Suggested guidelines for the diagnosis and management of chronic HCV infection in children

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ABSTRACT
HCV infection in children is different from the adult infection in many ways like natural course of the disease; duration, therapeutic response and side effects profile of the drug therapy; and prognosis. Special considerations include what is the appropriate time to investigate a suspected child, when to institute and choice of drug therapy and how to prevent vertical transmission. In this article, based on the current evidence suggested guidelines for the diagnosis and management of chronic HCV infection in children is given. Feedback to help improve/modify these recommendations by those experienced in dealing with the children will be welcome.

Keywords: Chronic Hepatitis C; Children; Guidelines; Antiviral Therapy

1. INTRODUCTION
Antiviral therapy for chronic hepatitis C has traditionally been considered contraindicated in children. A review of the recent literature however suggests that this view is no more true. Many recent studies have suggested that antiviral therapy can be safely given in children with excellent results, though some important diagnostic and therapeutic considerations need to be addressed. In the light of the current evidence, this article presents a practical and succinct diagnostic and therapeutic approach to HCV-infected children.

2. DISCUSSION
Approximately, 0.2% and 0.4% of children under the age of 12 and between 12 - 19 years respectively are infected with hepatitis C in Pakistan [1] (roughly, 75% - 90% of them have HCV genotype 3). Based upon studies in adults, it is estimated that 75% - 80% of these children are HCV RNA positive as well (i.e. have active disease and potentially require treatment). In USA, an estimated 240,000 children (28,000 new each year) [2] are infected with HCV with viremia present in 50% - 80% of them [3]. The prevalence of HCV infection among women of childbearing age is estimated to be 1.2% and the risk of HCV transmission at the time of delivery is 2% - 5% (the higher the HCV viral load in mother [ > 1 x 10^6 ], higher the risk of transmission and vice versa) [4]. In mothers suffering from HCV/HIV coinfection, the risk further increases by at least four folds [5]. Whereas, in the developed world maternal drug use and vertical (perinatal) transmission appears to be the major mode of HCV transmission in children [6], in Pakistan we cannot overlook transmission by blood/blood products transfusion. Thus all children who have ever been transfused unscreened blood/blood products in Pakistan for any reason, and children born to infected mothers (all pregnant ladies should be screened for HBV & HCV) should be considered as potentially infected and investigated appropriately. Other potential modes of exposure in pediatric age-group patients include hemodialysis, extracorporeal membrane oxygenation, surgery for congenital heart disease and high-risk behaviours such as intravenous or intranasal drug use and use of shared tattoo equipment, Seroprevalence rates as high as 10% - 20% have been reported in such cases [7,8]. In quite an appreciable percentage (63% in one study) [9] of HCV-positive pediatric age-group patients, no obvious cause of viral exposure is found.

2.1. Natural Course of HCV Infection in Children
The natural course of the disease is different in children as compared to the adults. As compared to vertically-transmitted HCV infection in whom most patients are asymptomatic [10] with normal or near-normal ALT levels, transfusion-acquired pediatric HCV infection is more commonly associated with symptomatology (jaundice in 1/3rd of the cases) and raised ALT levels (in almost all cases). In cases of vertically-transmitted HCV infection, although ALT levels are often normal at birth, many studies have reported that the levels may rise either transiently or persistently at 4 - 6 months of age, and may
continue to remain high till 2 years of age with substantial fall thereafter [11,12]. Nonetheless, it is pertinent to mention here that ALT concentration is not a criterion to suspect or rule out the presence of significant liver damage. Many studies have repeatedly shown that ALT levels may be persistently normal in patients who otherwise are HCV infected with high viral loads and evidence of severe hepatocellular damage or even significant fibrosis on liver biopsy [13-15]. Therefore, normal ALT levels should never be interpreted as normal liver. Unlike adults, higher rates of spontaneous resolution (ranging from 20% - 45% especially in genotype 3 cases) have been demonstrated in children [16,17]. It appears that children with transfusion-acquired infection are more likely to undergo spontaneous resolution than those who acquired the disease vertically. Also, unlike adults, in children the disease progression per se is slower and there is less probability of development of end-stage-liver disease or hepatocellular carcinoma [18]. Data however shows that the frequency of development of fibrosis is no different in children than adults, although progression to cirrhosis is slower (most children develop advanced liver disease >30 years after infection) [19-21]. Interestingly, periportal fibrosis appears to be commoner in children; it may worsen with age [20,21]. It appears that the probability of persistent viraemia and development of end-stage liver disease is relatively higher in children who are infected with genotype 1a, are polymerase chain reaction (PCR)-positive after the first year of life [22], are obese, have HCV/HIV co-infection or those whose mothers abuse drugs [9]. This probably represents the groups of patients who should be offered the benefits of antiviral therapy early in the course of the disease. Conversely, spontaneous viral clearance is more likely with genotype 3 cases as depicted in one study by Cox regression analysis (hazard ratio 6.44; 95% confidence interval: 2.7 - 15.5) [9]. In this group of patients, it is reasonable to give some time for spontaneous resolution to take place. Children who present with symptomatic acute HCV infection are probably less likely to develop chronic infection and thus should be given time for spontaneous resolution to take place [23].

