An international survey on the interpretation of pigmentation using the C class of the Clinical, Etiological, Anatomical, Pathophysiological Classification

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Abstract

Skin changes over the gaiter area like pigmentation, lipodermatosclerosis and eczema are a clinical sign of advanced chronic venous disorder. This is documented as C4 in the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification. The hypothesis was that there is great variability whether skin changes are recorded as early or advanced disease. The aim was to evaluate different patterns of skin changes by delegates at 3 international venous conferences. Seven high-definition, A4-sized, color photographs were taken of untreated legs with skin changes from patients attending a public hospital venous clinic. They all had venous disease confirmed on duplex with deep or superficial vein reflux >0.5 s. The photographs were displayed and a questionnaire was provided. Delegates familiar with CEAP were asked to choose from 3 C class options for each photograph. The responses were summarized by grouping them into mild (C0-3) and severe (C4-6). A total of 117 delegates completed the questionnaire from 30 countries. A percentage of 60 had practiced phlebology >10 years. The percentages of responders scoring mild (C0-3) and severe disease (C4-6) were: mild/severe=3/96 (photo 1), 65/33 (photo 2), 31/67 (photo 3), 56/44 (photo 4), 74/21 (photo 5), 89/10 (photo 6) and 37/69 (photo 7). The median percentage measure of agreement was 36.8 [95% confidence interval (CI): 24.8-48.9]. The range was 23.2 (95% CI: 10.5-36.0) to 94.8 (95% CI: 90.7-98.9%), P=0.001/image, Fisher exact test). This indicates a significant difference of opinion between the appearances of mild and severe clinical disease. Clinical decisions using the C class as a sign of advanced disease may be unreliable if used alone for recording severity, grouping patients or rationing treatment.

Introduction

The Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification for chronic venous disorders (CVD) was set up following an international ad hoc committee.1,4 It was revised in 2004 when it was stated that revision of CEAP is an ongoing process and that recommendations for change in the CEAP standard be supported by solid research.3 In 2007, a Joint Statement of the American Venous Forum and the Society of Interventional Radiology reported that this revision should be included as a baseline patient characteristic prior to endovenous treatments.3 This would facilitate comparison between the results of different studies and improve the overall quality of research on venous disease.

The C component is the most widely used part of the CEAP classification and it is based solely on clinical appearance. Skin changes secondary to CVD are classified as C4 with C4a representing pigmentation or eczema and C4b representing lipodermatosclerosis (LDS) or atrophie blanche. In 2004, a questionnaire study without photographs was sent to 3681 phlebologists around the world. They concluded from 206 responders that future work would be required on discriminating between C4 and varicose vein sizes and which C (C1-3) to assign for corona phlebectatica.5,6 Discrepancies on the C placement of varicose veins of differing sizes were also apparent in an international consensus from experts on the C scale. This is because wide variations in interpretation of skin changes could inaccurately place a leg into a mild (C0-3) or severe (C4-6) category. The aim was to investigate the definition of C4 by asking dedicated phlebologists to use their judgment and experience to classify 7 color photographs of skin changes using the C of CEAP.

Materials and Methods

Study design

This was an international observational study involving experienced phlebologists familiar with the CEAP classification. The majority of delegates were vascular surgeons/angiologists with an interest in phlebology. There were no responders whose main practice was dermatology. They were asked to complete a short questionnaire in order to grade 7 photographs on the C of CEAP. These photographs were displayed on a table, placed at strategic locations, throughout the duration of 3 international venous conferences: the Royal Society of Medicine venous forum (RSM-VF), the European Venous Forum (EVF) and the venous section of the World Congress of the International Union of Angiology (IIA). Participants were either self-selected when they took an interest in the display table or when known specialists, prominent in the venous world, were invited specifically to complete the questionnaire.

Patients

All 7 photographs were from patients with

[Veins and Lymphatics 2013; 2:e15]
leg symptoms who were attending the varicose vein clinic at a single public hospital. Patients were referred in the later stages of their disease because uncomplicated varicose veins do not fill the referral criteria under the current public health rationing system. Five patients had duplex evidence of reflux in the saphenous trunks greater than 0.5 s without evidence of deep venous reflux. Two photographs were taken from the same patient (leg elevated and dependant) who had a previous calf vein thrombosis with significant tibial vein reflux. None of the patients had a healed venous ulcer or had received endovenous intervention for their condition.

