Case definitions for acute hepatitis C virus infection: A systematic review

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Background & Aims: Case definitions for recent hepatitis C virus (HCV) infection vary considerably between studies. The aim of this systematic review was to characterize case definitions for recent HCV and explore the heterogeneity in studies performed to date.

Methods: A systematic literature search of MEDLINE, SCOPUS, and ISI Web of Knowledge was performed covering all studies of recent HCV infection cited between January 2000 and June 2011. The criteria used by each study to define cases of recent HCV infection were extracted, structured, and analyzed.

Results: Overall, 195 articles were included, with 87% (n = 169) providing a clear case definition for recent HCV infection. The most frequently used individual criteria for defining a case included HCV antibody seroconversion (77%), alanine aminotransferase (ALT) elevation (68%), and HCV RNA detection (63%). In studies using HCV antibody seroconversion, the window period between the last negative and the first positive antibody test varied widely across studies (4 weeks to 4 years). Considerable diversity was also observed with respect to the ALT threshold used to characterize ALT elevations, ranging from 2 to 20 times the upper limit of normal. HCV antibody seroconversion was used as a single criterion in 41% of the studies, while all other studies used at least two criteria (range: 2–9). Epidemiology/surveillance studies mostly used a more sensitive case definition, whereas treatment studies, natural history studies, and diagnosis studies used more specific case definitions.

Conclusions: Marked heterogeneity in case definitions for recent HCV infection was observed. Although a single case definition for recent HCV is not warranted, a degree of standardization within specific study categories would enable improved cross-study comparison and more uniform evaluation of HCV prevention and management strategies.

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Keywords: Hepatitis C; HCV; Acute; Newly acquired; Case definition; Systematic review.

Introduction

Our knowledge of recently acquired hepatitis C virus (HCV) infection has been hampered for two reasons: (1) the majority of cases with recent HCV infection are asymptomatic [1–3], and (2) the identification and follow-up of those at the highest risk of infection, such as people who inject drugs (PWID), have been difficult. Despite these limitations, a large number of studies have been performed in the setting of acute or recent HCV infection. Case definitions for recent HCV in these studies are highly variable. Although guidelines are available for the diagnosis, management, and treatment of HCV infection [4,5], these guidelines do not contain any recommendations of case definitions for recent HCV infection.

Accurate case definitions for recent HCV infection are essential for ensuring standardized surveillance of HCV incidence and enabling the assessment of the impact of policies designed to reduce HCV transmission [6,7]. Well-defined cases of recent HCV infection can also provide valuable insight into HCV pathogenesis, which is important for vaccine design. Lastly, early identification of recent HCV infection provides the opportunity for enhanced HCV treatment outcomes [8,9].

Traditionally, the acute-phase of HCV infection is defined as 6 months following infection acquisition [1,10]. This definition is generally based on evidence that the majority of individuals who spontaneously clear HCV (73–86%) do so within the first 6 months following infection (reviewed in [8,11]). There is no definitive test available to distinguish acute or recent HCV infection from chronic infection. The most accurate case definition for identifying recent HCV infection is the detection of HCV RNA in an individual with documented HCV antibody seroconversion, preferably with a narrow window period [2,12]. However, detection of HCV antibody seroconversion needs longitudinal monitoring of at-risk individuals, which is difficult in practice. Other criteria such as marked serum alanine aminotransferase (ALT) elevation or acute hepatitis clinical symptoms (particularly jaundice) have been suggested as the secondary criteria to diagnose acute HCV infection [1,4,12,13]. However, these additional criteria are insufficient as only 15–30% of patients develop a symptomatic acute hepatitis illness [3,14] and ALT elevation does not differentiate acute HCV infection from exacerbation of chronic HCV infection or other causes of acute hepatitis in a patient with chronic HCV infection [3]. Detection of HCV RNA with negative HCV antibody (and subsequent seroconversion) accurately diagnoses very recent HCV infection [4,15], but is uncommon in clinical practice.
Review

Previous studies attempting to review existing evidence in natural history or treatment of recent HCV infection reported considerable heterogeneity in case definitions for recent HCV infection [8,9,16]. The aim of this systematic review was to characterize case definitions for recent HCV infection and explore the heterogeneity in studies performed to date.

