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Original Research

Outcomes and costs of single-step hepatitis C testing in primary care, Birmingham, United Kingdom

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ABSTRACT

Objectives: In UK laboratories, the diagnostic algorithm for chronic hepatitis C (HCV) infection commonly requires two serological assays to confirm anti-HCV–antibody positivity in a serum sample followed by HCV RNA detection in a second whole-blood sample (two-step testing algorithm). A single-step algorithm (both anti-HCV antibodies and RNA tested on an initial serum specimen) has been advocated to reduce attrition rates from the care pathway.

Study design: To investigate the feasibility, clinical impact and relative costs of switching from a two-step to single-step testing algorithm in the laboratory, a pilot study on unselected primary care requests was undertaken.

Methods: All primary care patients tested for HCV infection from December 2013 to April 2016 were included. The single-step testing algorithm was introduced in March 2015. Before this, the two-step algorithm was used. Patients were followed up until August 2016.

Results: RNA quantitation in plasma was within one log of serum values for 21 paired samples. Although all patients in the single-step algorithm received an RNA test, only 70% completed the two-step testing algorithm; differences in referral rates to specialist care was due to 30% of HCV antibody–positive patients in the two-step algorithm not having follow-up whole-blood sampling for HCV RNA testing. Costs per new diagnosis and new diagnosis referred to specialist care were lower in single-step testing by £94.32 and £144.25, respectively.

Conclusion: This study provides further evidence that a single-step testing algorithm, as recommended in the UK Standards for Microbiology Investigation, works in practice and should be the standard of care for screening for chronic HCV.

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Introduction

Chronic hepatitis C (HCV) infection is a public health burden that has only recently gained attention. In 2016, the World Health Organization set global targets for viral hepatitis (including HCV infection) elimination by 2030.[1] The upscale of highly effective, short course (8–12 weeks) treatment with direct acting antivirals[2–4] is an important component of the elimination strategy.

Another key component in HCV elimination is targeted HCV antibody testing in at risk groups.[2,3] Among injecting drug users in the UK, an estimated 50% remain undiagnosed.[5] In addition, a large gap exists between testing and linkage into care and treatment. For example, among patients with new detection of HCV antibody in a single centre in the UK, approximately 50% were not evaluated further in specialist clinics.[6] Thus, the overall proportion of patients with chronic HCV infection accessing treatment in the UK is estimated to be only 3%, although the National Health Service (NHS) England treatment target is >3% of all infected patients.[5]

A laboratory intervention to simplify diagnosis of chronic HCV infection can help address the gap between testing and treatment. The traditional laboratory algorithm was a two-step process: first, serum was tested for HCV antibody; and second, if serum was positive for HCV antibody, a plasma sample was requested to test for HCV RNA. A national evaluation of this two-step algorithm in the US found that 50% of patients with new detection of HCV antibody did not have HCV RNA testing.[7] Consequently, reflex laboratory testing, i.e. detection of HCV RNA on the same serum sample testing positive for HCV antibody, is now recommended.[8–10] Perceived higher costs of RNA testing on all antibody positive sera, a proportion of which are falsely positive, may be a barrier to switching algorithms.

We conducted a pilot study of switching to the single-step testing algorithm to calibrate HCV RNA quantitation in plasma versus serum, compare the proportion completing the two-step with single-step testing algorithm, proportion referred to specialist care, and estimate the relative costs of testing algorithms.

Methods

Study setting

The study was conducted at Public Health Laboratory, Birmingham, UK, which provides diagnostic services for a catchment population of 1.2 million. To provide conservative estimates of HCV infection prevalence, only HCV testing requests from primary care were evaluated. Testing requests from secondary care, drug and alcohol and prison services were excluded because of the likely higher rates of HCV infection in these populations.

Study design and testing algorithm

Prospective observational study

From December 1, 2013 to February 28, 2015, all HCV antibody–positive sera had a second confirmatory antibody test before a second whole-blood specimen was requested for HCV RNA testing, defined as 'two-step testing algorithm' (Fig. 1). During the 'single-step testing algorithm' from March 1, 2015 to April 30, 2016, all HCV antibody–positive sera were tested for HCV RNA on the same sample. Both laboratory algorithms comply with national standards for diagnosis of HCV infection.[10] Antibody-positive HCV RNA undetectable samples had the second confirmatory antibody test to determine true positivity of the first antibody assay.

Hepatitis C testing

In both time periods, the laboratory method for first antibody, second antibody and HCV RNA detection were the same (Architect anti-HCV assay [Abbott], LIAISON HCV assay [DiaSorin] and RealTime HCV [Abbott], respectively).

The RealTime HCV test (Abbott) is licensed for quantitative HCV RNA measurement in serum and plasma. Paired serum and plasma samples taken within one week of each other were used to evaluate the performance of RNA detection in plasma compared with serum.