Photographs

The photographs were high-resolution, taken at close range and printed in color on high-quality photographic A4 print-paper (Figures 1-7). Dissimilar backgrounds were chosen to avoid direct comparisons between the pictures. Each photograph was cropped to highlight the gaiter and ankle areas. The first photograph of lipodermatosclerosis was used as a quality control to determine the standard of the participants at classifying skin changes and to familiarize them with the task. The remaining 6 were selected to highlight controversial areas in the C-class. Although they were considered to be representative of venous disease, it is for the reader to decide on the prevalence of these skin changes in their day-to-day practice. All 7 photographs were displayed simultaneously on a table which enabled each participant to pick them up and view each from different angles in order to make their judgment. Conferring was not forbidden and occurred occasionally. A copy of the clinical classification of the revision of CEAP summary was also placed on the table for information purposes to remind each person of its precise wording as shown below.3

Clinical classification (C class)

According to CEAP classification, C class is divided as follows:
- C0: no visible or palpable signs of venous disease;
- C1: telangiectasies or reticular veins;
- C2: varicose veins;
- C3: edema;
- C4a: pigmentation or eczema;
- C4b: lipodermatosclerosis or atrophie blanche;
- C5: healed venous ulcer;
- C6: active venous ulcer.

Questionnaire design

The questionnaire occupied half a page of A4 paper from which participants were asked to check 9 boxes and state their country of practice (Figure 8). This restriction on 10 questions/replies was purposeful to prevent lapses of concentration or questionnaire fatigue thereby ensuring data quality with maximal completion.10 Participants were given 3 C-class options for each photograph from which to pick their answer. They also had the option of stating an alternative C-class option or checking the don’t know box for whatever reason, including poor quality of photographs. The question on whether a clinical history would influence their judgement was included because it is uncertain whether clinicians should rely on clinical appearance alone or use supplementary information in deciding the C of CEAP. This may be relevant because pigmentation could be the result of treatment. Discoloration could also be caused by extensive telangiectasiae following a deep venous thrombosis (DVT). The clinical history in both of these situations may encourage an enthusiastic C class score of C4a rather than C4 or C5.

Data analysis

Data were transferred manually from the questionnaires onto spreadsheets at the end of the study and then imported into the IBM® SPSS® statistics software version 19 (IBM Corp., Armonk, NY, USA) for statistical analysis. The results on the C-class determination from the 7 pictures were reported in 2 ways. Firstly, specifically, as the percentage of responders choosing each C-class and/or stratification into mild and severe venous disease. Similarly, the results were reported in two ways. Firstly, specifically, as the percentage choosing mild (C0-3) or severe (C4-6) venous disease (binary outcome). The percentage agreement between mild versus severe disease was determined using the risk difference value of the Fisher exact test. Full agreement, where all the raters scored either mild or severe, would be represented as 100%, whereas equivalence would be represented as 0% agreement.

Results

Participant characteristics

A total of 117 delegates completed the questionnaire out of the 120 that were returned. Three were excluded because the answers to the 7 picture questions were incomplete. It was interesting that 2 responders ticked multiple boxes for each question in line with the recommendations of the advanced CEAP. In this case the single highest descriptor was used for the clinical classification.3 Delegates of 30 different nationalities completed this questionnaire, the top 5 being: UK (17), Italy (16), USA (10),...
Czech Republic (8) and France (7). This distribution reflected the location of the conferences: London (RSM-VF: 20/117 responders, 17%), Florence (EVF: 63/117 responders, 54%) and Prague (IUAP: 34/117 responders, 29%).

