CRSA Clinical Practice Guidelines Manual
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PRACTICE GUIDELINE FOR BONE ANCHORED HEARING AID (BAHA)

Patient Selection:

1. Minimum age is five (5) years.
2. Conductive or mixed conductive and sensorineural hearing loss, where an air conductive hearing aid is not workable such as: Malformation of the external ear canal or middle ear including, but not limited to, microtia which makes wearing an external aid impossible, stenosis or atresia of the external auditory canal, chronic middle ear infection and drainage, severe otitis externa and allergic reactions to external hearing aids.
3. Audiologic criteria:
   a. Pure tone average bone conduction threshold of up to 70 db;
   b. Speech discrimination score better than 60%.

Psychosocial Evaluation:

1. Patient's cognitive function must be sufficient to allow him/her to understand and participate in the decision-making process and in the care/maintenance of the implant unit.
2. Patient/family must have been compliant with previous medical and audiological management at CRS.
3. Patient/family must commit to necessary otologic, audiologic, educational and therapeutic follow-up outlined in the treatment plan.

References:

1. Clinical Policy Bulletin: Bone-anchored Hearing Aid, Aetna, 7/20/2007, www.aetna.com/cpb/medical/data/400_499/0403.html.
2. TA 6.38 Bone-Anchored Hearing Aid (BAHA), 5/2005, Harvard Pilgrim Health Care.
3. Bedford and Hertfordshire INTERIM Priorities Forum Statement Number 30: Bone Anchored Hearing Aids (BAHAs), October 2006.

GUIDELINES FOR USE OF BOTOX FOR CHILDREN WITH SPASTICITY

Basic Requirements:

1. The decision to use Botox treatment will, in all cases, be a team decision, the result of collaboration among appropriate team members and the family. The team will include appropriate physician(s), i.e. orthopedics, neurology or neurosurgery and therapists, OT/PT.
2. All Botox treatment will be guided by a formal treatment plan. The treatment plan and any subsequent changes to the plan will be reviewed by the team.
3. All children receiving Botox treatment will undergo pre and post treatment evaluations of physical status (i.e. ROM, spasticity, pain) and function (i.e. gait, activities of daily living).
4. All children will receive physical or occupational therapy following Botox injection.
5. Patients will receive Botox injections no more frequently than once every three months.
6. Overall, Botox injection dosage will not exceed 20 units per kg.
7. Children under 18 months of age will be considered candidates for Botox treatment only after review by the medical directors.
8. A witnessed Consent to Treat form will be signed by the patient's parent/legal guardian.

Patient Selection Criteria/Prerequisites:

1. Child must have documented increased muscle tone which clearly puts him/her at risk for joint deformity and which causes one or more of the following:
   a. Pain
   b. Interference with <u>one or more</u> of the following functions:
      i. Proper positioning
      ii. Standing
      iii. Gait
      iv. Patient ability to perform activities of daily living
      v. Caregiver ability to maintain hygiene, care, or positioning

      OR
2. To provide diagnostic information regarding probable outcome of surgical treatment of targeted muscle group(s).
3. There must be documentation that less invasive approaches to spasticity management (i.e. serial casting, night splinting, a reasonable course of physical or occupational therapy, oral medication) have not adequately reduced the influence of spasticity on function during the previous 12 months and that the relative merits of surgical intervention have been considered.
4. Patient must be receiving ongoing medical/habilitative management through CRS and have been evaluated in a related clinic within the previous three months.
5. It must be clear that there are no psycho-social contraindications (i.e. poor attendance to medical or therapy appointments, family instability, lack of access to reliable transportation for follow-up care) in the recent patient/family history.

Request-Approval Process:

The Team (see 1. under Basic Requirements above) should approve all Botox therapy and should have evidence of the following:

1. Evidence that the patient meets III.A. and/or III.B and III.C. through E., above.
2. Documentation that the child's candidacy for Botox treatment has been discussed in a staffing which includes all relevant team members. This team will include, at least, the managing neurologist and therapist.
3. Documentation of physical and/or occupational therapy evaluation within the previous three months to record pre-treatment status and function, as related to the goals of Botox injection. This evaluation will have included:
    a. Classification of deformity, established measures of ROM, spasticity and, if appropriate, pain.
    b. Measures of functional ability.
    c. Videotape of pre-treatment function.
4. Documentation that the family has been provided with balanced information on the mechanisms of Botox treatment as well as the minor discomfort and minimal side effects of the treatment. They must have been given reasonable expectations for outcomes, and have committed to all necessary pre and post injection assessment and therapy.
5. Information regarding previous treatment approaches (therapy, casting, splinting, bracing, etc.) and outcomes.
6. Treatment plan which includes:
    a. Functional and physical treatment goals, how and when they will be measured, and by whom.
    b. Target muscle (group) and planned dosage, as well as preliminary estimate of total number of future injections.
    c. Post-injection therapy treatment recommendations, including frequency of sessions.
    d. Time at which post-injection physical and functional evaluations will take place and when child will return to appropriate neurology, orthopedic, and/or multi-disciplinary clinics.

Treatment Outcome Assessment:

Evaluation of treatment outcomes will differ somewhat depending upon the individual outcome goals established as part of the child's treatment plan. In all cases, however, outcomes will be assessed in each of four areas:

1. Technical/Musculoskeletal Outcomes. Assessed by physicians and therapists.
    Examples:
    a. Increased ROM
    b. Tone reduction
    c. Pain reduction, if appropriate
    d. Increased tolerance for bracing or splinting
2. Functional Outcomes. Assessed by therapists.
    Examples:
    a. Improved speed or quality of gait
    b. Improved positioning for healthy posture and function
    c. Improved ability to transfer
    d. Increased ability to perform activities of daily living such as feeding, grooming, hygiene

   e. Post treatment - video taping

3. Patient/Family Satisfaction. Assessed by therapist and/or social worker. Examples:
   a. Patient/family perception of disability change
   b. Increased ease of care
   c. Patient commitment to treatment plan
4. Cost Effectiveness. Assessed and estimated by Case Eligibility Review. Examples:
   a. Short-term costs of injection, pre and post-treatment medical and habilitative management.
   b. Estimates of possible long-term cost-savings related to delay or prevention of contractures, deferred surgery, etc.

References:

Botulinum Toxin for Spasticity in Children with Cerebral Palsy: A Comprehensive Evaluation. Kristie Bjornson, PhD, PT[a]. Ross Hays, MD[b], Cathy Graubert, PT[a], Robert Price, MS[b], Francine Won, PT[a], John F. McLaughlin, MD[c], Morty Cohen, RPh[a]. PEDIATRICS Volume 120, Number 1, July 2007.

BTX-A. Pediatric Dosing Guidelines Management of Spasticity with Botulinum Toxin Type A (Botox), August 2005, www.mdvu.org/library/dosingtables/btxa.

CLEFT LIP — CLEFT PALATE

ORGANIZATIONAL GUIDELINES

Organizational Guidelines represent the minimum requirements for providing care for individuals with cleft lip / left palate. Care and treatment should be provided in a manner that includes adherence to and consistency with each of the following guidelines.

CRS Enrollment:

Patients diagnosed with cleft lip/cleft palate and craniofacial anomalies must be enrolled at a site with a cleft lip/cleft palate and craniofacial anomalies clinic.

Interdisciplinary Team Membership:

The following team members must be available to attend clinics and team conferences, review patient information, determine the need to see the patients at a clinic site and be available for inpatient consultation or coordinate care with inpatient staff at CRS contracted hospitals. It may not be necessary for each member to see the patient at each visit. One team member can fill more than one role if properly trained.

- Audiologist
- Child Life Specialist
- Child Psychologist
- CRS Member / caregiver
- Dentist
- Educator
- Genetic Counselor (Optional)
- Geneticist
- Nutritionist
- Oral and Maxillofacial Surgeon
- Orthodontist
- Otolaryngologist
- PCP (Invited)
- Pediatrician
- Plastic Surgeon
- RN Nurse Coordinator
- Social Worker
- Speech Therapist

Consultative Personnel:

The clinic must have access for consultation to specialists as identified by the Team.

Outreach Clinics:

Outreach Clinics are designed to provide a limited specific set of services including evaluation, monitoring and treatment in settings closer to the family than a clinic. Major treatment plan changes must be communicated to the clinic. Members with cleft lip / cleft palate and craniofacial anomalies may be seen in related specialty field clinics such as plastic surgery or nutrition clinics. Field clinic records must be provided to the clinic serving the member.

Community-Based Services:

Community-based services means all local services including provider agencies, schools, private physician offices, hospitals, and / or any other local setting. The following community based services may be provided from a community-based setting:

- Lab Services
- Pharmacy Services
- Speech Therapy
- General Dentistry (The dental services associated with cleft lip / cleft palate and craniofacial anomalies are specialized; they need to be provided at the clinic site or in private dental offices with the Interdisciplinary Team involved).

Facilities and Services:

- Age-appropriate setting for all patients
- Defined age-appropriate services, i.e., Pediatrics, Adolescent Medicine, and/or Internal Medicine
- Pediatric and / or Adult Intensive Care Units appropriate to the age and complexity of the medical condition as determined by the orthopedic surgeon with medical consultation as needed
- Social Work Department
- Child Life Services
- Physical Therapy
- General Dentistry- Oral and Maxillofacial Surgery, Orthodontic, and Prosthodontic pediatric services available
- Identified clinic area for outpatient services
- X-ray services
- Equipment and expertise to measure height and weight

- Access to the pharmacy

Team/Staff Meetings:

Team and staff meetings will be held based on the age of the patient and their diagnosis. At a minimum the following will occur:

1. Interdisciplinary Team Meetings ï Evaluate patient at regularly scheduled intervals, the frequency and specific content of those evaluations being determined by the condition and needs of the patient and family. Hold regularly scheduled face-to-face meetings for discussion of findings, treatment planning, and recommendations for each patient. Develop a longitudinal treatment plan for each patient that is modified as necessitated by craniofacial growth and development, treatment outcomes, and therapeutic advances. CRS sites are encouraged to perform periodic chart reviews with documentation to ensure that all patients are reviewed and planned appropriately, and according to, their underlying condition.
2. Staff meetings once a year to focus on issues of clinic patient care and clinic administration.

Lead Physician Specialists:

Qualifications: The Lead Physician Specialist should be a Team Member with experience and expertise in serving members with cleft lip/cleft palate and craniofacial anomalies.

GUIDELINES FOR PATIENT SERVICES, EVALUATION, AND MONITORING FOR CLEFT LIP/CLEFT PALATE

The purpose of these guidelines is to promote a uniform level of care at CRS Clinics for members with cleft lip / cleft palate and craniofacial anomalies and to provide a general framework for excellence in patient care. Their relevance to specific situations will depend on individual variations in clinical course and professional judgment, growth and development, and treatment techniques. In addition, this document should serve as an outline to assess programs, secure resources needed to enhance patient care and education, and guide the future development of treatments for patients with cleft lip / left palate and craniofacial anomalies.

Diagnosis & Treatment:

Goal: To provide accurate and timely diagnosis of patients with cleft lip/cleft palate and craniofacial anomalies.

Goal: To habilitate the patient through appropriately timed multidisciplinary interventions and monitor treatment progress and provide proactive treatment as appropriate.

Infancy:

- Consultation with plastic surgeon

- Consultation with pediatrician (Peds Screening)
- Contact made with Orofacial Team Coordinator
- Contact made by Social Services
- Evaluation by a Feeding specialist
- Contact with other specialty as necessary
- Visit with plastic surgeon
- Otolaryngology screening
- Audiology screening
- Follow-up with pediatrician (Peds Screening)
- Orthodontics for palatal control device if required
- Contact with other specialty as necessary
- Consultation with a geneticist
- Repair cleft lip
- Audiology follow-up
- Social Service Follow-up
- Pediatrician / PCP Follow-up
- Contact with other specialty as necessary

Age 12 to 18 months:

- Cleft palate repair or when determined as necessary
- PE Tube placement or evaluation
- Speech / language evaluation
- Developmental Screening
- Pediatric dentist for oral examination, preventive education/procedures, speech/language evaluation
- Contact with other specialty as necessary

Age 2 to 3 years:

- Cleft palate repair or when determined as necessary
- PE Tube placement or evaluation
- Speech / language evaluation
- Developmental Screening
- Pediatric dentist for oral examination, preventive education/procedures, speech/language evaluation

- Contact with other specialty as necessary

Age 4 to 6 years:

- Evaluation for VPI (velopharyngeal incompetence)
- Surgical procedures as needed such as pharyngeal flap or palatal lift
- Orthodontia-dental/facial orthodontia treatment initiation
- Evaluation by craniofacial team for future orthognathic surgery
- Screening for developmental and special education needs and referral as appropriate
- Contact with other specialty as necessary

Age 6 to 9 years:

- Screening for self esteem and teasing issues and referral to psychology as needed
- Contact with other specialty as necessary

Age 9 to 11 years:

- Bone grafting of alveolar cleft
- Contact with other specialty as necessary

Age 11 to 18 years:

- Orthodontia (alveolar ridge notch & CP palate patients only)
- Prosthodontic Dentistry
- Lip revision / rhinoplasty
- Orthognathic surgical procedures with post op evaluation of VP function and articulation by speech pathologist
- Contact with other specialty as necessary

Children Entering System at Older Ages:

For patients enrolled in CRS after early childhood, the treatment parameters will be modified as appropriate for the patientôs individual needs.

Transition Planning:

Planning for transition to adulthood should begin at age 14 years and continue until age 21 years.

Ongoing Patient Evaluation and Monitoring:

Goal: To anticipate and treat psychosocial problems and management of the condition.

Psychosocial support with periodic assessment of patient and family needs. This can be performed by various specialists with referrals as indicated.

References:

Parameters for Evaluation and Treatment of Patients with Clept Lip/Palate or Other Craniofacial Anomalies. Official Publication of the American Cleft Palate-Craniofacial Association. Revised Edition October 2004. http://www.acpa-cpf.org/teamcare/parameters04rev.pdf

Annex 1: European Collaboration on Craniofacial Anomalies (EUROCRAN). 2004 http://www.eurocran.org/content.asp?contentID=105&sid=211448

East Carolina University . Cleft Lip/Cleft Palate / Craniofacial. http://www.surgery.ecu.edu/plas_clc.htm. December 2006.

CYSTIC FIBROSIS

ORGANIZATIONAL GUIDELINES

CYSTIC FIBROSIS[1] Organizational Guidelines represent the minimum requirements for providing care for individuals with Cystic Fibrosis. Care and treatment should be provided in a manner, which includes adherence to and consistency with each of the following Guidelines.

CRS Enrollment:

All members with a cystic fibrosis diagnosis must be enrolled in clinics meeting these Guidelines. Care provided to members under CRS in any other part of the state must be coordinated with the designated Cystic Fibrosis Team.

Interdisciplinary Team Membership:

The following Team Members must attend clinics and team conferences, review patient information, determine the need to see the patients at a clinic site and are available for inpatient consultation or coordinate care with inpatient staff. It may not be necessary for each member to see the patient at each visit:

- Pulmonologist ï Lead Physician
- Registered Nurse Coordinator
- Social Worker
- Respiratory Therapist
- Dietitian/Nutritionist
- Child Psychologist
- CRS Member / Caregiver
- Primary Care Physician[2]

Available Personnel:

Below are personnel who must be available to the member / adult at the clinic during a scheduled specialty clinic. These personnel may or may not be called in by the Interdisciplinary Team members to see the member or they may choose to see the member based on prior knowledge of the members needs:

- Advocate

[1] These Guidelines of care are consistent with the Cystic Fibrosis Foundation, Minimum Criteria for CF Center Qualifications with minor revisions to reflect the Children's Rehabilitative Services delivery system.
[2] The Primary Care Physician will be invited to all Team meetings; however, it is understood that PCP will not always be able to attend.

- Child Life Specialist
- Educator
- Translator

Consultative Personnel:

The clinic must have access to personnel for consultation including but not limited to the following:

- Allergist / Immunologist
- Anesthesiologist
- Angiographer
- Cardiologist, pediatric and adult
- Endocrinologist
- Gastroenterologist
- Geneticist / Genetic Counselor
- Infectious Disease Specialist
- Internist
- Nuclear Medicine specialists
- Otorhinolaryngologist
- Pediatrician
- Pulmonologist
- Radiologist
- Surgeon, pediatric, general thoracic
- Urologist

Outreach Clinics:

Outreach Clinics are designed to provide a limited specific set of services including evaluation, monitoring and treatment in settings closer to the family than a clinic. Major treatment plan changes must be communicated to the clinic. Cystic Fibrosis Outreach / Field Clinics must include the following personnel:

- Pulmonologist
- Clinic Coordinator
- Respiratory Therapist

Community-based Services:

Community-based services means all local services including provider agencies, schools, private physician offices, hospitals, and/or any other local setting. The following community-based services may be provided for patients with cystic fibrosis:

- Pharmacy services
- Respiratory therapy
- Lab work
- Any other appropriate extension of services as approved by the Interdisciplinary Team and approved by the CRS Medical Director.

Services to Adults with Cystic Fibrosis:

1. Clinic times separate from the member clinics will be scheduled for adults.
2. Child Life Specialist should be removed from the Team.

Facilities & Services:

1. Age-appropriate setting for adult patients
2. Defined age-appropriate services/ i.e. Pediatrics, Adolescent Medicine and/or Internal Medicine
3. House Officers when the hospital is a teaching institution
4. Pediatric and Adult Intensive Care Units
5. Respiratory Care Department
6. Nutrition or Dietary Department
7. Social Work Department
8. Identified clinic area
9. Laboratories performing:
    a. Sweat test by quantitative pilocarpine iontophoresis as stated in the Cystic Fibrosis Foundation guidelines
    b. Pulmonary function tests, including ability to measure long volumes
    c. Daily, round the clock availability of:
        i. bacteriology
        ii. blood chemistries
        iii. arterial blood gases
        iv. imaging studies including radiographic, ultrasonographic, and nuclear medicine studies.
10. Respiratory therapy available 24 hours a day, 7 days a week

Other Criteria:

1. Written patient records to include, but not limited to:
   a. Documentation of positive sweat test and/or genetics
   b. Copies of outpatient clinic visits
   c. Discharge summaries
   d. Growth chart
   e. Laboratory data
2. Sweat Test results reviewed by Lead Physician
3. Referral plan for procedures or services not available through CRS, such as oxygen at home, equipment, supplements, therapy vest, etc
4. All outpatient clinic reports and discharge summaries sent to the referring physician
5. A plan for the care of adult patients
6. 24-hour coverage by a lead physician
7. A minimum of 50 CF patients

Team/Staff Meetings:

1. Case Planning Meetings- a meeting of the specialists involved in the care and treatment of the member is to be held after each specialty clinic
2. Interdisciplinary Team Meetings/ review and planning meetings (patient specific):
   a. Every three (3) months with the regular assessment
   b. Once a year for planning and review with the family
3. Staff meetings at least annually to focus on issues of clinic patient care and clinic administration
4. Internal education meetings annually to focus on new information regarding the care and treatment of persons with Cystic Fibrosis
5. A yearly note by Social Services, Dieticians, and Child Life required

Lead Physician Specialists:

Qualifications: The lead physician specialists for members with cystic fibrosis will be a pulmonologist or pediatrician with experience in the care of cystic fibrosis patients. Board certification in Pulmonary Medicine is recommended.

GUIDELINES FOR PATIENT SERVICES, EVALUATION AND MONITORING FOR CYSTIC FIBROSIS

The purpose of these guidelines is to promote a uniform level of care and teaching services at CF Centers, and to provide a general framework for good patient care. Their relevance to specific situations will depend on individual variations in clinical course and

professional judgment. In addition, this document should serve as a tool to assess programs, secure resources needed to enhance patient care and education, and guide the future growth and development of CF care.

Diagnosis:

Goal: To provide accurate and timely diagnosis of CF.

The diagnosis of cystic fibrosis is based on clinical and laboratory findings. These may include but are not limited to: a) chronic obstructive pulmonary disease, b) intestinal malabsorption, c) electrolyte loss through sweat, d) family history of CF, e) meconium ileus at birth, f) male infertility due to azoospermia, g) presence of staphylococcus aureus or mucoid pseudomonas aeruginosa in the respiratory tract.

Confirmation of the diagnosis currently requires two positive sweat tests, done on different days, by quantitative pilocarpine iontophoresis (Gibson-Cooke) according to Cystic Fibrosis Foundation approved methods or 2 CF mutations. A positive test is defined by sweat chloride measurements in excess of 60 milliequivalents per litre in an adequate sample of sweat (minimum of 75 milligrams in gauze or filter paper, or 15 microliters for the Wescor Collection system, collected over a 30 minute period). Repeat borderline sweat electrolyte measurements (40-60 meq/ml) require clinical correlation and judgment for diagnosis.[1]

Evaluation and Education of Newly Diagnosed Patients:

Goal: a) To provide accurate assessment of physical and emotional status, and to begin patient family education.

b) To help families cope with the emotional impact of diagnosis and formulate an appropriate therapeutic plan.

