Obrovskobuněčná myokarditida / giant cell myocarditis

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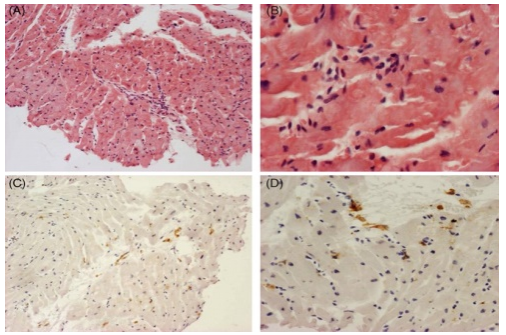
I. INTERNÍ KARDIOANGIOLOGICKÁ KLINIKA FNUSA A LF MU

MUNI MED

Myokarditidy - úvod

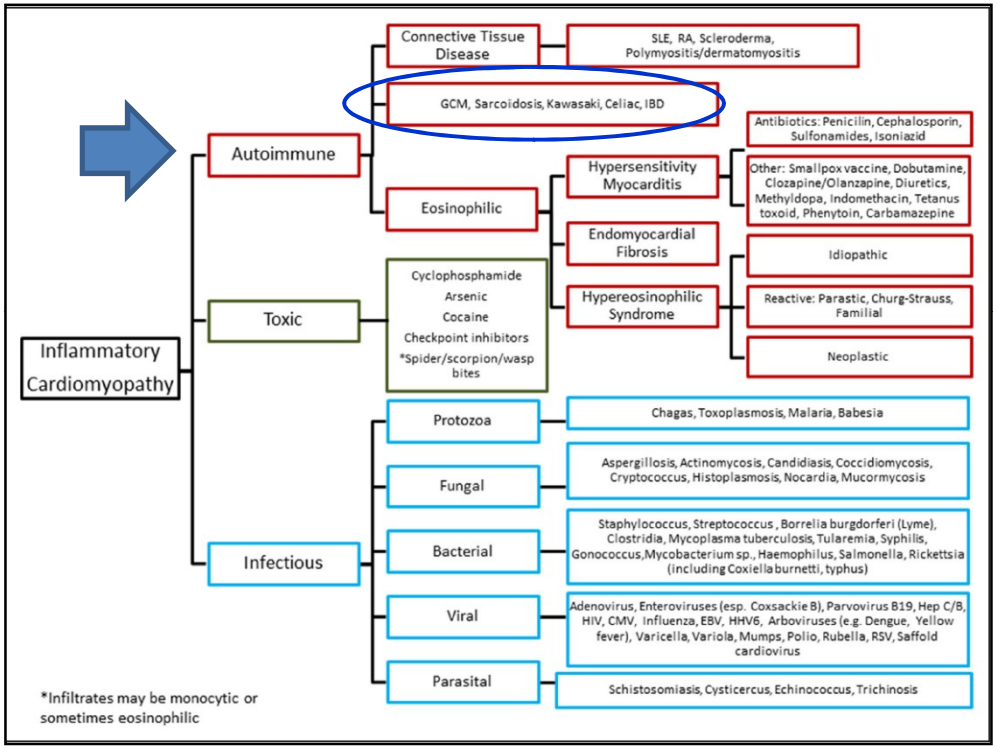
Myokarditida je akutní či chronický zánět myokardu s řadou infekčních a **neinfekčních příčin.**



Myokarditidy a zánětlivé kardiomyopatie - etiologie

Inflammatory Cardiomyopathic Syndromes

Barry H. Trachtenberg, Joshua M. Hare



Circ Res. 2017;121:803-818.

Myokarditidy – dělení dle délky symptomů

Akutní myokarditida – doba od začátku symptomů do 1 měsíce

- **fulminantní myokarditida** je akutní myokarditida s těžkým srd. selháním až kardiogenním šokem vyžadující terapii inotropy či MCS

Subakutní myokarditida – doba od začátku symptomů 1-3 měsíce

Chronická myokarditida – doba od začátku symptomů více než 3 měsíce

⇩

Zásadní pro agresivitu diagnostických i terapeutických přístupů

Clin Med 2021 Sep; 21(5): e505–e510.

GCM – epidemiologie

- Vzácná, ale nejdramatičtější forma myokarditidy
- Incidence GCM z autoptických sérií se pohybuje mezi 0.007% a 0.051% (Vaideeswar 2013)
- „Detection rate“ 0.13 případů na 100,000 osob (Heymans 2016)
- Tvoří cca 1% ze všech případů myokarditid
- Postihuje nejčastěji osoby mezi 40-60 lety, pod 20 let věku spíše výjimečně
- Častěji jedince s jinou autoimunitou, muže i ženy stejně často

GCM – klinický obraz

- **Akutní rychle progredující srdeční selhání, často ústící během 24-48 hod do obrazu kardiogenního šoku.**
- **Přítomnost refrakterních komorových dysrytmií či AV bloku vyššího stupně, které mohou být iniciálním projevem předcházejícím rozvoj těžké systolické dysfunkce LK.**
- **Před zavedením imunosupresivní léčby se jednalo o prakticky vždy smrtelné onemocnění!**

GCM – patofyziologie

- **Patofyziologie GCM není zcela objasněna**
- **T-lymfocyty zprostředkovaná autoimunitní myokarditida**

- U lidí i v animálních modelech je patrná infiltrace myokardu dominantně T-lymfocyty a makrofágy.
- U experimentální GCM produkují CD4+ T lymfocyty interferon-γ, který stimuluje produkci NO a TNFα- v makrofázích. To vede k upregulaci syntézy NO a produkci volných radikálů, které mají negativně inotropní efekt.

Klinický obraz a indikace EMB

Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy

Table 3 Indications for endomyocardial biopsy

Clinical presentation
• Suspected fulminant myocarditis or acute myocarditis with acute HF, LV dysfunction and/or rhythm disorders. • Suspected myocarditis in haemodynamically stable patients.
Dilated cardiomyopathy with recent onset HF, moderate-to-severe LV dysfunction, refractory to standard treatment (following exclusion of specific aetiologies).
Suspected ICI-mediated cardiotoxicity: acute HF with/without haemodynamic instability early after drug initiation (~ first 4 cycles)
High-degree atrioventricular block, syncope and/or unexplained ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia, frequent multifocal premature ventricular complexes), refractory to treatment, without obvious cardiac disease or with minimal structural abnormalities.
Autoimmune disorders with progressive HF unresponsive to treatment with/without sustained ventricular arrhythmias and/or conduction abnormalities.
MINOCA/takotsubo syndrome with progressive LV dysfunction and HF with/without ventricular arrhythmias or conduction abnormalities.