### 2.2. Investigative Work-Up

Only those children whose mothers are both anti-HCV antibody & HCV-RNA positive should be investigated for possible vertical transmission of HCV infection. Mothers who are anti-HCV antibody positive but HCV-RNA negative virtually never transmit infection to their infants [24-30]. Diagnostic work-up of children suspected of having chronic HCV should proceed similar to that of adults. A sensitive serological test (3rd generation enzyme linked immunoassay—ELA) for the detection of anti-HCV antibodies (not done during the first year of life due to the presence of maternal IgG antibodies) followed by a sensitive HCV RNA assay for definite confirmation is the usual diagnostic protocol [31,32]. Presence of HCV-RNA in both the mother and the infant is the most reliable indicator of vertical transmission of HCV infection. In anti-HCV positive persons, a single positive HCV RNA assay confirms the diagnosis. Having said this please remember that false positive result is also a possibility from contamination due to errors in sampling, storage, or extraction of RNA. Since, HCV RNA is normally present only intermittently in the circulation, a single negative assay doesn’t rule out the diagnosis of HCV infection. Thus, all negative test results should be reconfirmed with a repeat test done approximately 1 - 2 months later so as to reliably rule out the presence of ongoing HCV infection. If HCV RNA is lost due to errors in sampling, storage, or extraction of RNA, or insensitivity of the assay (caused by improperly selected probes or primers), false negative results can come. The special precautions that need to be observed in all such cases include urgent shipping of the samples on dry ice; rapid separation of the serum within 2 to 4 hours of collection; and storage at −20°C.

Unlike hepatitis B virus (HBV) cases, no test is currently available to determine infectivity in a HCV-infected case. Therefore, all patients who are anti-HCV positive should be taken as potentially infectious.

Because of the probability of spontaneous clearance of HCV RNA from circulation during the first few years of life, infants born to HCV-infected mothers (particularly genotype 2 & 3 cases, which represent most of the Pakistani patients) should best be given time for spontaneous resolution to take place. Investigative work up can thus be deferred till 18 months of age or later. There is 80% probability that children who are PCR-positive at the age of 18 months won’t develop spontaneous resolution and will end up having chronic infection albeit asymptomatic [22]. Since antiviral treatment is contraindicated in children under the age of 3 years, there is no need to induce undue anxiety in the family just to have an earlier diagnosis. However, if parents insist on an earlier diagnosis, a qualitative PCR for HCV RNA may be performed at or after the infant’s first well-child visit at 4 months of age [33]. Anti-HCV antibodies passively acquired by infants from the infected mothers may persist in the circulation for up to 12 months. Therefore, serological testing (anti-HCV detection by enzyme immunoassay—ELA) should better be avoided in infants <1 year of age [34]. Because of the possibility of contamination with the maternal blood, cord blood should never be used for any HCV-related testing [35].

Adolescents/young adults who need to be screened for HBV/HCV include those who were transfused blood before 1992 or who had had admission in a neonatal intensive care unit (NICU) prior to 1992 for any reason. This
represents a large risk group (approximately 500,000 in the United States). Although there is a documented [36] seroprevalence of about 3% in this group, whether systematic screening of all NICU graduates for HCV to identify previously unrecognized cases is practicable &/or cost-effective is not yet clear [37].

2.3. Role & Utility of Liver Biopsy in Hepatitis C

The role and utility of liver biopsy in hepatitis C cases is still debatable and no definite consensus exists in any guideline. Subgroup of patients in which liver biopsy may be useful include:

1) >5 years olds who have acquired HCV infection vertically in which aminotransferase levels remain persistently normal and parents are unsure about whether or not to proceed to treatment [15]. As is well known that ALT levels do not correspond accurately to the degree of hepatic fibrosis, [38] in patients with persistently normal aminotransferase levels, the only way to reliably determine the extent and severity of liver disease and thus to make timely decisions regarding therapeutic interventions is to go for liver biopsy.

2) >5 years olds who have acquired HCV infection vertically and are suffering from HCV genotype 1 (less likely to respond to treatment) and parents are unsure about whether or not to proceed to treatment; [liver biopsy is not routinely recommended for genotype 2 or 3 cases because these patients respond very favorably to antiviral therapy regardless of the stage of liver disease and degree of fibrosis].

