

**DoD Clinical Guidelines for Post-Smallpox Vaccine Associated Myopericarditis
Vaccine Healthcare Centers Network (VHC)**

Vaccine(s) administered in past 30 days

**Clinical symptoms: Chest pain, shortness of breath, palpitations,
syncope, dry cough**

Initial Evaluation

History: Characterize symptoms ¹ Past medical history ² <ul style="list-style-type: none"> Include detailed vaccination hx Risk factors for cardiac symptoms ³	Physical Examination ⁴ Laboratory ⁵ (Troponin I/T, BNP, ESR, UltraS CRP, CK-MB, CBC, Viral surveillance) Diagnostics [Electrocardiogram, Echocardiogram, CXR, Imaging studies (MRI with gad)] ⁶
--	--

A. Symptoms only

B. Symptoms + objective abnormality¹¹

A. Cardiology Consultation

- Document normal ECG, CXR, troponin, CK-MB, CRP, other studies as indicated during acute symptoms^{5,6}
- Consider non-cardiac etiology⁷

Therapeutic options⁸:
NSAIDs +/- colchicine; other Rx, such as acetaminophen (pain)

Management & Recovery⁹

- No strenuous activity until 6-12 week follow-up
- 6-12 week clinical F/U visit, ECG, and exercise stress test to clear for return to duty
- For ongoing or persistent symptoms, refer to cardiology
- Permanent exemption from future smallpox vaccines unless exposed to variola major

B. Cardiology Consultation

- Differential includes myo-pericarditis and acute coronary syndrome^{7,11}
- Special labs and diagnostics^{5,6} as indicated

B1. Symptoms with objective abnormality but without positive biomarkers or LV dysfunction¹¹

Therapeutic options⁸: NSAIDs +/- colchicine; other Rx, such as acetaminophen (pain)

Management & Recovery⁹

- No strenuous activity until 6-12 week follow-up
- 6-12 week clinical F/U visit, ECG, exercise stress test to clear for return to duty; repeat abnormal studies
- For ongoing or persistent symptoms, refer to cardiology
- Permanent exemption from future smallpox vaccines unless exposed to variola major

B2. Symptoms with positive biomarkers, mild depressed LV function, and/or imaging c/w myocarditis¹¹

Therapeutic options⁸: NSAIDs; other Rx, such as acetaminophen (pain)

Management & Recovery⁹

- No strenuous activity until 6-12 week follow-up
- 6-12 week clinical F/U visit, ECG, exercise stress test as clinically indicated; repeat abnormal studies
- Activity as tolerated & deployment restriction for 6 months
- Cardiology F/U at 6-12 month intervals until symptom resolution
- Permanent exemption from future smallpox vaccines unless exposed to variola major

B3. Symptoms with objective abnormality and LVEF < 45%, sustained dysrhythmias, hemodynamic instability¹¹

- Transfer to Tertiary Care Center when stabilized

Therapeutic options: see Footnote 8

Management & Recovery⁹

- No strenuous activity until 6-12 week follow-up
- 6-12 week clinical F/U visit, ECHO, ECG, exercise stress test as clinically indicated; repeat abnormal studies
- Activity as tolerated & deployment restriction for a minimum of 6 months
- Cardiology F/U at 6-12 month intervals until symptom resolution
- Permanent exemption from future smallpox vaccines unless exposed to variola major

Refer **all** cases to VHC Network for case review, entry into DoD Smallpox Vaccine Myopericarditis Registry, filing of VAERS report and long-term case management. Please include patient and provider contact information, Echocardiograms, ECG, cardiac isoenzyme results, & copies of pertinent records.

Consultation: Call the DoD Vaccine Clinical Call Center at 866-210-6469 to request VHC and/or military cardiology clinical consultation.