European Journal of Heart Failure (2021) **23**, 854–871

Diagnostika myokarditid vs GCM

- **Klinická diagnóza - za základě symptomů a jednoduchých klinických vyšetření - zánět v myokardu není známý**
- **Využití neinvazivních dg metod - využití MRI**
  - **podezření na přítomnost zánětu bez určení jeho typu**
  - **nelze určit virovou přítomnost v myokardu**

Diagnostika myokarditid vs GCM

- Klinická diagnóza - za základě symptomů a jednoduchých klinických vyšetření - zánět v myokardu není známý
- Využití neinvazivních dg metod - využití MRI
  - podezření na přítomnost zánětu bez určení jeho typu
  - nelze určit virovou přítomnost v myokardu

Invazivní dg u susp. myokarditid v HF Guidelines 2021

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 27 Dilated cardiomyopathy or hypokinetic non-dilated cardiomyopathy: specific aspects of diagnosis and treatment

Endomyocardial biopsy[97,907,917–919]
Indication. In suspected phenotypes requiring specific treatments (i.e. giant cell myocarditis, eosinophilic myocarditis, sarcoidosis, vasculitis, SLE, other systemic, auto-immune inflammatory conditions, or storage diseases).

Table 32 Endomyocardial biopsy in patients with suspected myocarditis

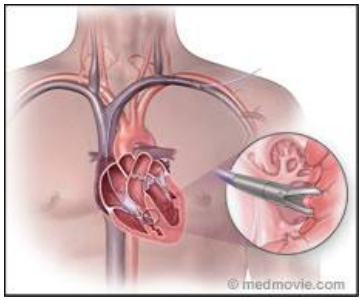
Indication (see also Section 4.3). Progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 second-degree or higher AV block with lack of short-term (<1-2 weeks) expected response to usual medical treatment.
The aim is to identify aetiology and to indicate specific treatment (e.g. giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, systemic inflammatory disorders).[97,98,917,918,958]

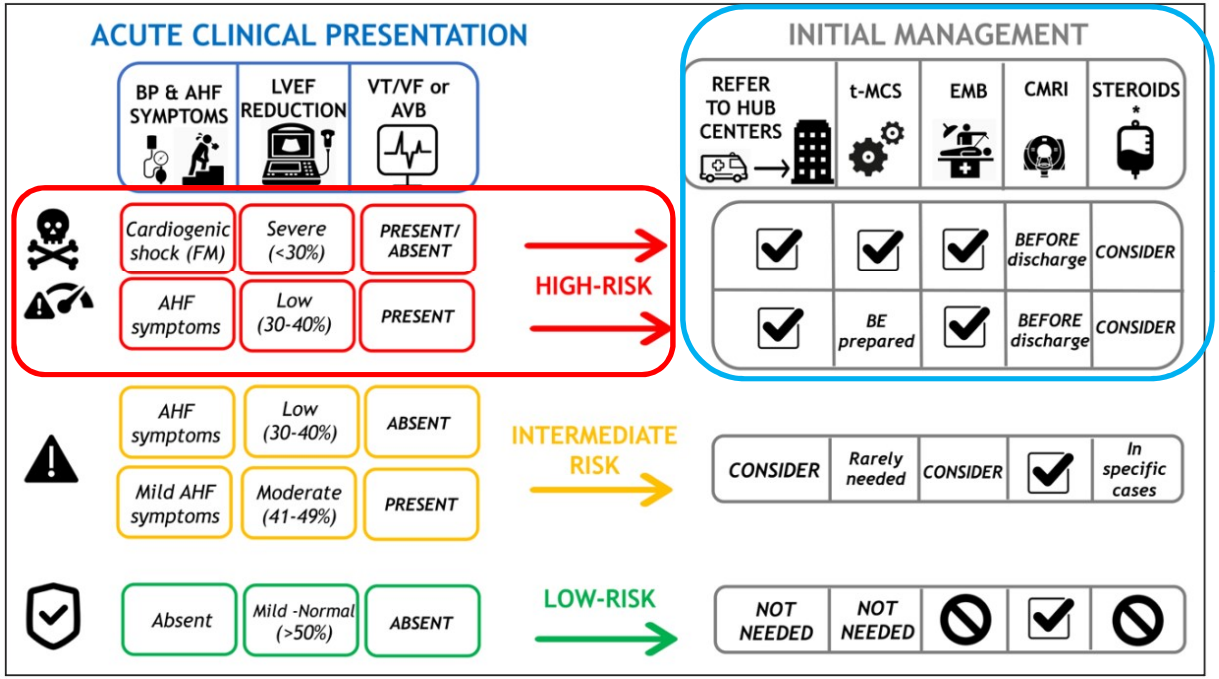
Eur Heart J. 2021;42(36):3599-3726.

Indikace EMB u nemocných s podezřením na myokarditidu

Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

An Expert Consensus Document



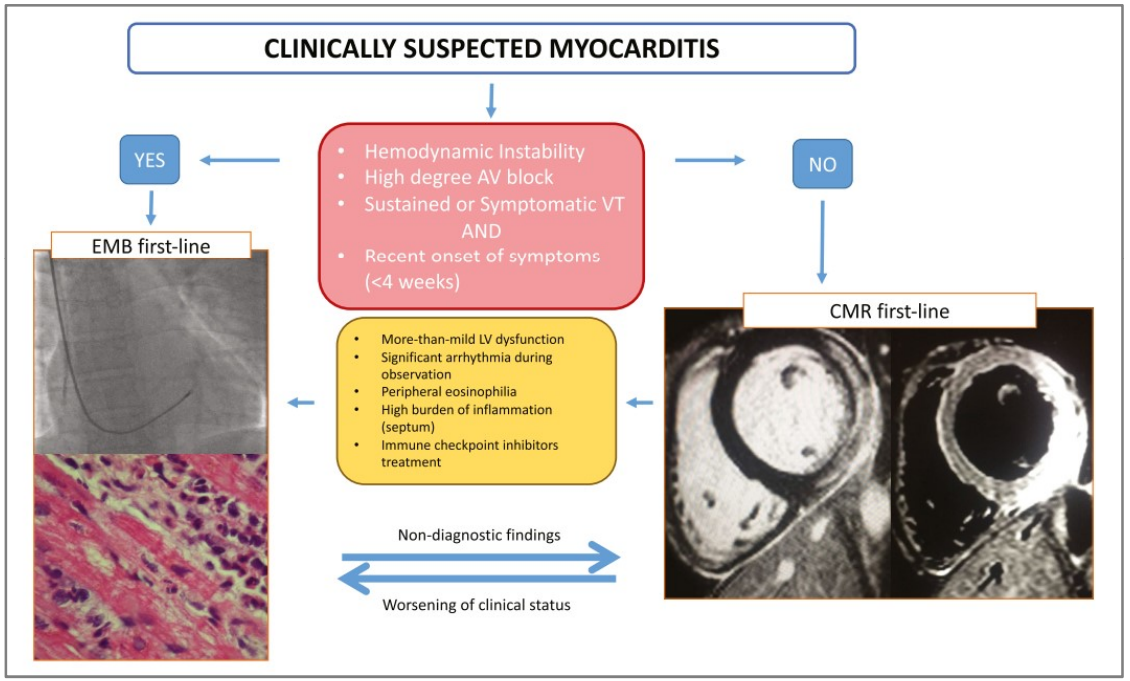


Circ Heart Fail. 2020 Nov;13(11):e007405.

