Transfusion-related acute lung injury : etiological research and its methodological challenges

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Chapter 2

The role of donor antibodies in the pathogenesis of transfusion-related acute lung injury

A systematic review

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Abstract

Background

The majority of cases of transfusion-related acute lung injury (TRALI) are thought to be caused by the presence of leukocyte antibodies in the blood of the donor. We performed a systematic search of the literature to quantify the contribution of donor antibodies to the occurrence of TRALI.

Study design and methods

We conducted a systematic search of the PubMed and EMBASE databases. Retrieved articles were judged by three authors independently. Reference lists of all articles were subsequently screened for relevant references. All articles in English, German, French and Dutch, published at any time before December 2007 were eligible for inclusion.

Results

Of 77 articles, on leukocyte antibodies in donors involved in a case of TRALI, 14 articles contained sufficient data. These 14 articles reported leukocyte antibodies in 24 of 51 donors (47%) associated with 24 of 28 TRALI cases (86%). Of 15 articles that reported the prevalence of leukocyte antibodies in the general donor population, 2 articles reported a prevalence of 17% in (452) randomly selected donors. The odds ratio for developing TRALI was 15 (95% CI 5.1 to 45) for patients who received a transfusion from a donor who tested positive for leukocyte antibodies, compared to donors who tested negative. Leukocyte antibodies contributed to 80% (95% CI 51% to 92%) of all TRALI cases.

Conclusion

Leukocyte antibodies were more prevalent in donors involved in TRALI cases than among randomly selected donors. These findings suggest that donor antibodies contribute to four fifths of all TRALI cases.

Introduction

Transfusion-related acute lung injury (TRALI) is clinically indistinguishable from acute respiratory distress syndrome (ARDS) and develops during, or shortly after, transfusion of one or more blood products.[1] TRALI is currently recognized as the most common, severe side effect of blood components transfused.[2-5] It has an estimated incidence of 1 in 5000 transfusions and a mortality of 6%.[1] It is thought to often be caused by donor derived leukocyte antibodies, which can be directed either against the human leukocyte antigens (HLA) or against the human neutrophil antigens (HNA). These antibodies could activate the recipient's pulmonary neutrophils, which in turn damage the pulmonary endothelium. This causes pulmonary edema.[1,6,7]

Since these antibodies are most frequently found in parous women and are present primarily in plasma rich blood products,[8,9] it has been proposed to exclude parous women from donating plasma for transfusion.[10] In many countries, among others the United Kingdom and the Netherlands, plasma from female donors is no longer used for transfusion, when possible.[3] Although the situation does call for preliminary caution, other etiologies have also been suggested for TRALI.[11-15]

The importance of other potential causes and the contribution of leukocyte antibodies to the occurrence of TRALI is unclear. Therefore, it is not possible to estimate the benefits, expected to be gained, by measures directed at the elimination of products containing these antibodies from the blood supply.

Leukocyte antibodies do not always cause TRALI which is in part due to the heterogeneity of the HLA system. The presence of leukocyte antibodies in blood products is not particularly uncommon either,[88,9] which raises the possibility that their presence is merely a chance finding in some TRALI cases.

Therefore, to estimate the contribution of leukocyte antibodies to the occurrence of TRALI, the prevalence of these antibodies in a control group of randomly selected donors is needed, in addition to the prevalence in donors associated with a TRALI case. Unfortunately, this control group is generally not included in the TRALI literature, which consists mainly of case reports and case series.

Furthermore, evidence from the literature might be biased by circular reasoning and publication bias, causing only those cases where leukocyte antibodies were identified to be diagnosed and published as TRALI cases. Given that leukocyte antibodies are present by coincidence in a certain portion of TRALI cases, publication bias would ensure an overestimated association of these antibodies with TRALI cases.

To quantify the contribution of donor antibodies to the occurrence of TRALI, we compared the reported prevalence of leukocyte antibodies, in donors associated with cases of TRALI, with the reported prevalence in the general donor population.

Methods

We performed a literature based study into the role of donor leukocyte antibodies in TRALI. Case reports and case series from the literature were included to obtain data on antibody prevalence in donors associated with TRALI cases. These data were compared to a control group provided by reports on the prevalence of leukocyte antibodies in the donor population in general. Leukocyte antibody prevalences in these two groups were compared as described below in more detail.

To correct for differences between patients in the number of received transfusions, all prevalences determined in donors were recalculated to the number of patients that could potentially be transfused with antibody containing components, assuming all patients received the same number of transfusions. From this comparison we obtained the odds ratio, as an estimate of the relative risk for TRALI associated with the presence of leukocyte antibodies in transfused blood product.

