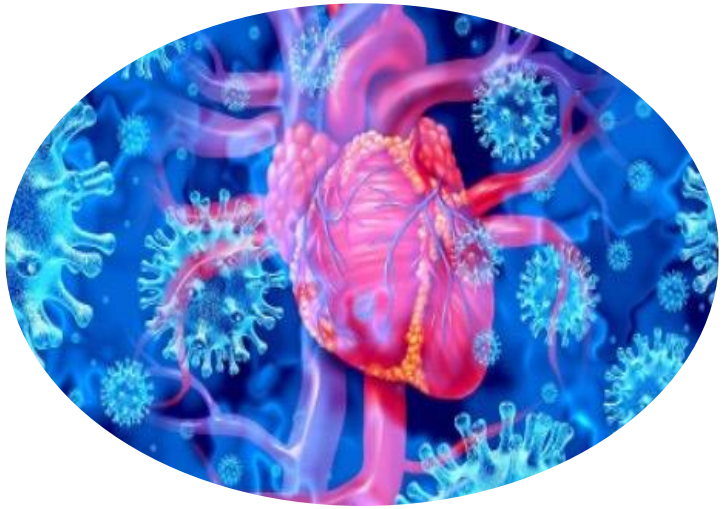
MYOCARDITE



Journée régionale du DES MIR

MODULE INFECTIEUX – INFECTIONS COMMUNAUTAIRES

Lara JOSLOVE (5ÈME SEMESTRE DES MIR)

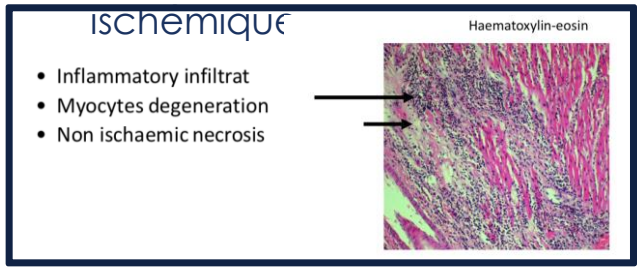
MYOCARDITE – MODULE INFECTIEUX

- Myocardite : définition, épidémiologie
- Etiologies des myocardites
- Focus sur les myocardites d'origine infectieuse
- Stratégie diagnostique
- Prise en charge initiale d'une myocardite aigüe
- Myocardite virale : des traitements spécifiques ?
- Pronostic et suivi

GÉNÉRALITÉS : MYOCARDITE

DÉFINITION

- Atteinte inflammatoire du muscle cardiaque
- Histologique, Immunologique, Immunohistochimique
  - Infiltrat inflammatoire
  - Nécrose myocytaire non ischémique



EPIDIEMIOLOGIE

- Incidence ≈ 22/100000 patients/an
  - ↗ lors des épidémies virales
- 2ème cause cardiaque de douleur thoracique (3%) aux urgences
- 33% des IDM à coronaires non obstruées sont des myocardites
- Séries autopsiques – prévalence :
  - Morts subites + jeunes : 6-10%
  - Tout venant : 1 – 3,5%
- Prévalence 10% sur biopsie pour cardiomyopathie dilatée non ischémique
- Sex-ratio myocardite aïgue : 6 pour 1 ♂

CLASSIFICATION CLINIQUE

- **Myocardite fulminante**
- **Myocardite aiguë/subaïgue**
- Myocardite chronique active
- Myocardite chronique persistante

Aretz et al, The Dallas Criteria, Human Pathology, 1987
WHO/ISFC. Circulation. 1996;93:841-842
Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. Eur Heart J. 2013 Sep; 34(33):2636-48.)
Charpentier S, et al Management of chest pain in the French emergency healthcare system: the prospective observational EPI- DOULTHO study. *Eur J Emerg Med*. 2018;25:404–410.
Pasupathy S, et al, Systematic review of patients presenting with suspected myocardial infarction and non- obstructive coronary arteries. *Circulation*. 2015;131:861–870.
Ammirati E et al, Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. Circ Heart Fail. 2020 Nov;13(11):e007405.

ETIOLOGIES

Dysfonction VG du sepsis ?

Table 1 Causes of myocarditis/inflammatory cardiomyopathy

1. Infectious myocarditis	
Bacterial	*Staphylococcus, Streptococcus, Pneumococcus, Meningococcus, Gonococcus, Salmonella, Corynebacterium diphtheriae, Haemophilus influenzae, Mycobacterium* (tuberculosis), *Mycoplasma pneumoniae, Brucella*
Spirochaetal	*Borrelia* (Lyme disease), *Leptospira* (Weil disease)
Fungal	*Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporothrix*
Protozoal	*Trypanosoma cruzi, Toxoplasma gondii, Entamoeba, Leishmania*
Parasitic	*Trichinella spiralis, Echinococcus granulosus, Taenia solium*
Rickettsial	*Coxiella burnetii* (Q fever), *R. rickettsii* (Rocky Mountain spotted fever), *R. tsutsugamuschi*
Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
2. Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)
3. Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)
Miscellaneous	Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Phaeochromocytoma, vitamins: beri–beri
Physical agents	Radiation, electric shock

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. Eur Heart J. 2013 Sep; 34(33):2636-48.)

