Appendices
Appendix A

GUIDELINES FOR DATA COLLECTION, ANALYSIS AND PRESENTATION OF MYOCARDITIS AND PERICARDITIS

It was the consensus of the Brighton Collaboration *Myocarditis and Pericarditis Working Group* to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about myocarditis and pericarditis. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and whether the source of information is a prospective clinical trial, a post-marketing surveillance or epidemiological study, or an individual report of myocarditis and pericarditis. These guidelines have been developed by the Working Group for guidance only, and are not to be considered a mandatory requirement for data collection, analysis, or presentation.

1.1. Data collection

These guidelines represent a desirable standard for the collection of data on adverse events following immunization to favorize comparability of data and are recommended as an addition to data collected for the specific study question and setting. The guidelines are not intended to guide the primary reporting of myocarditis and pericarditis to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition, which are not repeated in these guidelines.

Guidelines 1-43 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,[a] and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences.[b] These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of myocarditis or pericarditis following immunization. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of myocarditis or pericarditis following immunization.

1.1.1. Source of information/reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

1) Date of report.
2) Name and contact information of person reporting[1] and/or diagnosing the myocarditis or pericarditis as specified by country-specific data protection law.
3) Name and contact information of the investigator responsible for the subject, as applicable.
4) Relation to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

1.1.2. Vaccinee/control

1.1.2.1. Demographics

For all cases and/or all study participants, as appropriate, the following information should be recorded:

5) Case/study participant identifiers (e.g., first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).
6) Date of birth, age, and sex.
7) For infants: gestational age and birth weight.

1.1.2.2. Clinical and immunization history

For all cases and/or all study participants, as appropriate, the following information should be recorded:

8) Past medical history, including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma.
9) Any medication history (other than treatment for the event described) prior to, during, and after immunization including prescription and non-prescription medication as well as medication or treatment with long half-life or long-term effect. (e.g., immunoglobulins, blood transfusion and immunosuppressants).
10) Immunization history (i.e., previous immunizations and any adverse event following immunization (AEFI)), in particular, occurrence of myocarditis or pericarditis after a previous immunization.

[a] https://www.ich.org/
[b] https://cioms.ch/wp-content/uploads/2019/11/Fillable-Form_CIOMS-to-E2B.pdf

1.1.3. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

11) Date and time of immunization(s).
12) Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose (e.g., 0.25mL, 0.5 mL) and number of dose (if part of a series of immunizations against the same disease).
13) The anatomical sites (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
14) Route and method of administration (e.g., intramuscular, intradermal, subcutaneous, needle-free, other injection devices).
15) Needle length and gauge.

1.1.4. The adverse event

16) For all cases with any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

The following should be specifically documented:

17) Clinical description of signs and symptoms of myocarditis or pericarditis, and if there was medical confirmation of the event (i.e., patient seen by physician).
18) Date/time of onset[2], first observation[3] and diagnosis[4], end of episode[5] and final outcome[6].
19) Concurrent signs, symptoms, and diseases.
20) Measurement/testing
    - Values and units of routinely measured parameters (e.g. temperature, blood pressure, cardiac enzymes, ECG values), in particular, those that indicate the severity of the event;
    - Method of measurement (e.g., type of thermometer, oral or other route, duration of measurement);
    - Results of laboratory examinations, surgical and/or pathological findings and diagnoses if available.
21) Treatment given for myocarditis or pericarditis, especially the following:
    Myocarditis: supportive treatment (extracorporeal membrane oxygenation, pacing), prednisone, Intravenous immunoglobulin.
    Pericarditis: pericardiocentesis, aspirin, colchicine, prednisone.
22) Outcome[6] at last observation.
23) Objective clinical evidence supporting classification of the event as 'serious'[7].
24) Exposures, other than the immunization, 24 hours before and after immunization (e.g. other treatments or procedures, environmental) considered potentially relevant to the reported event.

