REGIONE DEL VENETO
Azienda Ospedale Università Padova

European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/847176/2022

Agenda – Workshop on myocarditis post COVID-19 vaccination
16 January 2023 13.00 – 18:10 CET

800 1222 • 2022 ANNI

UNIVERSITÀ DEGLI STUDI DI PADOVA

Mechanisms of myocarditis post-COVID vaccination

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Nothing to disclose

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ESC REPORT

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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Myocarditis – *ESC 2013 Task Force diagnostic criteria*

Table 4 Diagnostic criteria for clinically suspected myocarditis

Clinical presentations[a]

- Acute chest pain, pericarditic, or pseudo-ischaemic
- New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
- Unexplained cardiogenic shock

Diagnostic criteria

I. ECG/Holter/stress test features

- Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

II. Myocardiocytolysis markers

- Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

- New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

- Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis – *ESC 2013 Task Force diagnostic criteria*

Clinically suspected Myocarditis in the presence of:

➔ **1 or more of the clinical presentations**

and

1 or more of the diagnostic criteria from different categories *

➔ **in asymptomatic patients at least 2 diagnostic criteria should be met**

*after exclusion of coronary heart disease, cardiac defect, congenital cardiac anomaly etc.

- Accuracy of CMR is low in biopsy-proven myocarditis with CHF/DCM or arrhythmia presentation

- CMR does not provide etiological diagnosis in myocarditis

Caforio A et al., Eur Heart J 2013;34:2636-2648

What is myocarditis?

- **Definition**

  Myocarditis is an inflammatory disease of the myocardium and is diagnosed by established histological, immunological and immunohistochemical criteria.

  (Circulation, 1995 WHO/ISFC classification; Eur Heart J, 1999; AHA statements 2006, 2016; ESC 2008, Eur Heart J 2013)

- **Histological features** (Dallas criteria on EMB)

- **Myocarditis forms**

  - *idiopathic,*

  - *infectious (mainly viral) and/or autoimmune*

Etiological forms of biopsy-proven myocarditis

Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (*Table 1*).

Autoimmune myocarditis

Histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies (aabs) (*Table 2*).

N.B. There are autoimmune diseases (e.g. Hashimoto's thyroiditis) where aabs are mainly biomarkers, autoantibody-mediated forms (e.g. Graves' disease), in which aabs are pathogenic, and cell-mediated autoimmune diseases, which are negative for aabs. In all cases, autoimmune diseases are negative for infectious agents.

Viral and immune myocarditis

Histological myocarditis with positive viral PCR and positive cardiac aabs (*Table 2*).

N.B. A follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac aabs, e.g. post-infectious autoimmune disease.

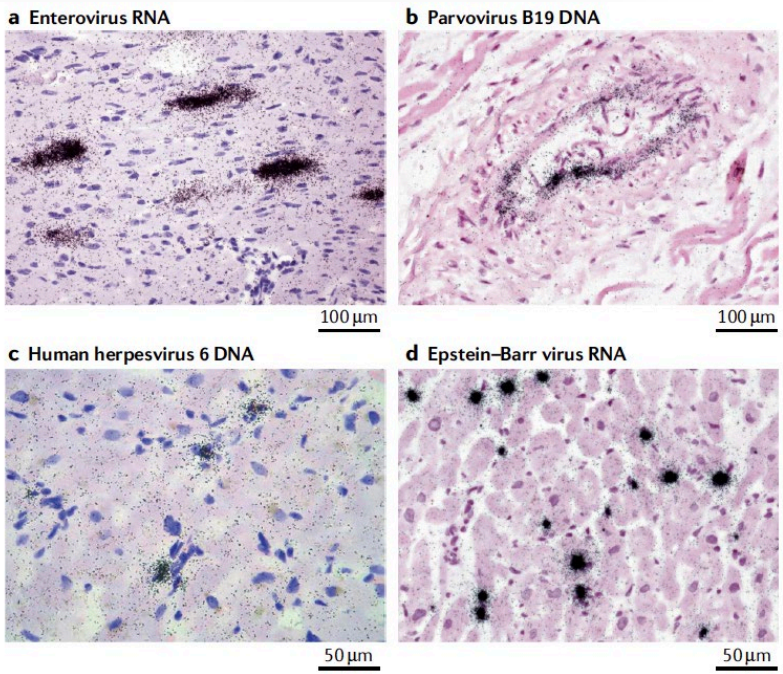

Fig. 4 | **Visualization of viral nucleic acids in acute myocarditis.** Viral nucleic acids in heart tissue samples from patients with acute myocarditis can be detected with radioactive in situ hybridization (black spots). Cell nuclei (purple) and cell cytoplasm and extracellular matrix (pink) are visualized with haematoxylin and eosin staining. Enteroviruses (panel **a**) infect and lyse cardiomyocytes, parvovirus B19 (panel **b**) infects endothelial cells, and human herpesviruses (panel **c**) and Epstein–Barr viruses (panel **d**) replicate in immune cells. Panels **a** and **b** ×400, panels **c** and **d** ×630.