ETIOLOGIES - INFECTIEUX

Table I Causes of myocarditis/inflammatory cardiomyopathy

1. Infectious myocarditis

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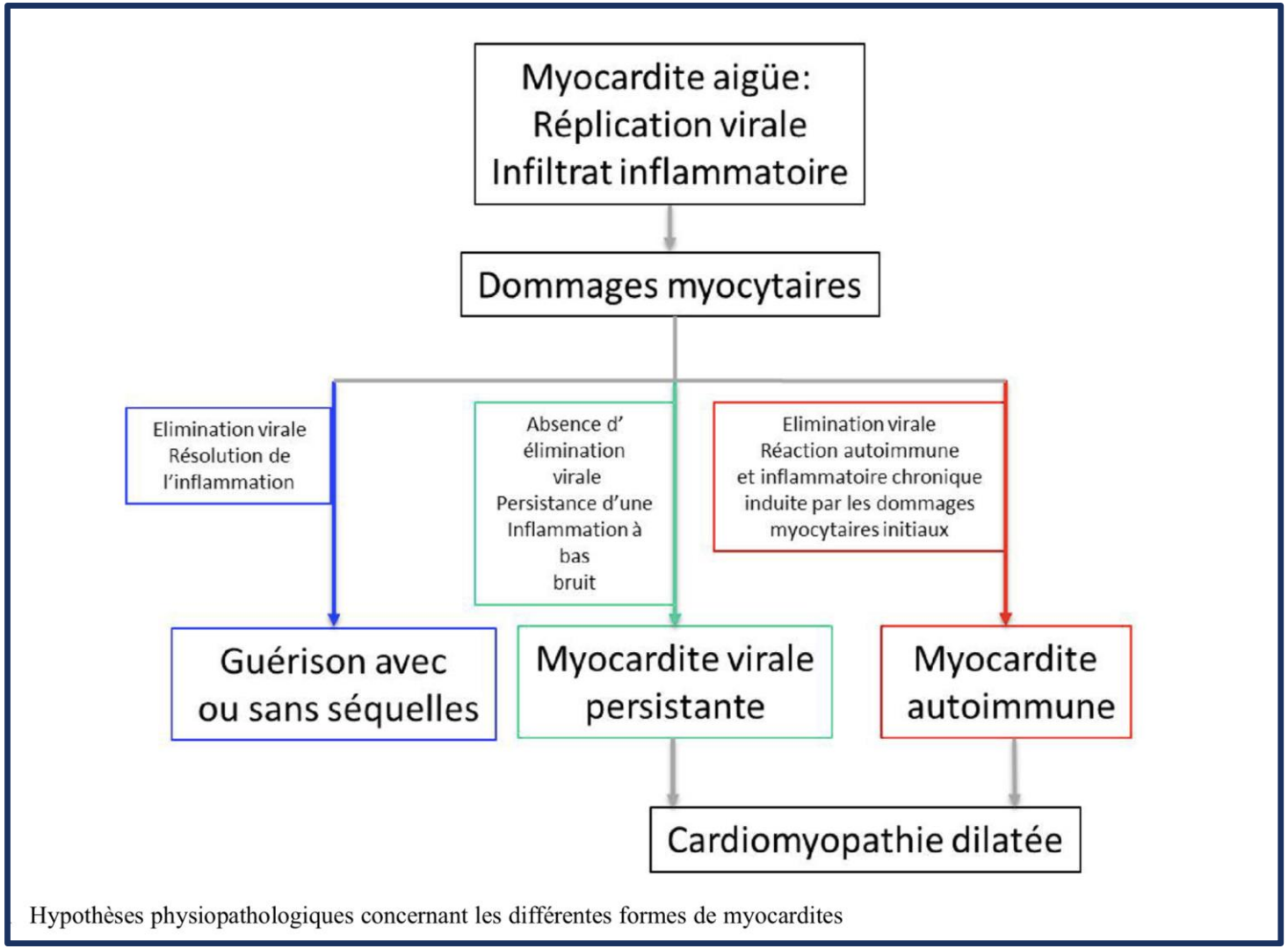
Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. Eur Heart J. 2013 Sep; 34(33):2636-48.)

MYOCARDITE VIRALE

- La + fréquente
- *Enterovirus* +++
- Plusieurs phases évolutives



Hypothèses physiopathologiques concernant les différentes formes de myocardites

G. Hékimian et al, Diagnosis and Management of Myocarditis, Méd. Intensive Réa (2017) 26:196-206

MYOCARDITES INFECTIEUSES NON VIRALES

- Bactériennes
  - Mécanisme direct (salmonelloses, gangrène gazeuse, méningococcies, tuberculose, borréliose…)
  - Mécanisme indirect : toxiques (fièvre typhoïde - endotoxine ou la diphtérie - exotoxine).
  - (Par contiguité, endocardites avec microabcès endomyocardiques

- Parasitaires:
  - *Trypanosoma cruzi*
  - *Toxoplasma gondii*

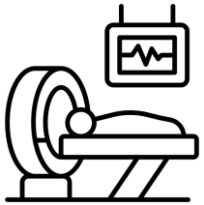
- Fongiques : exceptionnelles

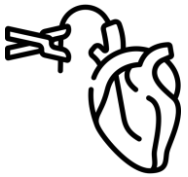
DIAGNOSTIC

- Clinique évocatrice :
  - Douleur thoracique, dyspnée, syncope
  - Signes associés
- ECG, troponine +
- ETT

- ELIMINER UNE ORIGINE CORONAIRE

- Caractériser les anomalies tissulaires
  - IRM
  - Biopsie endomyocardique





DIAGNOSTIC

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.

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. Eur Heart J. 2013 Sep; 34(33):2636-48.)

DIAGNOSTIC

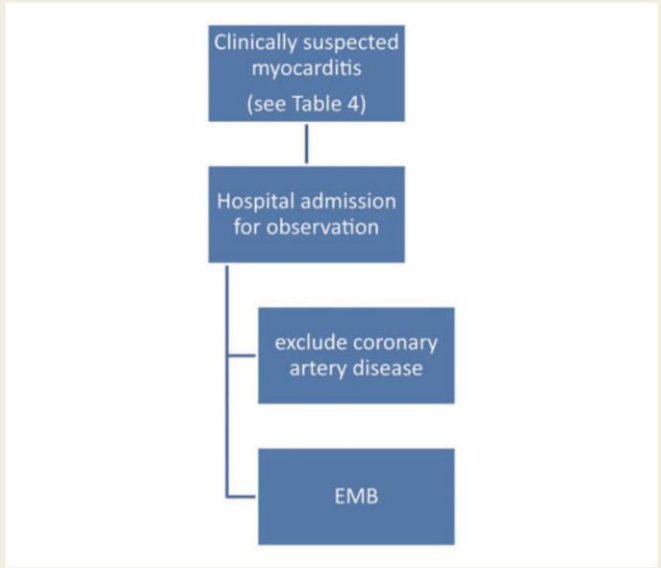
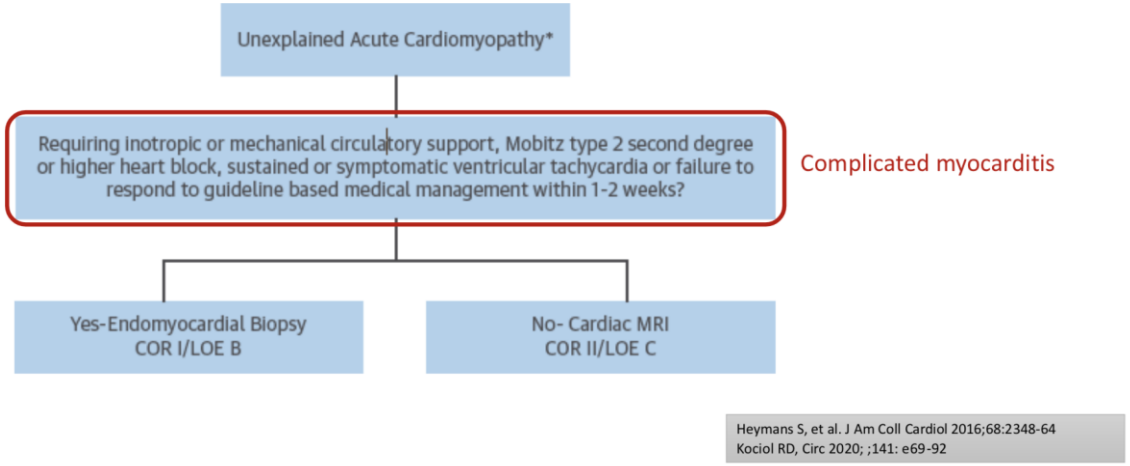


Figure 3 The flow chart shows the proposed diagnostic approach for patients with clinically suspected myocarditis according to *Table 4*.

