
CHAPTER 11 – CARDIOVASCULAR SYSTEM

First Nations and Inuit Health Branch (FNIHB) Pediatric Clinical Practice Guidelines for Nurses in Primary Care.

The section on Rheumatic Fever (Carditis) has been updated as of December 2017.

The remaining content of this chapter was reviewed in September 2011.

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INTRODUCTION

Cardiovascular disease is uncommon in childhood. The major problems seen include congenital heart disease (usually abnormalities of the great vessels, hypoplastic heart, pulmonary or aortic atresia and tetralogy of Fallot), cardiac failure, rheumatic fever, carditis and myocarditis.

Functional or innocent heart murmurs are common.

Congestive heart failure at birth is rare and usually suggests severe valvular deformities.

Symptoms of ventricular septal defect, including heart failure, usually occur at approximately 6 weeks of age.

For more information on the history and physical examination of the cardiovascular system in older children and adolescents, *see the chapter “Cardiovascular System” in the adult clinical practice guidelines.*

ASSESSMENT OF THE CARDIOVASCULAR SYSTEM

Symptoms of cardiovascular disease vary with the age of the child.

Ask about:

- Rapid or noisy breathing
- Cough
- Cyanosis
- Sleeping patterns
- Exercise tolerance: indicated in a young child by ability to feed and in an older child by ability to keep up with peers during play

IN INFANTS

CYANOSIS

- An abnormality of oxygen transport related to heart, lungs or blood or inadequate oxygenation of blood due to mixing of venous and arterial blood. Transport problems include impairment of the oxygen-carrying capacity of hemoglobin, as for example, in carbon monoxide poisoning, and hypoxemia secondary to ventilation/perfusion mismatches as for example in pneumonia
- Causes bluish discoloration of mucous membranes, nail beds and skin, is a significant clinical finding and is related to inadequate oxygenation of arterial blood
- May be transient (related to increased oxygen demand by tissues, for example, during feeding in infants or during play in toddlers) or permanent from birth

EXERCISE INTOLERANCE

- Eats slowly or poorly
- Tires easily during feeding and with poor weight gain
- Cyanosis appears with feeding (exertional)
- Often described by parents or caregiver as a “good baby”: always quiet, sleeps a lot, parents may find baby less energetic compared to siblings at same age

DIFFICULTY BREATHING

- Tachypnea
- Chest retractions
- Nasal flaring
- Anxious appearance
- Grunting

EXCESSIVE PERSPIRATION

- Infant’s head described as “always wet”
- Infant perspires freely and easily, especially with excretion and feeding

SLOW GROWTH

- Child usually exhibits slow weight gain, relative to height gain; difficulty in feeding may contribute to this problem
- Metabolic demands increased

RESPIRATORY INFECTIONS

- More common with congestive heart failure
- More severe with increased pulmonary flow

IN CHILDREN

- Slow growth
- Respiratory infections
- Chest pain
- Palpitations
- Dizzy spells or blackouts
- Exercise intolerance
- Squatting with cyanotic episodes (“tetralogy spells”)

MEDICAL HISTORY (SPECIFIC TO CARDIOVASCULAR SYSTEM)

- Prematurity (associated with a higher prevalence of congenital cardiac malformation)
- History of illnesses related to heart disease (for example, strep throat)
- “Flu-like” illness
- Joint pains or swelling
- Down syndrome (associated with a higher prevalence of congenital heart disease)

PHYSICAL FINDINGS

An examination of the cardiovascular system involves more than just examining the heart. The examination generally covers two systems: the central cardiovascular system (head, neck and precordium [anterior chest]) and the peripheral vascular system (extremities). Examination of the cardiovascular system must also include a full assessment of the lungs and neuromental status (for signs of confusion, irritability or stupor).

VITAL SIGNS

- Heart rate
- Respiratory rate
- Blood pressure (in both an upper and a lower limb, if possible)
- Temperature (may be elevated with myocarditis or acute rheumatic fever)
- Cardiovascular problems may present as failure to thrive (weight and height below specified percentiles for age) or as a sharp decline in the growth curve across a major percentile line, therefore always document height and weight for all well baby and child examinations

INSPECTION

- Respiratory distress
- Cyanosis: central and peripheral
- Hands and feet: cyanosis, clubbing
- Precordium: visible pulsations
- Edema (hands, feet, sacrum)

PALPATION

- Apical beat is located at fourth intercostal space, lateral to the mid-clavicular line in infants, and at fifth intercostal space, lateral to the mid-clavicular line in older children
- Brief, localized apical tap is normal
- Apical beat may be laterally displaced, which indicates cardiomegaly
- Thrills or heaves may be palpable through chest wall; check supraclavicular area for thrills (in children with a thin chest wall, normal heart movements can be easily palpated and should not be confused with true thrills and heaves)
- Hepatomegaly
- Check for presence, rate, rhythm, amplitude and equivalence of peripheral pulses, especially femoral pulses (which are bounding in patent ductus arteriosus, absent in coarctation of aorta)
- Check for synchrony of radial and femoral pulses
- Capillary refill (normal < 3 seconds)
- Edema: pitting (rated 0 to 4) and level (how far up the feet and legs the edema extends); sacral edema
- Skin: temperature, turgor

AUSCULTATION

- S₁ and S₂ heart sounds
- Physiologic splitting of S₂ heart sound
- Added heart sounds (S₃ and S₄): determine their location and relation to respiration
- Murmurs: determine location (where murmurs are best heard), radiation, their timing in cardiac cycle, intensity, grade (*see Table 1, “Characteristics of Heart Murmurs of Various Grades”*) and quality
- Bruits: may occur in carotid arteries, abdominal aorta, renal arteries, iliac arteries, femoral arteries
- Crackles in lungs: may indicate heart failure (in infants and children, this usually occurs as a late sign)

Table 1 – Characteristics of Heart Murmurs of Various Grades

Grade	Characteristics
I	Very quiet, barely audible
II	Quiet but audible
III	Easily heard
IV	Thrill can be felt, murmur is easily heard
V	Thrill can be felt and loud murmur can be heard with stethoscope placed lightly on chest
VI	Thrill can be felt and very loud murmur can be heard with stethoscope held off the chest wall

COMMON PROBLEMS OF THE CARDIOVASCULAR SYSTEM

HEART MURMURS

Most murmurs are innocent flow murmurs, which are present in up to 50% of children; see “*Innocent Heart Murmur*.”

