HRC3 Partner Center Clinical Care and Program Building Toolkit

Contents

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General clinical program information

Heterotaxy Partner Center overview

Heterotaxy Research and Clinical Care Collaborative (HRC3) in partnership with Heterotaxy Connection (HC) will oversee the development and implementation of Heterotaxy Parter Centers ("Partners") to ensure standardized and quality clinical care and research collaboration and innovation. The goal of the Partners will be to improve clinical outcomes and quality of life of persons with heterotaxy and develop a foundation and infrastructure for clinical and translational research, including a national Heterotaxy Registry.

Partners recognized by HRC3 and HC will be featured on our website and will be invited to contribute to research and registry initiatives. Partners will be expected to provide a high level of clinical and research expertise but absence of some of the clinical tools listed below does not necessarily preclude a center from becoming a Partner.

Partners should be directed by one or two co-directors from different pediatric or adult subspecialties. Partner directors will be expected to offer local and regional expertise to patients, families and other providers, stay up to date on clinical and research innovations, and offer scholarly contributions to the literature and at the yearly Facing Heterotaxy Together conference.

Although HRC3 and HC cannot provide financial effort to Partner site directors, this designation will create many opportunities for collaborative scholarship, publication authorship, and conference presentations. Most importantly, successful development of a network of Partners will provide the best care for our patients and their families.

Clinical specialty requirements

Partner centers will require local champions in each of the following specialties:

- Pediatric Cardiology
- Pediatric Pulmonology
- Genetics
- Genetic Counseling
- Pediatric General Surgery
- Pediatric Immunology, Hematology or Infectious Disease

Other strongly suggested subspecialties at Partner Centers:

- Cardiothoracic Surgery
- Electrophysiology
- Pediatric Neurology
- Otorhinolaryngology

- Radiology
- Gastroenterology or Hepatology
- Adult Cardiology
- Palliative Care
- Patient and family advocate

Diagnostic resources

Required

- Echocardiography
- Advanced cardiac imaging (i.e., cardiac CTA and/or MRI)
- ECG and Holter monitoring
- Local and/or sendout genetic testing and interpretation
- Abdominal ultrasound
- Splenic function testing (sendouts acceptable)
- Nasal nitric oxide testing
- Transmission electron microscopy

Suggested

- 3D cardiovascular modeling (print or virtual reality)
- Exercise and metabolic testing
- Invasive electrophysiology studies/ablations
- Neurodevelopmental testing
- Upper GI radiography

Support services

- Clinical administrative coordinator
- Clinical nursing
- Social worker
- Nutritionist/dietician
- Physical therapist
- Respiratory therapist
- Exercise physiologist (especially for complex cardiac disease)
- Psychologist
- Research Coordinator
- Speech Language Pathologist

Heterotaxy Partner Center application process

Prospective Partners will be required to complete a formal Request for Application (RFA) form which will be found on the HRC3 website. RFAs will include faculty

representatives of the required subspecialties and a list of available clinical resources at the center. Completed RFA forms will be submitted to the HRC3 Partners subcommittee and HC representative for formal review.

Genetics and Genomics
Kathryn Chatfield, Children's Hospital Colorado; Gabrielle C. Geddes, Indiana University School of Medicine; Sarah U. Morton, Boston Children's Hospital; Amy E. Roberts, Boston Children's Hospital; Stephanie M. Ware, Indiana University School of Medicine (Authors Listed Alphabetically)

Genetics and Genomics

Introduction

Heterotaxy can be a sign of a genetic syndrome, a primary manifestation of a disrupted gene, or apparently sporadic without a clearly identifiable genetic cause.[1-3] From a genetics and genomics standpoint, the most important question to answer is whether heterotaxy results from or is associated with an underlying genetic syndrome in the patient. This is best answered through a comprehensive assessment by a medical geneticist, in conjunction with broad genomic testing that assesses both structural and sequence variants.[1,4] The reason a medical geneticist's assessment is critical is that their evaluation can identify syndromic patterns that have actionable clinical screening or management guidelines, as these are not always detectable with molecular testing. In addition, medical geneticists ensure the most appropriate genetic and/or genomic testing is completed, interpret those testing results, assess family history and other family members as indicated, and provide estimates of recurrence risk.

Team composition

1. Medical Geneticist: All patients with heterotaxy should have access to a medical geneticist familiar with heterotaxy for evaluation, diagnostic clarification, and coordination of genetic testing. The medical geneticist plays a critical role in guiding the clinical team regarding syndromic associations, recurrence risks, and management of familial cases.

2. Genetic Counselor**:** Genetic counselors are essential in supporting patients and families by providing education, counseling, and assistance with navigating the complexities of genetic testing. They ensure that patients and their relatives understand the implications of the results, inheritance patterns, and reproductive options.

3. Genetic Counseling Assistant: A genetic counseling assistant can provide vital support to the counseling team by managing intake, coordinating communication, and assisting with administrative and testing logistics to streamline care.

4. Clinical Coordinator: A clinical coordinator helps organize appointments, testing workflows, and communication across the care team. For patients with heterotaxy, the coordinator ensures multidisciplinary input is integrated and that family members requiring genetic evaluation are appropriately scheduled.

5. Testing/Insurance Support: Dedicated support for prior authorization and insurance navigation is essential to prevent delays in care. This role also includes sample coordination and tracking, which is especially important when testing relatives of the patient to clarify inheritance or recurrence risks.

6. Scheduling and Billing Support**:** Patients and their families benefit from staff who manage registration and scheduling, including for relatives who may require evaluation. This support also encompasses billing for genetic counseling services, where permitted by state law and institutional policies, to ensure that the program remains sustainable and accessible.

Tips and tricks

- Remember not to refer to variants as "mutations" [5,6]
  In 2015, the American College of Medical Genetics and Genomics published variant interpretation guidelines, classifying them into five categories: Pathogenic Variants, Likely Pathogenic Variants, Variant of Uncertain Significance, Likely Benign Variants, and Benign Variants. At this time, it was also recommended that the word "mutation" not be used in clinical settings to avoid confusion and to use the more precise variant classification terminology.
- Variants of uncertain significance are not diagnostic
  If someone previously had genomic testing, be sure to record what test was completed (for example, exome or genome sequencing), when the test was last analyzed, as well as what lab
- Remember that genomic testing is never "whole" [6-9]
  There is no genetic or genomic test available that can assess for all genetic diseases. Due to a number of technical limitations, clear pathogenic coding variants may not be detected on exome or genome sequencing.

