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Diagnostic Technology: Point-of-care testing for Hepatitis C virus

Clinical Question:

In the primary care setting, what is the analytical performance and utility of point-of-care tests for hepatitis C virus infection compared to standard practice?

Advantages over Existing Technology:

Current clinical practice for testing patients for the presence of hepatitis C involves taking a blood test to detect antibodies to the virus using enzyme immunoassays (EIAs). EIAs occasionally produce false positive results and a proportion of patients clear the virus spontaneously, therefore a positive EIA test is confirmed either with recombinant immunoblot assay (RIBA) or with a molecular (polymerase chain reaction) test to confirm the presence of viral RNA.

Rapid point-of-care devices require little technical equipment and expertise and can be used in a clinic setting. Laboratory immunoassay is often performed in batches to minimise cost and results are only available several days after testing. Rapid tests allow patients to receive the results of their test at the same consultation and decrease the problem of patients not returning for test results. Rapid point-of-care testing for hepatitis C can be performed on small volumes of whole blood or oral fluid. This reduces the need to obtain venous blood samples from patients with poor access, such as intra-venous drug users.

Details of Technology:

There are several rapid hepatitis C test units available, which all use immunochromatography to show the presence of anti-hepatitis C antibodies in the test fluid. Test fluid is collected (whole blood, serum or oral fluid) and mixed with a developing solution such as colloidal gold labelled with protein-A (1). This mixture is then applied to the absorbent membrane of the test device, which contains immobilised hepatitis C antigens (such as core, NS3 and NS4 antigens) in a test zone. As the test fluid migrates through the test zone, a coloured line or dot appears if anti-hepatitis C antibodies from the test fluid react at the test zone, indicating a positive result. A control area is also present, which contains a control monoclonal antibody, and confirms that the test solution has adequately passed through the test zone by showing another coloured line or dot (2). If there is no control line then the test is invalid. If there is a control line only then the test is valid and negative. The tests take between 3 and 40 minutes to give a result and generally require no equipment other than the test device and a pipette to apply fluid. Tests for use with either whole blood or oral fluid and their properties are summarised in Table 1. Of these, CE marking is reported for the OraQuick HCV Rapid Antibody Test and Hexagon HCV. The OraQuick is currently the only test approved by the US Food and Drug Administration (June 2010) for use in high risk individuals or individuals with symptoms consistent with hepatitis C infection (3). Other available tests are for use with serum only and are therefore not listed as they are considered to be not appropriate for most primary care settings.

Table 1: Rapid HCV tests available and their specifications:

Product	Test fluid	Volume of test fluid	Time (min.)	Nature of Device
OraQuick HCVrapid antibody test (OraSure Technologies, USA)	Oral fluid/whole blood/serum/plasma	1 drop of blood or oral swab	20-40	Cassette encased test strip
SM-HCV Rapid Test (SERO-Med, Germany)	Whole blood/serum	30-40 µl (~2-3 drops)	3	Cassette encased test card
Anti-HCV Ab rapid test (Tema Ricerca, Italy)	Whole blood	1 drop	3	Cassette encased test card
SD Bioline HCV (Standardia Diagnostics Inc, Korea)	Whole blood/ serum/plasma	10 µl (~1 drop)	5-20	Cassette encased test strip
One Step HCV Rapid Test (Inter-chemical Ltd, China)	Whole blood/ serum/plasma	2-3 drops	10	Cassette encased test strip
Rapid Anti-HCV Test (InTec, China)	Whole blood/ serum/plasma	1 drop	1	Test card
Hexagon HCV (Human Diagnostics Worldwide, Germany)	Whole blood/ serum/plasma	10 µl (~1 drop)	5-20	Immunochromatographic test of unknown type
Multiplo rapid HBV/HIV/HCV antibody test (MedMira Laboratories Inc., Canada)	Whole blood/ serum/plasma	1 drop	3	Cartridge with test membrane
Dual Path Platform (DPP) HCV rapid assay (Chembio Diagnostic Systems Inc., USA)	Whole blood, oral fluid	Prototype currently under development		

Patient Group and Use:
The point-of-care anti-hepatitis C virus test has the potential to be used in primary care settings, such as general practice and accident and emergency. The main use would be to test patients with high-risk lifestyles who are offered hepatitis and HIV testing and/or those requesting tests, e.g. after a suspected exposure to hepatitis C (to look for pre-existing infection) or those presenting with symptoms of acute or chronic hepatitis. It could be used in genitourinary medicine and specialist drug addiction clinics, which have a high proportion of high risk individuals.

