Infective Endocarditis
Emergency Department & Inpatient

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Inclusion Criteria

Patients with suspected infective endocarditis (IE), with suspicion raised by (but not limited to) any of the following:

- Pathogenic blood culture positivity in setting of a new or previously known murmur, or prior hx of congenital heart disease
- Daily fever without a know source > 38 C for > 7 days in the presence of a new murmur
- Presence of septic embolization
- Fever in patients at high risk for IE

Signs & Symptoms

- Fever ***without*** source
- New murmur or change in existing murmur
- Evidence of Janeway lesions; Osler's nodes; Petechiae; Splinter hemorrhages under nails

Suspected Endocarditis based on History, Signs and Symptoms and/or Recent Positive Blood Culture

Definition and Diagnostic Criteria

Differential Diagnosis

Patient at risk for sepsis?

Yes →
- Sepsis evaluation and treatment as clinically indicated
- Consider ACT if patient is on inpatient unit

Hx of congenital heart disease?

No → **Admit to PICU**

If no source of infection identified, proceed with Endocarditis Order Set, TTE & Cardiology consult

Yes → **Admit to CTICU and obtain TEE**

No → Use "**Endocarditis ED Orders**" Cardiology consult, labs, and Transthoracic Echocardiogram (TTE)

Hx of congenital heart disease?

No → TTE Results

- **Right-sided Endocarditis** → Clinical judgment to admit to ID vs Cardiology—in consultation with Cardiology
- **Left-sided Endocarditis** → **Admit to CTICU and obtain TEE**
- **Negative** → Recent (within 48 hours) positive blood culture identified from prior facility, prior ED workup, or in-hospital (non-cardiology service)?
  - No → **Off Pathway** Consider other diagnoses
  - Yes → **Admit to ID** See Confirmed Infective Endocarditis algorithm

Yes → TTE Results

- **Right-sided Endocarditis or is negative**
  - **Admit to Cardiology**
  - See Confirmed Infective Endocarditis algorithm
  - Consider ICE if prosthesis involved
- **Left-sided Endocarditis** → **Admit to CTICU and obtain TEE**

Admission Criteria

Confirmed Infective Endocarditis

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[1]Criteria for ICU:

- Hemodynamic instability (stability for ≥24 hours reqired for transfer to floor)
- ICU level of care reqired for treatment, lesion type, risk for embolic phenomena or monitoring (Determined in discussion with Cardiology, ID & nursing)
- Dysfunction level none or mild
- Significant arrhythmias (absence of significant arrhythmia for ≥24 hours reqired for floor)
- Surgical intervention scheduled or reqired
- See **Admission Criteria**

Reqire ICU level care[1]? — Yes → **CTICU or PICU**

No

Admit/transfer to ID or Cardiology Service
(see "Suspected Endocarditis" algorithm for guidance)

- Cardiology or ID consult
- Initiate recommended **empiric antibiotics** or continue antibiotics per ID recommendation
- Repeat cardiac and embolic imaging as determined on a case by case basis
- Consult CT surgery whenever indicated[2]
- Left-sided lesions to be discussed in a multi-disciplinary forum (Cardiology Case Management Conference)
- consider intracardiac echocardiogram (ICE) for prosthetic pulmonary valve or right-sided conduit
- Transesophageal echocardiogram (TEE) needed for any native or prosthetic mitral valve lesions (consider for aortic valve as well)

[2]Surgical Indications:

- Congestive heart failure
- New or progressive valvar dysfunction that is usually seen as increased regurgitation
- Periannular extension of infection
- Sinus of Valsalva rupture
- Myocardial dysfunction
- Any prosthetic material in the presence of IE and/or positive blood cultures
- Embolic complications
- Persistent bacteremia despite appropriate antibiotic therapy
- Unstable prosthesis
- Location of vegetation: anterior leaflet of mitral valve higher risk than aortic valve for embolization, but all left-sided lesions should be carefully considered
- Persistent vegetations >10mm in adult-sized individuals, case-by-case consideration of size for smaller children