If liver biopsy in such patients shows only a minimal fibrosis limited to the portal tract (Metavir [39] score < 2 or Ishak [40] score < 3), initiation of interferon therapy may be delayed/individualized. Repeat biopsies done at 4 - 5 years intervals can be used to monitor the progression of fibrosis in such cases. If repeat biopsies show worsening of fibrosis, especially more- than-portal fibrosis (i.e. Metavir score ≥ 2 or Ishak score ≥ 3), patients should be offered antiviral therapy lest fibrosis worsens and cirrhosis develops when the treatment success rate and prognosis will be relatively poorer [41].

In children who have recently acquired HCV infection horizontally (via IV drug abuse etc), liver biopsy may not be necessary. This is because such patients are unlikely to develop advanced liver disease within a few years of transmission. If a decision to treat such a case is being made, determining the degree of fibrosis on histology is irrelevant.

2.4. Treatment

One rule of thumb that must be kept in mind while making a treatment decision in pediatric age-group HCV-infected cases is that although less common than adults, cirrhosis, end-stage liver disease and HCC do develop in some cases during childhood/adolescence. Therefore, deferring antiviral treatment on the assumption that these complications may not develop till 3rd/4th decade of life is not a very safe and prudent approach. Nonetheless, treatment plan may be deferred in patients suffering with genotype 1 who are approaching their 18th birthday in the near future because at least one of the protease inhibitors (telaprevir) is likely to be available to adults soon.

Monitoring for HCC is only recommended in patients who have already developed advanced cirrhosis (a rarity) and those coinfected with HBV (which can cause HCC without first causing cirrhosis). Liver ultrasonography and serum alpha fetoprotein levels both done annually generally suffice to monitor for HCC. Importantly the monitoring business should continue even after institutional and successful completion of antiviral treatment. This is because successful treatment of HCV infection in cirrhotic patients probably does not eliminate the risk of development of HCC.

It is suggested that all ≥3 years old patients with positive serology & HCV RNA be offered antiviral therapy. Children with persistently normal ALT levels repeatedly 6 monthly, however, can be monitored with serial liver biopsies as mentioned above.

Controversy exists regarding who to treat and who not to treat amongst infected children. Since disease progression is less likely in children, it appears reasonable not to expose the children to the adverse events associated with antiviral therapy. On the other hand, when we look at the life expectancy of an average infected child, it doesn’t seem rational and ethical to let a patient live for 40 or more years with ongoing infection and suffer its potentially avoidable complications.

Antiviral therapy should not be given in children <3 years of age [31,42]. The reason is potential neurotoxicity of interferon and thus its deleterious effects on the developing brain [31]. Because of the high rate of spontaneous resolution, the need for interferon therapy, if any, is only minimal in children <3 years of age. Children aged 3 - 17 who are infected with hepatitis C and are considered appropriate candidates for treatment may be offered antiviral therapy [31,42,43]. Encouragingly, compared to adults, antiviral therapy in children yields relatively higher SVR rates [genotype 2/3 (84%); genotype 1 (36%)] [44,45] and fewer adverse events. This is probably due to earlier stage of the disease, higher relative IFN dosage, & relative lack of comorbid conditions in pediatric patients [46].

Earlier studies recommended treating with non-pegylated interferon alfa-2b (3 MU/m² three times a week) and ribavirin (15 mg/kg) for 24 and 48 weeks in genotypes 2 & 3 and 1 cases respectively [31,32,42,44]. A recent comparative analysis of efficacies of different therapeutic
options available for children however has revealed that PEG-IFN-alpha-ribavirin combination therapy yields better results (in terms of % ETR & SVR achieved) as compared to non-pegylated interferon monotherapy or its combination with ribavirin [47].

US Food and Drug administration (FDA) approved PEG-IFN-alfa-2b-ribavirin combination therapy for use in children ≥3 years old with compensated liver disease in 2008. Although not yet approved, Peg-IFN alfa 2a can be used in doses of 180 micrograms/1.73 m² subcutaneously once weekly in combination with ribavirin in children ≥5 years of age. The approval of Peg-IFN use in children came following the publication of the results of a large multicenter trial [48] which evaluated the efficacy and safety of PEG-IFN-alpha-ribavirin combination therapy in 107 children with chronic HCV infection. The dosage regimens used in this trial were pegylated interferon alfa-2b 60 micrograms/m² subcutaneously once weekly & ribavirin 15 mg/kg/day in two divided doses orally. Children with genotype 2 or 3 were treated for 24 or 48 weeks depending upon the viral load—less than or more than 600,000 IU/mL respectively. Those with genotype 1 or 4 were treated for 48 weeks regardless of the viral load. As expectedly much higher SVR rates of 93% were attained in patients with genotypes 2 or 3 compared to 53% in those with genotypes 1 or 4. Although anxiety and depression were reported in 28% of the cases, in great majority of them the side effects were not serious enough to warrant starting antidepressant treatment. Hematological side effects i.e. anemia & neutropenia serious enough to require dose reductions were reported in 25% of the subjects.