Kdy u myokarditidy diagnostikovat invazivně a kdy neinvazivně?

State-of-the-Art of Endomyocardial Biopsy on Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

Enrico Ammirati[1] · Andrea Buono[2] · Francesco Moroni[3] · Lorenzo Gigli[1] · John R. Power[4] · Michele Ciabatti[5] · Andrea Garascia[1] · Eric D. Adler[4] · Maurizio Pieroni[5]

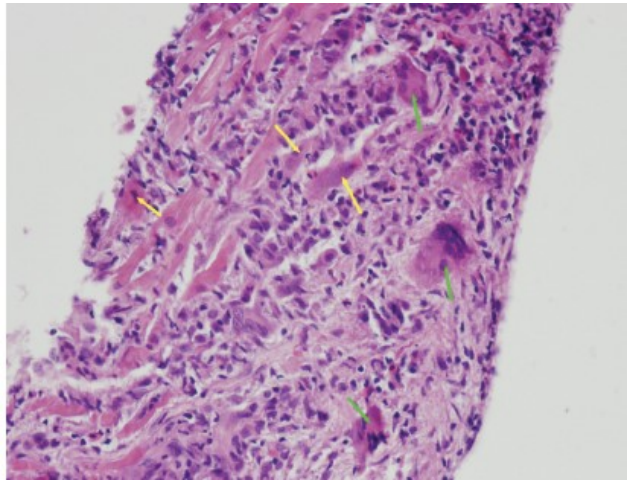


Current Cardiology Reports
https://doi.org/10.1007/s11886-022-01680-x

Bioptická dg je pro průkaz GCM nezbytná

- Na základě histologického/bioptického nálezu - průkaz a specifikace typu zánětu, ev. detekce a určení inf. agens
  - Histologicky podle Dallaských kritérií
  - Imunohistochemicky
  - PCR diagnostika

- Jen na základě (imuno)histologického nálezu lze stanovit definitivní dg!



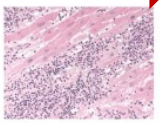
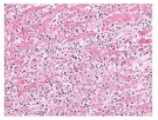
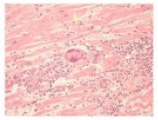
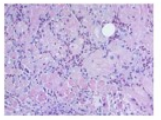
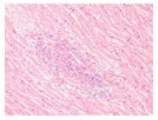
Máme pacienta s fulminantní myokarditidou…co dělat?

IS/IM terapie u fulminantní myokarditidy

Immunomodulating Therapies in Acute Myocarditis and Recurrent/Acute Pericarditis

SUSPECTED FULMINANT OR COMPLICATED ACUTE MYOCARDITIS

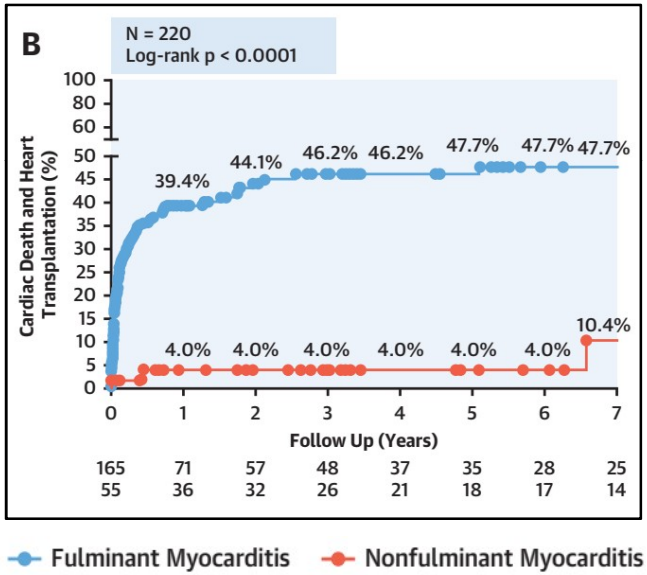
FIRST-LINE: i.v. pulse methylprednisolone 7–14 mg/kg/day for 3 d, then 1 mg/kg/day

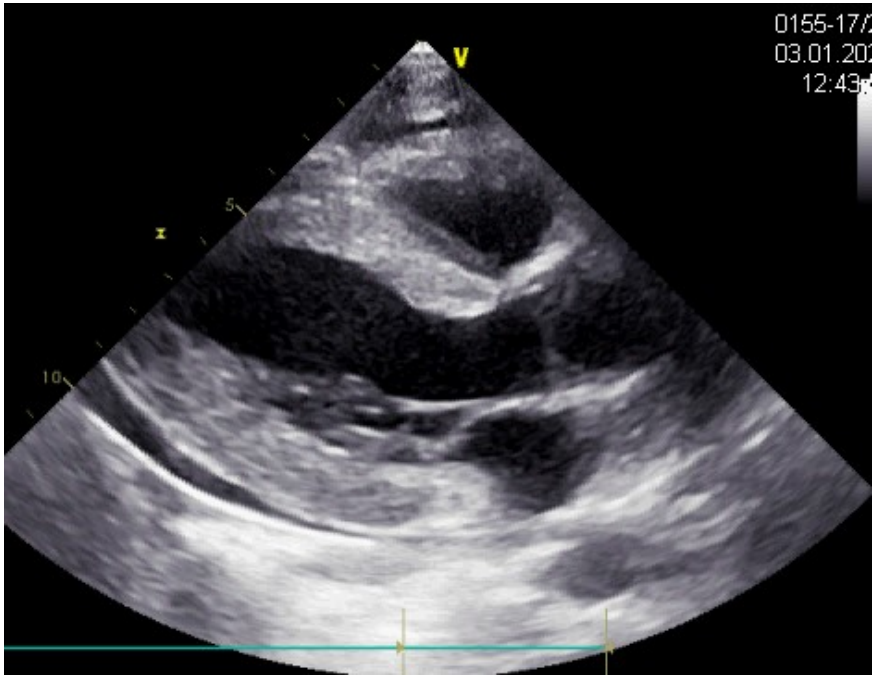
	 LYMPHOCYTIC	 ICI-ASSOCIATED	 GIANT CELL	 EOSINOPHILIC	 SARCOIDOSIS
ADDITIONAL	- If associated systemic autoimmune disorders (eg. SLE and APS): add aggressive treatment of associated conditions	**Hold ICI** therapy Confirm ICI-myocarditis via definitive imaging and/or endomyocardial biopsy	- If hemodynamically unstable pts: **ATG**, from 1 mg/kg, usually single-dose to 300 mg in 3 days or (alternative) i.v. **alemtuzumab** (anti-CD52 antibody) single dose of 30 mg plus oral **CyA**, BID, target through levels 150–250 ng/mL - If hemodynamically stable pts: only oral **CyA**, BID, target trough levels 150–250 ng/mL	- If EGPA: consider i.v. **cyclophosphamide** (especially in ANCA-positive pts), 600 mg*m² at days 1, 15, and 30 - If clonal (myeloproliferative) HES: **imatinib** 100–400 mg OD - If helminthic infection: **albendazole** 400 mg BID for 2–4 wk - If hypersensitivity reaction: **withdraw suspected drug**	
SECOND-LINE	**IVIG** (2 g/kg), single continuous infusion in 24–48 h or divided in 4 d or **plasmapheresis**, 3–5 sessions in 5–10 d	i.v. **abatacept** (a CTLA- 4 agonist) or **ATG**, 1 mg/kg, usually single dose or i.v. **alemtuzumab** (anti-CD52 antibody), 30 mg, single dose	i.v. **rituximab** 375 mg×m² (BSA) mg (once a wk for 4 wk and then every 4 mo as maintenance therapy) for 1 yr	- If DRESS, EGPA or idiopathic HES: anti-IL5 agents (e.g., **benralizumab** 30 mg s.c./4–8wk or **mepolizumab** 100-300 mg/4wk)	s.c. **methotrexate** 15–20 mg/wk or i.v. **infliximab** 5 mg/kg (up to 500 mg) at time 0 and after 2 and 4 wk and then every 6–8 wk or s.c. **adalimumab** 40 mg/2wk

