psychiatric causes of irritability including GI disorders (constipation, reflux, gallbladder disease), dental issues (cavity, tooth eruption), orthopedic disorders (fractures, dislocations) and/or sleep disturbance. Insufficient caloric intake is another frequently overlooked cause of irritability that needs to be considered. Treatable medical causes of irritability need to be excluded and managed accordingly before attributing to a mood disorder. Importantly, frustration from inability to communicate wants/needs is another contributor to irritability that should be addressed with early initiation of speech therapy emphasizing both low-tech and high-tech communication aids.

- **Abnormal attention and sensory processing:** Auditory/language processing is delayed and may be misinterpreted as disinterest, attention deficit, or lack of ability; allow for this delay when assessing non-verbal language by providing additional time for responding to questions or commands.

Sleep

- Screen for disrupted sleep by inquiring about bedtime, time required to fall asleep, time of awakening, and nocturnal awakenings. Inquire about sleep environment.
- Screen for symptoms of sleep disorders. Ask about snoring, respiratory pauses, nighttime gasping, restless sleep, and paroxysmal behaviors out of sleep.
- Referral to Sleep Medicine or Neurology when appropriate.

- **Sleep dysregulation:** Disrupted sleep is very common including inability to fall asleep as well as frequent awakenings throughout the night[28]. While primary insomnia is a common cause, disrupted sleep can also be a consequence of other sleep disorders such as sleep disordered breathing, sleep-related movement disorders, parasomnias, or nocturnal seizures. It is important to screen for symptoms of these disorders (inquire about snoring, respiratory pauses, nighttime gasping, restless sleep, and paroxysmal behaviors out of sleep) which will require further assessment/management by Sleep Medicine or Neurology[29-32]. Consider obtaining labs to assess for iron deficiency if family endorses restless movements during sleep: ferritin, serum iron, TIBC, and transferrin saturation (fasting labs preferred).
- **Primary insomnia:** Good sleep hygiene (which includes consistent bedtime routine and timing as well as achieving an appropriate level of comfort and safety in the sleeping environment) is critical for optimal sleep health in Rett Syndrome. Behavioral interventions are often overlooked but can be quite effective[33,34]. Given the significant sleep problems those with Rett Syndrome may experience, the use of medications to treat these may be appropriate. No medications for the treatment of insomnia in children are currently approved by the US Food and Drug Administration (FDA), and the literature on their efficacy is limited. Melatonin has been used effectively to improve sleep efficiency and sleep latency in certain people with Rett Syndrome[35,36], but studies on other agents are lacking. Further study is needed to better determine medication efficacy and dosing in those with Rett Syndrome. Medications such as guanfacine, clonidine, gabapentin and trazodone can be considered[37]. Carefully consider the nature of the sleep disturbance when selecting a medication, as certain agents are better suited to address issues of sleep onset, sleep maintenance, sleep consolidation, or sleep phase[38].

Pain

- Discuss potentially higher pain threshold and atypical response to pain in Rett Syndrome.
- Document patient's response to common sources of pain (i.e. bumping head, stubbing toe, etc.).

- **Pain assessment and sensitivity:** Pain is common in Rett Syndrome. Many individuals have an atypical response to pain including a delayed response, decreased response, or occasionally an increased response[39-41]. Common subtle responses to pain include wrinkling the forehead, wide eyes, grinding or gnashing teeth, sudden increase in vocalization, crying, screaming, tremors, rocking, tension in the upper limbs, and increased movement/kicking of the lower limbs[42].
- **Increased risk of acute and chronic pain:** When pain is suspected, important to correlate pain symptoms with specific activities such as meals, changes in stooling pattern, positioning, and trauma to uncover potential sources of pain. A thorough physical exam should be performed with heighted attention to GI and musculoskeletal problems. Commonly identified sources of pain/discomfort in Rett Syndrome include gastrointestinal (constipation, reflux, abdominal distension due air swallowing, gall stones, hunger); dental problems (bruxism, TMJ pain, dental carries); skin (breakdown from mouthing/rubbing stereotypies or pressure sores); musculoskeletal problems (fractures, hip subluxation, painful spasticity, dystonia, contractures); gynecology (dysmenorrhea); renal (urinary tract infections, kidney stones)[42].