Methods

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. Given the PRISMA statement was originally developed for systematic reviews of studies evaluating healthcare interventions, components of this statement have been customized to fit the scope of the current systematic review.

Eligibility criteria

All primary research papers investigating any aspect of recent HCV infection were included if they were:

(a) published in English

and

(b) conducted on human individuals

The case definition of recent HCV infection was chosen to include individuals in both the acute and early chronic phases. A broader definition of recent HCV infection is consistent with evidence that spontaneous HCV clearance occurs up to 2 years following infection acquisition [16] and that HCV treatment response may be enhanced in both acute and early chronic HCV infection [8].

Information sources

A literature search of MEDLINE (Pubmed), SCOPUS, and ISI Web of Knowledge was performed on June 20th, 2011, covering all studies published and cited since January 1, 2000. Reference lists of selected articles and the relevant review articles found during the initial search were hand searched and forward citation checks were carried out to identify further potentially relevant studies.

Search strategies

Given the various terminology used in studies referring to recent HCV infection, we used a wide range of search terms in search strategy to ensure all relevant studies were captured. The search strategy used was “acute hepatitis C” OR “acute HCV” OR “acute-phase hepatitis C” OR “acute phase hepatitis C” OR “acute-phase HCV” OR “acute phase HCV” OR “early hepatitis C” OR “early HCV” OR “recent hepatitis C” OR “recent HCV” OR “incident hepatitis C” OR “incident HCV” OR “newly acquired HCV” OR “newly acquired hepatitis C”. The search strategy was employed by looking for search terms in the title, abstract or keywords of the studies. Indexed subject heading terms were not used because no specific term was found in MeSH and Emtree thesauruses for recent HCV infection.

Study selection

Citations found during the primary search were merged using EndNote X4 (Thomson Reuters, New York, NY, USA). The abstracts of potentially eligible articles were reviewed to determine the relevance, of which relevant full texts were retrieved and examined.

Studies reported only in abstract form were excluded, given an insufficient case definition of recent HCV infection often reported in abstracts. Case reports and small case series reporting on fewer than 10 study participants were also excluded to avoid the inclusion of uncharacteristic or non-representative case definitions. Moreover, studies were excluded if they presented a subgroup or reanalysis of data from another included study unless they either used a different case definition of recent HCV infection or were classified in a different study category, as described below and in Fig. 1.

Data collection and analysis

All criteria used by each study for case definition of recent HCV infection were extracted. Based on each set of criteria, the number of individuals enrolled was recorded (if this information was provided in the paper). In addition, the following information was extracted from each article: country, study name (if

<table>
<thead>
<tr>
<th>Study category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology/surveillance</td>
<td>Investigating:</td>
</tr>
<tr>
<td>Natural history</td>
<td>• incidence of recent HCV infection</td>
</tr>
<tr>
<td></td>
<td>• demographic, behavioural, and/or clinical characteristics of individuals with recent HCV infection</td>
</tr>
<tr>
<td></td>
<td>• transmission patterns of recent HCV infection or risk factors associated with recent HCV acquisition</td>
</tr>
<tr>
<td></td>
<td>• accuracy of a surveillance system of recent HCV infection</td>
</tr>
<tr>
<td></td>
<td>• efficacy of a prevention program on incidence of recent HCV infection</td>
</tr>
<tr>
<td></td>
<td>• conducting phylogenetic analysis of HCV in recent HCV infection</td>
</tr>
<tr>
<td>Treatment</td>
<td>Investigating:</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>• validity, accuracy or practical usefulness of a diagnostic test for recent HCV infection</td>
</tr>
<tr>
<td></td>
<td>• comparison of two or more recent HCV infection diagnostic tests regrading the validity, accuracy or practical usefulness</td>
</tr>
</tbody>
</table>