Caforio et al. Eur Heart J 2013; 34:2636-48

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NON-COVID 19 myocarditis: facts

- **Myocarditis may be suspected by noninvasive cardiac imaging, including CMR, but diagnosis of certainty is based upon EMB.**

- **Etiologic diagnosis of infectious/viral vs immune-mediated/autoimmune myocarditis is based on EMB.**

Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis temporally associated with Sars-Cov2 infection or anti-Covid vaccine: diagnostic criteria

Case definition by the recommended classifications based on **Brighton Collaboration Myocarditis Case Definition** (Pandemic Emergency Response Process)

Definitive case (Level 1):

1. Histopathologic examination showing myocardial inflammation *(no mention to viral PCR).*

OR

2. Elevated troponin AND EITHER

a. cMRI with myocarditis specific changes

OR

b. Abnormal echocardiography. Evidence of focal or diffuse depressed left ventricle (LV) function identified by an imaging study, i.e. echocardiogr aphy, or that is documented to be of new onset or increased degree of severity. In the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow-up studies, these findings resolve, improve, or worsen.

Barda N, et al. N Engl J Med 2021; 385: 1078-90.
Mevorach, et al. N Engl J Med. 2021;385:2140–9.
Witberg G, et al. N Engl J Med. 2021;385:2132–9.
Ammirati et al, Circulation 2022, 45:1123–1139

Myocarditis temporally associated with Sars-Cov2 infection or anti-Covid vaccine: diagnostic criteria

Case definition by the recommended classifications based on Brighton Collaboration Myocarditis Case Definition (Pandemic Emergency Response Process)

Probable case (Level 2):

1. Clinical symptoms as for the possible case

AND

2. Any 1 of the following 3 findings

a. Elevated troponin I or T, or CPK MB

OR

b. Echocardiogram abnormalities

OR

c. EKG changes

Possible case (Level 3):

1. One of the following symptoms: dyspnea, or palpitations, or chest pain or pressure, or diaphoresis, or sudden death in a patient

