ESC Working Group on Myocardial and Pericardial Diseases

Questions from the live webinar - 15 Sept 2015 "Clinical presentation, Diagnosis and Treatment of Myocarditis: the ESC 2013 Task Force Criteria"

Hi is there any new study according to the immunoglobilin IV management in post Myocarditis induced CMP.
R: Yes, There is a pilot study demonstrating that IVIg significantly reduces viral load and improves cardiac function in patients with DCM related to increased PVB19 viral load in the heart. Dennert at al. Antivir Ther. 2010;15(2):193-201.

Should iECA be considered in patients with acute Myocarditis without left Ventricular dysfunction or heart failure symptoms?
R: yes, If the patient meets the 2013 ESC Task Force criteria of clinically suspected myocarditis an endomyocardial biopsy should be considered.

In your clinical pratcice you consider EMB in all the patients with suspected myocarditis?
Yes, as without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral or immunosuppressive).

Endomyocardial biopsy for all in the era of cardiac magnetic resonance?
Yes, EMB but not CMR reveals the etiology (e.g. viral or autoimmune) of myocarditis and, thus the adequate therapy (antiviral or immunosuppressive).

Using High sensitive troponin the diagnosis of Myocarditis can be made without positive troponin?
R: Clinically suspected or definite (biopsy-proven) myocarditis may occur even with a negative high sensitive troponin assay.

Every suspected myocarditis without hemodinamic instability need EMB to sustain the diagnosis?
R: YES, if the patient meets the 2013 ESC Task Force criteria of clinically suspected myocarditis an endomyocardial biopsy should be considered.

May myocarditis presents clinically as a condition mimicking HCM? Are there red flags that could help us in differential diagnosis?
Only the EMB is helpful, here the HCM AND the myocarditis can be diagnosed in parallel. In acute fulminant myocarditis there can be an increase in ventricular wall chamber thickness due to oedema (mimicking HCM)

If we have a patient with clinical ECG blood tests suggestive of myocarditis and working in a cenetr without endomyocardial biopsy facility should we refer to a cenetr with EMB for biopsy or treat empirically as myocarditis?
R: It is not possible to treat empirically myocarditis with antiviral or immunosuppressive therapy without an EMB diagnosis. It is possible only symptomatic heart failure and arrhythmia management according to ESC guidelines for heart failure and arrhythmia. Therefore, particularly if the patient is unstable because of heart failure and/ or arrhythmia it is recommended to refer the patient to a centre with EMB capability.

But do you defend that all patients with suspected myocarditis should get an EMB?
R: Yes, as without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral or immunosuppressive).

Is EMB mandatory for the diagnosis of myocarditis or can we use less invasive method like cardiac MRI. Thanks.
Without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral or immunosuppressive). In addition, MRI is not as sensitive as EMB in heart failure presentations of myocarditis.

ACE inhibitors and betablockers for patients with preserved LVEF myocarditis?
R: there are no controlled clinical trials for ACE inhibitors and betablockers in patients with preserved LVEF myocarditis. Therefore prescription of ACEinhibitors should be in keeping with current ESC guidelines on heart failure. Betablockers are most commonly prescribed in myocarditis with preserved LVEF is there is evidence of cardiac arrhythmia.Also in this case prescription should be in keeping with current arrhythmia guidelines.

Whis is your opinion about the immunoadsorcion in acute myocarditis episodes?
R: Immunoadsorption has been reported mainly in chronic inflammatory cardiomyopathy/DCM in small series of patients with beneficial effects on LVEF and NYHA. A multicenter randomised trial is approaching completion and we will see what are the results. So far immunoadsorption has not been tested in acute myocarditis.

Do you know wich is the sensibility of inmunohistochemical criterias when you take the samples from the right side of the septum?
It is comparable to that of the left ventricle

What about sampling error of EMB ie false negative or non-diagnostic EMBs, would GdCMR be helpful or even diagnostic?
Usually not as by GdCMR we do not know the etiology or pathogenesis of myocarditis and cannot treat the patients adequately. If clinically indicated EMB can be repeated.

Which is the meaning if you find a positive pcr for parvovirus? What do you do if you find positive pcr for parvovirus and limfocitic infiltrate?

Then, the patient has a viral myocarditis and the patient must not be treated by immunosuppressive therapy.
As many hospitals will not test for all viruses or other infectious agents (many use different panels) in EMBs how can we be sure the inflammation is virus-negative and initiate therapy if indicated?
You should send the biopsy to a lab where the most relevant infections can be determined.