1.1.5. Miscellaneous / general

25) The duration of surveillance for myocarditis or pericarditis should be predefined based on:
    - Biologic characteristics of the vaccine e.g., live attenuated versus inactivated or other type of vaccines;
    - Biologic characteristics of the vaccine-targeted disease;
    - Biologic characteristics of myocarditis or pericarditis including patterns identified in previous trials (e.g., early-phase trials); and
    - Biologic characteristics of the vaccinee (e.g., nutrition, underlying disease, immunodepressive illness).
26) The duration of follow-up reported during the surveillance period should also be predefined. It should aim to continue until the resolution of the event.
27) Methods of data collection should be consistent within and between study groups, if applicable.
28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 24.
29) Investigators of patients with myocarditis or pericarditis should provide guidance to reporters to optimize the quality and completeness of information provided.
30) Reports of myocarditis or pericarditis should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

1.2. Data analysis

The following guidelines represent a desirable standard for myocarditis or pericarditis data analysis to favorize comparability of data and are recommended in addition to data analyzed for the specific study question and setting.

31) Reported events should be classified in one of the following five categories according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

Event classification in five categories[8]

Event meeting case definition

Level 1: *Criteria as specified in the* myocarditis or pericarditis *case definition*

Level 2: *Criteria as specified in the* myocarditis or pericarditis *case definition*
Level 3: *Criteria as specified in the* myocarditis or pericarditis *case definition*

Event not meeting case definition

Additional categories for analysis

Level 4: Reported myocarditis or pericarditis with insufficient evidence to meet the case definition[9]
Level 5: Not a case of myocarditis or pericarditis

32) The interval between immunization and reported myocarditis or pericarditis could be defined as the date/time of immunization to the date/time of onset[2] of the first symptoms or signs consistent with the definition. If only a few cases are reported, the actual time course could be analyzed for each. If a large number of cases are reported, data can be analyzed using the following intervals:

Patients with myocarditis or pericarditis by interval to presentation

Interval	**Number (%)**
< 7 days after immunization	
8 - < 42 days after immunization	
> 42 days after immunization	
TOTAL	

33) The duration of a possible myocarditis or pericarditis could be analyzed as the interval between the date/time of onset[1] of the first symptoms and/or signs consistent with the definition and the end of episode[5] and/or final outcome[6]. Whatever start and ending dates/times are used, they should be used consistently within and across study groups.
34) If more than one measurement of a particular criterion is taken and recorded, the highest value for the adverse event could be used as the basis for analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.
35) The distribution of data (such as numerator and denominator data) could be analyzed in predefined increments (e.g., measured values, times), where applicable. Increments specified above should be used. When only a small number of cases are analyzed, the respective values or time course can be presented for each case.
36) Data on myocarditis or pericarditis obtained from patients receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analyzed by study arm and dose where possible, e.g., in prospective clinical trials.

1.3. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on myocarditis or pericarditis following immunization to favorize comparability of data and are recommended in addition to data presented for the specific study question and setting. It is also recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology[c] (e.g., statements of consolidated standards of reporting trials (CONSORT), of improving the quality of reports of meta-analyses of randomized controlled trials (QUORUM), and of meta-analysis of observational studies in epidemiology (MOOSE), respectively).

37) All reported events of myocarditis or pericarditis should be presented according to the categories listed in guideline 31.
38) Data on possible myocarditis or pericarditis events should be presented in accordance with data collection guidelines 1-24 and data analysis guidelines 31-36.
39) Terms to describe myocarditis or pericarditis such as ‘mild’, ‘moderate’, ‘severe’ or ‘significant’ are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.
40) Data should be presented with numerator and denominator (n/N) (and not only as percentages), if available.

Although denominator data are usually not readily available in immunization safety surveillance systems, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates be described (e.g. manufacturer data like total doses distributed, reporting through Ministry of Health, coverage/population based data).

41) The incidence of cases in the study population should be presented and clearly identified as such in the text.

[c] https://www.equator-network.org/

42) If the distribution of data is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, the mean and standard deviation should also be provided.
43) Any publication of data on myocarditis or pericarditis should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:
- The study design;
- The method, frequency and duration of monitoring for myocarditis or pericarditis;
- The trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- The type of surveillance (e.g., passive or active surveillance);
- The characteristics of the surveillance system (e.g., population served, mode of report solicitation);
- The search strategy in surveillance databases;
- Comparison group(s), if used for analyses;
- The data collection instrument (e.g., standardized questionnaire, diary card, report form);
- Clear indication if the day of immunization was considered to be 'day one' or 'day zero' in the analysis;
- Whether the date of onset[2] and/or the date of first observation[3] and/or the date of diagnosis[4] were used for analysis; and
- Use of this case definition for myocarditis or pericarditis, in the abstract or methods section of a publication[11].