A heart murmur may signify congenital anatomic, infectious or inflammatory damage to valves and outlets of the four chambers of the heart.

PHYSICAL FINDINGS: AUSCULTATION

Auscultation helps to distinguish significant murmurs from innocent murmurs.

Murmurs must be recognized in relation to other physiologic and pathologic sounds of the cardiac cycle.

- The S_1 sound is caused by the closure of the mitral and tricuspid valves, which usually occurs simultaneously. The S_1 sound is best heard at the cardiac apex
- The S_2 sound occurs with the closure of the aortic and pulmonary valves. Because the closure of these two valves is somewhat asynchronous, what is known as the S_2 sound actually consists of two sounds. The separation of the two component sounds is often difficult to detect in young children, although it is more pronounced during inspiration. Wide separation of the S_2 sound is often a significant pathologic finding. The S_2 sound is best heard in the second and third left intercostal spaces

- An S_3 sound may occur after the second heart sound. This may be found in healthy children. It is a sign of heart failure in a symptomatic child. The S_3 sound is best heard when listening at the apex of the heart (in the fourth and fifth intercostal spaces); a left side-lying position may accentuate the sound. Use the bell part of the stethoscope
- Ejection “clicks” may be present in certain conditions; they are always abnormal

If a murmur is present, several characteristics should be determined.

Timing within Cardiac Cycle

- Systolic ejection murmurs occur after the first sound. They are caused by turbulence in the blood as it leaves the heart
- Pansystolic murmurs begin with the first heart sound and end with the second. They most often occur in association with ventricular septal defects
- Diastolic murmurs begin with the second heart sound. They are always abnormal

Shape or Contour

- Qualifies the intensity over time: murmurs can be crescendo, decrescendo, or crescendo-decrescendo

Location on the Thorax

There are four general auscultatory areas:

- *Aortic*: left ventricular outflow murmur (usually ejection)
- *Pulmonary*: right ventricular outflow murmur, patent ductus arteriosus
- *Tricuspid*: tricuspid murmurs increase on inspiration; ventricular septal defects are heard best in this area
- *Mitral*: murmur at the cardiac apex

Radiation

Radiation of the murmur to the back, sides and neck should be carefully auscultated. Radiation of the murmur may give important diagnostic clues (for example, aortic stenosis radiates to the neck).

Intensity of Murmur

- Intensity expressed as a fraction of VI (for example, I/VI, II/VI), where a very loud murmur = V/VI or VI/VI, a loud murmur = III/VI or IV/VI, and a soft murmur = I/VI or II/VI (*see Table 1, “Characteristics of Heart Murmurs of Various Grades”*)
- Intensity (loudness) does not necessarily correlate with the severity of the condition. Soft murmurs may be dangerous, whereas loud murmurs are not necessarily so. A murmur associated with a thrill has an intensity of at least IV/VI
- Intensity may also increase with increased blood flow, as with exercise

Pitch

- Can be low, medium or high and is determined by whether it can be auscultated best with the bell or the diaphragm of a stethoscope

Quality

- Blowing
- Harsh
- Musical
- Rumbling
- Clanging

INNOCENT HEART MURMUR

Heart murmur that occurs in the absence of anatomic or physiologic abnormalities of the heart and therefore has no clinical significance. Such murmurs occur in 50–80% of children.

TYPES OF INNOCENT HEART MURMURS

Still’s murmur – vibratory, systolic ejection murmur (SEM), lower left sternal border (LLSB) or apex; ages 3 to 6 years.

Venous hum – infraclavicular hum, continuous, heard on right side more than left side; ages 3 to 6 years.

Peripheral pulmonic stenosis – pulmonic area, systolic, low pitched, radiates to axilla and back, seen in neonates; disappears usually by 3 to 6 months of age.

Pulmonary ejection – soft, blowing, upper left sternal border, systolic ejection murmur (SEM).

PATHOPHYSIOLOGY

Most innocent heart murmurs are produced by the forward flow of blood, which creates turbulence in the chambers of the heart or the great vessels. These murmurs are often more pronounced in high-output states, such as during a fever. Because the intensity of the murmur parallels the ejection velocity of blood from the ventricles, innocent murmurs usually occur during early to mid-systole, are short in duration, have a crescendo-decrescendo contour (especially an ejection murmur), are less than 3/6 in intensity and are never diastolic.

CLINICAL FEATURES

Innocent heart murmurs are asymptomatic and are usually found on routine physical examination.

DIAGNOSTIC TESTS

- Electrocardiogram (ECG)
- Echocardiography (only as ordered by a physician)

MANAGEMENT

Reassure the parents or caregiver that no immediate treatment is necessary.

Referral

Refer the asymptomatic child electively to a physician for assessment when a murmur is found.

EMERGENCY PROBLEMS OF THE CARDIOVASCULAR SYSTEM

CARDIAC FAILURE

The inability of the heart to pump blood commensurate with the body's needs. The symptoms and signs correlate with the degree of failure.

CAUSES

- Congenital abnormality of cardiac structures
- Inflammatory (for example, rheumatic fever)
- Infectious (for example, viral cardiomyopathy, subacute bacterial endocarditis)
- Severe anemia (that is, hemoglobin < 40 g/L)
- Other high-output states (for example, thyrotoxicosis, arteriovenous malformation)
- Extracardiac disease (for example, chronic pulmonary disease, pulmonary hypertension)

HISTORY

The history varies according to the child's age.