Standard diagnostic evaluation and modalities

Test	Looks For	Test Considerations
Karyotype	Large chromosomal anomalies and structural anomalies	Not generally helpful in assessment of heterotaxy patients without clinical suspicion for aneuploidy, translocations, inversions, or mosaicism detected best with karyotype. Can only be completed on samples with actively dividing cells.
Chromosomal Microarray	Genome wide copy number variants	Good coverage for copy number variants, cannot detect sequence variants such as those causative of primary ciliary dyskinesia. Resolution of chromosomal microarrays can vary widely, especially for prenatally completed microarrays which often restrict to reporting larger abnormalities or very well characterized pathogenic copy number variants.
Heterotaxy Panels, Ciliopathy Panels, Congenital Heart Disease Panels	Sequence variants and copy number variants (if deletion/duplication analysis is included) of a specific list of genes	The utility of the panel depends on the genes that are included. As the primary question of the test is, “Are there variants in this gene list?” larger panels are likely to result with variants of uncertain significance.
Genomic Testing:		
Exome Sequencing (Short Read)	Sequence variants and typically copy number variants of most coding areas of nuclear genes	This test allows for broad molecular testing, and if parents or other relatives are available they may be included as part of the test to assist with variant interpretation. The primary question of the test is, “Are there variants that could explain the patient’s features?” which means that providing all information about a patient to the lab is critical. Copy number variant coverage is more limited than with chromosomal microarray and is dependent on individual labs’ bioinformatics pipelines. Data can be reanalyzed after at least a year or if a major new clinical issue is identified.
Genome Sequencing (Short Read)	Sequence variants and typically copy number	This test allows for broad molecular testing, and if parents or other relatives are available

	variants of most of the nuclear genome Analysis variable by testing lab: Often includes mitochondrial genome analysis Some genomes cover specific repeat expansion disorders	they may be included as part of the test to assist with variant interpretation. The primary question of the test is, "Are there variants that could explain the patient's features?" which means that providing all information about a patient to the lab is critical. Copy number variant coverage is improved over exome sequencing. Data can be reanalyzed after at least a year or if a major new clinical issue is identified.
Genome Sequencing (Long Read)	Sequence variants and copy number variants of most of the nuclear genome Analysis variable by testing lab: May include structural anomalies May include mitochondrial genome May include repeat expansion disorders May include methylation analysis	This method of genome sequencing is currently emerging as a clinical test. As opposed to short read genome sequencing, long read genome sequencing has improved ability to get structural context. This means long read genome sequencing has the potential to identify differences such as translocations, inversions, chromothripsis, and repeat expansion disorders. Some long read genome analyses also have capacity to detect methylation status

Management

- Based on specific diagnosis or findings
- Periodic follow up for reassessment and/or reanalysis of genomic testing data

Summary

Every patient with heterotaxy should be evaluated by a Medical Geneticist and Genetic Counselor to help identify syndromic patterns, order appropriate testing and offer counseling.

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Immunological Management in Heterotaxy
Douglas McDonald, Boston Children's Hospital Jo Wilson, University of Wisconsin-Madison (Authors Listed Alphabetically)

Immunological Management

Introduction

The spleen plays a vital role in filtering and removing old red blood cells and white blood cells and is an important site of immune responses that protect against infection. Absent or impaired splenic function results in increased susceptibility to certain types of bacterial infections due to "encapsulated" bacteria (*Streptococcus pneumoniae, Haemophilus influenzae type b, Neisseria meningitidis, Capnocytophaga canimorsus*). Heterotaxy can manifest as "right isomerism," which is characterized by asplenia (no spleen) or "left isomerism," which is characterized by polysplenia (multiple spleens which may or may not function normally). Immunologic management of heterotaxy syndromes involves assessing the presence or absence of splenic function and preventing life-threatening bacterial infections.

Team composition

1. Immune system specialist: All patients with heterotaxy should be evaluated by an immunologist, hematologist or infectious disease expert to assess for immune dysfunction, given the known association of heterotaxy with functional asplenia, polysplenia, or hyposplenism. The immunologist is responsible for guiding appropriate immune work-up, including laboratory assessment of splenic function, lymphocyte subsets, immunoglobulin levels, and vaccine responses when indicated.

2. Nursing or Clinical Support Staff: Nursing or dedicated clinical support is essential for coordinating vaccines, prophylactic antibiotics, and follow-up immune monitoring. These staff members also play a crucial role in educating families on infection prevention, recognizing the warning signs of sepsis, and ensuring adherence to prophylactic regimens.

Immunological abnormalities encountered in heterotaxy

- Asplenia, functional hyposplenism
- Low immunoglobulin levels, reduced vaccine responses

- Decreased numbers of total T cells (CD4+, CD8+), naïve T cells, T-cell receptor repertoire diversity
- Premature immunosenescence in the T cell compartment, autoimmunity, neoplasms, increased infections—potential late effects

Screening and diagnostic evaluation

Assessment of spleen anatomy and function

Abdominal imaging (ultrasound, CT scan, MRI scan) is the preferred method of assessing the presence or absence of splenic tissue, but does not assess splenic function.

Preferred methods for assessing *splenic function* include **pitted red cell count*** and assessment of CD27+ **IgM+ memory B cell count***. Pitted red blood cells are red cells in which damaged proteins have accumulated underneath the cell surface, forming "pits". These "pits" are typically removed from red blood cells, and the presence of an increased percentage of pitted red cells in the blood (>4%) is indicative of impaired splenic function. IgM memory B cells are a type of B cell found in the spleen that are important as a first line of defense against encapsulated bacteria. IgM memory B cells secrete IgM antibodies against encapsulated bacteria, which provides protection against infection. Reduction in IgM memory B cell count is another measure of impaired splenic function.

All patients with heterotaxy should have splenic function testing, as functional hyposplenism in heterotaxy is possible even with normal spleen anatomy. All patients with asplenia on imaging should be assumed to have functional hyposplenism and testing is not necessary.

*if these tests are not available at your center, reliable send out assessments are available at Cincinnati Children's Hospital (RBC Pits Count: Erythrocyte Diagnostic Laboratory Test code: 2700100, B Cell Development Panel: Cincinnati Children's Diagnostic Immunology Laboratory, Test Code: 2094400)

Normal range for RBC pit count < 6 months of age is not validated. Due to immune immaturity, it can be elevated in the neonatal period. If low, this is reassuring for appropriate splenic function. If high, it may normalize over time so medical providers are recommended to trend this over time. This test will be falsely normal in the setting of packed RBC transfusions—delay testing if patients have received transfusions.

The decision to treat with antibiotic prophylaxis without confirmatory testing of splenic function should be made in consultation with an immunologist, hematologist or infectious disease expert.

For patients with more severe defects of the heart and great vessels that require surgical correction and thymectomy (particularly in patients less than 1 year of age), immune surveillance should:

- Evaluate for decreased numbers of total T cells (CD4+, CD8+), naïve T cells, TCR repertoire diversity
- Monitor for premature immunosenescence in the T cell compartment, autoimmunity, neoplasms, and increased infections.