Screenings

- Laboratory evaluations: CBC, chemistry panel, 25-OH-vitamin D (yearly), baseline lipid screen (fasting if possible), UA (every 2 years).
- Referral to an Ophthalmologist for vision screening that includes acuity, ocular alignment, visual fields, and cortical visual impairment.
- Audiology ABR at birth. Referral to ENT for further assessment if chronic otitis media.
- Annual dental health screening.

- **Screening - Ophthalmology:** Difficult vision assessment: Since eye gaze is expected to be the primary means of communicating, thorough assessment and optimization of vision is essential. Given that cortical visual impairment[43] (CVI) is emerging as a recognized comorbidity in Rett Syndrome, important to refer to an Ophthalmologist familiar with developmental disabilities and CVI.
- **Screening - Auditory:** Auditory processing delay is typically present. Refer to ENT for chronic otitis media.
- **Screening - Dental:** Teeth grinding, increased risk of caries: The most common oral finding in Rett Syndrome is teeth grinding (bruxism) that can potentially lead to non-physiologic tooth wear and hypertrophy of the masseter muscles. Other oral manifestations of Rett Syndrome include high arch palate, mouth breathing, tongue thrusting, and digit/thumb sucking leading to anterior open bite[44]. Routine cleanings are needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at a major medical institution. Regular preventive dental care is important to avoid the need for tooth extraction which can significantly interfere with oral function.

Education/Therapies

- Review for presence of current IEP and goals addressing academics, including literacy, communication, mobility, and socialization, as well as 504 accommodations for neurosensory regulation and apraxia. (See info on RettSyndrome.org)
- Document current therapies (type and frequency).

- **Educational Needs:** Educators often do not have experience with Rett Syndrome. The school environment needs to provide opportunities for developing a student's communication ability, academic learning, literacy, mobility, socialization with adults and neurotypical peers, and the building of friendships, beginning in preschool onwards. An understanding of and attention to apraxia and the importance of supporting neurosensory regulation is essential to promoting learning and progress across all areas as outlined in "Rett Syndrome Communication Guidelines: a handbook for therapists, educators, and families"[45]. Inclusion in the classroom and school community is more than occupying the physical space and should focus on active engagement and participation in the same learning and social activities as provided to classmates. In accordance with Free Appropriate Public Education (FAPE) rules, families should insist that literacy instruction be included in the IEP based on research-based practices. FAPE is an educational right of children with disabilities in the United States that is guaranteed by the Rehabilitation Act of 1973 and the Individuals with Disabilities Education Act (IDEA). The US Supreme Court has determined that services must be provided that will allow children to learn and make progress. The book, "Comprehensive Literacy for All: Teaching Students with Significant Disabilities to Read and Write" is a useful resource for families and educators.
- **Therapy Needs:** Therapists need to be informed that the approach to therapy in Rett Syndrome is different compared to children with nonspecific developmental delays. The focus in Rett Syndrome is about maintaining and optimizing the skills that are present. Attainment of new skills should not be a requirement to continue in therapy. Therapies routinely employed in Rett Syndrome include speech therapy involving augmentative and alternative communication (AAC) training, feeding therapy, physical therapy[22], occupational therapy, vision therapy, therapeutic horseback riding (hippotherapy) and swim/aqua therapy[46]. Additionally, if CVI is diagnosed, then

involvement of a Teacher of the Visually Impaired (TVI) along with orientation and mobility services will also be required at school. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potential. Families should work with schools to develop an IEP that recognizes and addresses all educational and therapy needs; referral to a Rett Specialist may provide additional assistance in this regard.

