MYOCARDITIS UPDATE AND GUIDELINE 2021

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FELLOWSHIP OF HF AND HEART TRANSPLANTATION
Background: Myocarditis is an inflammatory disease of cardiac myocytes that generally results in bradyarrhythmia, abnormalities of ventricular systolic function, and cardiogenic shock. Acute myocarditis can be caused by various infections, immune-mediated processes, and cardiotoxins.
1. Epidemiology and diagnosis

The incidence of acute myocarditis is estimated to be 1.5 million cases per year globally. The contribution of myocarditis as a cause of HF varies by age and region from approximately 0.5% to 4.0%. Chronic, EMB proven, inflammation can be found in 9% to 30% of adult patients with a DCM. The clinical presentation of acute myocarditis may vary from mild symptoms to cardiogenic shock.
Table 30  Aetiologies to be considered triggering acute myocarditis

<table>
<thead>
<tr>
<th>Aetiologies</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Infectious</strong></td>
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<tr>
<td><strong>Viral</strong></td>
<td>Parvovirus B19, human herpes virus-6, Epstein-Barr virus, enteroviruses, (coxsackievirus, adenovirus), CMV, HIV, SARS-CoV-2</td>
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<tr>
<td><strong>Others</strong></td>
<td><em>Borrelia, Coxiella burnetii</em> (Q-fever)</td>
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<tr>
<td><strong>Auto-immune and others</strong></td>
<td>Sarcoïdosis, giant cell myocarditis, eosinophilic myocarditis, SLE, ANCA-positive vasculitis, rheumatoid arthritis, any other auto-immune disease</td>
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<tr>
<td><strong>Toxic</strong></td>
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<tr>
<td><strong>Medications</strong></td>
<td>Immune check point inhibitors, anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil</td>
</tr>
<tr>
<td><strong>Other agents</strong></td>
<td>Alcohol, amphetamines, cocaine</td>
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Figure 20 Management of patients with heart failure and suspected myocarditis

ACS = acute coronary syndrome; CAD = coronary artery disease; CAG = coronary artery angiogram; CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; MCS = mechanical circulatory support. *TS exclude CAD/ACS.

- **Management of patients with heart failure and suspected myocarditis**
  - Clinical history, signs and symptoms, ECG, laboratory, echocardiography, cardiac MRI, coronary CT/CAG
    - Treatment of CAD if present and indicated
    - HF treatment
    - Clinical stabilization
      - Maintain HF treatment
      - Consider MCS
  - Suspected auto-immunity, infectious, toxic
    - BMB if any doubt about diagnosis
    - Consider immunosuppressive therapy or anti-infection
**Indication.**
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 inflammation).

**Number and sites of the samples**
A minimum of 5 but possibly at least 7 samples, 3 for pathology, 2 for infections (DNA, PCR) and 2 for RNA viruses/viral replication. Left and/or right ventricle. CMR or PET guided sampling may be considered.

**Aetiology**
Quantitative PCR viral genome analysis for common cardiotrophic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackievirus) by rtPCR. Viral mRNA for active viral replication may be assessed although it has low sensitivity. On indication, search for CMV, HIV, Borrelia, Coxiella burnetii (Q-fever) and SARS-CoV-2.

**Diagnosis of inflammation**
Immunohistochemistry with staining for anti-CD3-, CD4-, CD8- or CD45 antibodies for lymphocytes and anti-CD68 antibodies for macrophages and anti-HLA-DR antibodies.

**Therapeutic implications**
Immunosuppressive therapy may be indicated based on the results of EMB as in giant cell myocarditis or eosinophilic myocarditis and, possibly, also in sarcoidosis, vasculitis or selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling. Antibiotics: *Borrelia* (Lyme disease). Antiviral therapy: HIV, CMV, HHV6 pending on load and viral replication (mRNA).
HF therapy should be started if LV systolic dysfunction is present at presentation and should be continued for at least 6 months upon complete functional recovery (EF >50%).

Immunosuppression for at least 6—12 months is required in acute myocarditis with clinical or EMB evidence of auto-immune disease, including giant cell myocarditis, vasculitis or sarcoidosis.

Immunosuppression is not advised on a routine basis in acute myocarditis without clinical or EMB-based evidence of auto-immune disease. Initial empirical administration of i.v. corticosteroids may be taken into consideration in cases of high suspicion of immune-mediated myocarditis especially if complicated by acute HF, malignant arrhythmias and/or high degree AV block.

Intense sporting activities should be avoided as long as symptoms, cardiac enzymes elevated or ECG/imaging abnormalities are present and last for at least 6 months since complete recovery.