Surgery reqired? — Yes → **Off Pathway** Individualized management

No

Monitoring & Signs of Deterioration

- Patients should be on telemetry (PICU, CTICU, H4A) or CR monitoring (ID), with continuous pulse ox
- RN to report for tachycardia worsening for age, hypotension for age, inappropriate saturation for physiology (<92% for biventricular anatomy patients), new arrhythmia
- PEWS ≥ 5 Watcher Status: Huddle and mitigation/escalation plan
- PEWS ≥ 7 Call Act

Discharge when meeting criteria:

- Stable antibiotic levels, if indicated (e.g., therapeutic vancomycin/gentamicin levels)
- If PICC required, appropriate support available (family teaching, home nursing, medication delivery etc)
- Patient has means to monitor antibiotic levels at home, i.e. home health or designated lab/orders
- Use **Discharge Checklist** to verify discharge readiness

Duration and route of antibiotics per ID recommendation

Sepsis Risk Identification

***Sepsis Risk Criteria:**

- Clinical concern for sepsis
- Sepsis Alert in ED
- Sepsis Watcher in ED
- Sepsis inpatient screening met

Suspected Endocarditis Algorithm

Confirmed Endocarditis Algorithm

Inclusion & Exclusion Criteria

- Inclusion criteria: Patients with suspected infective endocarditis (IE), with suspicion raised by (but not limited to) any of the following:
  - Pathogenic blood culture positivity in setting of a new or previously known murmur, or prior hx of congenital heart disease
  - Fever (including fever of unknown origin, defined as daily fever > 38 C for > 7 days) in the presence of a new murmur
  - Presence of septic embolization
  - Fever in patients at high risk for IE (i.e. prior infective endocarditis, congenital heart disease, prosthetic material in heart, or intravenous drug user)

- Exclusion criteria: Patients with fever and known source and who do not meet **Duke Criteria**

Suspected Endocarditis Algorithm

Confirmed Endocarditis Algorithm

Definitions & Diagnostic Criteria

- Infective endocarditis occurs when virulent microorganisms colonize the endocardium and cardiac valves.
- Diagnosis is based upon history and physical exam, presence of bacteremia/ fungemia on blood cultures, laboratory results, and echocardiogram showing active valvulitis. Some patients may present with septic emboli if a late diagnosis is made
- The modified Duke criteria is used in diagnosing definite IE: 2 major criteria, 1 major criteria & 3 minor criteria, or 5 minor criteria.

MAJOR CRITERIA:

- **Blood culture positive for one of the following:**
- Typical microorganisms consistent with IE from 2 separate blood cultures, including but not limited to:
  - Viridans streptococci
  - Streptococcus bovis
  - HACEK group (Haemophilus, Aggregatibacter—previously Actinobacillus—Cardiobacterium, Eikenella, Kingella)
  - Staphylococcus aureus
- Community-acqired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows:
  - At least 2 positive cultures of blood samples drawn >12h apart or,
  - All 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
- **Single positive blood culture for Coxiella burnetii or anti–phase 1 IgG antibody titer ≥ 1:800**
- **Evidence of endocardial involvement:**
  - Transthoracic echocardiogram consistent with may include:
    - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jet, or an implanted material in the absence of an alternative anatomic explanation
    - Abscess
    - New partial dehiscence of prosthetic valve
    - New valvular regurgitation

MINOR CRITERIA:

- **Predisposition for IE in the pediatric and adolescent age groups include:**
  - Prosthetic cardiac valves or conduits
  - Cyanotic congenital heart lesions (baseline saturations < 92%, including all single ventricle patients)
  - Systemic-to-pulmonary shunts
  - Valve lesions with significant regurgitation
  - IV drug abuse
  - Prior infective endocarditis
- **Fever defined as temperature >38°C**
- **Vascular phenomena:**
  - Major arterial emboli
  - Septic pulmonary infarcts
  - Mycotic aneurysm
  - Intracranial hemorrhage
  - Conjunctival hemorrhages
  - Janeway lesions
- **Immunological phenomena:**
  - Glomerulonephritis
  - Osler nodes
  - Roth spots
  - Rheumatoid factor
- **Microbiological evidence:**
  - Positive blood culture that does not meet a major criterion as noted above (excludes single positive cultures for coagulase negative staphylococci and organisms that do not typically cause IE)
  - Serological evidence of active infection with organism consistent with IE