In another study aimed at ascertaining the efficacy and safety of PEG-IFN-alpha-ribavirin combination therapy in children, [49] 30 children between 3 - 6 years of age were selected for antiviral therapy based on positive HCV RNA for ≥3 years and elevated ALT levels. They received PEG-IFN-alpha2b 1.0 µg/kg/wk plus ribavirin 15 mg/kg/d for 24 weeks (genotype 2/3) or 48 weeks (genotype 1/4). Primary endpoint i.e. attainment of SVR (defined as undetectable HCV RNA (<50 IU/mL) at week 24 of follow-up) was achieved in 50% of the patients - (3/3 genotype 3; 12/27 genotype 1/4). No patient required ribavirin dose reduction; because of neutropenia, PEG-IFN-alpha-2b dose was reduced in 23% of the patients and stopped in 3 subjects.

In a multicenter trial (called PEDS-C trial), [50] comparative efficacies of pegylated interferon-ribavirin combination and pegylated interferon-placebo combination were compared in 114 children with chronic HCV infection. Former combination yielded higher SVR rates (53%) compared to the latter (21%).

It is not clear at this point whether to use early virologic response (EVR) as a criterion, similar to adults, to stop therapy at week 12 or not. Refer to Table 1 for definitions of treatment responses, and Tables 2 and 3 for a schematic lay out of the management plan in children with genotypes 2 & 3 (the most prevalent genotypes in Pakistan) and genotype 1 (the most prevalent genotype in West) respectively [51,52].

2.5. Nonresponders & Relapsers

Nonresponders are those cases in whom the qualitative HCV RNA assay done at 12 weeks into the therapy shows either no decline in the HCV RNA titer (compared with the pre-treatment assay) or a decline of <2 log [31]. Relapsers, on the other hand, are those cases in whom the qualitative HCV RNA assay done at the end of the treatment course comes out to be negative (<50 IU/mL) i.e. end-of-treatment response (ETR) achieved, but 24 weeks later, qualitative HCV RNA assay done to ascertain sustained virologic response (SVR) comes out to be positive [31]. In Pakistani patients, since genotype 3 accounts for almost 75% - 90% of all cases, we (rightly) only do qualitative PCR at week 12 to see achievement of early

| Rapid virologic response (RVR) | Qualitative HCV RNA assay done at 4 weeks comes out to be negative (<50 IU/mL). |
| Early virologic response (EVR) | Qualitative HCV RNA assay done at 12 weeks: |
| Nonresponders | Quantitative HCV RNA assay done at 12 weeks showing either no decline in the HCV RNA titre (compared with the pre-treatment assay) or a decline of <2 log—called partial virologic response (PVR) or viremic response. |
| End of treatment response (ETR) | Qualitative HCV RNA assay done on completion of the recommended duration of the course comes out to be negative. |
| Sustained virologic response (SVR) | Qualitative HCV RNA assay done 24 weeks after completion of the recommended duration of the course comes out to be negative. |

Relapsers | Qualitative HCV RNA assay done on completion of the recommended duration of the course came negative, but 24 weeks later, the assay done to confirm SVR comes out to be positive.  

Achievement of SVR is generally considered as the marker of eradication of HCV infection. Almost all such patients show EVC or PVR on 12 weeks assay.

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Table 2. Suggested management plan in children with genotypes 2 & 3.

<table>
<thead>
<tr>
<th>HCV RNA Assay:</th>
<th>Recommendation as per the HCV RNA Assay result:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 4 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay (&lt;50 IU/mL) <em>i.e. a case of RVR</em></td>
<td>Institute a standard treatment course of 24 weeks. Although, a few studies have shown attainment of comparable SVR rates in this subgroup with shortened treatment courses of 12 - 16, more data is needed to validate this recommendation in pediatric age group.</td>
</tr>
<tr>
<td>Positive assay</td>
<td>Give treatment for the standard duration of 24 weeks* (may be 36 - 48 weeks).</td>
</tr>
<tr>
<td><strong>Week 24 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay <em>i.e. a case of ETR</em></td>
<td>Successful therapy. Needs a repeat qualitative HCV RNA assay at week 48 (24 weeks after ETR) to establish SVR.</td>
</tr>
<tr>
<td>Positive assay</td>
<td>Treatment failed.</td>
</tr>
<tr>
<td><strong>Week 48 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay <em>i.e. a case of SVR</em></td>
<td>HCV infection got eradicated.</td>
</tr>
</tbody>
</table>

*The newly recommended week 4 qualitative HCV RNA assay helps modify the duration of the therapy based on viral kinetics. On one hand, this approach helps maximize the SVR rates and on the other hand, limits the toxicities and cost associated with the extended treatment courses. Achievement of RVR means that we can consider shortening the treatment course. SVR rates achieved in this subgroup are relatively poor. Thus prolonged therapy (>24 weeks) may be considered in this subgroup, although more evidence is needed at this time for a definite recommendation.