Yearly follow-up for at least 4 years, with an ECG and echocardiography, is needed as acute myocarditis may lead to DCM in up to 20% of cases.
Indication
Indicated at baseline, in all patients with clinical history, ECG, elevated troponin or echocardiographic abnormalities, and significant CAD excluded or unlikely. Advised at follow-up in patients with persistent dysfunction at echocardiography, arrhythmias or ECG abnormalities.a

Main findings
At baseline: T1-weighted (inflammation, injury) and T2-weighted (oedema) sequences, extracellular volume and LGE within 2 weeks after symptom onset.956,960
At follow up: LGE to evaluate the degree of scarring, T1 and T2 to identify persistent inflammation.a

Diagnostic significance
At least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted images), with at least one T1-based criterion (increased myocardial T1, extracellular volume, or LGE) in the acute phase. Only one (i.e., T2-based or T1-based) marker may still support a diagnosis of acute myocardial inflammation in an appropriate clinical scenario, albeit with less specificity in the acute phase.
À negative T1/T2 scan does not exclude a still ongoing inflammatory process in the chronic phase.a
THERAPY

MANAGEMENT OF HF AND ARRHYTHMIAS

Patients with myocarditis and reduced LVEF are treated with optimal medical care, according to guidelines for the management of HF\(^{234}\). However, many patients with myocarditis have preserved LVEF. Whether early initiation of treatment with inhibitors of the renin–angiotensin–aldosterone system or with β-blockers can reduce inflammation, adverse remodelling and scar formation in these patients is questionable. In particular, the risk of arrhythmia is increased in patients with myocarditis independently of LVEF.
ATRIOVENTRICULAR BLOCK IS LESS COMMON IN PATIENTS WITH ACUTE OR FULMINANT MYOCARDITIS THAN IN PATIENTS WITH CARDIAC SARCOIDOSIS, AND HAS A VARIABLE, BUT MOSTLY LOW PREVALENCE IN PATIENTS WITH GIANT-CELL MYOCARDITIS. THE FREQUENCY OF CARDIAC ELECTRICAL CONDUCTANCE DISTURBANCES DECREASES FROM GIANT-CELL MYOCARDITIS TO EOSINOPHILIC MYOCARDITIS TO LYMPHOCYTIC MYOCARDITIS. THE HIGH PREVALENCE OF CARDIAC ELECTRICAL CONDUCTANCE DISTURBANCES IN PATIENTS WITH MYOCARDITIS HIGHLIGHTS A CLINICAL NEED TO IDENTIFY PATIENTS WITH MYOCARDITIS AT RISK OF ARRHYTHMIA, INDEPENDENTLY OF LVEF AND LGE.
IN PATIENTS WITH MYOCARDITIS, LIFE-THREATENING BRADYARRHYTHMIAS AND TACHYARRHYTHMIAS CAN OCCUR AT ANY STAGE OF THE DISEASE AND LEAD TO SUDDEN CARDIAC DEATH.\textsuperscript{155,236} VENTRICULAR ARRHYTHMIAS (VA) ARE MOSTLY REPORTED IN PATIENTS WITH GIANT-CELL MYOCARDITIS OR CARDIAC SARCOIDOSIS, WITH A PREVALENCE OF 29%\textsuperscript{237} AND 55%\textsuperscript{238}, RESPECTIVELY. SUPRAVENTRICULAR ARRHYTHMIAS OCCUR MORE FREQUENTLY THAN VA IN PATIENTS WITH MYOCARDITIS AND CAN VARY IN PREVALENCE DEPENDING ON THE TYPE OF MYOCARDITIS.
POST-INFLAMMATORY, SCAR-RELATED VA CAN PRESENT AS MONOMORPHIC VENTRICULAR TACHYCARDIA IN PATIENTS WITH HEALED MYOCARDITIS. POST-INFLAMMATORY SCAR-RELATED VA OCCURS IN REGIONS OF MYOCARDIAL FIBROSIS, WHICH APPEAR AS LOW-VOLTAGE REGIONS ON ELECTROANATOMICAL VOLTAGE MAPPING OR AS LGE ON CARDIAC MRI. ALTHOUGH SYSTOLIC DYSFUNCTION IS A COMMON FINDING IN PATIENTS WITH MYOCARDITIS WITH VA, AN ARRHYTHMOGENIC SCAR CAN OCCUR IN PATIENTS WITH PRESERVED LVEF.
SEVERAL PATHOGENIC MECHANISMS HAVE BEEN POSTULATED TO EXPLAIN THE PRESENCE OF DIFFERENT ARRHYTHMIAS OBSERVED IN PATIENTS WITH ACUTE MYOCARDITIS, INCLUDING ELECTRICAL INSTABILITY DUE TO DIRECT CYTOPATHIC EFFECTS, ISCHAEMIA DUE TO CORONARY MICROVASCULAR OR MACROVASCULAR DISEASE, GAP JUNCTION DYSFUNCTION, ABNORMAL CALCIUM HANDLING AND INVOLVEMENT OF THE CARDIAC CONDUCTION SYSTEM. THE RISK OF SUDDEN CARDIAC DEATH IN PATIENTS WITH ACUTE MYOCARDITIS IS NOT ALWAYS ASSOCIATED WITH THE SEVERITY OF MYOCARDIAL INFLAMMATION, AND CAN PERSIST AFTER THE ACUTE PHASE OF MYOCARDITIS IS RESOLVED.
GIVEN THAT EMB FOR THE DIAGNOSIS OF CARDIAC INFLAMMATION IN PATIENTS WITH VA CAN HAVE A HIGH SAMPLING ERROR IN PATIENTS WITH FOCAL MYOCARDITIS AND ESPECIALLY IN PATIENTS WITH CARDIAC SARCOIDOSIS, ELECTROANATOMICAL VOLTAGE MAPPING CAN BE USED TO TARGET THE BIOPTOME (THE INSTRUMENT USED TO OBTAIN EMB SAMPLES) TO AREAS WITH <0.5 MV AMPLITUDE AND FRACTIONATED ELECTROGRAM SIGNAL).
EMB IS RECOMMENDED FOR THE DIAGNOSIS OF MYOCARDITIS IN PATIENTS WITH VA AND ACUTE CARDIOMYOPATHY BECAUSE THE RISK OF VA IS INCREASED IN PATIENTS WITH INFLAMMATION IN EMB SAMPLES. The presence of viral nucleic acids in EMB samples can also indicate an increased risk of VA and late myocardial damage with progressive electrical conduction defects.
SYMPTOMATIC VA IN PATIENTS WITH ACUTE MYOCARDITIS IS USUALLY MANAGED WITH \textbullet \ ANTIARRHYTHMIC DRUGS, BUT THE EFFICACY OF THIS APPROACH HAS NOT BEEN TESTED. CARDIAC DEVICE IMPLANTATION FOR THE MANAGEMENT OF VA SHOULD BE EVALUATED AFTER THE RESOLUTION OF REVERSIBLE ACUTE MYOCARDITIS, GENERALLY 3–6 MONTHS AFTER INITIATION OF THE ACUTE PHASE\textsuperscript{244}. HOWEVER, THE TIMINGS FOR THE PLACEMENT OF AN IMPLANTABLE CARDIOVERTER–DEFIBRILLATOR (ICD) REMAIN UNCLEAR.
Temporary pacing might be required on presentation, but decisions for chronic pacing typically require a period of observation, histological examination of EMB samples and assessment of the disease course. Early de novo ICD implantation in patients with reduced LVEF alone should be avoided, and the use of a wearable cardioverter–defibrillator (LifeVest, ZOLL) considered in patients at high risk of sudden cardiac death.
IN PATIENTS WITH LYMPHOCYTIC MYOCARDITIS AND IN PATIENTS WITH MYOCARDITIS AND VA IN THE ACUTE PHASE OF DISEASE. NEVERTHELESS, THE BEST TIMING OF WEARABLE CARDIOVERTER–DEFIBRILLATOR USE HAS NOT BEEN PROSPECTIVELY INVESTIGATED. PATIENTS WITH GIANT-CELL MYOCARDITIS AND VA WITH A HEART TRANSPLANT-FREE LIFE EXPECTANCY OF >1 YEAR SHOULD RECEIVE AN ICD. RISK MANAGEMENT IN PATIENTS WITH CARDIAC SARCOIDOSIS IS MOST PROBABLY INDEPENDENT OF LVEF, INDICATING THAT LVEF-INDEPENDENT MARKERS NEED TO BE IDENTIFIED.
KNOWLEDGE GAPS AND FUTURE DIRECTIONS