How to draw line between Myocarditis and Dilated cardiomyopathy ?
R: the differential diagnosis is based upon EMB. Acute or chronic myocarditis can be present in a patient with an imaging picture of non-ischemic DCM

Aspirin is contraindicated in myocarditis? should we use it in myopericarditis
R: there are experimental data in viral myocarditis indicating that aspirin and other NSAIDs do not improve myocarditis and may actually be harmful. Aspirin and NSAIds are not indicated in isolated clinically suspected or biopsy-proven myocarditis. In cases of clinically suspected myocarditis with pseudo-infarct presentation (abnormal troponin and normal coronary arteries) and clearly associated pericarditis (pericardial effusion and increased C reactive protein) the lowest dose of aspirin or other NSAIDs to control chest pain is generally used. However, cases of clear "myopericarditis" are uncommon. Most patients have either pure myocarditis with pseudo-infarct presentation without pericarditis (no pericardial effusion, no increased C reactive protein) or pure pericarditis (no troponin increase, pericardial effusion, increased C reactive protein).

How can we prevent Parvovirus infection not to become myocarditis?
You cannot prevent this infection. More than 70% of people get this infection during childhood and often it persists in different tissues and organs; so far there is no possibility to eliminate it from the body.

Do you recommend to test for mRNA as well to evaluate virus replication?
No, the sampling error is too high when measuring viral mRNA. It is easier to determine the copy numbers of PVB19 DNA, usually a copy number of less than 500 copies/ug myocardial DNA is not associated with cardiac inflammation and represents a latent infection which must not be treated.

Is there any genetic factor that predispose to the development of non-infective myocarditis? And any gender specific form on non-infectious myocarditis? Thanks. Andrea.
R: Yes, There are genetic factors of the immune system which predispose to myocarditis even viral myocarditis, eg. mutations in TLR3. It has also been shown that specific HLA alleles (e.g. DR4) are predisposing genetic markers of susceptibility to immune-mediated non-infectious myocarditis and DCM. Both myocarditis and inflammatory DCM can be familial, and other extra-cardiac immune-mediated disorders can occur in the index case or in family members, in keeping with other autoimmune disorders.

Do you still recommend antiviral treatment of symptomatic patients with suspected myocarditis/DCM not demonstrating inflammation on EMB but do show a high viral load?
Usually there is no high virus load without cardiac inflammation. Enterovirus infections should always be treated with type I interferons.

Do we need to perform myocardial biopsy if virus IgM antibodies are detected in blood in a patient suspected with myocarditis?
Yes, it was clearly shown that antiviral antibodies do not correlate well with the presence of the specific viral DNA/RNA in the heart.

The severity of the clinical presentation has any role in considering EBM?
R: Yes, in hemodinamically severe or life-threatening presentations EMB should not be delayed, since some of these patients may have specific autoimmune forms, such as giant cell myocarditis or cardiac sarcoidosis, in whom immunosuppression is mandatory and can stabilise the patient either as a bridge to recovery or to heart transplantation.

EMB is sometimes not feasible.I work in a district hospital with no specif cardiac pathologist. What do you suggest?
Convince the head of your hospital to send it to cardiopathologists. As an alternative, refer the patient to a centre with EMB expertise.

In post infectious myocarditis is corticosteroid has benifit?
R: in biopsy-proven post-infectious myocarditis, meaning virus-negative on EMB, steroids are used in combination with other immunosuppressive therapies, for instance azathioprine. Steroids or other immunosuppressive drugs are not indicated without having the diagnosis confirmed by biopsy.

Do we need routinely look for the aetiology with EMB(all of them will need coronary angiograms) in all patients and are they enough data to justify different management accordingly?
R: In all patients with clinically suspected myocarditis according to the ESC 2013 Task Force criteria it is recommended to consider coronary angiography and EMB.

When do you decide to do biopsy?
R: As soon as you have a patient fulflling ESC 2013 Task Force criteria for clinically suspected myocarditis.

Is it feasible to performe EBM to all patients with cl'nical suspected Myocarditis?
Yes, as without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral oder immunosuppressive).

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In which patients should we consider EBM?
R: As soon as you have a patient fulflling ESC 2013 Task Force criteria for clinically suspected myocarditis.

Steroids could be used in treatment of myocarditis?
R: in biopsy-proven non-infectious myocarditis, meaning virus-negative on EMB, steroids are used in combination with other immunosuppressive therapies, for instance azathioprine. Steroids or other immunosuppressive drugs are not indicated without having the diagnosis confirmed by biopsy.

When should the CMR be done after the acute presentation to help the diagnosis? Should we repeat the test at some point? Any difference i prognosis?
R: CMR may be used at follow-up to compare with the baseline test in terms of possible evolution of abnormal tissue changes, often at 1 year. Preliminary data suggest that extent of LGE may be a negative prognostic factor, but more data are needed. CMR does not replace EMB in patients who are on immunosuppressive or anti-viral therapy to decide when to stop such therapies.

Can MRI rule out the diagnosis of myocarditis?
No, the sensitivity is not high enough to exclude a myocarditis which is found by the microscope. In particular the sensitivity of CMR is low in heart failure and arrhythmia presentations of biopsy-proven myocarditis.