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Differential Diagnoses

- IE may imitate other diagnoses, therefore a broad differential is reqired.
  - Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection
  - Fever of unknown origin (FUO):FUO may have multiple potential etiologies, including that of IE, in the correct clinical context.
  - Rheumatologic and vascular phenomenon may also have demonstrable peripheral skin changes that can overlap with septic emboli
  - Stroke/TIAs from primary vascular issues may also present similarly
  - Isolated pulmonary embolism

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Testing

- Blood cultures
  - **Paired blood cultures** (2 peripheral, or 1 central (implanted port, PICC line, etc.) and 1 peripheral) should be obtained simultaneously.
  - Blood cultures should be repeated every 8 hours until 3 sets of paired blood cultures have been obtained.
    - These three serial sets of cultures are obtained to broaden our ability to grow potential infectious organisms, not to rule-in or -out endocarditis.
    - Ideally, these three sets of cultures are obtained before starting antibiotics. In patients with strong suspicion of IE for whom early antibiotic therapy is needed, 3 sets of paired blood cultures, each obtained 1 hour apart from another, is an appropriate method for blood culture collection. Antibiotic therapy should not be delayed for blood culture collection (ex. all 3 sets of paired cultures) if sepsis is present.
- C-Reactive Protein, Sedimentation rate, Procalcitonin
- CBC w/ differential
- Urinalysis and Urine culture
- Transthoracic Echocardiogram (TTE) is considered the first line cardiac imaging modality
  - A transesophageal echocardiogram is recommended for patients with:
    - Conduits and prosthetic valves
    - Rated at least possible IE by clinical criteria (Duke Criteria)
    - Complicated IE [paravalvular abscess]
    - Confirmed native or prosthetic mitral valve lesion
  - Intracardiac echocardiogram (ICE) for prosthetic pulmonary valve or right-sided conduits
- CT chest if echo shows a right-sided lesion
- Brain MRI if echo shows left-sided lesion
- Abdominal US/CT if echo shows a left-sided lesion (modality at discretion of treating team)
- If there is presence of hematuria, proteinuria, or abnormal renal function, additional diagnostic considerations including obtaining:
  - Protein/Creatinine ration (urine)
  - Serum C3, C4
  - Rheumatoid factor may be considered
  - Renal US (with Doppler) should be obtained to evaluate for embolic disease

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Severity Assessment

- Patients with left-sided lesions (i.e. mitral valve and aortic valve) are at higher risk for emboli to the coronary arteries and brain, which can cause stroke and death. These patients need to be observed very closely on telemetry for rhythm & ST segment changes, as well as for changes in mental status with frequent neurologic checks. Vegetation size should be monitored and an abrupt change in vegetation size should indicate close consultation with the CT surgical team.
- Patients are at highest risk of showering emboli during first 24-48 hours of presentation and antibiotic therapy.
- Patients who reqire an increase in respiratory support, remain febrile despite antibiotics, have changes in mental status, or vital sign instability should be managed in an ICU setting to manage sepsis, prevent embolic phenomena, and monitor rhythm on telemetry.

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Admission Criteria

Generally speaking, patients with existing cardiac conditions will be admitted to Cardiology services (either H4A or CTICU). Patients with left-sided (systemic circulation) lesions (regardless of history), will be admitted to the CTICU. All other patients will be admitted to the ID service or PICU, pending severity of illness. Only patients who are hemodynamically stable (normotensive, without oxygen reqirement, without mental status change) should be admitted to the Cardiology or Infectious Disease Floors.