ASSESS THE ROLE OF CLASSIC HF MEDICATIONS FOR THE PRIMARY PREVENTION OF HF IN PATIENTS WITH MYOCARDITIS.

CHARACTERIZE THE ROLE OF LVEF FOR PREDICTING THE RISK OF SUDDEN DEATH IN PATIENTS WITH MYOCARDITIS.

ASSESS THE INFLUENCE OF THE DIFFERENT FORMS OF INFLAMMATORY CARDIOMYOPATHY ON THE RISK OF SUDDEN CARDIAC DEATH (FOR EXAMPLE, CARDIAC SARCOIDOSIS VERSUS LYMPHOCYTIC MYOCARDITIS).

ASSESS THE BEST TIMING FOR CARDIAC PACING DEVICE IMPLANTATION.

INVESTIGATE THE ROLE OF A WEARABLE CARDIOVERTER–DEFIBRILLATOR IN PATIENTS WITH MYOCARDITIS WITH PRESERVED LVEF AND WITH SIGNS OF CLINICALLY SIGNIFICANT CARDIAC RHYTHM ABNORMALITIES.

DEVELOP A PATIENT STRATIFICATION MODEL FOR THE RISK OF SUDDEN DEATH IN PATIENTS WITH MYOCARDITIS.

PERFORM CLINICAL TRIALS TO ASSESS THE EFFICACY OF ANTIARRHYTHMIC DRUGS IN PATIENTS WITH CARDIAC INFLAMMATION.