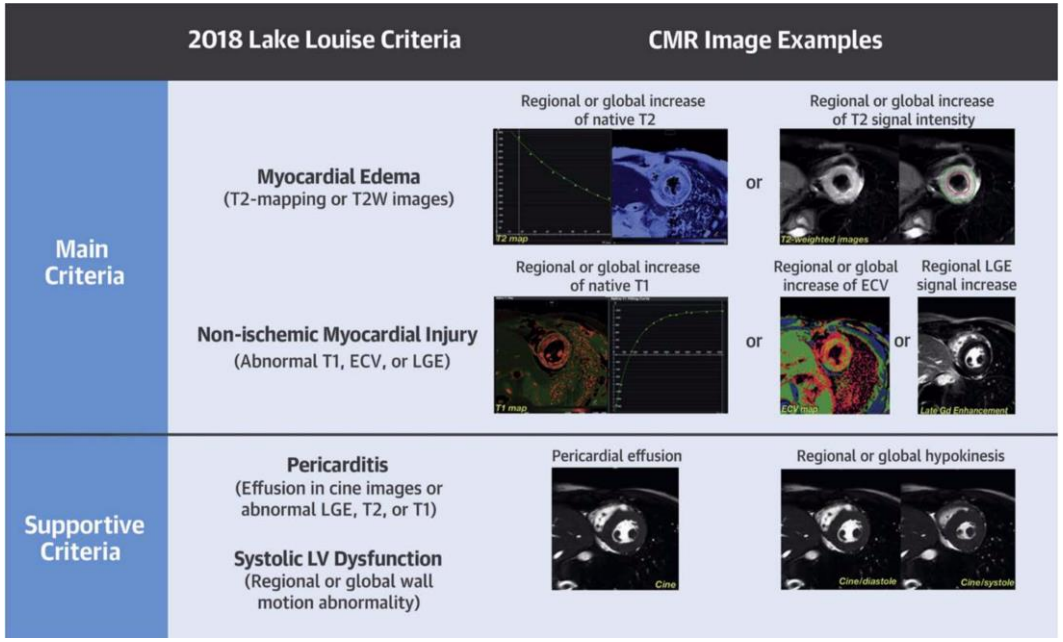


Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. Eur Heart J. 2013 Sep; 34(33):2636-48.)

STRATÉGIE DIAGNOSTIQUE

IRM cardiaque

- Œdème myocardique, lésions non



Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72(24):3158-76.

Biopsie endomyocardique

- >4 échantillons
- - de complications si centre expert
- Histologie (critères de Dallas), immunohistochimie, PCR

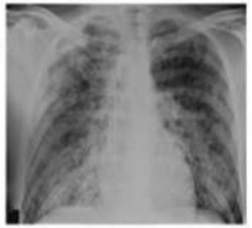
→ Permet un diagnostic étiologique plus précis

SUSPECTED INFLAMMATORY MYOCARDIAL DISEASE

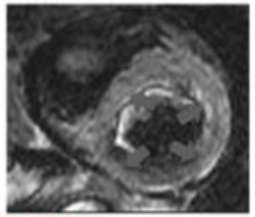
ACUTE STIMULI

ACUTE MYOCARDITIS

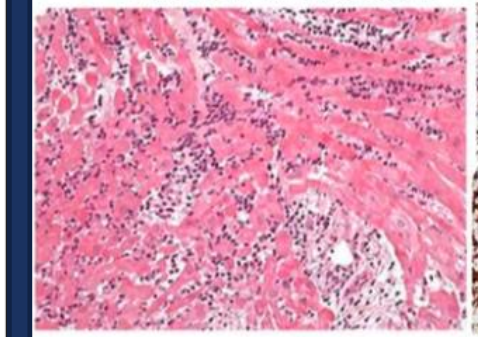
- Onset of symptoms < 30d
- Potential fulminant presentation, need for hemodynamic support
- Release of cardiac biomarkers: +++

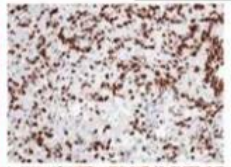


- LV size: normal or mildly dilated
- Wall thickness: +/++
- Signs of edema at CMRI sequences: ++

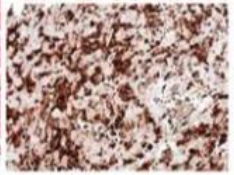


- Inflammatory infiltrate: +++
- Fibrosis: +/- and necrosis: ++





T-cells



Macrophages

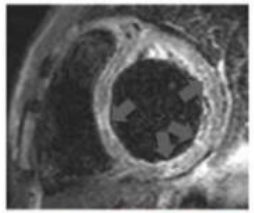
Acute Diffuse Lymphocytic Myocarditis

PERSISTENT STIMULI

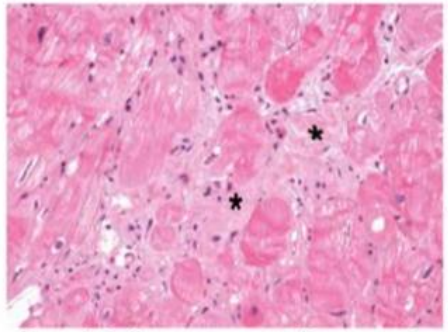
GENETIC PREDISPOSITION

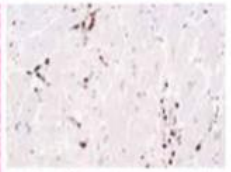
CHRONIC INFLAMMATORY CARDIOMYOPATHY

- Onset of symptoms > 30d
- Often presenting with HF symptoms
- Release of cardiac biomarkers: +/-



- LV size: dilated
- Wall thickness: often normal
- Signs of edema at CMRI sequences: +/-
- Inflammatory infiltrate: +/-
- Fibrosis, ++; necrosis - and myocyte abnormalities ++





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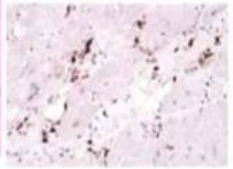


Macrophages

Chronic Inflammatory cardiomyopathy

Ammirati E et al, Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. Circ Heart Fail. 2020 Nov;13(11):e007405.

BIOLOGIE

Quel bilan biologique ?