Our question concerns the role of leukocyte antibodies in general and does not distinguish the relative contribution of anti-HNA or anti-HLA antibodies, nor does it focus on the role of antibodies that match with cognate antigens in the recipient. The available literature does not allow these additional comparisons to be made.

We performed an automated search of the literature and subsequently used predetermined criteria to include or exclude articles retrieved by this literature search. These criteria were chosen to select articles that would provide all data necessary for our comparison in the least biased way possible.

Search strategies

We conducted a systematic search of the PubMed and EMBASE databases, searching for articles mentioning either “lung” or “pulmonary” in combination with either “injury” or “edema” and mentioning “blood transfusion” while also mentioning either “antibodies” or “antigens” in any way. The complete search strategy is given in Appendix I. The resulting list of titles was judged for relevance by three authors independently and, of these selected articles, the abstracts were judged similarly. Exclusion criteria were: review (non-original data), animal study, *in vitro* study, stem cell transplantation or “different topic”. The reference lists of all articles, that were thus selected, were subsequently screened for relevant references, which had not been retrieved by the search.

An automatic search of the PubMed and EMBASE databases, for articles containing information on the prevalence of leukocyte antibodies in the general population, returned no articles with relevant information (see Appendix I for search strategy). Therefore, articles on this subject were selected solely from the reference lists of the articles selected

from the TRALI literature. Subsequently, we continued checking reference lists of referred articles until no relevant new references were found.

A flowchart of the selection process is presented in Figure 1. All articles in English, German, French and Dutch, published before December 2007 were eligible for inclusion.

Definitions

Articles that reported on measuring leukocyte antibodies in donors involved in TRALI cases (TRALI donors) were judged, in several steps, for the type of data available and the definition of TRALI used. A flowchart of the exclusion process is presented in Figure 2.

In each of these steps articles were excluded if they did not contain the information required for our analyses. In the successive exclusion steps, articles were excluded if they failed to report the number of TRALI cases tested, the number of donors tested, or the definition of TRALI used. Furthermore, articles were excluded if the presence of leukocyte antibodies was included in the definition of TRALI, the definition did not correspond to the clinical definition of TRALI that was agreed upon at the Canadian consensus conference in Toronto,[16,17] or if not all involved donors were tested.

In each successive step we documented the number of articles excluded during this step. For the remaining articles we assessed the number of TRALI cases reported, the number and percentage of TRALI cases with at least one donor tested positive for leukocyte antibodies, the number of donors tested, and the number and percentage of donors tested positive for leukocyte antibodies (Figure 2).

Articles that reported on the prevalence of leukocyte antibodies in the general population were included if the study population consisted of randomly selected donors. All articles reporting on specific subpopulations, such as female donors, (multi-)parous donors or previously transfused donors were excluded.

Analyses

The weighted average of the reported prevalences of leukocyte antibodies, among randomly selected donors, was calculated. This prevalence was used to estimate the number of donors with leukocyte antibodies that would be expected among donors not involved in TRALI cases. This expectation was corrected for the number of components transfused (Table 1, row 2), which was set as equal to that of the TRALI cases. The resulting expected number was subsequently compared to the observed number of donors with leukocyte antibodies among the donors that were involved in TRALI cases (Table 1, row 1).

Furthermore, the odds ratio (OR), and corresponding 95% confidence interval (CI), were calculated. The calculated OR was the ratio of the odds for developing a TRALI after being transfused with at least one product containing leukocyte antibodies, compared to the odds of developing a TRALI after being transfused only with products not containing

leukocyte antibodies, given that patients in both situations had an equal number of components transfused. This odds ratio is an estimation of the relative risk of developing a TRALI after being transfused with at least one product containing leukocyte antibodies, compared to the risk of developing a TRALI after being transfused as many products without leukocyte antibodies.

Finally, given the assumption that an observed association between leukocyte antibodies and TRALI was causal, the excess presence of antibodies could be used to calculate the fraction of TRALI cases explained by these antibodies. This was done by calculating the population attributable risk (PAR), i.e. the percentage of all TRALI cases that could be attributed to the presence of leukocyte antibodies, and the corresponding 95% CI. The OR and its variance were entered into the appropriate formulas to calculate the PAR and the corresponding 95% CI.[18]

Results

A total of 82 articles contained information on the prevalence of leukocyte antibodies in donors who had donated blood that was transfused to TRALI patients. A further 15 articles contained information on the prevalence of these antibodies in either the general population or a donor population. Figure 1 shows a flowchart of the selection process of these 97 articles. The complete lists of references for both searches are given in Appendix II.