INVESTIGATE THE EFFECT OF (INTENSIVE) EXERCISE ON THE PROPENSITY TO SUDDEN CARDIAC DEATH AND HF.
SEVERAL TREATMENT OPTIONS HAVE BEEN STUDIED IN SPECIFIC COHORTS OF PATIENTS WITH INFLAMMATORY CARDIOMYOPATHY THAT HAVE BEEN DEVELOPED ON THE BASIS OF THE EMB-DEFINED PRESENCE OF VIRAL GENOME (VIRUS TYPE AND VIRAL LOAD) AND IMMUNE CELL INFILTRATES.
VIRUS-NEGATIVE INFLAMMATORY CARDIOMYOPATHY

STUDIES AND REGISTRIES OF EMB SAMPLES FROM PATIENTS WITH VIRUS-NEGATIVE, CHRONIC INFLAMMATORY CARDIOMYOPATHY SUGGEST THAT THE USE OF IMMUNOSUPPRESSIVE THERAPY WITH PREDNISONE AND AZATHIOPRINE CAN IMPROVE CARDIAC FUNCTION. THESE FINDINGS CONTRAST WITH RESULTS FROM EARLIER STUDIES IN PATIENTS WITH ACUTE CARDIOMYOPATHY IN WHICH VIRAL PATHOGENS WERE NOT ASSESSED. A SINGLE-CENTRE, OBSERVATIONAL STUDY FOUND THAT 53% OF PATIENTS WITH INFLAMMATORY CARDIOMYOPATHY WHO DO NOT RESPOND TO STEROID-BASED THERAPY HAD CD20+ B CELLS IN EMB SAMPLES.
IN THIS SUBSET OF SIX PATIENTS WITH VIRUS-NEGATIVE INFLAMMATORY CARDIOMYOPATHY AND CD20⁺ B CELL-POSITIVE EMB RESULTS, TREATMENT WITH RITUXIMAB IMPROVED CARDIAC FUNCTION AND ALLEVIATED SIGNS AND SYMPTOMS OF HF FROM BASELINE, SUGGESTING THAT RITUXIMAB THERAPY HAS BENEFICIAL EFFECTS IN THIS PATIENT POPULATION.
ALTERNATIVE TREATMENT REGIMENS FOR PATIENTS WITH VIRUS-NEGATIVE OR AUTOIMMUNE INFLAMMATORY CARDIOMYOPATHY INCLUDE STEROID-BASED TREATMENT COMBINED WITH CYCLOSPORINE\textsuperscript{250} OR MYCOPHENOLATE MOFETIL\textsuperscript{251}, OR IMMUNOADSORPTION WITH SUBSEQUENT INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY (IMMUNOADSORPTION–IVIG). REMOVAL OF CIRCULATING ANTIBODIES BY NON-SPECIFIC IMMUNOADSORPTION HAS BEEN SUCCESSFUL IN THE TREATMENT OF SEVERAL AUTOIMMUNE DISEASES. PILOT STUDIES INDICATE THAT IMMUNOADSORPTION–IVIG IMPROVES MYOCARDIAL FUNCTION IN PATIENTS WITH DCM\textsuperscript{252} AND REDUCES MYOCARDIAL INFLAMMATION\textsuperscript{257}.
HOWEVER, THESE NOVEL FINDINGS SHOULD BE VIEWED AS HYPOTHESIS-GENERATING AND MORE DATA ARE REQUIRED FROM RANDOMIZED TRIALS. INDEED, A LARGE, PLACEBO-CONTROLLED MULTICENTRE STUDY TO INVESTIGATE THE EFFECTS OF IMMUNOADSORPTION–IVIG ON LV FUNCTION IN PATIENTS WITH DCM OR INFLAMMATORY CARDIOMYOPATHY IS ONGOING.\textsuperscript{258} THE RANDOMIZATION PHASE OF THIS STUDY WAS COMPLETED IN 2019. AN ALTERNATIVE TO IMMUNOADSORPTION IS THE INTRAVENOUS ADMINISTRATION OF SMALL SOLUBLE MOLECULES (SUCH AS PEPTIDES OR APTAMERS) THAT SPECIFICALLY TARGET AND NEUTRALIZE AUTOANTIBODIES AGAINST THE $\beta_1$-ADRENERGIC RECEPTOR.\textsuperscript{259} OF NOTE, THE USE OF ANTIBODY-TARGETING APPROACHES DOES NOT DEPEND ON THE PRESENCE OF CARDIAC INFLAMMATION.
AUTOANTIBODY TARGETING IS ALSO UNDER INVESTIGATION FOR THE TREATMENT OF NON-PRIMARY INFLAMMATORY HEART DISEASES, IN WHICH AUTOIMMUNITY COULD HAVE A ROLE IN DISEASE PROGRESSION. HOWEVER, KNOWLEDGE GAPS REMAIN ABOUT THE TYPE AND LENGTH OF IMMUNOSUPPRESSION AND ON NOVEL BIOLOGICAL AGENTS TO TARGET SPECIFIC IMMUNE PATHWAYS OR AUTOANTIBODIES.
Patients with myocarditis or inflammatory cardiomyopathy can be classified into four groups on the basis of endomyocardial biopsy (EMB) results: inflammation-negative, virus-negative; inflammation-positive, virus-negative; inflammation-negative, virus-positive; and inflammation-positive, virus-positive.