Fig. 1. Criteria used to categorize selected studies based on the main objectives of the studies.
Study selection

The studies included and excluded through the review process are summarized in Fig. 2. Overall, the initial search yielded 2211 citations. Of these, 2035 were excluded for the following reasons: non-relevant or duplicate articles (identified through searching multiple databases), not primary research papers, repeating reports, available only in abstract, and case reports or low sample size (Fig. 2). The remaining 176 citations were retained for full text review. Nineteen further articles were added through backward/forward citation check. Following the full text review, 26 articles (13.3%) were excluded because no clear or sufficient case definition for recent HCV infection was provided in the full text. Thus, 169 articles were included for data analysis [18–186].

Results

Study selection

The studies included and excluded through the review process are summarized in Fig. 2. Overall, the initial search yielded 2211 citations. Of these, 2035 were excluded for the following reasons: non-relevant or duplicate articles (identified through searching multiple databases), not primary research papers, repeating reports, available only in abstract, and case reports or low sample size (Fig. 2). The remaining 176 citations were retained for full text review. Nineteen further articles were added through backward/forward citation check. Following the full text review, 26 articles (13.3%) were excluded because no clear or sufficient case definition for recent HCV infection was provided in the full text. Thus, 169 articles were included for data analysis [18–186].

Study characteristics

The characteristics of included studies are summarized in Table 1. A total number of 16,814 individuals with recent HCV infection were enrolled in the studies ranging from 10 to 2075 (mean: 99; median: 36). Within study populations, the main mode of HCV acquisition was injecting drug use (51 studies, 38%) followed by unsafe sexual intercourse (27 studies, 20%). Fifty-four studies (32%) exclusively enrolled people from one high risk population among which the major populations included men who have sex with men (16 studies, 36%), PWID (15 studies, 34%), and hemodialysis patients (13 studies, 29%). Moreover, about one third of the studies (25 studies, 34%) enrolled exclusively HCV mono-infected individuals, but in 29 studies (40%) all enrolled individuals were HIV co-infected.

Among the 169 studies included in this systematic review, 71 studies (42%) focused on epidemiology/surveillance, 61 (36%) on natural history, 39 (23%) on treatment, and 18 (11%) on diagnosis. Twenty studies (12%) were categorized in more than one study category.

Various terms were used to describe recent infection, with the most common being “acute HCV infection” (140 studies, 83%). Other terms included “incident HCV infection” (14 studies, 8%), “newly acquired HCV infection” (seven studies, 4%), “recent HCV infection” (four studies, 2%), “early HCV infection” (three studies, 2%), and “HCV seroconversion” (one study, 1%). Use of “incident HCV infection” was restricted to epidemiology/surveillance studies but the other terms were used in all four study categories.

Criteria of case definition for recent HCV infection

The frequency of each criterion used for recent HCV infection case definition is presented in Table 2. The three most frequently used criteria included HCV antibody seroconversion (131 studies, 77%), ALT elevation (115 studies, 68%), and HCV RNA detection (107 studies, 63%).

Within studies using HCV antibody seroconversion as a case definition criterion, the reported window period of HCV exposure (time between the last negative antibody test and the first positive antibody test) was very wide, ranging from 4 weeks to 4 years (Fig. 3A). Many studies among those using HCV antibody
seroconversion as a case definition criterion (53 studies, 41%) did not report the window period length. Among the studies reporting the window period length, the most commonly used were 6 and 12 months. Among the studies categorized under one study category and reporting the window period of HCV exposure (n = 69), 38% of epidemiology/surveillance studies used a window period of <6 months as compared to 80% of treatment studies (p = 0.003) and 100% of diagnosis studies (p = 0.005).