Leukocyte antibodies and TRALI

Of 82 articles, eight were excluded because they failed to state the number of cases in which one or more donors tested positive for leukocyte antibodies. The 74 remaining articles showed 75% of 258 cases to involve at least one donor that tested positive. A total of 57 articles reported both the number of donors tested and the number of donors tested positive. From these the prevalence among 364 donors involved in 122 TRALI cases was estimated to be 32%. As shown in Figure 2, further stepwise exclusion of articles affected both these percentages.

Only 14 articles met all criteria for containing necessary data, reporting an average prevalence of 47% (24 donors positive of 51 tested), resulting in 86% of 28 cases in which at least one donor was tested positive for leukocyte antibodies (Table 1). Of these 14 articles eleven were case reports,[19-29] two reported on two cases each,[30,31] and one reported on 13 cases.[32] The average leukocyte antibody prevalence among the 13 articles reporting on 2 cases or less was 42%, while the prevalence reported in the case series of 13 cases was 62%. This corresponded to 93% and 77% of cases in which one or more donors tested positive for leukocyte antibodies, respectively. TRALI patients had an average of 1.8 (51/28) blood components transfused.

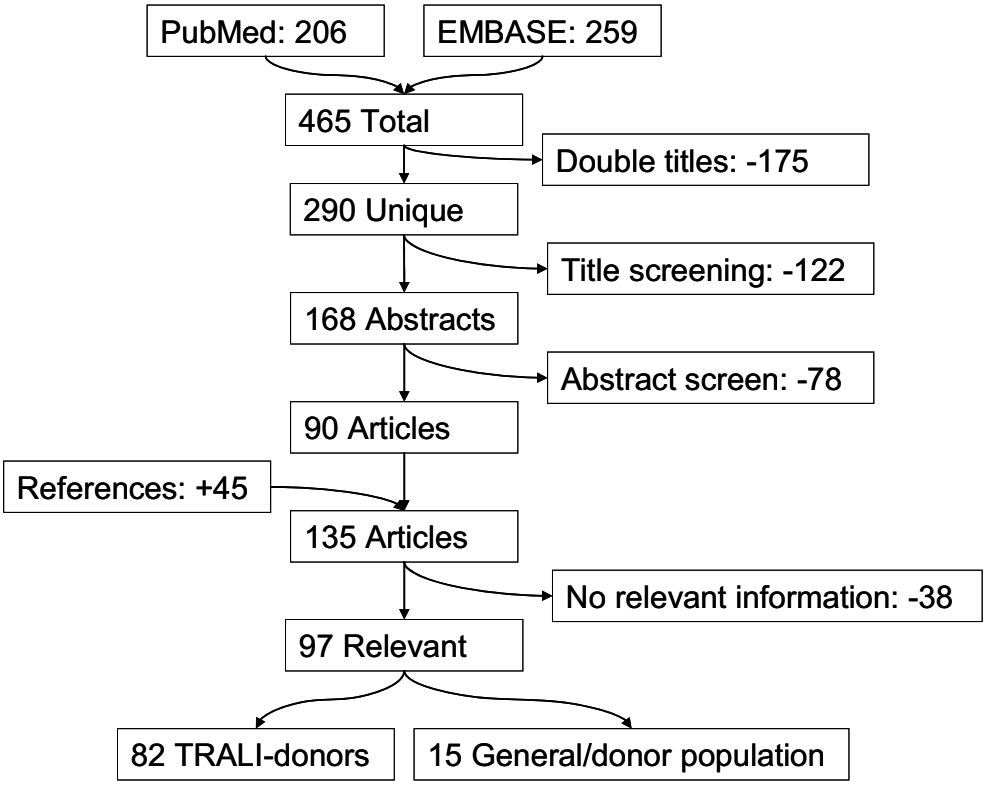

Figure 1: Flowchart of selection of relevant articles from the literature search. Values are numbers of articles. The literature search for leukocyte antibodies in the general population returned 309 articles. These were not included in this chart, since none contained relevant information. Articles on this subject were, instead, selected from reference lists only (see text for details).

Leukocyte antibodies in the donor population

The literature search for leukocyte antibodies in the general population returned 309 articles. None contained relevant information. Articles on this subject were, instead, selected from reference lists only.

