Author's response to reviews

Title: Dynamics of c-reactive protein and white blood cell count in critically ill patients with nosocomial gram-positive vs. gram-negative bacteremia: a historical cohort study

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Title: Dynamics of C-reactive protein and white blood cell count in critically ill patients with nosocomial Gram positive vs. Gram negative bacteremia: a historical cohort study

Authors: Dominique M Vandijck, Eric A Hoste, Stijn I Blot, Pieter O Depuydt, Renaat A Peleman, Johan M Decruyenaere

Dear Editor / Referee

We have addressed each of the reviewers’ comments in turn to the above-mentioned manuscript, and numbered our responses sequentially according to the reviewer questions.

REFEREE 2:

Major Compulsory Revisions

Question 1a:
When were the antibiotics prescribed, after the clinical diagnosis of BSI, after blood cultures became positive or in some patients was the first criteria and in some other patients was the second; and in the case of coagulase-negative staphylococci BSI, in
whom two successive positive blood cultures yielding coagulase-negative Staphylococcus on separate occasions within a 48-h period, as well as confirmation of clinical significance of bacteremia by the attending intensivist to have the final confirmation of BSI, when were the antibiotics prescribed in those patients; all these factors could have a significant influence in the changes of CRP and WCC after D0 once some patients were already on antibiotics while others were still with an untreated BSI.

- **Response 1a.** In our unit, empiric antibiotics are prescribed in case of clinical signs of sepsis and after blood cultures are sampled. Microbiological results are not awaited. The policy is to de-escalate antimicrobial therapy if possible. Here for, microbiological results are revised daily in communication with an infectious diseases specialist and a clinical microbiologist. In our ICU a restricted antibiotic strategy is conscientious followed. The empiric antibiotic regimen administered is based on the underlying pathology, patients’ history, local ecology, length of hospitalization, colonization status, presumed inciting focus, and hemodynamic status of the patient. Last-line antibiotics such as carbapenems and glycopeptides are only given to those patients colonized with multi-drug-resistant pathogens or those with a fulminated septic shock. Through mutual deliberation, different specialists (i.e. intensivist, infectious disease specialist, and microbiologist) daily verify whether narrowing the antibiotic spectrum is possible.

Further, in our ICU prophylactic antibiotics are only given to those patients at high-risk for acquiring infectious complications. For those already receiving antibiotic therapy, a new infectious event such as a nosocomial BSI will provoke an inflammatory response expressed by CRP and/or WCC changes.

In the text we added this information in the methods section:

“In our ICU a restricted antibiotic strategy is conscientiously followed. The empiric antibiotic regimen administered is based on the underlying pathology, patients’ history, local...
ecology, length of hospitalization, colonization status, presumed inciting focus, and hemodynamic status of the patient. Last-line antibiotics such as carbapenems and glycopeptides are only given to those patients colonized with multi-drug-resistant pathogens or those with a fulminated septic shock. Through mutual deliberation, different specialists (i.e. intensivist, infectious disease specialist, and microbiologist) daily verify whether narrowing the antibiotic spectrum is possible. Further, prophylactic antibiotics are only given preoperatively. For those already receiving antibiotic therapy, onset of BSI should be interpreted as a new outbreak of infection which on its turn will provoke an inflammatory response expressed by CRP and/or WCC changes in the blood.”

Question 1b:

Initial choice of antibiotics (p.7, 2nd paragraph): the authors should defined this concept; do the authors mean “the initial empiric antibiotic therapy” or is “the therapy started after the results of blood cultures became available”

- Response 1b. The reviewer is correct. It is important to clearly define what is meant when writing “the initial choice of antibiotics”. We indeed mean the “initial choice of empiric antibiotic therapy”, so changed it this way in the manuscript.

We certainly did not mean that “the therapy was started after culture results became available”. In our unit antibiotic therapy is started in case of clinical suspicion of infection, but main efforts have been made in terms of ICU staff education to perform blood culture sampling before infusion of antibiotics.

We changed to text to:

“Overall, 90.5% vs. 90.5% of episodes were treated adequately (P=0.999), however, there was a significant delay to initiation of appropriate therapy in patients with Gram positive aetiology of bacteremia; 52.4% in patients with GPB compared to 76.6% in patients with
GNB within 24-hrs after onset of bacteremia (P=0.010), and 70.7% compared to 89.6% within 48-hrs (P=0.037).”

**Question 1c:**
Definition of appropriate antibiotic therapy (page 6, 2nd line); one of the authors’ definitions of inappropriate antibiotics is no antibiotic being administered; I think that the correct definition of this situation is an untreated infection that is something different; the authors should give the numbers of BSI patients not treated empirically as well as the criteria to start antibiotics in some patients and on the opposite not to start in others.