Evaluation of the newly diagnosed patient should include medical, nursing, nutritional, psychosocial, respiratory, and physical therapy assessments as well as laboratory evaluation and genetic counseling. A comprehensive education program must be developed to promote optimum understanding of the disease, adherence to treatment plans and adequate coping with the demands of chronic illness.

Ongoing Patient Evaluation and Monitoring:

Goal: To anticipate and treat physical and psychosocial problems and complications of the disease.

At least four visits per year to the Clinic are recommended. The number of visits will vary with factors such as age, degree of illness; time elapsed from diagnosis, and distance from a clinic. Use of clinical scoring at every visit is encouraged. In addition, interim visits to the primary care physician for general pediatric care are necessary. The primary care practitioner has an important role in administering immunizations, evaluation and treatment of milder pulmonary exacerbation in consultation with the CF Center physician, advocacy and assessment of family dynamics. Every patient should

[3]The CF gene and some of its mutations have been recently characterized. This finding is foreseen to contribute to confirmation of the diagnosis of CF in the future.

be encouraged to be seen on a regular basis at a CF Clinic and by a physician in the community.

Respiratory Evaluation and Therapy:

Goal: To achieve optimum respiratory status. To anticipate and treat progression and complications of pulmonary disease.

Complete respiratory history and examination should be obtained at every visit (including nasal examination for nasal polyps).

Spirometry is recommended to quarterly and more often if clinically indicated and during hospitalizations for pulmonary exacerbation. Spirometry is done at every visit at many centers. Complete pulmonary function testing (including lung volumes) should be done at least once a year (performed according to American Thoracic Society Guidelines) .[2]

Arterial blood gases or pulse oximetry needs to be done at least annually on patients whose forced expiratory value in one second (FEV1) is less than 40% of predicted normal and additionally, when clinically indicated (i.e. exacerbation, oxygen therapy).

Respiratory tract culture and sensitivity should be done at least four times per year but preferably at each quarterly visit, before initiation of intravenous antibiotic therapy and at sick visits when clinically indicated.

Chest roentgenogram should be obtained annually and on pulmonary-related hospital admissions. Scoring of radiographs is encouraged.

All clinics should have written protocols for managing respiratory complications (hemoptysis and pneumothorax).

Knowledge and performance of respiratory and physical therapy techniques should be evaluated annually.

Gastrointestinal System/Nutrition:

Goal: To anticipate and treat nutritional deficits and complications. The ultimate goal is to achieve optimum growth and nutrition.

Measurements should include height and weight, plotted on Guideline growth chart, for all patients, every visit. Other measurements such as triceps skin fold thickness and mid-arm circumference can be useful.

Nutritional assessment should be carried out annually and when there is evidence of weight loss or poor weight gain. This assessment should include, but not be limited to, protein, fat, carbohydrate, vitamin and mineral intake. Other measures include: a) Assessment of pancreatic enzyme and vitamin supplementation and measurement of albumin and/or prealbumin levels at diagnosis, and when indicated; b) Abdominal examination with particular attention to liver and spleen size and consistency; c) A protocol for the management of diabetes mellitus; d) Laboratory measurements to include evaluation of metabolic and liver status, complete blood count, and fat soluble vitamin levels.

[2] Am. Rev. Resp. Dis. 1987; 136; 1285-96

Psychosocial Issues:

Goal: To anticipate and treat social and emotional problems of patients and their families.

Psychosocial assessment should be carried out annually. The CF Clinic staff should be available for genetic counseling, crisis management, ongoing support and anticipatory guidance, when indicated. Sexuality, fertility and pregnancy should be discussed at age-appropriate intervals.

Adult Issues:

Goal: To ensure that the changing needs of the growing population of adult patients are met by caregivers.

Adult patients have specific needs different from those of the pediatric patients. Clinics should have clear plans for the care of adults including identification of appropriate caregivers and preparation for transition to adulthood and adult care. Adequate actions to address these needs include the incorporation of adult care specialists in the clinic program, establishment of inpatient services in internal medicine wards, creation of transition teams or creation of parallel adult care teams. The specific activities undertaken will depend on clinic size, geographic factors, local institutional idiosyncrasies and availability of specialists in the community.

Specific areas requiring services include: obstetrics and gynecology, urology, cardiology, endocrinology, adult nutrition, vocational counseling, independent living, family planning, sexuality, medical insurance and other special counseling.

Facilities:

Goal: To provide adequate inpatient, outpatient and laboratory facilities to meet special needs of the CF patient population.

These include a) inpatient facilities that provide separate quarters for older patients (i.e. adolescent ward or wing). Personnel trained in the care of CF patients and sensitive to their needs; b) In-house physician 24 hours per day, 7 days per week; c) A specified, identifiable outpatient area with adequate space (providing privacy) for interviews and consultations, team conferences, equipment for nutritional assessment, height/weight measurement, and other pertinent outpatient activities; d) Laboratories capable of completing pulmonary functions by ATS Guidelines, including body plethysmography, microbiology studies according to the Centers for Disease Control guidelines, sweat testing according to CFF guidelines, and blood gas determinations and non-invasive oxygen monitoring.

PRACTICE GUIDELINE FOR DEEP BRAIN STIMULATION (DBS) FOR DYSTONIA

Policy:

ADHS/CRSA considers unilateral or bilateral deep brain stimulators as medically necessary durable medical equipment for the treatment of patients seven years of age or above with medically intractable/refractory primary dystonia, including generalized dystonia, hemidystonia, and cervical dystonia.

At this time, the U.S. Food and Drug Administration Humanitarian Device Exemption H020007 applies only to the treatment of medically intractable/refractory primary dystonia (USFDA, 2003). Therefore, the deep brain stimulator is not a CRS covered benefit for other diagnoses, and ADHS/CRS considers unilateral or bilateral deep brain stimulators for all other diagnoses experimental and investigational. These include, but are not limited to, trauma, hypoxic-ischemic encephalopathy, multiple sclerosis, degenerative disorders, metabolic disorders, infectious diseases, drug-induced, epilepsy, chronic cluster headaches, obsessive-compulsive disorder, Tourette syndrome, and secondary dystonia of unknown etiologies.

CRSA can not authorize or provide payment for this procedure for any condition other than the treatment of patients seven years of age or above with medically intractable/refractory primary dystonia, since the treatment cannot be considered reasonable and medically necessary.

Under the U.S. Food and Drug Administration Humanitarian Device Exemption provision, deep brain stimulators can only be placed at a clinical facility with IRB approval for the use of the device for the FDA approved indication (USFDA, 2003).

Description of Product or Service:

Deep brain stimulation (DBS) is a neurosurgical procedure that involves the stereotactic implantation of an electrode into a specific region of the brain, delivering chronic, high frequency electrical stimulation/impulses to several deep brain nuclei. Deep brain stimulation therapy uses a device with three implantable components: a quadripolar brain lead, a computerized neurostimulator, and an extension wire that connects the two.

Generally, DBS lead implantation is done using local anesthesia while the patient is awake to optimize the mapping procedure and avoid stimulation-induced adverse effects during intraoperative test stimulation of the lead. For younger patients or those with extreme dystonia, this procedure can be done with general anesthesia. Leads can be implanted unilaterally or bilaterally depending on the distribution of the patientâs symptoms.

Often, the electrode is attached to a temporary cable on the skin for short-term stimulation to validate treatment effectiveness. After effectiveness is determined, a permanent electrode is placed and the neurostimulator is implanted subcutaneously with the patient under general anesthesia. The neurostimulator is typically implanted in the subclavicular region, but can be located elsewhere.

Days to weeks after device implantation, stimulation is activated using the DBS programmer, and the frequency and amplitude of the electrical pulses can be adjusted according to the patientôs symptoms. Setting the neurostimulation parameters involves a balance between optimal efficacy and avoidance of side effects of neurostimulation.

DBS is an adaptable procedure that provides an alternative to more permanent surgical procedures that are ablative or lesioning, such as thalamotomy and pallidotomy. Ideally, DBS should interrupt the pathways responsible for the abnormal movements, functioning to reduce the overactive brain regions without destroying them.

Background:

In August 1997, the U.S. Food and Drug Administration (USFDA) approved DBS for medically refractory essential tremor and medically refractory Parkinsonôs Disease. Although these two diagnoses are not typically seen in the pediatric population, this information is included in this document to help the reader understand the different levels of FDA approval of DBS.

Effective October 1996, USFDA regulations regarding Humanitarian Use Devices (HUDôs) became effective as a result of provisions of the Safe Medical Devices Act of 1990. A HUD is defined by the FDA as ña device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year.òThis regulation provides an incentive for the development of devices for use in these small patient populations.

For the USFDA, the HUD regulation provides for the submission of a Humanitarian Device Exemption (HDE) application, which is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose, but must contain ñsufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury,òand that the probable benefit to health outweighs the risk of injury or illness from its use.

In April 2003, the FDA granted approval for the Activa® Dystonia Therapy System (Medtronic, Minneapolis, MN) under the HDE process, for medically refractory intractable primary dystonia. This HDE approval authorizes marketing of the Activa® Dystonia Therapy System. However, according to USFDA guidelines, ñan HUD may only be used after Internal Review Board (IRB) approval has been obtained for the use of the device for the FDA approved indication.ò Furthermore, the labeling for a HUD must state that the device is a humanitarian device and the ñeffectiveness of the device for the specific indication has not been demonstrated.ò

Dystonia:

The term ñdystoniaò covers a diverse group of movement disorders, all of which are characterized by involuntary muscle contractions that may cause twisting and repetitive movements or abnormal postures. Dystonia can be classified by its distribution on clinical examination or its known or inferred etiology. Regarding the former, focal dystonia affects a single body part, segmental dystonia involves adjacent body parts, hemidystonia involves one side of the body, and generalized dystonia is more widespread, affecting two or more body

segments. Regarding etiologic classifications two broad categories occur, primary and secondary dystonia. Marks (2005) defines these classifications as follows:

- Primary Dystonia: (idiopathic dystonia) is diagnosed when dystonia is the only sign present and there is no identifiable exogenous cause, degenerative disorder, or inherited condition underlying the dystonia. Several genetic mutations have been linked to some of the primary dystonia syndromes such as DYT1.

- Secondary Dystonia: is associated with acquired or exogenous causes and frequently has other neurologic findings in addition to dystonia. Acquired or exogenous causes may include: perinatal-hypoxic-ischemic insult, stroke, encephalitis, neurodegenerative disorders, or traumatic brain injury. Hereditary neurologic syndromes may also cause secondary dystonia, and can include Huntington's disease, Wilson's disease, pantothenate kinase-associated neurodegeneration, and many others.

Those with dystonia usually have normal intelligence and no associated psychiatric disorders. Dystonia is the most severe form of a group of movement disorders called dyskinesias.
At this time, the FDA approved indication for the use of DBS in the treatment of dystonia is for medically refractory, intractable primary dystonia in patients seven years of age or older. In addition, the clinical facility implanting DBS for primary dystonia under the HDE provision must have IRB approval for this FDA HDE indication.

Treatment of Dystonia

The primary goal of all treatments for dystonia is to provide symptomatic relief, improve function, and reduce disability. Currently, there is no cure for dystonia. Treatment options include medical treatment and surgical procedures, with surgery reserved for medically intractable dystonia.

Medical treatment includes oral medications such as dopaminergic and anticholinergic medications, and Baclofen. Chemodenervation is the use of chemicals such as botulinum toxin injection therapy to interrupt the flow of nerve impulses to the abnormal muscle. Botulinum toxin injection for the treatment of focal dystonia has been used for over a decade, and is considered the current standard of care for focal dystonia.

Surgical treatment for dystonia includes ablative/lesioning procedures, cervical rhizotomy, and now functional brain surgery with DBS for medically intractable primary dystonia.

Patient Selection:

- The patient must have medically intractable/refractory primary dystonia, with adequate documentation of previous medical failure.
- The patient must be an appropriate candidate for stereotactic procedures.
- The patient must be physically able to endure the surgical procedure.
- The patient must be able to cooperate by answering questions and following directions during the surgery.
- The patient must understand the nature of therapy and be able to operate the neuro-stimulator control magnet or therapy controller.
- The patient must be available for periodic follow-up visits, and must have demonstrated exceptional compliance with previous medical therapies.

- The patient should not be suffering from advanced dementia or have other independent diagnoses that could explain the failure to respond to medical treatment. There should not be any focal lesion of the basal ganglia, such as a space-occupying lesion or lacunae, at the target site that would nullify the result of the DBS.
- The patient will be fully aware of the risks and benefits of the surgery, including mortality and morbidity experience of the center and the performing surgeon.
- The patient must not have a medical condition that requires repeated magnetic resonance imaging (MRI).
- Various medical or environmental devices may generate enough electromagnetic interference to change the parameters of a neurostimulator; to turn it on or off, or it may cause a surge, shock, or jolt.
- Patients treated with DBS systems must never receive Diathermy.
- The use of cerebellar stimulation or pacing is considered investigational or not medically necessary.
- There will be no coverage for patients who have had previous thalamotomy, or when simultaneous DBS of the Ventralis Intermediate Nucleus of the Thalamus (VIM) is planned.
- The patient must not have other operating pacemakers.

Patients will be advised to avoid games, sports, and other pastimes where a strain to the lead connector assembly or a percussive injury to system components may be likely to occur (soccer, football, rugby, etc).

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PROTOCOL FOR EPILEPSY SURGERY

Introduction:

Epilepsy is a common disorder of childhood. It affects 0.5% of the pediatric population, and approximately 70% of all epilepsies begin in childhood. The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs). However, with the currently available medications, including the "new" AEDs, seizures can be satisfactorily controlled in only 70% of children.

In view of the current CRS eligibility criteria, which include treatment-resistant epilepsy, most children with epilepsy seen in the various CRS clinics have seizures that are difficult to control. Many of these patients have neurological and intellectual disability on the basis of co-morbid neurological problems, such as cerebral palsy. However, for all of these patients, and their families, poorly controlled seizures results in significant day-to-day struggles, and compromised quality of life. Intractable epilepsy has distressing medical, financial, social, and psychological consequences.

Over the years, resective brain surgery has proved to be an important alternative treatment for children with intractable epilepsy. Epilepsy surgery in specialized centers has been successful in controlling seizures in 50-80% of children undergoing surgery. It is also realized that the success of epilepsy surgery, both medically and psychosocially, is significantly better when the procedure is performed in childhood. Improved technology has made it possible to accurately identify the site of origin of seizures in the brain, making surgery feasible for more patients.

Proposals for standards and guidelines for the field of epilepsy surgery (and for epilepsy surgery in children) have evolved, beginning with the National Institutes of Health (NIH) Consensus Development Conference in 1990. As with most surgical therapies, controlled, randomized trials regarding surgical outcomes are relatively rare. Criteria for the referral and evaluation of children for surgical treatment of epilepsy have been addressed most recently by the Subcommission for Pediatric Epilepsy Surgery, Commission on Neurosurgery, of the International League Against Epilepsy (ILAE).[1] This CRS protocol rests upon these consensus statements.

There is no single definition of intractable (or treatment-resistant) epilepsy that is suitable for all patients. The decision about the need to look beyond conventional AED therapy is always highly individualized. Seizure frequency, the type of seizures, and the severity of seizure events each bear significantly on quality of life, and are thus important determinants about the need to consider epilepsy surgery. The frequency of seizures varies considerably between patients. However, even infrequent seizures may result in significant disability if they are likely to be associated with physical injury due to falls, brain injury due to status epilepticus, or social disability such as the inability to drive or work. For some patients, seizures can be controlled, but only by utilizing high doses of AEDs, which renders the patient chronically over-medicated, or prone to other significant side effects. These patients, likewise, are considered to be failures of medical management, and are potential candidates for pre-surgical evaluation. In brief, patients whose seizures are incompletely controlled, **or** who have unacceptable side effects of conventional AEDs, are candidates for epilepsy surgery evaluation.

The number of AEDs that must be tried to determine that the patient is refractory (or ñtreatment-resistantò) has recently been the subject of several studies that have added clarity to this important question. The study of Kwan and Brodie is most frequently cited, in which newly diagnosed epilepsy patients were followed prospectively within an epilepsy specialty clinic, and outcomes with respect to AED management were determined.[2] In this large newly treated cohort, 47% of patients achieved seizure control with the first AED tried, 13% with the second, and only 5% with the third. This study demonstrates that the most effective AED for any patient is the first one that they try. Second, and subsequent, AED choices are much less likely to be effective, and the likelihood of effectiveness diminishes with the number of AEDs that are prescribed. This has led to a ñthree-drug ruleò, used by many epilepsy centers, to establish the minimum number of AEDs that qualify a patient as treatment-resistant. (Some epilepsy specialists promote a ñtwo-drug ruleò as the minimum number of AEDs prior to epilepsy surgery, since the likelihood of success with the third drug is low.) The proper AED for the seizure type under treatment, and proper use of the AED with respect to dosage and blood levels, must be present to consider the AED trial as adequate.

Please note that this protocol does not address patient suitability for surgical placement of the vagal nerve stimulator, but is restricted to intracranial procedures.

Selection of Patients:

The following criteria should be considered in referring patients to the pediatric epilepsy specialist for consideration of epilepsy surgery:

1. The patient has refractory (treatment-resistant) epilepsy. Treatment failure is present if a) the number or severity of seizures is unacceptable to the patient, family, and treating physician, or b) AED treatment results in unacceptable side effects, including excessive sedation.
2. The patient has failed conventional management with at least three AEDs that are appropriate for the seizure type, and were used with adequate dosing.

Patients meeting the above criteria should be evaluated by one of the pediatric epilepsy specialists at CRS before initiating an evaluation as a potential candidate for epilepsy surgery. Patients will be reviewed on a case-by-case basis, either with a clinic visit with the pediatric epileptologist to determine suitability for further evaluation, or by chart review by one of the pediatric epilepsy specialists.

This evaluation will include consideration of the following issues:

1. The diagnosis of epilepsy is secure. The possibility that the clinical spells may represent a different disease process, such as syncope or psychogenic seizures, requires additional evaluation prior to initiating a pre-surgical work-up.
2. The seizure type (or types) is appropriate for consideration of epilepsy surgery. Brain resection for treatment of epilepsy is appropriate for partial, or localization-related, seizures. Epilepsy surgery for generalized seizures may be appropriate under restricted circumstances, such as corpus callosotomy for patients with frequent epileptic drop attacks.
3. Surgery should be appropriate in light of the natural history expected for each patientõs seizure type and epilepsy syndrome. For example, epilepsy surgery is generally not

indicated for benign focal epilepsies of childhood, which are expected to remit around the time of puberty.

4. The etiology of the epilepsy should be clarified if possible. Appropriate diagnostic tests should be performed in an attempt to define the structural abnormality, if present.
5. The patient should have had a reasonable trial of at least three appropriate AEDs with adequate monitoring of compliance and effects of treatment. Exceptions to this õthree-drug ruleò are rare, but may include circumstances such as refractory status epilepticus in which a surgically treatable lesion is found.
6. The family (and patient) should be fully informed of all available options for treatment. The patient and/or family must make an informed decision accepting the possibility of surgical therapy. Pre-surgical evaluation is not appropriate in circumstances where the family (or patient) is not willing to consider surgical therapy.
7. In general, the issue of epilepsy surgery in patients with significant co-existing disorders such as profound developmental retardation, progressive neurodegenerative disease, and/or severe psychiatric disorders should be approached with sensitivity to the likelihood of benefit (improved quality of life) for the patient and family.
8. The patient should have a reasonable potential of being a candidate for one of the available surgical procedures (as detailed below).

Evaluation of Epilepsy Surgery Candidates:

1. Pediatric Epilepsy Program

   Epilepsy surgery for CRS patients requires that evaluation and treatment be performed under the supervision of a pediatric neurologist in an epilepsy program that provides comprehensive diagnostic and treatment services.

   An epilepsy program should have the following staff and facilities[1]:

   a. a pediatric neurologist with special training and expertise in the field of childhood epilepsy,
   b. a neurosurgeon with expertise in epilepsy surgery in children,
   c. technical and professional staff, and physical infrastructure, to provide for EEG services necessary for pre-surgical evaluation, including continuous inpatient video-EEG monitoring,
   d. brain imaging resources, most importantly, MRI,
   e. professional resources for neuropsychological or developmental testing, and
   f. ancillary staff, to include nursing, social services, and child life, to provide support services and referral to appropriate community agencies, as a component of the epilepsy surgery process.

   Additional resources that are desirable include intraoperative cortical mapping, and non-invasive imaging modalities such as functional MRI (fMRI), positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG).

2. Rationale for Resective Surgery

   In order for resective brain surgery to be effective for patients with refractory epilepsy, the seizure focus must be located, and the risk associated with removing this region of the brain must be acceptable. Most of the testing and evaluation that goes into the

process of determining the suitability of a patient for surgery addresses one or both of these issues. Patients are good candidates for epilepsy surgery if the seizure focus has been successfully localized **and** the region is established as relatively safe to remove without causing new unacceptable deficits for the patient.