Do you recommend a MRI before biopsy for select the site of the biopsy?
R: we do not use CMR to select the site of the biopsy.

Is it absolutely imperative to get myocardial biopsy in all suspected and provisionally diagnosed myocarditis ?
Yes, as without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral oder immunosuppressive).

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Yes, as without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral oder immunosuppressive).

How many biopsies from how many regions of myocardium are needed?
R: According to the Task force recommendations at least 3 samples for histology and immunohistology,each 1 to 2 mm in size, additional samples (at least 2) from different regions for viral PCR.

But after the results of biopsy in 99% of subjects there are no changes in the therapy. So why send the general patients to a very small but definite risk with the biopsy?
R: IN all prospective studies with biopsy-proven myocarditis majority of patients have virus-negative myocarditis, which is already treatable

How would you treat Parvo B 19 myocarditis with 500 cpoies and deterioation of LV function.
R: There are no established specific therapies for PVB19 cardiac infection at the moment. The general indication up to now is to avoid immunosuppression. There is a pilot study demonstrating that IVIg significantly reduces viral load and improves cardiac function in patients with DCM related to increased PVB19 viral load in the heart. Dennert at al. Antivir Ther. 2010;15(2):193-201.

10 yr old girl with Ebstein Bar documented infection who presents ventricular ectopics more than 1000/24hr bur meanwhile the infection is in remission and there are no signs of heart failure. CMR with Gd LE is negative would you insist to endomyocardial biposy?
R: This patient will not reach the criteria for a clinically suspected myocarditis provided that there are no cardiac symptoms, normal echo and CMR, no troponin rise. The ventricular ectopics accounts for only 1 criterion. You need more than 2 features from different diagnostic categories if the patient is asymptomatic to consider EMB.

Should iECA be considered in patients with acute Myocarditis without left Ventricular dysfunction or heart failure symptoms?
R. Yes, without EMB the etiology (e.g. viral or autoimmune) of myocarditisand the stage (acute or chronic) cannot be determined and, thus the adequate therapy (antiviral oder immunosuppressive).

In our inststution usually we defier EMP anddepend on CMR for DD between ischemic and non ischemic CM with normal coronary.
R: As shown in the clinical case presented in this webinar, and in keeping with published work CMR is unreliable to detect myocarditis with heart failure presentation or with nonischemic DCM. In addition, without EMB the etiology (e.g. viral or autoimmune) of myocarditis and the stage (acute or chronic) cannot be determined and, thus the adequate therapy (antiviral oder immunosuppressive).

Inadequate CMR - look at Moon papers on T1 mapping, IR-GRE only detects focal scar.
R: without EMB the etiology (e.g. viral or autoimmune) of myocarditis cannot be determined and, thus the adequate therapy (antiviral or immunosuppressive). So far even the more advanced CMR sequences cannot differentiate between virus-positive and virus-negative patients.

What is the complication rate of endomyocardial biopsy in non-transplanted patients?
It is very low. It is published that in 3000 EMB there was no death and in one case a complete AV block

Is this Churg Strauss Syndrome?
R: No, it is not.

What is the histologic pattern in alcohol related dilated cardiomyopathy
There is no specific pattern of alcohol dilated CMP. We see degeneration of myocytes, fibrosis and sometimes some inflammation.

We usually think of myocarditis when the heart is normal in size or not significantly dilated. Here the EDD is 82 mm. Does this suggest that we should biopsy all our dilated myopathy patients???
R: Yes, indeed, correct. In our experience as well as in other transplant centers performing EMB in all patients with non-ischemic DCM the frequency of inflammatory cardiomyoapathy/myocarditis is fairly common in non - ischemic DCM. We now treat every patient with inflammatory virus-negative DCM with immunosuppression with very good results, as shown in the clinical case described here. This is why we would like to draw the attention of the cardiological community in order to perform EMB in all non ischemic DCM patients, even at an apparently advanced stage, because we have seen reverse remodeling and recovery of biventricular function with a simple immunosuppressive regimen as described in the Webinar.

I joined in late, where did you take the biopsies?
R: from the right ventricle.

Should EMB take place in every newly diagnosed DCM in young or middle-aged patients with normal coronary arteries?
R: Yes, indeed, correct. In our experience as well as in other transplant centers performing EMB in all patients with non-ischemic DCM the frequency of inflammatory cardiomyoapathy/myocarditis is fairly common in non - ischemic DCM. We now treat every patient with inflammatory virus-negative DCM with immunosuppression with very good results, as shown in the clinical case described here. This is why we would like to draw the attention of the cardiological community in order to perform EMB in all non ischemic DCM patients, even at an apparently advanced stage, because we have seen reverse remodeling and recovery of biventricular function with a simple immunosuppressive regimen as described in the Webinar.