- **Response 1c.** The reviewer is correct. After reconsidering this part of our definition of ‘inappropriate therapy’ this part is, however, somewhat confusing. Because in all patients empiric antibiotics were started we deleted this particular part of the definition.

We changed the text to:

“Therapy was considered ‘inappropriate’ when there was no in-vitro activity against isolated strains.”

**Question 1d:**
Timing of appropriate antibiotics (page 7, 2nd paragraph), again the authors have to define in the Methods this concept; do they refer to the time delay between blood cultures and antibiotics prescription; what was the reason of such differences; why those differences were so marked between BSI caused by Gram negative and Gram positive pathogens that are both severe clinical conditions.
- **Response 1d.** The reviewers comment is correct. “Time to appropriate antibiotics” is defined as the “*time delay between a blood culture that became positive and the time adequate antibiotics were administered*”. This information was added in the methods section.

Next, the reviewer refers to the reason of observing significant differences in starting appropriate antibiotics between BSIs caused by Gram positive and Gram negative pathogens, respectively. These observed differences are particularly due to the high prevalence of coagulase-negative *Staphylococcus* in the GPB-group. In all cases these pathogens were resistant, requiring the initiation of a glycopeptide, however, in our unit empiric therapy does not consists a glycopeptide (see also above: response to question 1a ‘empiric antibiotic strategy’). Only when suspicion of methicillin resistant *Staphylococcus aureus* involvement exists, or in case of unequivocal septic shock a glycopeptide is started empirically.

In the discussion section, we further elucidated on this issue:

> “Further, in the GPB-group, coagulase-negative Staphylococci were the most frequently isolated pathogens. In addition to the above, this may also explain the high observed rate of inappropriate choice of empirical antibiotics.”

**Question 2:**

From the manuscript my guess is that this study is a retrospective analysis of data prospectively collected, as the authors selected a cohort of patients from the years 2003 and 2004. Additionally, the authors should explain how the data was collected from a central database or another methodology. This issue should be better clarified in the methodology.
**- Response 2.** The reviewer is correct. This is a historical observational study, which is a retrospective study of prospectively collected data. As requested, we further clarified this issue in the methods section, as well as the way the data were collected.

This has been changed in the text as follows:

“All data (i.e. demographic, clinical, laboratory, and physiological) were gathered by reviewing the charts and the computerized hospital laboratory and administrative databases.”

**Question 3:**

The period of observation was very short, on the whole were 4 days of follow-up, and before BSI diagnosis only 3 days. This is a major limitation of the present study because infection could have started some days before blood cultures sampling and as a result of the short period of observation the authors could have missed the very beginning of the infection. This could be the explanation of the finding that both patients with Gram positive and Gram negative BSI have already very elevated CRP (>12mg/dL) at D-2. If the period of observation could be expanded to 5 or 7 days before D0 the results could have been different. Besides, the authors should elucidate the reason of lengthened the period of observation till D+1 when patients should be already on empiric antibiotics that for sure could have some influence on CRP and WCC levels. Additionally the authors should give some information of the criteria to perform blood cultures that could have effect on infectious markers if they are performed later or earlier in infection course.

**- Response 3.** We agree with the reviewers’ opinion that the period of observation (four days of follow-up, respectively) is short, and as a fact is a shortcoming of this investigation. Patients were on average already 9.0 days (GPB) and 8.0 days (GNB) admitted to the ICU explaining the high baseline CRP and WCC levels on D-2. Further, the reviewer is correct when stating that a longer period of observation would have resulted in additional
information. Additionally, (i) a considerable part of our study cohort developed BSI within the first few days of ICU admission, and (ii) there are many factors associated with increased CRP or WCC levels, however, not of any infectious origin, thereby potentially confounding the interpretation of trends in CRP and WCC levels in these patients.

Expanding the period of observation up to for instance 7 days is interesting in order to follow the individual clinical course; however, for the purpose of this study (research question), to our opinion this adds no extra information. We do have data of serial measurements of both parameters for longer period (until D+7 after onset of BSI); however, after 48-hrs culture results are usually available. Here, we wanted to examine if the dynamics of both biomarkers could help the physician when making this assessment and this before microbiological results are know. Consequently, reporting on the values of D+2 until D+7 is of minor importance with regard to the research question.

We added this shortcoming in the limitations of our study:

“The short period of observation (4 days, respectively) includes another limitation of this study. Taken into account a longer period could have resulted in additional information, though in an ICU setting, many other factors associated with increased CRP and/or WCC levels, however, not of infectious origin, are frequently observed.”

