

**Journal of Pediatric Infectious Diseases**  
**Intravenous Immunoglobulin for congenital parvovirus Myocarditis**  
 --Manuscript Draft--

<b>Manuscript Number:</b>	JPID-D-17-00105
<b>Full Title:</b>	Intravenous Immunoglobulin for congenital parvovirus Myocarditis
<b>Article Type:</b>	Case Report
<b>Keywords:</b>	congenital parvovirus infection, myocarditis, immunoglobulin
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<b>Abstract:</b>	Congenital Parvovirus infection has diverse presentation ranging from asymptomatic infants to intrauterine demise secondary to red cell aplasia or myocarditis. Treatment is aimed at correcting anemia with intrauterine and postnatal transfusions. We report a case of fetal hydrops with severe atrioventricular regurgitation and myocardial dysfunction secondary to parvovirus infection in a preterm infant. Myocarditis and myocardial dysfunction responded to immunoglobulin administration.

## Intravenous Immunoglobulin for Congenital Parvovirus Myocarditis

### Introduction:

Congenital Parvovirus infection has a diverse range of clinical presentation ranging from asymptomatic infants to intrauterine demise secondary to red cell aplasia or myocarditis.

[1, 2] Current treatments are primarily aimed at correcting anemia, using intrauterine red cell transfusions and prenatal or post-natal intravenous immunoglobulin (IVIG) with varying success. [3 - 7] We report a case of severe atrioventricular valves regurgitation secondary to myocardial dysfunction in a preterm female infant with congenital parvovirus infection responding to IVIG administration.

### Case Summary:

A premature female infant was born at 31 weeks' gestation with a birth weight of 2041g to a 34 year -old mother with no family history of cardiac diseases. At 26 weeks' of pregnancy, the mother reported that her five year-old son was clinically diagnosed with fifth disease. Her blood testing showed elevated parvovirus B19 IgM and IgG. The rest of her prenatal tests were unremarkable. Weekly fetal ultrasounds, including middle cerebral artery Doppler for fetal anemia were normal until 30 weeks of gestation when a fetal echocardiogram showed severe mitral and tricuspid regurgitation and severe bi-atrial enlargement. At 31 weeks' gestation, the fetus developed hydrops fetalis with placentomegaly, ascites, and pericardial and pleural effusions. The patient was then delivered at 31 weeks' gestation after maternal administration of two betamethasone doses. Apgar scores at 1, 5 and 10 minutes were 5, 7 and 8. She was intubated after delivery because of respiratory insufficiency. Vital signs showed hypotension and

tachycardia. Cardiac auscultation revealed a holosystolic murmur and hepatomegaly. A diastolic murmur and gallop were appreciated on the third day. Echocardiogram showed severe bi-atrial and right ventricular enlargement, moderate-to-severe tricuspid and mitral regurgitation, flat interventricular septum with decreased systolic function, and patent ductus arteriosus with low velocity left to right shunt (Fig.1 & 2). She received milrinone, dopamine and furosemide. Hemoglobin was 13 g/dL. 2 doses of IV IG at 750 mg/kg/dose were administered on day of life (DOL) 5 and 17. Quantitative parvovirus PCR, and Brain Natriuretic Peptide (BNP) levels were monitored following IVIG infusion (table 1).

The patient's condition improved with resolution of gallop on day 8, and diastolic murmur on day 20. Her cardiorespiratory function progressively improved, and she was extubated after 30 days. Milrinone and dopamine were discontinued on DOL 35, and the patient was maintained on captopril and furosemide. Her clinical improvement correlated temporally with a decreasing parvovirus load (Fig. 3). Echocardiogram performed during a follow up visit at 4 months of age demonstrated mild mitral and tricuspid regurgitation, mild bi-atrial enlargement with normal biventricular size and systolic function; hence medications were discontinued. The patient was last seen at 22 months follow-up visit and was developing and growing appropriately.