Front Med (Lausanne). 2022 Mar 7;9:838564.

Prognóza fulminantní vs nefulminantní myokarditidy

Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction



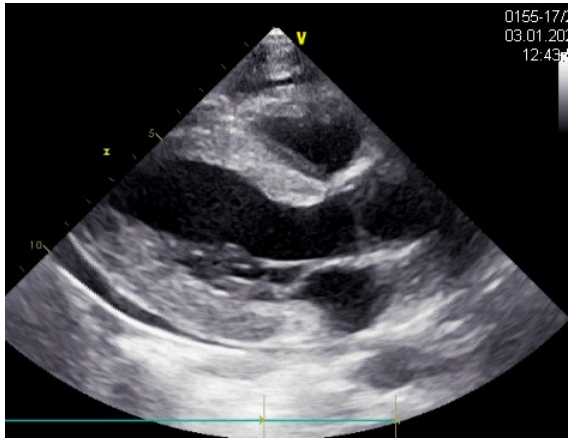


Ammirati, E. et al. J Am Coll Cardiol. 2019;74(3):299-311.

Myocarditis

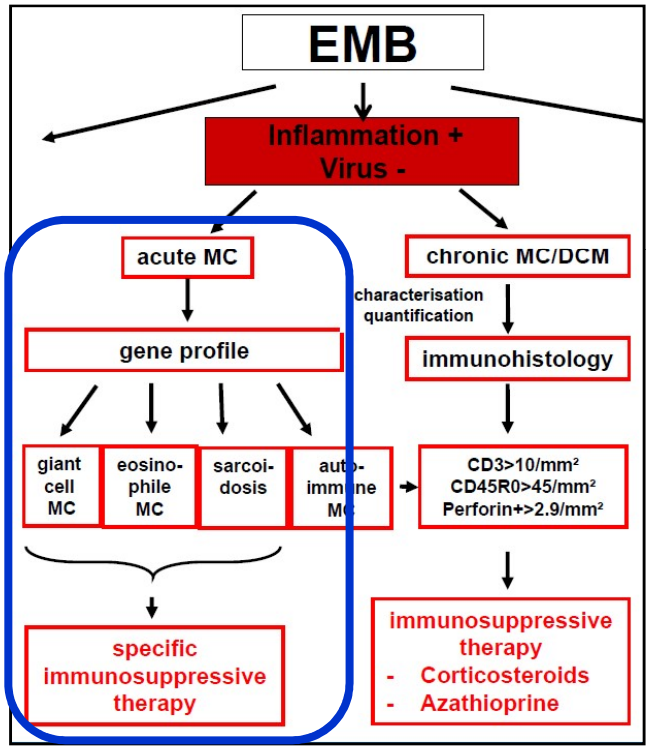
Cristina Basso, M.D., Ph.D.

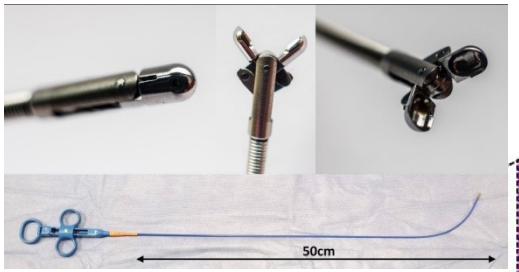
N Engl J Med 2022;387:1488-500.

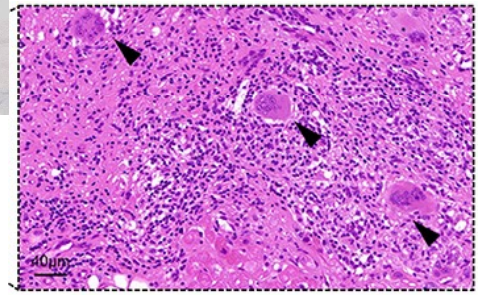


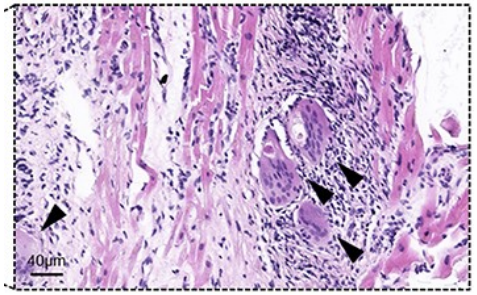
Presentation	High-risk profile	Intermediate-risk profile	Low-risk profile
Symptoms	Cardiogenic shock Symptoms of acute HF	Symptoms or mild symptoms of acute HF	No symptoms of acute HF
Left ventricular ejection fraction	<30% (severely low) or 30–40% (low)	30–40% (low) or 41–49% (moderately low)	≥50% (mildly low or normal)
Arrhythmias	VT, VF, or AVB absent or present	VT, VF, or AVB absent or present	VT, VF, and AVB absent
Immediate management			
Referral to expert center	Yes	Consider	No
Mechanical circulatory support	Consider	No	No
Temporary pacing	Consider	Consider	No
Immunosuppression	Consider	Consider	No
Diagnostic workup			
Cardiac MRI	After stabilization	Yes	Yes
Coronary angiography to rule out CAD	If needed	If needed	If needed
Endomyocardial biopsy	Yes	Consider	No

Imunosuprese u GCM – jednoznačně ANO!!