The prevalence of leukocyte antibodies in the general population or donor populations, as reported in the 15 articles included on this subject, ranged from 3% to 48%. Only two of these articles reported on 452 randomly drawn donors,[33,34] therefore representing the male-female-ratio found in those donor populations. The weighted average of the prevalence of leukocyte antibodies reported in these two articles was 17% (75 of 452; 95% CI 13% to 20%).

Transfusion of 452 products to control patients, each receiving 1.8 transfusions, would have resulted in the transfusion of 248 patients. Of these 248 control patients 70 would have been transfused with at least one product from a donor with leukocyte antibodies (Table 1).

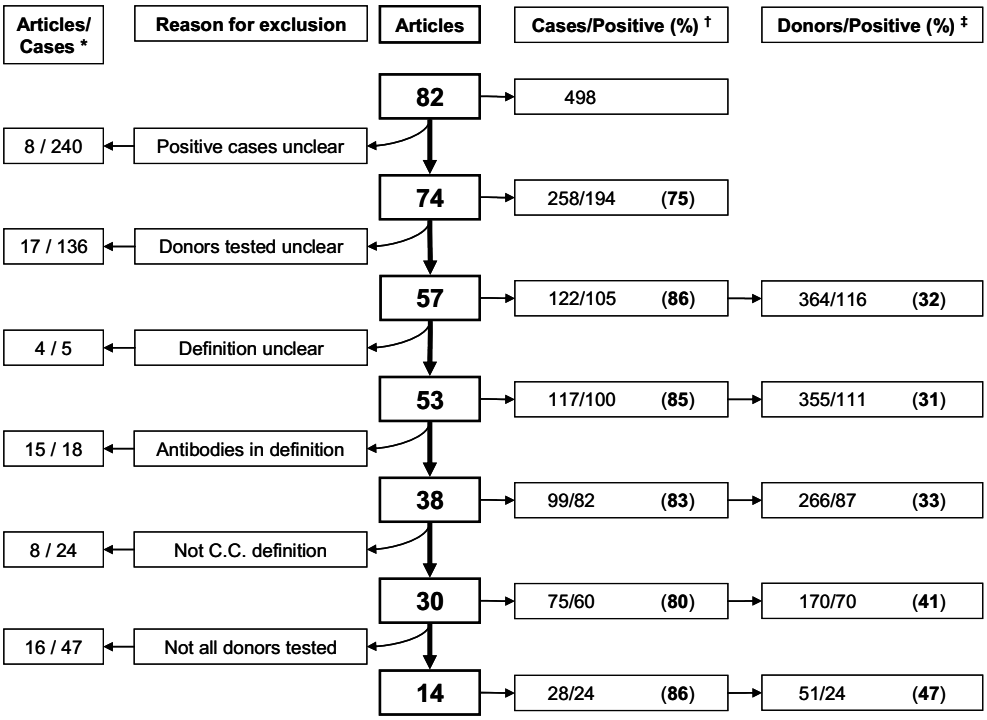

Figure 2: Flowchart of stepwise exclusion of 68 articles on TRALI donors in which insufficient information was reported. Values are numbers or percentages, as indicated below. The central column shows the number of articles decreasing stepwise from 82 to 14. *Articles/Cases: Numbers of articles and cases that were excluded in this step. †Case/Positive (%): Number of TRALI cases with information about the presence of leukocyte antibodies in one or more donors / Number of TRALI cases in which one or more donors were tested positive for leukocyte antibodies (TRALI cases in which ≥1 donor tested positive as percentage of all TRALI cases in which ≥1 donor was tested). ‡Donors/Positive (%): Number of donors tested / Number of donors tested positive (donors tested positive as percentage of total donors tested). C.C. definition: Canadian Consensus definition.

Comparison of observed and expected prevalences

The prevalence of leukocyte antibodies in donors involved in TRALI cases was higher than the prevalence in a group of randomly selected donors (47% versus 17%). Leukocyte antibodies were detected in 24 of 28 TRALI cases (86%). In each of these cases only one donor was tested positive, resulting in 24 of 51 donors (47%) testing positive.

The odds ratio for developing TRALI was 15 (95% CI 5.1 to 45) for patients who received a transfusion from at least one donor who tested positive for leukocyte antibodies, compared to patients who received an equal number of transfusions from donors who tested negative (Table 1). The population attributable risk was 80% (95% CI 51% to 92%).