Management of immunological disease in heterotaxy

Immunizations

- Immunization against encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenza type b, Neisseria meningitidis*) is essential in patients with absent or impaired splenic function, who are at increased risk of sepsis from these bacteria. Patients with absent or impaired splenic function must be up to date with routine childhood immunizations as well as CDC AICP guidelines for impaired splenic function. These include:
    - *Streptococcus pneumoniae* (CDC recommends 4 dose series of **20** 2, 4,6, and 12-15 months)
        - 1 dose of **PPSV 23 or PCV-20 after 2 years of age**
            - *If PPSV-23 given, need to repeat every 5 years regardless of antibody levels*
            - *If PCV-20 given (preference based on decreased bacterial carriage in the airway) – limited guidance on timeline to repeat at this time. Recommend following antibody levels.*
    - *Haemophilus influenza type b* (**Hib**) – standard infant series recommended
    - *Neisseria meningitidis using the **Menveo** vaccine should be given with patient's primary series (2,4,6, 12-15 months). If the patient is diagnosed after 2 years, can give **Menactra** series.*
        - *If first series < 7 years old, first booster at 3 years, then repeated every 5 years*
        - *If the first series is> 7 years old, repeat every 5 years.*
    - The serogroup B meningococcal vaccine (**Bexsero**) is recommended for children once they reach 10 years of age, and those with asplenia require a three-dose series. This should be repeated every 5 years.

Antibiotic prophylaxis against bacterial infection

- The incidence of overwhelming bacterial infections is best characterized in patients undergoing splenectomy. The incidence of fulminant sepsis is fairly low (3-7%), but mortality from sepsis is high (up to 70%). Antibiotic prophylaxis is recommended:
  - Amoxicillin: 10 mg/kg BID (until at least age 5 and recommendations for lifelong antibiotics are appropriate in certain clinical situations), maximum dose 500 mg BID. Some patients might need lifelong antibiotic prophylaxis. This decision should be made in consultation with local immunologist, hematologist or infectious disease expert.
  - Penicillin VK 125 mg BID (<3yo), 250 mg BID (>3yo).
- For patients with allergies, cephalexin and macrolides can be alternatives.
- Immediate medical care following animal bites (*Capnocytophaga canimorsus), even if the bite wound is minor.*

Management of fever in patients with asplenia and impaired splenic function

- Infections in patients with impaired splenic function can progress rapidly. All patients with impaired splenic function should have a written fever plan from their immunology provider.
- Patients who develop fever (e.g., temperature ≥101°F/38.3°C) or other signs of systemic infection (e.g., chills, rigors, vomiting/diarrhea, headache) should present to the nearest emergency department immediately.
- Patients with symptoms suggestive of viral upper respiratory illnesses (e.g., rhinorrhea, nasal congestion) who lack fever do not need to seek immediate care and can be managed similarly to patients with normal splenic function.
- If families live > 30 minutes from the closest emergency room, we do recommend "stand-by" antibiotics for home. Age/weight appropriate Augmentin dosing is first line with alternatives options given for penicillin allergic patients.

Summary

1. All patients with heterotaxy should be evaluated by an expert in immunology, hematology or infectious disease
2. Spleen anatomy should be determined by abdominal imaging
3. Spleen function should be assessed with pitted red blood cells and IgM+ Memory B cell count unless asplenia is confirmed on imaging
4. Patients with suspected or proven hyposplenism should receive vaccinations to prevent sepsis.
5. Patients with suspected or proven hyposplenism should be treated with prophylactic antibiotics to prevent sepsis.
6. Parter centers should develop and distribute fever protocols and educate families of patients with suspected or proven hyposplenism.

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Gastroenterology, including Hepatology and General Surgery
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Gastroenterology, Including Hepatology and General Surgery

Introduction

Gastrointestinal manifestations are commonly seen in heterotaxy and can range from the rare congenital portosystemic shunts to the routinely encountered abnormalities of abdominal situs and intestinal rotation anomalies (IRAs). The clinical implications of such abnormalities have an equally broad range from asymptomatic intestinal malrotation to liver transplant for biliary atresia. Familiarity with the full spectrum of gastrointestinal manifestations and their complications as well as access to standard resources for timely diagnosis and effective management are essential for improving outcomes in this complex patient population.

Team composition

Team members with the following expertise are appropriate.

1. Gastroenterology/Hepatology: Timely diagnosis of conditions such as biliary atresia is vital for improving outcomes, yet the diagnostic evaluation may be challenging in patients with significant underlying cardiac disease (i.e., concomitant congestive heart failure and chronic parenteral nutrition dependence). Efficient and effective diagnosis or elimination of diagnoses is especially important in coordination of neonatal care for many of these complex patients.
2. General Surgery: Many intestinal malformations listed below may present with obstructive symptoms. Balancing the risk of complications from the underlying malformation with those of any given surgical intervention are important to consider.
3. Transplant Surgery: With abdominal situs abnormalities and complex vascular anatomy, it is vital to have appropriate imaging capabilities and ability for the surgeons to appropriately plan for the complex anatomy that may be encountered (i.e., abdominal situs inversus or interrupted inferior vena cava) should patients progress to end-stage liver disease requiring transplantation.

Gastrointestinal manifestations

As can be seen in other organ systems, certain malformations may be more commonly seen in either left or right isomerism phenotypes; however, significant overlap between the types can be commonly seen and is by no means a rule.[1,2] Right atrial isomerism is commonly referred to as the "asplenia" type given the increased incidence of absent splenic tissue. Left atrial isomerism is commonly referred to as the "polysplenia" subtype given the association with multiple splenules. Patients with heterotaxy may also have normal left-sided spleen or abdominal situs inversus with a single right-sided spleen. Patients can commonly have an enlarged, midline liver. In such patients, the usual anatomic landmarks may be absent which can make identification of a spleen or lack thereof challenging. Visualization of the splenic artery and vein can aid in identification of splenic tissue in such cases. The implications of anatomic or functional asplenia are discussed separately in the immunology section.

Left atrial isomerism or "polysplenia" is more likely to be associated with biliary atresia.[3] Biliary Atresia is a rare, progressive, fibroinflammatory liver disease that only affects infants. Approximately 10-15% of all patients with biliary atresia have associated laterality defects such as interrupted IVC, polysplenia, malrotation, preduodenal portal vein and congenital heart disease (Biliary Atresia Splenic Malformation Syndrome, BASM).[4] Early (<60 days of life) identification and treatment of biliary atresia is imperative, as outcomes of Hepatoportoenterostomy (Kasai Procedure) improve with decreasing age of the patient. Testing conjugated or direct bilirubin shortly after birth has been shown to be a screening tool for infants at risk of having biliary atresia.[5] Therefore, we recommend laboratory testing shortly after birth in infants with heterotaxy and, if persistently elevated, the patient should be evaluated by pediatric gastroenterology/hepatology.