3. Testing Procedures for Pre-Surgical Evaluation
   Evaluation for surgery requires several standard procedures: electroencephalography, usually with inpatient video-EEG monitoring, MR imaging of the brain, and neuropsychological testing. These core studies (often supplemented by others) provide complementary information, and concordance between these tests increases the confidence level for performing successful surgery.[3]

Video-EEG Seizure Monitoring:

Video-EEG recordings are studied for both interictal and ictal findings, both of which offer information with respect to seizure localization. Patients are often taken off their AEDs for seizure monitoring. The duration of monitoring is highly variable, and is dependent upon how quickly informative seizures are captured. The number of seizures that need to be studied is also highly variable, but typically six or more is a conventional goal.

For some patients, the non-invasive testing (seizure monitoring with electrodes on the scalp, MRI, and neuropsychological studies) fails to adequately localize the seizure focus. Some of these patients may then be candidates for invasive monitoring with depth electrodes, and/or subdural strips or grids. Selecting patients for intracranial monitoring is highly individualized, with careful consideration of potential risks, and the likelihood of surgical success.

1. Brain Imaging Techniques
   Radiological techniques to image the brain include computerized tomography (CT), MRI, PET and SPECT scanning. MRI is clearly recognized as the most important of these modalities, and advances that have come with improved MR imaging have revolutionized the field of epilepsy surgery, particularly for children. The pre-surgical work-up often requires the use of specialized MR imaging sequences, such as protocols maximizing the likelihood of detecting cortical dysplasia, or temporal lobe abnormalities.

   PET, usually with injection of flourodeoxyglucose (FDG), demonstrates the distribution of cerebral metabolism by visualizing regional glucose uptake by the brain. In patients with focal seizures, interictal PET imaging may identify the epileptogenic zone by showing a region of hypometabolism. Conversely, an ictal PET study may localize the seizure focus by demonstrating a hypermetabolic region. In some instances, PET may obviate the need for intracranial EEG monitoring, or perhaps more commonly, may help localize the correct region to be studied further with intracranial grids. PET scanning is appropriate in non-lesional cases where the brain MRI is either normal or non-specific, or in some cases where functional assessment of the ñnormalò brain regions is required. PET imaging for lesional cases requires approval by the Regional Medical Director.

   SPECT, which measures regional cerebral blood flow, can also be a useful functional imaging technique of the brain. Since blood flow is linked to cerebral metabolism, SPECT can also be used to identify possible epileptogenic areas. It is useful to have

both an ictal and an interictal study; a change from hypoperfusion during the interictal period to hyperperfusion in the ictal period is more reliable than an abnormality in either stage alone. However, SPECT is less sensitive than PET in localizing the epileptic region.

2. Neuropsychological Testing
Detailed neuropsychological testing is essential for the evaluation of various cerebral functions, including memory and language prior to surgical treatment. It defines the degree and pattern of pre-existing neuropsychological deficits, and may assist in the localization or lateralization of the area of abnormality.

The intracarotid amobarbital (ICA) test (also known as the Wada test) is used in developmentally cooperative patients to lateralize language and memory function prior to surgical treatment, and can help determine the extent of resection once the decision to proceed with surgery has been made.

3. Additional Brain Mapping Techniques
Functional MRI (fMRI) is an increasingly accepted technique for mapping particular brain functions in selected patients[4]. Brain functions that can now be visualized (mapped) with fMRI include language, motor function, and sensory function (tactile and visual). Imaging the mesial temporal lobe structures for activation with short-term memory tasks is now also feasible. The significance of fMRI is that it may enable the pre-surgical evaluation process to õskipò intracranial seizure recording or an intracranial brain mapping (grid mapping) stage, or otherwise provide information that is critical for best surgical planning. In general, however, fMRI requires the participation of an awake and cooperative patient, and so its use is limited with younger children, or those with developmental or behavioral impairments.

Surgical Procedures for Specific Epilepsies:

Various types of operations are performed for treatment of epilepsy. This decision is highly individualized.

1. Temporal Lobectomy/Amygdalohippocampectomy
This procedure, in its many variations, is the single most common epilepsy procedure in the adolescent and adult population. The vast majority of such cases are for refractory epilepsy associated with mesial temporal sclerosis (MTS), which is now identifiable in many cases with high-resolution MR imaging. MTS also occurs in the childhood population, and has been described in children as young as one year of age. Long-term surgical success with this group can be as high as 80%.

2. Lesion Resection
Focal lesions affecting the neocortex commonly cause refractory epilepsy. There are many responsible pathologies, but common entities include focal cortical dysplasia, cavernous malformations, and benign tumors such as gangliogliomas and dysembryoblastic neuroepithelial tumors (DNETs). The identification of the lesion by structural imaging greatly simplifies the surgical process with respect to localization of the seizure focus. Success with this group can be as high as 70-80%.

3. Tailored Neocortical Resection

These cases, usually non-lesional by high-resolution MR imaging, usually prove to be due to focal or regional cortical malformations, and are particularly common with epilepsy surgery performed on children less than 10 years of age. Many of these patients have ñcatastrophicò epilepsy, with multiple daily seizures, and deterioration of developmental milestones.

The region of surgical resection is always highly individualized in this group, often determined by functional imaging such as PET, and guided further by the use of intracranial grid electrodes for seizure and functional mapping. Long-term success (complete seizure control) in this group is approximately 50%, although many more are significantly improved by surgery.

4. Multiple Subpial Transection

This technique is utilized for identified seizure foci affecting the neocortex when surgical resection is deemed ill advised due to the presence of the seizure focus within eloquent cortex, and the associated high risk of new neurological deficits if resection is performed. The brain surface in the affected cortical region, usually the crown of the gyrus, is incised with a probe, disrupting the horizontal fibers needed for seizure propagation, but without removing cortical tissue, and therefore preserving function. Multiple subpial transection (MST) is often paired with cortical resection in adjacent areas that are determined to be safe to remove.

5. Hemispherectomy

This procedure, and its technical variants, is usually restricted to the pediatric age range, specifically for children with catastrophic epilepsy associated with disease affecting one cerebral hemisphere. Examples of disease processes appropriate for hemispherectomy include hemimegalencephaly, porencephaly resulting from intrauterine stroke or injury, Rasmussenõs encephalitis, Sturge-Weber syndrome, and others. Patients are most suitable when the contralateral hemisphere is completely normal. These patients require rehabilitation following surgery, but usually recover to their pre-operative baseline with respect to motor function on the opposite side of the body. Long-term success for this procedure can be up to 80%.

6. Corpus Callosotomy

A palliative procedure, with surgical transection of a portion of the corpus callosum, in an effort to reduce the number of drop attacks that result in injury, in patients with refractory epilepsy who are not candidates for resective surgery. This procedure is commonly performed in stages, with transection of the anterior half or two-thirds of the corpus callosum, followed by transection of the posterior half if needed. Less than 5% of patients will experience complete seizure control, but 60% may have improvement in drop attacks.

7. Gamma Knife

Gamma knife (GK) is suitable for selected lesions visualized by MR imaging that result in epilepsy. While the treatment effect may be delayed by 6-12 months, this radiosurgical technique largely avoids the complications that can occur with open surgery. GK is an

option for selected pathologies, among them hypothalamic hamartoma and arteriovenous malformations.

Surgical treatment of epilepsy has developed and progressed over the last sixty years. Advances in neurophysiology, neuroimaging, specific understanding of epilepsy mechanisms, and refinement of surgical techniques has made surgery possible for many patients with intractable epilepsy. In some patients it is the only treatment that may offer the possibility of a long-term cure. The outcome data acquired by many epilepsy centers around the world has clearly established that surgery has a major role in the treatment of intractable epilepsy.

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ILIZAROV PROCEDURE PRACTICE GUIDELINE

Patient Selection:

1. Established Criteria

    1. Limb lengthening when limb length (upper or lower) discrepancy $\geq$ 5 cm
    2. Angular and multiplanar deformities
    3. Foot deformities, including lengthening of the metatarsals
    4. Congenital anomalies of the lower limbs (such as fibular and tibial hemimelia) that require both lengthening and correction of angular deformities
    5. Joint contractures
    6. Reconstruction of large bony defects secondary to tumors, trauma, infection, or other causes by means of bony transport. Congenital pseudoarthrosis of the tibia is a typical example where the Ilizarov method may be indicated
    7. Non-union and infected non-union of fractures
    8. Some acute fractures
    9. Fusion of joints
    10. Distraction of joints
    11. Amputation stump elongation

2. Other criteria are considered investigational and not allowed at this time.

Protocol for Treatment:

All patients who are felt to have the indications for the Ilizarov procedure and together with their family have been appropriately counseled by the involved physicians and desire to undergo this treatment for the above clearly-eligible conditions shall be scheduled for the following:

1. General pediatric clinic
2. Psychological evaluation
3. Social service evaluation
4. Physical therapy evaluation

These evaluations should be completed prior to the procedure being scheduled. Results of these evaluations will be reviewed by the involved orthopaedic staff physician. If there are not obvious contraindications to proceeding with the surgery, all information, including the orthopaedic surgery consultation, pediatric consultation, psycho-social and physical therapy evaluations will be forwarded to the Medical Director for approval. Following approval, the patient will be scheduled for surgery in a timely manner.

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MAXILLO MANDIBULAR OSTEODISTRACTION PRACTICE GUIDELINE

Patient Selection Criteria:

Patients with severe maxillary or mandibular deformity for which no other osteotomy technique is appropriate and who have at least one of the following:

1. Respiratory problems to the extent of producing clinically significant dynamic or static airway obstruction.

2. Serious verbal communication disturbance as determined by a speech therapist. The report must indicate that the deformity is the primary etiology for the speech impairment and that speech therapy alone cannot further improve speech.

3. Mastication abnormality affecting the nutritional status of the individual resulting in growth abnormalities.

Protocol:

Patients who meet selection criteria for maxillo-mandibular osteodistraction shall be scheduled for consultation with the interdisciplinary craniofacial team at the CRS site where the procedure is to be performed.

Pre-procedure status is to be documented by chart photographs, 3D CTscan and/or 1 CAT and when appropriate, speech tape.

All patients undergoing distraction need pre-operative orthodontic treatment for appropriate alignment of dentition.

<u>Out of Region Patients:</u>

Prior to scheduling the procedure, the procedure site interdisciplinary team shall consult with the home site team to ensure home site CRS clinic involvement and follow up. If there are no obvious contraindications to proceedings with osteodistraction related to intersite management, all information from the procedure site team shall be forwarded to the Medical Director of the home site for approval. Following home site approval, the patient shall be scheduled for the procedure in a timely manner.

The purpose of the interdisciplinary evaluation at procedure and home sties shall be an attempt to clearly establish that the patient and family are capable of accepting and following through with the extensive post operative care, procedure modifications, and therapy.

Interdisciplinary Team Membership:

The team shall include:

- craniofacial surgeon,
- oral surgeon,
- orthodontist,
- pediatrician,
- psychologist,
- speech pathologist,
- social worker, and
- nutritionist.

Outcome Evaluation:

It shall be the responsibility of the craniofacial surgeon managing the osteodistraction procedure to provide periodic outcome progress reports at intervals determined by the craniofacial team, but at a minimum of 6, 12, 24 and 48 months post procedure. Reports must include documentation of:

- Any change in airway status,
- Any change in speech status,
- Any change in mastication status, and
- Photographs of facial reconstruction.

METABOLIC DISEASE

ORGANIZATIONAL GUIDELINES

Organizational Guidelines represent the minimum requirements for providing care for individuals with metabolic disease. Care and treatment should be provided in a manner with includes adherence to and consistence with each of the following Guidelines.

CRS Enrollment:

All members with metabolic disease diagnoses must be enrolled in metabolic clinics meeting these Guidelines.

Interdisciplinary Team Membership:

Interdisciplinary Team Members must be present during regional clinics and team conferences to review the patient information and determine the need to see the patient at a clinic site and must be available for inpatient consultation or coordination of care with inpatient staff.

Two Interdisciplinary Team Guidelines are identified, one for those conditions which are amenable to nutritional management and one for conditions which are not amenable to nutritional management. The following Team Members must attend outpatient clinics and team conferences and must be available for inpatient consultation or coordination of care with inpatient staff:

Conditions which are amenable to nutritional management:

- Lead Physician - Geneticist with expertise in metabolic disorders, preferably a biochemical geneticist.
- Genetics Counselor or Genetics Nurse
- Metabolic Nutritionist
- Child Psychologist (available)
- Registered Nurse Coordinator (may be the same as the Genetics Nurse)
- CRS Member / Caregiver
- Primary Care Physician[1] (invited)

Conditions not currently amenable to nutritional management:

- Lead Physician - Geneticist
- Genetic Counselor or Genetics Nurse

[1] The Primary Care Physician will be invited to all Team meetings; however, it is understood that PCP will not always be able to attend.

- CRS Member / Caregiver
- Registered Nurse Coordinator (may be the same as the Genetics Nurse)

Available Personnel:

The following personnel must be available during the specialty clinics as needed to see the patient:

- Advocate
- Child Life Specialist
- Educators (education advocacy)
- Social Worker
- Translator

Consultative Personnel:

Consultation may be obtained as needed for an eligible patient when the consultation is related to the diagnosis or regarding a potential condition that is CRS eligible. The list of disciplines which the CRS Clinic must have access to for consultation includes but is not limited to the following:

- Pediatric Neurologist
- Orthopedist
- Neurosurgeon
- Ophthalmologist
- Physical Therapist
- Nutritionist
- Child Psychologist
- Cardiologist
- ENT
- Physical Therapist
- Occupational Therapist
- Pediatrician
- Audiologist

Outreach Clinics:

Outreach clinics are designed to provide a limited specific set of services including evaluation, monitoring, and treatment in settings closer to the family than a regional clinic. Major treatment plan changes must be communicated to the regional clinic.

Members with metabolic conditions may attend neurology, genetics, or other Outreach Clinics as determined by the Interdisciplinary Team.

Facilities & Services:

1. Age-appropriate settings for all patients
2. Defined age-appropriate services, i.e., Pediatrics, Adolescent Medicine, and/or Internal Medicine
3. Pediatric and Adult Intensive Care Units
4. Nutrition or Dietary Department
5. Social Work Department
6. Identified clinic area
7. Laboratories:
   a) performing pediatric phlebotomy
   b) performing routine pediatric lab evaluations (if contracted, the contracts must address quality and time requirements)
   c) performing or providing specialized genetics testing relevant to the condition
8. Access to the pharmacy and/or a distribution point for metabolic formula.

Team/Staff Meetings:

Team and staff meetings will be held based on the age of the patient and their diagnosis. At a minimum the following will occur:

1. Interdisciplinary Team Meetings - patient specific meetings held with the family for review of the status and planning the course of treatment:
   a) At the time of initial diagnosis and
   b) Once every three years thereafter (at a minimum.)
2. Staff meetings annually to focus on issues of clinic patient care and clinic administration.
3. Education meetings annually to focus on new information regarding the care and treatment for patients with metabolic diseases.

Lead Physician Specialists:

Qualifications: The lead physician for patients with metabolic diseases amenable to nutritional management shall be a Board Eligible/Board Certified in genetics, preferably a biochemical geneticist, with pediatric experience.

The lead physician for patients with metabolic disease not related to dietary conditions/treatment shall preferably be a biochemical geneticist with pediatric experience.

GUIDELINES FOR PATIENT SERVICES, EVALUATION AND MONITORING FOR METABOLIC DISEASE

The purpose of these guidelines is to promote a uniform level of care at CRS Clinics for members with metabolic disease, and to provide a general framework for good patient care. Their relevance to specific situations will depend on individual variations in clinical course and professional judgment. In addition, this document should serve as a tool to assess programs, secure resources needed to enhance patient care and education, and guide the future growth and development of metabolic care.

Diagnosis:

Goal: There is a vast, and ever increasing, number of medically defined inborn errors of metabolism. Diagnosis of specific conditions will be dictated by the biochemical basis for the individual condition. To provide accurate and timely diagnosis of metabolic disease the following guidelines are offered recognizing that diagnosis for specific conditions will be individualized:

Defects of Intermediary Metabolism such as Amino Acid and Organic Acid Disorders - Documentation of inborn error of metabolism, including but not exclusive of abnormalities in amino acid and organic acid metabolism, includes the following information needs:

1. Complete medical history
2. Complete physical examination
3. Copies of laboratory reports documenting the purported inborn error of metabolism, including but not limited to quantitative plasma amino acids and quantitative urinary organic acids

Metabolic Storage Diseases - Documentation of metabolic storage disease requires the following information:

1. Complete medical history
2. Complete physical examination
3. Laboratory data documenting the metabolic storage disease including but not limited to pathologic demonstration of stored material and enzymatic confirmation of a specific defect

Confirmation of the diagnosis requires:

Confirmation of diagnosis by a pediatric geneticist, pediatrician, or pediatric neurologist.

Evaluation and Education of Newly Diagnosed Patients

Goal: To provide accurate assessment of physical and emotional status, and to begin patient and family education.

The following assessments should be completed:

1. Psychological Evaluation including family members and family issues initially and on an ongoing basis as determined by the Interdisciplinary Team.
2. Psychometric Evaluation using nationally accepted instruments appropriate to the age of the patient and family member(s). Baseline and periodic assessments should be completed.

Goal: To help families cope with the emotional impact of diagnosis and formulate an appropriate therapeutic plan.

1. Information should be provided to the family following a positive newborn screen by the Newborn Screening Follow-up Staff if suspected metabolic condition is one identified by the newborn screen. If the metabolic disease is one suspected because of the clinical presentation, information shall be provided as iterated in #2 below.
2. Prior to or concomitant with the confirmation testing, experienced metabolic personnel should provide families with information about the suspected metabolic disease including the diagnosis and treatment.
3. Following confirmation, a geneticist and/or a genetic counselor should provide appropriate genetics counseling to the family.

   If available, written information regarding the condition should be provided, such as diagnostic requirements, inheritance concerns, possible treatment regimens, and prognosis.
4. A nutritionist should provide general information about nutritional management and respond to questions regarding their specific nutritional program.
5. Information about the CRS experience; i.e., what is CRS, who does CRS serve, what is a metabolic clinic like, who will be there, what is the family's role, etc.
6. Information regarding support groups and how to contact them.

Ongoing Patient Evaluation and Monitoring:

Goal: The ongoing patient evaluation and monitoring will be dictated by the biochemical basis for individual condition. However, some generalizations are appropriate to iterate as guidelines for the care of this group of disorders as a whole and to anticipate and treat physical and psychosocial problems and complications of the disease.

Clinic Visits:

1. For disorders of Intermediary Metabolism Amenable to Nutritional Management including but not limited to Amino and Organic Acid Disorders:
   a. Monthly for the first 6 months of life
   b. Bimonthly from 6 months to a year
   c. Quarterly from one year to 3 years

d. Semiannually thereafter

2. For Storage Disorders

a. Bimonthly for the first 6 months

b. Quarterly from 6 months to a year of age

c. Semiannually from one year to 3 years

3. For Conditions Not Amenable to Nutritional Management

a. Quarterly to one year of age

b. Annually thereafter

Monitoring:

Metabolic patients are monitored by laboratory analysis including but not limited to metabolic analysis of blood and urine.

Treatment:

Goal: The treatment for inborn errors of metabolism will be determined by the specific condition. However, some generalizations are appropriate to iterate as guidelines for the care of this group of disorders as a whole. Broadly, the inborn errors can be divided into two groups: those amenable to treatment by nutritional management (including inborn errors of vitamin metabolism) and those not amenable. The following are given as guidelines for these two categories recognizing that treatment will be individualized to the specific condition.

The Lead Physician of the Metabolic Team and Team members must be involved in decisions regarding all major procedures.

1. For Conditions Amenable to Nutritional Management (Including Inborn Errors of Vitamin Metabolism):

a. Provide metabolic formula and foods to limit the intake of the offending metabolite while supporting optimum growth and development.

b. Provide pharmacologic administration of vitamin(s) to correct or improve the metabolic disruption.

2. For Conditions <u>Not</u> Amenable to Nutritional Management:

Consequences and complications are managed within the specialty clinics. These actions must be coordinated with the Interdisciplinary Metabolic Clinic Team.

Gastrointestinal System/Nutrition:

Goal: To anticipate and treat nutritional deficits and complications. The ultimate goal is to achieve optimum growth and nutrition. Continued monitoring of growth

parameters in conjunction with appropriate metabolic nutritional guidance is extremely important.

NEUROFIBROMATOSIS

ORGANIZATIONAL GUIDELINES

Organizational Guidelines represent the minimum requirements for providing care for individuals with neurofibromatosis. Care and treatment should be provided in a manner that includes adherence to and consistency with each of the following Guidelines.

CRS Enrollment:

Neurofibromatosis patients must be enrolled in an NF Clinic. The patient may be seen at other clinics as appropriate as determined by the Interdisciplinary Team. All treatment must be consistent with the goals set in the Neurofibromatosis Clinic and records from other clinics must be sent to the NF Clinic Site.