Table 1: Number of TRALI cases and control patients with and without leukocyte antibodies present in at least one donor

	Leukocyte antibodies				
TRALI	+	-	Total	OR*	95% CI
+	24	4	28		
-	70†	178†	248†	15	5 to 48
Total	94	182	276		

*The OR has been calculated by the cross-product: (24*178)/ (4*70)=15

†Number of control patients that would have been transfused (in each group) with the 452 products from the randomly drawn donors, if each of them would have received 1.8 transfusions, the same number as received by the 28 TRALI cases.

Discussion

Our systematic review of the literature shows that the prevalence of leukocyte antibodies in donors involved in reported TRALI cases was higher than the prevalence reported among randomly selected donors. Our findings suggest four fifths of all cases of TRALI are explained by the presence of antibodies in donors.

Many articles on TRALI cases did not contain all the required information, or did not define TRALI according to the Canadian consensus definition.[16,17] Furthermore, to avoid the pitfall of circular reasoning, we excluded all reports in which the diagnosis of TRALI was made with knowledge of the antibody status of associated donors. This left us with only a minority of the TRALI publications. Data from only 28 of a total of 498 reported TRALI cases could be included in this review. Although this represents only a limited fraction of the total literature data, it gives the least biased estimate, due to systematic selection based on objectively predetermined criteria.

We could not include several large, well designed studies because they did not report on all data required for our analyses. One of these studies was the important publication by Popovsky and Moore in Transfusion, 1985.[1] Since this one study alone included a similar number of cases as the combination of all studies included in this review, we contacted the authors. Although the individual, case-specific data are no longer available after 22 years, averages could still be obtained. In 89% of cases one or more donors tested positive for leukocyte antibodies. In two or three of these cases more than one donor tested positive and

two to three donors were tested per case (personal communication, Mark A. Popovsky, august 2007). This leads to an estimation of the leukocyte antibody prevalence of between 32% and 49%, which is very similar to the results we obtained in our analyses.

Our study does not take into account antibody specificity, since our primary aim is to quantify the risk imposed by antibodies in the blood supply. From the perspective of the blood bank the presence of cognate antigens is not relevant, since it can not be known beforehand whether a future recipient will have the cognate antigen. The chance of antibodies causing TRALI can therefore be viewed as composed of both the chance of a recipient expressing cognate antigens and the chance of a recipient with cognate antigens being sensitive to developing TRALI. We use the prevalence of leukocyte antibodies in randomly selected donors as a control group. Therefore the calculated contribution of these antibodies to the occurrence of TRALI reflects the excess presence of antibodies, above the expected value. This excess presence can be explained only by biological significance, statistical variation and bias. Statistical variation is controlled for in the calculation of the 95% CI, which leaves only bias as an alternative to biological significance to explain our results. Possible causes of bias are further discussed below.

A large part of the literature reporting on TRALI cases is comprised of reports of one or two cases only, while larger case series remain relatively rare. Of the 14 articles that were included in this study only one reported on more than two cases. This article reported a lower fraction of positive cases (77%) than that reported in the case reports (93%). This is suggestive of publication bias in favor of reports of cases in which at least one donor was tested positive for these antibodies. Such bias may have lead to overestimation of the contribution of antibodies to the occurrence of TRALI in this systematic analysis.

Furthermore, it should be noted that other etiologies of TRALI have been suggested more recently[35] and may have a less severe clinical presentation.[7] Therefore, in these cases chest X-rays, which are required according to the Canadian consensus definition, may be performed less often. These studies would therefore be excludes from this review. Strict adherence to objectively predetermined criteria does result in the least biased estimate of the contribution of leukocyte antibodies to the occurrence of TRALI as defined according to the Canadian consensus definition.[16,17] However, less severe TRALI, which could still be clinically relevant, might not meet all criteria of this definition. Therefore, an etiological difference between less severe and severe TRALI can not be excluded based on our results.

The presented prevalence in the general donor population is based on only two studies, which could raise questions about the extrapolation of these results to other donor populations. Although there is not enough information to judge this in detail, one of these studies mentions 40% of the donors to be female. This does not seem a particularly unexpected percentage and thereby suggests the data from this study to be likely to apply to other donor populations as well.

The last possible source of bias is the presence of uncontrolled confounding. This would require there to be an unmeasured factor that is associated with the presence of leukocyte antibodies, but is causing TRALI by a mechanism unrelated to these antibodies. However, there seems no alternative biological mechanism readily identifiable that could convincingly explain the observed association of leukocyte antibodies with the occurrence of TRALI by means of confounding.