#### Discussion:

Parvovirus B19 is a non-enveloped single stranded DNA virus that is highly prevalent and presents with varying symptoms depending on the age and immunocompetence of the host. Children can present with characteristic “slapped cheek” rash of Erythema Infectiosum (Fifth Disease).<sup>[1]</sup> Fetal outcomes as a result of primary maternal infection

during gestation can range from asymptomatic full term birth to myocarditis, non-immune hydrops fetalis or intrauterine fetal death. <sup>[2]</sup> The overall risk of adverse fetal outcome is estimated at less than 10%. <sup>[1]</sup> Diagnosis is made by PCR detection of viral DNA, which has a 94% sensitivity. Fetal serology can be unreliable and detection of IgM is only 29% sensitive. <sup>[8]</sup>

Heart failure and the ensuing hydrops in congenital parvovirus infection are usually caused by severe anemia from red cell aplasia leading to high output cardiac failure resulting in hydrops. The presence of hydrops in our patient cannot be explained solely because of anemia as Hb level was 13g/dL. We attributed it to myocardial dysfunction and severe atrio-ventricular valve regurgitation associated with parvovirus infection. The exact mechanism of parvovirus induced myocardial and valvular dysfunction is unknown. The likely mechanics could be similar to what is described in cases of myocardial damage caused by other viral infections such as Coxsackie B involving immune-mediated and direct viral cytotoxicity. <sup>[9]</sup>

In our patient, IVIG treatment was associated with both clinical and echocardiographic response. Prior to IVIG treatment, parvovirus by PCR was positive. Following two courses of IVIG, cardio-respiratory status improved and the patient weaned off the ventilator and medications. Her quantitative PCR showed an increase several days after the first dose but consistently trended downward following the second dose. We elected to administer IVIG to treat myocarditis due to severity of the clinical presentation in lieu of its reported efficacy in other immune-mediated diseases, as supported by experimental data in which polyclonal immunoglobulin protects against myocardial damage in mouse models of viral and autoimmune myocarditis. <sup>[10]</sup> IVIG may replace antibodies, enhance

viral clearance, neutralize pathogens, and enhance clearance of inflammatory cytokines that contribute to myocytes destruction. <sup>[11]</sup> IVIG has been used successfully to treat parvovirus myocarditis in adults and children outside the neonatal period. <sup>[12, 13]</sup>

There are no current treatment guidelines for congenital parvovirus infection myocarditis in the early neonatal period. Treatment of congenital Parvovirus infection is directed at correcting anemia via intrauterine transfusion of blood, which reduces the risk of fetal demise. <sup>[8]</sup> Selbing et al administered IVIG to a mother at 22 weeks gestation and reported an improvement in fetal ascites and fetal pericardial effusion. <sup>[3]</sup> Matsuda, et al transfused B19-rich IVIG into the peritoneal cavity of a 22-week gestation fetus and reported similar findings. <sup>[4]</sup> Postnatally, IVIG was used to treat congenital parvovirus in the setting of anemia. <sup>[5, 6, 14]</sup> Lejeune, et al treated severely anemic twins with IVIG 0.4g/kg/day for 5 days and documented resolution of anemia and decreasing viral load. <sup>[5]</sup> Nadimpalli, et al documented an improvement in viremia and anemia in a 3 month-old treated with 3 courses of IVIG administered at 3-4 day intervals. <sup>[6]</sup> To our knowledge, this is the first case reporting the use of IVIG to treat parvovirus related myocarditis.

Limitations of our report include the uncertainty of the outcome had IVIG not been administered as the natural history of the disease process is still not well studied. In addition, our patient did not show improvement until after the second dose; however, this is consistent with the case reports by Lejeune and Nadimpalli, as discussed above.

Overall, our patient with myocarditis and anemia due to congenital parvovirus demonstrated improvement in clinical status after administration of IVIG. Uniquely, our patient's disease process was primarily myocarditis with severe mitral and tricuspid regurgitation, as opposed to pure red cell aplasia. Our case adds to the evidence base

suggesting that IVIG may be an effective treatment for congenital parvovirus, although it remains difficult to make a strong recommendation without a randomized controlled trial.