All types of heterotaxy can have various degrees of intestinal malrotation or incomplete rotation. Multiple single-center studies have found that the majority of asymptomatic heterotaxy patients (up to 70% or more) have signs of malrotation on routine upper GI studies.[6] However, symptomatic malrotation is quite rare and is seen in <5% of patients with heterotaxy. This paucity of symptoms has been attributed to a broad-based mesentery more commonly seen in patients with heterotaxy compared to the more narrow mesentery in isolated cases of malrotation. Ladd's procedures are associated with increased risk of morbidity and mortality in the heterotaxy population, especially in higher risk cardiac patients with shunted/single ventricular physiology.[7] Current data do not support the routine radiographic screening or routine prophylactic Ladd's procedure in asymptomatic patients.[8-12] For the symptomatic patient with either bilious emesis, feeding intolerance, or need for enteral access, additional testing and surgical consultation is warranted. If malrotation with volvulus is identified in a patient with bilious emesis, immediate surgical notification is paramount to expedite emergent operative intervention. Routine upper GI with small bowel follow through should be performed

in patients with feeding intolerance (intolerance of gastric feeds) or planned enteral access surgery (gastrostomy or gastrojejunostomy tube). If malrotation is encountered in a child with feeding intolerance, the general surgeon should review the risks and benefits of a therapeutic Ladd's procedure with the family and the primary team. If malrotation is identified for a child with planned enteral access surgery, the general surgeon should review the risks and benefits of mesenteric width assessment at the time of the enteral access operation (and the potential to proceed with a prophylactic Ladd's procedure if a narrow mesentery or obstructive Ladd's bands are encountered) with the family and the primary team. All families should also receive education about the lifelong risk of volvulus or symptomatic malrotation including indications for immediate medical evaluation. Other gastrointestinal malformations seen in heterotaxy and associated with risk of intestinal obstruction include annular pancreas, duodenal atresia, preduodenal portal vein, microgastria, anal atresia ("asplenia" subtype), or tracheoesophageal fistula.[13]

Finally, patients with heterotaxy also appear to be at higher risk of congenital portosystemic shunts (CPSS). CPSS are abnormal connections between the portal veinous system and systemic venous circulation. They are rare with a prevalence that is unknown. In one case series of 29 patients with CPSS, 14% had laterality defects.[14] CPSS can be intrahepatic or extrahepatic. Extrahepatic shunts are further divided based on the absence or presence of portal vein flow (type 1 vs type 2). Complications of CPSS can include encephalopathy, cholestasis, hypoglycemia, hypergalactosemia, liver masses, and hepatopulmonary syndrome. CPSS should be considered in patients with unexplained hypoxemia or evidence of chronic volume load. The timing and indications for closure are controversial since some will spontaneously close. Asymptomatic shunts can be followed conservatively and closed if spontaneous closure does not occur. Symptomatic shunts can be closed surgically or endovascularly depending on center experience and underlying type of CPSS. Staged closure should be considered in patients with little portal vein flow, as complete occlusion of the shunt could cause portal hypertension. CPSS should not be closed in the setting of complete absence of the portal vein and would require liver transplant in symptomatic cases.

Standard diagnostic evaluation and modalities

In all patients with a new diagnosis of heterotaxy, a complete abdominal ultrasound should be obtained with particular attention to spleen status, liver size and position, and biliary anatomy. Of note, the presence of a gall bladder does not rule out biliary atresia. Neonates should have a fractionated bilirubin level measured within the first days of life as part of their routine newborn screening. Levels above the upper limit of normal per institutional reference ranges should have repeat levels obtained at least within 2 weeks of age with prompt hepatology referral for persistent elevations in direct bilirubin levels. If there are imaging findings suggesting biliary atresia or a direct/conjugated bilirubin >1, hepatology should be consulted urgently. For

intestinal malrotation, there is insufficient data to recommend routine upper GI screening in asymptomatic individuals. However, any patient with bilious emesis should undergo emergent upper GI contrast study for diagnosis. In all other symptomatic patients, an upper GI study with small bowel follow-through increases the diagnostic yield. Abdominal X-ray remains the first line study for assessment of possible bowel obstruction in symptomatic patients with subsequent evaluation and surgical consultation to determine the site of obstruction given the numerous points of potential obstruction previously described in heterotaxy. Finally, if suspicious for possible CPSS, cross sectional imaging of the abdomen with either computed tomographic angiography (CTA) timed to the portal venous phase or magnetic resonance angiography should be performed. Special consideration is needed in patients with single ventricle congenital heart disease (i.e., Fontan physiology) to determine appropriate contrast timing for CTA.

Specific scenarios

Neonates with persistent direct hyperbilirubinemia

Early consideration for definitive testing of biliary atresia in neonates with persistent direct hyperbilirubinemia. Many patients with significant cardiac disease may have multiple reasons for direct hyperbilirubinemia such as TPN cholestasis and/or congestive hepatopathy (from valvular dysfunction, over-circulation in shunted physiology, and/or ventricular dysfunction as can be seen in non-compaction cardiomyopathy). However, the association of biliary atresia, especially in cases of polysplenia, should be aggressively pursued to aid in the timely diagnosis and management of the condition.

Atypical location of abdominal pain

Patients with malrotation or incomplete rotation may have atypical locations of abdominal pain. For instance, patients with appendicitis may have epigastric pain as the presenting symptom and could lead to a delay in diagnosis.[15] Awareness of the unique anatomy seen in heterotaxy and clinical suspicion should be maintained.

Congenital portosystemic shunt

Characterizing the shunt with a specific focus on presence or absence of portal vein flow is important. Cross sectional imaging is often required. Screening for complications, specifically hyperammonemia, should be done in all patients with CPSS. In cases of CPSS with need for cardiac intervention or heart transplant, multidisciplinary discussions between hepatology, cardiology, and surgery are necessary to determine if and when the shunt should be closed. Shunts should not be closed without hepatology consultation to ensure liver function is normal

and for monitoring after shunt closure. In general, liver transplant is not indicated for type I Abernethy unless there are complications attributable to the shunt.

Summary

Recommended Gastroenterology Staffing and Resources for Patients with Heterotaxy

- Gastroenterologist or hepatologist with expertise in heterotaxy manifestations
- General surgeon
- Consideration of a liver transplant team

Recommended Routine Evaluation:

- **At Diagnosis:**
  - Complete abdominal ultrasound
  - Fractionated bilirubin level in all neonates with heterotaxy
  - No routine evaluation for malrotation or intestinal obstruction is recommended unless clinical concerns surrounding the GI tract exist.
- **Longitudinal Follow-up:**
  - Upper GI for bilious emesis.
  - KUB and surgical consult for signs/symptoms of obstruction.
  - GI consult for vomiting, feeding intolerance, or poor weight gain.

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Pulmonology and Sleep Medicine
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Pulmonology and Sleep Medicine

Introduction

Patients with heterotaxy may have respiratory disease secondary to a genetic abnormality (i.e., primary ciliary dyskinesia (PCD)) or secondary to other comorbidities of heterotaxy itself, including congenital heart disease (CHD) or infections from functional hyposplenism (i.e, asplenia, polysplenia).