- Difficulty with feeding
- Shortness of breath
- Excessive sweating
- Poor weight gain
- Anxious appearance

PHYSICAL FINDINGS

- Tachycardia
- Tachypnea
- Blood pressure (assessed in both arms) usually normal but may be reduced (if so, this is cause for concern, as it may indicate cardiogenic shock)
- Temperature: if higher than normal, consider inflammatory or infectious cause
- Irritable
- Anxious
- Fontanel full
- Nostrils flared
- Cyanosis
- Peripheral swelling (in older children)
- Increased jugular venous distention
- Displaced, diffuse apical impulse (cardiomegaly)
- Heave or thrill
- Gallop rhythm (with extra S₃ heart sound)
- Increased murmurs

- Crackles in lung fields
- Hepatomegaly
- Diminished peripheral pulses

DIFFERENTIAL DIAGNOSIS

- Respiratory disease (for example, bronchiolitis or pneumonia)
- Metabolic abnormality (for example, hypoglycemia; poisoning, as with salicylates) also consider hyperglycemia with ketosis, head injuries
- Sepsis including meningitis

COMPLICATIONS

- Decreased cardiac output (shock)
- Death

DIAGNOSTIC TESTS

- Pulse oximetry

MANAGEMENT

Goals of Treatment

- Improve hemodynamic function
- Prevent complications

Appropriate Consultation

Consult with a physician regarding emergency treatment.

Nonpharmacologic Interventions

- Nurse the child in head-elevated position (do not allow neck to become kinked)
- Restrict oral fluids to no more than the quantity required to maintain hydration (*see chapter "Fluid Management"*)

Adjuvant Therapy

- Start IV therapy with normal saline to keep vein open (unless this would stress the child too much)
- Give oxygen 6–10 L/min or more by non-rebreather mask.¹ Titrate to keep oxygen saturations > 97%²

Pharmacologic Interventions

Drugs used to treat heart failure in children are to be ordered by a physician.

- Diuretics to decrease volume:
furosemide (Lasix), 1 mg/kg IV stat (may be given PO if IV access not available)
- ACE inhibitors may be prescribed by a physician for afterload reduction
- Digoxin may be used in some cases to increase contractility

Monitoring and Follow-Up

Acute Phase

Monitor ABCs (airway, breathing and circulation), vital signs, pulse oximetry (if available), heart and lung sounds, intake and output until child is transferred to hospital.

Over the Long Term

Children with cardiac illness should be monitored regularly within the community to ensure normal growth and development and to watch for complications. Frequency of follow-up depends on the severity of the condition.

Referral

Medevac immediately.

CYANOSIS IN THE NEWBORN (BIRTH TO 6 WEEKS)

Bluish discolouration of the skin and mucous membranes secondary to hypoxia.

CAUSES

Congenital Heart Disease

Cardiac cyanosis is due to left-to-right shunting, so that systemic venous blood bypasses the pulmonary circulation and enters the arterial systemic circulation.

Findings of increased risk for congenital heart disease:

- Genetic syndromes (for example, Down syndrome)
- Certain extracardiac anomalies (for example, omphalocele)
- Maternal diabetes that is poorly controlled in the first trimester
- Exposure to a cardiac teratogen (for example, lithium, isotretinoin [Accutane], alcohol)
- Family history of significant congenital heart disease

Non-cardiac Causes

- Pulmonary infection (for example, group B streptococcal infection)
- Intrauterine infection or systemic viral infection (for example, Rubella or Coxsackie B5)
- Aspiration of meconium
- Pulmonary hypoplasia
- Respiratory distress syndrome (for example, in premature infants)
- Hypoventilation (for example, neurologic depression)
- Persistent fetal circulation: seen in post-term infants with perinatal distress or pulmonary disease

Clinical Features of Infants with Cyanotic Heart Disease

The clinical features usually present in the first week of life but may present later:

- Difficulty feeding; infant appears to tire easily
- Lethargy
- Cyanosis when feeding or active (for example, while crying)
- Perspiration on face or forehead, especially when feeding or active
- Rapid, noisy breathing

PHYSICAL FINDINGS

- Lethargy
- Cyanosis, initially of the oral mucosa; in severe cases, the cyanosis becomes generalized
- Reduced oxygen saturation
- Tachypnea
- Poor perfusion (for example, pallor or gray, ashen appearance; extremities cool; capillary refill diminished; peripheral pulses diminished)
- In coarctation of aorta, pulse quality and blood pressure may differ in different extremities
- Heart sounds may be loud
- Precordium may appear hyperdynamic (heaves or thrills may be present)
- Heart murmur may be present
- Hepatomegaly (if infant is in heart failure)

DIFFERENTIAL DIAGNOSIS

- Pulmonary causes as listed above
- Sepsis

COMPLICATIONS

- Cardiac failure (*see* “Cardiac Failure”)
- Failure to thrive (*see* “Failure to Thrive” in the pediatric chapter “Hematology, Endocrinology, Metabolism and Immunology”)
- Death

DIAGNOSTIC TESTS

- Pulse oximetry

MANAGEMENT***Appropriate Consultation***

Consult a physician immediately and prepare to medevac.

Adjuvant Therapy

- Give oxygen 6–10 L/min (or more, if necessary) by non-rebreather mask. Titrate to keep oxygen saturations $> 97\%^2$
- Consider intravenous (IV) therapy with normal saline if infant is feeding poorly or is in significant clinical distress

Nonpharmacologic Interventions

- Nurse in an upright position
- Feed small amounts frequently

Monitoring and Follow-Up

- Monitor level of consciousness, vital signs, heart and lung sounds, perfusion, pulse oximetry
- Hydration status (intake and output) (*see* “Clinical Features of Dehydration” in the chapter “Fluid Management”)
- Watch for signs of cardiac failure (*see* “Cardiac Failure”)

Referral

- Medevac as soon as possible

RHEUMATIC FEVER (CARDITIS)

OVERVIEW

Please refer to provincial/territorial guidelines for Acute Rheumatic Fever where available

Acute rheumatic fever is a serious illness that may require medical evacuation. Consult with physician/nurse practitioner immediately when there is suspicion of acute rheumatic fever.

