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Consensus guidelines on managing Rett syndrome across the lifespan

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ABSTRACT

Background Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical comorbidities extending beyond the nervous system requiring the attention of health professionals. There is no peer-reviewed, consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods Informed by the literature and using a modified Delphi approach, a consensus process was used to develop guidance for care in RTT by health professionals.

Results Typical RTT presents early in childhood in a clinically recognisable fashion. Multisystem comorbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist health professionals and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions The overall multisystem issues of RTT require primary care providers and other health professionals to manage complex medical comorbidities within the context of the whole individual and family. Given the median life expectancy well into the sixth decade, guidance is provided to health professionals to achieve current best possible outcomes for these special-needs individuals.

What is known about the subject?

- Rett syndrome (RTT) is a multisystem and rare genetic disorder with similarities to other developmental encephalopathies.
- There is no peer-reviewed, consensus-based therapeutic guidance to care in RTT.

What this study adds?

- Primary care providers and other health professionals caring for patients with RTT frequently have limited first-hand experience managing the disorder due to its rare prevalence.
- A consensus on guidance for health professionals caring for patients with RTT was developed based on literature review and expert opinion.
- This guidance is applicable to other rare and often severe neurodevelopmental disorders.

INTRODUCTION

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of 1 in 20 000–40 000 people. RTT is one of the most common genetic causes of developmental and intellectual impairment in girls,[2] affecting up to 1 in 10 000 girls under the age of 12. RTT is not a neurodegenerative condition,[3] rather it is a progressive disorder involving multisystem symptom evolution over time. Following demonstration of symptom reversal in mouse models,[4 5] there is flourishing hope for further disease-modifying therapies.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X chromosome.[6] This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment.[7] Complete genetic testing involves sequencing and methods to detect larger deletions (eg, multiplex ligation-dependent probe amplification) of the *MECP2* gene. Likely owing to the random nature of X chromosome inactivation[8] and other genetic modifiers,[9–11] genotype–phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X and R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared with other mutation groups (R133C, R294X, R306X and C-terminal truncations).[12] *MECP2* mutations causing RTT are almost always de novo (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first 2 years of life, involving developmental delays and hypotonia on examination, but

Box 1 Classic (or typical) and atypical Rett syndrome (RTT) diagnostic criteria[1]

Classic or typical RTT diagnostic criteria.
A period of regression followed by recovery or stabilisation.
- Partial or complete loss of acquired purposeful hand skills.
- Partial or complete loss of spoken language.
- Gait abnormalities: impaired or absence of ability.
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms.

Atypical RTT diagnostic criteria.
A period of regression followed by recovery or stabilisation.
- At least two of the four main criteria.
- Five of eleven supportive criteria.
  - Breathing disturbances while awake.
  - Bruxism while awake.
  - Impaired sleep.
  - Abnormal muscle tone.
  - Peripheral vasomotor disturbances.
  - Scoliosis/kyphosis.
  - Growth retardation.
  - Small cold hands and feet.
  - Inappropriate laughing/screaming spells.
  - Diminished response to pain.
  - Intense eye communication: 'eye pointing'.

subsequent symptom evolution between 18 and 30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking.[13] The core clinical diagnostic features of RTT (Box 1, typical and atypical)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies, causing lifelong dependence.[14 15] The average age at RTT diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing.[16] The multisystem nature of the disorder has been documented within multiple observational studies, with symptom risk evolving across the lifespan.

MECP2 mutations have been identified rarely in boys with neurodevelopmental disorders, termed 'male RTT encephalopathy'. The resulting developmental outcome is quite variable, although with symptomatology distinct from RTT, and ranges in severity from a severe neonatal encephalopathy with minimal developmental improvement to a mild intellectual disability.[17] Male RTT encephalopathy[18] and other distinct developmental encephalopathies (historically linked to RTT)[19] such as *MECP2* duplication syndrome,[20–22] *CDKL5* deficiency disorder[23–26] and *FOXG1* syndrome[27–30] may have similar approaches (but distinct therapeutics) as more is learnt about specific aspects of their clinical care. Alterations in *MECP2*, *CDKL5* and *FOXG1* should be considered in all individuals, male and female, with developmental delays and intellectual disability.