In patients with virus-positive inflammatory cardiomyopathy, a clear distinction between virus-active and virus-associated inflammatory cardiomyopathy is required. Given the different aetiologies and clinical presentations of the four groups, specific therapy regimens are suggested for each group (blue boxes), in addition to approved optimal medical therapy for heart failure and risk-adjusted therapy.
IMMUNOSUPPRESSIVE THERAPY IS MANDATORY FOR SPECIFIC FORMS OF VIRUS-NEGATIVE AUTOIMMUNE MYOCARDITIS, SUCH AS EOSINOPHILIC MYOCARDITIS, GIANT-CELL MYOCARDITIS AND CARDIAC SARCOIDOSIS. IMMUNOSUPPRESSIVE THERAPY IS ALSO SAFE AND EFFECTIVE IN CLINICALLY UNSTABLE OR NON-RESOLVING LYMPHOCYTIC VIRUS-NEGATIVE MYOCARDITIS AND IN LYMPHOCYTIC VIRUS-NEGATIVE MYOCARDITIS REFRACTORY TO STANDARD HEART FAILURE THERAPY. AUTOANTIBODY TARGETING CAN BE ACHIEVED WITH IMMUNOADSORPTION OR WITH NEWLY DEVELOPED SMALL MOLECULES (APTAMERS) THAT NEUTRALIZE SPECIFIC AUTOANTIBODIES.
FIG. 7: GAPS IN EVIDENCE FOR ENDOMYOCARDIAL BIOPSY-GUIDED THERAPY IN MYOCARDITIS AND INFLAMMATORY CARDIOMYOPATHY.
VIRUS-POSITIVE INFLAMMATORY CARDIOMYOPATHY