ALT elevation was also commonly used to identify individuals with recent HCV infection. However, considerable diversity was observed with respect to the ALT threshold used, ranging from 2 to 20 times ULN. Many studies among those using ALT elevation as a case definition criterion (22 studies, 19%) did not report a threshold value. Among the studies reporting the ALT elevation threshold, the most common level was 10 times ULN (Fig. 3B). Among the studies categorized under one study category and reporting ALT level threshold as ULN (n = 71), 41% of epidemiology/surveillance studies used an ALT threshold of 10 times ULN or higher as compared to 89% of natural history studies (p <0.001).

HCV antibody seroconversion was the only criterion used in some studies as a single criterion for a case definition of recent HCV infection. Criteria other than HCV antibody seroconversion (e.g., HCV RNA positive, ALT elevation, etc.) were used within case definitions comprising two or more criteria (Tables 3 and 4). While 69 studies (41%) used one criteria set, the other 100 studies (59%) used more than one criteria set ranging from 2 to 9 sets. HCV antibody seroconversion was used in 55 studies (42%) as a single criterion and in 76 studies (58%) in conjunction with other criteria to define a case (Table 3). The largest number of study subjects was identified with HCV antibody seroconversion as a single criterion (mean: 69 per study). A more restricted criteria set, with HCV antibody seroconversion in conjunction with HCV RNA detection and ALT elevation, was the second most frequently used criteria set, which was used in 25 studies (19%), and identified an average of 53 individuals in each study.

A total number of 43 criteria sets were used as case definitions for recent HCV infection. The most frequently used criteria sets in all studies and in each study category are presented in Table 4. HCV antibody seroconversion as a single criterion was the most frequently used case definition in epidemiology-surveillance studies which was used in almost half of the studies in this category (33 studies, 46%). In natural history studies, HCV antibody seroconversion was also the most commonly used case definition (15 studies, 25%). However, the frequency of using HCV RNA

Table 1. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Male (%)</th>
<th>Number of studies (%) Total number = 169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD Median (Inter-quartile range)</td>
<td>63.4 ± 23.9 61.3 (46.7-79.3)</td>
</tr>
<tr>
<td>Age (mean or median)</td>
<td>20 (16.4) 63 (51.6) 39 (32.0)</td>
</tr>
<tr>
<td>Main mode of HCV acquisition</td>
<td>51 (38.4) 27 (20.3) 23 (17.3) 14 (10.5) 10 (7.5) 4 (3.0) 6 (4.5)</td>
</tr>
<tr>
<td>HIV co-infection</td>
<td>25 (34.3) 19 (26.0) 29 (39.7)</td>
</tr>
</tbody>
</table>

Data was provided by: *132 studies (78.1%); †122 studies (72.2%); ‡133 studies (78.7); §73 studies (43.2%).

*Data presented as percentage.

**Percentages do not total 100% because in two studies more than one risk factor was reported as the main mode of HCV acquisition among enrolled individuals.

Table 2. Individual frequency of each criterion used in the studies for case definition of recent HCV infection.

<table>
<thead>
<tr>
<th>Number of studies (%)</th>
<th>Total number = 169</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody seroconversion</td>
<td>131 (77.5)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>115 (68.0)</td>
</tr>
<tr>
<td>HCV RNA positive</td>
<td>107 (63.3)</td>
</tr>
<tr>
<td>Exposure</td>
<td>46 (27.2)</td>
</tr>
<tr>
<td>Definite exposure</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td>Probable exposure</td>
<td>4 (8.7)</td>
</tr>
<tr>
<td>Both or not reported</td>
<td>28 (60.9)</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>40 (23.7)</td>
</tr>
<tr>
<td>Fever or jaundice + general symptoms</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>General symptoms + fever or jaundice</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>Both used in various sets of criteria</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>HCV antibody positive</td>
<td>40 (23.7)</td>
</tr>
<tr>
<td>HCV RNA positive + HCV antibody negative</td>
<td>32 (18.9)</td>
</tr>
<tr>
<td>Increasing HCV antibody titre</td>
<td>8 (4.7)</td>
</tr>
<tr>
<td>HCV RNA fluctuation &gt;10 fold (1 log10)</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>
detection with initially negative HCV antibody, which detects individuals with early acute HCV infection, was comparable (13 studies, 21%). This criteria set was also the most frequently used case definition in diagnosis studies (7 studies, 39%). In treatment studies more restricted criteria sets were generally used.