In the past two decades the natural history of RTT has been extensively studied.[31] Perhaps most important to all health professionals managing this complex disorder is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age.[14 32] As such, health professionals are often presented with the daunting task of effectively managing the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding RTT symptomatology that identified the most relevant primary care concerns through a modified Delphi consensus approach, we developed recommendations regarding guidance for best practice. These recommendations have been organised based on an age-dependent health supervision approach to facilitate the goal of effective and meaningful care for individuals with RTT across all ages.

METHODS

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation-sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 and September 2018 with input obtained from 22 clinical sites. An initial draft was presented in January 2017 for external review by the network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett centres (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the National Institutes of Health-funded Natural History Study of Rett and Related Disorders (NHS, U54 HD061222; ClinicalTrials.gov: NCT00299312/NCT02738281) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously.[33] The partners were chosen based on clinical experience across primary care, multiple subspecialties, healthcare delivery, and importantly patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the group. A consensus led by the group leader surrounding relevant guidance based on published data and clinical opinion was developed through six further rounds of modifications. The results of a literature review were used to inform the guidance (C. Fu et al., BMJ Paediatrics Open, 2020, in press). The recommendations were created based on an age-dependent health supervision approach to assist health professionals in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages

(tables 1 and 2). Items are organised by prevalence at each age group. Consistent with the International Classification of Functioning, Disability and Health guidelines (WHO 2001),[34] this guidance recognises the interrelatedness of body function/structure, environment and personal factors to maximise activities and participation (online supplementary table 1). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental and educational concerns need to be assessed frequently to achieve the goal of family-centred service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impact.[35 36]
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programmes for which the individual may be eligible.
- Government-sponsored income and other support benefits.
- Personal financial, community and emotional support available to the family.

Patient and public involvement

Patient family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (PN and MC), were involved in the development of the patient care guidance and writing of this manuscript. Their organisations will assist with dissemination of the guidance.

RESULTS

The guidance was formulated into a checklist (table 1) with further details and references (tables 2–6) that informed the checklist and the consensus process. The guidance for management by health professionals was grouped by relevant features and therapeutic approaches at different ages. The checklist (table 1) is suitable for use by health professionals as well as the family as part of their healthcare records, with tables 2–6 providing further detailed guidance.

Diagnosis to 5 years old: early childhood

Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[37–39] begin during this age. Additional treatable gastrointestinal issues, including dysmotility, gastro-oesophageal reflux, constipation and gas bloating, often presenting as irritability or apparent discomfort, manifest commonly at this age.[37 40] The development of microcephaly or head growth stagnation (as early as 1.5 months)[39] is a common feature, although macrocephaly has also been seen.[41] Tone issues at this age are typically characterised by hypotonia[42]; early referral to therapists (physical, occupational, speech language including augmentative communication[43]) and establishment of an individualised education programme[44] are necessary. Severe hearing loss is uncommon in RTT,[45] but there may be delayed auditory processing[46 47] that mimics hearing impairment. There is increased risk of cortical visual impairment and ocular apraxia in RTT.[48] There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[49–51] and may develop with time.[52] The frequency of epileptic and non-epileptic spells[53 54] waxes and wanes throughout the course.[53 55] Individuals with RTT generally respond to anticonvulsants,[53 55 56] but there have been no randomised controlled trials of specific anticonvulsants for RTT. If hospitalised, it is important to inform hospital staff of important issues in individuals with RTT that could potentially confound or complicate care. These include a heightened sensitivity to the effects of anaesthetics, potentially requiring lower doses of anaesthetic medications to achieve sedation,[57 58] or longer time to awaken from general anaesthesia.[59] Although response to pain is altered in RTT,[60] the approach to analgesia should not be altered. Hospital staff should also be aware of cold extremities,[61] irregular and disordered breathing with oxygen desaturations,[62 63] impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the prepubescent stage: late childhood