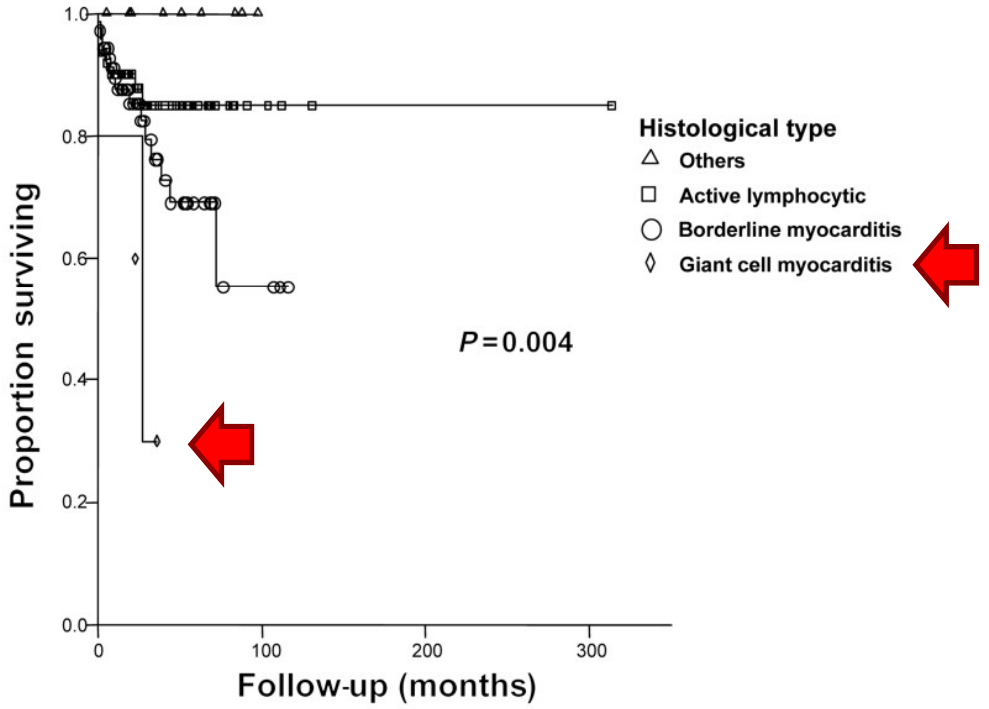






Prognóza GCM ve srovnání s jinými typy myokarditid

A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogeneti features at diagnosis



Neléčená GCM prakticky vždy končí fatálně!

European Heart Journal (2007) **28**, 1326–1333

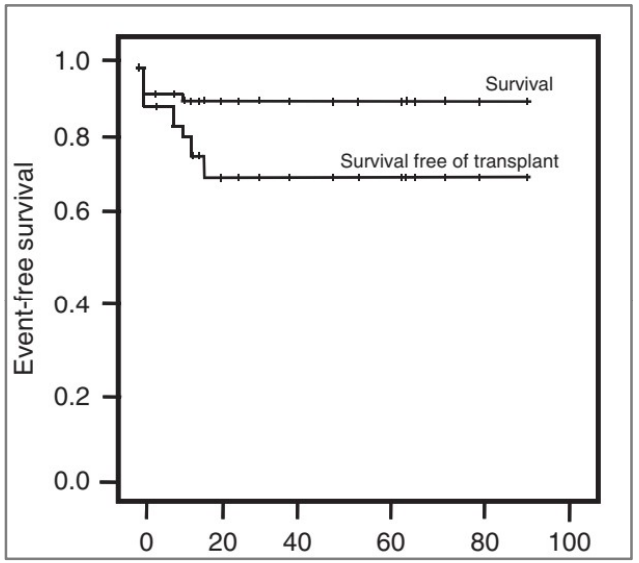
Efekt včasné diagnostiky a IS léčby u GCM

Diagnosis, Treatment, and Outcome of Giant-Cell Myocarditis in the Era of Combined Immunosuppression

Riina Kandolin, MD; Jukka Lehtonen, MD; Kaisa Salmenkivi, MD; Anne Räisänen-Sokolowski, MD; Jyri Lommi, MD; Markku Kupari, MD

Table 1. Immunosuppressive Treatment of the 26 Patients With Biopsy-Diagnosed GCM

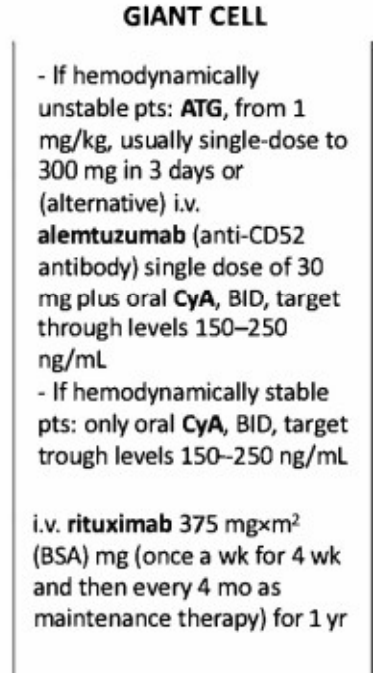
Corticosteroid + Azathioprine + Cyclosporine 17 (65%)
Corticosteroid + Azathioprine 4 (15%)
Corticosteroid + Azathioprine + Muromonab + Gammaglobulin 1 (4%)
Corticosteroid + Azathioprine + Myocophenolate mofetil 1 (4%)
Corticosteroid + Cyclosporine+ Myocophenolate mofetil 2 (8%)
Corticosteroid + Cyclosporine + Azathioprine/Methotrexate* 1 (4%)



Conclusions—Repeat endomyocardial biopsies are frequently needed to diagnose giant-cell myocarditis. On contemporary immunosuppession, two thirds of patients reach a partial clinical remission characterized by freedom from severe heart failure and need of transplantation but continuing proneness to ventricular tachyarrhythmias. **(*Circ Heart Fail*. 2013;6:15-22.)**

Praktický přístup k terapii u GCM

- Iniciálně Solumedrol - 1g i.v. /den po 3 dny
- U stabilních pacientů - CyA nebo Tac + MMF + Pre
- U nestabilních pacientů
  - ATG 1mg/kg i.v. po 3 dny
  - alemtuzumab (anti-CD52) + CyA / Tac
  - rituximab (anti-CD20) i.v. 1x týdně 375mg/m2
- Dostupnost MCS a došetření k transplantaci



GIANT CELL

- If hemodynamically unstable pts: **ATG**, from 1 mg/kg, usually single-dose to 300 mg in 3 days or (alternative) i.v. **alemtuzumab** (anti-CD52 antibody) single dose of 30 mg plus oral **CyA**, BID, target through levels 150–250 ng/mL
- If hemodynamically stable pts: only oral **CyA**, BID, target trough levels 150–250 ng/mL

i.v. **rituximab** 375 mg×m^2 (BSA) mg (once a wk for 4 wk and then every 4 mo as maintenance therapy) for 1 yr

Front Med (Lausanne). 2022 Mar 7;9:838564.