Formule sanguine : éosinophiles
Myocardite à éosinophiles
Haptoglobine, LDH, schizocytes
Microangiopathie thrombotique
Recherche d'anticoagulant circulant lupique
Syndrome des anticorps antiphospholipides
Laboratoire de biochimie

EPP, calcémie, ECA
Sarcoïdose
Triglycéride, ferritine dont fraction glycosylée
Maladie de Still de l'adulte
TSH, T3L, T4L
Hypothyroïdie, hyperthyroïdie
Catécholamines sanguines et urinaires
Phéochromocytome
Laboratoire de microbiologie

Hémocultures
Cardiomyopathie septique

Anticorps anti-nucléaires (ANA, FAN)
Toute maladie auto-immune systémique
Anti-ENA
Permet le « sous-typage » des maladies auto-immunes systémique
Anti-ADN, anti-nucléosome
Lupus systémique
Anticorps des sclérodermie (dot-sclérodermie)
Sclérodermie systémique, myocardites associées aux anti-RNApol3
Anti-centromères
Sclérodermie systémique
Anticorps des myosites (dot-myosite)
Myosites inflammatoires
Anti-CCP
Polyarthrite rhumatoïde
Facteur rhumatoïde
Polyarthrite rhumatoïde, Sjogrën ou cryoglobulinémie
Recherche de cryoglobulinémie
Cryoglobulinémie
Anti-cardiolipine et anti-B2GP1 (IgG/IgM)
Syndrome des anticorps antiphospholipides
ANCA (PR3/MPO)
Vascularites associées aux ANCA

PCR multiplex (nez, pharynx, voies aériennes)
Virus respiratoires : SARS-CoV-2, grippe A et B, adénovirus
Bactéries respiratoires : légionellose, chlamydia et mycoplasme

Sérologies et PCR
Virus : SARS-CoV-2, herpes-virus (EBV, CMV, HSV1-2, VZV), parvovirus B19, VIH, hépatites (A, B, C, E)
Parasites : toxoplasmose, Maladie de Chagas (Trypanozoma cruzi)
Bactérie : leptospirose (PCR sang et urine)
Sérologies uniquement
Virus : HTLV1-2
Bactéries : Bartonelle, légionellose, mycoplasme et chlamydia pneumoniae, coxiella burnetii, brucellose, syphilis, maladie de Lyme
PCR uniquement
Virus : enterovirus, HHV-6, HHV-8, Whipple (sang, selles, salive)

Appel Genetique si Récidive

Diapo : Dr Pineton de Chambrun

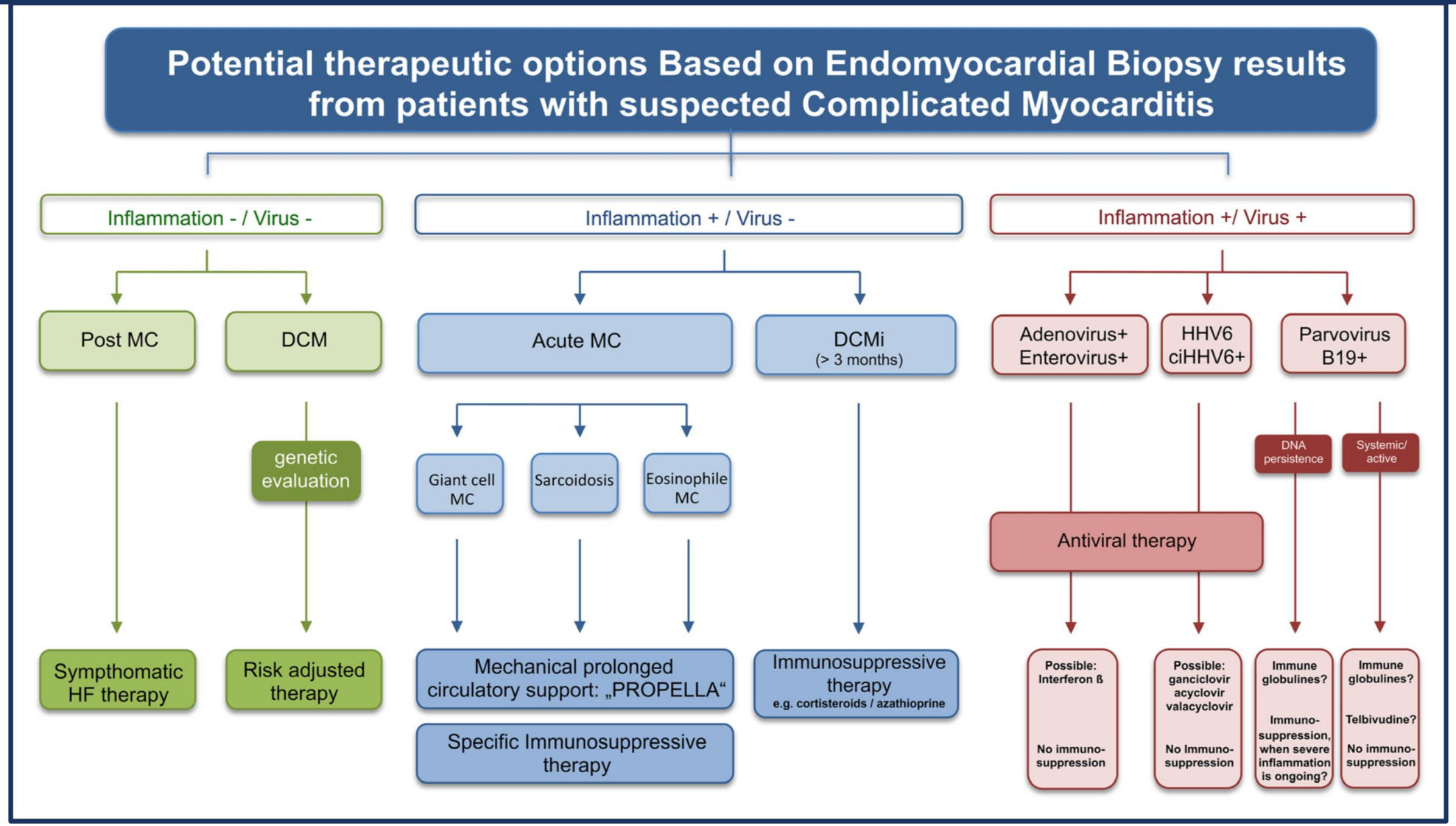
PRISE EN CHARGE

- Traitement symptomatique (catécholamines, diurétiques…)
- Si choc cardiogénique, rapprochement d'un centre d'assistance (avant défaillance multiviscérale)

  en *bridge to recovery*

- Si cause reconnue et curable, traitement spécifique précoce (antibiotique, antifongique, antiviral)
- Après la phase aigue, traitement de l'insuffisance cardiaque

PRISE EN CHARGE SPÉCIFIQUE



Tschöpe C et al, Management of Myocarditis-Related Cardiomyopathy in Adults, (Circ Res. 2019;124:1568-1583.

MYOCARDITE AIGUE VIRALE

- **Corticothérapie** (Bolus puis entretien) non efficace et aggrave le pronostic dans des études anciennes

  … mais mis en pratique si dysfonction VG qui s'aggrave

- **IgIV** : au cas par cas…
- PHRC CORIUM : Corticoïdes ou corticoïdes associés aux immunoglobulines dans le traitement de la myocardite fulminante: un essai randomisé adaptatif en double aveugle.
  - comparer un traitement par bolus de corticoïde + immunoglobulines vs corticoïde seul vs placebo
  - 120 patients au sein de 14 services de réanimation ou unités de soins intensif de cardiologie
  - sur une période maximale de 4 ans.
  - Le critère de jugement principal sera un critère hiérarchique composite incluant la mortalité ou transplantation cardiaque à J28 et le nombre de jours vivants sans assistance extracorporelle et sans inotrope à J28.