During the early school years, children with RTT typically have stabilised developmentally; the regression phase has ended.[39] Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and maintaining a healthy body mass index are important, as these have been associated with better functioning.[38 64] Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity.[65] Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche.[66] Difficulties with abnormal tone in this age range typically are characterised by hypotonia evolving to rigidity.[67 68]

Postpuberty to the end of school (~21 years old): postpuberty

Surveillance for scoliosis continues to be an important preventive measure, although this lessens with completion of puberty.[66] Surveillance for urinary retention is important.[69 70] Biliary tract disease is seen in young adulthood at rates similar to the general population, but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting.[71 72] Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood.[73] Longitudinal supervision is required in RTT as physical, behavioural and cognitive limitations will not allow for independent living.[14 15] This may include day programmes and respite care.

Table 1 Health supervision guidance as a checklist for individuals and primary care providers (PCP)

- **Individuals with Rett syndrome should be seen for regular wellness check-ups, screenings and immunisations (especially influenza vaccinations)*.**
- **Inform staff that extra time will be needed for visit, especially for inspecting the individual without braces, shoes and outer clothing.**
- **Parents and caregivers should keep a binder of health records to include genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, X-ray reports and other imaging results.**

Areas of assessment	Assessment details	Yearly wellness visit	Primary care every 6 months*	Baseline
Genetics/*MECP2* testing results	Counsel family on genetic test results and refer to genetic counsellor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			√
General	Update current medications and allergies.	At every visit		
	Weight.	At every visit		
	Height or body length. Body mass index.	At very visit At every visit		
	Head circumference†.	At every visit		
	Tanner stage.	At yearly wellness		
	Laboratory evaluations (see below).	See below		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	√	√	
	Screen for gastro-oesophageal reflux, gas bloating, biliary tract disease, constipation and haemorrhoids, skin tags, or fissures.	√	√	
Nutrition	Review nutritional and herbal supplements. Nutrition screening‡: energy, protein, fluids, sodium, potassium, calcium and vitamin D intake. Consider nutrition-related laboratory screening (yearly): complete blood count, electrolyte panel, 25-OH vitamin D, fasting lipids.	√	√	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, colour change) and air swallowing.	√		
Neurology	Screen for presence of paroxysmal events (seizures or non-epileptic spells suspicious for seizures). Advise caregivers to keep a log with description of distinct event types and frequency. Refer to neurology if an event occurs repeatedly for diagnostic clarification. Encourage follow-up with neurologist routinely; every 6 months if treated for seizures. If the individual's weight fluctuates (more than 10%–20%), request the neurologist to consider adjusting anticonvulsant doses accordingly. Laboratory follow-up as needed for use of antiseizure medications.	√	√	√
	Screen for abnormal movements (stereotypies and dystonia) and level of impact on daily activities.	√		√
Cardiology	12-lead ECG to screen for prolonged QTc interval; if abnormal, refer to cardiology.	√		√
Skin	Document temperature and colour of hands and feet. Screen for skin breakdown from hand mouthing or ill-fitting braces. Screen for pressure ulcers.	√	√	

Continued

Table 1 Continued

- **Individuals with Rett syndrome should be seen for regular wellness check-ups, screenings and immunisations (especially influenza vaccinations)***.
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- **Parents and caregivers should keep a binder of health records to include genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, X-ray reports and other imaging results**.