Importance:
The prevalence of hepatitis C in the United Kingdom is between 200 000 and 500 000, although a large proportion of infected individuals remain undiagnosed (4). The major risk factor for infection in the UK is injecting drug use (5). Of those who develop acute hepatitis C infection, around 80% will become chronically infected and 30% will develop liver cirrhosis within 20 – 30 years. In the UK, alcohol and hepatitis C are now the most common causes of cirrhosis; chronic hepatitis C infection leads to cirrhosis and hepatocellular carcinoma in approximately 20% of cases (6). If diagnosed however, chronic hepatitis C infection can be treated with interferon and ribavirin, which can result in viral clearance in approximately 50% of patients with genotype 1 disease and 80% of cases with genotypes 2 or 3 (7).

Previous Research:
Accuracy compared to existing technology:
The initial standard test for hepatitis C antibody detection is laboratory immunoassay, therefore most accuracy studies of rapid tests compare their performance with immunoassay. Most of the following studies do not compare rapid tests in a point-of-care setting, but use only those test kits which would be appropriate for point-of-care testing comparing the accuracy to laboratory tests in the laboratory setting.
The OraQuick rapid anti-hepatitis C test was compared with laboratory immunoassay (1). Five different fluids from 122 known HCV positive patients and 450 low risk subjects with unknown status were tested. 121 of 122 known hepatitis C positive cases were detected by OraQuick in all fluid types (99.2% sensitivity). One subject was negative for oral fluid but positive on venous blood, finger prick blood, plasma and serum. Results from OraQuick compared to immunoassay (EIA) testing in samples from 450 low risk subjects were 99.8% concordant (449/450 cases) for all 5 specimen types per individual. OraQuick gave one false negative result and detected one previously undiagnosed hepatitis C positive subject,

which was confirmed with recombinant immunoblot assay and PCR. Sensitivities and specificities for each fluid type in the low risk group with OraQuick were as follows: oral fluid, 99.2% and 100%; venous whole blood, 100% and 100%; finger prick blood, 100% and 100%; plasma, 100% and 99.8%; serum, 100% and 99.8%. A series of 19 seroconversion panels were also tested and OraQuick detected HCV antibody at the same time as EIA in 9 cases and earlier than EIA in 10 cases. Overall OraQuick detected HCV antibody 4.9 days before EIA (95% CI: 1.4-8.3).

A follow-up study conducted at 8 clinical testing sites compared OraQuick with laboratory assays (EIA, RIBA and PCR) on blood, serum, plasma and oral fluids from 2206 subjects recruited from outpatient clinics specialising in hepatology, gastroentereology or infectious diseases (8). All subjects were either symptomatic for hepatitis or had one or more risk factors for HCV infection. Overall sensitivities were virtually identical for venous blood, fingerstick blood, serum and plasma (99.7–99.9%) and specificities were all 99.9%. For fingerstick blood (considered to be the most useful in the primary care setting) sensitivity was 99.7% (95% CI, 99.0% - 100%) and specificity was 99.9% (95% CI, 99.6% - 100%). Sensitivity was slightly lower for oral fluid at 98.1% (95% CIs, 96.9% - 99.0%) and specificity was 99.6% (95% CI, 9.2% - 99.9%). Of 12 HCV positive subjects (1.6%) who gave nonreactive OraQuick results in oral fluid alone, only four were positive for HCV RNA when tested by PCR (0.5%). In this population with a relatively high prevalence of HCV (34%), the positive and negative predictive values (PPV, NPV) ranged from 99.7% to 99.9% for the different specimen types, with PPV of 99.9% and NPV of 99.9% for fingerstick blood, and PPV of 99.3% and NPV of 99.0% for oral fluid. This was the only study that appears to have been conducted in the clinical setting.