The experience of the delegate was determined by their number of years in phlebology practice which were: less than 2 (6%), between 2 and 10 (31%), between 10 and 30 (43%), over 30 (17%) and failure to answer (3%). Of the 27 original members of the ad hoc committee on the revision of the CEAP classification, 12 (44%) were recognized and invited in person into the study. Nine members completed the questionnaire and 3 were unable to take part for whatever reason. A further index of experience was provided by the answers to the quality control picture 1 depicting lipodermatosclerosis. A total of 96% of delegates recognized this correctly as C/C \(a/C_{fa} \) with 3% as edema (C \(_1 \)) and 1% checking don’t know for whatever reason.

**C class response stratification**

The percentage of participants checking each of the three given choices is displayed in the legends underneath each picture for convenience (Figures 1-7). Pictures 4, 5 and 7 caused the greatest amount of uncertainty with the percentage of participants checking the don’t know box at 10%, 5% and 4%, respectively. The full spectrum is illustrated in Table 1.

**Mild and severe response stratification**

The percentages of participants scoring mild (\(C_{m} \)) and severe disease (\(C_{s} \)) for each photograph from 1 to 7 were: mild/severe= 3/56 (photo 1), 65/33 (photo 2), 31/67 (photo 3), 56/34 (photo 4), 74/21 (photo 5), 89/10 (photo 6) and 37/59 (photo 7), respectively. Apart from the control picture 1 which was classed as severe according to 96% of participants, there was a significant lack of agreement between mild and severe clinical disease for the remaining legs. The percentage agreement (risk difference) of mild versus severe disease is displayed in the last column of Table 1. There was clinical uncertainty in classifying pictures 2 (Figure 2) with 32% of participants choosing advanced disease. However, when the same leg was elevated in picture 6 (Figure 6), this was reduced to 10%.

**Importance of a clinical history**

In response to the influence a clinical history had to judgment of C class (Figure 8) the participants chose YES (67%), NO (26%), don’t know (3%) with 4% leaving this question unanswered. The fact that two-thirds of participants stated that they would use a history was surprising because the C of CEAP was designed to be judged solely from clinical appearance.

**Discussion**

The CEAP classification remains the gold standard classification of CVD. This was confirmed in a recent review article at which they conducted a Medline analysis retrieving 266 publications using CEAP. This review also discussed the limitations of CEAP firstly stating that CEAP was not a severity classification and then pointed out the controversial areas as \(C_{fa} \). The current study has demonstrated that the controversial areas can extend into the higher categories of CEAP. The reality is that C of CEAP is frequently used to group patients into categories and is also used to discriminate patients with mild and severe disease. The \(C_{fa} \) group has been discussed as an individual disease. The C stratification has been used in epidemiological studies, longitudinal studies and as a comparator against symptoms and signs, quality of life questionnaires and hemodynamic assessments. Many clinical papers stratify patients’ legs into mild/severe or uncomplicated/complicated based on this division between \(C_{m} \) and \(C_{fa} \). This stratification is also used for rationing treatment in most public hospitals and in cost calculations.

The CEAP and venous clinical severity score (VCSS) are different tools and do not measure the same items equally. The existence of similar items with different definitions revised or otherwise should be clear in the mind of the assessor to avoid substitution error. For example, \(C_{fa} \) uses a definition of \(>3 \) mm for a varicose vein whereas the VCSS uses a cut-off point of \(4 \) mm. Furthermore, pigmentation defined by the VCSS is more strict than the CEAP because focal pigmentation over varicose veins does not qualify, and a focal low intensity (tan) is not considered by the VCSS as indicative of significant skin pigmentation. Eczema is \(C_{fa} \) but not a VCSS attribute unless it is synonymous with inflammation.

The current research demonstrates that there are substantial discrepancies in the clinical classification of CVD using the C of CEAP and the distinction between mild and severe venous disease is also unclear. Each photograph is commented upon below in order to focus on the controversial areas.

**Picture 1:** This is the control photograph which was correctly identified as \(C/C_{fa}/C_{a} \) by 96% of participants. A plaque of LDS is seen in the gaiter region with deeply situated varicose veins above this area. Although LDS is confirmed by palpation, this was not possible using photographs, a fact probably realized by 16% of participants who decided on choosing \(C_{fa} \) alone. Nevertheless, the highest percentage score was \(C_{fa} \) (42%) indicative of LDS.