Areas of assessment	Assessment details	Yearly wellness visit	Primary care every 6 months*	Baseline
Orthopaedics rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to orthopaedics if >20°.	√	(if scoliosis present √)	
	Screen for abnormal hip abduction, range of motion and leg length.	√	√	
	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	√		
	Discuss risk of fractures due to osteopaenia.	√		
	Screen for needs and use of mobility aids.	√		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to urology for frequent urinary tract infections or urinary retention. Consider urology-related laboratory screening (every 2 years): urinalysis.	√		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing and walking. Language: coo, babble, laugh, words.	√		√
Communication	Screen communication methods used by family and school: eye pointing, vocalisations, switches, iPad, eye gaze device.	√		√
Behavioural	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Enquire about sensory processing difficulties.	√	√	√
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom. Consider laboratory evaluation for iron deficiency if concerns arise about disrupted sleep or restless leg syndrome: ferritin, serum iron, total iron binding capacity, transferrin.	√	√	√
Pain	Discuss delayed pain response and describe the individual's response to pain.	√		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	√		
Screenings	Screen for vision concerns and consider referral for formal vision assessment, including acuity, spatial, depth, visual fields and cortical visual impairment.	√		
	Review newborn ABR results at baseline, consider repeating ABR if history of chronic otitis media, consider evaluation for auditory processing delay.	√		√
	Annual dental health screening; refer for cleaning every 6 months.	√		

Continued

Table 1 Continued

- **Individuals with Rett syndrome should be seen for regular wellness check-ups, screenings and immunisations (especially influenza vaccinations)*.**
- **Inform staff that extra time will be needed for visit, especially for inspecting the individual without braces, shoes and outer clothing.**
- **Parents and caregivers should keep a binder of health records to include genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, X-ray reports and other imaging results.**

Areas of assessment	Assessment details	Yearly wellness visit	Primary care every 6 months*	Baseline
Education/therapies	Review for presence of current educational plan (see information on RettSyndrome.org). Documentation of therapies (type and frequency).	√		√
Family/social	Assess for family stress (financial, social, fatigue).	√	√	√
Resources	Review available community and insurance resources (disabled parking permit, respite care and so on). In adolescent individuals review plans for obtaining guardianship. Clinician may be required to write letters of medical necessity for equipment and sign school medication forms.	√		

*6-month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention.
†Please see Centers for Disease Control and Prevention or Nellhaus head circumference chart for age 0–18 years.
‡Please see Food and Drink Log (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, energy and fluid intake.
ABR, auditory brainstem response; IEP, individualised education programme.

21 years and older: adulthood

Overall, individuals with RTT tend to stabilise clinically in young adulthood.[74–76] Frequent causes of hospitalisation for women with RTT include pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation or refusal/inability to eat or drink.[15] While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake.[32] With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants raises the risks for osteoporosis and bone fractures,[77–79] necessitating continued supplementation and monitoring of 25-OH vitamin D status.[80 81] Musculoskeletal problems and gross motor function may worsen overall,[75] possibly due to more parkinsonian features,[67] but with overall preservation of intellect and memory[15]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features and high prevalence of social withdrawal behaviours lead to abnormal or decreased social interactions consistent with anxiety or depression.[82] Although the majority of women with RTT in the USA live at home,[14] in other countries only about one-third of women over age 16 with RTT live at home (either full time or part-time), with the majority living in a residential facility.[15] Long-term and individually tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration.[83]

DISCUSSION

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomised clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardised. While evaluation of annual ECG for prolonged QT appears supported by the literature,[49–52] the impact and outcomes of such surveillance need further study. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation, such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the lifespan of gynaecological concerns. Additional studies should also address the role and utility of palliative care and banking of postmortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older women with RTT and for those more severely affected who are not routinely captured in most studies.[76] Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics.[84] It is

Table 2 Detailed approaches to management and therapy for RTT: genetics, neurology, cardiology, respiratory and urology