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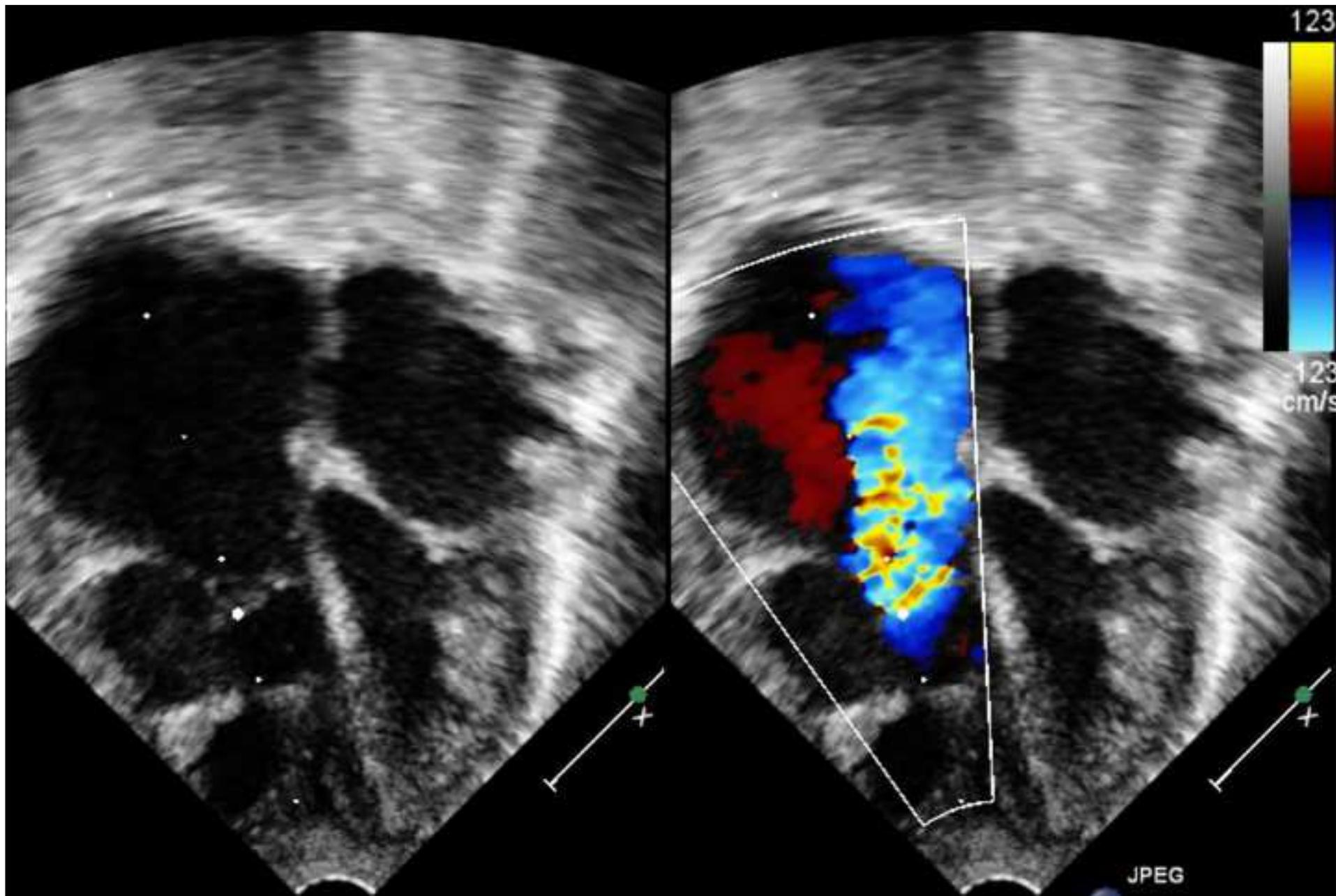