FOOTNOTES:

Footnote 1	Characterize symptoms, including chest pain type	Specify symptom location, character, onset, duration, intensity/severity, frequency, accompanying/associated symptoms, and alleviating/aggravating factors. Categorize patient's chest pain type if present (choose one): <ol style="list-style-type: none"> Pericarditis chest pain: Chest pain that is typical and made worse by supine position, improved with leaning forward, pleuritic, constant <ol style="list-style-type: none"> Detailed history is critical to case definition of suspect pericarditis – see case definitions, page 5 Myocarditis chest pain: angina-like, diffuse; not necessarily positional or pleuritic Atypical chest pain: Pain, pressure, or discomfort in the chest, neck, or arms not clearly exertional or not otherwise consistent with pain or discomfort of myocardial ischemic origin. Reference: http://www.guideline.gov/summary/summary.aspx?doc_id=6534
Footnote 2	Assess past medical history	Detailed review of all systems, with attention to the following disorders: <ul style="list-style-type: none"> Lung disease Gastrointestinal disease Vascular disease (e.g., stroke, transient ischemic attack, peripheral arterial disease) Musculoskeletal disorders (e.g., impingement syndrome, thoracic outlet syndrome) Reference: PMH study guide http://medinfo.ufl.edu/year1/bcs96/clist/history.html Include vaccination history and adverse events (specify site of vaccination and lot number, if available)
Footnote 3	Risk Factors for Cardiac Symptoms	<ol style="list-style-type: none"> Personal History of angina, myocardial infarction (MI), congestive heart failure (CHF), percutaneous coronary intervention (e.g., balloon angioplasty, stent, atherectomy), coronary artery bypass graft (CABG), catheterization with stenosis \geq 50% Age, sex, race/ethnicity (African American, Mexican American, American Indian, Native Hawaiian, some Asian American), diabetes, hypertension, smoking, dyslipidemia, family history of CAD (especially prior to age 55), obesity, physical inactivity, stress, and excessive alcohol consumption Reference: http://www.americanheart.org/presenter.jhtml?identifier=4726
Footnote 4	Physical Examination	Perform a focused PE to include: gender and race/ethnicity, vital signs, ht, wt, detailed exam to include vaccination site, cardiac (jugular venous pressure if able), pulmonary, peripheral edema and lymphadenopathy. Reference: http://medicine.ucsd.edu/clinicalmed/introduction.htm
Footnote 5	Laboratory studies	Report normal range as defined by individual hospital laboratory standards.
Laboratory studies: All patients		
	Complete blood count	CBC at presentation, to include differential, with emphasis on eosinophil and lymphocyte count should be noted.
	Brain natriuretic peptide	BNP at presentation to assess for heart failure
	Cardiac enzymes	All Creatinine Kinase (CK), CK-MB, and troponin (I/T) values should be noted.
	Inflammatory markers	All erythrocyte sed rate and C-reactive protein (CRP) (ultrasensitive, if available) values should be noted.
Laboratory studies as clinically indicated:		
	Immune complex screening	All C3, C4, CH50, Raji cell/C1q assay, and C3D values should be noted.
	Viral surveillance	Smallpox related myopericarditis is a diagnosis of exclusion. No smallpox vaccine related cases have exhibited viral etiology to date. When considering other etiologies, viral surveillance is indicated.
	Serologies	Consider ID consultation; PCR for vaccinia if available (consult CDC/VHC). All coxsackie A/B (enteroviruses), adenovirus, CMV, Parvovirus B19, influenza A/B, HHV-6, HSV-1, HIV, RSV , dengue, echovirus, encephalomyelitis, Epstein-Barr, Lyme, rhabdovirus, varicella, variola, yellow fever, hepatitis A/B/C IgM, and core IgG values and titers during the evaluation should be noted; obtain