Tomioka N., et al C. Effects of prednisolone on acute viral myocarditis in mice. J Am Coll Cardiol. 1986;
Frishman W.H et al . Innovative drug treatments for viral and autoimmune myocarditis. Heart Dis. 2002
https://sante.sorbonne-universite.fr/actualites/presentation-des-programmes-de-recherche-lies-la-faculte-de-medecine-sorbonne-universite

INTERFERON BETA

- Myocardite « chronique » : 6 mois d'évolution
- Phase 2, 143 patients, insuffisance cardiaque, biopsie avec PCR virale + (enterovirus, adenovirus, parvovirus B19)
- randomisés en 3 groupes (placebo, 4 Mio IU IFNβ, 8 Mio IU IFNβ)

Table 5 Analyses of binary efficacy parameters, treatment effects

Response variable	Treatment effect	
	Odds ratio IFN-β-1b vs. Placebo (adjusted for strata)	*p* (two-sided)
Overall response (virus elimination, primary)	**2.33**	**0.0487**
NYHA improvement		
Week 0–12	**3.19**	**0.013**
Week 0–24	2.08	0.073

Differences were considered to be statistically significant at a value of <0.05 (bold values)

Heinz-Peter Schultheiss et al, Betaferon in chronic viral cardiomyopathy (BICC) trial: Effects of interferon-b treatment in patien, ts with chronic viral cardiomyopathy, Clin Res Cardiol 2016

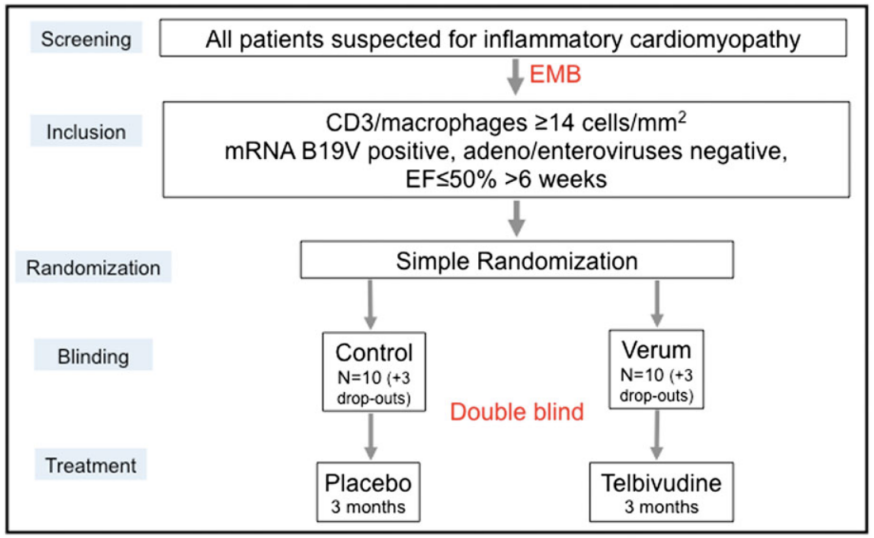
TELBIVUDINE

ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 818–830
Published online 11 August 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12341

ORIGINAL RESEARCH ARTICLE

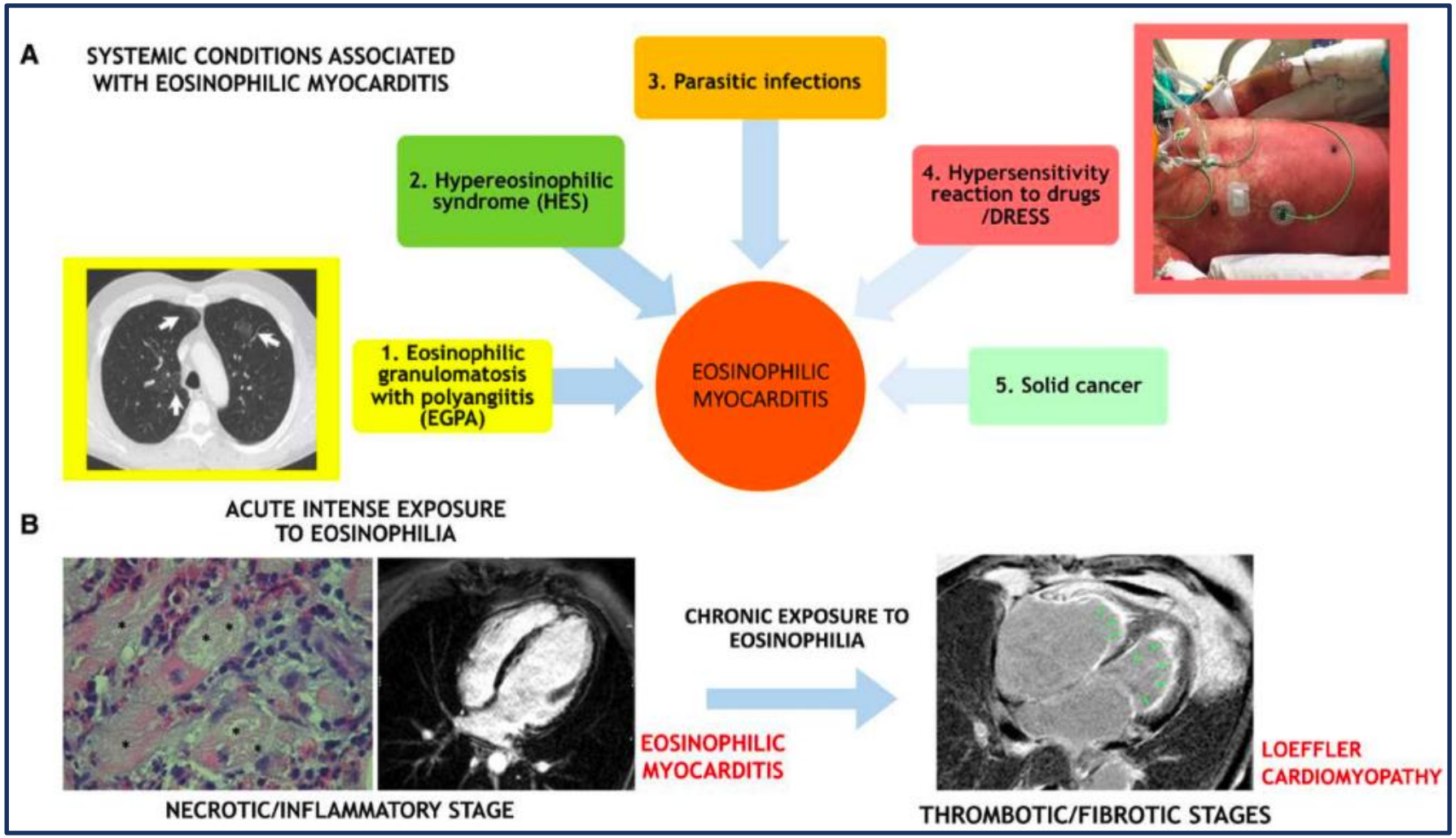
Telbivudine in chronic lymphocytic myocarditis and human parvovirus B19 transcriptional activity

Sophie Van Linthout[1,2†], Ahmed Elsanhoury[1†], Oliver Klein[1], Marzena Sosnowski[1], Kapka Miteva[1], Dirk Lassner[3], Mohamed Abou-El-Enein[1], Burkert Pieske[2], Uwe Kühl[2†] and Carsten Tschöpe[1,2*†]



Van Linthout S, et al Telbivudine in chronic lymphocytic myocarditis and human parvovirus B19 transcriptional activity. ESC Heart Fail. 2018 Oct;5(5):818-829.