In 29 studies exclusively enrolling HIV co-infected participants, the most frequently used case definitions was HCV antibody seroconversion as a single criterion (12 studies, 41%) followed by HCV antibody seroconversion in conjunction with ALT elevation (8 studies, 28%) and HCV RNA positive with a past RNA/antibody negative (8 studies, 28%). In 25 studies exclusively enrolling HCV mono-infected participants, the most common case definition criteria sets included HCV antibody seroconversion in conjunction with HCV RNA positive and ALT elevation (6 studies, 24%) followed by HCV antibody seroconversion (5 studies, 20%) and HCV RNA positive plus ALT elevation (5 studies, 20%).
Review

Table 4. The most frequently used criteria sets for case definition of recent HCV infection in the studies.

<table>
<thead>
<tr>
<th>Criteria Set</th>
<th>Number of studies (%)</th>
<th>Number of individuals identified using the criteria set * Total number (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies (n = 169)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>55 (32.5)</td>
<td>2345 (69.0)</td>
</tr>
<tr>
<td>Seroconversion + HCV RNA positive + ALT elevation</td>
<td>25 (14.8)</td>
<td>1061 (53.0)</td>
</tr>
<tr>
<td>HCV RNA positive + HCV antibody negative</td>
<td>23 (13.6)</td>
<td>625 (41.7)</td>
</tr>
<tr>
<td>Seroconversion + HCV RNA positive</td>
<td>22 (13.0)</td>
<td>615 (36.2)</td>
</tr>
<tr>
<td>HCV RNA positive + ALT elevation</td>
<td>21 (12.4)</td>
<td>548 (49.8)</td>
</tr>
<tr>
<td>Epidemiology/surveillance (n = 71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>33 (46.5)</td>
<td>1862 (81.0)</td>
</tr>
<tr>
<td>HCV RNA positive + ALT elevation</td>
<td>11 (15.5)</td>
<td>316 (45.1)</td>
</tr>
<tr>
<td>HCV RNA positive + past RNA/antibody negative</td>
<td>11 (15.5)</td>
<td>84 (28.0)</td>
</tr>
<tr>
<td>Natural history (n = 61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>15 (24.6)</td>
<td>321 (64.2)</td>
</tr>
<tr>
<td>HCV RNA positive + HCV antibody negative</td>
<td>13 (21.3)</td>
<td>216 (43.2)</td>
</tr>
<tr>
<td>Seroconversion + HCV RNA positive + ALT elevation</td>
<td>10 (16.4)</td>
<td>263 (52.6)</td>
</tr>
<tr>
<td>Treatment (n = 39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>11 (28.2)</td>
<td>97 (24.2)</td>
</tr>
<tr>
<td>HCV RNA positive + ALT elevation + exposure</td>
<td>10 (25.6)</td>
<td>83 (27.7)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>8 (20.5)</td>
<td>156 (39.0)</td>
</tr>
<tr>
<td>Seroconversion + ALT elevation</td>
<td>8 (20.5)</td>
<td>59 (29.5)</td>
</tr>
<tr>
<td>Diagnosis (n = 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA positive + HCV antibody negative</td>
<td>7 (38.9)</td>
<td>374 (53.4)</td>
</tr>
<tr>
<td>Seroconversion + HCV RNA positive + ALT elevation + symptoms</td>
<td>3 (16.7)</td>
<td>103 (34.3)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>3 (16.7)</td>
<td>50 (16.7)</td>
</tr>
</tbody>
</table>

Data was provided by: *34 studies (61.8%); *20 studies (80.0%); *15 studies (65.2%); *17 studies (77.3%); *11 studies (52.3%); *23 studies (69.7%); *7 studies (63.6%); *3 studies (27.3%); 5 studies (33.3%); 5 studies (38.5%); 5 studies (50.0%); 4 studies (36.4%); *3 studies (30.0%); *4 studies (50.0%); *2 studies (25.0%); *7 studies (100%); *3 studies (100%).