		specimens for convalescent titers at 4 week interval.
	Other Cultures	Consider ID consultation; all viral cultures (nasal wash, urine, feces) for adenovirus, influenza viruses, parvovirus B19 or enteroviruses should be noted.
	Collagen vascular screening	Note all ANA, Anti-DS DNA, ENA, and similar values during the evaluation.
	Myocardial biopsy	Auto-antibodies for myocardium; special studies, including PCR for vaccinia, parvovirus B19, etc. Consult VHC Network working group for updated information
Footnote 6	Diagnostics	
Diagnostics: All patients		
	Electrocardiogram (ECG)	Note date, time, rate, rhythm, the presence of ectopy and abnormalities in waves, intervals and segments Typical ECG manifestations: Pericarditis: Acute <ol style="list-style-type: none"> 1. Diffuse ST segment elevation, particularly leads I,II, III, aVF, aVL, and V5-V6 2. Diffuse PR segment depression 3. PR segment elevation in lead aVR Evolving <ol style="list-style-type: none"> 1. T-wave changes: notched, biphasic. Or low-voltage inversions. Myocarditis: <ol style="list-style-type: none"> 1. Diffuse T-wave inversions without ST segment abnormality 2. Incomplete atrioventricular conduction blocks (usually transient) 3. Intraventricular conduction blocks (usually transient) *When myocarditis and pericarditis occur together, ST segment abnormalities also may be evident. Reference: Demangone, D. (2006) ECG manifestations: Noncoronary heart disease. <i>Emergency Medicine Clinics of North America.</i> (24) pp.113-131.
	Chest X-ray	PA and Lateral
	Echocardiogram	If only a range is estimated for ejection fraction (EF), note the midpoint of the range.
Other diagnostics as clinically indicated:		
	Pulmonary functions	With DLCO if indicated; diffusion capacity corrected for hemoglobin is a sensitive measure of pulmonary interstitial disease and increased risk for hypoxia with activity.
	Stress test	Indicate whether an exercise tolerance, stress-echocardiogram, or nuclear/pharmacological stress test was performed during the hospital stay and the result of the testing. Clinical correlation is recommended in the cases of a negative stress test result.
	Cardiac catheterization	If vessel occlusion identified, note the anatomical region affected and the degree of stenosis present.
	Holter & Event Monitor	Consider for dysrhythmia evaluation
	Imaging	MRI with gadolinium; consider indium scan for detection of patchy inflammation If not available locally, contact VHC Network
Footnote 7	Differential Diagnosis	Consider acute coronary syndrome (myocardial infarction), aortic dissection, pneumothorax, pulmonary embolism , musculoskeletal pain, esophageal disorder (gastroesophageal reflux, esophageal spasm), systemic autoimmune disease.
Footnote 8	Therapeutic options	Consult recent literature for any updates in treatment options
	Symptoms only (A) OR symptoms with objective findings, but without positive biomarkers or LV dysfunction (B1)	Non-steroidal anti-inflammatory therapy with or without colchicine; acetaminophen for pain (Colchicine in addition to Conventional Therapy for acute pericarditis: Results of the COLchicine for acute PERicarditis (COPE) trial. Imazio M, et al. <i>Circulation</i> 2005; 112:2012-16.)
	Symptoms w/ positive biomarkers or mild depressed LV function or imaging c/w myocarditis (B2)	Non-steroidal anti-inflammatory therapy; other Rx, such as acetaminophen (pain)
	Progressive symptoms (LVEF	▪ Conventional heart failure treatments (e.g., ACE inhibitors, nitrates, diuretics,