MYOCARDITE ÉOSINOPHILIQUE



Ammirati E et al, Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. Circ Heart Fail. 2020 Nov;13(11):e007405.

MYOCARDITE AIGUE : PRONOSTIC, SUIVI

PRONOSTIC

- Mortalité : 15-20% à 5-10 ans
- Facteurs pronostiques :
  - Présentation clinique
  - Réhaussement tardif (après injection) en IRM
  - Histologie
  - Co-infections
- Facteurs de récupérations incomplète :
  - Stade dyspnée NYHA, âge, NtproBNP, FEVG
- Récurrences :
  - 10% dans les 10 ans
  - Surtout la première année

SUIVI

- CI sport pendant 6 mois +++
- Réévaluation à 6 mois :
  - ETT
  - IRM
  - ETT d'effort à 6 mois
- Arrêt du traitement bétabloquant/IEC si tout est normalisé

Anzini *et al.* Circulation. 2013 Nov 26;128(22):2384-94
Kindermann *et al.* Circulation. 2008;118:639–648
Ammirati *et al.* Circulation. 2017;136:529–545
Ammirati *et al.* J Am Coll Cardiol. 2019 Jul 23;74(3):299-311
Grün *et al.* J Am Coll Cardiol. 2012 May 1;59(18):1604-15
Caforio *et al.* European Heart Journal (2007) 28, 1326–1333
V. Kytö *et al.* European Journal of Internal Medicine 25 (2014) 946–950

MYOCARDITE – *MODULE INFECTIEUX*

Circulation: Heart Failure

ADVANCES IN HEART FAILURE

Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

An Expert Consensus Document

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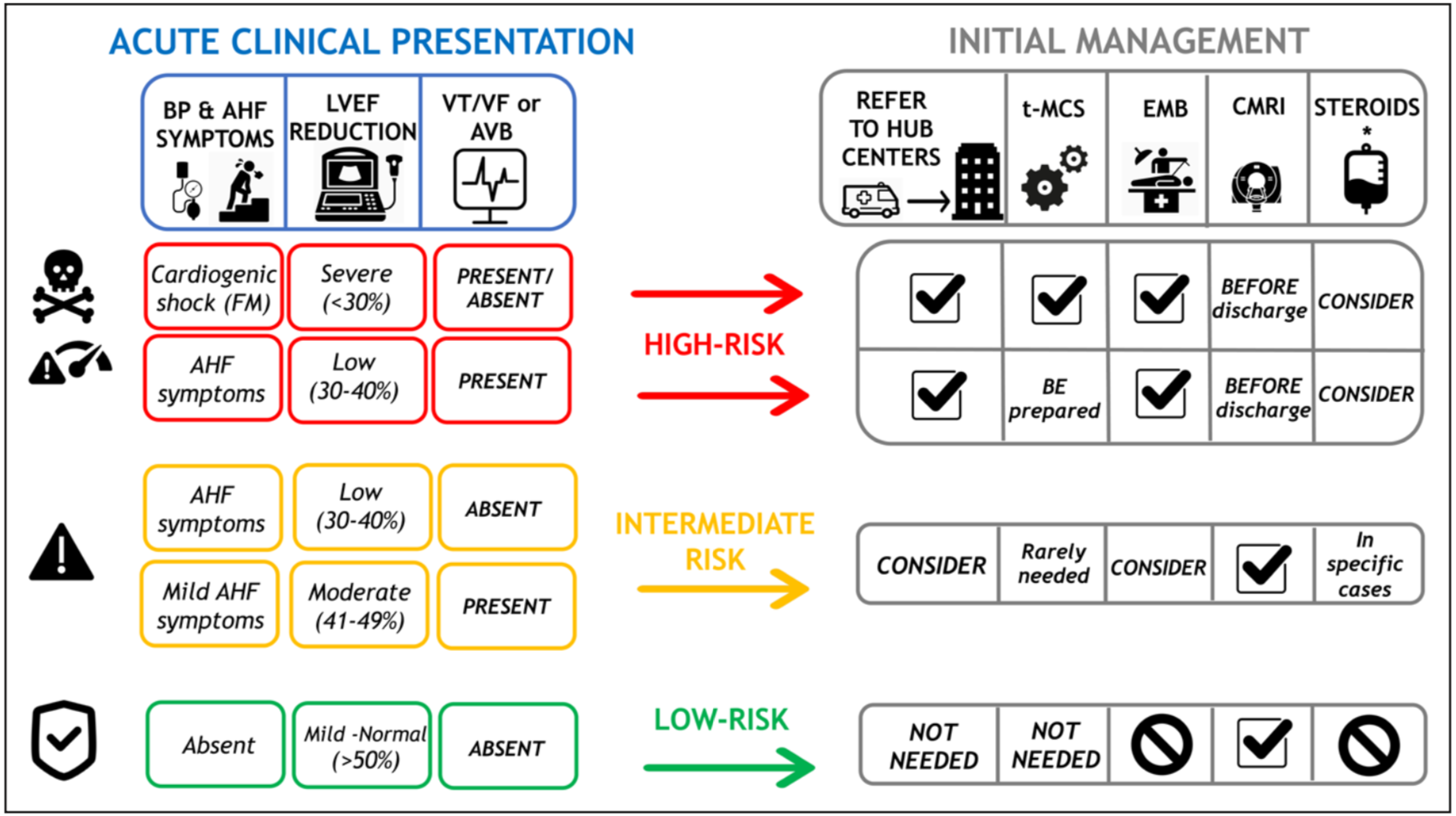
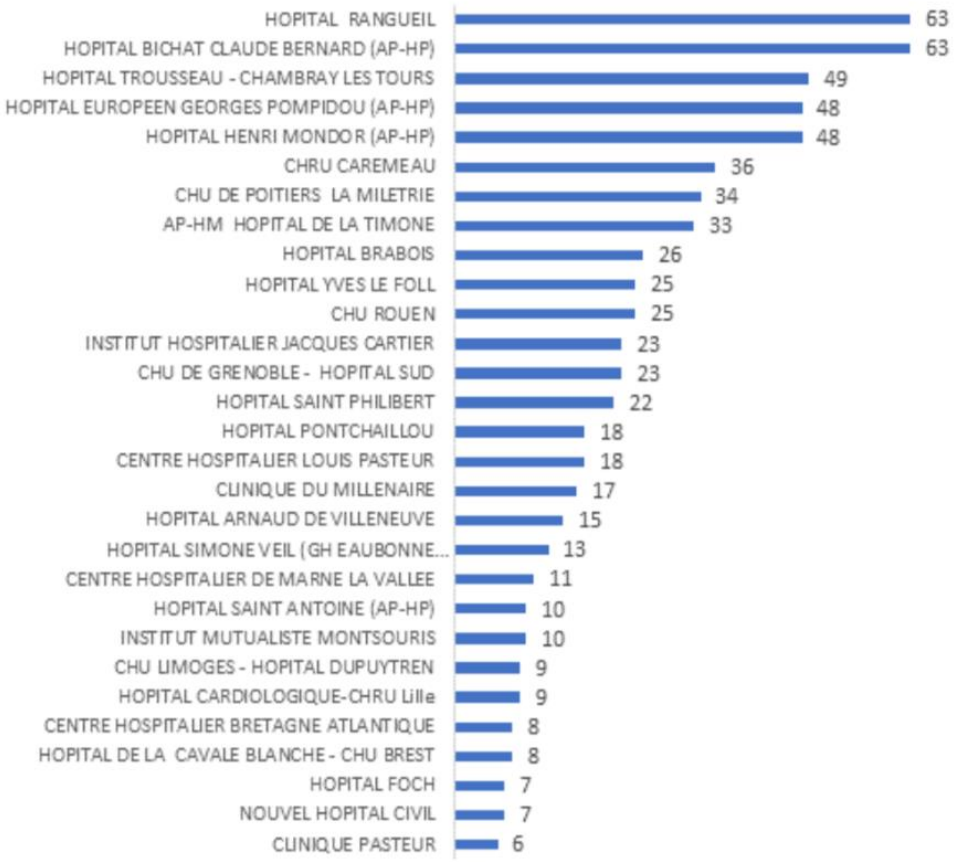