Data collection and follow-up

All patients were followed up until August 1, 2016, i.e. 3 months after inclusion of the last patient in the single-step testing period. For those with a first diagnosis of chronic HCV infection as searched through our laboratory records, referral to specialist care was ascertained by electronic records of attendance at the viral hepatitis service at Heart of England NHS Foundation Trust and/or telephone enquiry to patients' general practitioners. No HCV RNA results three months after a positive antibody test (two-step testing algorithm) or no evidence of specialist care referral by the end of follow-up on August 1, 2016 (either in two-step or one-step testing algorithms) were considered as lost to follow-up. Referral to other specialist centres within and outwith the study area were included.

Cost estimates

Costs of HCV antibody (initial and confirmatory) and RNA testing at April 1, 2016 were used. The total cost per HCV screen was calculated by summing all test components (Fig. 1). In the two-step testing algorithm, additional costs for the second plasma sample collection was calculated for phlebotomy only and did not include additional equipment or transportation costs. Total costs for the number of tests performed during the two-step and single-step testing period were calculated. This sum was divided by the number of new diagnoses and number referred to specialist care in each time period to obtain cost per new diagnosis/new diagnosis referred to specialist care. Adjusted costs per new diagnosis/new diagnosis referred to specialist care for each testing algorithm were also calculated assuming the prevalence of HCV infection and referral rates were the same in both time periods, i.e. the overall prevalence and referral rates during the study period (December 2013–April 2016).

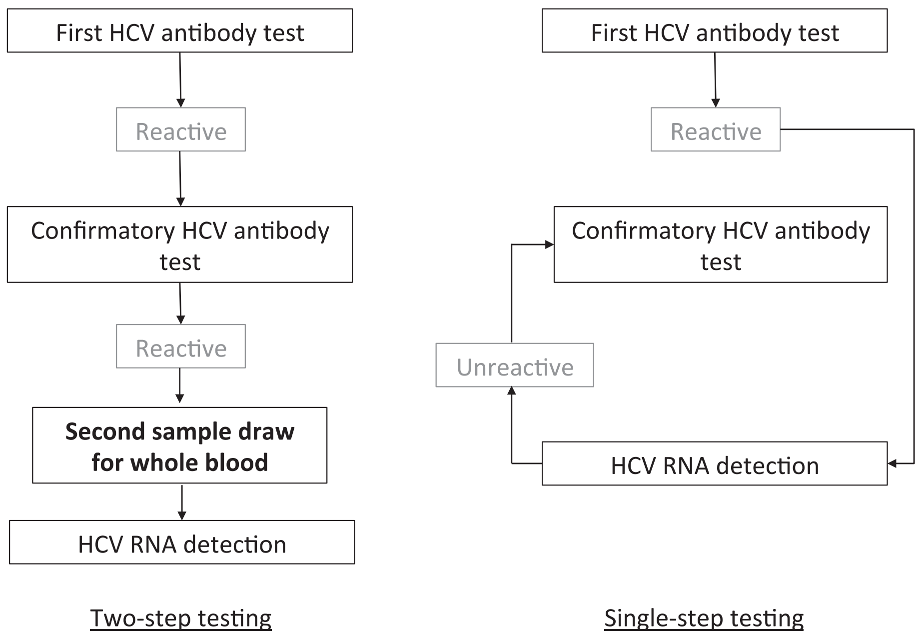

Fig. 1 – A schematic flowchart for two-step and single-step testing algorithm in the laboratory.

Results

The manufacturers licence to use either serum or plasma for HCV RNA detection was initially verified in our laboratory. Twenty-one paired serum and plasma samples were tested for quantitative HCV RNA, and results were within one log for all pairs (R^2 0.97). The number of requests for HCV antibody testing from primary care was higher during the two-step testing algorithm than single-step testing algorithm ($n = 4524$ and $n = 4152$, respectively, Table 1). The prevalence of HCV-antibody positivity was similar in the two periods (overall 3% [273/8676, 95% confidence interval {CI} 3–4%]).

Only 70% (107/154, 95% CI 62–76%) completed the two-step testing algorithm; 111/154 antibody-positive or discrepant sera requiring HCV RNA confirmation had a plasma specimen sent, but three plasma specimens did not meet minimum requirements for correct patient identification and one specimen was inhibitory. In contrast, 99% (118/119, 95% CI 95–100%) completed the single-step testing algorithm (two-proportion z-test, $P < 0.01$). Except for this difference, further findings were similar in both algorithms (Table 1). The overall prevalence of HCV RNA in antibody-positive or discrepant specimens was 51% (114/225, 95% CI 44–57%). When only new diagnoses were considered, the proportion referred to specialist care in both the two-step and single-step testing

Table 1 – Number of primary care patients tested for HCV infection, positive cases identified, number of new diagnoses referred to specialist care and costs per testing algorithm, from December 1, 2013 to April 30, 2016.

