Neonatal Myocarditis: A Review
Mohammad Abdullah Al Mamun¹, Manzoor Hussain²

Abstract
Neonatal myocarditis is a rare and life-threatening disease with clinical symptoms suggesting bacterial sepsis, accompanied by congestive heart failure, cardiogenic shock and arrhythmias. Enteroviruses and adenoviruses are the most frequent pathogens isolated in myocarditis in neonate. Due to extensive myocyte necrosis in the left ventricle, symptoms may mimic myocardial infarction and circulatory collapse. The diagnosis is suggested by an ischaemic electrocardiogram, raised cardiac enzymes and left ventricular dysfunction. These infants are best managed by early recognition of heart failure, avoidance of hypotension and transfer to an ECMO center. No specific antiviral treatment exists for neonatal myocarditis. Even in the presence of sufficient respiratory and circulatory support, the mortality among neonates with viral myocarditis is high. Majority of survivors develop serious cardiac sequelae. Since neonatal myocarditis is a devastating disease and is not often in the differential diagnosis of neonatal collapse, clinicians should keep a high index of suspicion.

Introduction
Neonatal myocarditis may present with symptoms mimicking bacterial sepsis, accompanied by congestive cardiac failure, cardiogenic shock, arrhythmia, cardiovascular collapse requiring inotropes and mechanical ventilation suggested by an ischaemic electrocardiogram, raised cardiac enzymes and left ventricular dysfunction on echocardiography with normal coronary arteries.¹⁻³ Enterovirus (EV) and adenoviruses are the most frequent pathogens isolated, but parvovirus B19, influenza virus, respiratory syncytial virus and herpes viruses have been reported to cause neonatal myocarditis.⁴ It may be an under recognised cause of neonatal collapse. As EV infection is common in neonate⁵ and are the most frequent cause of myocarditis in neonate and infant⁶, in this review we will discuss about EV myocarditis in neonate. The incidence of neonatal EV infections may reach up to 12% during epidemics.⁶ Human EV belong to the family Picornaviridae and were previously classified into echoviruses, coxsackie viruses A and B, polioviruses, and the 'numerated' enteroviruses. A more recent classification system distinguishes four species (A,B,C,D) of non-polio enteroviruses. EV infection is increasingly reported in cases of sudden unexplained death in infancy, raising the possibility that it may be more common than previously thought.⁷ This devastating disease predominantly occurs within the first 2 weeks of life and in the majority of cases maternal disease existed prior to or shortly after the delivery.⁸ Approximately 75% of infected infants remain asymptomatic and less than 5% require hospitalization. The majority of EV infections are mild and selflimiting, with non-specific manifestations such as febrile illness, mild upper respiratory tract infection or gastroenteritis. Conjunctivitis and a fine blanching or occasionally petechial rash may be observed. However, progression to severe disease such as viral sepsis...
syndrome, myocarditis, hepatitis and meningoencephalitis may occur. Severe EV diseases such as meningoencephalitis, severe hepatitis and myocarditis occur mostly in the neonatal period\(^2,8,9\). Coxackie viruses of group B (CVB) are the predominant causative agents of acute and chronic EV myocarditis which damage the heart primarily via direct lysis of infected myocytes.\(^10\)

Neonates may acquire EV infections either vertically during maternal viremia; during delivery through contact with infected maternal blood, stool or vaginal secretions; or postnatally by close contact to infected mothers, visitors or health-care workers. The optimal treatment for neonates with EV myocarditis remains poorly studied and prognosis is also poor.\(^4,11,12\)

**Pathogenesis**

EV damages the myocardium primarily via direct lysis and apoptotic degeneration of infected myocytes in the absence of a localized ischaemic event.\(^13,14\) This myocyte necrosis is mimicking myocardial infarction and replaced by a scar. Later in life this may turn into an aneurysm of the left ventricle as it frequently occurs in patients with myocardial infarction.\(^13\) Akinetic, hypokinetic and hyperechogenic areas may found in the left ventricle on echocardiography and may develop dilated cardiomyopathy with mild or severe aneurysm formation within the left ventricular wall and mild to severe left ventricular dysfunction.\(^3\)

**Risk factor**

Risk factors for severe complications include premature birth, maternal illness prior to, at or shortly after delivery and onset of symptoms within the first 2 weeks of life.\(^8,9\)

**Clinical findings**

The clinical signs of EV infection are fever, lethargy, poor feeding, respiratory distress, irritability, poor peripheral perfusion, tachycardia, lactic acidosis and enlarged liver. The median day of onset of symptoms is 6 days (range 1-18 days) after birth.\(^9\) May present with arrhythmias, congestive heart failure and cardiogenic shock and can mimic any other neonatal infection. The cardiovascular collapse due to myocarditis may occur several days after EV sepsis/ meningitis during the second wave of a biphasic pattern of EV infection.\(^3\) Rapid deterioration may ensue, leading to shock, multiorgan failure and death.