The SM-HCV rapid test was compared to a third generation laboratory immunoassay using serum and whole blood samples from 195 subjects in a hepatitis clinic (The University of Hong Kong) and 95 healthy controls (2). Of the 101 patients testing positive for hepatitis C antibody with laboratory immunoassy, 98 tested positive with SM-HCV. In the 95 healthy controls, all tested negative with laboratory and SM-HCV tests. The laboratory immunoassay results were taken as gold standard in this study and SM-HCV accuracy was calculated as: sensitivity 97%, specificity 100%, positive predictive value 100%, negative predictive value 97.9%.

The Tema Ricerca rapid anti-HCV Antibody test was compared to laboratory hepatitis C immunoassay on 100 whole blood samples which had been collected routinely at a central laboratory (Bologna) (9). 50 were hepatitis C immunoassay antibody positive and 50 were hepatitis C immunoassay antibody negative as confirmed with a recombinant immunoblot assay. The sensitivity and specificity for the rapid test were 100% and 98%, respectively, using whole blood. When diluting the whole blood the sensitivities and specificities were as follows: 1:20 dilution, 96% and 100%, 1:50 dilution, 30% and 100%, 1:100 dilution, 4% and 100% which suggests that the test may not be as useful in early disease with lower antibody titres.

One study measured the accuracy of the Hexagon HCV test compared to laboratory immunoassay using 161 HCV positive plasma samples and reported a sensitivity 64.0% (95% CI, 56.0–71.4%) and specificity of 100% (95% CI, 97.8% - 100%), and a PPV and NPV of 100% and 97.4%, respectively (10).

A recent Centers for Disease Control and Prevention (CDC) study evaluated the OraSure, Chembio and MedMira tests compared to laboratory immunoassay and RIBA using 1100 serum samples previously drawn from patients reporting injection drug use (11). The sensitivities of the Chembio, MedMira, and OraSure assays compared to the 2 laboratory assays were 96.2%–98.0%, 86.8%–88.3%, and 97.8%–99.3%, respectively. The 3 assays had specificity of 99.5% or higher with no differences between assays.

We have not found published accuracy studies for the following devices: SD Bioline HCV (Standardia Diagnostics Inc, Korea), One Step HCV Rapid Test (Inter-chemical Ltd, China), and Rapid Anti-HCV Test (InTec, China).

Impact compared to existing technology

We have not found any studies which used point-of-care anti-hepatitis C antibody testing in the primary care setting.
A cluster randomized controlled trial among 28 specialist drug clinics and 6 prisons in England and Wales comparing capillary dried blood spot hepatitis C testing to usual care showed the uptake of hepatitis C antibody testing among

injecting drug users increased by an average of 14.5% (95% CI, 1.3-28%, paired t-test p = 0.03) (12). Although testing was laboratory-based in this study, the increased uptake in testing with the dried blood spot sampling may indicate a role for point-of-care hepatitis C testing.
The Centers for Disease Control are currently evaluating the performance of rapid HCV assays at four different clinical sites in the USA (13).

Guidelines and Recommendations
The Health Protection Agency's Hepatitis C in UK Report 2011 indicates that alternative testing technologies continue to contribute to the increased uptake of testing in intravenous drug users, particularly using dried blood spot (DBS) and oral fluid testing. The report recommends "Testing in those attending specialist services for drug users needs to be sustained and enhanced, and the potential use of non-invasive specimens (e.g. oral fluid) for testing in other settings should be considered." (14)
The Department of Health gives guidance for detection and diagnosis of hepatitis C in primary care, but point-of-care testing is not included in the testing pathway (15).
NICE guideline: Hepatitis B and C: ways to promote and offer testing is expected to be published in December 2012.
SIGN Guideline no. 92: Management of hepatitis C. December 2006: the testing algorithm uses EIA as a first line test followed by viral PCR on positive samples. Point-of-care testing is not included though use of saliva and dried blood spots is discussed as a potential alternative to serum/plasma (16).