Notes for guidelines

[1]If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

2The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for myocarditis or pericarditis occurred. This may only be possible to determine retrospectively.

3 The date and/or time of first observation of the first sign or symptom indicative for myocarditis or pericarditis can be used if date/time of onset is not known.

[4]The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.

[5]The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.

[6] E.g. recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.

[7]An AEFI is defined as serious by international standards if it meets one or more of the following criteria: 1) it results in death, 2) it is life-threatening, 3) it requires inpatient hospitalization or results in prolongation of existing hospitalization, 4) it results in persistent or significant disability or incapacity, 5) it is a congenital anomaly or birth defect, 6) it is a medically important event or reaction.

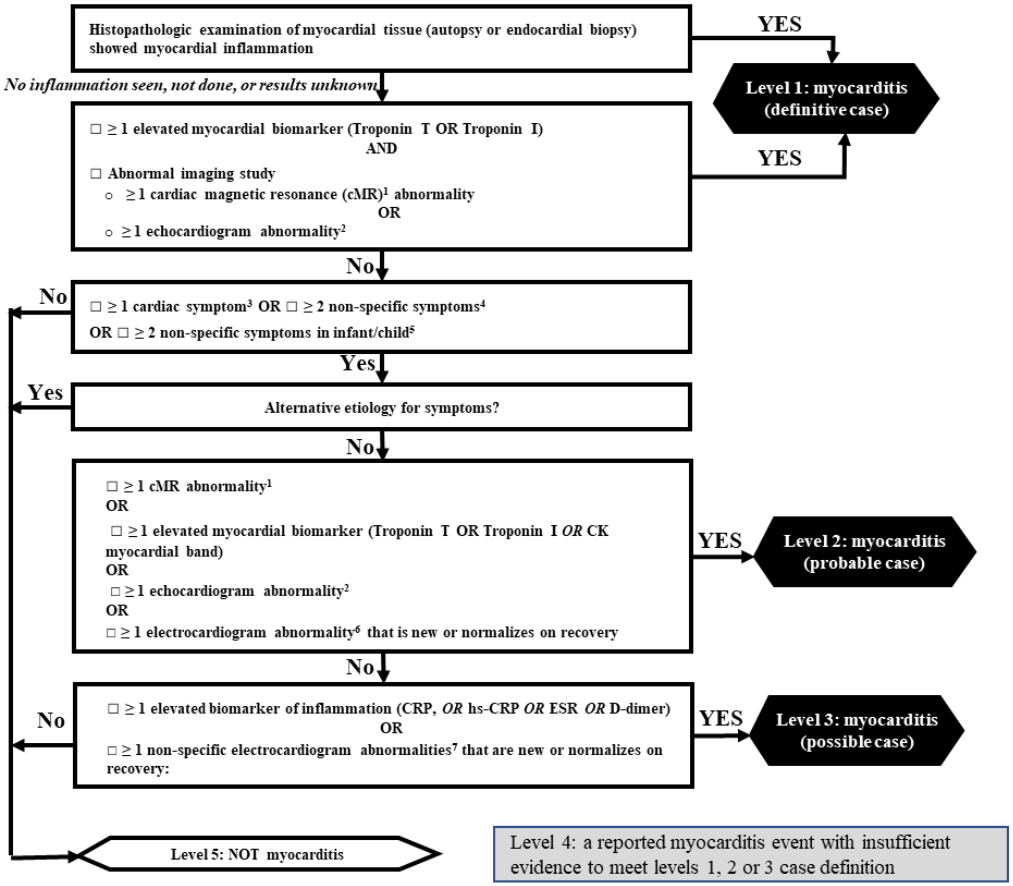
[8]To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level 3. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined. Major criteria can be used to satisfy the requirement of minor criteria. If the lowest level of the case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified as either Level 4 or 5.

[9]If the evidence available for an event is insufficient because information is missing, such an event should be categorized as 'Reported myocarditis or pericarditis with insufficient evidence to meet the case definition' (Level 4).

[10]An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as 'Not a case of myocarditis or pericarditis' (Level 5).

[11]Use of this document should preferably be referenced by referring to the link to the Brighton Collaboration website (https://brightoncollaboration.us/).