Interdisciplinary Team Membership:

The following Team Members must be present during regional clinics and team conferences to review the patient information and determine the need to see the patient at a clinic site and must be available for inpatient consultation or coordination of care with inpatient staff:

- Pediatrician/PNP
- Geneticist/Genetic Counselor
- RN Nurse Coordinator
- Child Psychologist
- Pediatric Neurologist
- Social Worker
- Child Psychiatrist
- CRS Member / Caregiver
- Primary Care Physician[1]
- Vocational Rehabilitation for teenagers[2]

Available Personnel:

The following personnel must be available to the member/adult at the neurofibromatosis clinic:

- Advocate
- Audiologist

[1] The Primary Care Physician will be invited to all Team meetings; however, it is understood that PCP will not always be able to attend.
[2] Vocational Rehabilitation Services representatives are to be invited to the Clinic.

- Child Life Specialist
- Translator

Consultative Personnel:

The Regional Clinic must have access for consultation to specialists including, but not limited to the following:

- Cardiologist
- Neurosurgeon
- Nephrologist
- Occupational Therapist
- Oncologist
- Otolaryngologist
- Ophthalmologist
- Orthopedist
- Pediatric Surgeon
- Physical Therapist
- Plastic Surgeon
- Speech Therapist

Outreach Clinics:

Outreach clinics are designed to provide a limited specific set of services including evaluation, monitoring and treatment in settings closer to the family than a regional clinic. Major treatment plan changes must be communicated to the regional clinic.

Members with neurofibromatosis may attend neurology, genetics, or orthopedic outreach clinics as determined by the Interdisciplinary Team.

Facilities & Services:

1. Age-appropriate setting for all patients
2. Defined age-appropriate services (i.e., Pediatrics, Adolescent Medicine and/or Internal Medicine)
3. Pediatric and Adult Intensive Care Units
4. Social Work Department
5. Identified clinic area for NF outpatient services
6. Access to the pharmacy

Team/Staff Meetings:

Team and staff meetings will be held based on the age of the patient and their diagnosis. At a minimum the following will occur:

1. Interdisciplinary Team Meetings / review and planning meetings (patient specific meetings) are to be held at least once every two years for planning and review.
2. Staff meetings annually to focus on issues of clinic patient care and clinic administration.
3. Education meetings annually to focus on new information regarding the care and treatment for persons with neurofibromatosis. These may be off site meetings.

Lead Physician Specialists:

Qualifications: The lead physician for patients with neurofibromatosis should be a geneticist, pediatrician or a Pediatric Neurologist with knowledge and experience in the evaluation, care and treatment of patients with neurofibromatosis.

GUIDELINES FOR PATIENT SERVICES, EVALUATION & MONITORING FOR NEUROFIBROMATOSIS

The purpose of these guidelines is to promote a uniform level of care at CRS Clinics for members and adults with neurofibromatosis, and to provide a general framework for good patient care. Their relevance to specific situations will depend on individual variations in clinical course and professional judgment. In addition, this document should serve as a tool to assess programs, secure resources needed to enhance patient care and education, and guide the future growth and develop treatment of neurofibromatosis.

Diagnosis

Goal: To provide accurate and timely diagnosis of neurofibromatosis.

Diagnostic Criteria NF1: As developed by the NIH Consensus Development Conference and subsequent changes, specified that 2 or more of the following be present: [1, 3]

1. 6 or more cafe-au-lait macules more than 5 mm in greatest diameter in prepubertal individuals and more than 15 mm in greatest diameter after puberty
2. 2 or more neurofibromas of any type or 1 plexiform neurofibroma
3. freckling in the axillary or inguinal regions (Crowe sign)
4. an optic pathway tumor
5. 2 or more Lisch nodules (iris hamartomas)
6. a distinctive, osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of the long bones (with or without pseudarthrosis)

7. a first-degree relative (parent, sibling, or offspring) with NF1 that met criteria 1-6 above

The diagnosis of NF1 cannot be made on the presence of cafe-au-lait spots alone; however, the family should be told that NF1 is by far the most likely diagnosis, since familial cafe-au-lait spots are an exceedingly rare condition. Additional criteria are almost always met by the age of 10 years. [3]

Confirmation of the diagnosis for NF 1 must be established prior to entry into the CRS program. Follow up within CRS requires the following activities:

- History

  Focus on symptoms associated with NF1, such as cognitive or psychomotor deficits, pain, visual complaints, progressive neurologic deficits, changes in bowel and bladder function, weakness, seizures, headaches, and childhood development history. [1]

- Family History

  Should include grandparents, great aunts and uncles and their descendants. When possible, an effort should be made to locate medical records of affected 1st and 2nd degree relatives. [1] Parents and siblings should be referred (this is not a covered CRS service) for examination for signs and symptoms of NF1. [3]

- Physical Examination

  Should give particular attention to possible manifestations of the disorder such as hypertension, scoliosis and other skeletal anomalies, Macrocephaly, focal neurological deficits (impaired vision, ptosis, optic atrophy), developmental disabilities, proptosis, Lisch nodules, short stature, signs of precocious puberty or hypogonadism, cafe-au-lait macules, and neurofibromas. [1]

- Tests

  Should be dictated by findings on clinical evaluation. Laboratory tests in asymptomatic patients are unlikely to be of value, particularly computerized tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), and evoked potentials. As an option, DNA testing may be provided at the Discretion of the NF Team.

- Counseling

  Must be provided for all patients and their families and should include: [1]
  1. Prognosis
  2. Genetics
  3. Psychological and Social Adjustment
  4. Family members
  5. Follow-up
  6. Resources

  Modified counseling is indicated for preadolescents who are likely to have NF1. [3]

- Written Report

Should summarize clinical findings, test results, and information conveyed through counseling.[1]

Diagnostic Criteria for NF2 per the Manchester Conference: Individuals with the following clinical features have confirmed (definite) NF2:[3]

- Bilateral vestibular schwannomas (VS) OR
- First-degree relative with NF2 AND EITHER
- Unilateral VS < 30 y OR
- 2 of the following:
  - Meningioma
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular lenticular opacity
  - Individuals with the following clinical features should be evaluated for NF2:
  - Unilateral vestibular schwannomas < 30 y AND
  - At least one of the following:
    - meningioma
    - glioma
    - schwannoma
    - juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
    - Multiple meningiomas (2 or more) AND
    - Unilateral vestibular schwannomas <30y OR
    - One of the following:
      - glioma
      - schwannoma
      - juvenile posterior subcapsular lenticuolar opacities / juvenile cortical cataract

Diagnostic Activities for NF2[1] (unless otherwise indicated): Evaluation for NF2 should never represent a single point in time but should include long term follow up.[3] Screening can be relaxed if there are no further tumors developing during a 5 to 10 year period or if NF2 molecular testing becomes more reliable for exclusion.[3] MR should be performed to rule out bilateral vestibular schwannomas definitely.[3] Persons with retinal hamartomas or cortical wedge opacities should be evaluated by a trained neuro-ophthalmologist.[3]

- History

Focus on symptoms possible associated with hearing loss, tinnitus, dizziness, loss of balance, pain, headache and seizures

- Family History

  Include grandparents, great aunts and uncles and their descendants

  Should locate medical records for affected 1st and 2nd degree relatives

- Physical Examination

  Should give particular attention to possible manifestations such as cafe-au-lait macules and neurofibromas

  Neurological assessment should emphasize cranial nerves, balance and coordination

- Tests

  ✓ Must include audiogram and brain stem auditory evoked responses (BAER)

  ✓ High Resolution MRI with gadolinium should be used in patients with evidence of hearing impairments or abnormal BAER

  ✓ Tests of vestibular function may be useful adjuncts to BAER

  ✓ If no MRI has been performed by puberty, it should be obtained

  ✓ Other tests as indicated

- Counseling

  Must be provided for all patients and their families and should include:

  1. Prognosis
  2. Genetics
  3. Psychological and Social Adjustment
  4. Family members
  5. Follow-up
  6. Resources

- Written Report
  Should summarize clinical findings, test results and information conveyed through counseling

  Goal: To provide accurate assessment of physical, emotional, and behavioral issues and educational / vocational needs, and to begin patient and family education.

Education of Parents & Diagnosed Patients

NF 1:

Families and patients may require support in the following areas (but not limited to these areas). Services should be provided if they are included in the CRS policy regarding covered services.

1. Adjustment to the diagnosis

2. Coping with medical sequelae and medical procedures
3. Attention problems or ADHD (CRS will refer patients requiring Medication Management to Behavioral Health Systems)
4. Educational difficulties including learning disabilities fine motor deficits.
5. Increased risk for psychological disorders / adjustment problems such as depression, low self-esteem, etc.
6. Linkage to community services such as DDD, Behavioral Health, AzEIP, ALTCS, SSI, housing, food, transportation.

Ongoing Patient Evaluation and Monitoring

Goal: To anticipate and treat physical and psychosocial problems and complications of the disease.

NF1 Follow-up Examination Guidelines:

Should be performed annually for NF 1 patients and counseling should parallel assessment described above[1]

1. Infancy[3]

   Presence of tibial bowing should prompt referral to orthopedic surgeon familiar with management of NF1 related orthopedic problems in members

   Prevention of fracture is of paramount importance in individuals with tibial bowing.

2. Childhood[3]

   Annual vision evaluation by an experienced ophthalmologist during first decade of life.

   Cranial MR imaging should be used when there is any evidence of optic nerve dysfunction. There should be special attention to the orbits and appropriate management determined by a multidisciplinary clinical team.

   The role of surgery in the management of optic pathway tumors is limited and treatment usually involves chemotherapy and, less commonly, radiation therapy.

   All members should be evaluated for psychosocial issues with an emphasis on those members suspected of having learning disabilities. Some members manifest attention deficit disorder and may benefit from treatment with stimulant medication. Medication Management of ADHD will be referred to the Behavioral Health System.

   Monitor for blood pressure evaluations associated with renal artery stenosis or, rarely, pheochromocytomas.

   Decisions about surgical treatment and frequency of follow up on plexiform neurofibromas must be made judiciously and individualized for each patient. The Interdisciplinary Team should be consulted.

   Members with headache or abdominal pain should have a careful physical and neurologic examination to exclude other underlying causes.

Members with headache or abdominal pain should have a careful physical and neurologic examination to exclude other underlying.

3. Lifelong[3]

   (CRS Members to age 21)

   Specific lesions which are symptomic/function limiting may be removed as they occur by experienced surgeons. The long term benefit of removal of large numbers of neurofibromatomas by surgical excision or carbon dioxide laser is untested.

   Persons with persistent hypertension or classical signs of pheochromocytoma should be evaluated further

   Rapid growth of a plexiform neurofibromas or the development of de novo pain should prompt an immediate evaluation for bleeding or malignant transformation

NF 2 Follow Up Examination Guidelines:

1. The criterion Guideline for the identification of vestibular schwannomas is MR imaging of the head with 3-mm cuts through the internal auditory canals with and without gadolinium enhancement.
2. All patients with a new diagnosis of NF2 should undergo full spinal MR imaging with or without gadolinium enhancements to aid in prognostication.
3. Patients with intramedullary tumors should receive an annual follow up MR image.
4. If tumors are found, follow up MR imaging should be performed every 6 to 12 months.
5. Part of the evaluation of a person suspected to having NF2 should include review of pathology reports and review of original tumor sections when possible.
6. In families with early onset NF2, the screening protocol should begin in early childhood.
7. Individuals with NF2 should have an annual neurologic evaluation with cranial MRI as well as audiometry and brainstem auditory evoked responses for those with functional hearing.
8. Follow up ophthalmologic evaluations and spinal imaging are recommended for persons with problems in these areas.
9. Surgical treatment should be limited to specialty tertiary care centers with experienced otolaryngologists and neurosurgeons
10. The Interdisciplinary Team should work together to coordinate care and follow up
11. Surgical planning should be done by Neurosurgeon and/or Otolaryngologist. Referral by NF team can be based on MRI changes or clinical symptoms.
12. Radiation therapy should be considered carefully

13. Treatment of vestibular tumors should include counseling of the problems with balance. Drowning and near drowning caused by underwater disorientation is especially important
14. Hearing and speech augmentation is an important part of management of NF2. Lip reading and hearing aids may be useful
15. Review social adjustment development and appropriateness of school / vocational placement.

Treatment

Goal: To anticipate and treat progression and complications of the disease.

Management Options for NF 1 patients:

Management Options for Optic Glioma:

- Annual ophthalmologic examination using MR and CT imaging to document size, shape and extension
- Appropriate consultation will be made if special circumstances such as disfiguring orbital mass or large tumors compressing adjacent structures

Management Options for Other Neural Tumors:

- Manage these tumors in same manner as in general population

Management Options for Orthopedic Problems:

- Kyphoscoliosis and tibial bowing benefit from early intervention and should be managed by an orthopedist familiar with complications

Management Options for Vascular Problems:

- Thorough evaluation of hypertension
- Other vascular disorders must be handled on an individual basis in the same manner as they would be in the general population

Psychosocial Issues

Goal: To anticipate and treat social and emotional problems of patients and their families.

Patients and families should have available interdisciplinary multi specialty care as well as follow up services including community support research and referral services, education advocacy and placement assistance, -psychological and neuropsychological evaluations, and developmentally appropriate support and education to the member. This would include the services of a social worker, Member Psychologist, child life specialist and special educator.

1. Patient advocacy through education of personnel in schools, insurers, health care services, regional and national health organizations and welfare services.
2. In-service education of health professionals and health sciences students, social sciences students and others.

3. Assist in linking adults to Vocational Rehabilitation and Vocational education and training.

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SICKLE CELL DISEASE IN CHILDREN AND ADOLESCENTS:
DIAGNOSIS, GUIDELINES FOR COMPREHENSIVE CARE, AND CARE PATHS AND PROTOCOLS FOR MANAGEMENT OF ACUTE AND CHRONIC COMPLICATIONS*

Peter A. Lane, George R. Buchanan, John J. Hutter, Robert F. Austin,
Howard A. Britton, Zora R. Rogers, James R. Eckman, Michael DeBaun, Winfred C. Wang,
Prasad Mathew, Sarah Iden, Michael Recht, Jesse D. Cohen, Ernest Frugé,
Leanne Embry, Lewis Hsu, Brigitta Mueller, Robert Goldsby, Charles T. Quinn
for the Sickle Cell Disease Care Consortium**

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OPERATIONAL & SERVICE GUIDELINES
SICKLE CELL DISEASE

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INTRODUCTION

Much progress has been made during the past 20 years in the treatment of sickle cell disease. Identification of most affected infants by neonatal screening provides opportunities for educational and medical interventions that significantly reduce morbidity and mortality during childhood and adolescence. Comprehensive medical care includes extensive health maintenance with appropriate prophylactic measures, parental education, psychosocial support, and periodic medical assessment with monitoring for the development of chronic organ damage. Appropriate care also provides for the management of acute illness in a setting where knowledge and perspective about sickle cell disease is available and where physicians have ready access to baseline information about the patient, including results of previous physical examinations, laboratory work, and radiographs. Because acute illness in patients with sickle cell disease can prove rapidly life threatening, it is essential that patients have unimpeded access to providers who have the expertise necessary to quickly recognize and treat potentially catastrophic signs and symptoms. Such care not only reduces morbidity and mortality, but it also may reduce medical costs by preventing some manifestations of the disease and by limiting the severity or sequelae of others. Many acute complications can be managed safely on an outpatient basis, thus reducing the need for hospitalization.

This manual provides information about the diagnosis of sickle cell disease, an overview of comprehensive care, and clinical care paths and protocols for the management of some of the more common acute and chronic complications. The manual originally was developed in 1996 by the staff of the Colorado Sickle Cell Treatment and Research Center, University of Colorado School of Medicine and The Children's Hospital, Denver, CO. Subsequently, it has been revised and expanded annually, most recently by its current authors, pediatricians and hematologists from Arizona, Colorado, Georgia, Missouri, New Mexico, Tennessee, Texas, and Utah who met in November, 2001. Thus, it represents a broad consensus of providers with expertise in sickle cell disease. It is hoped that these guidelines will improve the consistency and quality of care, but the authors recognize that adherence to them does not assure a successful medical outcome and that deviations from them will be appropriate in individual cases. The guidelines are not intended to replace a physician's best medical judgment, nor should they be used as a substitute for hands-on care by providers with experience and expertise in the management of sickle cell disease.

The current revision of the manual was supported in part by a contract from the Genetic Services Branch, Maternal and Child Health Bureau, HRSA. The manual's authors encourage the widespread reproduction and distribution of these materials for any educational and/or patient care related purpose and ask only that the source of the materials be acknowledged. Individual institutions may wish to adopt some or all of the clinical care paths and protocols (with or without modification) for routine use in their outpatient clinics and inpatient units. To facilitate dissemination of this material, the manual is now available on the websites of the Mountain States Genetics Network (www.mostgene.org), the Texas Department of Health (www.tdh.state.tx.us/newborn/newborn.htm) and the Georgia Comprehensive Sickle Cell Center (www.scinfo.org). It is expected that this manual will continue to undergo periodic review with revisions posted on these websites. Its authors welcome comments and suggestions for improvement.

PRINCIPLES OF CARE FOR CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE

Sickle cell disease is a complex genetic disorder with multi-system manifestations that requires specialized comprehensive care to achieve an optimal outcome. Comprehensive medical care

includes ongoing patient and family education, periodic comprehensive evaluations and other disease-specific health maintenance services, timely and appropriate treatment of acute illness, and genetic counseling.

In addition to medical treatment, the management of sickle cell disease requires sensitivity to important psychosocial implications of the disease and services to address them. Barriers to appropriate health care include inadequate insurance coverage, transportation, and/or access to health care providers with expertise in the management of sickle cell disease. Important stresses that often affect a family's ability to cope with sickle cell disease include the economic and educational consequences of time lost from work and school and the impact of chronic illness on normal family functioning, including adjustment issues for non-affected siblings. Families live daily with the knowledge that unpredictable acute illnesses will interrupt daily life, and there are often feelings of powerlessness, frustration, and even anger. A general lack of community awareness about sickle cell disease and fear of stigmatization may limit the support available from extended family, friends, and the community at large. Prior experience with health care providers who lack knowledge, sensitivity, and compassion may contribute to delays in seeking appropriate health care and may engender adversarial relationships between families and providers. Failure to appreciate ethnic and cultural differences between providers and patients and families may also contribute to misunderstanding and lack of trust. Thus, it is imperative that providers take time to listen to the concerns of patients and families, that they be sensitive to psychosocial as well as medical needs, and that they assist families in accessing available resources as needed.

The federal Healthy People 2010 Objectives include six measures for Children with Special Health Care Needs.* These provide guiding principles for the care of CRS Program enrolled Members with sickle cell disease.

1. **All members with sickle cell disease will receive regular and ongoing comprehensive care within a medical home.**

   Optimal care requires the active involvement of professionals in pediatrics and hematology, nursing, social work, psychology, genetics, education, and counseling. The services they provide need to be coordinated through an appropriate medical home. For many patients, the medical home will be a multi-disciplinary sickle cell clinic that coordinates all aspects of comprehensive care in collaboration with the member's primary care physician or that provides specialty and primary care in one setting. In other cases, the medical home may be provided by a knowledgeable primary care provider from whom the patient receives day-to-day care, with periodic referrals to sickle cell specialists for comprehensive evaluations and for the management and treatment of severe, life-threatening complications. The location of the medical home and extent to which care is provided by the primary care provider versus the multi-disciplinary sickle cell clinic will vary among patients and communities and will depend in part on the expertise of the primary care provider, access to a multi-disciplinary sickle cell clinic, family preference, and the frequency and severity of disease manifestations. Good communication among the family, primary care providers, and subspecialists is essential to provide coordinated care and to establish and maintain trust.

2. **All families of Members with sickle cell disease should have adequate private and/or public insurance to pay for the services they need.**

   Almost every member in the U.S. with sickle cell disease is eligible for health care coverage by commercial insurance, Medicaid, Medicare, SSI, or the Childrenôs Health Insurance Plan (CHIP). It is imperative that providers assist families and patients to obtain and maintain adequate insurance coverage. For patients insured by managed care plans, ongoing access

to providers with expertise in sickle cell disease may require advocacy by primary care providers and anticipation of payer requirements for prior authorization for specialty services.

3. **All members with sickle cell disease will be screened early and continuously for special health care needs.**

   Individuals with sickle cell disease require ongoing screening for a variety of disease-related problems. All patients with sickle cell disease should have regularly scheduled comprehensive medical evaluations to review previous disease manifestations, document important baseline physical findings and laboratory values, monitor growth and development, and screen for signs of chronic organ damage. Comprehensive evaluations also provide an ideal setting for providing age-appropriate family and patient education and for evaluating and addressing psychosocial issues.