Many, but not all, cases of heterotaxy arise from genetic abnormalities in motile cilia. Motile ciliary dysfunction can lead to organ laterality defects, such as heterotaxy, and impairment of mucociliary clearance. This can result in chronic sinopulmonary disease and bronchiectasis. Primary ciliary dyskinesia is a congenital disorder of mucociliary clearance leading to chronic wet cough, chronic rhinosinusitis, neonatal respiratory distress, bronchiectasis, and subfertility. A milder form of motile cilia impairment, Heterotaxy Associated Ciliary Dysfunction (HACD), might also cause chronic respiratory symptoms and post-operative complications. The respiratory phenotype in HACD is milder compared to the classic phenotype of PCD. Symptoms and signs of motile ciliary impairment include chronic wet cough, chronic nasal congestion, recurrent otosino-pulmonary infections, neonatal respiratory distress without a causative cardiac lesion, cerebral ventriculomegaly/hydrocephalus, or unexpected/prolonged post-operative respiratory complications. Whereas the diagnosis of PCD is based on evidence-based clinical criteria with genetic testing, nasal nitric oxide measurement, and transmission electron microscopy of ciliary ultrastructure, HACD is suggested when there is an appropriate clinical phenotype and PCD testing is negative.

Common complications of cardiothoracic surgery can also contribute to lung disease. Fetuses with CHD are at risk of preterm birth, which is independently associated with lung disease. Surgical complications of cardiothoracic surgery, such as recurrent laryngeal nerve injury, can result in transient or chronic vocal cord paresis and/or chronic pulmonary aspiration. Pulmonary aspiration can lead to chronic lung disease, bronchiectasis, and recurrent

pneumonias. Diaphragm paresis can also occur secondary to phrenic nerve injury during cardiothoracic surgery. This can be transient or chronic and may be associated with respiratory insufficiency, chronic atelectasis, and ineffective airway clearance. Post-operative respiratory complications, including prolonged mechanical ventilation and/or tracheostomy, are more common among children with heterotaxy. Individuals with heterotaxy and functional hyposplenism are at a higher risk of developing recurrent or severe bacterial respiratory infections. Treatment of the respiratory complications of heterotaxy requires a multidisciplinary team and access to specialized services and testing to ensure an appropriate diagnosis and management.

Team composition

1. Pediatric Pulmonologist: All patients with heterotaxy should be consulted by a pediatric pulmonologist for evaluation of PCD, HACD, as well as other pulmonary conditions that can be associated with heterotaxy. Additionally, pediatric pulmonologists should participate in lower airway interventions when appropriate and collaborate with chest or pulmonary physical therapists to ensure that a proper airway clearance is prescribed.

2. Respiratory Therapist: Respiratory therapists should be involved in the care of patients with heterotaxy and suspected or confirmed ciliary dysfunction to provide expertise in airway clearance techniques. They can train families on the use of airway clearance devices, oscillatory vests, and inhalation therapies, ensuring that patients maintain optimal lung hygiene. They also play a key role in monitoring adherence, evaluating effectiveness, and adjusting regimens in coordination with pulmonologists and physical therapists.

3. Pediatric Radiology: Pediatric radiologists are essential for evaluating structural anomalies of the chest and abdomen commonly associated with heterotaxy. They should be consulted for advanced imaging of the lungs, airways, and sinuses in patients with suspected ciliary dysfunction. Their interpretation guides diagnosis identifies complications such as bronchiectasis and informs surgical or interventional planning.

4. Pediatric Otorhinolaryngology : Pediatric otorhinolaryngologists should evaluate patients with heterotaxy for chronic upper airway disease, including sinusitis, otitis media, and conductive hearing loss, which are frequent in ciliary dysfunction. They should provide guidance on medical and surgical management, including the use of tympanostomy tubes or sinus surgery, and collaborate with pulmonologists and speech-language pathologists to optimize airway health and hearing.

5. Speech-Language Pathology: Speech-language pathologists should be consulted for assessment and management of feeding, swallowing, and speech difficulties in patients

with heterotaxy and ciliary dysfunction. They can provide swallowing evaluations to prevent aspiration, recommend therapeutic strategies, and support speech development, especially in children with hearing loss secondary to chronic otitis media.

6. Dietician: Dieticians should be engaged to evaluate the nutritional status of patients with heterotaxy, especially those with chronic respiratory illness or feeding difficulties. They can develop individualized nutrition plans to support growth, optimize immune function, and prevent malnutrition, which can worsen respiratory outcomes. Coordination with speech-language pathology and gastroenterology may be necessary for comprehensive care.

7. Social Worker: Social workers play a critical role in supporting families navigating the complex care needs of children with heterotaxy and ciliary dysfunction. They should assist with care coordination, connect families with resources, and provide counseling for coping with chronic illness. They are also vital in addressing barriers to care, such as insurance, transportation, and access to specialized equipment.

8. Psychologist: Psychologists should be integrated into the care team to provide mental health support for patients and families coping with heterotaxy and chronic respiratory disease. They can offer therapy to address anxiety, depression, and medical trauma, and help children develop strategies for adherence to treatment regimens. Their role is crucial in enhancing the quality of life and promoting psychosocial resilience.

Respiratory manifestations of heterotaxy

- Primary ciliary dyskinesia
- Heterotaxy Associated Ciliary Dysfunction (HACD)
- Recurrent respiratory infections with immunosuppression
- Post-surgical lung disease
    - Chronic aspiration with iatrogenic vocal cord dysfunction
    - Diaphragm paresis
    - Ventilator-related lung injury
    - Decreased chest wall compliance
    - Chest wall weakness
    - Pulmonary hemorrhage
    - Pleural effusion
    - Arteriovenous malformations
- Lung diseases associated with specific cardiac pathophysiology
    - Plastic bronchitis
    - Immunoglobulin depletion in protein-losing enteropathy after Fontan procedure
- Chronic pulmonary vasculopathy

    - Pulmonary embolism
    - Pulmonary veno-occlusive disease
    - Pulmonary hypertension
- Sleep Disordered Breathing (SDB)
- Airway anomalies
    - Trachobronchomalacia

Standard diagnostic evaluations and modalities

- Pulmonology consultation for all patients with heterotaxy
    - Comprehensive history and physical exam exploring signs and symptoms of chronic upper and lower respiratory disease (see Common Manifestations)
    - Baseline full pulmonary function testing, including spirometry, diffusion capacity, inspiratory/expiratory pressures, plethysmography, pulse oximetr
    - Baseline chest radiography assessing for chronic lung disease and diaphragm abnormalities.
- Studies to consider based on history and physical exam
    - Primary ciliary dyskinesia screening in patients with consistent phenotypes*
        - Nasal nitric oxide (for children age 5 and older^), PCD genetic testing and/or ciliary transmission electron microscopy
    - Chest ultrasound to assess for diaphragm movement disorders
    - Video fluoroscopic swallow study, functional endoscopic evaluation of swallowing, or other study to evaluate for pulmonary aspiration
    - High resolution chest computed tomography (CT) with inspiratory and expiratory views if there are concerns for structural lung disease or bronchiectasis on chest radiography
    - Respiratory cultures (sputum, oropharyngeal or bronchoalveolar lavage) for surveillance of *Pseudomonas aeruginosa* and other organisms in patients with bronchiectasis, immunodeficiency, HACD or other chronic lung diseases.
    - Flexible bronchoscopy to assess for tracheomalacia and bronchomalacia
    - Polysomnography for patients with symptoms of sleep-disordered breathing.