DIFFERENTIATING BETWEEN VIRUS-INDUCED ACTIVE MYOCARDITIS (FOR EXAMPLE, CAUSED BY ADENOVIRUSES OR ENTEROVIRUSES) AND VIRUS-ASSOCIATED MYOCARDITIS (IN WHICH THE VIRAL GENOME IS DETECTED IN EMB SAMPLES BUT WHETHER THE VIRUS IS A BYSTANDER IS NOT CLEAR; FOR EXAMPLE, CAUSED BY LATENT INFECTIONS WITH HERPESVIRUSES OR B19V) IS IMPORTANT. TO DATE, THE THERAPEUTIC EFFICACY OF TARGETING THE VIRAL INFECTION IN ACUTE VIRAL MYOCARDITIS HAS NOT YET BEEN ESTABLISHED IN RANDOMIZED CLINICAL TRIALS.
THE PHASE II BICC TRIAL INVESTIGATED THE EFFECTS OF IMMUNOMODULATION WITH IFNB THERAPY ON VIRAL CLEARANCE IN PATIENTS WITH INFLAMMATORY CARDIOMYOPATHY AND MYOCARDIAL VIRAL PERSISTENCE (ADENOVIRUSES, ENTEROVIRUSES OR B19V). TRIAL PARTICIPANTS WITH ENTEROVIRUS-POSITIVE MYOCARDITIS OR ADENOVIRUS-POSITIVE MYOCARDITIS (AS ASSESSED WITH EMB) SHOWED VIRAL CLEARANCE AFTER TREATMENT WITH IFNB, BUT IFNB THERAPY WAS NOT ASSOCIATED WITH VIRAL DNA CLEARANCE IN PATIENTS WITH B19V-POSITIVE MYOCARDITIS
THE ANTIVIRAL DRUGS POCAPAVIR AND PLECONARIL AS WELL AS IVIG THERAPY ARE EFFECTIVE IN NEONATES WITH ENTEROVIRAL MYOCARDITIS. IN PATIENTS WITH LATENT INFECTION WITH EPSTEIN–BARR VIRUS, CYTOMEGALOVIRUS OR HHV6, THE USE OF ANTI-HERPESVIRUS DRUGS IS AN OPTION TO REDUCE VIRAL COPY NUMBERS\textsuperscript{261}. WHETHER A COMBINATION OF ANTIVIRAL AND IMMUNOSUPPRESSIVE DRUGS CAN BE AN OPTION IN SELECTED PATIENTS WITH VIRUS-POSITIVE INFLAMMATORY CARDIOMYOPATHY DEPENDING ON THE STAGE OF THE DISEASE NEEDS TO BE INVESTIGATED.
**IVIG** is often used in patients with severe B19V viraemia and clinical complications. New antiviral strategies against B19V infections are under investigation and include the synthetic nucleotide analogues cidofovir and brincidofovir, flavonoid molecules, and hydroxyurea. However, no therapy options are so far available for B19V-associated inflammatory cardiomyopathy. The consensus is that no therapy is needed if low B19V copy numbers are detected in cardiac tissue samples in the absence of cardiac inflammation.
EVIDENCE FROM SMALL OBSERVATIONAL STUDIES INDICATES THAT IMMUNOSUPPRESSIVE TREATMENT HAS BENEFICIAL EFFECTS IN PATIENTS WITH LOW B19V DNA LOAD IN THE MYOCARDIUM AND WITH CARDIAC INFLAMMATION (CAPACITY PROGRAMME)\textsuperscript{262}, AND IN PATIENTS WITH B19V RNA POSITIVITY, FROM TREATMENT WITH THE ANTIVIRAL DRUG TELBIVUDINE, Owing TO ITS IMMUNOMODULATORY PROPERTIES
HOWEVER, PLACEBO-CONTROLLED CLINICAL TRIALS ARE NEEDED TO VALIDATE THESE OBSERVATIONS. OF NOTE, IMMUNOADSORPTION–IVIG WAS FOUND TO BE SAFE AND EFFECTIVE IN IMPROVING CLINICAL SYMPTOMS IN PATIENTS WITH VIRUS-POSITIVE INFLAMMATORY CARDIOMYOPATHY, REGARDLESS OF B19V OR HHV6 PRESENCE IN EMB SAMPLES. BY CONTRAST, IVIG DID NOT SHOW ANY BENEFICIAL EFFECTS IN PATIENTS WITH DCM IN A STUDY THAT DID NOT EVALUATE CARDIAC VIRAL PERSISTENCE.
REGISTRY DATA INDICATE THAT IVIG IS ASSOCIATED WITH CLINICAL IMPROVEMENT IN PATIENTS WITH B19V-ASSOCIATED INFLAMMATORY CARDIOMYOPATHY\textsuperscript{265}. IVIG WAS ASSOCIATED WITH A REDUCTION IN CARDIAC INFLAMMATION WHEREAS CARDIAC B19V ERADICATION WAS LIMITED, AS ASSESSED ON EMB SAMPLES.
REGISTRY DATA INDICATE THAT IVIG IS ASSOCIATED WITH CLINICAL IMPROVEMENT IN PATIENTS WITH B19V-ASSOCIATED INFLAMMATORY CARDIOMYOPATHY. IVIG WAS ASSOCIATED WITH A REDUCTION IN CARDIAC INFLAMMATION WHEREAS CARDIAC B19V ERADICATION WAS LIMITED, AS ASSESSED ON EMB SAMPLES.
PATIENTS WITH HIV-ASSOCIATED, HCV-ASSOCIATED OR INFLUENZA-ASSOCIATED MYOCARDITIS OR INFLAMMATORY CARDIOMYOPATHY ARE TREATED WITH ESTABLISHED ANTIVIRAL DRUGS (TABLE 1), INCLUDING ANTIRETROVIRAL THERAPY FOR PATIENTS WITH HIV-ASSOCIATED MYOCARDITIS, A COMBINATION OF OMBITASVIR, PARITAPREVIR, RITONAVIR AND DASABUVIR FOR PATIENTS WITH HCV-ASSOCIATED MYOCARDITIS,46 AND NEURAMINIDASE INHIBITORS (PERAMIVIR AND ZANAMIVIR) FOR PATIENTS WITH INFLUENZA-ASSOCIATED MYOCARDITIS
FOR PATIENTS WITH COVID-19, SEVERAL ANTIVIRAL REGIMENS ARE UNDER INVESTIGATION AND INCLUDE STRATEGIES TO PREVENT VIRAL ENTRY INTO THE HOST CELL (SUCH AS CHLOROQUINE, HYDROXYCHLOROQUINE, CAMOSTAT MESYLATE AND UMIFENOVIR), PROTEASE INHIBITORS (LOPINAVIR–RITONAVIR AND DARUNAVIR), RNA POLYMERASE INHIBITORS (REMDESIVIR) AND ANTI-CYTOKINE AGENTS (SUCH AS IL-6 RECEPTOR ANTAGONISTS AND IL-1B INHIBITORS)\textsuperscript{269}
KNOWLEDGE GAPS AND FUTURE DIRECTIONS

• Perform large, prospective, randomized controlled studies to explore new or existing (repurposed) immunosuppressive or immunomodulatory regimens and antiviral regimens in patients with myocarditis or inflammatory cardiomyopathy.

• Perform multicentre, EMB-guided or cardiac MRI-guided trials to assess optimal treatment duration with conventional HF drugs and, particularly, with treatment regimens that still need to be approved for clinical use.