4. **Services for member's with sickle cell disease and their families should be organized in ways that families can use them easily.**

   Important health and other services may be available but difficult to access because of problems with transportation or parking or a lack of insurance coverage or prior authorization from managed care plans. Access to multidisciplinary comprehensive evaluations can be facilitated by the provision of outreach clinics in communities distant from tertiary care centers. Because acute illness can prove rapidly life threatening, it is imperative that every member with sickle cell disease have a plan for around-the-clock access to a medical facility where knowledge and perspective about sickle cell disease is available, where evaluation and treatment can be promptly delivered, and where providers have access to baseline information about the patient. Other important services include social services, neurocognitive evaluations, and educational and vocational planning and counseling - all of which require communication and coordination among providers, educators, patients, and families. In many communities, patient and family support groups and other valuable supportive, educational, and counseling services are organized and provided by community-based groups, such as local chapters of the Sickle Cell Disease Association of America.

5. **Families of members with sickle cell disease will participate in health care decision-making at all levels and will be satisfied with the services they receive.**

   Parents are ultimately responsible for decisions about their children. In order for parents to participate in decisions regarding their children's health care, they must receive accurate and ongoing education about the disease and about a variety of treatment options. Education should be provided in an open, non-judgmental, and mutually respectful environment. Providers should recognize that personal and cultural beliefs about illness and existing stresses and support systems may greatly impact the family's ability to cope with sickle cell disease and may appropriately influence their decisions. Patients and families should be encouraged to provide feedback about the care they receive and suggestions to improve it.

6. **All members with sickle cell disease will receive the services necessary to make appropriate transitions to all aspects of adult life, including adult health care, work, and independence.**

   The families of members with sickle cell disease should be encouraged to set appropriate goals for their children and to develop realistic strategies to achieve those goals. School personnel must be educated about sickle cell disease and encouraged to accommodate repeated and often unpredictable absences. During middle childhood and adolescence,

education about sickle cell disease is increasingly directed towards the patient, as well as the family, with the expectation that adolescents will be knowledgeable about their disease and its management. Counseling about higher education and vocational choices should be realistic but avoid underestimating the patient's potential. The transition from pediatric to adult health care providers and institutions can be traumatic and requires prior discussion, preparation, and planning. The current shortage of health care providers with interest and expertise in the treatment of adults with sickle cell disease is a major problem that must be addressed.

* A National Agenda for Children with Special Health Care Needs. Measuring Success for Healthy People 2010: A working document. Material and Child Health Bureau, HRSA, September, 1999.

DIAGNOSTIC TESTING COMMON SICKLE CELL SYNDROMES*

Syndrome	Neonatal Screening[2]	Hemoglobin Separation by age 6 weeks[2]	Hemoglobin Separation in Older Members (≤ 5 yr)				
			Hb A (%)	Hb S (%)	Hb F (%)	Hb A_2 (%)	Hb C (%)
Sickle cell anemia (HbSS)	FS	FS	0	75-95	2-25[4]	<3.5	0
Sickle β^0-thalassemia[1]	FS	FS	0	80-92	2-15	3.5-7.0	0
Sickle-hemoglobin C disease (Hb SC)	FSC	FSC	0	45-50	1-5	NA[5]	45-50
Sickle β^+-thalassemia[1]	FSA or FS[3]	FSA	5-30	65-90	2-10	3.5-6.0	0
Sickle cell trait	FAS	FAS	50-60	35-45	<2	<3.5	0
Normal	FA	FA or AF	95-98	0	<2	<3.5	0

* Table shows results of hemoglobin separation tests (i.e., hemoglobin electrophoresis, isoelectric focusing and/or HPLC). In selected cases, DNA analysis or testing of parents may be helpful.

1 β^o indicates thalassemia mutation with absent production of β-globin (i.e. no Hb A); β^+indicates thalassemia mutation with reduced (but not absent) production of β-globin

2 Hemoglobins reported in order of quantity (e.g., FSA=F>S>A); F, fetal hemoglobin; S, sickle hemoglobin; C, hemoglobin C; A, hemoglobin A. Abnormal results require confirmation with Hb electrophoresis, isolectric focusing, HPLC, and/or DNA studies (see p. 7).

3 Quantity of Hb A at birth sometimes insufficient for detection.

4 Hb F levels in rare cases of Hb SS may be high enough to cause confusion with Hb S-pancellular Hereditary Persistence of Fetal Hemoglobin (S-HPFH), a benign disorder not usually associated with significant anemia or vaso-occlusion. In such cases, family studies and laboratory tests to evaluate the distribution of Hb F among red cells may be helpful.

5 Quantity of Hb A_2 cannot be measured by electrophoresis in presence of Hb C

NEWBORN SCREENING FOLLOW-UP GUIDELINES[1]

Follow-up of Infants with Probable Hemoglobin Disease (i.e. newborn screening results FS, FSC, FSA, FC, FE, FU, F Other, F only, etc.[2])

1. The newborn screening laboratory reports positive results promptly to the hospital, sample submitter, and/or to the Newborn Screening Program follow-up coordinator (varies by state). The laboratory or follow-up coordinator (depending on the state) notifies the primary care physician and/or the parents by telephone, FAX, or certified mail of the infant's test results. Whenever possible, contact with the family will be accomplished within 2-3 weeks.

2. The primary care physician or follow-up coordinator will arrange for confirmatory testing (hemoglobin separation by electrophoresis, isoelectric focusing and, and/or HPLC or DNA analysis) in an appropriate laboratory by two months of age, unless the diagnosis has already been confirmed. Testing of parents or DNA analysis may help establish the correct diagnosis in some infants. Consultation with a pediatric hematologist is strongly encouraged.

3. Parents will be notified promptly when a clinically significant hemoglobin disorder has been confirmed. Infants with confirmed sickle cell anemia or sickle β^0-thalassemia (or with screening results FS not yet confirmed) should be started on prophylactic penicillin (VK 125 mg po bid)[3] by 2-3 months of age. Education and written information about the disorder and its treatment and a medical referral to a physician knowledgeable about sickle cell disease (ideally a pediatric hematologist and/or sickle cell clinic) will be provided. Early education about sickle cell disease should emphasize the importance of prompt medical evaluation for fever and for signs and/or symptoms of splenic sequestration. Genetic counseling should be provided (see p. 10).

4. As part of appropriate education, the role of testing parents, siblings, or other family members should be discussed.

5. If the family declines follow-up and confirmatory testing, all follow-up attempts will be thoroughly documented. It may be appropriate to notify Member Protective Services in some instances.

Follow-up of Infants with Probable Hemoglobin Trait (i.e., newborn screening results FAS, FAC, FAE, FAU, FA Other, etc.[2]) (does not include Hb Bart's)

1. The newborn screening laboratory reports screening results to the hospital, sample submitter, and/or to the Newborn Screening Program follow-up coordinator (depending on the state) within two to three weeks of the screening test.

2. The primary care physician or follow-up coordinator (depending on the state) will contact the parents to recommend confirmatory testing (hemoglobin separation by electrophoresis, isoelectric focusing, and/or HPLC) in an appropriate laboratory by 2-3 months-of-age, unless this has already been accomplished with routine neonatal screening samples (varies by state). As part of appropriate education, the role of testing parents and other family members should be discussed.

3. Education and written materials about the hemoglobin trait and its genetics should be provided to the family when a hemoglobin trait has been confirmed. Education should emphasize the lack of illness associated with these genetic carrier conditions and their potential genetic implications (see p. 10).

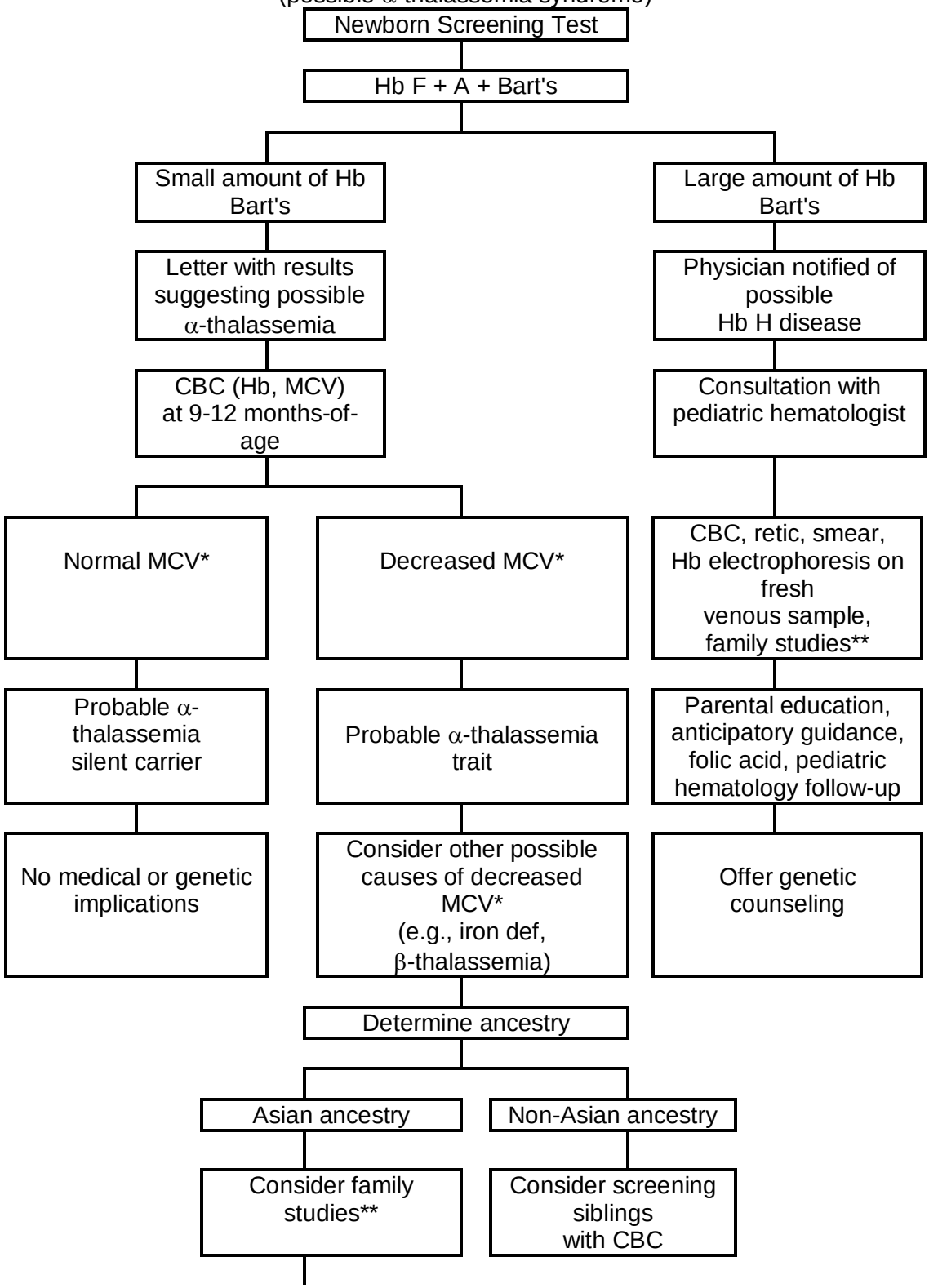
4. If the family declines follow-up and confirmatory testing, the case will be closed.

[1] Modified from Newborn Screening Practitioner's Manual, 2nd edition, Mountain States Regional Genetics Services Network, 1996, p. 35.

[2] Hemoglobins (Hb or Hgb) are reported in order of quantity (e.g., FSA = F>S>A). F=fetal Hb, A=adult Hb, S=sickle Hb; C=Hb C, E=Hb E; U (Other)=unidentified or other Hb (includes Hb D, G, and others)

[3] Tablets have a longer shelf life than suspension, which must be reconstituted with water, kept refrigerated, and expires in 14 days.

Follow-up Procedures for Infants with Hemoglobin Bart's on Neonatal Screen
(possible α-thalassemia syndrome)



Offer genetic counseling

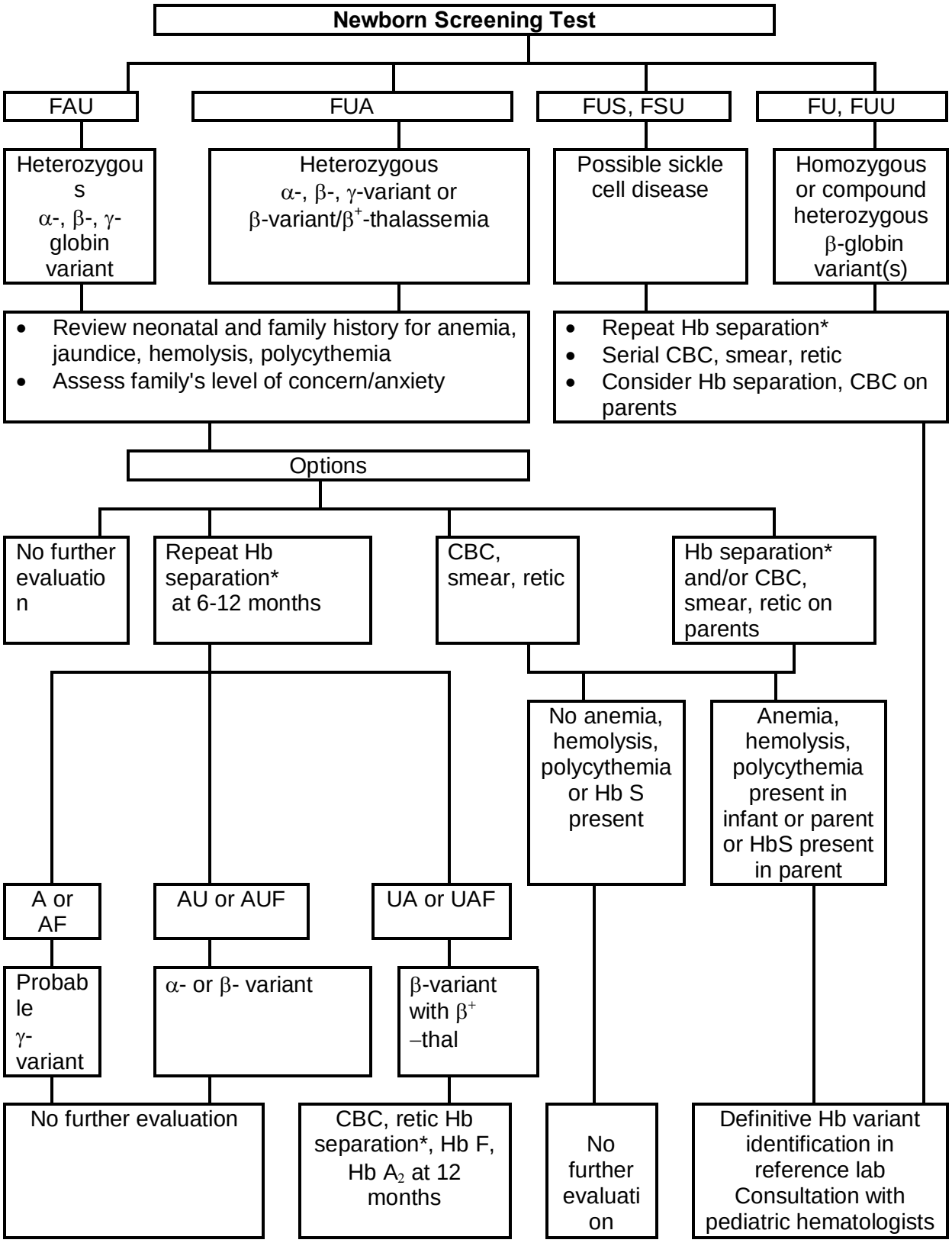
* Normal MCV for infants 9-12 months-of-age is ≥ 70 ft. Phone consultation with pediatric hematologist may prove helpful in interpreting results.

** Family studies. Initially CBC on parents and other siblings. Subsequent evaluation of couples possibly at risk for hydropic fetus requires DNA studies and possible referral to a perinatal genetics center.

Unidentified Hemoglobin Variants

Each year unidentified (U or "other") hemoglobin variants are detected by neonatal screening in thousands of U.S. infants. Most of these infants are heterozygotes (i.e., screening results FAU). These variants may be caused by mutations in α-, β-, or γ-globin genes. Most have no clinical or hematologic consequence, but a few may show altered oxygen affinity or be chemically unstable. Most unidentified Hb variants have no significant genetic implications, but a few may cause sickle cell disease when co-inherited with hemoglobin S. At present time, there is limited reference laboratory capacity in the United States, such that the majority of unidentified hemoglobin variants identified by screening cannot be definitively identified. Thus, while the overwhelming numbers have no clinical or genetic significance, uncertainty about the identity of variants may lead to frustration and anxiety for families and health care providers.

The following strategy is suggested for the follow-up of unidentified hemoglobin variants identified by newborn screening. The algorithm is intended to provide a common-sense approach that should limit laboratory expense and reserve definitive hemoglobin variant identification in reference labs for situations where definitive identification is needed for specific clinical or genetic concerns in a given family.



* Hb separation by hemoglobin electrophoresis, isoelectric focusing, or HPLC

Genetic Counseling
Hemoglobinopathies and Hemoglobin Traits

1. Genetic counseling should be provided by a medical specialist who has been trained in genetic counseling for hemoglobinopathies. Counseling can be provided by a genetic counselor with expertise in hemoglobinopathies or by a hematologist, pediatrician, nurse, or other medical specialist with expertise in the inheritance of hemoglobinopathies.

2. Patients with clinically significant disease should already be under medical management of a primary care physician, pediatrician and/or hematologist. If possible, all pertinent laboratory tests should have been done previously: newborn screening results (initial and confirmatory), DNA, and/or other hemoglobinopathy testing. (For details of testing potential hemoglobinopathy carriers, see #3 below.) Additional testing may be recommended after evaluation of the family history. These tests may be ordered immediately after counseling or may need to be arranged individually depending upon each person's medical resources.

3. Genetic counseling information should include a review of genetic inheritance, specifically autosomal recessive mode of inheritance, provision of accurate recurrence risk information to parents of an affected member, evaluation of the family history, and discussion of the importance of testing other family members who are at risk for a hemoglobinopathy or to be a carrier. Accurate recurrence risk counseling for parents of a member identified as having sickle cell trait, hemoglobin C trait, or β-thalassemia, etc. requires knowledge of the parents' carrier status. Testing of potential carriers requires a CBC and hemoglobin separation by electrophoresis, isoelectric focusing, and/or HPLC (including accurate quantization of Hb F and Hb A_2 if the MCV is borderline or decreased). Solubility testing (i.e. Sickledex, Sickleprep, Sicklequik) is inadequate for hemoglobinopathy screening, and should never be used.

4. Accurate information about the clinical course, treatment, and medical complications of the specific hemoglobin disorder relevant to the family must be provided, with emphasis on the importance of continuing medical follow-up and health maintenance strategies which can help decrease the number and severity of medical complications.

5. If a pregnancy is in progress for a couple at-risk for a member with a hemoglobinopathy, a referral to a prenatal genetics center or to an obstetrician with expertise in prenatal diagnosis should be offered.

SICKLE CELL DISEASE - ROUTINE COMPREHENSIVE EVALUATIONS

(In conjunction with a pediatric hematologist and/or sickle cell program)

Age	Hx(ROS) Psychosocial Exam Education	CBC Retic	Hb Electro	RBC Phenotype	Chemistry[1]	U/A	Pulse Ox	CXR	EKG Echo PFT's	CNS	Gallbladder Ultrasound	Ophth Consult
2 mo	X	X										
4 mo	X	X										
6 mo	X	X	2									
9 mo	X	X										
12 mo	X	X	2	X	X		X					
15 mo	X	X										
18 mo	X	X					X					
2-9 yr	3	3	2		4	4	4	5	6	7	8	
≥10 yr	4	4			4	4	4	5	6	7	8	9
New pt	X	X	2	X	X	10	X	10	10	7	10	10

Table provides general guidelines: Schedules for routine clinic visits and studies will need to be modified for individual patients.

1 Consider creatinine, BUN, liver function tests. Consider adding ferritin and/or iron and TIBC for any patients at risk for iron deficiency or for those at risk for hemosiderosis secondary to multiple transfusions.
2 Patients without documented confirmation of diagnostic testing or for whom diagnosis is unclear (e.g. FS or FSA on neonatal screen without subsequent anemia or hemolysis); review of other hematologic studies and family studies may also help establish accurate diagnosis.
3 2-3 times per year
4 Yearly
5 Consider every other year; yearly if history of recent acute chest syndrome or evidence of chronic cardiac or pulmonary disease

6 Consider to document baseline status and evidence of chronic cardiac or pulmonary disease in patients with history of severe or recurrent acute chest syndrome or unexplained cardiopulmonary symptoms.
7 May include CNS imaging such as MRI, MRA, and TCD ultrasonography and/or neurocognitive testing. Consider especially for patients with poor school performance or developmental or behavioral concerns.
8 prn clinical suspicion of cholelithiasis every 1-2 years as appropriate for age

SICKLE CELL DISEASE - IMMUNIZATIONS AND PROPHYLACTIC MEDICATIONS

(Routine immunizations should be administered per standard guidelines. For issues not covered by the table, consult the latest guidelines of the American Academy of Pediatrics.)