System/area	Common concerns and questions	Details and suggested approach	References
Genetics	*MECP2* gene	For suspicion of RTT, *MECP2* gene sequencing and MLPA testing are recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counsellor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrolment in clinical trials. Referral to a Rett centre if feasible may be useful to provide multidisciplinary care and access to clinical trials.	16 85 86
Neurology	Seizures and spells	Refer to neurologist for seizures and spells suspicious for seizures, with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett spell and a seizure (both may be present). Individuals can have multiple types of seizures. 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 a video electroencephalogram (EEG) to accurately characterise whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	53–56
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand wringing, mouthing and so on) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	67 68 87 88
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (ie, fluoxetine). A current ECG is recommended before anaesthesia.	49–52
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	61 89 90
Respiratory	Hyperventilation, air swallowing, breath-holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for these. If night-time apnoeas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	62 63 91–93
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of urinary tract infections. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increased risk of kidney stones.	69 70 See: 94

References not specific to RTT noted as 'See'.
MLPA, multiplex ligation-dependent probe amplification; OT, occupational therapy; RTT, Rett syndrome.

therefore important for families, caregivers and health professionals to reach out to Rett centres and family support group resources to stay up-to-date on clinical trials, drug approvals and how this impacts this current care guidance. While a primary care provider may not be able to counsel on the suitability of different clinical trials,

Table 3 Detailed approaches to management and therapy for RTT: gastroenterology and nutrition

System/area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease or constipation; these can be empirically diagnosed and managed (see entries below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, and burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	37 38 40 72
	Constipation	*This is a very common problem*. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often part of long-term treatment with a goal of one soft bowel movement per day.	37 40
	Reflux	*This is a very common problem*. Proton pump inhibitor or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as oesophagitis, ulcer, strictures or Barrett's oesophagus.	37 40
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met; consider energy dense foods (oils, syrups, avocado), and gastroenterologist and nutrition consults. Gastrostomy button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	37–39 95 96
	Calcium/vitamin D	Ensure supplemental vitamin D intake: 600–1000 IU or more daily. Target serum levels of 25-OH-vitamin D greater than 30–40 ng/mL. Ensure milk and dairy products to provide age-appropriate dietary calcium intake: 1–3 years, 700 mg/day; 4–8 years, 1000 mg/day; 9–18 years, 1300 mg/days; 19 years and older, 1000 mg/day. 240 mL (8 oz) of milk or 240 mL (8 oz) of yoghurt contains 300 mg of calcium.	77–79See: 97
	Prolonged feeding times	Long feeding times (more than 30 min) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	64 96 See: 98
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration, or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	37 38

References not specific to RTT noted as 'See'.
BMI, body mass index; CDC, Centers for Disease Control and Prevention; RTT, Rett syndrome.

actively engaging individuals with RTT and their families and referring to clinical trials at specialty centres are necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate delivery of more thorough and well-rounded management and comprehensive surveillance by primary care providers and other health professionals caring for individuals with RTT. Importantly, the guidance also helps to outline considerations in which health professionals may want to refer the individual with RTT for more specialised management.

In conclusion, RTT is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the sixth decade of adulthood. Primary care providers and other health professionals tasked with coordinating care play an essential role in ensuring the long-term health and well-being of these individuals through effective screening practices, active management and thoughtful coordination of subspecialty requirements. The accumulating knowledge regarding the natural history of RTT

Table 4 Detailed approaches to management and therapy for RTT: orthopaedics, rehabilitation, skin, endocrine and hospitalisation

System/area	Common concerns and questions	Details and suggested approach	References
Orthopaedics, rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating reobservation every 6 months if present. Supine X-ray and orthopaedic referral when scoliotic curvature greater than 20°; correction may be indicated when greater than 40°. Kyphosis is more common in ambulatory individuals.	65 99–102
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray anterior-posterior views of pelvis may be needed to evaluate femoral head coverage.	103
	Contractures	Encourage families and caregivers to inspect all joints and practise daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalisation). Consider occupational therapy (OT) and physical therapy (PT) consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	104 105
	Osteopaenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider bone density (DEXA) scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH vitamin D levels). Cause for fractures beyond osteopaenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	77–81 95 97 106 107
	Equipment	There is risk of injury due to outgrown equipment (see 'Skin'). Family and caregivers may need lifts, shower accommodations, bedside toilets and so on; these needs may be best assessed by a physiatry referral.	See: 108
Skin	Breakdown from mouthing or equipment or lack of repositioning	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 refit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	105
Endocrinology, gynaecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4 and TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; intrauterine device is a consideration. Avoidance of Depo-Provera is a consideration. Well-woman examination should include breast examination.	66 109 See: 110
Hospitalisation	Anaesthesia sensitivity, impaired proprioception	Individuals may be more sensitive to effects of anaesthetics. They may take longer to awaken from anaesthesia. It is important to ensure anaesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities, and risk of presence of prolonged QTc; a recent ECG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalised, family or hospital should perform daily range of motion to prevent contractures.	49–51 57–59 62 63