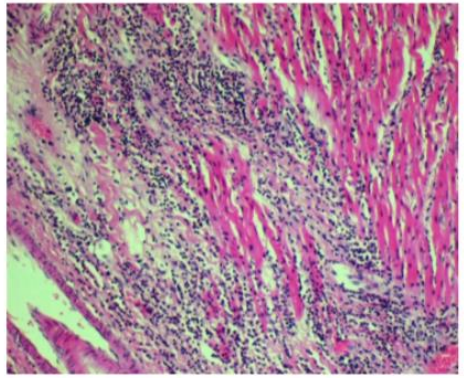
Merci de votre attention

MyocarditIRM registry



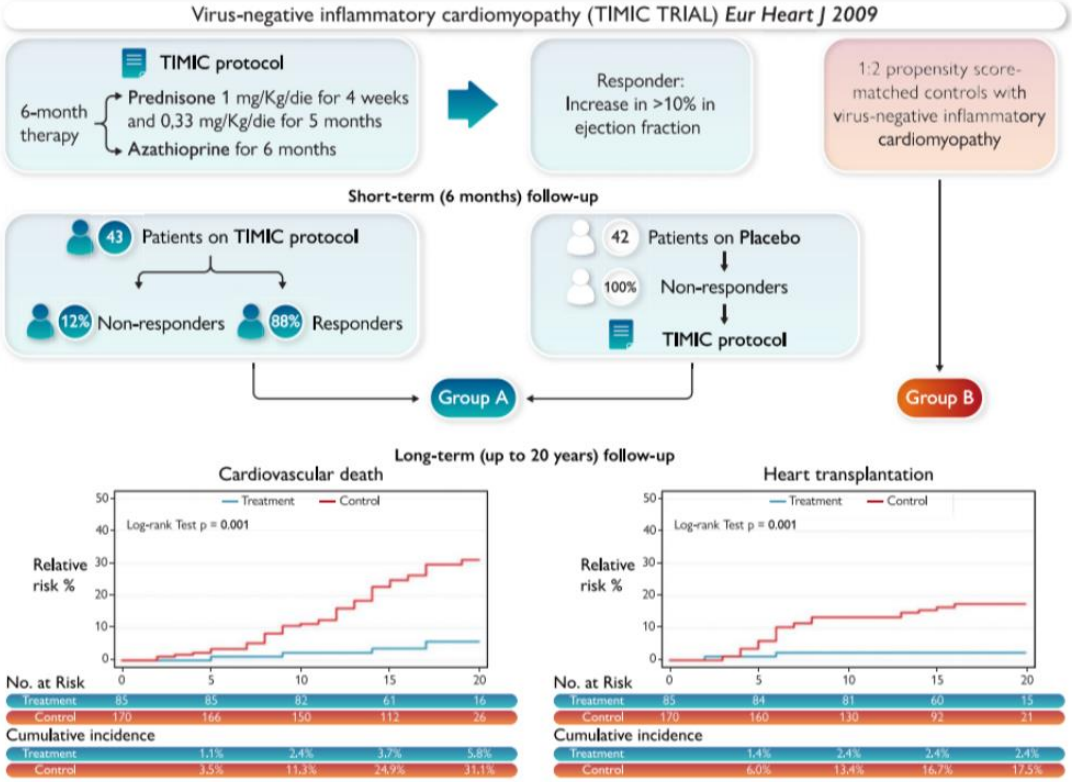
808 patients with acute viral myocarditis included in 2016-2019
In 52 French centers (ICCU)

EMB in 13 patients (1.6%)



Diagnosis of acute myocarditis

3. Benefits of a specific treatment in myocarditis with virus negative EMB



Frustaci et al, EHJ.2009.30;16:1995–2002

Chimenti et al EHJ (2022) 43, 3463–3473

2018 Lake Louise Criteria

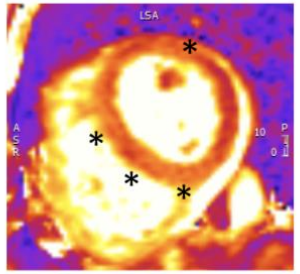
A) BASELINE

B) FOLLOW UP at 4 months

MAIN CRITERIA

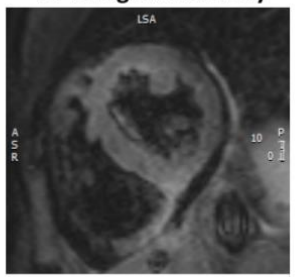
Myocardial Edema
(REGIONAL or GLOBAL T2-mapping or T2W images)

Global increase of **native T2**



T2 map 62ms -increased

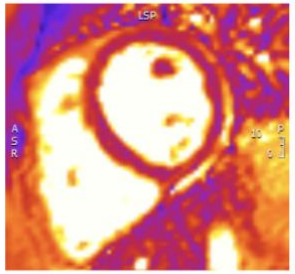
Global increase of **T2 signal intensity**



S.I. ratio 2.4 (n.v.<2)

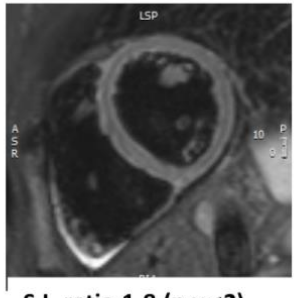
CMR FINDINGS SUPPORTING THE DIAGNOSIS OF ACUTE MYOCARDITIS

Normal **native T2**



T2 map 49ms - normal

Normal **T2 signal intensity**

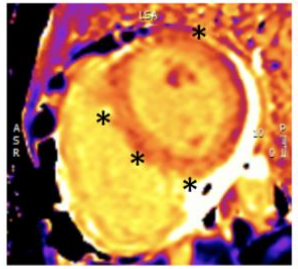


S.I. ratio 1.8 (n.v.<2)