Inmunosuppresive therapy for past myocarditis diagnosed in a late manner?
R: Sorry, the question is unclear to us. Immunosuppressive therapy may be considered if acute or chronic myocardial inflammation is found at EMB, and infectious agents (mainly viruses) are not detectable on EMB by molecular tools (as described by Prof. Klingel in the second talk). We hope we answered your question.

EMBs- where (LV/IVS/RV) and how many ? CMR or PTE guided
R: According to the Task force recommendations at least 3 samples for histology and immunohistology,each 1 to 2 mm in size, additional samples (at least 2) from different regions for viral PCR. From the RV or LV according centre preference and expertise. No need for CMR or PTE guide.

What do you think about using micofenolate instead of azathioprine?
R: we used azathioprine because the available trials used this drug, which is also effective and safe, as well as not expensive. However, in some patients without an adequate response, for instance in myocardits of SLE patients we have also used MMF with good results. More clinical trials are needed to establish the role of MMF as well as many other newer immunosuppressive and immunomodulatory agents, including biologic agents.

In Parvo virus myocarditis how sensitive is the blood test alone for viral load compared to in combination with myocardial biopsy as suggested by speaker?
The amount of virus load in the blood does not necessarily correlate with virus load in the blood.

We understand that byopsy is mandatory and that not preforming it is not ethical. Anyway in absence of myocardial biopsy whath type of therpay we can impement?
R: prescription of ACEinhibitors, beta-blockers, diuretics, antiarrhythmic etc, should be in keeping with current ESC guidelines on heart failure and arrhythmia. Betablockers are most commonly prescribed in myocarditis even with preserved LVEF if there is evidence of cardiac arrhythmia.

Is ist possible to miss a viral infection utilizing a myoc. biopsy of the RV? how to overcome?
Take an adequate number of biopsies, as recommeded by the Task Force, e.g. at least 3 samples for histology and immunohistology,each 1 to 2 mm in size, additional samples (at least 2) from different regions for viral PCR. From the RV or LV according centre preference and expertise. No need for CMR or PTE guide. However, current molecular techniques for viral genome detection are very sensitive and it is unsual that a clinically significant viral infection is missed.

How long should beta blockers and ACE inhibitors be continued in myocarditis with impaired LV systolic function?
R: Good question, no definitive answer for the moment. We use a tailored approach and generally keep them until LV function is entirely normal.However, if there is fibrosis (healed myocarditis) on a follow-up EMB and/or extensive LGE on F-u CMR we keep the patients on therapy life-long especially if these drugs are well tolerated. Autoimmune diseases are chronic, often life-long conditions and relapses may occur, therefore we tend to keep beta blockers and ACE inhibitors also after immunosuppression is stopped. So far the longest relapse of autoimmune myocarditis occured in a female patient after 10 years of immunosuppressive discontinuation, with worsening of LV function in spite of ACE inhibitors and with arrhythmia (NSVT) in spite of beta blockers, and responded to reinstitution of immunosuppression with azathioprine.

Is there any ongoing clinical trials on immunosuppressive therapy? Thank you!
R: The WG on Myocardial and Pericardial Disease is actively engaged in trying to set up a European Myocarditis Immunosuppression trial in biopsy-proven cases. Stay tuned!

Beside the medication what the patients with myocarditis have to follow (healthy behaviors)
R: good question, again little controlled data. However, we give the following recommendations: 1) sigarette smoking cessation; 2) no use of illlict drugs (e.g. cocaine can cause toxic myocarditis);3) restrict alcohol intake; 4) no sport activity in the first 6 months from diagnosis (both in biopsy-proven and clinically suspected myocarditis), 4) if recurrent cardiac symptoms, especially in the first months from diagnosis, e.g chest pain in the pseudo-infarct presentation, go to the nearest emergency department, 5) dedicated multidisciplinary outpatient follow-up (cardiologist, clinical immunologist, rheumatologist or internist with expertise in autoimmune disease)

How long would you defer an ICD during treatment of confirmed myocarditis in the context of severe LVSD in the absence of a life vest option i.e. when you're not sure that it will recover?
R.: Good question, again not enough data. If you do not have a life-vest option you should not defer the ICD implantation if there are indications according to arrhythmia guidelines.

What about the use of corticoids in miopericarditis?
R: Cases of clear "myopericarditis" are uncommon. Most patients have either pure myocarditis with pseudo-infarct presentation without pericarditis (no pericardial effusion, no increased C reactive protein) or pure pericarditis (no troponin increase, pericardial effusion, increased C reactive protein). Both in pericarditis and in clinically suspected myocarditis with pseudo-infarct presentation corticosteroids should not be used in the absence of etiological diagnosis, which in the case of clinically suspected myocarditis requires an EMB.