**ECG findings**

ECG changes in neonatal myocarditis are variable and include ST-segment elevation or depression, T wave inversion or flattening, prolonged QTc, QRS widening, abnormalities in atrioventricular conduction and brady or atrial or ventricular arrhythmias (i.e., supraventricular or ventricular ectopic beats) are frequent findings. The dominant and consistent ECG features of subendocardial injury are the development of a new Q-wave and an absence of R-wave in I, II and in the left precordial leads and poor R wave progression. Although the sensitivity of ECG findings in myocarditis is low, a pathological Q-wave mimicking myocardial infarction has been described in adults.\(^3,9,15\) This uniform ECG feature representing severe myocardial ischaemia has an important additional value in the diagnosis of myocarditis in infants.

**Fig 1** Electrocardiogram showing ST segment depression in the anterior chest leads with poor R wave progression

**Echocardiography findings**

Echocardiography includes morphology, diastolic and systolic diameter of the left ventricle and left atrium, fractional shortening of the left ventricle, presence or absence of mitral and tricuspid regurgitation.\(^9\) There may be extensive areas of bright myocardium (hyperechogenicity) suggesting necrosis of the left ventricle and calcifications.\(^16\) Left ventricular dysfunction in the neonatal period is recognized as a complication of sepsis, birth asphyxia, metabolic disease, or structural abnormalities such as aberrant left coronary artery or hypoplastic left heart syndrome. So these should be excluded. There may be global ventricular dysfunction whereas severe left ventricular dysfunction may also present.\(^3\) Aneurysm of the left ventricle may also present.\(^17\)
Viral diagnosis
Viral diagnosis may be confirmed by positive real-time EV polymerase chain reaction (RT-EV PCR) on blood and/or cerebrospinal fluid, nasopharyngeal swab or stool. RT-EV PCR may be performed by using viral RNA extracted from different specimens. In recent years PCR testing has replaced culture techniques as the preferred diagnostic method, given the excellent sensitivity of >90%.

Prognosis
Very little information is available regarding the long-term cardiac outcome of neonates who survive EV myocarditis. There may be long term sequelae like chronic heart failure, mitral regurgitation and aneurysm formation within the left ventricle requiring long-term cardiac drug therapy. Mortality and long-term cardiac prognosis for survivors of EV myocarditis in the neonatal period have not been well studied. A review on this issue by Abzug et al mentioned that the prognosis for survivors of myocarditis is favourable.

Treatment
No specific antiviral treatment exists for EV myocarditis. While inotropic agents improve cardiac contractility, they may increase myocardial oxygen consumption and exacerbate arrhythmias. Afterload reduction is one of the mainstays of treatment and can be achieved with milrinone, dobutamine or levosimendan. Treatment with intravenous immunoglobulins has been advocated in the past, assuming that neutralizing antibodies could enhance virus clearance and attenuate the detrimental inflammatory response in the early phase of myocarditis. The therapy should be started as early as possible before severe necrosis of the myocytes has occurred. Treatment with ECMO in neonatal EV myocarditis has been sporadically reported but the benefit of ECMO is controversial. Pleconaril represents a potential antiviral treatment available against EV infections. However, several pediatric and adult studies reported conflicting results, and so far, no pediatric randomized controlled trial has been performed.

Outcome
The prognosis of enteroviral myocarditis in neonates is poor, with a mortality in the range of 30 to 83%, but it remains unknown how many cases with mild myocarditis are left undiagnosed. However, the rapid deterioration of ventricular function caused by myocarditis can lead to sudden instability and collapse. In these cases, mortality without ECMO is likely to approach 100%. Therefore, patients showing rapid clinical and echocardiographic deterioration despite adequate inotropic support should be considered early for ECMO.
**Conclusion**

Neonatal myocarditis may be an under recognized cause of neonatal collapse. The diagnosis is suggested by an ischaemic electrocardiogram, raised cardiac enzymes, and left ventricular dysfunction on echocardiography. As it is a devastating disease with high mortality and is not often in the differential diagnosis of neonatal collapse, clinicians should keep a high index of suspicion for neonatal myocarditis.

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