Age	Pneumococcal Conjugate Vaccine (PCV7)*	Pneumococcal Polysaccharide Vaccine	Meningococcal Vaccine	Influenza Vaccine	Penicillin	Folic Acid
2 mo	X				8	
4 mo	X				8	
6 mo	x (1)			7	8	9
12-15 mo	x (2)			7	8	
2 yrs.	3	x (3)	6	7	8	
5 yrs.	4	x (4)	6	7	8	9
>10 yrs.	4	5		7	8	9

* Two different pneumococcal vaccines are now licensed, a new 7-valent pneumococcal conjugate vaccine (PCV7) and the old 23-valent pneumococcal polysaccharide vaccine (PPV23). Four doses of PCV7 are now recommended for all infants and members < 2 yrs. of age. Because of different serotype coverage, members with sickle cell disease should receive both vaccines, but always ≥ 2 months apart.

1. For members 7-11 months of age not previously immunized with PCV7, 2 doses 2 months apart followed by a third dose at 12-16 months.
2. For members 12-23 months of age not previously immunized with PCV7, 2 doses 2 months apart.
3. For members 24-59 months of age previously immunized with PPV23 but not PCV7, 2 doses of PCV7 2 months apart ≥2 months after PPV23 Second PPV23 3 years after first PPV23 and ≥2months after second PCV7.

For members 24-59 months of age not previously immunized with PCV7 or PPV23, 2 doses of PCV7 2 months apart, followed by 1 dose of PPV23 ≥2 months later and second dose PPV23 3-5 years after the first PPV23.

4. For members ≥ 5 years of age previously immunized with PPV23 but not PCV7, 1 dose of PCV7 ≥ 2 months after last dose of PPV23. If not previously given, second dose of PPV23 ≥ 2 months after PCV7 and 3-5 years (< 10 years of age) or ≥ 5 years (> 10 years of age) after first dose of PPV23.

   For members ≥ 5 years of age not previously immunized with PPV23 or PCV7, 1 dose of PCV7 followed by first dose of PPV23 ≥ 2 months later and second dose PPV23 3-5 years (< 10 years of age) or ≥ 5 years (> 10 years of age) after first PPV23.
5. Some centers recommend third dose of PPV23 ≥5 years after second dose PPV23.
6. Recommended for asplenic patients by AAP Red Book, but not considered routine standard-of-care at many sickle cell centers.
7. Yearly for members ≥ 6 months of age.
8. Penicillin prophylaxis (125 mg PEN VK po bid < 3 yr; 250 mg po bid > 3 yr) from 2 months to 5 years of age in all infants with Hb SS and S β^o-thalassemia. Prophylaxis considered on case by case basis for older members (especially those with previous invasive pneumococcal infection or surgical splenectomy) and for those with Hb SC and S β+-thalassemia. Note: tablets have a longer shelf life

than suspension, which must be reconstituted with water, kept refrigerated, and expires in 14 days. Erythromycin may be used as a substitute for members with proven or suspected penicillin allergy.

9. Controversial. Folic acid 400 mcg or 1 mg po q.d. may be considered for members with significant hemolysis (Hb SS, $S\beta^o$-thalassemia).

CRS MANAGED HEALTHCARE SERVICES

SICKLE CELL PATIENT & FAMILY NEEDS ASSESSMENT
Please answer the following questions by circling Y=yes or N=no

Do you have any problems getting good health care for your child? **Y N**

Do you feel comfortable with how well you can treat and control your childôs pain at home? **Y N**

Do you know how to take your childôs temperature? **Y N**

If your child is less than 5 years old, can you feel the belly for enlargement of the spleen? **Y N**

Are you comfortable with your understanding of sickle cell? **Y N** Do you want more general information? **Y N**

Do you need more information on how sickle cell is inherited? **Y N**

Do you have problems with health insurance? **Y N** with parking? **Y N** with transportation? **Y N**

Do you feel your childôs pain problems are treated well when your child is in the hospital? **Y N**

Which emergency room do you use? _____ Are you comfortable with the staffôs knowledge of sickle cell disease and the way they control your members pain? **Y N**

Do you feel that the people who work at our clinic understand and are sensitive to your cultural background and needs? **Y N?** Do you feel that you have the opportunity to take part in making decisions about your childôs health care? **Y N**

Do you get the kind of help from others that you need? **Y N** If yes, from whom? (circle) Family, Friends, Church, Other: _____

Would you like more contact with another family who has children with sickle cell disease? **Y N**

What is your childôs grade in school? _____ Is your child enrolled in special education? **Y N**

Do you feel there is a need for a better understanding of your childôs special needs at school? **Y N**
About how many days did your child miss from school last year? _____

If your child is more than 12 years old, are you receiving services to help your child prepare for an independent adult life? **Y N**

Are your other children having any problems because of their brother or sister with sickle cell disease? **Y N**

Are there any other worries in your life? **Y N**

Would you be willing to work toward getting better care and more research on sickle cell disease? **Y N**

Are you a member of the Sickle Cell Association? **Y N**

What are the hardest things about sickle cell disease that you have to deal with?

_____

_____

What else can we do for you?

_____

Name of child: _____ Age: _____

Date of Birth: _____

Who completed this form? (Name, relationship to patient) _____

Date _____

ACUTE ILLNESS IN SICKLE CELL DISEASE: Illness Requiring Urgent Medical Care

Definition of illness requiring immediate medical care, including emergencies

Any of the following:

- T > 101°F or 38.5°C
- Pain inadequately relieved by home measures
- Significant respiratory symptoms (e.g., severe cough, shortness of breath, chest pain)
- Abdominal pain, distension, and/or acute enlargement of the spleen
- Any neurologic symptom or sign - even if transient
- Significant increase in pallor, fatigue, and/or lethargy
- Priapism episode lasting > 2-3 hr
- Significant vomiting or diarrhea

Acute illness characterized by any of the signs or symptoms listed above can prove rapidly life-threatening. Thus it is essential that sickle cell patients have unimpeded access to the providers / facility in their community that are best prepared to provide appropriate care. Ideally, every patient should have a predetermined plan to rapidly access an appropriate provider / facility that can provide:

- Expertise in sickle cell disease and/or immediate contact/consultation with a pediatric hematologist or the patient's primary care physician with expertise in sickle cell disease
- Access to patient's baseline data (past problems, exam, lab, radiographs)
- Access to appropriate transfusion support

It is essential that providers of urgent care make contact with the patient's continuity physician or service during the acute illness visit to be certain that appropriate treatment is provided (see clinical care paths, p. 16-25) and that continuity of care is maintained.

TRANSFUSION THERAPY FOR ACUTE COMPLICATIONS

Red blood cell transfusions play an important role in the treatment of some acute illnesses in patients with sickle cell disease. For severe complications, timely transfusions may be life saving. Specific guidelines for the use of transfusions for individual complications are provided in the clinical care paths throughout this manual. In general, appropriate use of red cell transfusions require attention to the following issues:

Indications:
Indications for red cell transfusions include acute exacerbations of the patient's baseline anemia that require increased oxygen carrying capacity, acute life or organ-threatening vaso occlusive episodes, and preparation for surgical or radiographic procedures that involve general anesthesia or the use of ionic contrast.

- Acute exacerbation of baseline anemia
    1. Aplastic crisis
    2. Splenic sequestration
    3. Hepatic sequestration
    4. Hyperhemolysis

- Severe vaso-occlusive events
    1. Acute chest syndrome
    2. Stroke
    3. Severe infection
    4. Acute multiorgan failure syndrome

- Preparation for procedures
    1. General anesthesia and surgery
    2. Radiographs with ionic contrast

Selection of transfusion products
Leukocyte-depleted, packed red blood cells are recommended. Where available, minor-antigen-matched, sickle-negative cells are preferred.

Transfusion method
A simple transfusion is appropriate for most situations characterized by acute exacerbation of anemia. Partial exchange transfusion, generally by erythrocytapheresis, may be needed for severe life-threatening illness or in situations where a relatively high baseline hemoglobin precludes a simple transfusion that would risk hyperviscosity by increasing the hemoglobin level to > 10gm/dl.

Volume considerations
Patients with severe chronic anemia (i.e. aplastic crisis) are at risk for volume overload and congestive heart failure from rapid infusion of RBC. Thus, slow correction of the anemia (e.g., 4-5 cc/kg packed RBC over 4 hr, often with furosemide) or isovolemic partial exchange transfusion may be needed to prevent precipitation of cardiovascular collapse.

Hyperviscosity
Because sickle red cells are poorly deformable, simple red cell transfusions that increase the hemoglobin levels to > 10gm/dl may be associated with hyperviscosity and should be avoided.

OUTPATIENT EVALUATION AND MANAGEMENT OF FEBRILE ILLNESS

($T \geq 101^{o}F$ or $38.5^{o}C$) IN MEMBER WITH SICKLE CELL DISEASE

1. Rapid triage - immediately upon presentation. Place immediately into exam room.

2. Brief history and physical exam with emphasis on:
   - vital signs
   - degree of pallor
   - evidence of systemic or localized infection
   - cardiopulmonary status
   - spleen size (compare with baseline exam)
   - neurologic exam

2. Laboratory:
   - Stat CBC, diff, platelet, reticulocyte count, and blood culture (use butterfly or angiocath and follow immediately with IV antibiotic).
   - Type and crossmatch if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
   - Urinalysis and urine, CSF, other cultures if clinically indicated.

4. Prompt administration of IV ceftriaxone (50-75 mg/kg, 2.0 grams maximum single dose) through butterfly or IV catheter used for phlebotomy. (For patients with known or suspected cephalosporin allergy, substitute clindamycin 10-15 mg/kg, 600 mg maximum single dose.)

   - Strongly consider adding vancomycin (10-15 mg/kg IV) for severe illness or if CNS infection is suspected.
   - Parenteral antibiotics should be given before other procedures, such as CXR, etc.
   - *The presence of a focus of infection (e.g. otitis) does <u>not</u> alter the urgency of giving parenteral antibiotics.*

5. Acetaminophen 15 mg/kg po (if not given in the last 4 hr) and/or ibuprofen 10 mg/kg po. Avoid ibuprofen if contraindication present (i.e. gastritis, ulcer disease, coagulopathy, or renal impairment).

6. Review summary of patient's last comprehensive evaluation or seek baseline information by phone.

7. Contact pediatric hematologist or patient's primary physician with expertise in sickle cell disease.

8. CXR and pulse ox (or blood gas), particularly if:

   - toxic appearance
   - any respiratory symptoms
   - chest and/or abdominal pain
     May use 0_2 by nasal cannula or face mask if signs of respiratory illness present. The etiology of a supplemental 0_2 requirement should be investigated.

9. Observation:

a) Admission:
   1. Most infants < 1 yr with HbSS or Sβ^o-thalassemia
   2. Most with previous episodes of bacteremia or sepsis
   3. Most with T > 40^0C, WBC > 30,000/mm^3 or < 5,000/mm^3, and/or platelet count < 100,000/mm^3
   4. Signs of systemic toxicity
   5. Patients who receive clindamycin or vancomycin
   6. Evidence of other acute complications including severe pain, aplastic crisis, splenic sequestration, acute chest syndrome, stroke, or priapism (see other Clinical Care Paths).
   7. Concerns about compliance / follow-up

b) Outpatients:
   Observe with repeat vital signs and assessment ≥2 hr post ceftriaxone. If non-toxic and clinically stable with reliable family and hematologist/PCP approval, discharge with a specific plan for outpatient follow-up. Minimum follow-up includes phone contact the next day. Repeat exam and 2nd dose of ceftriaxone (with or without repeat CBC and reticulocyte count) 24 hr later may be advisable in some cases.

INPATIENT MANAGEMENT OF FEVER IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:
Hematology

MONITORING:
1. Vital signs q 2 hr until stable, then q 4 hr (suspect septic shock)
2. Consider CR monitor and ICU for any signs of cardiovascular instability.
3. Record I & O, daily weight.
4. Pulse ox for severe illness or if respiratory signs or symptoms present.

DIAGNOSTICS (if not previously obtained):
1. CBC, diff, platelet, and reticulocyte count initially and daily until improving (compare with patient's baseline data).
2. CXR if tachypnea, cough, chest or abdominal pain, or any respiratory symptoms are present or subsequently develop.
3. Blood culture if febrile. Consider urinalysis, urine and other cultures (e.g. CSF).
4. Consider renal and liver function tests (BUN, creatinine, fractionated bili, ALT) and DIC screen for very severe pain or any evidence of encephalopathy (R/O acute multi-organ failure syndrome).
5. Consider abdominal ultrasound, liver function tests, amylase and lipase for RUQ, epigastric or severe abdominal pain (R/O cholelithiasis, cholecystitis, pancreatitis).
6. Type and crossmatch if Hb is 1-2 gm/dl or more below baseline or if evidence of acute chest syndrome present (see acute chest syndrome care path). Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
7. Consider orthopedic consult with aspiration for culture of bone or joint if osteomyelitis or septic arthritis suspected.

FLUIDS, GENERAL CARE:
IV + PO 1-12 x maintenance. Increased fluids may be needed if patient is dehydrated or if insensible losses are increased (e.g. persistent fever). Avoid excessive fluids, which may precipitate or exacerbate acute chest syndrome.

MEDICATION/TREATMENT:
1. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Certraxone 50 mg/kg/dose q 24 hrs.. Substitute clindamycin 10 mg/kg IV q 6 hr for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe illness and/or proven or suspected CNS infection. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
2. Acetaminophen 15 mg/kg po q 4 hr. May add ibuprofen 10 mg/kg po q 6-8 h if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
3. See other Clinical Care Paths for pain, acute chest syndrome, acute anemic crisis, stroke, priapism, if present.
4. 0_2 by nasal cannula or face mask if needed to keep pulse ox ≥92% or ≥ patient's baseline value (if > 92%). The etiology of a new or increasing supplemental 0_2 requirement should be investigated. Avoid excessive or unnecessary 0_2, which may suppress the reticulocyte count and exacerbate anemia.

5. Consider transfusion with RBC if Hb is 1-2 gm/dl or more below baseline and patient shows any signs of cardiovascular compromise.

DISCHARGE CRITERIA:

1. Afebrile ≥24 hr with negative cultures ≥24-48 hr.
2. Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air.
4. No evidence of anemic crisis (aplastic or sequestration): stable hemoglobin/hematocrit.
5. Follow-up arranged.

OUTPATIENT EVALUATION AND MANAGEMENT OF PAIN IN MEMBER WITH SICKLE CELL DISEASE

1. History:
   - Nature, location, duration, and severity of pain
   - Character of pain similar to previous sickle pain?
   - Analgesics already used for this episode
   - Associated symptoms - especially fever or evidence of dehydration
   - Consider etiologies other than sickling (e.g., cholecystitis, appendicitis, trauma)
   - Previous experience with analgesics (efficacy and side effects). What does patient/family feel best alleviates pain?

2. Physical Exam: Complete with emphasis on:
   - vital signs
   - hydration status
   - degree of pallor
   - evidence of infection
   - cardiopulmonary status
   - spleen size (compare with baseline exam)
   - penis (priapism)
   - neurologic

3. Lab:
   - CBC, diff, platelet, and reticulocyte count (compare with patient's baseline values)
   - Blood cultures if febrile (see fever care path)
   - Type and crossmatch if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
   - CXR and pulse ox (or blood gas) if:
   - Fever
   - chest pain
   - tachypnea
   - respiratory symptoms
   - Consider abdominal ultrasound and liver function tests for RUQ, epigastric pain (R/O choletithiasis /cholecystitis).

4. Contact pediatric hematologist or patient's primary physician with expertise in sickle cell disease.

5. Treatment (discuss with patient, family, and hematologist or primary physician on-call)

   a) Mild to moderate pain:

   - Å Acetaminophen with codeine 1 mg/kg po (and then q 4 hr) and oral fluids
   - Å Consider starting ibuprofen 10 mg/kg po q 6-8 h or other anti-inflammatory agent if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
   - Å If adequate relief and no other acute complications present, discharge on oral analgesics (acetaminophen with codeine and/or ibuprofen).

Å If inadequate relief within 30 min, follow b, below
Å Ibuprofen or other NSAID as first line treatment for mild to moderate pain.

b) Moderate to severe pain:

- Morphine 0.1-0.15mg/kg IV. Reassess pain q 15-30 min. Patients with severe pain may require repeated doses of morphine 0.02-0.05 mg/kg IV q 15-30 min to achieve pain relief. Alternative analgesics, such as hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV, may be appropriate in individual cases. Ketorolac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV may be used in addition to opioid analgesia if no contraindication (i.e., gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures.
- IV fluids: 10 cc/kg bolus over 1 hr then maintenance rate. Excessive fluids should be avoided unless patient is judged dehydrated.
- Monitor pulse ox. Use 0_2 by nasal cannula or face mask if needed to keep 0_2 saturation $\geq$ 92% or $\geq$ patient's baseline value (if > 92%). The etiology of a supplemental 0_2 requirement should be investigated.
- If adequate pain relief with one or two doses of morphine, consider giving acetaminophen with codeine (1 mg/kg) as outpatient therapy.
- Consider hospitalization for around-the-clock parenteral analgesics if more than one or two doses of morphine required.

INPATIENT MANAGEMENT OF VASO-OCCLUSIVE PAIN IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:
Hematology

MONITORING:
1. Vital signs q 4 hr
2. Record I+0, daily weight
3. Strongly consider continuous pulse ox if any respiratory symptoms present or if on parenteral narcotics
4. Consider CR monitor

DIAGNOSTICS (If not previously obtained):
1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline data.)
2. CXR if cough, chest pain, hypoxemia or any respiratory symptoms present or develop after admission. Patients with severe vaso-occlusive pain are at increased risk for acute chest syndrome (see p. 20).
3. If febrile, blood culture and other cultures (e.g. urine, CSF) and urinalysis as indicated.
4. Consider renal (BUN, Creat) and liver (fractionated bili, ALT) function tests for very severe pain or any evidence of encephalopathy (R/O acute multi-organ failure syndrome).
5. Consider abdominal ultrasound, liver function tests, and/or amylase and lipase for RUQ, epigastric or severe abdominal pain (R/O cholelithiasis, cholecystitis, pancreatitis)
6. Type and crossmatch if Hb is 1.5-2.0 gm/dl or more below baseline and/or if evidence of acute chest syndrome (see acute chest syndrome care path) or cardiovascular compromise present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.

FLUIDS, GENERAL CARE:
1. IV + P.O. 1-12 x maintenance. Increased fluids may be needed if patient is dehydrated and/or insensible losses are increased (e.g., persistent fever). Avoid excessive fluids, which may precipitate or exacerbate acute chest syndrome.
2. Incentive spirometry - 10 breaths q 2 hr when awake
3. Encourage ambulation and activity

MEDICATION/TREATMENT:
1. Morphine sulfate 0.05 - 0.15 mg/kg/dose IV q 2 hr or 0.05 - 0.1 mg/kg/hr continuous infusion or via PCA. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion, with 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. In most cases, prn analgesic orders are not appropriate. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketoralac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV q 6-8 hr in addition to opioid analgesia if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures. Base choice of analgesics in part or prior experience of patient with efficacy and side effects. Consider the addition of naloxone (Narcan) drip at 0.25 mcg/kg/hour with continuous drip opioids to prevent itching and constipation.

2. Ibuprofen 10 mg/kg po q 6-8 hr or other anti-inflammatory agent if no contraindication (i.e. ketoralac, gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
3. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Certriaxone 50 mg/kg/dose q 24 hours if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 h for severe febrile illness or for proven or suspected CNS infection.
4. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
5. Consider pain team consultation.
6. 0_2 by nasal cannula or face mask as needed to keep pulse ox $\geq$ 92% or $\geq$ patient's baseline value (if > 92%). The etiology of a new or increasing supplemental 0_2 requirement should be investigated. Avoid excessive or unnecessary 0_2, which may suppress the reticulocyte count and exacerbate anemia.
7. Offer heating pads or other comfort measures previously used by patient.
8. Consider colace or laxative for narcotic-induced constipation.
9. See other Clinical Care Paths for acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, priapism, if present.
10. Reassess pain control on a regular basis (at least twice daily) by discussing efficacy and side effects with patient/family. Analgesics may be weaned as tolerated by decreasing dose, <u>not</u> by prolonging interval between doses. Discuss analgesic changes with patient/family.

<u>DISCHARGE CRITERIA</u>:
1. Adequate pain relief on oral analgesics.
2. Taking adequate oral fluids and be able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Afebrile $\geq$2 4 hr. with negative cultures for $\geq$ 24-48 hr. if applicable.
4. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air.
5. Stable hemoglobin/hematocrit
6. Follow-up arranged.

CRS MANAGED HEALTHCARE SERVICES

ACUTE CHEST SYNDROME IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:
An acute illness associated with lower respiratory symptoms, hypoxemia, or new infiltrate on CXR.