Communication

- Screen communication methods used by family and school: eye pointing, vocalizations, augmentative communication system (switches, iPad, eye-gaze device).

- **Communication:** Refer for augmentative and alternative communication (AAC) assessment at time of diagnosis. Verbal speech is unlikely to develop so all modalities of communication should be explored (eye gaze, body language, vocalizations, AAC device) as part of a comprehensive treatment plan. The Rett Syndrome Communication Guidelines (IRSF, 2020) should be recommended to all families. A referral to an AAC specialist is recommended as many speech pathologists do not have specialized experience with AAC. Eye gaze is the preferred modality of communication for individuals with Rett Syndrome as it is least likely to be affected by apraxia. A communication system should be established as early as possible with both low-tech (i.e. Yes/No choice board, BIGmack switch, PECS board, etc), and high-tech (i.e. iPad, eye-gaze tracking AAC) interfaces. Age is not a barrier for development of communication so a referral should be made regardless of age if someone does not have an effective communication system. Ideally, identical AAC systems should be used both at home and school to reinforce its role as the primary means of communication. If an electronic communication system is used, a back-up non-electronic system should always be available in the event of technology failure. Families should own their own system that can be used in all settings, including home, school, and the community; however, ideally, a second system can be kept at school to avoid needing to transport back and forth[45].

Family/Social Concerns and Community Resources

DEVELOPMENT
- Assess for sources of family stress (financial, social, care fatigue).
- Discuss long term care plans and counsel on the importance of documenting plans in a will and establishing a legal trust/estate.
- Introduce the concept of palliative care. Consider referral to Palliative care service for patients with high medical complexity.
- Discuss end-of-life care concerns including DNR, advance care directives and goal setting with family.

COMMUNITY RESOURCES
- Review available social support resources including disability parking permit, respite care, legal assistance for people with disabilities, etc.
- Review community options for long term care in adult patients with aging caregivers.

- **Increased family stress:** This arises from many sources including financial, family/social interactions, and care fatigue. Parents and caregivers may need respite care and should be encouraged to take breaks from solely providing medical care. Social work referral should be considered to identify respite care options, address financial needs, help apply for Medicaid and/or waivers to support respite care or home nursing and needed supplies at home. Sibling stress can be significant and coping can be a challenge[47]. Consider referral to a Family counselor to help siblings with their adjustment to the diagnosis. Older siblings of childbearing age may have concerns about recurrence in their own children. When appropriate, consider referral to a Genetic counselor to review the genetics of Rett Syndrome and heritability. Parents should be encouraged to engage with patient advocacy groups for additional social support and use online resources (i.e. rettsyndrome.org) to provide education for extended family and friends that want to learn more about the disorder.

- **Discussions of palliative care:** Providers should introduce the concept of palliative care early as an additional means of providing ongoing symptomatic care with emphasis on improving quality of life for the patient and family rather than solely for end-of-life care[48]. Consider referral to Palliative care service for patients with high medical complexity to help facilitate care coordination. Palliative care referral should also be considered when there are questions among the clinical providers, family and caregivers about overall goals of care. Advance care directives and DNR orders can be set up and changed at any point of care as patient condition changes to align with the family's goals.
- **Guardianship:** Families of adolescents with Rett Syndrome should be encouraged to investigate as soon as possible the guardianship rules relevant to their state/governing entity. Establishing guardianship is necessary to continue to provide care to children after they reach the age of majority. Caregivers should be referred to a Social worker to explore options in their state. There are many options including shared guardianship that can also be considered.
- **Care outside the home and care options for aging caregivers:** These difficult discussions are important to have early in order to help parents and families coordinate future care needs that best serve the individual with Rett Syndrome[49-51].
- **Wills/estates/trusts:** Families should begin to look into this regardless of their financial means as soon as possible.