Table 3. Suggested management plan in children with genotypes 1.

<table>
<thead>
<tr>
<th>HCV RNA Assay:</th>
<th>Recommendations as per the PCR results:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 4 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay (&lt;50 IU/mL) <em>i.e. a case of RVR</em></td>
<td>Predictors of poor response* absent: Shorten the treatment duration to a total of 24 weeks*; †; ‡. Predictors of poor response present: Give treatment for the standard duration of 48 weeks.</td>
</tr>
<tr>
<td>Positive assay</td>
<td>Continue treatment and repeat HCV RNA at 12 weeks.</td>
</tr>
<tr>
<td><strong>Week 12 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay <em>i.e. a case of EVC</em></td>
<td>Continue treatment for a total of 48 weeks.</td>
</tr>
<tr>
<td>HCV RNA fall by ≥2 logs <em>i.e. a case of PVR</em></td>
<td>Repeat qualitative HCV RNA at 24 weeks.</td>
</tr>
<tr>
<td>HCV RNA fall by &lt;2 logs <em>i.e. a case of non-responder</em></td>
<td>Stop treatment.</td>
</tr>
<tr>
<td><strong>Week 24 qualitative HCV RNA assay (only done in cases which show PVR at week 12 assay):</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay (this subgroup is called “slow responders”)</td>
<td>Continue treatment for a total of 48 - 72 weeks. 72 weeks therapy has generally shown superior results as compared to 48 weeks therapy in slow responders [84-86].</td>
</tr>
<tr>
<td>Positive assay</td>
<td>Stop treatment as probability of attaining SVR is negligible.</td>
</tr>
<tr>
<td><strong>Week 48 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay <em>i.e. a case of ETR</em></td>
<td>Successful therapy. Needs a repeat qualitative HCV RNA assay at week 72 (24 weeks after ETR) to establish SVR.</td>
</tr>
<tr>
<td>Positive assay</td>
<td>Treatment failed.</td>
</tr>
<tr>
<td><strong>Week 72 qualitative HCV RNA assay:</strong></td>
<td></td>
</tr>
<tr>
<td>Negative assay <em>i.e. a case of SVR</em></td>
<td>HCV infection got eradicated.</td>
</tr>
<tr>
<td>Positive assay <em>i.e. a case of relapse</em></td>
<td>Previously treated with non-pegylated interferon: Treat with peginterferon and ribavirin. If EVR is not achieved at week 12, stop the treatment.</td>
</tr>
</tbody>
</table>

*Old age (> 50 yrs); male gender; African American race; obesity; alcoholism; HIV confection or immunosuppression; more-than-portal fibrosis on liver biopsy (Metavir ≥ 2 or Ishak ≥ 3); a pretreatment viral load of >800,000 IU/mL. †SVR rates of 80% - 89% can be achieved in this subgroup. ‡In case of relapse, re-treatment with the standard 48 weeks course is recommended.
virologic response (EVR) [52]. Quantitative PCR is only reserved for genotype 1 cases and the above-mentioned definition of non-responders is primarily true for this group of patients.

How do we approach nonresponders and relapers basically depends upon the previous drug regimen administered in the patients (peginterferon-ribavirin combination; nonpegylated interferon-ribavirin combination; peginterferon monotherapy; nonpegylated interferon monotherapy) and the presence of negative predictors to drug therapy. In patients who were prescribed any regimen other than peginterferon-ribavirin combination therapy can be prescribed this regimen regardless of the genotype, [31] and sustained virologic response rates of 25% - 40% for nonpegylated interferon monotherapy cases, and 10% for nonpegylated interferon-ribavirin combination therapy cases can be expected [45].

2.6. Acute HCV Infection in Children

There is limited data and experience available to treat acute HCV infection in children. This is because except in rare outbreaks, [23] acute symptomatic HCV infection is rarely encountered in pediatric clinical practice. Based on empirical evidence a reasonable recommendation would be to allow 6 - 8 weeks observation time for spontaneous resolution to take place and treat only those who demonstrate persistent viremia in the form of positive PCR for HCV RNA after this period.