CONSULTS:
Hematology

MONITORING:
1. Hospitalize
2. Vital Signs q 2-4 hr
3. Continuous pulse ox
4. Record I+O, daily weight

DIAGNOSTICS:
1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline values.)
2. CXR initially, repeat for clinical deterioration
3. Consider:
   a) Type and crossmatch for severe illness or if Hb > 1 gm/dl below baseline. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
   b) Blood cultures if febrile or history of recent fever
   c) Blood gas for severe illness
   d) Renal (BUN, creat) and liver (fractionated bili, ALT) function tests for severe illness or if diffuse encephalopathy present (R/O acute multiorgan failure syndrome)

FLUIDS, NUTRITION, GENERAL CARE:
1. Maintain "euvolemia". IV + P.O. 1-13 x maintenance. More fluid is appropriate only if patient is dehydrated or if insensible losses are increased (e.g., persistent fever).
2. Incentive spirometry - 10 breaths q 2 h when awake
3. Encourage ambulation, activity

MEDICATIONS/TREATMENTS:
1. Oxygen to pulse ox ≥ 92% or ≥ baseline value (if > 92%).
2. Acetaminophen 15 mg/kg po q 4 hr. or prn T > 38.0^{o}C
3. Ibuprofen 10 mg/kg po q 6-8 hr if no contraindication (i.e., ketorolac, gastritis, ulcer, coagulopathy, renal impairment). Limit more frequent dosing to 72 hr maximum duration.
4. Morphine 0.05 - 0.15 mg/kg IV q 2 hr or 0.05 - 0.1 mg/kg/h continuous infusion or PCA for severe pain. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion and 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketorolac 0.5 mg/kg (30 mg maximum dose) IV q 6-8 h (72 h maximum duration) to reduce or avoid opioids. Do not use ibuprofen with ketorolac.

5. Cefotaxime or cefuroxime 50 mg/kg q 8 h IV or Ceftriaxone 50 mg/kg/dose q 24 hours. Substitute clindamycin 10 mg/kg IV q 6 h for patient with known suspected cephalosporin allergy. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
6. Azithromycin 10 mg/kg po first dose, then 5 mg/kg qd, erythromycin 10 mg/kg q 6 h po, or other macrolide antibiotic
7. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe illness, or nafcillin or vancomycin if large infiltrate with pleural effusion present.
8. Consider one dose of furosemide 0.5-1.0 mg/kg IV if signs of fluid overload present.
9. Consider trial of bronchodilators, especially if patient has history of reactive airway disease or wheezing on exam.
10. Consider red cell transfusion:
    a. Simple transfusion for moderately severe illness, especially if Hb > 1 gm/dl below baseline (do <u>not</u> transfuse acutely to Hb > 10 gm/dl, Hct > 30%).
    b) Partial exchange transfusion to Hb 10 gm/dl and Hb S or Hb S+C (patient's RBC) ≥ 30% for severe or rapidly progressive disease (may require transfer to ICU and transfusion medicine consult for erythrocytapheresis). Remove femoral or central venous catheters as soon as possible after exchange transfusion to reduce risk of thrombosis.
11. See other Clinical Care Paths for acute splenic sequestration, aplastic crisis, stroke, priapism, if present.

<u>DISCHARGE CRITERIA</u>:

1. Off supplemental 0_2.
2. Afebrile ≥ 24 hr. and negative cultures for ≥ 24-48 hr if applicable.
3. Stable hemoglobin/hematocrit.
4. Taking adequate oral fluids and able to take po medications if applicable.
5. Adequate pain relief, if needed, with oral analgesics.
5. Follow-up plans coordinated with hematology service. On a case by case basis, consider follow-up pulmonary function testing and the possibility of chronic transfusions (p. 27) or hydroxyurea (p. 28).

ACUTE SPLENIC SEQUESTRATION IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:
An acute illness associated with Hb 2 gm/dl or more below patient's baseline value with acutely enlarged spleen. Mild to moderate thrombocytopenia is often present. Reticulocytosis equal to or greater than baseline is usually present. If reticulocyte count is decreased, consider coexistent aplastic crisis (see p.22).

CONSULTS:
Hematology

MONITORING:
1. Hospitalize
2. Consider ICU admission for signs of cardiovascular compromise.
3. Vital signs q 2 hr until stable, then q 4 hr.
4. CR monitor
5. Continuous pulse ox
6. Record I+O, daily weight
7. Serial exams (initially q 2-4 h) to reassess cardiovascular status and spleen size

DIAGNOSTICS:
1. CBC, diff, platelet count, and reticulocyte count initially, then q 4-12 hr depending on severity of anemia, rate of fall in Hb level, changes in spleen size.
2. Type and crossmatch RBC stat. Time permitting, consider if available minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Blood culture, urinalysis, and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness present.

FLUIDS, GENERAL CARE:
1. IV + PO @ 1 X maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever) or to support intravascular volume before transfusion.
2. Incentive spirometry - 10 breaths q 2 hr when awake if on parenteral narcotics.

MEDICATION/TREATMENT:
1. RBC transfusions 10 cc/kg for Hb < 4-5 gm/dl and/or signs of cardiovascular compromise; will often give 5ml/kg or PRBCõs in 2 increments to prevent volume overload if cells released from the spleen. *In severe cases, urgent initiation of transfusion prior to inpatient admission may be life-saving.*
2. Cefotaxime or cefuroxime 50 mg/kg IV q 8 hr or Certriaxone 50mg/kg if febrile. Substitute clindamycin 10 mg/kg IV q 6 h for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
3. If applicable, continue prophylactic penicillin. Penicillin prophylaxis should be discontinued while patient is receiving broad-spectrum antibiotics.
4. 0_2 by nasal cannula or face mask if needed to keep pulse ox ≥ 92% or ≥ patient's baseline value (if > 92%). The etiology of a new or increasing supplemental 0_2 requirement should be investigated. 0_2 @ 2 liters by nasal cannula or 35% by face mask can be given empirically for the severely anemic member who is to receive RBC transfusions.

5. Acetaminophen 15 mg/kg po q 4 hr and/or ibuprofen 10 mg/kg po q 8 hr for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia.)

6. Morphine sulfate 0.05-0.15 mg/kg IV q 2 hr or 0.05-0.1 mg/kg/hr continuous infusion or via PCA for severe pain. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion and 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases.
7. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, aplastic crisis, stroke, priapism, if present.

DISCHARGE CRITERIA:
1. Stable hemoglobin/hematocrit.
2. Taking oral fluids well and able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Afebrile ≥ 24 hr. and negative cultures for ≥ 24-48 hr. if applicable.
4. Adequate pain relief, if needed, with oral analgesics.
5. Follow-up arranged.
6. Consider surgical splenectomy and/or chronic transfusions for severe or recurrent events.

APLASTIC CRISIS IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:
An acute illness associated with Hb below patient's baseline value with a substantially decreased reticulocyte count (often < 1%). Most cases are caused by acute infection with human parvovirus. If acute enlargement of spleen is present, consider coexistent splenic sequestration (see p. 21). Parvovirus also has been associated with other acute complications of sickle cell disease which may occur during aplastic crisis, including pain, bone marrow necrosis, acute chest syndrome, and stroke.

CONSULTS:
Hematology

MONITORING:
1. Hospitalize for evidence of cardiovascular compromise, for inability to provide appropriate transfusion support as outpatient, and/or for concerns about reliability of follow-up.
2. Vital signs q 2 hr until stable, then q 4 hr. if hospitalized.
3. Consider CR monitor and continuous pulse ox
4. Record I+O, daily weight

DIAGNOSTICS:
1. CBC, diff, platelet count, and reticulocyte count initially, then q 12-24 hr.
2. Type and crossmatch. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Blood culture, urinalysis, and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness present.
5. Consider diagnostic tests for parvovirus.

FLUIDS, GENERAL CARE:
1. IV + PO @ 1 X maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever). Avoid excessive fluids which may precipitate congestive heart failure.
2. Contact isolation for presumed parvovirus infection (no pregnant care providers).
3. Incentive spirometer 10 breaths q 2 hours while awake.

MEDICATION/TREATMENT:
1. RBC transfusions for symptomatic anemia and/or Hb < 5 gm/dl with no evidence of erythroid recovery; usually 5-6 cc/kg over 4 hrs with close observation for fluid overload. Transfusion may need to be repeated.
2. Cefotaxime or cefuroxime 50 mg/kg IV q 8 hr if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness and/or for proven or suspected CNS infection.
3. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
4. 0_2 by nasal cannula or face mask if needed to keep pulse ox ≥92% or ≥ patient's baseline value (if > 92%). The etiology of a new or increasing supplemental 0_2 requirement should be investigated. 0_2, 2 liters by nasal cannula or 35% by face mask, can be given empirically for the severely anemic member who is to receive RBC transfusions.
5. Acetaminophen 15 mg/kg po q 4 hr and/or ibuprofen 10 mg/kg po q 8 hr for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia.)
6. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, acute splenic sequestration, stroke, priapism, if present.

7. CBC and reticulocyte count now and again in 10-14 days on siblings or close contacts with sickle cell disease or other chronic hemolytic anemias to exclude simultaneous or sequential parvovirus infection.

DISCHARGE CRITERIA:

1. Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable.
2. Adequate pain relief, if needed, with oral analgesics.
3. Afebrile ≥ 24 hours with negative cultures for ≥ 24-48 hr. if applicable.
4. Adequate hemoglobin/hematocrit with reliable family and outpatient follow-up in place, including arrangements for follow-up clinical and laboratory monitoring and for additional transfusions if needed.

ACUTE STROKE OR NEUROLOGIC EVENT IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:
Hematology
Neurology
Physical Medicine and Rehabilitation

MONITORING:
1. Rapid triage - urgent hematology consultation
2. Hospitalize. Consider ICU admission and/or CR monitor first 24 hr and until stable.
3. Vital signs, neuro checks q 2 hr.
4. Record I & O, daily weight.

DIAGNOSTICS:
1. Type and crossmatch for partial exchange transfusion (erythrocytapheresis). Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
2. CBC, diff, platelet count, and reticulocyte count initially and as clinically indicated (compare with patient's baseline data).
3. RBC minor-antigen phenotype if not previously documented.
4. Consider screening coagulation profile.
5. Blood and urine cultures if febrile.
6. Electrolytes initially and daily until stable.
7. MRI and MRA. If not immediately available, CT without contrast to exclude intracranial hemorrhage. Initiation of transfusion therapy should not be delayed by arrangements for imaging studies.
8. Consider CSF culture if febrile and no contraindication present.

FLUIDS, GENERAL:
1. IV + PO 1 x maintenance

MEDICATION/TREATMENT:
1. Partial exchange transfusion or erythrocytapheresis to Hb 10 gm/dl and Hb S (patient's RBC) ≤30% (may require transfusion medicine consult for erythrocytapheresis). Remove femoral or central venous catheter as soon as possible after exchange transfusion to reduce risk of thrombosis.
2. Simple transfusion with RBC to Hb approximately 10 gm/dl may be considered as an alternative to partial exchange transfusion for stable patients with Hb < 6-7 gm/dl (do not transfuse acutely to Hb > 10 gm/dl, Hct > 30%).
3. Rx seizures if present.
4. Rx increased intracranial pressure if present.
5. 0_2 by nasal cannula or face mask if needed to keep pulse ox ≥ 92% or ≥ patient's baseline (if > 92%). The etiology of a new or increasing supplemental 0_2 requirement should be investigated.
6. Consider hemoglobin electrophoresis after partial exchange transfusion or at discharge.
7. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Certriaxone 50mg/kg/dose q 24 hours if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
8. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.

9. See other Clinical Care Paths for pain, acute chest syndrome, acute splenic sequestration, aplastic crisis, priapism, if present.

DISCHARGE CRITERIA:
1. Clinically and neurologically stable > 24 hr. after transfusions.
2. Afebrile > 24 hr. with negative cultures for ≥ 24-48 hr. if applicable.
3. Taking adequate oral fluids and able to take oral medication if applicable.
4. Hematology rehabilitation, and physical therapy follow-up organized.
5. Initiate chronic transfusion program (see p. 27).

OUTPATIENT MANAGEMENT OF PROLONGED PRIAPISM IN MEMBER WITH SICKLE CELL DISEASE

Priapism is a prolonged painful erection of the penis that commonly occurs in children and adolescents with sickle cell disease, often starting during the early morning hours. It occurs in two forms: (a) stuttering episodes that last less than 2-4 hours but are often recurrent and may precede a severe episode, and (b) severe events that last more than 2-4 hours and may eventually result in impotence. Simple maneuvers such as increasing oral fluids, taking analgesics, urination, moderate exercise, and/or taking a bath or shower may help end an episode of priapism, and no further specific intervention may be required. Patients who have frequent episodes (≥2 within one month or ≥4 within one year) should contact their sickle cell program for elective evaluation. For such patients, priapism prophylaxis with pseudoephedrine 30 mg/po hs (< 10 years) or 60 mg/po hs (> 10 years) should be considered. **Any episode that lasts longer than 2-4 hours should be considered an emergency that requires prompt medical intervention as described below.**

1. Rapid triage - immediately upon presentation. Place immediately into exam room.

2. History with emphasis on:
   - length of current episode
   - associated symptoms - especially fever, dysuria, evidence of dehydration, or pain in other locations
   - history of prior episodes of priapism, previous treatments and effectiveness

3. Physical Examination with emphasis on:
   - vital signs
   - hydration status
   - degree of pallor and cardiopulmonary status
   - genitourinary (severity of pain, any evidence of detumescence)

4. Laboratory:
   - consider CBC, diff, platelet, reticulocyte count (compare with patient=s baseline values)
   - blood cultures if febrile (see fever care path, p. 16)
   - urinalysis and urine culture for history of dysuria or fever
   - type and cross match if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor antigen matched, sickle negative, and leukocyte-depleted RBCs.

5. Immediately contact urologist to perform aspiration and irrigation, described below.

6. Review summary of patients last comprehensive evaluation or seek baseline information by phone.

7. Contact pediatric hematologist or patient's primary care physician with expertise in sickle cell disease.

8. Treatment (discuss with patient, family, and hematologist or primary physician on-call)
   - IV fluids: 10 cc/kg bolus over one hour then at maintenance rate

- analgesia: for moderate to severe pain, morphine 0.1-0.15 mg/kg IV. Reassess pain q 15-30 minutes. Patients with severe pain may require repeated doses of morphine 0.02-0.05 mg/kg IV q 15-30 minutes to achieve pain relief
- monitor pulse ox for patients receiving opioid analgesia
- use O_2 by nasal cannula or face mask as needed to keep O_2 saturation ≥92 or ≥ patient's baseline value (if > 92%).

9. Aspiration and irrigation: The following procedure should be performed by a staff urologist or experienced urology resident <u>as soon as possible</u> for episodes that have lasted more than 4 hours from onset of erection. Conscious sedation may be appropriate for selected patients if administered by experienced staff, but usually is not required.

- the lateral side of the penis is prepped with betadine and approximately 0.5 ml of 1% lidocaine is infiltrated subcutaneously into the lateral surface of the penis and then more deeply into the tunica albuginea.
- a 23 gauge needle is inserted into the corpora cavernosa and as much blood as possible is aspirated into a dry 10 ml syringe through a three-way stopcock.
- another 10 ml syringe containing 1:1,000,000 solution of epinephrine (i.e. 1ml of 1:1,000 epinephrine diluted in 1 liter of normal saline) is attached to the three-way stopcock. The corpora cavernosa are irrigated with 10 ml of the 1:1,000,000 epinephrine solution, with additional blood aspirated via dry syringes until detumescence has occurred
- the needle is withdrawn and five minutes of firm pressure (timed by the clock) is applied by the physician doing the procedure to prevent hematoma.
- if the patient retains detumescence for ≥1 hour they may be discharged home with hematologist/urologist/PCP approval and a specific plan for outpatient follow-up.
- any recurrent episode lasting > 2 hours should be treated with repeat aspiration and irrigation.
- If the episode fails to respond to aspiration and irrigation, the patient should be hospitalized for inpatient management (p. 25).

INPATIENT MANAGEMENT OF PROLONGED PRIAPISM IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:
Prolonged priapism is a painful erection of the penis that lasts more than 2-4 hours and may result eventually in impotence. Most episodes are successfully treated with outpatient aspiration and irrigation with epinephrine (see p.24). This inpatient care path is for patients who fail to respond to outpatient management.

CONSULTS:
1. Hematology
2. Urology

MONITORING:
1. Vital signs q 2-4 h.
2. Record I+O, daily weight.
3. Strongly consider continuous pulse ox if receiving parenteral narcotics.

DIAGNOSTICS (if not previously obtained):
1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline data.)
2. Consider type and crossmatch. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Urinalysis and urine culture.
4. Blood culture if febrile. Consider other cultures (e.g. CSF).

FLUIDS, GENERAL CARE:
1. IV fluids - 10 cc/kg over 1 hr, then IV + PO = 1½ x maintenance
2. Encourage ambulation
3. Incentive spirometry - 10 breaths q 2 hr when awake if on parenteral narcotics

MEDICATION/TREATMENT:
1. Never use ice or cold packs.
2. Morphine sulfate 0.05-0.15 mg/kg/dose IV q 2 hr or 0.05-0.1 mg/kg/hr continuous infusion or via PCA. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion, with 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. In most cases, prn analgesic orders are not appropriate. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketoralac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV q 6-8 hr in addition to opioid analgesia if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures.
3. Mild to moderately severe pain - acetaminophen with codeine (1 mg/kg) po q 4 hr.
4. Ibuprofen 10 mg/kg po q 6-8 h if no contraindication (i.e. ketorolac, gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
5. Reassess pain control at least twice daily. Analgesics may be weaned as tolerated by decreasing dose, not by prolonging interval between doses.

6. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h if febrile. Substitute clindamycin 10 mg/kg IV q 6 h for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
7. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
8. 0_2 by nasal cannula or face mask if needed to keep pulse ox ≥92% or ≥ patient's baseline value (if > 92%). The etiology of a new or increasing supplemental O_2 requirement should be investigated. Avoid excessive or unnecessary 0_2, which may suppress the reticulocyte count and exacerbate anemia.
9. Consider transfusion if no evidence of detumescence within 12 hrs:
   a) Partial exchange or erythrocytapheresis to Hb 10 gm/dl and Hb S (patient's RBC) ≤30%.
   b) May consider simple transfusion as alternative to partial exchange transfusion if Hb < 6-7 gm/dl (do <u>not</u> transfuse acutely to Hb > 10 gm/dl, hct > 30%).
10. Winter shunt (spongiosum-cavernosum shunt) may be considered if priapism persists for > 24 hrs, unresponsive to supportive care, drainage and irrigation, and transfusions, but is controversial.
11. Observe for severe headache or neurologic signs or symptoms. (Ischemic stroke may occur 1-10 days after onset of priapism, especially following transfusion.)
12. See other Clinical Care Paths for acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, if present.

<u>DISCHARGE CRITERIA</u>:

1. Priapism resolving (complete detumescence may take 1-2 weeks)
2 Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable
3. Adequate pain relief on oral analgesics
4. Afebrile ≥24 hr. with negative cultures ≥ 24-48 hr. if applicable.
5. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air
6. Consider starting pseudoephedrine 30 mg po hs (< 10 years) or 60 mg po hs (> 10 years) for priapism prophylaxis.
7. Follow up arranged.

GENERAL ANESTHESIA AND SURGERY

General anesthesia is associated with a significant risk for post-operative complications, especially acute chest syndrome. Thus, it should be planned carefully with good communication between the hematologist, anesthesiologist, surgeon, and blood bank. Surgery should only be performed at a center with expertise in sickle cell disease. General principles include:

1. Pre-op evaluation
   CBC, retic, pulse ox
   Consider CXR
   Consider pulmonary function tests for patients with prior history of acute chest syndrome or with suspicion of chronic lung disease.

2. Pre-op transfusion: Simple or partial exchange transfusion should be strongly considered for all members with Hb SS or S β^o-thalassemia prior to any procedure requiring general anesthesia. Data from a prospective, randomized, multicenter trial suggest that simple transfusion is as efficacious as partial exchange transfusion in most cases. The need for pre-op transfusions must be individualized. Use minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC if available.
   - Simple transfusion : RBC's to increase Hb to 10 gm/dl.
   - Aggressive transfusion: Erythrocytapheresis or serial simple transfusions to decrease Hb S to 30% with Hb approximately 10 gm/dl.

   Surgery without pre-op transfusion in members with Hb SS and S β^o-thalassemia may be considered in selected cases for <u>minor</u> procedures (e.g. PE tubes) with brief anesthetics. Pre-op transfusions may also be appropriate for selected members with Hb SC or S β^+-thalassemia, especially if they have a history of recurrent acute chest syndrome or evidence of chronic organ damage.

3. Prior to surgery (within 72 h)
   CBC, retic
   Consider Hb electrophoresis to document Hb S% (after pre-op transfusions)
   Hydration (1-1½ x maintenance) ≥12 hr before procedure.
   Teach incentive spirometry

4. Intraoperative
   Minimum 50% 0_2 with anesthetic agent
   Avoid hypoxia (continuous pulse ox), hypercarbia, or hyperventilation.
   Avoid or minimize tourniquets

5. Post-operative
   0_2 by nasal cannula @ 2L or by face mask @ 35% for 18-24 hr regardless of pulse oximetry.
   Pulse oximetry for 18-24 hr to ensure supplemental 0_2 is sufficient to keep saturation > 95%.
   IV + PO 1-1½ x maintenance. Avoid excessive hydration, which may precipitate acute chest syndrome.
   Aggressive pain management.
   Incentive spirometry - 10 breaths q 2 hr while awake. Encourage early ambulation and activity.