CMR FINDINGS SUPPORTING THE COMPLETE RESOLUTION OF MYOCARDITIS WITH MINIMAL RESIDUAL FIBROSIS

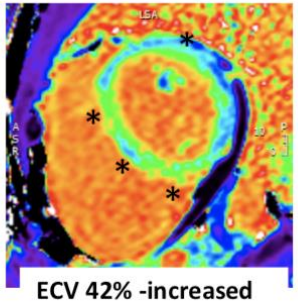
Non-ischemic myocardial injury
(REGIONAL or GLOBAL abnormal T1, ECV or LGE)

Global increase of **native T1**



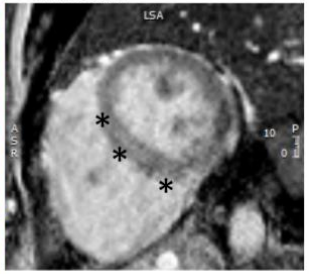
T1 map 1360ms -increased

Global increase of **ECV**



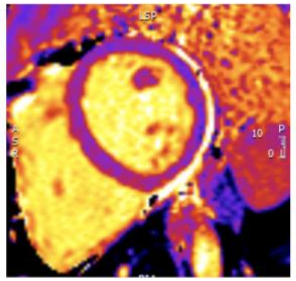
ECV 42% -increased

Diffuse **LGE signal** increase



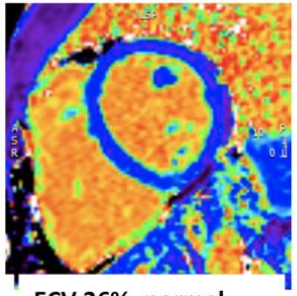
Diffuse LGE distribution

Normal **native T1**



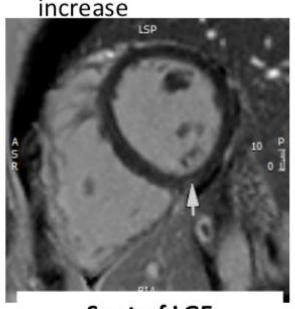
T1 map 1047ms -normal

Normal **ECV**



ECV 26% -normal

Localized **LGE signal** increase



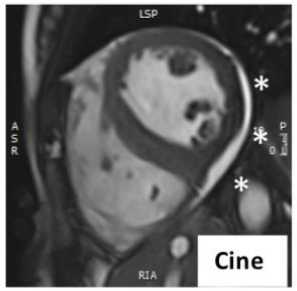
Spot of LGE

SUPPORTIVE CRITERIA

Pericarditis
(Effusion in cine images or abnormal LGE, T2 ot T1)

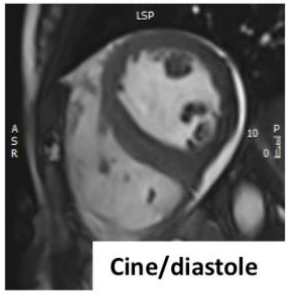
Systolic LV Dysfunction
(Regional or global wall motion abnormality)

Mild Pericardial effusion



Cine

Global hypokinesis – **LVEF 33%**



Cine/diastole

Cine/systole

NO Pericardial effusion

Cine

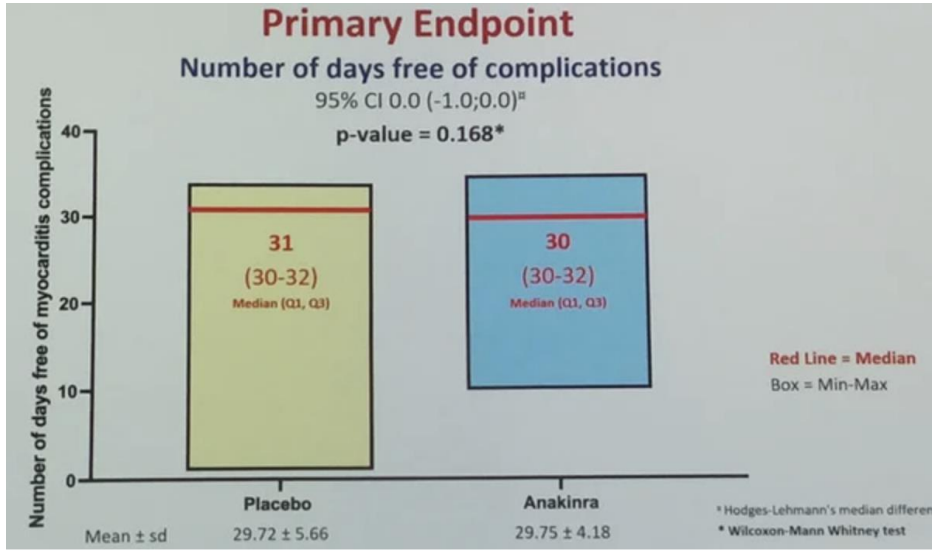
Normal systolic function – **LVEF 67%**

Cine/diastole

Cine/systole

ARAMIS - ANAKINRA VERSUS PLACEBO IN ACUTE MYOCARDITIS

- essai clinique de **phase IIB multicentrique randomisé de supériorité contre placebo en double aveugle**.
- Les **critères d'inclusion** comprenaient :
  - Présence d'une douleur thoracique
  - **ET** élévation de troponine
  - **ET** myocardite confirmée à l'IRM cardiaque réalisée dans les 72h (critères de Lake Louise)
  - Angiographie coronaire (coroscanner/coronarographie) normale à partir de 40 ans ou en cas de FDRCV.
- Étaient **exclus** les patients présentant une forme grave d'emblée, nécessitant une assistance hémodynamique/ventilatoire, certaines étiologies (auto-immunes, cellules géantes, éosinophilique, sarcoïdose, COVID-19), ceux traités par un autre anti-inflammatoire dans les 2 semaines, ainsi que ceux présentant une contre-indication à l'Anakinra.
- Ils étaient randomisés en 1:1 dans deux bras :
  - Traitement standard* + **100 mg d'anakinra en injection sous cutanée quotidienne jusqu'à la sortie d'hospitalisation (maximum 14 jours)**
  - Traitement standard* + placebo

•Pas de bénéfice du traitement anti-inflammatoire par anakinra chez les patients présentant une forme simple de myocardite aiguë
•Des essais à grande échelle sur des patients à plus haut risque sont maintenant nécessaires

- Le **critère de jugement principal** était un critère composite de survie sans complication à 28 jours de la sortie d'hospitalisation :
  - arythmies ventriculaires (TV/FV)
  - insuffisance cardiaque nécessitant l'hospitalisation
  - douleur thoracique modifiant les thérapeutiques,
  - dysfonction VG < 50 % en ETT.