Acute rheumatic fever (ARF) is a diffuse inflammatory disease of the connective tissues involving the heart, joints, skin, central nervous system and subcutaneous tissue. ARF is the immunologic sequela to untreated Group A Streptococcal (GAS) infection. While acute rheumatic fever leaves no lasting damage to the brain, joints or skin, damage to heart valves may be permanent which lead to a chronic heart condition called rheumatic heart disease (RHD).⁽¹⁾ In the absence of secondary antibiotic prophylaxis, recurrence of rheumatic fever is likely and each subsequent episode may cause further cardiac damage to the valves.⁽¹⁾

CAUSES

Untreated GAS pharyngitis infection⁽²⁾

ASSESSMENT

Medication review: Review current medications, including over-the-counter, complementary and alternative medicines, as well as any chemical or substance intake that may impact management.

Allergy history: Screen for medication, latex, environmental or other allergies and determine approximately when and what type of reaction occurred.

RISK FACTORS

- Personal and family history of acute rheumatic fever; most common in those aged 5 to 15 years, but can occur in children as young as 3 years of age⁽²⁾

- Overcrowding⁽³⁾
- Socioeconomic disadvantage⁽⁴⁾
- Lack of access to medical/health care⁽⁴⁾

HISTORY OF PRESENT ILLNESS

Review risk factors and collect history of present illness.

- Preceding GAS pharyngitis⁽²⁾
- Joint pain, redness and swelling (migratory arthritis, typically involving the large joints)
- Signs and symptoms of heart failure include:⁽⁵⁾
 - Exertional dyspnea and/or dyspnea at rest
 - Orthopnea
 - Chest pain/pressure and palpitations
 - Cough
 - Fatigue and weakness
 - Nocturia and oliguria
 - Anorexia, weight loss, nausea
- Involuntary, uncoordinated muscular movements (Sydenham's chorea) (typically presents 2 to 6 months after initial infection)⁽⁶⁾
- Emotional lability⁽⁶⁾
- Non-pruritic, painless rash⁽¹⁾
- Fever⁽⁷⁾

PHYSICAL FINDINGS

Perform a physical examination using the IPPA approach.

Major Manifestations

Carditis

- Carditis may be clinical or subclinical.⁽¹⁾
- New or changing heart murmurs. For more information on heart murmurs, see *Heart Murmurs* in *Appendix, Section A* of this guide.
- Rubs may be audible with inspiration and expiration if disease is associated with pericarditis.⁽¹⁾
- Muffled heart sounds (consistent with pericardial effusion).⁽⁸⁾
- Tachycardia at rest;⁽¹⁾ may be out of proportion to fever⁽⁸⁾

- Tachypnea, orthopnea, jugular venous distention, crackles, hepatomegaly, a gallop rhythm, edema and swelling of the peripheral extremities if the client is in heart failure.⁽⁹⁾
- Cardiomegaly, pulmonary congestion and other findings consistent with heart failure may be observed on chest x-ray.⁽¹⁰⁾

Arthritis

- Large joints are usually affected, especially the knees and ankles.⁽¹⁾
- Classified as swelling of the joint in the presence of 2 or more of the following:⁽¹⁾
 - Limitation of movement
 - Hot joint
 - Pain in the joint and/or tenderness

Sydenham's Chorea

- Jerky, uncoordinated movements of the extremities that disappear during sleep,⁽¹⁾ dysphonia and possible emotional lability⁽⁶⁾
- Female predominance⁽⁷⁾
- Can be a standalone criterion for the diagnosis of acute rheumatic fever without additional manifestations⁽¹⁾

Subcutaneous Nodules

- Usually located over a bony prominence or near tendons⁽¹¹⁾
- 0.5 to 2 cm in diameter, round, firm, occasionally painful protuberances found on extensor surfaces at specific joints including

the knees, elbows, and wrists; also seen in the occiput and along the spinous processes of the thoracic and lumbar vertebrae⁽⁷⁾

Erythema Marginatum

- Rare and difficult to detect (especially on dark-skinned people)⁽¹⁾
- An evanescent, pink rash with a pale center and rounded or serpiginous margins⁽⁷⁾
- The rash is usually present on the trunk and proximal extremities; it is almost never on the face⁽⁷⁾
- Blanches with pressure⁽⁷⁾
- Not affected by anti-inflammatory medication⁽¹⁾
- Rarely seen as the sole major criterion for acute rheumatic fever and should be accompanied by additional major criteria in order to make the diagnosis⁽¹⁾

Minor Manifestations

- Fever⁽⁷⁾
- Arthralgia⁽⁷⁾
- Raised C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)⁽⁷⁾
- Prolonged PR interval on electrocardiogram (ECG)⁽⁷⁾

DIFFERENTIAL DIAGNOSIS

Consult physician/nurse practitioner when practice is outside legislated scope and without authorized delegation.

TABLE 2

Differential Diagnoses of Arthritis, Carditis and Chorea

ARTHRITIS	CARDITIS	CHOREA
<ul style="list-style-type: none"> - Septic arthritis - Connective tissue and other autoimmune diseases such as juvenile idiopathic arthritis - Lyme disease - Infective endocarditis 	<ul style="list-style-type: none"> - Physiological mitral regurgitation - Mitral valve prolapse - Congenital valve disease - Infective endocarditis - Myocarditis, viral or idiopathic - Kawasaki disease 	<ul style="list-style-type: none"> - Drug intoxication - Tic disorder - Intracranial tumor - Lyme disease - Autoimmune: Systemic lupus erythematosus, systemic vasculitis

The diagnosis is based on a collection of signs known as Jones' criteria; see Table 3, *Revised Jones' Criteria*.