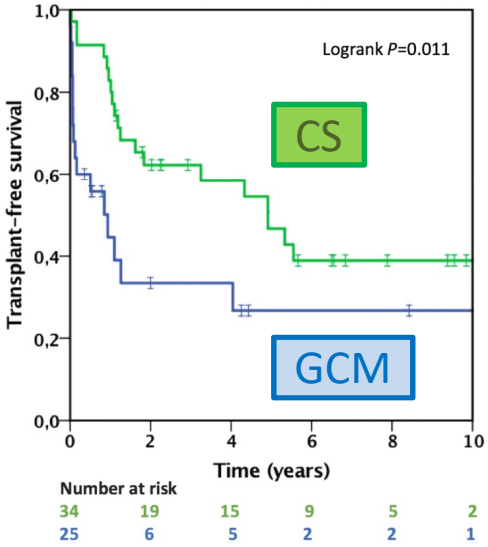
Diferenciální dg GCM a CS

Idiopathic giant cell myocarditis or cardiac sarcoidosis? A retrospective audit of a nationwide case series

Aims Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) are inflammatory cardiomyopathies sharing histopathological and clinical features. Their differentiation is difficult and susceptible of confusion and apparent mistakes. The possibility that they represent different phenotypes of a single disease has been debated.

Methods and results We made a retrospective audit of 73 cases of GCM diagnosed in Finland since the late 1980s. All available histological material was reanalyzed as were other examinations pertinent to the distinction between GCM and CS. Finding granulomas in or outside the heart was considered diagnostic of CS and exclusive of GCM. Altogether 45 of the 73 cases of GCM (62%) were reclassified as CS. In all except one case, this was based on finding sarcoid granulomas that either had been originally missed (n = 29) or misinterpreted (n = 11) or were found in additional posttransplant myocardial specimens (n = 3) or samples of extracardiac tissue (n = 1) accrued over the disease course. Supporting the reclassification, patients relocated to the CS group had less heart failure at presentation (prevalence 20% vs. 46%, P = 0.017) and better 1 year transplant-free survival (82% vs. 45%, P = 0.011) than patients considered to represent true GCM.

Conclusions Recognizing granulomas in or outside the heart remains a challenge for the pathologist. Given that CS and GCM are considered distinct diseases and granulomas exclusive of GCM, many cases of GCM, if thoroughly scrutinized, may need reclassification as CS. However, whether CS and GCM are truly different entities or parts of a one-disease continuum has not yet been conclusively settled.

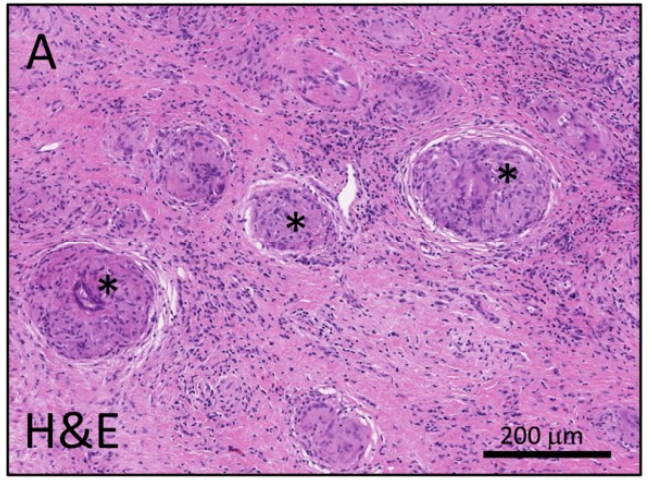


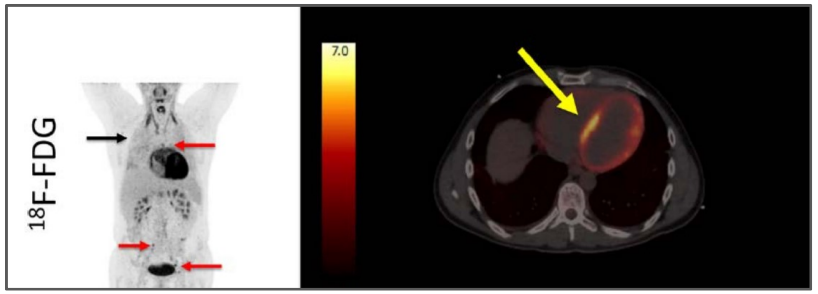
ESC Heart Failure 2020; **7**: 1362–1370

Histologie u srdeční sarkoidózy

Idiopathic giant cell myocarditis or cardiac sarcoidosis?
A retrospective audit of a nationwide case series

- **Myokardiální granulomy bez nekrózy ale s fibrózou jsou typickými histologickými znaky srdeční sarkoidózy.**
- **V dif. dg. může pomoci detekce extrakardiálního postižení.**





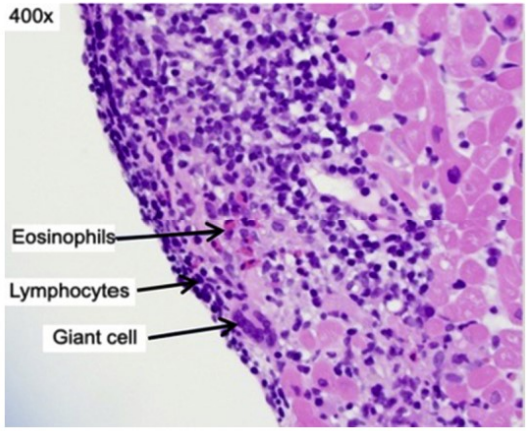
Histologie u GCM

Management of Patients With
Giant Cell Myocarditis

JACC Review Topic of the Week

- **Přítomnost multinukleárních obrovských buněk spolu s výraznou smíšenou celulární inflamatorní infiltrací včetně eozinofilů a také přítomnost rozsáhlé nekrózy myocytů jsou typické pro GCM.**