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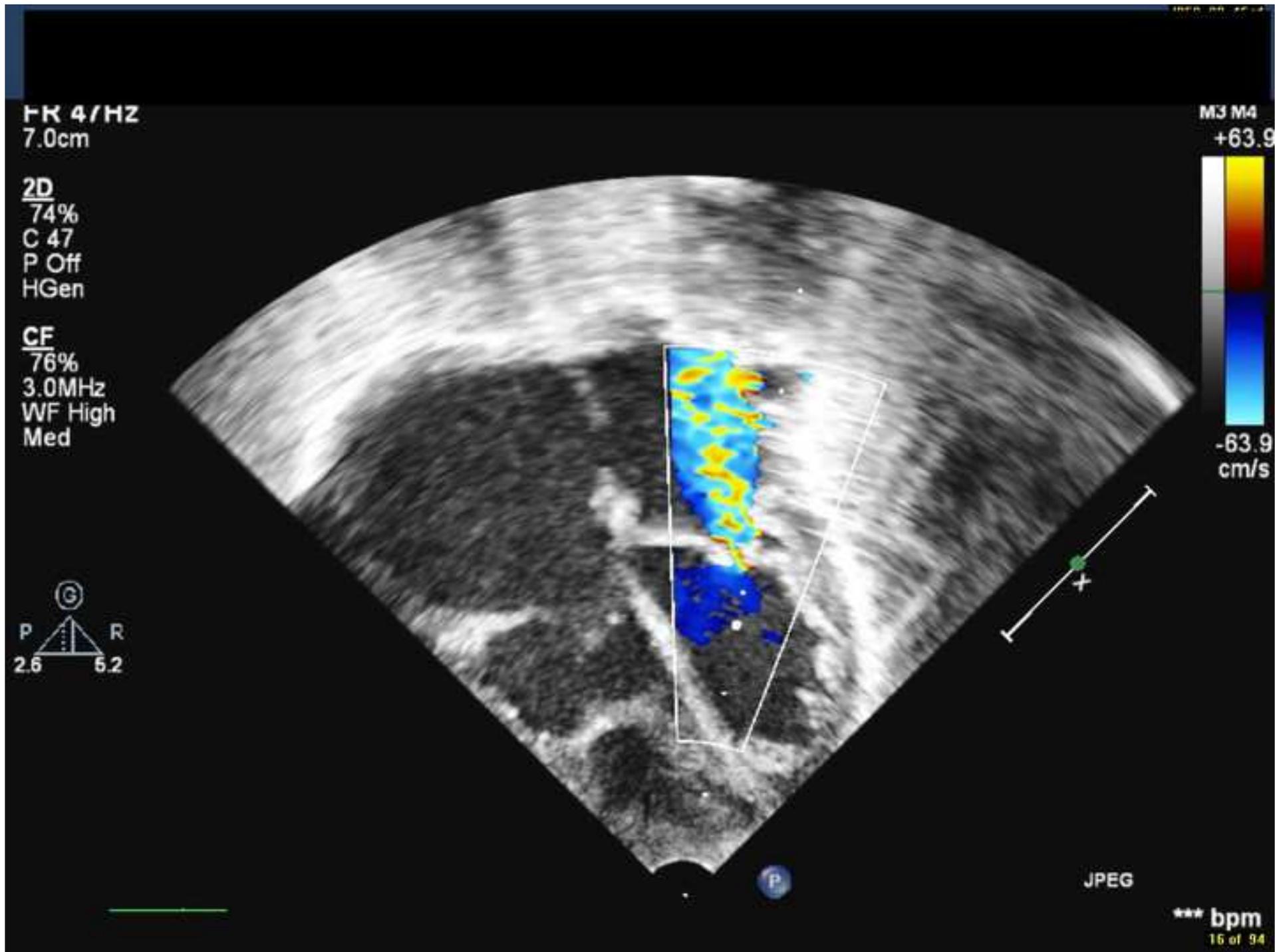
Table 1: Sequential laboratory data