Appendix B Brighton Collaboration case definition and levels of diagnostic certainty for myocarditis



CRP: c-reactive protein ; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity CRP

[1]cMR abnormalities:
- Edema on T2 weighted study, typically patchy
- Late gadolinium enhancement on T1 weighted images with an increased enhacement ratio between myocardial and skeletal muscle typically involving ≥1 non-ischemic regional distribution with recovery (myocyte injury)

[2]Echocardiogram abnormalities:
- New focal or diffuse left or right ventricular function abnormalities (e.g., decreased ejection fraction)
- Segmental wall motion abnormalities
- Global systolic or diastolic function depression/abnormality
- Ventricular dilation
- Wall thickness change

[3]Cardiac symptoms:
- Acute chest pain or pressure
- Palpitations
- Dyspnea after exercise, at rest, or lying down
- Diaphoresis
- Sudden death

[4]Non-specific symptoms:
- Fatigue
- Abdominal pain
- Dizziness or syncope
- Edema
- Cough

[5]Infant/child non-specific symptoms:
- Irritability
- Vomiting
- Poor feeding
- Tachypnea
- Lethargy

[6]Electrocardiogram abnormalities:
- Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or superventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages
- AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block
- Continuous ambulatory electrocardiographic monitor that detects frequent atrial or ventricular ectopy

[7]Non-specific Electrocardiogram abnormalities:
- ST-segment of T-wave abnormalities (elevation of inversion
- Premature atrial and ventricle contraction
- Newly reduced r-wave height, low voltage or abnormal q waves

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Definitions related to acute symptoms

Chest pain: Pressure, tightness, soreness, pain, or a squeezing or aching sensation in the chest or arms that may spread to the neck, jaw, throat, back or to the shoulders and arms. May present as throat or jaw or arm or shoulder pain alone. Pain can be described like a heavy weight or pressure on the chest or pinching oe burning. Positional changes in chest pain: May or may not worsen with different positions or movement.

Dyspnea: Shortness of breath at rest and/or with exercise.

Gastrointestinal: Nausea, indigestion, heartburn, or abdominal/stomach pain.

Diaphoresis: Cold sweats usually without fever

Fatigue or exhaustion: Often with marked change in exercise tolerance

Palpitations: Irregular heartbeat, skipping beats

Syncope, near-syncope: Lightheadedness or sudden dizziness or fainting

Cough: Usually persistent ("won't quit") dry cough without sputum production

Leg and feet swelling Acute/rapid onset rarely associated with fulminant myocarditis

Sudden death: Cardiogenic shock is clinical diagnosis rather than a symptom

Electrocardiogram abnormalities

ST-segment or T wave (elevation or inversion): Note that in younger healthy populations early repolarization as a normal variant is frequently normal but it can be abnormal if it returns to normal rhythm or if there are time evolving changes (Courtesy of Dr. Atwood, Cardiology, Walter Reed National Military Medical Center).

Paroxysmal or sustained atrial or ventricular arrhythmias: Premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages.

AV nodal conduction delays or intraventricular conduction defects: Atrioventricular block (grade I-III), new bundle branch block