OR

2. Two of the following symptoms: fatigue, gastrointestinal, dizziness or syncope, edema, or cough.

AND

3. Supportive laboratory biomarkers: elevated CRP, or elevated D-dimer, or elevated ESR

AND

4. Nonspecific EKG abnormalities: St-T or T waves changes, or premature complexes.

AND

5. The absence of evidence of any other likely cause of symptoms or findings

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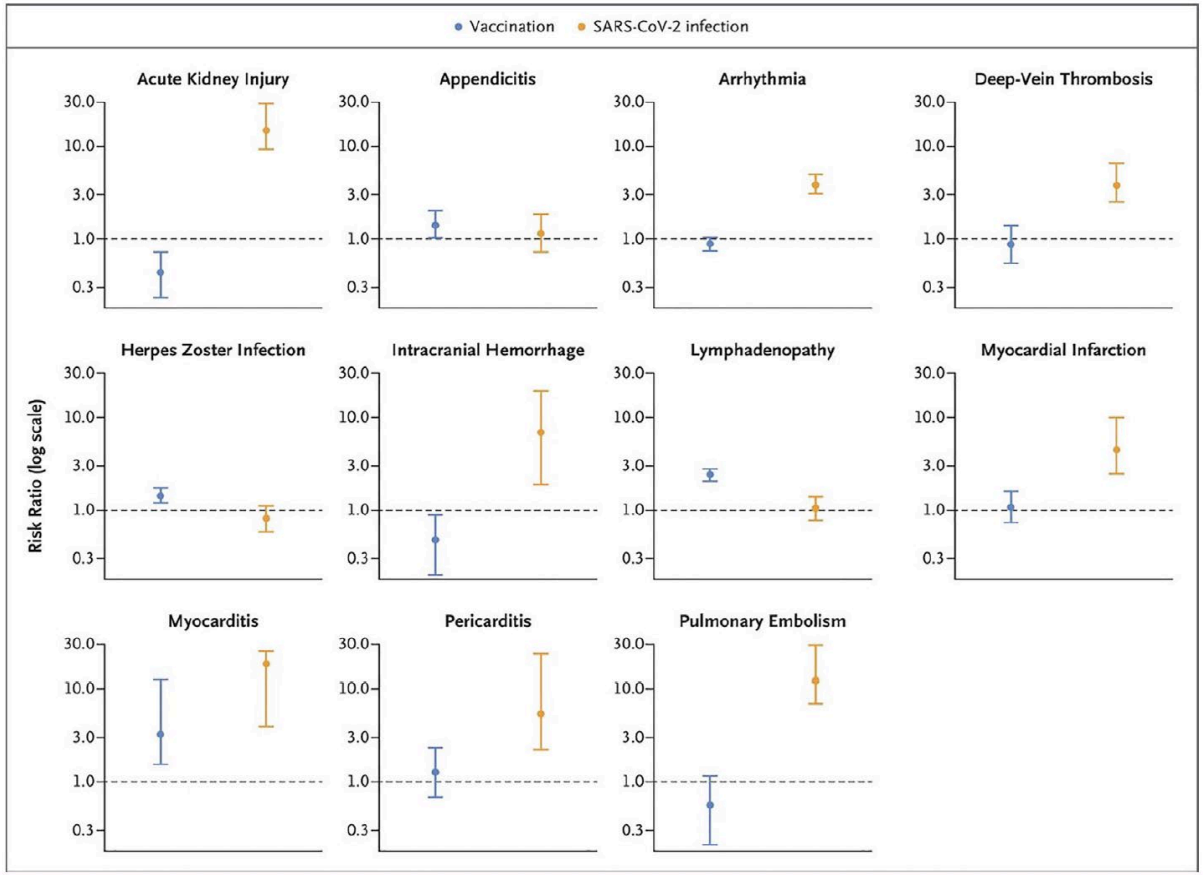

Figure 1 Risk of complications after COVID-19 vaccine versus with COVID-19 infection: data were obtained from a national study in Israel. Each cohort consisted of more than 800 000 individuals. Relative risk for developing myocarditis after vaccine was 3.2, while it is 18.3 after getting COVID-19. From Barda *et al.*[11]

Barda N, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021; 385: 1078-90.

Placing the risk of myopericarditis following COVID-19 vaccination into perspective

Giovanna Liuzzo [1,2]* **and Carlo Patrono** [3]

Key Points

- This systematic review and meta-analysis identified 22 studies published between 1947 and 2021 that evaluated the risk of myopericarditis after vaccination.[1] Half of these studies looked at coronavirus disease 2019 (COVID-19) vaccines, nine of them specifying the type of COVID-19 vaccine, and half at other vaccines (six studies reported on smallpox, two on influenza, and three on a variety of non-COVID-19 vaccines).
- The primary outcome was the incidence of myopericarditis after any vaccination; secondary outcomes included the incidence of myocarditis, pericarditis, and mortality after any vaccination. Given the heterogeneity in case reporting, myopericarditis was defined as an umbrella term describing myocarditis, pericarditis, or cases with features of both. The incidence of myopericarditis was analysed among pre-specified subpopulations.
- The overall incidence of myopericarditis (405 million vaccine doses) was 33.3 cases (95% confidence interval 15.3–72.6) per million vaccine doses. Among 395 million vaccine doses (high certainty of evidence by GRADE approach)—nearly 300 million mRNA vaccines—the risk of myopericarditis following COVID-19 vaccination was comparable with or lower than the risk following non-COVID-19 vaccinations (9 million doses, moderate certainty). The overall incidence of myopericarditis following COVID-19 vaccination was 18.2 (10.9–30.3) cases per million doses, compared with 56.0 (10.7–293.7) cases per million doses for non-COVID vaccinations ($P = 0.20$). The incidence of myopericarditis was significantly higher following smallpox vaccinations (132.1 [81.3–214.6], $P < 0.0001$ vs. COVID-19 vaccinations) but not significantly different after influenza (1.3 [0–884.1], $P = 0.43$) or various other vaccinations (57.0 [1.1–3036.6], $P = 0.58$).
- Risk factors for myopericarditis included being under the age of 30 (40.9 cases per million doses), being male (23 cases per million doses), receiving an mRNA vaccine (22.6 cases per million doses), and receiving a second dose of vaccine (31.1 cases per million doses)—compared with all COVID-19 vaccines in the general population (all $P < 0.01$).

1. Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, *et al.* Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *Lancet Respir Med* 2022. Online ahead of print.

Myocarditis temporally associated with anti-Sars-Cov2 mRNA vaccines

Limitations of current studies

- No reliable estimates on clinically-suspected myocarditis frequency in the population prior to COVID19 pandemia.

- No reliable baseline estimate to compare to the frequency of clinically suspected myocarditis temporally associated with anti-COVID19 mRNA vaccines, but epidemiological data suggest lower frequency compared to other non-COVID vaccines.

- Definition (CDC-Brighton) of myocarditis temporally associated with mRNA vaccines **DOES NOT INCLUDE EMB** as mandatory, thus it is **NOT POSSIBLE** to have a **diagnosis of certainty** and of its **etiology** (other viruses, immune-mediated?).

Hypothetical immunopathogenic mechanisms of myocarditis triggered by mRNA vaccination

- **INNATE IMMUNITY**: (IL-1 mediated, neutrophil, monocyte-macrophages infiltration).
- **ADAPTIVE IMMUNITY**:

  - Molecular mimicry between the spike proteins of Sars-Cov-2 and self antigens (Type II reaction*, *autoimmunity*)

  - Immune complexes (Type III reaction*, *serum sickness*)

  - Delayed hypersensitivity mechanisms (Type IV reaction*, *DRESS Sdr/eosinophilic myocarditis*)

***Immunologic mechanisms as defined by the Gell and Coombs classification system**

Lack of evidence of significant homology of SARS-CoV-2 spike sequences to myocarditis-associated antigens

Daniel Marrama,[a] *Jarjapu Mahita,*[a] *Alessandro Sette,*[a,b,1] *and Bjoern Peters,*[a,b,1]*

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Summary

Background COVID-19 mRNA vaccines have proven to be highly safe and effective. Myocarditis is an adverse event associated with mRNA vaccination, especially in young male subjects. These events are rare and, in the majority of cases, resolve quickly. As myocarditis can be driven by autoimmune responses, we wanted to determine if the SARS-CoV-2 spike protein antigen encoded in the mRNA COVID vaccines had potential cross-reactivity with auto-antigens previously associated with myocarditis.

Methods We performed a sequence identity comparison between SARS-CoV-2 spike protein-derived peptides and myocarditis-associated antigens. We also performed a structural analysis of these antigens and the SARS-CoV-2 spike protein to identify potential discontinuous 3-D epitope similarities.

Findings We found no significant enrichment in the frequency of spike-derived peptides similar to myocarditis-associated antigens as compared to several controls.

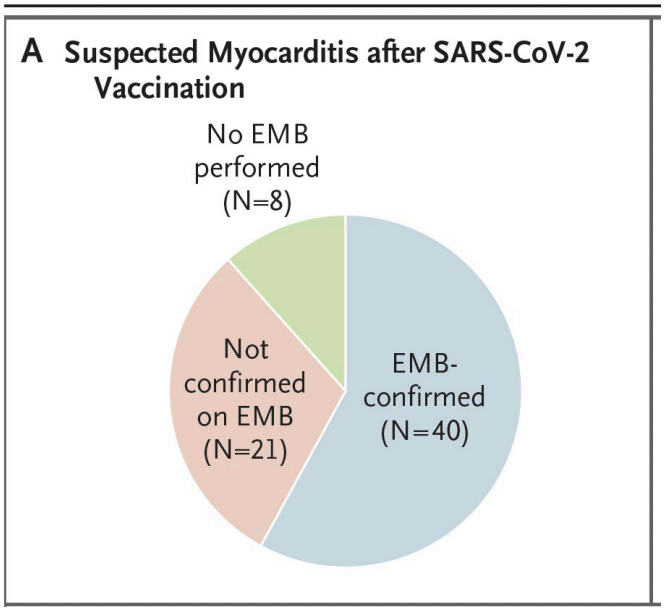
Interpretation Our results do not support the notion that increased occurrence of myocarditis after SARS-CoV-2-spike vaccination is mediated by a cross-reactive adaptive immune response.