The reason why we decided to lengthen the period of observation till D+1 is because results of microbiology are usually available after 36- to 48-hrs. Therefore, within this time interval, patterns in the evolution of CRP and/or WCC levels may indicate appropriateness of empiric therapy.

In our unit, the indication to perform blood cultures is when a patients’ body temperature rise above 38.4°C or in case of clinical suspicion of infection. As rightly stated by the reviewer,
the latter can have considerable effect on infectious markers, so this additional information is included in the manuscript.

*Blood cultures were routinely performed when the patients’ temperature was ≥38.5°C or when infection was suspected on clinical grounds.*

**Question 4:**
There is no information concerning previous antibiotic therapy as well as if the patients were antibiotics in the days before B0. This issue could have a major effect on the studied infectious markers. As a result the authors should fully clarify this issue. In a study designed to assess the value of serial infectious markers in the diagnosis of BSI, my opinion is that patients already on antibiotics should be excluded from the final analysis as the definition of the first day of the new infection, D0, is very uncertain. If the authors want to analysed these patients they have to make one analysis for patients without previous antibiotics and another for patients already on antibiotics. This factor, previous antibiotic therapy, could also hypothetically have influence on the type of bacteria, Gram-positive or negative, recovered from the blood cultures.

- **Response 4.** Here, we do not fully agree with the reviewers' comment. Patients under antibiotics, but who develop breakthrough BSI will react with an additional inflammatory response. Because in this particular very sick patient population, nearly all patients were already on antibiotics in the previous days (e.g. prophylactic treatment, etc.). Therefore, it is impossible to exclude all these patients. From a methodological point of view, this is not incorrect because we did not study the outcome of these patients. When only considering the evolution or patterns of laboratory variables, multiple episodes may be taken into account for analysis. Regarding our data concerning ‘in-hospital mortality’ (= outcome variable) (also
referring to the reviewer question 12), here only the first episode of a patient was taken into account, as a patient can only die once. In other words, in this setting it is correct that only the first episode might be considered for analysis.

Question 5:
The authors stated (page 7, 2nd paragraph) in Gram negative BSI CRP peaked at D1; however with such a short period of observation this could not be true as it could be later. Only with a longer period of observation the authors could identify the timing of peak concentration.

- Response 5. In our database, CRP and WCC levels are collected until D+7 after onset of BSI. As a matter of fact, we did analyse the evolution of both infectious markers over this period, and both (GPB and GNB) peaked on D+1. However, we decided to not report these data, because culture results are usually available on D+1 or at least on D+2 (which is 72-hrs). The need to wait for D+3-D+5-D+7 defeats the purpose of the study, which is (i) to differentiate between GPB and GNB based on the patterns of both infectious markers and hence prior to the availability of microbiological results, and (ii) to explore the early utility of CRP and WCC levels in patients receiving empiric antibiotics.

Therefore, we consider the reporting of serial measurements of both biomarkers (until D+7) as redundant and less relevant with regard to the research question of this study.

Question 6:
The logistic regression analysis should be reanalysed since the authors entered the variables in the model in an incorrect way. In the present manuscript the authors want to study several variables as predictors of Gram negative or Gram positive BSI. As a
result the dependent variable is BSI with a dichotomous result, Gram positive or Gram negative pathogen. CRP, WCC are the independent variables and moreover the model could be adjusted for age, sex, APACHE, etc. With the sample size of this study the authors could adjust the odds ratio without violation of the rules of multivariable logistic regression analysis.

- **Response 6.** We understand the reviewers’ remarks concerning the logistic regression analysis; however, there are arguments for both methods. In this study (historical cohort) it is important to clarify which the main exposure variables and the main outcome variables are. It is tacit that the main “exposure” variable is “aetiology of BSI” (Gram positive or Gram negative), and that the main outcome variables are “CRP changes” and “WCC changes”. We are convinced this is the appropriate interpretation, because in our study we are trying to link aetiology of BSI with the changes in both biomarkers. Therefore, aetiology of BSI takes place “before” the change in these biomarkers (cause precedes the effect).

As mentioned above, the outcome variables are CRP change and WCC change, not aetiology of BSI. The logistic regression model should therefore evaluate the predictors of the outcome variable, not the exposure variable.

**Question 7:**

Once the aim of the authors was to study the dynamics of CRP and WCC over time in BSI patients to differentiate between Gram positive and Gram negative pathogens the authors could have draw ROC curves for CRP and WCC in order to try find the best cutt-off of both markers.

