ORIGINAL ARTICLE

An audit of thrombophilia screens: results from the National Pathology Alliance benchmarking review

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Aims: The National Pathology Alliance benchmarking review has completed six years of data collection and analysis of the workload and organisation of haematology laboratories in the UK. This study audits national practice of routine thrombophilia screening against the current standards, as set out in the British committee for standards in haematology (BCSH) guidelines on investigation of heritable thrombophilia.

Methods: Each laboratory completed a standard data collection questionnaire about the number of routine thrombophilia assays performed each year. Information was collected on which thrombophilia tests were performed as part of a routine thrombophilia screen. These results were then compared against the BCSH guidelines on investigation of heritable thrombophilia.

Results: Of the 57 National Health Service trusts that submitted data for review in 2002/2003, 47 performed a routine thrombophilia screen. Ten laboratories complied with the guidelines but 37 laboratories did not.

Conclusion: There was variation in practice in the tests used in routine thrombophilia screens. There is evidence that some laboratories deviate from what may be regarded as "evidence based practice". The lack of compliance with the guidelines was in general associated with the performance of additional tests not recommended in the guideline. In a minority of laboratories, a clinically significant diagnosis would be missed by the failure to include one or more tests in a thrombophilia screen.

The National Pathology Alliance benchmarking review has completed six annual cycles of data collection and analysis of the workload and organisation of haematology departments in the UK.¹ The national definition of tests and requests in haematology and blood transfusion that is used by most laboratories has enabled a comparative analysis of workload between laboratories of similar type and size to be made. This analysis has identified a variation in diagnostic strategies used in different laboratories in areas such as testing for folate deficiency.² This report analyses the variation in practice in how laboratories respond to a clinical request to perform a thrombophilia screen. National guidelines for the investigation of heritable thrombophilias have been published, and these are the standards against which this audit was undertaken.³

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METHODS

The method for data collection and analysis for the National Pathology Alliance benchmarking study has previously been described in detail.^{2–4} Laboratories participate in this study on a voluntary basis. Each laboratory completes a data collection questionnaire with the number of tests that the laboratory performs on an annual basis. The haematology data collection proforma collects workload information on a range of 63 laboratory tests, and data on laboratory activity in relation to the preparation of blood components and blood products. For the purposes of our study, a structured proforma was included in the data collection analysis. The clinical scenario used for this audit was: "As part of a thrombophilia screen, which of the following tests would you perform in your

department, assuming that the patient is not on anticoagulants and has no other clinical problem that might affect the result?". Tests performed both on site and those referred to other laboratories were included as part of the profile offered by an individual laboratory. Data were also collected on tests that were only performed sometimes, such as when another test shows an abnormality, or when appropriate clinical details are given on the request. Those laboratories that referred out all routine thrombophilia screens were excluded from our audit.

RESULTS

Fifty seven National Health Service (NHS) trusts submitted data for the annual National Pathology Alliance benchmarking review in 2002/2003, 47 of which (13 were teaching hospital trusts) declared that they performed a routine thrombophilia screen; these 47 trusts are subject to further analysis. Of these 47 NHS trusts, many had laboratories on several sites and the total sample size was 99 individual laboratory sites. For the purposes of our study, however, the 47 NHS trusts were assessed as 47 laboratories because the testing patterns were the same within each trust.

Ten laboratories performed thrombophilia screens that complied with the minimum recommendations of the guidelines published by the British committee for standards in haematology (BCSH), and these results are summarised in table 1. Three laboratories routinely undertook both total protein S and free protein S assays. The BCSH guidelines suggest that only the total protein S assay should be used as a screening test, and if this is abnormal, then a free protein S assay should be performed. Seven laboratories complied with the guidelines and only performed a free protein S assay when the total protein S assay was abnormal. It should be noted that only two laboratories fully complied with the

Abbreviations: APC:SR, APC resistance sensitivity ratio; BHSC, British committee for standards in haematology; NHS, National Health Service

[illegible]

in thrombophilia profiles that lead to non-compliance with the guidelines. In addition, other tests not recommended in the guideline were also performed by most laboratories. A separate analysis of trends in testing patterns over the six-year period of the benchmarking study showed no change after publication of the BCSH guidelines.

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DISCUSSION

BCSH guidelines on the investigation and management of heritable thrombophilia recommend a set of standard assays for thrombophilia assessment.³ Our audit demonstrates wide variation in the application of these guidelines. Ten of the 47 laboratories questioned complied with the guideline by performing a range of 13 tests as part of a routine thrombophilia screen. However, only two of these laboratories fully complied with the guideline, with the other eight laboratories performing additional tests that are not recommended for routine thrombophilia screens. Thirty seven laboratories performed a thrombophilia screen that did not comply with the minimum requirements of the guideline, with most of the laboratories performing additional tests not recommended in the guideline. Therefore, most laboratories appear to "interpret" the guidelines, with 44 of the 47 laboratories questioned performing at least a prothrombin time, activated partial thromboplastin time, antithrombin, protein C, factor V Leiden, PT20210A, and lupus anticoagulant assays.