**Pictures 2 and 6:** This is the same leg

**Figure 4.** Mild pigmentation with eczema at the gaiter region. Survey result: \(C_{a} \) (32%), \(C_{fa} \) (21%), \(C_{fa} \) (34%).

**Figure 5.** Mild retro-malleolar pigmentation over a normal vein. Survey result: \(C_{fa} \) (50%), \(C_{fa} \) (16%), \(C_{fa} \) (21%).

**Figure 6.** The same as shown in Figure 2 but the leg is now elevated. Survey result: \(C_{fa} \) (86%), \(C_{fa} \) (8%), \(C_{fa} \) (2%).
dependent (Figure 2) and elevated (Figure 6) in a patient who has deep venous reflux in the calf veins following a DVT. The dependent ankle is discolored with a venous flare/corona phlebectatica and small varicose veins but on elevation pigmentation is not present which confirms the C1-2 status of this leg. The dependent leg was reported as C4a by 28% of participants but this reduced to 8% after elevation. Elevation was used here to discriminate apparent pigmentation from venous congestion against true pigmentation from extravasation. Although corona phlebectatica is currently C1, there are recommendations by many phlebologists to consider it as C4a. The lack of a marker scale prohibits the sizing of varicose veins. This may be necessary for establishing if they are >3 mm in diameter, in which case they would belong to C2. However, skin thickness and depth of vein should also be taken into consideration. For example it would be difficult to compare vein size in Figure 1 with those in Figure 2.

Picture 3: Obvious mid-calf pigmentation over extensive varicose veins was reported by only 66% of participants using C4a in comparison to the 29% who reported C3. This may be because pigmentation in CEAP is defined as brownish darkening of the skin and occurs in the ankle region but may extend to leg and foot. Should pigmentation arising de novo over a mid-calf varicose vein without having extended from the ankle be classed as C4a? These factors may explain the reluctance of choosing C4a as an option.

Picture 4 and 5: These legs demonstrate mild (Figure 4) and very mild (Figure 5) degrees of pigmentation with eczema. This is reflected in the percentage of participants choosing C4a at 32% and 50%, respectively. Once again, it has been left for the observer to decide on what constitutes brownish darkening and how much eczema is significant to qualify as C4a. Both patients also had a normal looking vein present beneath the medial malleolus which may have prompted the choice of C4a at 21% and 16%, respectively.

Picture 7: Many patients have different baseline skin colors which may cause additional problems in defining increased pigmentation rather than basing a judgment on its presence or absence. This has been highlighted in this picture of gaiter telangiectasiae where 56% of participants classified the accompanying hyperpigmentation as C4a.

In cases of doubt there are two additional ways to evaluate pigmentation. The first is to compare vein size in Figure 1 with Figure 2. The second is to confirm a real pigmentation that does not disappear.

A published limitation of CEAP is that the patient’s venous history is not taken into account. The C class according to the current definition is about clinical appearance, not medical history. It is clear from the current study that 67% of participants would use a clinical history in making their judgment on C. This supports the rationale of this study because the C of CEAP is nothing more than clinical appearance and was not intended to co-ordinate historical features. However, in everyday practice the judgment of a C class cannot be devoid of a clinical history. Pigmentation in the gaiter region may have other etiological factors like post-inflammatory hyperpigmentation occurring after trauma or a skin infection. Similarly, eczema may be caused by an allergic reaction or an insect bite rather than venous insufficiency. A C classification assessed by a doctor in the morning may become a C1 in the evening. These may only become apparent from the clinical history. Furthermore, the presence of minor reflux within a small caliber vein may not be enough to cause pigmentation. It would be interesting if a group of dermatologists were asked to complete the survey since they have a focused interest in pigmentation disorders.

The pictures represent legs seen in common practice, which are difficult to classify because of lack of agreement using the C class. Improvements in C stratification could be

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Table 1. Percentage of C classes chosen by 117 participants for each picture. The 3 given choices are highlighted in italics. Risk difference represents agreement, from no agreement (0%) to full agreement (100%).