2.7. Monitoring of Antiviral Therapy

Although unlike adults, children surprisingly appear to tolerate interferon therapy much better, [53,54] antiviral therapy needs to be monitored to look for the development of potentially serious side effects and also to determine the response to therapy (see Table 4) [51]. Monitoring of antiviral therapy includes checking complete blood counts (CBC) at weeks 1, 2, 4, 6, 8 and then monthly; every 3 months, all baseline investigations should be repeated including LFT’s, creatinine, glucose and TSH.

Since retinopathy & uveitis have been reported in 2% - 3% of the patients treated with IFN, a baseline ophthalmologic examination prior to the commencement of treatment, and repeat examination thereafter if symptoms develop is recommended in all patients.

Interference with both linear growth and weight gain have been reported in children during the months of treatment [55]. Almost 80% of the children catch-up the growth following completion of the antiviral course. In 20% of the cases however growth velocity remains inhibited (<3rd percentile) six months after cessation of the treatment. Data regarding recovery of growth after longer time periods are awaiting publication.

Obesity is known to be inversely related to the success of antiviral therapy in both adults and children. In one study [56], each standard deviation (1 z-score unit) increase in BMI was associated with a 12% reduction in the probability of SVR attained. Based on this we recommend that a period of weight loss for several months or a year be given to obese children before commencing antiviral treatment. Since the disease progression is appreciably slow in children, this delay in the commencement of antiviral treatment is unlikely to affect the SVR except positively.

As with ribavirin therapy, the incidence of hemolytic anemia appears to be less than that in adults [57]; also it appears that the incidence doesn’t rise when higher doses (15 mg/kg) are used as compared to lower doses (8 - 12 mg/kg) [43]. Anemia, however, is a particular problem in those having renal insufficiently, cirrhosis, thalassemia, or HIV co-infection. There are reports of ribavirin-induced worsening of anemia in such patients with consequent rise in transfusion requirements (especially, in thalassemia patients) [4]. Anemia usually develops within the first 4 weeks of starting antiviral therapy and persists till the end of the course [58]. Almost 40% patients suffer a drop in Hb concentration of ≥3 gm/dl [58]. Most published studies recommend RBV dose-reduction if Hb level falls to or below 10g/dl, and discontinue it if it falls to <8 g/dl. [42,59]. The current recommendation is to reduce IFN dose if neutrophil count falls to <0.5 × 10^9/L, and discontinue it if it falls to <0.3 × 10^9/L [31,59]. Regarding platelet count, it is recommended to reduce IFN dose if platelet count falls to <30 × 10^9/L, and discontinue it if it falls to <20 × 10^9/L [42,59]. Because of the risk of development of life-threatening infection (very low!),

Table 4. Monitoring of anti-viral therapy.

<table>
<thead>
<tr>
<th>For nthly:</th>
<th>CBC at weeks 1, 2, 4, 6, 8 and then monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4:</td>
<td>Qualitative HCV RNA assay at week 4 in both genotype 1 and 2 &amp; 3 cases to assess for RVR.</td>
</tr>
<tr>
<td>Week 12:</td>
<td>Quantitative HCV RNA assay at week 12 in genotype 1 cases only to assess for EVR.</td>
</tr>
<tr>
<td>Every 3 months:</td>
<td>LFT’s, creatinine, glucose and TSH.</td>
</tr>
<tr>
<td>Week 24:</td>
<td>• Qualitative HCV RNA assay at week 24 in only those genotype 1 cases who attained EVR at week 12.</td>
</tr>
<tr>
<td>Week 48:</td>
<td>• Qualitative HCV RNA assay at week 48 in genotype 2 &amp; 3 cases to determine ETR.</td>
</tr>
<tr>
<td>Week 72:</td>
<td>• Qualitative HCV RNA assay at week 48 in genotype 1 cases to determine ETR.</td>
</tr>
</tbody>
</table>

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patients who already have neutropenia or thrombocytopenia below the permissible limits (neutrophil count > 1500/mm³ & thrombocyte count > 75,000/mm³) should not be started with antiviral therapy. Although haematopoietic growth factors (erythropoietin and filgrastim) have been used in adults to help avoid antiviral dose reductions and attain optimum adherence (defined as the administration of interferon-ribavirin combination therapy in an optimum dose for more than 80% of the prescribed duration), [60] our experience with these drugs in children is almost non-existent. Therefore, despite of promising results in adults, the use of these agents as adjuncts to antiviral therapy is not recommended at this moment.