TABLE 3Revised Jones' Criteria^{*(7)}

MAJOR CRITERIA		MINOR CRITERIA	
Low-risk populations**	High-risk populations	Low-risk populations**	High-risk populations
<ul style="list-style-type: none"> - Carditis (clinical and/or subclinical) - Polyarthrititis - Chorea - Erythema marginatum - Subcutaneous nodules 	<ul style="list-style-type: none"> - Carditis (clinical and/or subclinical) - Arthritis (monoarthrititis or polyarthrititis, polyarthralgia) - Chorea - Erythema marginatum - Subcutaneous nodules 	<ul style="list-style-type: none"> - Polyarthralgia - Fever ($\geq 38.5^{\circ}\text{C}$) - ESR ≥ 60 mm in the first hour and/or CRP ≥ 30 mg/L - Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion) 	<ul style="list-style-type: none"> - Monoarthralgia - Fever ($\geq 38^{\circ}\text{C}$) - ESR ≥ 30 mm/h and/or CRP ≥ 30 mg/L - Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

*For all client populations with evidence of preceding group A *Streptococcal* pharyngitis infection:

- Diagnosis of initial acute rheumatic fever is:
 - 2 major manifestations or
 - 1 major plus 2 minor manifestations
- Diagnosis of recurrent acute rheumatic fever is:
 - 2 major or
 - 1 major and 2 minor or
 - 3 minor manifestations

**Low-risk populations are those with acute rheumatic fever ≤ 2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤ 1 per 1,000 population per year.

COMPLICATIONS

- Rheumatic heart disease due to permanent damage to the heart valves, which leads to valvular disease, cardiac myopathy and sequelae such as:⁽¹⁾
 - Heart failure
 - Atrial fibrillation
 - Systemic embolism
 - Stroke
 - Endocarditis
 - Need for cardiac surgery
- Recurrent attack, which worsens the damage to the heart⁽¹²⁾
- Death⁽²⁾

DIAGNOSTIC TESTS

Consult physician/nurse practitioner when practice is outside legislated scope and without authorized delegation.

Diagnostic test selection is based on client history, risk factors, physical examination findings and test availability. Testing should be carried out as per provincial/territorial policies and procedures. The tests below are for consideration. Currently, there is no single laboratory test to confirm the diagnosis of ARF.⁽¹⁾ ARF remains a clinical diagnosis and relies on health professionals being aware of its diagnostic features.⁽¹⁾

Laboratory

- Rapid Antigen Detection Test (RADT) (if available)
- Throat culture and sensitivity (C+S) for group A *Streptococcus*⁽¹⁰⁾
- WBC, ESR⁽¹³⁾
- Blood culture and sensitivity (C+S) if febrile⁽¹³⁾

Other Diagnostic Tests

- Chest x-ray⁽¹³⁾
- ECG to assess for prolonged PR interval⁽¹⁾

MANAGEMENT

Consult physician/nurse practitioner when practice is outside legislated scope and without authorized delegation.

Note: The diagnosis and treatment of rheumatic fever requires medical evacuation. Emergency treatment of heart failure may be necessary; see *FNIHB Pediatric and Adolescent Care Clinical Practice Guidelines – Chapter 11 – Cardiovascular System – Cardiac Failure*.

GOALS OF TREATMENT

- Provide symptomatic relief
- Prevent complications

NON-PHARMACOLOGIC INTERVENTIONS**Interventions**

- Bed rest while awaiting medical evacuation

PHARMACOLOGICAL INTERVENTIONS

In addition to consulting a physician/nurse practitioner, review the drug monograph, the FNIHB Nursing Station Formulary or provincial/territorial formulary before initiating treatment.

Note: With the exception of acetaminophen or medications to treat heart failure (if required), medications should not be started until the diagnosis has been clearly established. After consultation with receiving facility, antibiotics may be started after throat swab(s) have been collected.⁽¹⁾

Antipyretic/Analgesic**Acetaminophen⁽¹⁴⁾**

- Acetaminophen 10 to 15 mg/kg/dose PO q4-6h PRN
- [caution-hepatic, INR, renal]
- Maximum from all sources: acetaminophen 75 mg/kg/day or 4,000 mg/day, whichever is less

Antibiotic Therapy

- Antibiotics should be initiated to eradicate residual GAS infection in all cases while the diagnosis of ARF is being established.⁽¹⁾
- A full course of antibiotics should be given.⁽¹⁾
- Oral therapy such as penicillin, amoxicillin, cephalexin or clindamycin may be considered.

For specific dosing recommendations, see *FNIHB Pediatric and Adolescent Care Clinical Practice Guidelines – Chapter 9 – Ears, Nose, Throat and Mouth – Bacterial Pharyngotonsillitis – Antibiotic Therapy*.

MONITORING AND FOLLOW-UP

Consult physician/nurse practitioner when practice is outside legislated scope and without authorized delegation.

MONITORING

- Monitor vital signs as indicated by client's condition, including oxygen saturation.
- Monitor intake and output.
- Monitor for signs of cardiac failure. If client is in cardiac failure, see *FNIHB Pediatric and Adolescent Care Clinical Practice Guidelines – Chapter 11 – Cardiovascular System – Cardiac Failure*.
- If administering an agent with risk of anaphylaxis, monitor the client closely for 30 minutes.

FOLLOW-UP**Post-acute Phase**

- All clients should receive regular follow-up. The frequency and duration of review is dependent on individual clinical needs and should become more frequent in the event of symptom onset, symptomatic deterioration or a change in clinical findings.⁽¹⁾

- Discuss the importance of ongoing secondary prophylaxis during every health professional interaction with the client.⁽¹⁾
- Because of the risk of recurrence, continual antibiotic prophylaxis with benzathine penicillin G must be maintained.
- The risk of recurrence is greatest in the 5 years after the initial episode.
- Prophylaxis is initiated immediately after completion of a full therapeutic course of antibiotics, as initiated by a physician/nurse practitioner.
- The physician/nurse practitioner should also determine any discontinuation of prophylaxis.
- The duration of antibiotic prophylaxis can range from 5 years to 30 years, as it depends on a number of factors, including age, clinical pattern, environment and time elapsed since the last episode of ARF.⁽¹⁾
- Clients may need to be on other cardiac and anticoagulation therapies, depending on the severity of the heart damage due to ARF.