However, there are several concerns with the approach taken by some of the laboratories. All laboratories provide some form of screening for the factor V Leiden mutation: 46 of the 47 laboratories surveyed performed factor V Leiden polymerase chain reaction testing and 34 used the modified APC:SR (APC resistance sensitivity ratio) technique. However, the BCSH guidance suggests that the modified APC:SR technique should be the initial screening test for the factor V Leiden mutation in conjunction with a free protein S assay. The logic behind this is to identify the 5% of abnormal APC:SR tests that are not secondary to the factor V Leiden mutation—for example, factor V Cambridge. Another concern is the potential waste of resources, with universal factor V Leiden molecular screening in the face of potentially normal modified APC:SR screening, which is 100% specific and sensitive.³ Similarly, many laboratories continue to use both the modified and unmodified techniques. This practice is contrary to the BCSH guidance and is a waste of resources.

Only 11 of the 47 laboratories surveyed routinely carried out a total protein S assay. When scrutinising the assays performed, many laboratories now perform the more clinically relevant free protein S assay instead of a total protein S assay. This approach has a logical basis because modern enzyme linked immunosorbent assay free protein S assays are insensitive to APC resistance⁶; however, they may miss rare cases of type II protein S deficiency. Furthermore, the total protein S assay is now not recommended as a routine test after the 1996 consensus conference

recommended the measurement of free protein S for the diagnosis of protein S deficiency.^{7,8} When considering this evidence based practice in the context of the BCSH guidelines, it means that only 10 of the 47 laboratories surveyed carry out thrombophilia screening in accordance with BCSH guidance.

"Only 11 of the 47 laboratories surveyed routinely carried out a total protein S assay"

Six laboratories offer no routine free or total protein S estimates and two do not perform routine functional antithrombin assays. This does not appear to have a logical basis. It is also inappropriate to offer a protein C, protein S, or antithrombin assay without a baseline prothrombin time, as is the routine practice in three laboratories surveyed. These laboratories would fail to pick up individuals with vitamin K deficiency and patients taking oral anticoagulation treatment.

All laboratories questioned perform a lupus anticoagulant as a standard assay but only 31 laboratories perform IgG and IgM anticardiolipin antibody assays as part of the standard thrombophilia screen. This departure from standard practice cannot be justified, because the identification of the antiphospholipid syndrome is clinically important.⁹

The thrombin clotting time was only performed routinely in just over half of the laboratories surveyed. Heritable dysfibrinogenemia is exceedingly rare and the link between it and thrombosis is not robust.¹⁰ The thrombin clotting time also lacks sensitivity and specificity for this disorder.¹¹ This, we believe, has led many haematologists to doubt the value of the thrombin clotting time in routine thrombophilia testing, thus making it difficult to criticise those laboratories that do not routinely perform this assay.

The results of the audit show a wide variation in practice but our study does not attempt to ascertain the reasons behind this deviation. Our results undoubtedly show deviation from what may be regarded as evidence based practice. This is particularly important for those laboratories that failed to include one or more of the recommended tests in a thrombophilia screen, with the potential for missing a clinically relevant diagnosis. However, those laboratories that performed tests not recommended in the guideline could also usefully review their practice, because discontinuing the performance of these tests may reduce unnecessary expense. The final point for consideration should be that, with such wide deviation from the BCSH guidelines, is it now time to update this guidance?

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REFERENCES

- 1 **Galloway M**, Osgerby J, Rushworth L, et al. *Pathology benchmarking report—haematology and blood transfusion 2002/2003*. London: Newchurch, 2004.
- 2 **Galloway M**, Rushworth L. Red cell or serum folate? Results from the National Pathology Alliance benchmarking review. *J Clin Pathol* 2003;**56**:924–6.
- 3 **British Committee for Standards in Haematology**. Guideline. Investigation and management of heritable thrombophilia. *Br J Haematol* 2001;**114**:512–28.
- 4 **Galloway M**, Nadin L. Benchmarking and the laboratory. *J Clin Pathol* 2001;**54**:509–7.
- 5 **Trossaert M**, Conard J, Horellou MH, et al. Modified APC resistance assay for patients on oral anticoagulants. *Lancet* 1994;**344**:709.

Take home messages

- There was variation in practice in the tests used in routine thrombophilia screens: only 10 of 47 laboratories complied with the British committee for standardisation in haematology guidelines
- Some laboratories appeared to deviate from what may be regarded as "evidence based practice"
- The lack of compliance with the guidelines was often associated with the performance of additional tests not recommended in the guideline, which can be wasteful of resources
- In a few laboratories, a clinically significant diagnosis would be missed by the failure to include one or more tests in a thrombophilia screen

- 6 **Goodwin A**, Rosendaal FR, Kottke-Marchant K, *et al*. A review of the technical, diagnostic and epidemiologic considerations for protein S assays. *Arch Pathol Lab Med* 2002;**126**: 1349–66.
- 7 **Lane DA**, Mannucci PM, Bauer KA, *et al*. Inherited thrombophilia: part 1. *Thromb Haemost* 1996;**76**:651–62.
- 8 **Lane DA**, Mannucci PM, Bauer KA, *et al*. Inherited thrombophilia: part 2. *Thromb Haemost* 1996;**76**:824–34.
- 9 **Greaves M**, Cohen H, MacHin SJ, *et al*. Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol* 2000;**109**:704–15.
- 10 **Haverkate F**, Samama M. Familial dysfibrinogenemia and thrombophilia. Report on a study of the SSC subcommittee on fibrinogen. *Thromb Haemost* 1995;**73**:151–61.
- 11 **Hayes T**. Dysfibrinogenaemia and thrombosis. *Arch Pathol Lab Med* 2002;**126**:1387–90.