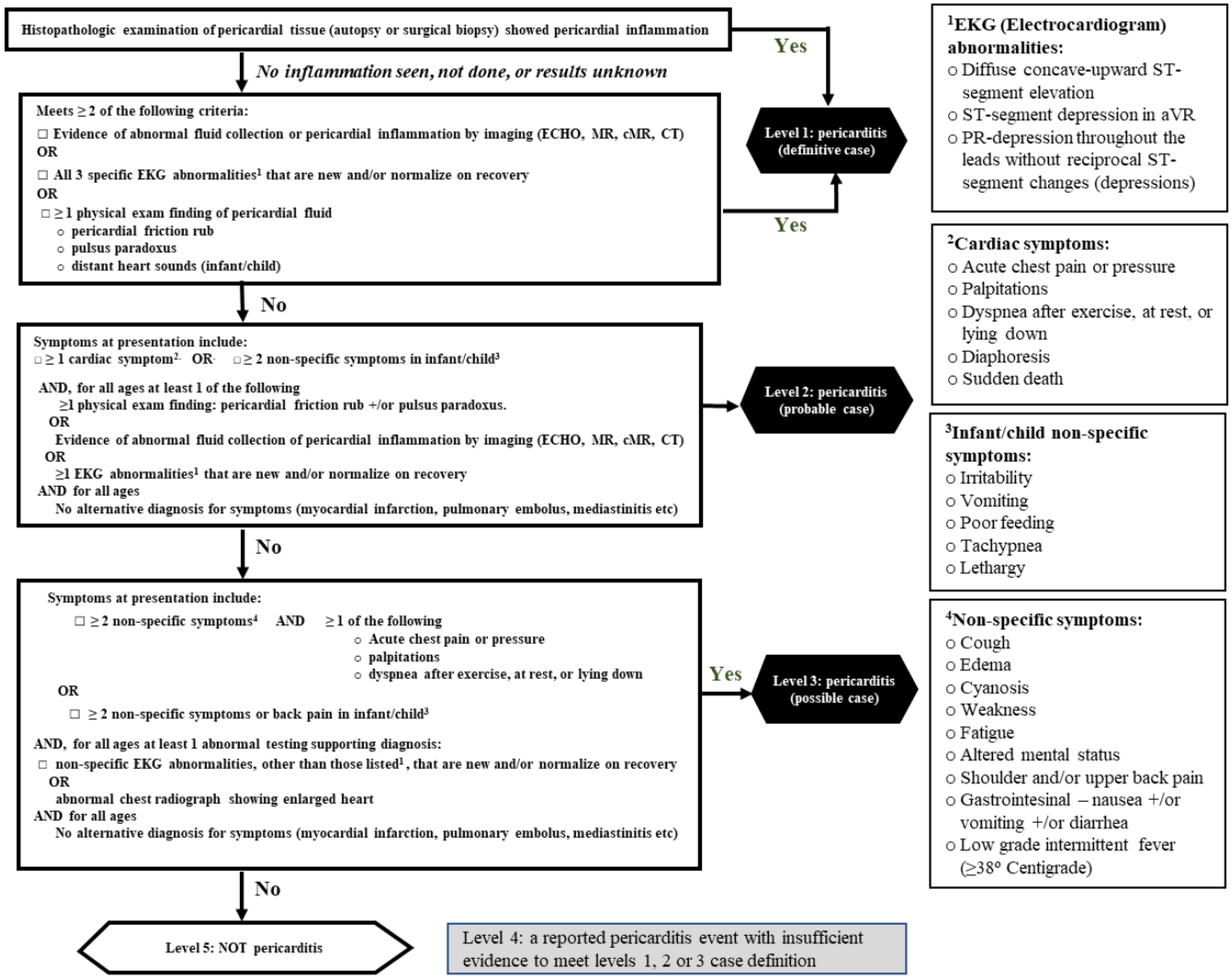
Continuous ambulatory electrocardiographic monitoring: To detect frequent atrial or ventricular ectopy

Echocardiogram abnormalities

Ventricular function abnormalities (right or left): Segmental wall motion abnormalities, global systolic or diastolic function depression/abnormality, ventricular dilation, wall thickness changes, pericardial effusion, and intracavitary thrombi. **Ejection fraction** (EF): Low <50%; Low Normal = 50-55%; Normal = >55% [**Note**: confirmed abnormality if it normalizes after recovery or was documented previously as higher] Include: Bedside or portable ultrasound documenting EF

Cardiac magnetic resonance abnormalities: Edema (T2-weighted), typically patchy in nature or late gadolinium enhancement (T1-weighted) with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-ischemic regional distribution with recovery (myocyte injury).

Appendix C Brighton Collaboration case definition and levels of diagnostic certainty for pericarditis



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Definitions related to acute symptoms

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Dyspnea: Shortness of breath at rest and/or with exercise.

Gastrointestinal: Nausea, indigestion, heartburn, or abdominal/stomach pain.

Diaphoresis: Cold sweats usually without fever

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Cough: Usually persistent ("won't quit") dry cough without sputum production

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Sudden death: Cardiogenic shock is clinical diagnosis rather than a symptom

Electrocardiogram findings

ST-segment or T wave (elevation or inversion): Note that in younger healthy populations early repolarization as a normal variant is frequently normal but it can be abnormal if it returns to normal rhythm or if there are time evolving changes (Courtesy of Dr. Atwood, Cardiology, Walter Reed National Military Medical Center).

Echocardiogram abnormalities

Presence of a pericardial effusion: Fluid collection in the pericardial sac surrounding the heart

Include: Bedside or portable ultrasound documenting presence or absence of fluid