Referral

- Arrange for medical evacuation.

APPENDIX

SECTION A: SUPPLEMENTAL CLINICAL MANAGEMENT INFORMATION

Heart Murmurs

- Those most commonly heard during acute rheumatic fever are:⁽⁸⁾
 - Apical pansystolic murmur is a high-pitched, blowing-quality murmur of mitral regurgitation that radiates to the left axilla. The murmur is unaffected by respiration or position.
 - Apical diastolic murmur (known as Carey-Coombs murmur) is heard with active carditis and accompanies severe mitral insufficiency.
 - Basal diastolic murmur is an early diastolic murmur of aortic regurgitation and is a high-pitched, blowing, decrescendo heard best along the right upper and mid-left sternal border after deep expiration while the client is leaning forward.

Approaches to Disease Prevention

Effective control programs for acute rheumatic fever integrate features of primordial, primary and secondary prevention.

Primordial Prevention

- Primordial prevention refers to broad social, economic and environmental initiatives undertaken to prevent or limit the impact of GAS infection in a population.

Primary Prevention

- Primary prevention refers to medical intervention using antibiotics to reduce GAS transmission, acquisition, colonization and carriage, or treating GAS infection effectively to prevent the development of acute rheumatic fever.⁽¹³⁾

Secondary Prevention

- Secondary prevention refers to medical intervention using long-term prophylactic antibiotics to reduce repeated acquisition of GAS that might induce recurrent episodes of acute rheumatic fever in order to prevent the development of rheumatic heart disease, or for those clients who have established rheumatic heart disease in order to prevent disease progression.

BIBLIOGRAPHY

The following references and other sources have informed the updating of this Clinical Practice Guideline.

REFERENCES

1. Heart Foundation of New Zealand. New Zealand guidelines for rheumatic fever: Diagnosis, management and secondary prevention of acute rheumatic fever and rheumatic heart disease: 2014 update. [Internet] Auckland (NZ): The National Heart Foundation of New Zealand; 2014 [cited 2015 May 20]. Available from: <http://assets.heartfoundation.org.nz/shop/marketing/non-stock-resources/diagnosis-management-rheumatic-fever-guideline.pdf>

2. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, et al. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease. *Circulation*. [Internet] Hagerstown, MD : Lippincott Williams & Wilkins; 2009. 119(11), 1541–1551. doi:10.1161/CIRCULATIONAHA.109.191959. Available from: <http://www.circ.ahajournals.org/content/119/11/1541>
3. Gordon J, Kirlew M, Schreiber Y, Saginur R, Bocking N, Blakelock B, et al. Acute rheumatic fever in First Nations communities in northwestern Ontario. *Canadian Family Physician*. Don Mills, Ont.: College of Family Physicians of Canada; 2015. 61(10), 881–886. Available from: <http://www.cfp.ca/content/61/10/881>
4. Victoria State Government. Rheumatic heart disease. Department of Health and Human Services. [Internet] Melbourne, Victoria (AU): Department of Health and Human Services, State Government of Victoria (AU); 2014 [cited 2015 May 6]. Available from: <http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/rheumatic-heart-disease>.
5. Dumitru I, Baker MM. Heart Failure: Practice Essentials, Background, Pathophysiology. [Internet] New York, NY: Medscape; 2015 [cited 2015 December 14]. Available from: <http://emedicine.medscape.com> with authorized username and password.
6. Madden S, Kelly L. Update on acute rheumatic fever: It still exists in remote communities. *Canadian Family Physician*. [Internet] Don Mills, ON: College of Family Physicians of Canada; 2009. 55(5), 475–478. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682299/> with payment.
7. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Kaplan EL. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of doppler echocardiography: A scientific statement from the American Heart Association. *Circulation*. [Internet] Hagerstown, MD : Lippincott Williams & Wilkins; 2015 May 19. doi:10.1161/CIR.0000000000000205. Available from: <http://circ.ahajournals.org/content/early/2015/04/23/CIR.0000000000000205>
8. Chin TK, Chin EM. Pediatric Rheumatic Heart Disease: Background, Pathophysiology, Epidemiology. [Internet] New York, NY: Medscape; 2014 [cited 2015 December 14]. Available from <http://emedicine.medscape.com> with authorized username and password.
9. Colucci WS. Evaluation of the patient with suspected heart failure. [Internet] Waltham, MA (US): UptoDate; 2016. [cited 2017 January 12]. Available from: <http://www.uptodate.com> with authorized username and password.
10. Chin TK, Li D. Pediatric rheumatic fever: Background, pathophysiology, epidemiology. [Internet] New York, NY: Medscape; 2014 [cited 2015 December 7]. Available from: <http://reference.medscape.com> with authorized username and password.
11. Steer A, Gibofsky A. Acute rheumatic fever: Clinical manifestations and diagnosis. [Internet] Waltham, MA (US): UptoDate; 2015. Available from: <https://www.uptodate.com> with authorized username and password.
12. World Heart Federation. Rheumatic heart disease. [Internet] Geneva, Switzerland: World Heart Federation; 2012 [cited 2016 May 17]. Available from: <https://www.world-heart-federation.org/programmes/rheumatic-heart-disease/>

13. RHD Australia (ARF/RHD writing group). The Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease, 2nd ed. Quick reference guides. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. [Internet] Casuarina NT (AU): Menzies School of Health Research; c2014 [cited 2015 December 16]. Available from: http://www.rhdaustralia.org.au/sites/default/files/resources/quick_reference_guides_0.pdf

14. Acetaminophen. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 April 23]. Available from: <http://online.lexi.com> with authorized username and password.

OTHER SOURCES

Health Canada. First Nations and Inuit Health Branch (FNIHB) Nursing Station Formulary and Drug Classification System. 2016 April.