- **Response 7.** In our analysis ROC curves were used to determine the cutt-off values for CRP and WCC levels, however, we did not shown these figures to keep the paper as brief as
possible. We are also not convinced that showing these curves is of substantial value for the readers of an Infectious Diseases Journal.

Question 8:
In Methods (page 6, 2\textsuperscript{nd} paragraph) the authors described the criteria to assess the presence of organ dysfunction/failure. The authors should explain the choice of these criteria since there are several other methods, well studied and validated with critical care patients, like the SOFA or MODS score e.g., designed to assess the clinical evolution of patients independently of the cause, infectious or non-infectious.

- Response 8. The reviewer is quite correct. Because we do not dispose of SOFA and/or MODS scores for the patients with a nosocomial BSI in this database (period 2003-2004), we also could not calculate them retrospectively because of to many unreliable and missing data. Since recently, a new intensive care unit information system (ICIS) is installed in all our units; these scores will be available in the future. Nevertheless, the APACHE II score has already been proven to be a high-quality score to assess one’s organ dysfunction independently of the reason for admission. As a fact, we agree with the reviewer statement that there are also other scores available, though we think that using the APACHE II score is at least of the same significance.

Question 9:
In case of multiple determinations of CRP and WCC in the same day the authors recorded the highest value (page 6, 1\textsuperscript{st} paragraph). However, these criteria could give misleading results. We could hypothesized that a patient could have a CRP and WCC determination at 23:00 of one day; taking into account the biology of CRP (Pepys, JCI
2003;111:1805) and WCC my guess is that the value at 6:00 of the following day would be almost the same. My suggestion is to collect the values of CRP and WCC daily and ideally all collected at the same hour.

- Response 9. The reviewer is correct and his suggestion is valuable. In our unit, blood sampling for laboratory is performed daily at 6 am. Only in exceptional conditions additional determinations of laboratory parameters is performed. In this study cohort, the number of patients with several CRP and/or WCC determinations per 24-hrs are as a fact limited. After examining this issue, a strict minimum (~5%) of episodes more than one determination was performed and consequently taking into account for analysis. For all others (~95%) CRP or WCC levels retained for analysis were morning blood samples (sampled at 6 am, and as such one single determination on the same hour). On the other hand, using the highest levels in case of multiple determinations during the same day is maybe somewhat arbitrary, but most commonly used in literature.

Question 10:

In this manuscript the authors assessed 198 episodes of BSI however they give no information if those episodes were on different patients or if on the opposite there are several BSI episodes in the same patient. From a statistical point of view only one BSI episode per patient could be included in the study. This issue needs to be fully elucidated. From figure 1 it seems that the 198 BSI episodes included in the study were diagnosed in 110 patients. Consequently, at least 88 episodes were recurrent BSI episodes.

- Response 10. See also response to the reviewers question 4 (Response 4).
This is no outcome study. In epidemiological studies focused on outcome (for example, mortality) it is common to only take into account the first event under investigation. Though, for this particular purpose it is not incorrect to use consecutive episodes of BSI.

**Question 11:**

Another issue that should be fully explained is the exclusion criteria. From the initial 198 BSI episodes the authors excluded almost half, more precisely 42%! The Candida BSI (N=20, with a good sample size) were excluded even though they carry a very bad prognosis in every study. Besides, the polymicrobial (N=40, an excellent sample size) could have also a different clinical course as well as a different course of the infectious markers that I think also deserves to be evaluated.

- **Response 11.** The reviewer is correct stating that both, polymicrobial episodes of BSI as well as those caused by *Candida* spp. are of interest to evaluate; however, this was not the primary objective of this investigation. The purpose of this study was to evaluate CRP and WCC changes aiming to differentiate between GPB and GNB. Therefore, episodes caused by *Candida* spp. and polymicrobial BSIs were not considered for analysis. Here, we want to further elaborate on the latter. Polymicrobial episodes caused by two Gram positive or Gram negative strains were included in this study, but only those containing both (Gram positive and Gram negative strains) \(n=40\), see figure 1) were excluded. Concerning the episodes of candidemia \(n=20\) we think this sample is too small for making valuable interpretations.

**Question 12:**
The authors should include a table with the baseline patients’ characteristics including length of ICU stay and mortality rate as well as a table with the microbiologic data and eventually the appropriateness of antimicrobial therapy.

- **Response 12.** The reviewer is correct. In first instance, we did not include a table with the patients’ baseline characteristics and microbiologic data to keep the manuscript brief and concise (as we would submit our manuscript as a brief report). We now have included two tables with this additional information.