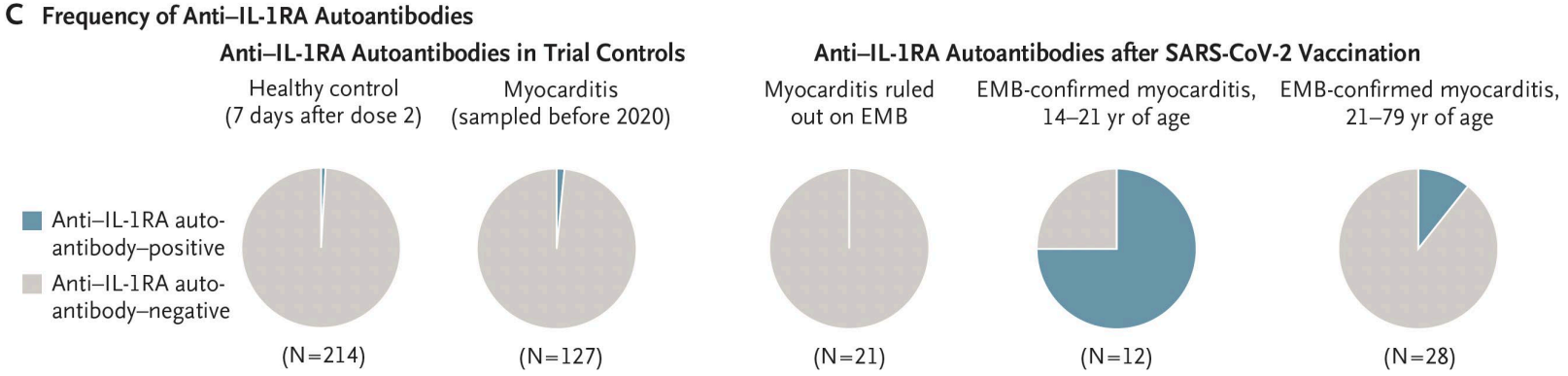
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination

- PCR for cardiotropic viruses: 7 patients(17%) (EBV, HHV6, PVB19 positive on EMB)
- Anti-IL-1 RA autoantibodies, mainly in young males





Hypothetical immunopathogenic mechanisms of myocarditis triggered by mRNA vaccination

- **INNATE IMMUNITY:** (IL-1 mediated, neutrophil, monocyte- macrophages infiltration):
  - No predominance of neutrophil/macrophagic infiltration on EMB .
  - AutoAb-mediated disinhibition of innate immunity (anti IL1-RA Ab)?

- **ADAPTIVE IMMUNITY:**
  - Molecular mimicry between the spike proteins of Sars-Cov-2 and self antigens (Type II reaction*, *autoimmunity*):
    - ruled out
  - Immune complexes (Type III reaction*, *serum sickness*):
    - absence of systemic involvement
  - Delayed hypersensitivity mechanisms (Type IV reaction*, *DRESS sdr/eosinophilic myocarditis*):
    - myocarditis is anecdotic,
    - absence of systemic involvement

*Immunologic mechanisms as defined by the Gell and Coombs classification

Prospective myocarditis and pericarditis Registry, **CARDIOIMMUNOLOGY, PADOVA**

Myocarditis **about 1000 patients on active FU**

Pericarditis **on avarage, 250 patients on active FU**

Biopsy-proven Myocarditis temporally associated to:

SARS-CoV-2 infection:	proven	0
	suspected	0
mRNA anti-COVID vaccines	proven	0
	suspected	0

(submitted)

Summary

- Myocarditis temporally related with mRNA anti-COVID19 vaccines:
  - very rare, self-limited, mainly in young males
  - temporal association does not imply causation
  - viral or new-onset immune-mediated or latent pre existing autoimmune forms, triggered or fostered by anti-COVID19 mRNA vaccines?

Caforio A. NEJM 2021; 385:2189-90

Conclusions

Endomyocardial biopsy (histology/immunohistology/molecular infection pathology) **is key** for:

1) definite **diagnosis**,

2) differential **diagnosis**,

3) etiological **diagnosis** of myocarditis,

4) **identification of possible pathogenic mechanisms** also in patients with Sars-CoV-2 infection and in patients following SARS-CoV-2 mRNA vaccination.

Caforio A. NEJM 2021; 385:2189-90

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Associazione Malattie Infiammatorie Cardiovascolari

The Padua Cardioimmunology Team

"There are three phases to treatment: diagnosis, diagnosis and diagnosis."

William Osler. Principles and Practice of Medicine, 1892