FIGURE 3 Histopathology of Giant Cell Myocarditis



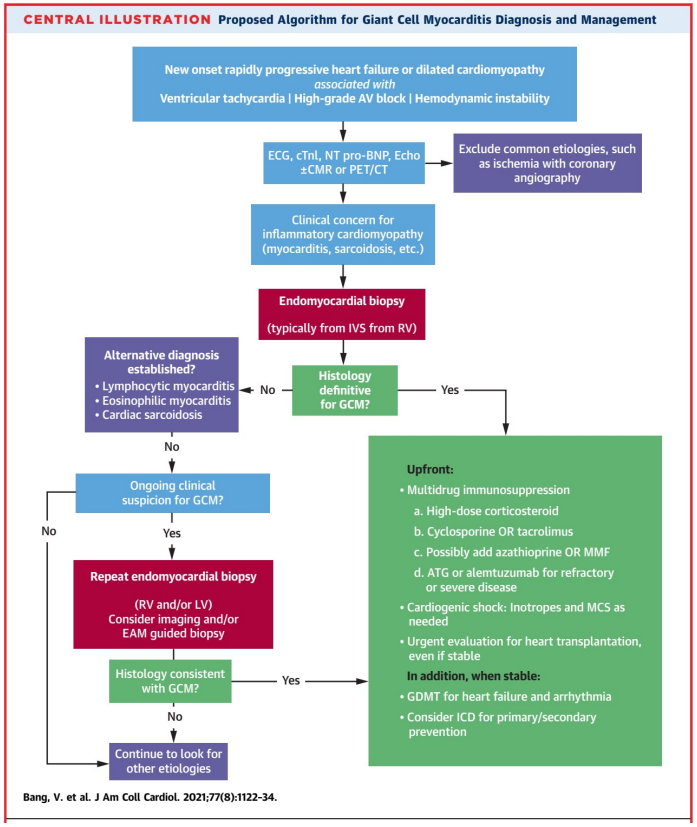
Courtesy of Dr. Juan Vilaro, University of Florida Medical Center. This is a high-power magnification of eosin and hematoxylin staining of cardiac myocytes affected by giant cell myocarditis. Multifocal inflammatory infiltrates consisting of lymphocytes with multinucleated giant cells and eosinophils are seen.

J Am Coll Cardiol 2021;77:1122-34

Shrnutí dg a th u GCM - „take-home messages“

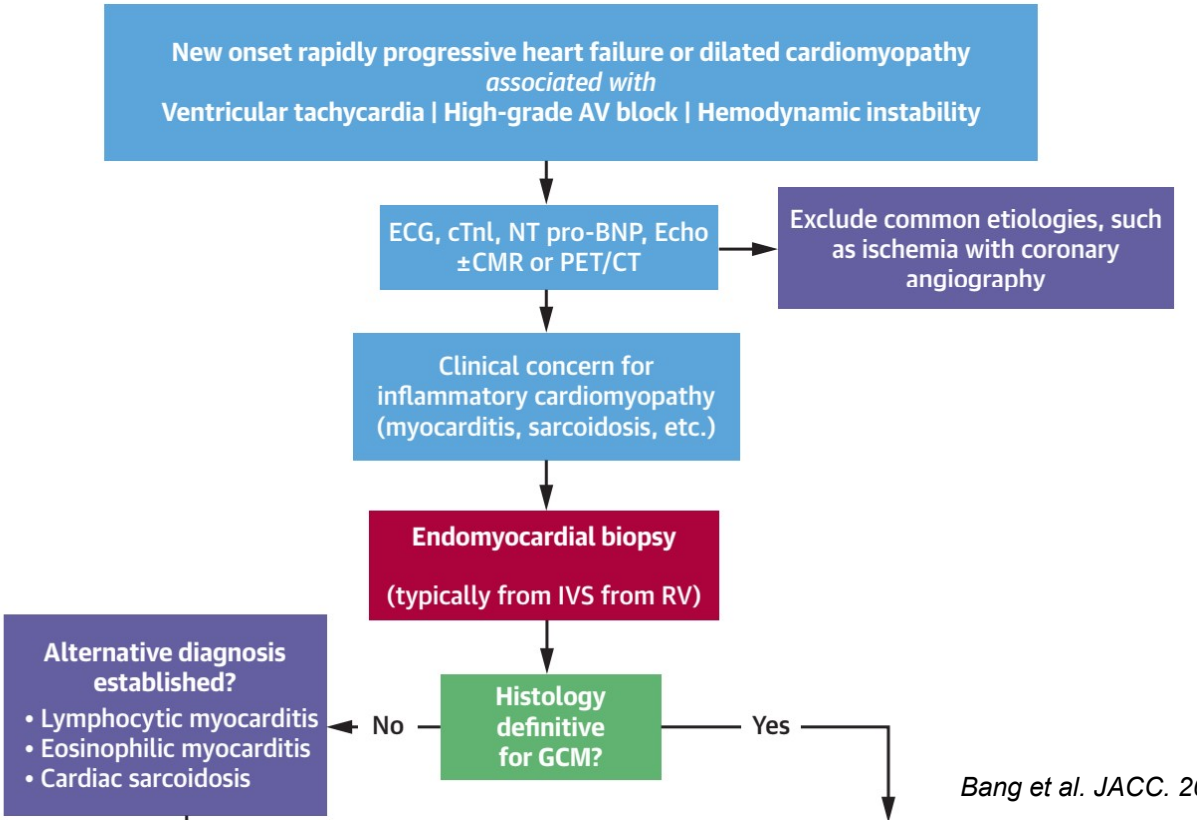
Management of Patients With Giant Cell Myocarditis

JACC Review Topic of the Week



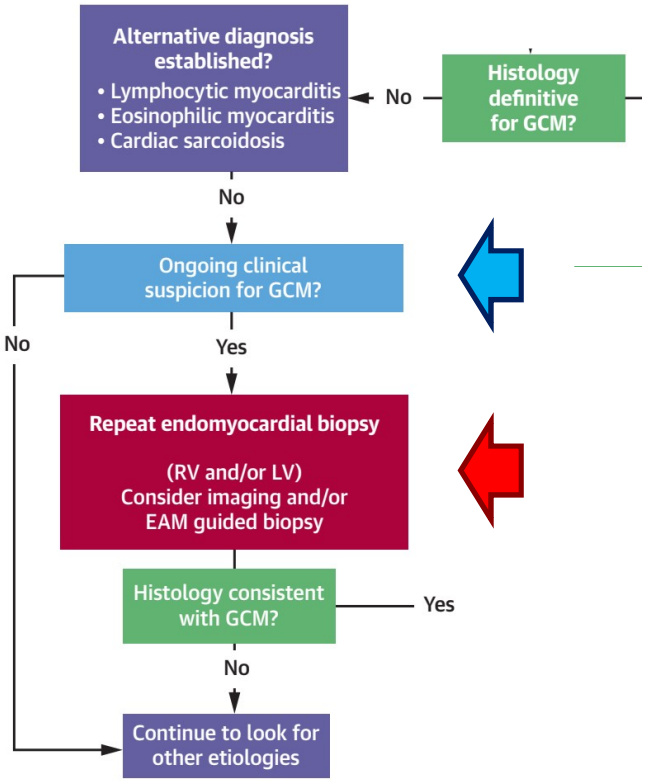
Bang et al. JACC. 2021 Mar, 77 (8) 1122–1134.