*Data was provided by the proportion of studies reporting the number of individuals identified using each criteria set.

Discussion

This systematic review demonstrates that there is marked heterogeneity in the case definitions used to define recent HCV infection. This heterogeneity in case definitions across studies is particularly evident in the broad range of HCV antibody seroconversion intervals and ALT thresholds employed in various studies. In addition, many studies incorporated several criteria sets within a given case definition. The findings from this study suggest that a greater standardization of definitions for recent HCV infection would be useful, particularly within specific study categories. Standardized definitions would enable improved cross-study comparison and more uniform evaluation of HCV prevention and management strategies.

HCV antibody seroconversion was the most frequently used case definition criterion, used in 77% of studies either as a single criterion or within a multiple criteria case definition. However, the time between the last negative antibody test and the first positive antibody test (window period) differed widely across studies. A narrower window period (e.g., ≤6 months) ensures that cases are within the acute HCV infection phase, but limits the number of enrolled cases as very frequent HCV antibody screening is uncommon among at-risk populations. Further, it biases the case definition toward those with a single exposure event (e.g., occupational exposure). A broader window period would increase case detection, enable evaluation of potentially improved therapeutic outcomes in both acute and early chronic HCV infection and should provide greater representativeness of individuals acquiring HCV infection.

Serum ALT elevation was the second most frequently used case definition criterion for recent HCV infection used in 68% of studies. Although most of these studies (36%) reported serum ALT level of 10 times ULN to characterize ALT elevation, a wide range in ALT threshold was reported. The ALT threshold affects both sensitivity and specificity of the criterion. A low threshold will result in possible measurement bias by inadvertently enrolling some chronic infection cases while a very high threshold will reduce case detection. Natural history and treatment studies tended to use higher ALT threshold ensuring greater specificity. On the other hand, epidemiology/surveillance studies mostly used a low ALT threshold to enhance sensitivity and thus overall case detection. Of note, the ALT threshold has been changed twice in the last decade for case definitions employed in the surveillance of acute viral hepatitis in the United States. In 2000, the ALT threshold was raised from 2.5 times ULN to seven times ULN and since 2007 the threshold has been higher than 400 IU/L [42,175,176,179].

The majority of the studies (59%) used more than one case definition criterion set for recent HCV infection. Eight studies used some criteria sets to define “definite/confirmed cases” and some others for “probable cases” [26,45,50,87,105,108,138,150]. In two further studies, the criteria sets were weighted in three levels consisting of “definite cases”, “probable cases”, and “possible cases” [54,104]. While in all these 10 studies, “definite/confirmed
cases” were defined based on either HCV antibody seroconversion or HCV RNA positive plus HCV antibody negative, a variety of criteria were used for “probable cases” and “possible cases”. In addition, several studies employed different case definitions to report findings from the same source cohort. [50,100,108,109,124,125,158,159].