• Perform sex-matched clinical studies, given the well-known sex-related differences in immune responses\textsuperscript{21,22} and outcomes in patients with myocarditis\textsuperscript{270}.
NOVEL THERAPEUTIC STRATEGIES

PATIENTS WHO DO NOT RESPOND TO GUIDELINE-DIRECTED NEUROHORMONAL INHIBITOR THERAPY AND HAEMODYNAMIC SUPPORT MIGHT BENEFIT FROM THERAPIES THAT EITHER INHIBIT ONE OR MORE OF THE EFFECTOR ARMS OF THE IMMUNE RESPONSE OR PROMOTE REGULATORY ELEMENTS OF THE IMMUNE SYSTEM. INSIGHTS FROM EXPLORATORY CLINICAL TRIALS SUGGEST THAT MULTIPLE SIGNALLING PATHWAYS CAN BE DIFFERENTIALLY ACTIVATED IN PATIENTS WITH MYOCARDITIS OR INFLAMMATORY CARDIOMYOPATHY.
IMPORTANTLY, CURRENT CLINICAL TRIALS ARE DESIGNED ON THE BASIS OF LESSONS LEARNED FROM PREVIOUS TRIALS ON HIGH-DOSE TNF INHIBITOR THERAPY IN PATIENTS WITH SYSTOLIC HF, WHICH DID NOT SHOW IMPROVEMENTS IN PATIENT OUTCOMES271. BY TAKING A SYSTEMATIC APPROACH TO PERSONALIZE TARGETED THERAPIES, THE CURRENT GENERATION OF THERAPEUTIC AGENTS ARE AIMED AT MINIMIZING TOXICITY AND MAXIMIZING THE LIKELIHOOD OF RECOVERY IN PATIENTS WITH SPECIFIC PHENOTYPES OF INFLAMMATORY CARDIOMYOPATHY.
TREATMENT WITH AN ENGINEERED SOLUBLE CAR FUSED TO THE CARBOXY TERMINUS OF HUMAN IGG, WHICH REDUCES VIRUS UPTAKE INTO HOST CELLS, HAS BEEN SHOWN TO LIMIT THE DEVELOPMENT OF ACUTE\textsuperscript{272} AND CHRONIC\textsuperscript{273} CVB3-INDUCED MYOCARDITIS IN MICE. THE POTENTIAL OF THIS APPROACH STILL NEEDS TO BE EVALUATED IN HUMANS.
ANTI-IL-1B AND ANTI-IL-1 RECEPTOR ANTIBODIES

FINDINGS FROM STUDIES IN ANIMAL MODELS OF VIRAL AND AUTOIMMUNE MYOCARDITIS • SUPPORT A CENTRAL ROLE FOR NLRP3 INFLAMMASOME ACTIVATION AND SUBSEQUENT IL-1B PRODUCTION IN THE PATHOGENESIS OF MYOCARDITIS. TREATMENT WITH AN ANTI-MOUSE IL-1B ANTIBODY AT DIFFERENT STAGES OF ENTEROVIRAL INFECTION PREVENTED THE DEVELOPMENT OF CHRONIC VIRAL MYOCARDITIS BY REDUCING INFLAMMATION, INTERSTITIAL FIBROSIS AND ADVERSE CARDIAC REMODELLING IN MICE. ONE CLINICAL TRIAL AND SEVERAL CASE SERIES SUPPORT THE USE OF AN ANTI-IL-1B MONOCLONAL ANTIBODY FOR THE TREATMENT OF RECURRENT PERICARDITIS. THE ONGOING ARAMIS AND RHAPSODY TRIALS ARE DESIGNED TO ASSESS THE EFFICACY OF IL-1B-BLOCKING AGENTS IN PATIENTS WITH MYOCARDITIS AND ASSOCIATED PERICARDITIS.
ANTI-IL-17 ANTIBODY

INCREASED IL-17-RELATED RESPONSES AND THE ACTIVATION OF PROFIBROTIC PATHWAYS HAVE BEEN ASSOCIATED WITH A GREATER RISK OF DEATH IN MICE WITH CVB3-INDUCED MYOCARDITIS AND WITH A LOWER RATE OF FUNCTIONAL RECOVERY IN PATIENTS WITH MYOCARDITIS. TH17 CELLS HAVE BEEN SHOWN TO PROMOTE THE PROGRESSION TO DCM IN MICE, WHEREAS TREG CELLS PROTECTED AGAINST MYOCARDITIS IN MICE BY ATTENUATING INFLAMMATION. A CLINICAL TRIAL OF SECUKINUMAB, AN ANTI-IL-17 MONOCLONAL ANTIBODY, HAS BEEN PROPOSED.
CELL-BASED THERAPIES