From this review the best estimate of the risk associated with the transfusion of leukocyte antibody containing blood products is a 15-fold increase in the odds of TRALI, compared to the transfusion of products not containing these antibodies. Of all TRALI cases, analyzed in this review, 80% are estimated to be attributable to donor derived antibodies. However, since the studies included in this review were not designed to investigate this specific question results could still be biased for several reasons, including publication bias. Therefore, new studies specifically designed to quantify the contribution of leukocyte antibodies to the occurrence of TRALI are necessary.

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Appendix I

Search strategy for TRALI and antibodies in PubMed

(“transfusion associated acute lung injury”[tiab] OR “transfusion related acute lung injury”[tiab] OR TRALI OR “transfusion associated respiratory distress”[tiab] OR ("Blood Transfusion/adverse effects"[Mesh] AND "Respiratory Distress Syndrome, Adult"[Mesh]) OR (“acute lung injury”[ti] AND transfusion[ti]) OR (“pulmonary reaction*”[ti] AND transfusion[ti]) OR “pulmonary transfusion reaction*”[tiab] OR (“pulmonary injury”[ti] AND transfusion[ti]) OR (“pulmonary edema”[ti] AND transfusion[ti]) OR (“lung edema”[ti] AND transfusion[ti]) OR (“pulmonary oedema”[ti] AND transfusion[ti]) OR (“lung oedema”[ti] AND transfusion[ti])) AND (Alloantibodies OR alloantibody OR Alloantigens OR alloantigen OR "Isoantigens"[MeSH] OR isoantigens OR isoantigen OR "Isoantibodies"[MeSH] OR isoantibodies OR isoantibody OR Alloantibod*[tiab] OR Alloantigen*[tiab] OR Isoantibod*[tiab] OR Isoantigen*[tiab] OR "Antibodies"[MeSH] OR antibody OR antibodies)

Search strategy for TRALI and antibodies in EMBASE

(((transfusion associated acute lung injury OR transfusion related acute lung injury OR TRALI OR transfusion-associated respiratory distress OR (acute lung injury AND transfus$)).ti,ab) OR exp Transfusion Related Acute Lung Injury/ OR (Acute lung injury/ AND exp Blood transfusion/) OR (exp Adult Respiratory Distress Syndrome/ AND exp Blood Transfusion/) OR (pulmonary reaction$.ti AND transfusion.ti) OR pulmonary transfusion reaction$.ti,ab OR (pulmonary injury.ti AND transfusion.ti) OR (pulmonary edema$.ti AND transfusion.ti) OR (lung edema$.ti AND transfusion.ti) OR (pulmonary oedema$.ti AND transfusion.ti) OR (lung oedema$.ti AND transfusion.ti)) AND ((alloantibod$ OR alloantigen$ OR isoantigen$ OR isoantigen OR isoantibod$ OR antibod$).ti,ab OR exp Antibody/ OR exp Alloantigen/)

Search strategy for prevalence of antileukocyte antibodies in PubMed

(Alloantibodies OR alloantibody OR Alloantigens OR alloantigen OR "Isoantigens"[MeSH] OR isoantigens OR isoantigen OR "Isoantibodies"[MeSH] OR isoantibodies OR isoantibody OR Alloantibod*[tiab] OR Alloantigen*[tiab] OR Isoantibod*[tiab] OR Isoantigen*[tiab] OR "Antibodies"[MeSH] OR antibody OR antibodies) AND ("anti-hla" OR "anti-hna" OR “anti-leukocyte” OR “anti-granulocyte” OR “anti-neutrophil”) AND ("Epidemiology"[MeSH] OR "Prevalence"[MeSH] OR "Incidence"[MeSH] OR prevalence [tiab] OR incidence [tiab])

Search strategy for prevalence of antileukocyte antibodies in EMBASE
((alloantibod$ OR alloantigen$ OR isoantigen$ OR isoantigen OR isoantibod$ OR antibod$).ti,ab OR exp Antibody/ OR exp Alloantigen/) AND (anti-hla OR anti-hna OR anti-leukocyte OR anti-granulocyte OR anti-neutrophil) AND (exp epidemiology/ OR prevalence.ti,ab OR incidence.ti,ab)

Appendix II

Complete reference lists for articles included in this review

Articles containing information on the prevalence of anti-leukocyte antibodies in the general population

1. Boulton-Jones R, Norris A, O'Sullivan A, Comrie A, Forgan M, Rawlinson PS, Clark P. The impact of screening a platelet donor panel for human leucocyte antigen antibodies to reduce the risk of transfusion-related acute lung injury. Transfus.Med. 2003 Jun;13(3):169-70.
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