- Cardiology Floor Admission:
  - Hemodynamically stable AND with a history of CHD (palliated or otherwise)
- CTICU Admission:
  - Confirmed or suspected left-sided (systemic circulation) lesion
    - Suspicion would be raised by evidence of systemic emboli even if no readily found left-sided vegetation
  - History of CHD (palliated or otherwise) AND hemodynamic instability regardless of location of lesion
- Infectious Disease Floor Admission (must meet all of the following):
  - Hemodynamically stable AND no history of CHD AND without concern for a left-sided (systemic circulation) lesion
- PICU Admission:
  - Hemodynamic instability in patients without a history of CDHand no concern for a left-sided (systemic circulation) lesion

Admission Matrix

Septic or Requiring Ventilatory Support	History of CHD	Site of Lesion	Unit
Yes	Yes	Any	CTICU
	No	Left	CTICU
		Right or Negative TTE	PICU
No	Yes	Left	CTICU
		Right or Negative TTE	Cardiology
	No	Left	CTICU
		Right	ID vs. Cardiology
		Negative	Off Pathway

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Assessment & Monitoring

- Teams to consult (at time of high suspicion or of definitive diagnosis):
  - Cardiology
  - Infectious Disease
  - Ophthalmology (especially with staphylococcal and fungal endocarditis)
  - CT Surgery
  - Hematology
  - Nephrology (if significant renal injury is observed)
- In patients with a positive blood culture (culture positive IE): Blood cultures will be obtained daily until 3 consecutive days of negative blood cultures.
- Consider the following assessments:
  - CBC with differential, LFTs, BUN/Cr, CRP 2x/week
  - Sedimentation rate weekly
  - For patients receiving vancomycin in the treatment of Staphylococcus aureus IE, the goal vancomycin AUC/MIC ratio is between 400-600. If unable to calculate AUC/MIC, target troughs of 15-20 ug/mL are considered acceptable. For other vancomycin susceptible Gram positive pathogens, target troughs of 10-15 ug/mL may be acceptable, though target troughs are at the discretion of the provider.
    - Vancomycin levels should be monitored per clinical pharmacy recommendations until achieving target levels.
    - Once achieving stable target vancomycin levels (defined as 2 vancomycin levels within target range separated by 72hours duration), vancomycin levels may be obtained weekly thereafter
    - Serum vancomycin trough levels should be obtained if evidence of worsening renal function, decreased urine output, or other clinical concern.
  - For patients receiving daptomycin, serum CK levels should be obtained at baseline and monitored weekly
- Echocardiograms may be done PRN based on location of vegetation, size of vegetation, presence of valve dysfunction, heart failure symptoms in close consultation with a Cardiology team
- If CT surgery is performed, specimen(s) should be sent for:
  - Histopathology
  - Bacterial Aerobic/anaerobic culture
  - Fungal cultures
  - AFB culture
  - Tissue specimens may also be submitted for (but not limited to) the following in discussion with ID:
    - Staphylococcus aureus PCR
    - Streptococcus pneumoniae PCR
    - Group A Streptococcus PCR
    - Bartonella henselae PCR
    - Universal PCR (XMIS)
    - Fungal nocardia culture

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Recommended Treatments

- In patients for whom IE is suspected, and who are non-toxic appearing, hemodynamically stable, without focal neurologic deficits, or other clinical concerns, antibiotic therapy may be withheld while serial paired blood cultures are obtained
- **Empiric antibiotic therapy** is indicated if not meeting the above criteria, and should be administered as soon as possible, AFTER paired blood cultures have been obtained (if clinically possible). Goals for timing of antibiotic administration should be consistent with other guidelines (ex. sepsis, etc), though should ideally be given within 60 minutes of arrival.
  - Empiric antibiotic therapy is dependent on a multitude of factors, including but not limited to:
    - The presence of foreign material (eg. prosthetic valves)
    - The timing of valve placement relative to current presentation
    - Identification of a vegetation on ECHO
    - Prior history of bacterial colonization
    - Accounting for desired tissue penetration (eg. presence of embolic disease. or need for CNS penetrating agents)
    - Drug allergies
    - Clinical presentation, appearance, and other various comorbidities
  - **In General**, empiric antibiotic therapy (if indicated, see above) is as follows, however consideration for other factors must be given. Infectious Diseases should be contacted with questions regarding empiric antibiotic therapy.
- Antibiotics should be tailored based upon culture results and susceptibility profile, accounting for comorbidities as above, as recommended per Infectious Diseases consultation.
  - If persistent bacteremia despite appropriate targeted therapy (>5 days if clinically stable, >3 days if reqiring vasopressor support), then adjunctive, combination, or alternative targeted therapy may be considered and directed as per Infectious Diseases.
  - If patient has progressive renal insufficiency that may impair the ability to proceed to the OR, or conditions for which the need for dialysis may result in substantial harm, then adjunctive, combination, or alternative targeted therapies may be considered as per Infectious Diseases.
- CT surgery determines surgical candidacy based on vegetation size, vegetation location, embolic phenomena, etc.