2.8. Antiviral Therapy in Decompensated Cirrhotic Patients

Traditionally, despite of the known theoretical benefits of antiviral therapy (improvement in liver histology, partial reversal of established cirrhosis, and prevention of life-threatening complications), many cirrhotic patients have not been offered antiviral therapy. Current literature review, however, shows that because of the unstandardized dosage schedules being administered over variable periods of time in the past studies, we have under- & overestimated the potential benefits & risks of antiviral therapy respectively, in decompensated cirrhotic patients. Based on the current literature review it is suggested that cirrhotic patients with a CTP score ≤9 and a decompensated event that abated with common management may be considered for antiviral therapy [61,62] although more data in pediatric age group is needed to recommend routine usage of this therapy. Because of the high risk of septic complications and low probability of attainment of an SVR, patients with Child-Pugh class C, CTP score ≥10 or MELD score 18 disease are not considered appropriate candidates to institute antiviral therapy [63]. The ideal candidate for antiviral therapy remains a patient with Child-Pugh class A disease in whom the risk of drug-induced side effects is almost identical to that of the controls [51]. Whether or not to institute antiviral therapy in Child-Pugh class B patients should be individualized on case-to-case basis giving due consideration to factors like genotype & pre-treatment viral loads with antiviral therapy discontinued after 4 or 12 weeks if there is no virological response [63]. Standard schedules of treatment may be considered in all patients with genotype 2 and 3 HCV infection; in genotype 1 cases, however, the risk-benefit ratio still needs to be defined. All cirrhotic patients on antiviral therapy need adjustment of the dosage schedule in accordance with the tolerability of the patient, especially in response to the development of haematologic side effects [64]. Additionally, norfloxacin prophylaxis has been shown to substantially reduce the risk of super-added infections. One thing that has increasing become clear from the existing trials date is that cirrhotic patients who achieve SVR are less likely to develop liver-related complications as compared to the non-responders [63]. Despite of the many encouraging studies in the recent past, however, data on the long-term disease progression, avoidance of transplantation, and most importantly, improvement of life expectancy is still sparse. Although liver functions have clearly been shown to improve with antiviral therapy (as indicated by significant reductions in CTP and MELD scores), the same are more likely to deteriorate within a few years in patients with advanced cirrhosis thus explaining the need to accumulate data on the survival benefit conferred by antiviral therapy in cirrhotic patients.

2.9. Vertical Transmission of HCV Infection

Vertical transmission primarily occurs in women with demonstrable HCV viremia during pregnancy or delivery (<10% risk) [65]. Transmission in non-viremic mothers is unusual. Similarly, the lower the level of viremia, the lesser is the risk of vertical transmission and vice versa. For example, many studies have demonstrated that a viral titer of <1 × 10⁵ copies per mL is associated with a much lower risk of vertical transmission [66-68]. Although HIV coinfection appears to be the single most important cofactor associated with almost fourfold increased risk of vertical transmission, [5] the increased risk at least in part may be explained by higher levels of viremia in infected cases [26]. In fact the increased risk of vertical transmission in HIV coinfected cases may possibly be abrogated after adjusting for viral titres. Also, antiretroviral therapy against HIV infection possibly reduces the risk of vertical transmission [30]. Although more validation studies are needed, at least one study [27] demonstrated increased risk (~40% - 50%) of vertical transmission in genotype 3 cases compared to genotype 1—a finding that may have important implications in the development of Pakistani guidelines (screen women of child bearing age and offer them antiviral therapy if found HCV infected before they marry/attempt to conceive!). Certain other studies, however, have failed to find an association between a given genotype and an increased risk of vertical transmission [24,26]. Doctors working in high HCV seroprevalence countries (like Pakistan) are recommended to conduct some statistically significant studies on this issue.

All pregnant women in Pakistan should undergo routine testing for HCV (this recommendation, however, is not valid for most of the western countries!). Because of the risk of teratogenicity both interferon alpha and ribavirin are absolutely contraindicated in pregnancy [47]. Since, vertical transmission usually occurs at the time of
birth, in order to reduce its risk, most pediatricians recommend going for delivery within 6 hours of membrane rupture in HCV infected mothers and avoidance of the use of invasive procedures on the fetus such as fetal blood sampling or internal fetal (fetal scalp) monitoring [69,70]. No measure, however, fully prevents vertical transmission [71,72]. Current evidence has not proved cesarean section to be a useful way of reducing the transmission risk. Thus most authorities in this field do not advise to have cesarean sections, other than for the usual obstetric indications [73]. Probably, the only valid exception to this recommendation are the HIV/HCV coinfected cases in whom breast feeding by HCV-infected mothers. The only exceptions are the HIV/HCV coinfected cases in whom the risk of vertical transmission appears to reduce if elective cesarean sections are done before membrane rupture [65,74]. Infant’s exposure to infected blood is more likely during vaginal delivery compared to cesarean section; [75] thus the need to go for as bloodless a cesarean section as possible in coinfected cases. In HCV mono-infection cases, however, cesarean section has not been proven to be protective [29].