Hospitalization Concerns

- **Anesthesia sensitivity, osteopenia, and motor impairment:** Patients with Rett Syndrome may need lower doses of anesthetics or analgesics. Patients may take longer to awaken from anesthesia. It is important to ensure all caretakers are aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of prolonged QTc; a recent EKG is essential. Hospital needs to be aware of fracture risks associated with osteopenia in patients with Rett Syndrome who will require careful support for many motor actions due to their lack of hand use, inability to change position and increased fall risk. Range of motion exercises to prevent contractures should be performed daily.

Alternative Medications

As management of Rett Syndrome remains primarily symptom directed at this time, families are often interested in learning more about or may have already started alternative, non-medicinal treatments to manage symptoms with the hope of improving quality of life[52]. Caregivers may be reluctant to share this interest with healthcare providers due to social stigma. Because alternative medicines can have side effects as well as interactions with prescription medicines, clinicians should proactively inquire about their usage and encourage transparency. Similar to prescription treatments, counseling on alternative medicines should cover known or possible side effects as well as potential benefits. Additionally, clinicians should encourage the caregiver to consider specific goals or expectations for a treatment along with a reasonable timeframe for assessing effectiveness. This thoughtful approach permits a more objective determination of response to treatment and minimizes the chances that an ineffective treatment will be continued unnecessarily which adds to the medication burden and potentially be detrimental to quality of life[53].

Males with MECP2 Mutations

- Adhere to guidelines for Rett Syndrome in patients with neonatal encephalopathy and Male Rett Encephalopathy.
- Patients with the milder phenotype of intellectual disability without regression are expected to have less complex medical needs.

- **Male patients:** Pathogenic *MECP2* mutations in males were once expected to primarily cause in utero or early postnatal demise. More recently, however, in large part due to more frequent use of gene sequencing panels for diagnosis, a growing number of male children with developmental disabilities are found to have *MECP2* mutations[54]. In fact, males with *MECP2* mutations may account for up to 3-5% of all patients meeting Rett Syndrome criteria55. However, the presentation in male children is very heterogeneous and more often will not meet typical Rett Syndrome criteria. The spectrum of presentation in males with *MECP2* mutations loosely falls into three categories: 1) those with a severe neonatal encephalopathy (and early death), 2) patients meeting typical Rett Syndrome clinical criteria though usually with worse symptom severity (termed "Male Rett Encephalopathy"), and 3) males with developmental delays/intellectual disability without regression[56]. Similar to females with Rett Syndrome males with *MECP2* mutations have complex medical needs and high healthcare utilization[55].

Epilepsy, dystonia, abnormal regulation of breathing, swallowing dysfunction, GI concerns and sleep disturbances are the most frequent comorbidities identified in males and should receive attention in their care. However, the same general guidelines for behavior, orthopedic concerns, nutritional health, education, habilitative therapies, and equipment considerations also apply as for females with Rett Syndrome.

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Resources for Families and Caregivers

International Rett Syndrome Foundation (IRSF) Website

rettsyndrome.org

A website dedicated to empowering families with the latest medical information, offering meaningful support and resources, and advocating for all those living with Rett syndrome.

My Rett Ally

rettsyndrome.org/myrettally

A web application specifically designed for Rett syndrome patients and families to simplify and enhance care coordination.

Rett Research Ready

rettsyndrome.org/rett-research-ready

A website to learn about the research and clinical trial process and search the latest Rett syndrome research opportunities.

Rett Syndrome Communication Guidelines

rettsyndrome.org/communication-guidelines

Guidelines that include the best information and strategies to facilitate your child's communication.

Transition of Care Toolkit

rettsyndrome.org/toctoolkit

A toolkit to empower parents and guide healthcare providers through the conversations necessary to transition a loved one to adult medical care.

RettEd Video Library

youtube.com/@IRSFoundation

A video library that features expert speakers on various Rett-related research and care topics.

International
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