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Infective Endocarditis:Recommended Empiric Antibiotics

Scenario	Antibiotic Recommendation	MISC
Suspected IE (+/- CHD), with or without known vegetation, hemodynamically stable, well appearing	• Consider holding antibiotic therapy pending serial paired sets of blood cultures	
Patient does not meet above clinical criteria		
Suspected IE (+/- CHD, without prosthetic material), with or without known vegetation	• IV vancomycin (refer to age specific dosing found in order set) **AND** • IV ceftriaxone 100mg/kg q24h (max dose 4000mg/dose)	Consider prior colonization and susceptibilities, drug allergies, and other comorbidities in empiric antibiotic choice Dose adjust all antimicrobials as per renal function Linezolid is not considered a first line therapy empiric or definitive treatment of IE irrespective of presence of AKI or other comorbidities If concerns re: antibiotic choice, please contact ID on call physician for recommendations.
Suspected IE (CHD with prosthetic material), no known vegetation	• IV vancomycin (refer to age specific dosing found in order set) **AND** • IV cefepime 50mg/kg q8h (max dose 2000mg/dose)	
Suspected IE, Hx of prosthetic material (< 1 year), known vegetation	• IV vancomycin (refer to age specific dosing found in order set) **AND** • IV cefepime 50mg/kg q8h (max dose 2000mg/dose) **AND** • IV gentamicin 1mg/kg/dose q8h **AND** • PO rifampin ~7mg/kg/dose q8h (max dose 300mg/dose)	
Suspected IE, Hx of prosthetic material (> 1 year), known vegetation	• IV vancomycin (refer to age specific dosing found in order set) **AND** • IV ceftriaxone 100mg/kg q24h (max dose 4000mg/dose) **WITH OR WITHOUT** • PO rifampin ~10mg/kg/dose q12h (max dose 300mg/dose)	
Suspected IE presenting with concerns of sepsis (ICU level admission)	**No Prosthetic Material, No High Risk* Criteria** • IV vancomycin (refer to age specific dosing found in order set) **AND** • IV ceftriaxone 100mg/kg q24h (max dose 4000mg/dose) **AND** • IV gentamicin (refer to age specific dosing found in order set) **Prosthetic Material or meets High Risk* Criteria** • IV vancomycin (refer to age specific dosing found in order set) **AND** • IV cefepime 50mg/kg q8h (max dose 2000mg/dose) **AND** • IV gentamicin (refer to age specific dosing found in order set)	
*High Risk as defined by NCH sepsis alert algorithm		

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Deterioration & Escalation of Care

- Identification of Deterioration
  - If the patient develops new embolic phenomena after effective antibiotics have been started, the patient should be transferred to the appropriate ICU if not already there and (re)evaluated by CT surgery
- Escalation of Care Protocol:
  - If patient is clinically deteriorating, they should be transferred to the CTICU and evaluated by CT surgery

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Discharge Criteria & Planning