Both tables as included in the manuscript as given below:

### Table 1: Patients’ baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Episodes of Gram positive bacteremia (n = 42)</th>
<th>Episodes of Gram negative bacteremia (n = 63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>55.6 (19.5)</td>
<td>58.3 (15.2)</td>
<td>0.905</td>
</tr>
<tr>
<td>Female, No (%)</td>
<td>15 (41.7)</td>
<td>16 (33.3)</td>
<td>0.497</td>
</tr>
<tr>
<td>APACHE II, mean (SD)</td>
<td>19.1 (6.7)</td>
<td>20.5 (7.8)</td>
<td>0.400</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease, No (%)</td>
<td>1 (2.8)</td>
<td>0 (0.0)</td>
<td>0.429</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate therapy ≤24-hrs, No (%)</td>
<td>22 (52.4)</td>
<td>48 (76.6)</td>
<td>0.010</td>
</tr>
<tr>
<td>Appropriate therapy ≤48-hrs, No (%)</td>
<td>30 (70.7)</td>
<td>56 (89.6)</td>
<td>0.037</td>
</tr>
<tr>
<td>Appropriate therapy, No (%)</td>
<td>38 (90.5)</td>
<td>57 (90.5)</td>
<td>0.999</td>
</tr>
<tr>
<td>Delay in the start of appropriate therapy, mean (SD)</td>
<td>1.6 (1.6)</td>
<td>0.6 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU LOS, median (range)</td>
<td>16.5 (5.5-31.0)</td>
<td>19.5 (3.0-30.3)</td>
<td>0.726</td>
</tr>
<tr>
<td>ICU LOS before onset of bacteremia, median (range)</td>
<td>9.0 (1.3-24.0)</td>
<td>8.0 (2.3-17.8)</td>
<td>0.544</td>
</tr>
<tr>
<td>In-hospital mortality, No (%)</td>
<td>13 (36.1)</td>
<td>22 (45.8)</td>
<td>0.503</td>
</tr>
</tbody>
</table>

*Only calculated on patients (n=84, 36 patients with GPB and 48 patients with GNB, respectively)
<table>
<thead>
<tr>
<th>Organism</th>
<th>n</th>
<th>Number of antibiotic susceptible bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Gram positive bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>42</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>11</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>23</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Streptococci / Enterococci</td>
<td>8</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td><strong>Gram negative bacteria</strong></td>
<td>63</td>
<td>53 (84.1)</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>20</td>
<td>13 (20.6)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>16</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>8</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>6</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>5</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>3</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>2</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>1</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td>1</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td><em>Flavobacterium</em></td>
<td>1</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Minor Essential Revisions

The manuscript also needs some English editing; examples: C-reactive protein and not c-reactive protein; Gram and not gram.

The units of WCC are not correct.

- **Response.** All grammatical comments were corrected as requested.

The authors wrote in Background that patients present “subtle signs of the hosts’ response” in the beginning of BSI. This statement should be more objective and ideally with a reference.

- **Response.** We changed the formulation of ‘subtle signs of the hosts’ response’ to “Early recognition of even the first minor signs of infection in case of a beginning bacteremia could therefore help to identify those patients who are more likely infected with either Gram-positive or Gram negative pathogens”.

As requested we included a reference (Levy et al.. Intensive Care Med 2003;29:530-538).

All abbreviations should be defined as NCCLS on page 5, ACCP/SCCM on page 9.

- **Response.** All abbreviations are now written in full. We apologize for both flaws.

NCCLS: “National Committee for Clinical Laboratory Standards”

ACCP/SCCM: “American College of Chest Physicians/Society of Critical Care Medicine”

This is a single centre study that also constitutes another limitation that should be stated.

- **Response.** In the discussion section we further elucidated the limitations of this study.

“Because our findings are based on a single centre study, one should be careful when interpreting or extrapolating these data”.
The authors stated on page 9 that the ACCP/SCCM sepsis criteria lack both sensitivity and specificity to define the presence or absence of sepsis. This affirmation is not entirely correct since these criteria are consensually considered very sensitive.;

- **Response.** The reviewer comment concerning the sensitivity and specificity of the sepsis criteria is warranted. We therefore changed this sentence to “Because these criteria are consensually considered to have high sensitivity and low specificity, we therefore selected a very homogeneous group of patients with unequivocal bacterial sepsis.”

**Discretionary Revisions**

The number of references is somewhat long.

- **Response.** We reduced the number of references to 27.

Concerning reference #5 the authors should present a declaration from the editorial board of the journal declaring that the particular paper is in press.

- **Response.** Concerning this reference, which was on time of submission of this manuscript to BMC Infectious Diseases, in press, has in meantime been published and referred to in a correct way.