References not specific to RTT noted as 'See'.
OT, occupational therapy; RTT, Rett syndrome.

Table 5 Detailed approaches to management and therapy for RTT: psychological, behavioural, sleep, pain and screenings

System/area	Common concerns and questions	Details and suggested approach	References
Psychological, behavioural	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioural inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (ie, bright lights, loud noises).	46 47
	Externalising/internalising behaviours	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (eg, sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with a selective serotonin reuptake inhibitor such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	15 76 82 111
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, total iron binding capacity and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	112 113 See: 114–116
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response giving appearance of decreased sensitivity and have variable indications of pain (ie, grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply.	60
	Increased risk of chronic pain	Often due to gastrointestinal problems (see Table 3), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	37 40 71 72
Screening: ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by a practitioner familiar with special-needs individuals and cortical visual impairment is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	48 104
Screening: auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain, but if chronic otitis media is present these are needed.	45
Screening: dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anaesthesia. Dental work under anaesthesia should be done with proper anaesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	88 117

References not specific to RTT noted as 'See'.
RTT, Rett syndrome.

Table 6 Detailed approaches to management and therapy for RTT: development, education, therapies, social and alternative medications

System/area	Common concerns and questions	Details and suggested approach	References
Development, education and therapies	Developmental milestones	Developmental regression (reduced hand use and language) typically stops between 2 and 3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy, feeding therapy, occupational therapy, augmentative communication therapy, vision therapy, hippotherapy (horse) and swim/pool therapy.	43 44 48 104 118
	IEP and therapy challenges	Educators may not have experience with RTT. Request they focus on communication, mobility and socialisation with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in RTT is different: it is about maintaining skills as well as recovery. Therapies for RTT should include occupational, physical, speech, swallowing and augmentative communication. Therapy that maximises physical activities should be lifelong, as these will minimise long-term complications and maximise long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a teacher of the visually impaired should be included in the IEP. These essential accommodations to facilitate education are in accordance with disability rights legislation enacted in many countries throughout the world as required by the United Nations (UN) Convention on the Rights of Persons with Disabilities. This international treaty signed by nearly all 193 UN Member States defines access to an inclusive, quality and free education as a basic human right of individuals with disabilities. Families should work with schools to develop an IEP that recognises this; referral to a Rett specialist may provide additional assistance in this regard.	43 44
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals both at home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	43 104
Social concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand RTT through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of childbearing age should be considered by referral to a genetic counsellor.	35 36 119 120
Alternative medications	Cannabis, St John's wort and so on	Families should be encouraged to disclose use of alternative medications (cannabis, oils and so on) to all specialists.	

CVI, cortical visual impairment; IEP, individualised education programme; RTT, Rett syndrome.

serves as a vital resource to help providers anticipate the complexities of this disorder.

Web links to regional RTT clinics for health professionals

- https://www.rettsyndrome.org/about-rett-syndrome/clinics
- https://reverserett.org/newly-diagnosed/#clinics-map
- https://www.rettsyndrome.eu/

Useful web links for families

- https://www.rettsyndrome.org/

- https://reverserett.org/
- https://www.rettsyndrome.org/for-families/resources-for-families
- https://www.rettsyndrome.eu/

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