Figure 1: Four chamber demonstrating atrial enlargement and severe atrioventricular regurgitation

Figure 2: Four chamber demonstrating atrial enlargement and severe atrioventricular regurgitation

Figure 3: Clinical course summary in relation to IVIG





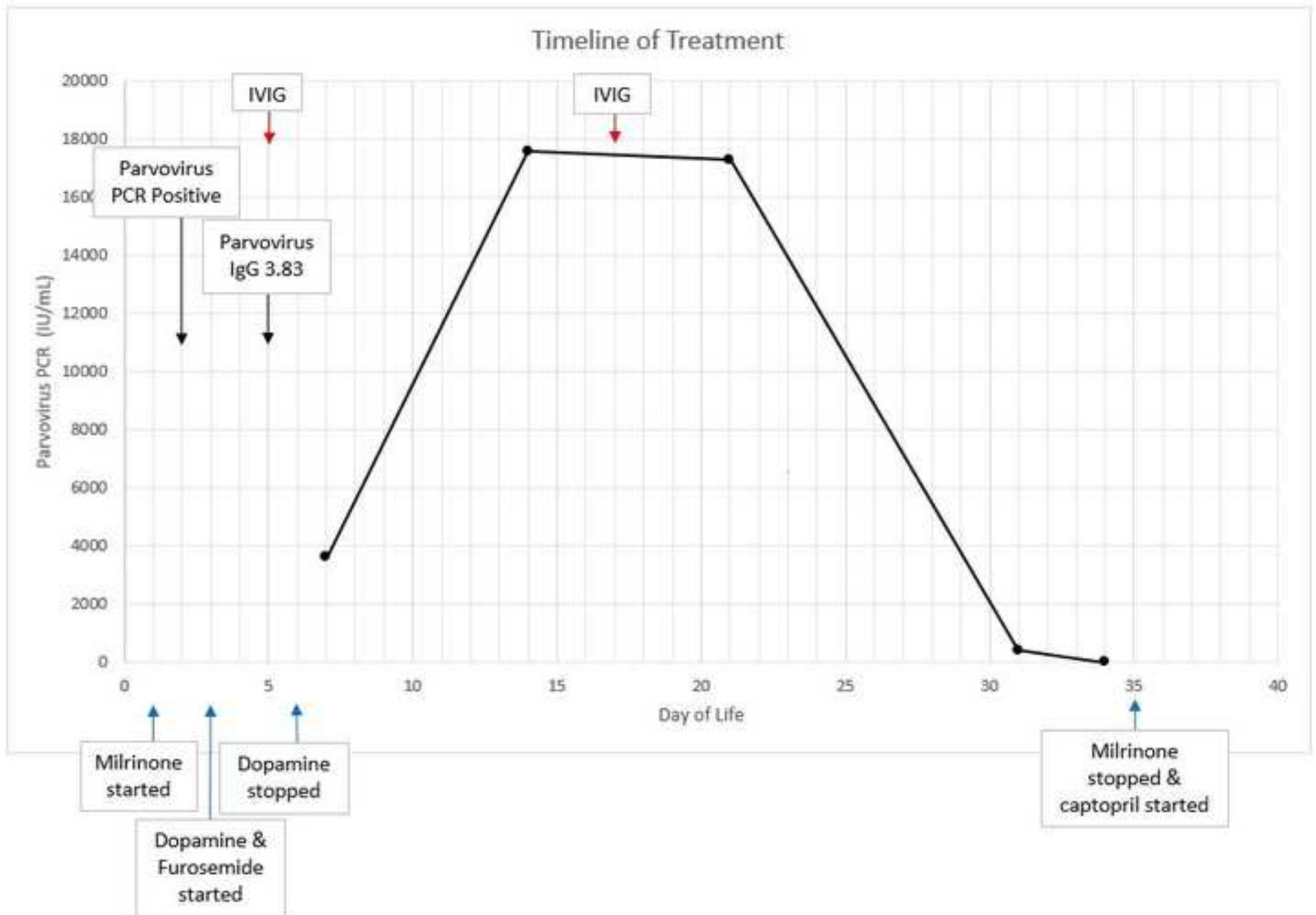


Table 1

Age in days	1	7	14	21	31	34	48
Hemoglobin (N = 13-21) g/dl	12.5						
Qualitative Parvovirus PCR	Positive						
Quantitative Parvovirus (IU/ml)		3600	17600	17300	409	< 199	
Brain natriuretic Peptide (pg/ml)		175			99		28

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