Consider daily CBC, diff, platelet count and reticulocyte count until stable.

CHRONIC TRANSFUSION PROTOCOL

Overview:
Some severe manifestations of sickle cell disease warrant maintenance therapy with chronic blood transfusions. The goal is to suppress erythropoiesis sufficiently and to provide enough normal red blood cells to maintain the percentage of the patient's cells (i.e. hemoglobin S) at less than 30%. Experience has shown that this approach significantly reduces the risk of recurrent stroke. Such transfusions also reduce markedly the incidence of many other sickle-related complications such as vaso-occlusive pain and acute chest syndrome. In addition to preventing acute complications, chronic transfusions may prevent the progression of chronic organ damage and even reverse some pre-existing organ dysfunction. This has been shown most clearly in patients with Hb SS and functional asplenia, some of whom show improved splenic reticuloendothelial function after receiving chronic transfusions. Many members with sickle cell disease treated with chronic transfusions also experience an increased sense of wellbeing, with improved energy levels, exercise tolerance, growth velocity and sexual development. Thus, transfusions to chronically replace sickle cells with normal erythrocytes can be considered a specific therapy that markedly ameliorates the disease.

Indications:
Stroke

Indications in Selected Patients
Transient ischemic attack
Abnormal TCD
Severe or recurrent acute chest syndrome
Severe debilitating pain
Following splenic sequestration (as alternative to observation or early surgical splenectomy)
Recurrent priapism
Chronic organ failure
Intractable leg ulcers
Severe chronic anemia with high output cardiac failure
Selected pregnancies

Outpatient Transfusions:
PRBC 10-15 ml/kg (minor-antigen-matched, sickle-negative, leukocyte-depleted) given over 3-4 hr with standard monitoring. Minor -antigen matching for Rh (C, D, E,) and Kell should be provided for all patients. More extensive matching should be provided if available, especially for patients with previous alloimmunization. Frequency of transfusions (usually q 3-4 weeks) is adjusted to maintain Hb S ≤30% (typically with nadir Hb > 9-10 gm/dl). For patients receiving chronic transfusions for stroke who have had no recurrent neurologic events for 3 years, consider decreasing frequency of transfusions to maintain Hb S ≤50%. Record volume of RBC transfused. Serial erythrocytapheresis is an alternative approach to chronic transfusions that is associated with substantially less or little iron loading and should be seriously considered for patients with adequate venous access.
Patients should be immunized to hepatitis A and B.
Continue prophylactic penicillin if applicable.

Iron Chelation:

Initiation of chelation with deferasirox (Exjade) should be considered after ≥ 1 year of chronic transfusions and/or serum ferritin is increased to 1500-2000 μg/L. Hepatic iron content > 4 mg/gm dry wt liver tissue (as determined by liver biopsy) also has been used as an indication for beginning iron chelation. Initial dose is 20-30 mg/kg/per day, orally, once per day . Use of serial erythrocytapheresis for chronic transfusions may delay or limit the duration or avoid entirely the need for chelation.
Counsel regarding avoidance of excess dietary iron.
Consider vitamin C supplementation, 100-250 mg/d, only at start of each dose of deferoxamine.

Monitoring:

Audiology evaluation if any symptoms present (e.g. tinnitus, difficulty hearing)
Ophthalmology consultation for any new visual symptoms
Prior to each transfusion:
CBC, reticulocyte count, type and cross, antibody screen. Consider serum ferritin and Hb S quantitation
Every 3-6 months
Height, weight, history, physical exam
Hb electrophoresis, ferritin, ALT
Yearly
Liver function tests including ALT. Consider Hepatitis C, HIV, and HTLV I-II serology, calcium, phosphorus, alkaline phosphatase, thyroid profile, fasting glucose, and other endocrine studies as indicated.
Audiology evaluation
Ophthalmology examination
Consider CXR, EKG, echocardiogram
Consider 24 hr urinary iron excretion with 12 hr dose of subcutaneous deferoxamine (usually 40-50 g/kg).
Consider metaphyseal and spinal radiographs.
Consider liver biopsy for histology and quantitative iron.
Consider CNS evaluation including MRI, MRA, and/or neurocognitive testing for patients with stroke

HYDROXYUREA PROTOCOL

Higher levels of fetal hemoglobin (Hb F) and lower leukocyte counts are thought to be beneficial in patients with sickle cell disease and can be achieved with daily oral administration of hydroxyurea (HU). A placebo-controlled, double blind, prospective trial in severely affected adults with Hb SS showed that HU significantly reduced the incidence of vaso-occlusive pain, acute chest syndrome, and blood transfusions. A multi-center phase I/II trial in members > 5 years-of-age showed safety and hematologic effects similar to those observed in adults. Clinical benefit in members with Hb SS has been suggested by a number of open-label trials. The drug is FDA-approved for selected adult patients, with the important caution that the drug is not curative and requires close hematologic monitoring for myelotoxicity and the strict use of contraception by both men and women who are sexually active. Use of HU in patients with Hb SC or β^+- thalassemia is under investigation.

The clinical course of each patient with sickle cell disease should be regularly reviewed by a pediatric hematologist/sickle cell program and the possibility of hydroxyurea treatment and its pros and cons considered. Many patients with severe complications may also be candidates for either a program of chronic transfusions (p. 27) or, if an HLA-matched sibling is available, stem cell transplantation (p. 29). HU is generally not considered appropriate for patients with stroke, and it is not useful in the treatment of acute sickle pain. No improvement is expected until the drug has been taken daily for 3-6 months. HU may alter the natural history of the sickle cell disease; for example splenomegaly or splenic sequestration may occur in relatively older patients. HU is a potentially toxic chemotherapeutic agent whose long-term toxicity (including concerns about carcinogenicity and teratogenicity) is unresolved. *Thus, the drug should be initiated and monitored only by hematologists with expertise in chemotherapy and sickle cell disease and after written documentation of patient education and consent.*

Indications (Inclusion criteria)
- Dx: Hb SS or S β^o-thalassemia
- ≥3 years-of-age
- ≥3 severe vaso-occlusive pain events/year, or
- ≥2 episodes of acute chest syndrome/year, or
- Any combination of ≥3 episodes of acute chest syndrome and severe pain/year

Exclusion criteria
- Pregnancy
- Inability to use reliable contraception if sexually active (men <u>and</u> women)
- Inability to comply with daily dosing and frequent laboratory monitoring

Dosage

Hydroxyurea 15-30 mg/kg p.o. q.d.(supplied as Droxia [200, 300, and 400mg] and Hydrea [500mg] capsules). All size capsules must be available for accurate dosing. Liquid suspensions, 100mg/ml in flavored syrup, are stable for 1 month and can be prepared for younger members. The dose may be increased by approximately 5 mg/kg/day every 8-12 weeks to a maximum dose of 30 mg/kg/day or until there is evidence of toxicity (see below). Consider folate supplementation, 0.4-1 mg p.o.q.d.

Monitoring

1. CBC, reticulocyte count: baseline, then every 2 weeks until maximum dose tolerated without toxicity f or 8-12 weeks; then every 4 weeks.
2. History and physical examination: baseline, then every 4 weeks until maximum dose tolerated for 8-12 weeks, then every 8 weeks. Be alert to the possibility of recurrent or new splenomegaly and risk of splenic sequestration.
   b. Fractionated bilirubin, ALT, and creatinine: baseline, then every 12-24 weeks.
   c. Quantitation of hemoglobin F: baseline, every 3 months x 2, then every 6 months.
   d. Pregnancy test (if menstruating): baseline, then prn. (Stop HU immediately for positive result and offer teratogen risk counseling. Information is available from the Organization of Teratogen Information Services at 888-285-3410 or www.otispregnancy.org).

Toxicity

Toxicity from hydroxyurea is generally defined as any of the following:

ANC < 2000 x 10^6/L
platelet count < 80,000 x 10^6/L
absolute reticulocyte count < 80,000 x 10^6/L if hemoglobin < 9.0 gm/dl
hemoglobin < 5 gm/dl or > 20% below baseline
serum creatinine > 1.0 mg/dl or 50% above baseline
100% increase in ALT

If toxicity occurs, treatment will be stopped for at least 1 week and until toxicity resolves. HU will then be resumed at the same dose or a dose decreased by 2.5-5 mg/kg/d. If toxicity does not recur after 12 wks on the lower dose, the dose may then be increased by 2.5-5 mg/kg/d. If toxicity recurs on the higher dose, then HU will be stopped again until toxicity resolves, and hydroxyurea can then be resumed at the lower dose without further dose escalations.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Successful allogeneic hematopoietic stem cell transplantation provides a hematologic cure for sickle cell disease. Published experience in children less than 16 years of age shows that about 80% with Hb SS who undergo bone marrow transplantation from an HLA-identical sibling donor will have sustained engraftment and elimination of all sickle-related symptoms. Ten to 15% of patients will reject the stem cell graft, and about 5% will succumb from complications of the procedure. Although not as rigorously studied, the success of transplantation from HLA-identical sibling cord blood or peripheral blood progenitor cells may be similar. There is currently a NIH-funded study to collect cord blood for stem cell transplantation from subsequent siblings of patients with sickle cell disease and other hemoglobinopathies (contact CHORI-Cord Blood Program at 510-450-7605 for further information).

Wide scale implementation of transplantation for sickle cell disease in the United States has been limited by our ability to predict the clinical severity of sickle cell disease for a given member and often by the lack of an HLA-match sibling without sickle cell disease. A consensus of opinion now suggests that allogeneic hematopoietic stem cell transplantation is an appropriate treatment option for patients who have an HLA-identical sibling donor and have experienced a severe clinical course. Such patients include those who have had a stroke or who are experiencing impaired neuropsychologic function with abnormal MRI, recurrent acute chest syndrome, osteonecrosis of multiple joints, and/or recurrent debilitating pain. The procedure should only be undertaken in centers with expertise in both sickle cell disease and transplantation.

Some of the early transplant patients partially rejected donor marrow and became stable mixed chimeras (a mixture of donor and host hematopoiesis) with amelioration of sickle-related symptoms. Non-myeloablative transplant protocols with less intensive and therefore less toxic conditioning regimens are currently under investigation to try to induce stable mixed chimerism in patients with sickle cell disease. Such approaches should decrease the toxicity and cost of transplantation and hopefully achieve clinical benefit. Others are investigating the use of alternative donor or unrelated hematopoietic progenitor cells in severely affected patients without an HLA-identical sibling donor. These approaches are promising, but are currently investigational.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Stroke, defined as an acute, clinically evident neurological event, occurs in 7-11% of patients with Hb SS. Most strokes are ischemic events caused by stenosis or occlusion of large cerebral arteries such as the intracranial internal carotids and middle cerebrals. Stroke typically occurs without warning and causes significant long-term neurologic sequelae in at least 50% of cases. Chronic transfusion after a first stroke reduces markedly the high risk of recurrent stroke, but this is a suboptimal approach because it does not prevent the initial neurologic injury.

Transcranial Doppler (TCD) ultrasonography provides a non-invasive method for identifying members with Hb SS who are at high risk for developing a first stroke. High-risk patients are those with increased blood velocity in large cerebral vessels, indicative of vascular narrowing. Patients with mean blood-flow velocity in the internal carotid or middle cerebral artery of >200cm/second are at highest risk. A prospective randomized study demonstrated that chronic transfusions reduce the risk of first stroke in such high-risk patients. These data have led some to the recommendation of routine TCD screening of members with sickle cell anemia, and the initiation of a chronic transfusion program for those with abnormal screening tests.

Initial transcranial Doppler (TCD) screening should be done between two and three years of age. It should be repeated yearly therafter.

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SPINA BIFIDA

CLINICAL PRACTICE GUIDELINES

Clinical Practice Guidelines represent the minimum requirements for providing care for individuals with Spina Bifida. Care and treatment should be provided in a manner that includes adherence to and consistency with each of the following Guidelines.

CRS Enrollment:

Patients diagnosed with Spina Bifida must be seen at a site with a Spina Bifida Clinic.

Interdisciplinary Team Membership:

The following Team Members must be present during regional clinics and team conferences to review the patient information and determine the need to see the patient at a clinic site and must be available for inpatient consultation or coordination of care with inpatient staff:

- Pediatrician
- Neurosurgeon
- Orthopedist
- Urologist
- Physical Therapist
- Nutritionist
- Social Worker
- Registered Nurse Coordinator
- Occupational Therapist
- Child Psychologist
- Genetic Counselor/Nurse
- Nurse with expertise in Bowel and Bladder Care
- CRS member / Caregiver
- Primary Care Physician (Invited)[1]

Available Personnel:

The following personnel must be available to the member at the Spina Bifida Clinic:

- Advocate

[1]The Primary Care Physician will be invited to attend all Interdisciplinary Team meetings.

- Child Life Specialist
- Orthotist
- Skin / Wound Specialist (may be RN/LPN with additional expertise in Wound Care)
- Translator
- Educator

Consultative Personnel:

The Regional Clinic must have access for consultation to specialists including, but not limited to the following:

- Audiologist
- Cardiologist
- Endocrinologist
- Gastroenterologist
- Geneticist
- Nephrologist
- Pediatric Neurologist
- Ophthalmologist
- Otolaryngologist
- Plastic Surgeon
- Pulmonologist
- Psychiatrist
- Physiatrist

Outreach Clinics:

Outreach Clinics are designed to provide a limited specific set of services including evaluation, monitoring and treatment in settings closer to the family than a Regional Clinic. Major treatment plan changes must be communicated to the regional clinic.

Members with spina bifida may be seen in other specialty clinics including Orthopedic, Urology, Neurosurgery and Neurology outreach clinics.

Outreach clinic records must be provided to the Regional Clinic serving the member.

Facilities & Services:

1. Radiology services of a quality and consistency to effectively monitor changes in spinal curve, full service neuroradiology lab and urodynamic lab availability.
2. Equipment and expertise to measure height and weight.
3. Access to the pharmacy.
4. Latex safe environment.

Team/Staff Meetings:

Team and staff meetings will be held based on the age of the patient and their diagnosis. At a minimum the following will occur:

1. Interdisciplinary Team Meetings: review and planning meetings (patient specific meetings) are to be held at least once a year. Based on the individual impairment, the Team may determine that once every two years is appropriate.

2. Staff meetings annually to focus on issues of clinic patient care and clinic administration.

3. Education meetings once a year to focus on new information regarding the care and treatment for persons with spina bifida. These may be off site meetings and are to be made available to staff and the CRS members and caregivers.

Lead Physician Specialists:

Qualifications: The Lead Physician Specialist should be a pediatrician with experience and expertise in spina bifida.

Radiation Exposure:

Care should be taken when ordering radiology studies to consider cumulative radiation exposure to the child. The technique that produces the best result with the least radiation exposure should be utilized.

GUIDELINES FOR PATIENT SERVICES, EVALUATION AND MONITORING FOR SPINA BIFIDA

The purpose of these guidelines is to promote a uniform level of care at CRS Clinics for members with spina bifida and to provide a general framework for good patient care. Their relevance to specific situations will depend on individual variations in clinical course and professional judgment. In addition, this document should serve as a tool to assess programs,

secure resources needed to enhance patient care and education, and guide the future development of treatment of spina bifida.

Diagnosis Treatment:

Goal: To provide accurate and timely diagnosis of spinal deformities.
Goal: To maintain maximum functioning and monitor for signs of deterioration in motor functioning, urinary and bowel continence, central nervous system functioning and skeletal alignment.

See Guidelines for Spina Bifida Health Care Services Throughout Life; Spina Bifida Association of America, Professional Advisory Council, June 1990, or updates as available.

Ongoing Patient Evaluation and Monitoring:

Goal: To anticipate and treat physical and psychosocial problems and management of the condition.

Make sure a social worker is available to the family.

Provide access to a nurse with experience in working with member's with spina bifida.

See Guidelines for Spina Bifida Health Care Services Throughout Life; Spina Bifida Association of America, Professional Advisory Council, June 1990 for monitoring / clinic scheduling.

GUIDELINES FOR SELECTING SURGICAL CANDIDATES FOR DISLOCATED HIPS IN CHILDREN WITH SPINA BIFIDA

1. Selection Criteria. Unilateral hip dislocation may be considered for surgical treatment in a child of any age when associated with one or more of the following:

   a) X-ray evidence of deterioration in scoliosis or pelvic obliquity

   b) Documented pain

   c) Ischial pressure sores

   d) Documented deterioration of sitting alignment which can no longer be addressed through the child's seating system

   e) Documented deterioration in standing or assisted ambulation

   f) Other well-documented, compelling clinical conditions may be presented to the child's team for consideration of surgical intervention.

Each of these areas will be assessed and documented in MM and /or Ortho Clinic at least annually, for every child with spina bifida, in order to provide a longitudinal record.

2. Manual muscle testing and sensory testing are performed at regular age-appropriate intervals on all children with spina bifida, and will be performed on any candidate for hip reduction surgery prior to making a decision regarding surgery.

3. A decision regarding CRS coverage of a hip reduction surgery will require consensus of the child's MM Clinic team, including orthopedic surgeon, the family, physical therapist, nurse, social worker, and other professionals as appropriate to the individual child's case, and approval by the Medical Director.

4. Clinical and functional goals of the surgical procedure and expected outcomes must be documented prior to the procedure.

SPINAL DEFORMITIES

Clinical Practice Guidelines represent the minimum requirements for providing care for individuals with scoliosis, kyphosis, and related spinal deformities. Care and treatment should be provided in a manner that includes adherence to and consistency with each of the following Guidelines.

CRS Enrollment:

Member's diagnosed with scoliosis, kyphosis, or other spinal related conditions must be enrolled in a regional scoliosis clinic. Based on the recommendations of the interdisciplinary team, the patient may be seen in regional orthopedic clinics and orthopedic outreach clinics. Information from the regional or outreach orthopedic clinics must be provided to the regional spinal deformities clinic.

For member's with multiple CRS diagnoses involved with multiple teams, the appropriate members of each interdisciplinary team shall review the patient status and refer to the Spinal Deformities Team when appropriate for treatment related to the spinal deformity.

Team Membership:

The following Team Members <u>must</u> be present during regional clinics and team conferences to review the patient information and determine the need to see the patient at a clinic site and must be available for inpatient consultation or coordination of care with inpatient staff:

- Orthopedic Surgeon with experience in treating member's with spinal deformities - Lead Physician

- Registered Nurse Coordinator
- Nurse with experience in spinal deformities (May be the same as the Nurse coordinator)
- CRS member / Caregiver
- Primary Care Physician[2]

Consultative Personnel:

- Educator
- Geneticist
- Nutritionist
- Occupational Therapist
- Pediatric Cardiologist
- Pediatric Neurologist
- Pediatric Neurosurgeon
- Pediatric Urologist

[2]The Primary Care Physician will be invited to attend all Interdisciplinary Team meetings.

- Pediatrics
- Child Psychologist
- Pulmonologist
- Radiologist
- Physical Therapists

Outreach Clinics:

Outreach clinics are designed to provide a limited specific set of services including evaluation, monitoring and treatment in settings closer to the family than a regional clinic. Major treatment plan changes must be communicated to the regional clinic.

Members with spinal deformities may receive monitoring services between site visits at the orthopedic outreach clinics. The outreach clinic must include an orthopedic surgeon with expertise in managing spinal deformities and an orthotist.

Outreach clinic records must be provided to the Regional Clinic serving the member.

Community Based Services not provided by CRS:

Community based services means all local services including provider agencies, schools, private physician offices, hospitals, and/or any other local setting.

Members with a diagnosis of idiopathic scoliosis with a curvature of less than 15 degrees who are skeletally mature may be monitored in the community.

The following community based services may be provided from a community based setting:

- Physical Therapy
- Radiology Services
- Lab Services
- Pharmacy Services
- Occupational Therapy
- Nutrition Services
- Social Work Services

Special Equipment:

Radiology services of a quality and consistency to effectively monitor changes in spinal curve.

Team/Staff Meetings:

Team and staff meetings will be held based on the age of the patient and their diagnosis. At a minimum the following will occur:

1. Interdisciplinary Team Meetings: review and planning meetings (patient specific meetings) are to be held as follows:

   All patients with spinal deformities should attend an interdisciplinary regional spinal deformities clinic at least once every 6 months except for patients with a curve of less than 15 degrees who are skeletally mature who should attend interdisciplinary regional spinal deformities clinics at least once every two years.

2. Staff meetings annually to focus on issues of clinic patient care and clinic administration.

3. Education meetings annually to focus on new information regarding the care and treatment for persons with spinal deformities. These may be off site meetings. The following individuals should be included in the education meetings: the lead

physician, the members of the Interdisciplinary Team, and any other interested persons.

Lead Physician Specialists:

Qualifications: The Lead Physician Specialist should be an orthopedic surgeon with experience in the managing of pediatric spinal deformities in members.

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