*Chronic wet cough, chronic nasal congestion, recurrent oto-sino-pulmonary infections, neonatal respiratory distress without a causative cardiac lesion, cerebral ventriculomegaly/hydrocephalus, or unexpected post-operative respiratory complications
^Nasal nitric oxide analysis, tested with tidal breathing technique, might be reliable in children 2 years of age and older if it is interpreted by an experienced provider at a PCD Clinical and Research Center.

Management of respiratory disease in patients with heterotaxy

- Management should be based on the underlying pulmonary conditions identified.

- If the patient satisfies diagnostic criteria for PCD, the patient should be managed according to the PCD Foundation consensus statement or referred to a hospital with a PCD Clinical and Research Network Center accredited by the PCD Foundation.
- Health providers should have a low threshold to implement regular airway clearance strategies and antibiotics as needed with acute respiratory illness and in the perioperative period.
- Airway clearance strategies:
    - Decisions regarding the age of initiation of airway clearance and use of bronchodilators should be made in coordination with other subspecialists involved (cardiologists, neonatologists, respiratory therapists, etc.)
    - The use and dose of additional mucolytic therapies should be determined based on the patient's response and tolerance on a case-by-case basis.
- Regular surveillance of respiratory cultures looking for pathogens found among patients with bronchiectasis (i.e. *Pseudomonas aeruginosa*), if the patient is found to have bronchiectasis, PCD, HACD, or an immunodeficiency
- Routine and supplemental vaccinations for patients with chronic lung disease, as recommended per local practices
- Follow-up determined by type of respiratory distress
    - Patients with PCD, HACD, or bronchiectasis should be seen quarterly.

Specialized management: Refer to the attached link

Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state-of-the-art review

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Cardiology and Cardiac Surgery
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Cardiology and Cardiac Surgery

Introduction

The cardiac manifestations of heterotaxy are strikingly diverse, ranging from minor vascular variants of little clinical consequence to complex single-ventricle physiology and complete heart block, which can result in fetal demise. This breadth makes a uniform approach to cardiac care challenging. Nevertheless, with heterotaxy comprising approximately 3% of patients with significant congenital heart disease—similar to the prevalence of hypoplastic left heart syndrome—coordinated, multicenter, data-driven, and, to the extent possible, standardized efforts are essential to guide care. Optimal management requires a team of cardiology and cardiothoracic surgery providers with dedicated expertise in this complex population.

The following sections provide practical guidance in four key areas: (1) team composition, (2) common cardiac manifestations, (3) standard diagnostic evaluations and diagnostic modalities, and (4) specific issues warranting targeted attention.

Team composition

Team members with the following expertise are appropriate. Overlap is certainly possible depending on the individual cardiologist's expertise.

1. Fetal Cardiology: Prenatal evaluation of heart disease in heterotaxy is uniquely challenging due to the wide variability in anatomy and physiology.[1–6] A fetal cardiologist

with expertise in accurately characterizing complex fetal cardiac and extracardiac findings is essential. Given the potential for serious postnatal physiology (e.g., obstructed total anomalous pulmonary venous return, ductus arteriosus–dependent outflow obstruction, or complete heart block), experience with perinatal planning and coordination across maternal–fetal medicine, neonatal, and cardiac intensive care teams is critical.[7,8] Equally important is close partnership with non-cardiology providers who can deliver comprehensive, longitudinal counseling that addresses the full spectrum of heterotaxy-associated comorbidities.

2. Pediatric Cardiology: A cardiologist (or small group) with expertise in heterotaxy should serve as an institutional resource. While not all patients with heterotaxy need to be managed directly by one individual, this dedicated heterotaxy cardiologist/team should provide consultative support and guidance to other cardiac providers involved in longitudinal care. This role includes coordinating multidisciplinary input, anticipating multiple organ system interactions, peri-procedural support, and helping navigate the variability inherent in this population. This role can include serving as the medical home for the patient or as member of a multidisciplinary team.

3. Electrophysiology: Conduction system disease in heterotaxy is common and complex.[9–12] Patients with polysplenia may develop sinus node dysfunction or complete heart block, even without surgical intervention. Those with asplenia may have twin AV nodes, predisposing them to re-entrant tachyarrhythmias.[13] Post-operative rhythm management often requires nuanced decision-making, making electrophysiology expertise essential from the outset. Increasingly, intraoperative electrophysiologic mapping has been used to define conduction tissue in heterotaxy, reducing the risk of complete heart block during surgical repair.[14–16]

4. Cardiothoracic Surgery – Surgical management in heterotaxy requires specialized experience. Surgeons must be experienced operating in abnormal cardiac positions (e.g., dextrocardia), managing anomalous systemic and pulmonary venous return, addressing complex intracardiac anatomy, and preserving the conduction system. Familiarity with the broad range of surgical strategies—including single-ventricle palliation and biventricular repair—is key to individualized care planning.

Common cardiac manifestations of heterotaxy

Cardiac anatomy in heterotaxy is extraordinarily variable. While summary tables can provide useful orientation, they should be viewed only as general guides. The table below outlines cardiac features most commonly associated with specific heterotaxy phenotypes, with the important caveat that exceptions are frequent.[17–21] For the purposes of this document, polysplenia is considered equivalent to left atrial isomerism, and asplenia to right atrial

isomerism. More recently, a third category—*situs inversus phenotype*—has been increasingly recognized within the heterotaxy/ciliopathy spectrum.[22] These patients typically exhibit predominantly abdominal, pulmonary, and atrial situs inversus in association with complex congenital heart disease. Historically, they may have been labeled as having *situs inversus totalis* and excluded from the heterotaxy spectrum. This terminology is misleading, however, as a proportion of these patients also demonstrate ciliary dyskinesia, intestinal malrotation, and genetic variants that overlap substantially with those observed in both asplenia and polysplenia phenotypes.