Canadian Pharmacists Association. Acetaminophen (Tylenol). [Internet] Ottawa, ON: e-Therapeutics; 2012 [cited 2015 December 13]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Canadian Pharmacists Association. Compendium of Therapeutic Choices: Canada's Trusted Reference for Primary Care Therapeutics (CTC 7). Ottawa: Canadian Pharmacists Association; c2014.

Acetaminophen. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 13]. Available from: <http://online.lexi.com> with authorized username and password.

Canadian Pharmacists Association. Penicillin V. [Internet] Ottawa, ON: e-Therapeutics; 2009 [cited 2015 December 6]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Penicillin V. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 6]. Available from: <http://online.lexi.com> with authorized username and password.

Canadian Pharmacists Association. Amoxicillin (Amoxicillin). [Internet] Ottawa, ON: e-Therapeutics; 2015 [cited 2015 December 6]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Amoxicillin. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 6]. Available from: <http://online.lexi.com> with authorized username and password.

Canadian Pharmacists Association. Cephalexin. [Internet] Ottawa, ON: e-Therapeutics; 2009 [cited 2015 December 6]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Cephalexin. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 6]. Available from: <http://online.lexi.com> with authorized username and password.

Canadian Pharmacists Association. Clindamycin (Dalacin C). [Internet] Ottawa, ON: e-Therapeutics; 2014 [cited 2015 December 6]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Clindamycin. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 6]. Available from: <http://online.lexi.com> with authorized username and password.

Canadian Pharmacists Association. Penicillin G. [Internet] Ottawa, ON: e-Therapeutics; 2009 [cited 2015 December 6]. Available from: <http://www.e-therapeutics.ca> with authorized username and password.

Penicillin G. [Internet] Hudson, OH: Lexi-Comp. Inc.; 2015 [cited 2015 December 6]. Available from: <http://online.lexi.com> with authorized username and password.

VIRAL MYOCARDITIS

Myocarditis is an inflammatory disorder of the myocardium with necrosis of the myocytes and associated inflammatory infiltrate.

PATHOPHYSIOLOGY

Myocarditis generally results in a decrease in myocardial function, with concomitant enlargement of the heart and an increase in the end-diastolic volume caused by increased preload. Progressive increase in left ventricular end-diastolic volume increases left atrial, pulmonary venous and arterial pressures, resulting in increasing hydrostatic forces. These increased forces lead to both pulmonary edema and congestive heart failure.

CAUSES

It is usually caused by a viral infection. Parvovirus B19 and human herpesvirus-6 are the most frequent pathogens in patients with acute myocarditis. Infecting organisms may include the following:

- Parvovirus B19
- Herpesvirus
- Coxsackievirus types A and B (especially type B)
- Adenovirus (most commonly types 2 and 5)
- Cytomegalovirus
- Echovirus
- Epstein-Barr virus
- Hepatitis C virus
- Human immunodeficiency virus
- Influenza and parainfluenza
- Measles
- Mumps, associated with endocardial fibroelastosis (EFE)
- Poliomyelitis virus
- Rubella
- Varicella

Risk Factors

Younger patients, especially newborns and infants and immunocompromised individuals may have increased susceptibility to myocarditis.

HISTORY

Clinical presentation varies widely. In mild forms, few or no symptoms are noted. In severe cases, patients may present with acute cardiac decompensation and progress to death.

In newborns and infants, symptoms may sometimes appear suddenly and may include:

- Irritability
- Failure to thrive
- Feeding difficulties
- Fever and other symptoms of infection
- Lethargy
- Low urine output (a sign of decreasing kidney function)
- Pale hands and feet (a sign of poor circulation)
- Rapid breathing
- Rapid heart rate

Symptoms in children over age 2 may also include:

- Belly area pain and nausea
- Cough
- Fatigue
- Swelling (edema) in the legs, feet and face
- Recent, nonspecific, flu-like illness
- Older children present with similar symptoms as above and may experience lack of energy and general malaise
- Chest pain: Although rare in young children, this may be the initial presentation for older children and adolescents and should be considered a serious symptom accordingly

PHYSICAL FINDINGS

Neonates/Infants

- Hypothermia or hyperthermia
- Tachypnea
- Tachycardia
- Cyanosis
- Cool extremities
- Decreased capillary refill
- Pale or mottled skin may be present
- Wheezing, and diaphoresis with feeding
- Irritability
- Somnolence
- Hypotonia
- Seizures
- Oliguria
- End-organ damage (for example, renal failure may develop because of direct viral infestation or because of low cardiac output)

Older Children

- Low grade fever
- Tachycardia, weak pulse
- Jugular venous distention and edema of the lower extremities may be present
- Heart sounds may be muffled, especially in the presence of pericarditis
- An S3 may be present
- Heart murmur caused by atrioventricular valve regurgitation may be heard
- Crackles may be heard in older children
- Hepatomegaly may be present in younger children
- Cool extremities
- Decreased capillary refill
- Pale or mottled skin may be present

Adolescents

Presentation in adolescents is similar to that of children between 6 and 12 years old. However, the following symptoms may be more prominent:

- Decreased exercise tolerance
- Lack of energy, malaise
- Chest pain
- Low-grade fever
- Arrhythmia
- Cough
- Low cardiac output

DIFFERENTIAL DIAGNOSIS

- Myocarditis, nonviral
- Pericarditis, viral
- Aortic stenosis, valvular
- Enteroviral infections
- Cardiomyopathy, dilated
- Glycogen-storage disease type I or type II
- Coarctation of the aorta
- Coronary artery anomalies

DIAGNOSTIC TESTS

Chest x-ray may show cardiomegaly and cardiac failure.

Electrocardiography (ECG)

In some patients with mild cardiac involvement, ECG changes may be the only abnormal findings suggestive of myocarditis.