Although HCV-RNA is detectable in maternal colostrum and breast milk, [76] the risk of HCV transmission via breast feeding has not been proven [77,78]. Probably, this is because of very low levels of HCV-RNA in breast milk, and its inactivation by gastric HCl. Thus both the American Academy of Pediatrics [79] and American College of Obstetricians and Gynecologists [74] support breastfeeding by HCV-infected mothers. The only exceptions are the HCV/HIV coinfected cases in which breast feeding should be avoided. If nipples are cracked or bleeding, breast feeding should be withheld temporarily [79].

Following observations have been made in different papers studying the effects of HCV infection on the mother/fetus:

1) Effects on mother: High ALT levels at the beginning of pregnancy may actually normalize in a significant proportion of pregnant ladies by 3rd trimester (probably due to the effects of pregnancy on the immune system) and rise again within a few months after delivery. Paradoxically, HCV RNA titre may actually rise during the 3rd trimester. Although Histologic Activity Index may show transient histological deterioration during pregnancy, [80] studies have shown pregnancy to be associated with improvement in long-term progression of fibrosis [81]. Increased risk of gestational diabetes (OR 2.5; 95% CI 1.0 - 6.0) especially if mother is overweight has also been suggested.

2) Effects on fetus (other than vertical transmission of HCV infection): Increased risk of low birth weight (OR 2.2; 95% CI 1.2 - 3.8), small for gestational age (OR 1.5; 95% CI 1.0 - 2.1), need for assisted ventilation (OR 2.4; 95% CI 1.4 - 3.9) or neonatal intensive care (OR 2.9, 95% CI 1.9 - 4.6).

More studies are needed to understand the significance of the above-mentioned observations.

2.10. Horizontal Transmission of HCV Infection

Unless blood is transmitted somehow, horizontal transmission from child to child within households, school, or daycare settings does occur and thus HCV infected children can intermingle with other children as otherwise [79,82]. In order to avoid the possibility of blood transmission, sharing of razors, toothbrushes, nail clippers, or other objects that may be contaminated with blood is highly discouraged. Since the risk of transmission through saliva appears to be minimal, avoiding sharing eating utensils, drinking glasses, towels or other potential sources of saliva transmission is not required [83]. Adolescents should be educated, encouraged and monitored to avoid high-risk behaviors including sex with multiple partners, body piercing, tattooing, IV drug abuse, intranasal cocaine etc. In adolescents who have already acquired HCV infection, measures should be taken to minimize disease progression. These include treating with antiviral therapy, avoiding alcohol consumption, checking hepatitis A and hepatitis B status and immunizing accordingly if required. NSAID’s should better be avoided; if required Paracetamol can be used as an analgesic agent although it’s recommended should never be exceeded.

3. CONCLUSION

A large-scale, population-based seroprevalence survey is the need of the hour in order to reliably estimate the true disease burden of hepatitis C in Pakistan. The study design should take into account the risk factors particularly strong in our population (e.g. unscreened blood transfusion). A well streamlined surveillance, data collection and reporting process should also be developed at national level in order to determine the true incidence of new cases. Diagnostic work-up (serology by 3rd generation EIA/ELIZA [not if <1 year of age] followed by qualitative HCV RNA assay) of children suspected of having chronic HCV should proceed similar to that of adults. Liver biopsy may be considered in HCV-positive children with persistently normal aminotransferase levels. Because of the potential interferon-induced neurotoxicity, antiviral therapy is contraindicated in children <3 years of age. Infected children aged 3 - 17 who are selected for treatment may receive therapy with pegylated interferon alfa-2b 60 micrograms/m² subcutaneously once weekly & ribavirin 15 mg/kg/day in two divided doses orally. Peginterferon-alfa-2a in a dose of 180 micrograms/1.73 m² subcutaneously once weekly can also be used in combination with ribavirin in children ≥5 years old. Non-pegylated interferon yields inferior therapeutic response in terms of ETR & SVR rates achieved, nonetheless, if chosen for affordability reasons the recommended dose...
regimen is interferon alfa-2b 3 MU/m² subcutaneously three times a week & ribavirin 15 mg/kg/day in two divided doses orally for 24 and 48 weeks in genotypes 2&3 and 1, respectively. In non-responding patients/relapsers, peginterferon-ribavirin combination therapy may be prescribed regardless of the genotype provided the same was not given beforehand. Cirrhotic patients with a CTP score ≤ 9 and a decompensated event that abated with common management may be considered for antiviral therapy, although more data in pediatric age group is needed to recommend routine usage of this therapy. Despite of promising results in adults, the use of hematopoietic growth factors (erythropoietin & filgrastim) as adjuncts in the management of HVC infection in children is not recommended at this moment.

REFERENCES