Standard diagnostic evaluation and modalities

Heterotaxy requires a flexible and dynamic approach to cardiac assessment. The clinical team's goal is to establish and maintain sufficient understanding of anatomy and physiology to guide appropriate management, anticipate complications, and inform longitudinal care. Given the complexity and potentially evolving nature inherent to heterotaxy, no single imaging or electrophysiologic modality suffices; rather, an optimal approach utilizes serial clinical assessment and utilization of complementary tools.

Echocardiography is the first-line modality that provides the foundation to understand pre- and postnatal anatomy and physiology. All anatomic aspects should be defined to the greatest extent possible. Information from fetal echocardiography, including heart rhythm assessment, is essential for prenatal counseling and delivery planning. Families in which a parent has heterotaxy or other situs abnormality, or with a prior pregnancy affected by heterotaxy, should undergo fetal echocardiography in all subsequent pregnancies. Postnatal transthoracic echocardiography typically provides sufficient detail for early management and is the primary tool for ongoing surveillance. In select cases, transesophageal or 3D echocardiography may be helpful. Transesophageal echocardiography is frequently used in the operative setting. Intraoperative epicardial echocardiography should be strongly considered when transesophageal windows—which are often limited in heterotaxy—are inadequate.

An electrocardiogram (ECG) should be obtained yearly at a minimum and more frequently as indicated. Because conduction abnormalities are often intermittent or progressive, a ten-second ECG may miss important findings. Extended rhythm assessment (e.g., Holter or ambulatory cardiac monitoring) should be considered at baseline, even in asymptomatic patients and thereafter as needed. Patients with significant arrhythmia may benefit from consultation with an electrophysiologist and potential invasive rhythm assessment (electrophysiology catheterization procedure).

Cross-sectional cardiac imaging is an essential diagnostic tool in heterotaxy. Cardiac magnetic resonance imaging (MRI) provides quantitative assessment of ventricular volumes, systolic function, flow dynamics, myocardial tissue characterization, and valve regurgitation. MRI also

plays a critical role in procedural planning, including decisions between single-ventricle palliation and biventricular repair pathways. In patients undergoing Fontan palliation, computational flow modeling can be used to optimize pulmonary blood flow distribution. Fetal cardiac MRI is an emerging adjunct for characterizing cardiac anatomy and physiology in utero.

Cardiac computed tomography (CT) is another excellent modality, offering rapid, high-resolution imaging of cardiac and vascular anatomy. Cine CT is possible and is particularly valuable in patients with pacemakers, when assessment of ventricular volumes and function is required. Importantly, advances in CT technology have significantly reduced radiation exposure, an important long-term consideration for patients with heterotaxy.

Cardiac catheterization remains essential in select cases. Although most anatomic information is now obtained from non-invasive imaging, catheterization continues to provide valuable diagnostic hemodynamic data, including assessment of pulmonary vascular resistance, diastolic function, and vascular obstruction. Cineangiography can also complement other imaging modalities by delineating complex anatomy, defining coronary anatomy, and unmasking collateral circulations—including systemic-to-systemic, systemic-to-pulmonary, and portal-to-systemic shunts. In addition, catheterization plays a key therapeutic role, offering opportunities for transcatheter interventions that can reduce surgical burden and optimize outcomes.

In all cases, cardiac evaluation in heterotaxy should be iterative and collaborative. Anatomic, physiologic, and rhythm assessments must be tailored to the individual patient, with an understanding that anatomy, physiology, and risk can change over time.

Specific scenarios

Prenatal complete heart block

Complete heart block can occur in a small subset of fetuses with polysplenia (left atrial isomerism). While ventricular function is often preserved during fetal life, prenatal complete heart block carries a guarded prognosis due to the risk of sudden decompensation. However, complete heart block is often treatable postnatally if the fetus tolerates gestation and delivery.[5]

Close fetal monitoring is essential. This includes serial echocardiography to assess ventricular function, careful surveillance of fetal movement, and close collaboration with maternal–fetal medicine. Delivery prior to term should be considered in consultation with maternal–fetal medicine if there are signs of decompensation (e.g., diminished ventricular function or decreased fetal movement) or concerns regarding maternal well-being. Maternal terbutaline may be considered to increase the fetal heart rate, although its benefit is often marginal and maternal tolerance may limit its use.[23]

Postnatally, patients should be stabilized with medications that have positive chronotropic effects (e.g., dopamine, dobutamine, epinephrine, or beta-agonists such as isoproterenol).

Emergency temporary pacing may be indicated in the early neonatal period. Indications for placement of a permanent pacemaker depend on the clinical course.

Prenatal obstructed totally anomalous pulmonary venous connection

Obstructed TAPVC represents one of the highest-risk lesions associated with heterotaxy, most commonly occurring in asplenia (right atrial isomerism). The most severe form involves an infradiaphragmatic connection to the portal venous system, although obstruction at other sites (e.g., the superior vena cava) is also possible.

Prenatal identification is critical for appropriate planning. While fetal echocardiography is usually sufficient, prenatal MRI may be considered in select cases to evaluate for pulmonary hypoplasia or lung injury secondary to longstanding pulmonary venous hypertension.

Immediate postnatal deterioration is possible, often within minutes to hours of birth. Delivery planning should include readiness for urgent evaluation and intervention. Early postnatal imaging must assess the anatomy and confirm obstruction with a plan for emergent surgical or catheter-based relief of obstruction as indicated.

Pulmonary vein stenosis

Pulmonary vein stenosis is a related and potentially progressive condition that may occur postnatally, even in patients whose pulmonary veins were initially unobstructed.[24,25] The pathophysiology is not fully understood but likely involves a combination of abnormal pulmonary venous anatomy, distortion from adjacent cardiac structures, maldistribution of pulmonary blood flow, and altered flow dynamics in single-ventricle or shunted circulations.

Infants with asplenia are particularly at risk, and careful longitudinal monitoring of pulmonary vein anatomy and flow is essential. If stenosis is identified, treatment options may include medical therapy, catheter-based interventions, or surgical repair. Outcomes are variable and depend heavily on the location, etiology, extent of the stenosis, the number of veins involved, as well as the overall anatomy of the pulmonary venous system.[26–28]

Biventricular repair versus single ventricle palliation

A central question in the management of patients with heterotaxy with congenital heart disease is whether to pursue single-ventricle palliation or biventricular repair (or, in some cases, 1.5-ventricle repair).[29–31] The key consideration is whether the potential long-term benefits of a biventricular circulation outweigh the risks and complexity of achieving the repair, or whether a single-ventricle pathway offers a safer and more reliable course.[32]

When two adequately sized ventricles and atrioventricular valves are present, biventricular repair is an appealing option. Important challenges include abnormal cardiac position, complex venous anatomy, an elongated left ventricle–to–aorta pathway, and the need to establish right ventricle–to–pulmonary artery continuity.[31,33,34] Conduit placement introduces the burden of future surgical or transcatheter interventions, and such procedures—including pulmonary valve

replacement—may be complicated by abnormal venous anatomy, such as interrupted inferior vena cava.