- Low-voltage QRS (< 5 mm throughout the limb leads) is the classic pattern
- Pseudoinfarction patterns with pathologic Q waves and poor progression of R waves in the precordial leads may also be present
- T-wave flattening or inversion is a common finding associated with small or absent Q waves in V5 and V6
- Left ventricular hypertrophy with strain may be present
- Other nonspecific findings include a prolonged PR segment and prolonged QT interval
- Sinus tachycardia is the most common finding
- Premature ventricular contractions and atrial tachycardia have been reported
- Junctional tachycardia is common and may worsen congestive heart failure
- Occasional second-degree and third-degree atrioventricular block may be present
- Ventricular tachycardia is commonly associated and may be the initial presentation

COMPLICATIONS

- Arrhythmia
- Cardiac failure (*see “Cardiac Failure”*)
- Thromboembolism
- Decrease in ventricular function
- Dilated cardiomyopathy

MANAGEMENT

Goals of Treatment

- Stabilize cardiovascular function
- Prevent complications

Appropriate Consultation

Consult a physician urgently if you suspect this condition.

Adjuvant Therapy

- Give supplemental oxygen as necessary via non-rebreather mask. Titrate to keep oxygen saturations > 97%
- Start an intravenous line with normal saline. Run at a rate sufficient to maintain hydration depending on oral intake of child. Do not overhydrate. Keep line open until consultation with an emergency physician. Always weigh infant before starting any intravenous fluids as a measure of hydration

Nonpharmacologic Interventions

- Bed rest is necessary during the acute phase of the illness
- Nurse in an upright position

Pharmacologic Interventions

Consult a physician for medication orders. Medications may include the following, when indicated: *see “Cardiac Failure”*.

- Diuretics to decrease volume:
furosemide (Lasix), 1 mg/kg IV stat (may be given PO if IV access not available)
- ACE inhibitors may be prescribed by a physician for afterload reduction
- Digoxin may be used in some cases to increase contractility
- Antiarrhythmics
- Anticoagulants

Monitoring and Follow-Up

Acute Phase

Monitor ABCs (airway, breathing and circulation), vital signs, pulse oximetry, heart and lung sounds, neuromental status, intake and output and medication response and adverse effects closely until child is transferred to hospital.

Over the Long Term

Children with cardiac illness should be monitored regularly within the community to ensure normal growth and development and to watch for complications. Frequency of follow-up depends on the severity of the condition.

Referral

Medevac to a facility with intensive and cardiology care.

SOURCES

Internet addresses are valid as of February 2012.

BOOKS AND MONOGRAPHS

Bickley LS. *Bates' guide to physical examination and history taking*. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999.

Cheng A, et al. *The Hospital for Sick Children handbook of pediatrics*. 10th ed. Elsevier; 2003.

Colman R, Somogyi R (Editors-in-chief). *Toronto notes – MCCQE 2008 review notes*. 24th ed. Toronto, ON: University of Toronto, Faculty of Medicine; 2008.

Gray J (Editor-in-chief). *Therapeutic choices*. 5th ed. Ottawa, ON: Canadian Pharmacists Association; 2007.

Health Canada. *Canadian immunization guide*. 7th ed. Ottawa, ON: Health Canada; 2006.

Jensen B, Regier L (Editors). *The Rx files*. 7th ed. Saskatoon, SK; 2008.

Rudolph CD, et al. *Rudolph's pediatrics*. 21st ed. McGraw-Hill; 2003.

Uphold CR, Graham MV. *Clinical guidelines in child health*. 3rd ed. Gainesville, FL: Barmarrae Books; 2003.

Repchinsky C (Editor-in-chief). *CPS Compendium of pharmaceuticals and specialties*. Ottawa, ON: Canadian Pharmacists Association; 2007.

JOURNAL ARTICLES

Arnold JMO, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol* 2006;22(1):23-45.

Birdi N, Hosking M, Clulow MK, Duffy CM, et al. Acute rheumatic fever and poststreptococcal reactive arthritis: Diagnostic and treatment practices of pediatric subspecialists in Canada. *J Rheumatol* 2001;28:1681-88.

INTERNET GUIDELINES / DOCUMENTS / OTHER PUBLICATIONS

Cilliers A, Manyemba J, Saloojee HH. (2003). *Anti-inflammatory treatment for carditis in acute rheumatic fever*. Available at: <http://summaries.cochrane.org/CD003176/corticosteroids-andimmunotherapy-to-prevent-heart-damage-as-a-result-of-rheumatic-fever>

Chin TK, Chin EM, Siddiqui T, Sundell, A-K. (2008, October). *Rheumatic Heart Disease: Treatment & Medication*. Available at: <http://emedicine.medscape.com/article/891897-overview>

Hong W, Tang W. (2008, September). *Myocarditis*. Available at: <http://emedicine.medscape.com/article/156330-overview>

Poothirikovil V. (2008, November). *Cardiomyopathy, Dilated*. Available at: <http://emedicine.medscape.com/article/895187-overview>

Rodriguez-Cruz E, Ross RD. (2008, October). *Myocarditis, Viral*. Available at: <http://emedicine.medscape.com/article/890740-overview>

Satou GM, Herzberg G, Erickson LC. (2006, June; updated 2009, March). *Heart Failure, Congestive*. Available at: <http://emedicine.medscape.com/article/901307-overview>

END NOTES

- 1 Emergency Nurses Association (ENA) (2007) Trauma Nursing Core Competencies Provider Manual. 6th Edition. p. 70.
- 2 Debbie M. Popovich, Nancy Richiuse, Gale Danek. Pediatric health care providers' knowledge of pulse oximetry *Pediatric Nursing*, Jan-Feb, 2004; p. 2. Available at: http://findarticles.com/p/articles/mi_m0FSZ/is_1_30/ai_n17206797/pg_2/?tag=content;coll
- 3 UpToDate Online 18.1. 2010. *Treatment and prevention of rheumatic fever*. And UpToDate Online 18.1. 2010. Antibiotic therapy of GAS pharyngitis, which is based on Gerber, MA, Baltimore, RS, Eaton, CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation* 2009;119(11):1541-51. Available by subscription: www.uptodate.com
- 4 *Secondary prevention of rheumatic fever (prevention of recurrent attacks)*. UpToDate Online 18.1. Available by subscription: www.uptodate.com