Diagnostika GCM



Bang et al. JACC. 2021 Mar, 77 (8) 1122–1134.

Diagnostika GCM



Senzitivita EMB v diagnostice GCM se pohybuje mezi 70-80%.

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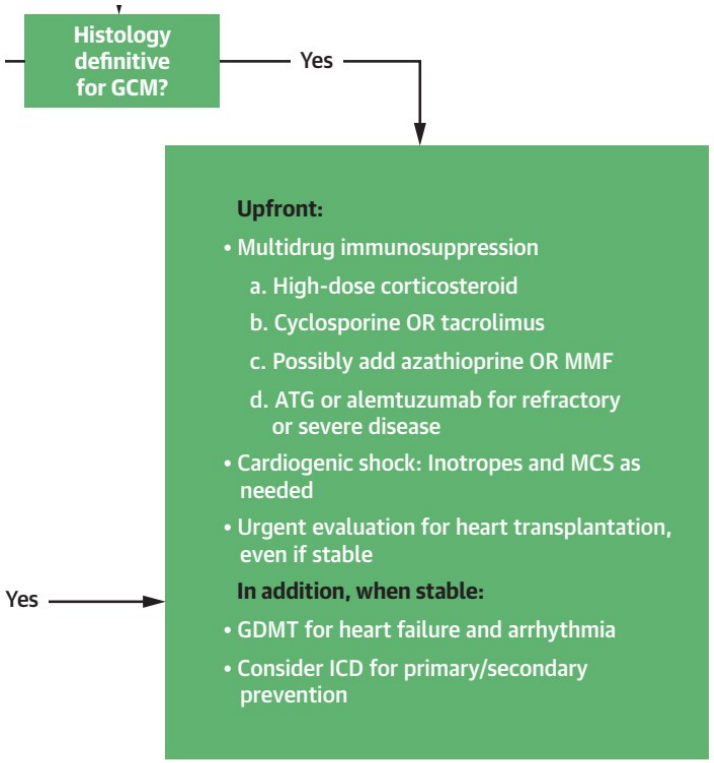
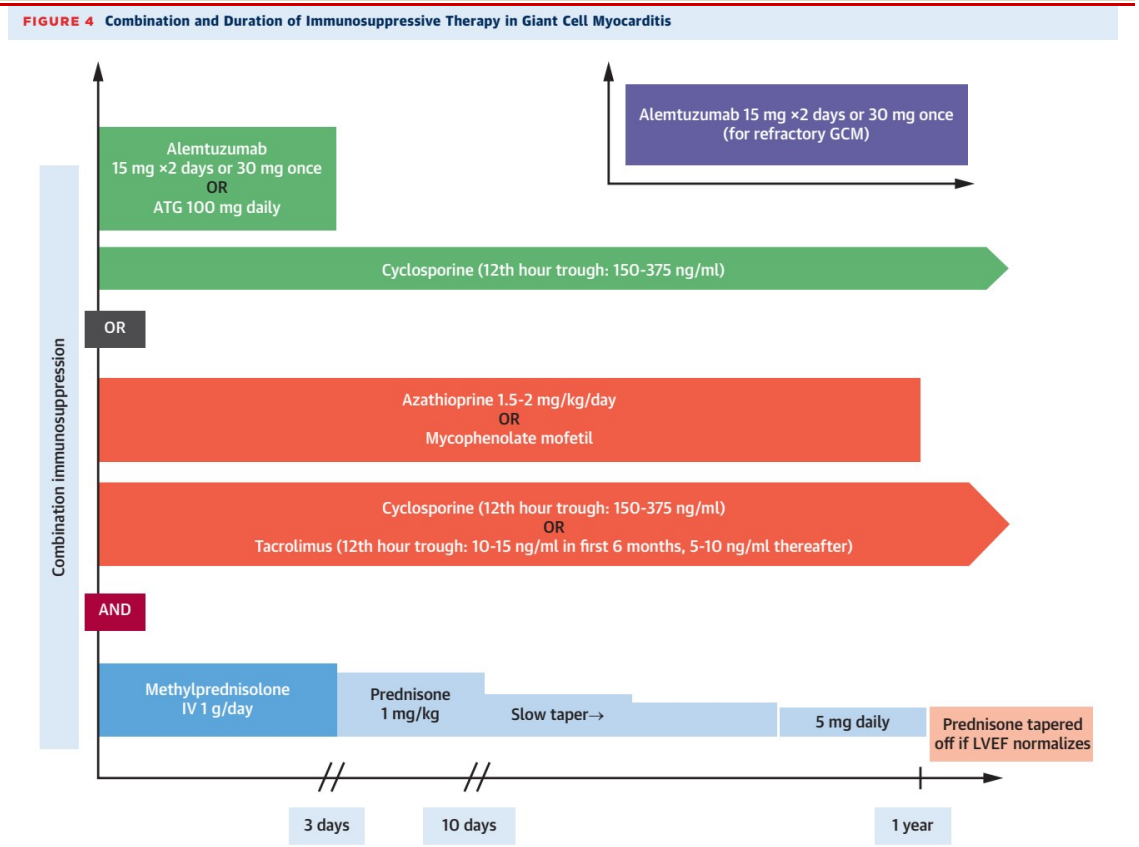
Je-li dg GCM potvrzena, začni okamžitě s léčbou!





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Závěr

- **Obrovskobuněčná myokarditida je vzácným, ale velmi závažným onemocněním.**
- **Diagnostika GCM vyžaduje vysoký stupeň podezření a rychlost vzhledem k akutnímu a potenciálně smrtelnému průběhu.**
- **EMB je základním kamenem diagnostiky, v případě nediagnostické první EMB je doporučeno její opakování.**
- **Imunosuprese spolu s komplexní léčbou zásadně zlepšují prognózu pacientů s GCM.**
- **MCS a transplantace srdce hrají důležitou roli ve zvládnutí akutního i střednědobého průběhu onemocnění.**

Děkuji za pozornost!

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