	Two-step testing		Single-step testing	
	N	% (95% CI)[a]	N	% (95% CI)[a]
Antibody requests on serum	4524	–	4152	–
Antibody positive/discrepant	154	3 (3–4)	119	3 (2–3)
RNA test performed	107[b,c]	70 (62–76)	118[c]	99 (95–100)
RNA detectable	54	51 (41–60)	60	51 (42–60)
New diagnosis of chronic HCV infection	46	85 (73–92)	49	82 (70–89)
Referred to specialist care	41	89 (77–95)	46	94 (84–98)
Cost per complete RNA positive screen	£69.71		£56.40	
Cost per complete RNA negative screen	£69.71		£67.71	
Cost per new diagnosis (assuming overall prevalence)[d]	£771.67	(£941.69)	£677.35	(£632.96)
Cost per new diagnosis referred to specialist care (assuming overall prevalence and referral rates)[d]	£865.77	(£1016.04)	£721.52	(£684.63)

CI, confidence interval.
[a] Denominator for percentages is the number of patients in the preceding step.
[b] Additional four plasma samples were received of which three could not be processed because of insufficient patient identification details.
[c] One specimen was inhibitory.
[d] Assumes the overall revalence and referral rates across the whole study period.

algorithm was high (89% vs 92%, respectively, two proportion z-test, $P = 0.64$).

The cost per two-step HCV screen, regardless of RNA result, was £69.71 (Table 1). The single-step HCV screen was £13.31 cheaper per RNA-positive specimen and £2 cheaper per RNA-negative specimen (the difference in the latter is due to phlebotomy costs of second blood sample drawn in two-step testing). The cost per new diagnosis of HCV infection and per new diagnosis referred to specialist care was £94.32 and £144.25 cheaper, respectively, in the single-step testing algorithm than in the two-step testing algorithm. The results were more pronounced when adjusted for differences in prevalence in the two testing periods (cost per new diagnosis was £308.73 cheaper and cost per new diagnosis referred to specialist care was £331.41 cheaper in single-step testing).

Discussion

Although the single-step testing algorithm is the recommended standard of care, as proposed by the UK Standards for Microbiology Investigations (UK SMIs) screening for hepatitis C infection,[10] no estimates of the number of UK laboratories complying with this standard are available. Where single-step testing is in place, there is evidence that it translates to clinical benefit, in conjunction with other measures.[11,12] Concerns regarding use of HCV viral load assays in a diagnostic algorithm when they are not specifically licensed for confirmation of HCV infection, the possibility of contamination associated with single sample testing and increased costs may constrain some laboratories from implementing single-step testing. We have shown that serum HCV RNA testing is robust. The additional cost of reflex RNA testing for laboratory users with a similar patient population is also cheaper overall per new diagnosis, because of the 30% attrition of patients who are antibody-positive but never RNA tested. Furthermore, our cost estimates used only minimum costs for second blood sample drawn in two-step testing and the cost of HCV RNA testing is likely to be lower with time. In addition, elimination of unnecessary specialist referrals for up to 50% of patients with no evidence of active infection would help recoup costs. As a concession to cost, HCV core antigen testing could be considered to determine viraemia, albeit less sensitive than HCV RNA testing.[13] HCV core antigen testing is part of some HCV testing algorithms, and it may show the same benefit as this study, providing clear instructions to refer patients to specialist services are placed on core positive reports. Patient convenience and quicker turnaround of conclusive results are other important benefits that have not been costed in this study.

The limitations of this study are two-fold: first, the cost estimates for laboratory testing prevents an accurate cost-benefit of single step vs two-step testing to be fully analysed; second, as the study was based in primary care with a low HCV RNA positivity rate, it also remains to be determined whether a single-step testing algorithm would be equally beneficial in a setting with a known higher chronic HCV prevalence, or where antibody positive cases would be more inclined to referral.

Conclusion

A single-step HCV testing algorithm enhances the recruitment of patients with potential chronic HCV infection from the primary care pathway. The expected increased numbers of new chronic HCV diagnoses and patients referred to specialist care in single-step testing outweigh the costs of increased reflex RNA testing for all antibody-positive patients. This approach also has much merit from a public health perspective as a way of shortening the length of time from HCV diagnosis to care, and minimising unnecessary interventions in the testing pathway towards cure, ultimately reducing the cases of onward transmission.

Author statements

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Ethical approval

The study was conducted as part of service evaluation of the algorithm switch. Approval from the Research and Development Department, Heart of England NHS Foundation Trust was sought and no ethical approval was necessary.

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Competing interests

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