<table>
<thead>
<tr>
<th>Picture</th>
<th>C3</th>
<th>C2</th>
<th>C1</th>
<th>C4</th>
<th>C4a</th>
<th>C5</th>
<th>Don’t know</th>
<th>Mild/severe*</th>
<th>P value</th>
<th>Risk difference % (CI: 95%)</th>
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<tr>
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<td></td>
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<td>16</td>
<td>39</td>
<td>42</td>
<td></td>
<td>1</td>
<td></td>
<td>3/113 &lt;0.0005 94.8 (90.7-98.9)</td>
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<tr>
<td>2</td>
<td></td>
<td>16</td>
<td>48</td>
<td>1</td>
<td>28</td>
<td>2</td>
<td></td>
<td>3</td>
<td>&lt;0.0005</td>
<td>33.3 (21.1-45.6)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0</td>
<td>29</td>
<td>1</td>
<td>66</td>
<td>1</td>
<td></td>
<td>3</td>
<td>&lt;0.0005</td>
<td>36.8 (24.8-48.9)</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>-</td>
<td>21</td>
<td>3</td>
<td>-</td>
<td>34</td>
<td></td>
<td>10</td>
<td></td>
<td>65/49 0.0009 23.8 (10.7-36.9)</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>4</td>
<td>16</td>
<td>4</td>
<td>21</td>
<td>-</td>
<td></td>
<td>5</td>
<td>&lt;0.0005</td>
<td>56.8 (45.9-67.6)</td>
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<td></td>
<td>86</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>8</td>
<td></td>
<td>2</td>
<td>&lt;0.0005</td>
<td>79.3 (71.5-87.2)</td>
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<tr>
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<td></td>
<td>21</td>
<td>15</td>
<td>1</td>
<td>56</td>
<td>3</td>
<td></td>
<td>4</td>
<td></td>
<td>43/69 0.0008 23.2 (10.5-36.0)</td>
</tr>
</tbody>
</table>

*Ratio in absolute numbers of C3/C1. Fish exact test. CI, confidence interval.
made by defining the controversial areas as this work has demonstrated. A consensus statement from a panel of experts using published photographs may improve the reliability and agreement of CEAP.

Limitations
This is an observational study where patients with an indeterminate C class were selected deliberately because they would invoke disagreement between different participants. However, the objective of this study was to highlight controversial areas because recognition of a limitation is an essential step prior to an improvement. Although all the patients were photographed within the same week the true prevalence of their leg appearances and the extent to which these patients are representative of a diseased venous cohort should be determined by the readers’ individual clinical practice. However, patients attend the clinic because of their varicose veins rather than hyperpigmentation per se.

A further limitation is that photographs are not patients. Differences in lighting, background and angles are known to have profound effects on the interpretation of varicose veins. The quality of the photographs appears poor from a professional viewpoint, and this is a factor which may have caused difficulties in participant’s choice. However, an A4 photograph at high resolution is much better than its on screen image. Each participant had the option to check the ‘don’t know’ box, for whatever reason, but this rarely happened. Care was taken to ensure that each photograph accurately represented the clinical features of each patient. This may have advantages over questionnaire studies which use descriptors without photographs and disadvantages in comparison to studies where patients are examined in a clinical setting. However, the use of photographs outside a clinical setting may be beneficial because it standardizes the available information from which judgments are made. Clinicians are therefore less likely to have their judgments on the C of CEAP influenced by the patients’ medical records, symptoms or duplex findings.

Conclusions
Clinical trials using the C class as a means of stratifying legs into mild and severe clinical disease should be interpreted with caution because of the difficulties in weighting the importance of pigmentation based solely on appearance. This information is of value in clinical situations where the C of CEAP may be used to ration treatment and in research situations were it is often used as a benchmark or comparator for hemodynamic and quality-of-life validations. The results of this work have also indicated that the C of CEAP may be improved by using the same rater throughout clinical studies, unifying the CEAP definitions with those of the VCSS and by using leg elevation to discriminate between telangiectasiae and pigmentation. This work also confirms that the C class should not be used as a severity classification.

References
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