Single-ventricle palliation may be more attractive in particularly complex two-ventricle hearts, or when ventricular and/or atrioventricular valve hypoplasia is present. It may be the only option when a single ventricle and/or a single atrioventricular valve is present. Fontan outcomes continue to improve, but in heterotaxy this pathway is rarely straightforward.[35,36] Ciliary dysfunction, pulmonary vein stenosis, and portosystemic venous connections can significantly compromise long-term outcomes and must be considered carefully. Even when technically successful, single-ventricle circulation carries additional risks such as maldistribution of pulmonary blood flow—particularly in polysplenia, interrupted IVC, or bilateral SVCs. Preferential streaming of hepatic venous return can predispose to pulmonary arteriovenous malformations and cyanosis. Strategies to address this include careful preoperative planning, computational flow modeling, and surgical innovations such as neo-innominate vein construction or hepato-azygos shunts.[37–39]

For select patients, a 1.5-ventricle circulation may be feasible. This is generally considered when right-sided atrioventricular valve and ventricular hypoplasia preclude routing the entire cardiac output through the hypoplastic chamber. In this approach, the hypoplastic ventricle handles IVC return to the lungs, while SVC return is directed via a cavopulmonary (Glenn) anastomosis to the lungs. A band or fenestrated membrane can protect the Glenn from pulsatile flow while maintaining hepatic factor delivery. In rare cases of left ventricular hypoplasia, the left ventricle may serve as the IVC ventricle while the right ventricle supports systemic output.[40]

Ultimately, optimal outcomes in heterotaxy—whether through biventricular repair or single-ventricle palliation—demand multidisciplinary expertise to guide decisions. Success hinges on collaboration, careful procedural planning, and individualized assessment of each patient's anatomy and physiology.[34]

Single ventricle palliation and underlying cilia dysfunction

A common misconception is that primary ciliary dyskinesia (PCD) is a contraindication to single ventricle palliation. This is not the case. As in other scenarios, the primary considerations remain anatomic feasibility and pulmonary vascular resistance. Nevertheless, patients with PCD benefit from close perioperative and postoperative collaboration with pulmonary specialists, particularly in managing airway clearance and optimizing respiratory function in the setting of compromised mucociliary transport.[41,42]

Portosystemic shunt (Abernethy malformation)

Abernethy malformation refers to a congenital portosystemic shunt (CPSS).[43,44] Though rare in the general population, CPSS are well described within the heterotaxy/ciliopathy spectrum and should be considered in any heterotaxy patient—particularly those with polysplenia/left atrial isomerism—who present with unexplained cyanosis or volume overload.

Normally, splanchnic venous return from the stomach, intestines, and spleen flows via the portal vein into the liver for nutrient processing and detoxification. In Abernethy malformation, this blood bypasses the liver (hepatofugal flow) and drains into the systemic circulation. Two subtypes are recognized: Type I, with complete absence of the portal vein, and Type II, with a portal vein of variable caliber with portal shunting to the systemic circulation of varying degree.

Clinical consequences are variable but important. Complications include (1) hyperammonemia with hepatic encephalopathy, (2) pulmonary arteriovenous malformations, and (3) pulmonary hypertension. As in patients with Glenn or Kawashima physiology who experience maldistribution of hepatic venous return, those with Abernethy malformation may develop AVMs that cause cyanosis and increase systemic ventricular volume load—even in patients with otherwise normal hearts or excellent surgical repairs.

Management requires multidisciplinary collaboration among hepatology, imaging, and interventional teams. Cross-sectional imaging (MRI/CT) defines anatomy, while catheterization or interventional radiology can both diagnose and treat shunts. For large shunts, surgical banding or ligation may be required; newer transcatheter strategies permit staged restriction and occlusion. In Type I (complete portal vein absence), liver transplantation may be the only definitive treatment but is generally reserved for patients with symptoms attributable to the shunt.[45]

In patients with CPSS undergoing superior cavopulmonary anastomosis (Glenn or Kawashima), altered resistance may unmask the shunt and redirect flow toward the liver (hepatopedal). Any post-Glenn/Kawashima catheterization should specifically assess for CPSS to guide management.

Table: Typical Cardiac Manifestations of Heterotaxy Subtypes

Cardiovascular Feature	Polysplenia / Left Atrial Isomerism	Asplenia / Right Atrial Isomerism	Situs Inversus Phenotype
Systemic Veins	Absence of the suprarenal IVC (“interrupted” IVC) with azygos continuation to the SVC	Bilateral SVCs Absent coronary sinus	Left-sided SVC and IVC
Pulmonary veins	Normal Ipsilateral	Totally anomalous (with or without obstruction)	Right-sided

Atrioventricular valves	Separate	Common valve	Separate
Ventricles	Biventricular	Single Unbalanced (usually AV canal)	Biventricular
Great arteries	Normally related	Malposed	Malposed
Outflow obstruction	Systemic	Pulmonary	Pulmonary
Rhythm	Sinus node dysfunction Complete heart block	Twin SA nodes Twin AV nodes	Inverted
Other	Congenital portosystemic shunts (Abernethy malformation) Ventricular noncompactions (left and right)	MAPCAs	NA

Listed findings are most often seen in the specified phenotype but overlap with other subtypes is common. AV, atrioventricular; IVC, inferior vena cava; MAPCAs, multiple/major aortopulmonary collateral arteries; SA, sinoatrial; SVC, superior vena cava.

Summary

Recommended Cardiology Staffing and Resources for Patients with Heterotaxy

Optimal care for patients with heterotaxy requires coordinated input from a multidisciplinary team with expertise in congenital cardiovascular disease.

Clinical personnel

- Fetal cardiologist with expertise in prenatal evaluation and perinatal planning
- Pediatric cardiologist
- Pediatric electrophysiologist
- Pediatric cardiothoracic surgeon
- Pediatric imaging cardiologist (or radiologist) experienced in complex congenital heart disease
- Cardiac intensive care physician

Cardiovascular imaging capabilities

- Comprehensive echocardiography (including 3D)
- Cross-sectional imaging with CTA and cardiac MRI
- 3D modeling (printing or virtual reality) to support advanced surgical planning

Electrophysiology assessment and management

- Standard and extended ECG monitoring
- Ambulatory rhythm monitoring (e.g., Holter)
- Exercise physiology lab with stress and metabolic testing
- Invasive electrophysiology studies and ablation capabilities
- Intraoperative and advanced EP mapping

Recommended routine evaluation:

- **At diagnosis**
  - Transthoracic echocardiogram
  - Electrocardiogram
  - Consideration of extended rhythm monitoring (e.g., Holter), particularly before cardiac surgery

- **Longitudinal follow-up**
  - Standard surveillance tailored to underlying anatomy and physiology
  - Consideration of invasive electrophysiology study or intraoperative AV node mapping during complex intracardiac repair

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