The most frequently used case definition criteria sets were different among study categories. While HCV antibody seroconversion as a single criterion was the most frequently used case definition in epidemiology/surveillance studies, the studies investigating diagnosis or treatment of recent HCV infection tended to use more restricted definitions (Table 4). Moreover, different study requirements and research questions would appear to strongly influence case definitions. For instance, studies investigating diagnosis or natural history of recent HCV infection generally need to detect individuals in the very early stage of HCV infection. The HCV RNA detection with initial negative HCV antibody criterion, which meets this requirement, was found as the most common and the second most common criterion used in these two study categories, respectively. However, epidemiology/surveillance studies mainly aimed at the investigation of transmission patterns, and prevention programs generally used HCV antibody seroconversion, often with prolonged window periods. Treatment studies tended to use the most restrictive case definitions, presumably to prevent use of suboptimal therapy among misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases. The Australian Trial in Acute Hepatitis C (ATAHC) Study, however, allowed cases with HCV antibody misclassified chronic HCV cases.

The case definition recommended by the European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel [13] states Preferred criteria, which are based on seroconversion or positive HCV RNA and a documented negative HCV RNA and negative HCV antibody in the previous 12 months. In addition, they recommend the Alternative criteria, which include a positive HCV RNA and an elevated ALT with various ALT thresholds according to the history of the patients. This guideline reports that no consensus has been reached to include a history of HCV transmission risk factors in the alternative case definition. No other standardized definitions have been proposed, but particularly within study categories, would provide enhanced capacity for cross-study comparison. Accurate reporting of all components within case definitions would also improve study comparison.

Various terms were used in the studies to describe HCV infection in early stage, including ‘acute’, ‘recent’, ‘incident’, ‘newly acquired’, and ‘early’ HCV infection. Standardization of the terms used to describe HCV infection in early stage is needed. We suggest using the term ‘acute infection’ to describe infections where the estimated duration is less than 6 months (26 weeks). This would include individuals with:

1. Initial detectable HCV RNA and negative HCV antibody, with subsequent HCV antibody seroconversion;
2. Clinical symptoms (including jaundice) or an ALT higher than 10 times ULN, with other causes of acute hepatitis excluded, and onset of symptoms or peak ALT being less than 20 weeks prior to diagnosis (symptom onset or peak ALT are around 6 weeks from exposure); or
3. Asymptomatic HCV antibody seroconversion with the midpoint between last negative HCV antibody and first positive HCV antibody is less than 26 weeks prior to diagnosis (unless single exposure event can more accurately define time of infection).

We suggest using the term “recent infection” for individuals with an estimated duration of more than 6 months (26 weeks) and less than 2 years.

The current study has some limitations. In this systematic review, our search was limited to the studies published after 2000. Moreover, conference abstracts and grey literature were not covered. Although a sensitive search strategy was employed in this review, it remains possible that some studies on recent HCV infection were not captured in our search.

Key Points

- Marked heterogeneity in case definitions to define recent HCV infection was found among studies
- HCV antibody seroconversion intervals and ALT elevations thresholds varied widely when used as criteria for defining recent HCV infection. The most frequently used HCV antibody seroconversion intervals were 6 months and 12 months. The most frequently used ALT elevations threshold was 10 times the upper limit of normal
- Studies in different categories mostly tended to use case definition criteria addressing the specific questions and requirements in that particular study category. Epidemiology/surveillance studies generally used HCV antibody seroconversion, often with prolonged window periods to enhance sensitivity. Studies investigating diagnosis or natural history of recent HCV infection generally used more specific case definitions to detect individuals in the very early stage of HCV infection. Treatment studies tended to use the most restrictive case definitions, presumably to prevent use of suboptimal therapy among misclassified chronic HCV cases
- More standardized case definitions for recent HCV within specific study categories are required

In summary, the current systematic review revealed considerable heterogeneity in case definition for recent HCV infection. Studies in different categories mostly tended to use case definition criteria, which addressed the specific questions and requirements in that particular study category. Although single case definition for recent HCV infection is not warranted, a degree of standardization, particularly within specific study categories, would be advantageous for clinical practice, research, and public health surveillance. More standardized case definition(s) for recent HCV infection will provide opportunities for comparison across studies. From a public health point of view, utilization of standard definition(s) to identify recently infected individuals facilitates the introduction of standard measures to evaluate the spread of HCV infection.
Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Review