Cost-effectiveness and economic impact:
Currently very limited evidence exists on the cost-effectiveness and economic impact of hepatitis C virus (HCV) point of care (POC) testing. Evidence suggests that HCV POC testing is likely to be cost-saving due to the following reasons:

- It requires minimum training since the procedure is not complicated;
- It does not require the use of expensive laboratory equipment to carry out the test;
- It is cheap; the costs of many currently available HCV rapid tests are no more expensive than the enzyme immunoassay tests (17);
- It provides rapid turnaround time for testing and finally, the simplicity and ease of use of the HCV POC test provides rapid diagnosis which is clinically relevant and has a direct positive impact on patient management and outcome.

A US study determining a cost-effective strategy for diagnosis of HCV infection in clinical laboratories showed that using a rapid anti-HCV kit would allow for a savings of US$ 65 000/year in reagent costs in a laboratory performing approximately 8000 HCV serological tests annually (18).

The benefits of using anti HCV rapid testing on patient outcomes were explored comparing a rapid HCV test (that can be used with venous blood, finger stick blood, serum, plasma, or oral fluid) with FDA-approved laboratory methods. The study concluded that OraQuick® HCV rapid Antibody test appears suitable as an aid in the diagnosis of HCV infection (1). The availability of HCV POC test increases number of cases diagnosed through increasing testing opportunities outside of traditional laboratory settings, such as clinics, community outreach centres and General Practices. HCV infection left undiagnosed may go on to cause other complications. Avoiding complications due to HCV infection through rapid diagnosis is likely to be cost saving.

No studies evaluating the cost-effectiveness of rapid HCV testing in a primary care setting were found in this review. This has highlighted the need for future research to be concentrated on undertaking cost effectiveness studies of HCV POC testing in both primary and secondary care settings. Evidence on health-related quality of life outcomes associated with HVC, and its long-term consequences, are required so that cost-effectiveness studies can use cost per QALY as the measure of outcome.

In order to demonstrate cost-effectiveness one would need to show that:

1. The tests significantly increase the uptake of Hep C antibody testing
2. Reduces the number of people currently not returning for results (follow-up)
3. Those who test positive go on to have PCR

4. Those who are PCR positive
    a. Take extra care to prevent transmission to others, thus reducing costs to the NHS; and/or
    b. go on to be referred to a Hep C clinic,
5. Those referred attend the Hep C clinic
6. Those attending the clinic are treated (which is expensive)
7. The treatment is completed and assures a good cure rate
8. Therefore the rate of cirrhosis / complications is reduced, saving money to the NHS.

There are so many steps that it is quite possible that the tests are not cost-effective if there is a "bottleneck" at one or more of the steps above.

Research Questions:
We did not identify sufficient or relevant research to be able to address the original research question.

Suggested next step:
1. Further accuracy studies of devices suitable for primary care are required before a systematic review of diagnostic performance can be carried out.
2. Studies which examine the roles of hepatitis C antibody POC testing in primary care settings are needed. Point-of-care testing may be used as an initial test, which is then confirmed with serum PCR testing. Studies should consider whether patient testing increases and if point-of-care testing improves hepatitis C diagnosis rates, as well as rates of referral to and successful completion of treatment at specialist hepatology clinics, and in which populations or settings this is most useful (e.g. prison, genitourinary medicine, GP).
3. Hepatitis C is only one of the triad of significant blood-borne viruses for which screening should take place in high-risk individuals (the others being hepatitis B and HIV), and in some settings (e.g. genitourinary medicine clinics) would occur at the same time as blood testing for syphilis. Therefore in most clinical settings, testing for these three or four pathogens is standard care, and POC tests for just one of them may be inappropriate or add little. Research studies therefore need to explore testing for combinations rather than individual pathogens.

Expected outcomes:
Point-of-care anti-hepatitis C virus antibody testing has the potential to be a valuable method of screening high risk patients for hepatitis C before confirming infection with laboratory based investigations. However there are many steps between diagnosis of hepatitis C infection and cure and each step carries a high attrition rate. Therefore increased uptake of testing may not affect disease outcomes.

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Comments:

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