	< 45%, sustained dysrhythmias, hemodynamic instability) (B3)	<p>select beta-blockers such as carvedilol or metoprolol succinate)</p> <ul style="list-style-type: none"> ▪ Consider corticosteroids if no evidence of active infection on endomyocardial biopsy or in blood/oropharynx. ▪ Consider Vaccinia Immune Globulin (VIG)/IVIG only with expert consultant case review via VHC Network.
Footnote 9	Management and Recovery	<p>Whenever possible, standardized follow up should occur at or be coordinated with Walter Reed Army Medical Center (WRAMC) or Brooke Army Medical Center (BAMC) in collaboration with VHC Network staff.</p> <p>Deployment restriction reference: Maron et al. Task Force 4: HCM, Other Cardiomyopathies, and Marfan. <i>JACC</i>;45 (8):1340–5.</p>
	Symptoms only (A) OR Symptoms with objective findings, but without positive biomarkers or LV dysfunction (B1)	<p>Asymptomatic at follow-up</p> <ul style="list-style-type: none"> ▪ No strenuous activity until 6-12 week follow-up ▪ Repeat any previously abnormal studies at 6-12 weeks ▪ Clinical evaluation to include stress test at 6-12 weeks to clear for return to duty with light physical activity at own pace ▪ Long-term follow-up, including risk-benefit assessments for future vaccines such as live influenza, will be completed by VHC Network <p>Symptomatic and/or persistent/abnormal findings at follow-up</p> <ul style="list-style-type: none"> ▪ No strenuous activity until 6-12 week follow-up ▪ Repeat any previously abnormal studies ▪ Clinical evaluation to include stress test at 6-12 weeks ▪ Consult cardiology for further recommendations ▪ Long-term follow-up, including risk-benefit assessments for future vaccines such as live influenza, will be completed by VHC Network
	Symptoms with positive biomarkers or mild depressed LV function or imaging c/w myocarditis (B2) OR Progressive symptoms (LVEF < 45%, sustained dysrhythmias, hemodynamic instability) (B3)	<p>Asymptomatic at follow-up</p> <ul style="list-style-type: none"> ▪ No strenuous activity until 6-12 week follow-up; activity as tolerated and deployment restriction for 6 months ▪ Clinical evaluation at 6-12 weeks and 6-12 months ▪ Repeat any previously abnormal studies at 6-12 weeks and 6-12 months ▪ Stress test at 6-12 weeks; repeat at 6-12 months to clear for deployment ▪ Long-term follow-up, including risk-benefit assessments for future vaccines such as live influenza, will be completed by VHC Network <p>Symptomatic and/or persistent/abnormal findings at follow-up</p> <ul style="list-style-type: none"> ▪ No strenuous activity until 6-12 week follow-up; activity as tolerated and deployment restriction for 6 months ▪ Clinical evaluation at 6-12 weeks to include enzymes, ultra sensitive CRP, ECG, ECHO, stress test (unless contraindicated) ▪ Repeat MRI with previous enhancements or if symptomatic at 6 months ▪ Clinical evaluation at 6-12 months to include repeat ECHO, stress test, and MRI <ul style="list-style-type: none"> ▪ If normal and asymptomatic, clear for deployment ▪ If normal and symptomatic, consult cardiology ▪ If abnormal MRI with continued symptoms, not clear for deployment ▪ Continue cardiology follow-up at 6 -12 month intervals until asymptomatic ▪ Long-term follow-up, including risk-benefit assessments for future vaccines such as live influenza, will be completed by VHC Network
Footnote 10	Disability Assessment	<p>The majority of patients have recovered within 1 year. The natural history of this condition remains unknown. Careful functional assessment post-acute phase has not yielded definitive objective parameters.</p>

Footnote 11	<p style="text-align: center;">Case Definitions for Myocarditis and Pericarditis (MMWR 2003;52:492-6, www.cdc.gov/mmwr/PDF/wk/mm5221.pdf)</p>		
	Suspect	Probable	Confirmed
Myo- carditis	<p>(1) Dyspnea, palpitations, or chest pain of probable cardiac origin, with either one of the following:</p> <p>(a) ECG abnormalities beyond normal variants, not documented previously, including</p> <ul style="list-style-type: none"> ■ ST-segment/T-wave abnormalities ■ Paroxysmal or sustained atrial or ventricular arrhythmias ■ AV nodal conduction delays or intraventricular conduction defects ■ Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy, <p>OR</p> <p>(b) Focal or diffuse depressed LV function of indeterminate age identified by an imaging study</p>	<p>(1) Meets criteria for suspected myocarditis and is in the absence of other likely cause of symptoms;</p> <p>(2) In addition, meets one of the following:</p> <p>(a) Elevated cardiac enzymes (Troponin I, Troponin T, or Creatine Kinase-MB), OR</p> <p>(b) New onset or increased degree of severity of focal or diffuse depressed LV function by imaging, OR</p> <p>(c) Abnormal imaging indicating myocardial inflammation (cardiac MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)</p>	<p>Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy.</p>
Peri- carditis	<p style="text-align: center;">Suspect</p> <p>(1) Typical chest pain (i.e., made worse by supine position, improved with leaning forward)</p> <p>(2) No evidence for alternative likely cause of such chest pain</p>	<p style="text-align: center;">Probable</p> <p>(1) Meets criteria for suspected Pericarditis, or case in a person with pleuritic or other chest pain not characteristic of any other disease, that in addition, has one or more of the following:</p> <p>(a) Pericardial rub, an auscultatory sign with one to three components per beat OR</p> <p>(b) ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions not previously documented, OR</p> <p>(c) Echocardiogram indicating presence of abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or large posterior pericardial effusion alone)</p>	<p style="text-align: center;">Confirmed</p> <p>Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy</p>