- Discharge Checklist
  - Patients going home with a PICC line with prolonged course antibiotics:
    - Medication, dose, and duration of antibiotic treatment is determined by Infectious Diseases, dependent on several factors including (but not limited to) the presence (or absence) of surgical intervention, pathogen, and evidence of disseminated infection.
    - Reqire in-house PICC line teaching prior to discharge.
    - Home nursing or medication delivery service if indicated
  - Patients going home on long-term IV or oral antibiotics:
    - If indicated, ensure stable antibiotic levels prior to discharge
    - Order weekly monitoring labs if patient going home on parenteral therapy
  - Patient has means to monitor antibiotic levels at home (home health service, designated outpatient laboratory, orders are placed)
  - Patient has ID follow-up appointment
  - Patient has Cardiology follow-up appointment
  - Patient has echocardiogram ordered at appointment, if indicated
  - Patient has had a discharge echocardiogram completed prior to discharge
- Outpatient Follow Up:
  - Infectious Diseases:
    - Serial laboratory monitoring includes weekly CBC with diff, BUN/Cr, LFTs
    - Additional laboratory considerations such as vancomycin levels (weekly if on stable dosing), and serum CK (weekly) dependent upon antibiotic choice.
    - Optional monitoring labs: sedimentation rate, CRP.
    - Follow up imaging of sites of dissemination (MRI of brain, abdominal U/S) are at the discretion of the provider.
    - Timing of outpatient follow up is at the discretion of the provider
  - Cardiology:
    - Timing of outpatient follow up and repeating imaging is at the discretion of the provider
  - Other follow-up may be indicated based on clinical course, involvement of other body systems, and other consultant recommendations
  - Primary care
    - Ideally, patients should see their primary care physician to follow-up recent admissions within a few weeks from discharge
- Patient should come to the ER after discharge if return of fever, issues infusing or aspirating PICC line, change in mental status.

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Patient & Caregiver Education

- Education should include
  - PICC line teaching to be done in-house prior to discharge
  - Dental health importance (antibiotics prior to dentist if indicated)

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Risk Awareness

Our goal is to create a standardized guideline to shorten the time to initiation of antibiotics, cardiac imaging, and surgery while lowering complications and death.

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Quality Measures

- To determine our success, measuring:
  - Average time to initial cardiac imaging
  - Average time to initiation of effective antibiotic therapy
  - Average use of anticoagulation
  - Average number of deaths and days between death
  - Average number of embolic complications
  - Average number of patients who experience renal insufficiency (from antibiotics)
  - Compliance with blood culture collection guidelines

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Pathway Team & Process

Pathway Development Team

Leader(s):

Cardiology:

Cristin Blaney, APRN

Deipanjan Nandi, MD

Cardiothoracic Surgery:

Sergio Carrillo Melendez, MD

Infectious Diseases:

Christopher Ouellette, MD

Members:

Cardiology:

Jessica Bowman, MDCT CT

Surgery:

Sergio Carrillo, MD

Patrick McConnell, MD

CTICU:

Richard Fernandez, MD

Neurology/PICU:

Melissa Chung, MD

Clinical Pharmacy:

Jessica Tansmore, PharmD

Hematology:

Amanda Sankar, MD

Emergency Medicine:

Terri Dachenhaus, RN

Emergency Medicine Fellow:

Courtney Coyle, MD

Resident:

Jaclyn Giafaglione, MD

Clinical Pathways Program:

Medical Director – Emergency Medicine:

Berkeley Bennett, MD, MS

Medical Director – Associate Chief Quality Officer, Center for Clinical Excellence:

Ryan Bode, MD, MBOE

Medical Director – Hospital Pediatrics:

Gerd McGwire, MD, PhD

Medical Director – Clinical Informatics & Emergency Medicine:

Laura Rust, MD, MPH

Business & Development Manager:

Rekha Voruganti, MBOE, LSSBB

Program Coordinators:

Tahje Brown, MBA

Tara Dinh, BS

Clinical Pathway Approved

Medical Director – Associate Chief Quality Officer, Center for Clinical Excellence:

Ryan Bode, MD, MBOE

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

For more information about our pathways and program please contact:ClinicalPathways@NationwideChildrens.org

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