Clinical application of T<sub>REG</sub> cells<sup>281</sup> or the use of IL-2 agonists<sup>282</sup> (which promote T<sub>REG</sub> cell production and increase survival and suppressor function of mature T<sub>REG</sub> cells<sup>283</sup>) are alternative approaches to elevate the T<sub>REG</sub> cell to T<sub>H17</sub> cell ratio. Another potential cell-based approach involves the use of mesenchymal stromal cells, which have been shown to increase the number of T<sub>REG</sub> cells<sup>85</sup> and have immunomodulatory and cardioprotective effects in mouse models of myocarditis<sup>69,78,284</sup>, such as by modulating the cardiosplenic axis. Therapy with allogeneic mesenchymal stromal cells has also been shown to be safe and effective in patients with non-ischaemic DCM in the Poseidon-DCM trial.
IN THIS TRIAL, A SIGNIFICANT IMPROVEMENT IN LVEF WITH AUTOLOGOUS MESENCHYMAL STROMAL CELL THERAPY WAS OBSERVED ONLY IN PATIENTS WHO DID NOT CARRY A PATHOGENIC GENE VARIANT ASSOCIATED WITH DCM, INDICATING THE RELEVANCE OF THE GENETIC PROFILE OF PATIENTS WITH NON-ISCHAEMIC DCM IN DictATING RESPONSIVENESS TO MESENCHYMAL STROMAL CELL THERAPY. THIS RESPONSE WAS ASSOCIATED WITH A MARKED REDUCTION IN CIRCULATING TNF LEVELS, SUGGESTIVE OF A THERAPEUTIC EFFECT GOVERNED BY IMMUNOMODULATION. TAKEN TOGETHER, THESE FINDINGS INDICATE THAT CELL-BASED THERAPY HAS A POTENTIAL ROLE IN THE TREATMENT OF PATIENTS WITH INFLAMMATORY CARDIOMYOPATHY. FUTURE TRIALS ARE WARRANTED TO TEST THIS HYPOTHESIS.
ALDOSTERONE ANTAGONISTS

EVIDENCE SHOWS THAT EARLY BLOCKADE (STARTING AT THE ACUTE PHASE OF CVB3 INFECTION) OF THE MINERALOCORTICOID RECEPTOR WITH EPLERENONE HAS PLEIOTROPIC EFFECTS, INCLUDING IMMUNOMODULATORY, ANTI-OXIDATIVE AND ANTI-APOPTOTIC EFFECTS, AND PREVENTS ADVERSE CARDIAC REMODELLING AND DYSFUNCTION WITHOUT AFFECTING VIRAL LOAD IN THE HEART IN A MOUSE MODEL OF PERSISTENT VIRAL MYOCARDITIS\textsuperscript{287}. THIS FINDING SUGGESTS THAT EPLERENONE IS AN IDEAL CANDIDATE AS AN ACUTE TREATMENT OF MYOCARDITIS, TOGETHER WITH HF TREATMENT. HOWEVER, CURRENT GUIDELINES DO NOT CONSIDER ALDOSTERONE ANTAGONIST THERAPY FOR ACUTE MYOCARDITIS, INDICATING THE NEED TO TEST THIS NEW THERAPEUTIC CONCEPT IN CLINICAL TRIALS.
CANNABIDIOL AND ANTAGOMIRS

Interventions that primarily promote regulatory functions of the immune system for the treatment of myocarditis are under investigation in experimental models. The approaches include therapy with cannabidiol and therapy with antisense mirna complements (known as antagomirs or anti-mirs). Antagomirs injected systemically or locally can be used as a therapeutic tool to reduce either inflammation or virus replication.
MODULATION OF THE GUT MICROBIOME

Accumulating findings demonstrate the contribution of the gut microbiome and its derived metabolites to the underlying inflammation associated with HF. In addition, a gut microbiota-derived myosin-mimic peptide has been linked to inflammatory cardiomyopathy. These findings suggest that modulation of the microbiome and its derived metabolites are potential preventive and therapeutic strategies for inflammatory heart diseases.
Myocarditis in a 16-year-old boy positive for SARS-CoV-2

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Interventions: The patient was managed early with antivirals, immunomodulatory agents, a high dose of ascorbic acid, melatonin, and immunoglobulin therapy. The patient’s clinical condition was improved with minute by minute hemodynamic monitoring and supportive care.
A 78-year-old man was brought to the emergency department with complaints of shortness of breath and moderate generalized edema. Upon admission, his vital signs were as follows: body temperature: 37.2 °C, oxygen saturation: 72%, heart rate: 110 beats/min, blood pressure: 170/80 mmHg, respiratory rate: 40 breaths/min, and glasgow coma scale (GCS): 12. Chest auscultation revealed bilateral rales over the lung fields. Lung parenchymal changes related to COVID-19 were seen on chest computerized tomography (CT) scan, and PCR for SARS-CoV-2 was positive. Moreover, there was cardiomegaly on his chest radiography. Initial echocardiography indicated left ventricular ejection fraction (LVEF) of 15%, pulmonary arterial pressure (PAP) of 50 mmHg, diastolic dysfunction grade 1, mild regurgitation mitral valve, and normal septal thickness. The diagnosis of acute myocarditis was thus confirmed based on the classic Lake Louise criteria.
Discussion & Conclusion

• we have two mechanisms of COVID-19 induced cardiac dysfunction:
  
direct and indirect. In direct mechanism viral fusion with host cell can cause by ACE 2 receptor, cellular proteases such as serine protease TMPRSS2 and cathepsins (cathepsin B and cathepsin L) that may play significant duty in viral entry. The ‘cytokine storm’, may indirectly result in cardiac damage. Clinicians should be aware of the potentially lethal cardiac complication of COVID-19 especially in geriatrics. The use of anti-inflammatory and Immunotherapy may be beneficial in critically ill patients with acute myocarditis in the context of severe inflammation.