The Challenge of Transfusion of Patients Infected with HIV/AIDS

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Submitted: 20 Jan 2019; Accepted: 28 Jan 2019; Published: 11 Feb 2019

Keywords: Blood Transfusion – HIV/AIDS Patients - Autoantibodies – Antiglobulin Test

Abstract
The transfusional support of human immunodeficiency virus-infected patients is a challenge both for the clinical physician and for the blood services, either because of the immunohematological problems or the microbiological/thrombotic risk associated.

The immunohematological risk caused by positive crossmatch is resolved by autologous adsorption; if the patient was recently transfused, the adsorption will be homologous.

The thrombotic risk (due to hypercoagulable state) is resolved by pretransfusion heparin administration and leukoreduction only in autoimmune hemolytic anemia cases; and the presumed microbiological risk is similar to HIV-negative patients.

Introduction
Infectious diseases are one of the most important public health problems of the world, reaching even 25% of annual cause of death. In developing countries, it represents the first cause of death [1].

Among infectious diseases, the Human Immunodeficiency Virus (HIV) still is one of the major public health problems in the world; more than 35 million deaths are attributed to this virus. In the world, 36, 7 million individuals are estimated to be HIV-infected [2].

Most of HIV-infected patients present some degree of anemia during the natural history of the disease [3]. The etiology of the anemia is frequently multifactorial and many times is refractory to conventional treatment of anemia (iron, erythropoietin, folate and vitamin B12), being the red blood cells (RBC) transfusion the main treatment for symptomatic anemia in these patients.

The transfusional support of HIV-infected patients is a challenge both for the clinical physician and for the blood services, either because of the immunohematological problems or the microbiological/thrombotic risk associated.

Immunohematological Risk
The HIV attacks the immune system and deteriorates the systems of defense against infections and certain types of cancer and the patient acquires a progressive immunodeficiency because the HIV destroys the immune cells. The most advanced stage of HIV infection is the Acquired Immunodeficiency Syndrome (AIDS) which, according to the person, can take between 2 and 15 years to manifest. The patients with AIDS can have certain types of cancer and infections or present other clinical manifestations of importance that might reach a high degree of lethality.

The immunohematological consequences of the direct and indirect action of HIV in the immune system of the patient or the associated infections are so diverse and heterogenous that the consequences are from clinical insignificance to life risking (Figure 1). To its adequate understanding, the alloimmune risks will be discussed first, then the ones concerning erythrocytes and serum.

Immune Response to Blood Group Antigens
One of the first consequences of the action of HIV on the immune system is the decrease of the alloimmune response to the exposition of “non-self” erythrocytes [4]. The general hospital population presents an incidence of irregular antibodies of 8-10% versus the HIV-infected of 0 – 2, 6% [5,6].
This situation is to be expected, since it expresses the inability to recognize and present blood group antigens by the antigen-presenting cells (APC) and the decrease of lymphocytes T CD4+ type 2, a subpopulation that’s essential to this process [7].

In animal models, viral infections or viral-like inflammation can potentiate the alloimmunization, whereas Gramm negative bacterial infection or sepsis suppress or diminish alloimmune response [5].

On the other hand, the levels of antibodies of ABO system, anti-A and anti-B are usually normal, a situation that’s compatible with the fact that the immune response that produces this anti-carbohydrates and anti-glycolipids antibodies is T independent (Figure 2).

Table 1: Blood group antigens receptors to microbes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Pneumoniae</td>
<td>I</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>P. vivax/ P.knowlesi</td>
<td>DARC (Fy6)</td>
<td>Malaria</td>
</tr>
<tr>
<td>P. Falciparum</td>
<td>A / B, GPA (MN), GPB (SsU), GPC (Ge), Banda3 (Dx), CR1, CD36, ICAM-1, XK, Ok^a</td>
<td>Malaria</td>
</tr>
<tr>
<td>HIV</td>
<td>H, P, Lu^a, Ok^a</td>
<td>AIDS</td>
</tr>
<tr>
<td>H. pilori</td>
<td>Le^a H</td>
<td>Pyloric ulcer</td>
</tr>
<tr>
<td>E. Coli</td>
<td>DAF (CROM); GPA (M); GLOB1 (P)</td>
<td>Urinary infection</td>
</tr>
<tr>
<td>Echovirus / Coxsackie</td>
<td>DAF (CROM)</td>
<td>Diarrhea, meningitis, pneumonia</td>
</tr>
<tr>
<td>M. Tuberculosis</td>
<td>CR1 (Knops)</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>M. Leprae</td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td>H influenzae</td>
<td>AnWj</td>
<td>Severe infection</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Glob1 (P)</td>
<td>RBC aplasia, Fifth disease</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>CD44 (IN)</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Pseudomonas aer</td>
<td>B, P1, Pk</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Giardia</td>
<td>A</td>
<td>Parasitism</td>
</tr>
<tr>
<td>Streptococcus suis</td>
<td>GLOB1 (P)</td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

Alteration in Blood Group Antigens
From the microbe-erythrocyte interaction, arise alterations in the structures of the cell membrane surface, these alterations very rarely modify in a clinically significant way the half-life of RBC.

The most affected structures tend to be the proteins or carbohydrates of blood group antigens and can potentiate, depress or acquire “de novo” blood group antigens (Table 2).

The blood group antigens are products of the expression of one or more inherited genes (genotype), this phenomenon (modification of phenotype) are usually passengers and remit spontaneously or by the action of medical treatment.

In some cases, the erythrocyte membrane can be modified by microbial enzymes (Neuraminidase, β-Galactosidase, Deacetylase) that can diminish the expression of blood group antigens. In the case of A and B antigens of ABO system, not always this diminution of expression may be detected by conventional agglutination test.
Table 2: Blood group antigens affected by microbes

<table>
<thead>
<tr>
<th>Action on antigens</th>
<th>Infectious agent or most important clinical manifestations</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>HIV/AIDS</td>
<td>CR1 / Knops</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>A, B, H, I, K, M, N</td>
</tr>
<tr>
<td></td>
<td>Epstein Barr Virus</td>
<td>Le</td>
</tr>
<tr>
<td>Potentiation</td>
<td>Sepsis</td>
<td>T, Tk, Th y Tn</td>
</tr>
<tr>
<td>Acquired</td>
<td>Sepsis</td>
<td>B_{adq}</td>
</tr>
<tr>
<td></td>
<td>E. Faecium</td>
<td>K_{skw}, J_{kb_{adq}}</td>
</tr>
<tr>
<td></td>
<td>Micrococcus</td>
<td>Jk_{skw}</td>
</tr>
</tbody>
</table>

In other cases and by a similar mechanism to the previously described (modification of membrane by bacterial enzymes) it may have the opposite effect that is to potentiate blood group antigens that are not generally detected by conventional test. These antigens are T, Tk, Th and Tn and responsible for the polyagglutination phenomenon. This problem is in general detected by “minor crossmatch”; resulting positive in saline medium at room temperature (patient’s erythrocytes vs donor’s plasma). Although in the case of “natural” antibodies not complement-activator IgM and non-reactive in anti-globulin medium, they usually do not have clinical significance and may be ignored.

More rarely, the detection of unexpected antigens is usually the result of the direct action of microbial enzymes or the adsorption of bacterial products in the surface of erythrocytes. In these cases, they often produce discrepancies in ABO typing or other blood group systems (Figure 2).

Positive Direct Antiglobulin Test and Non-Reactive Eluate
Since the beginnings of the HIV/AIDS pandemic the high incidence of positive Direct Antiglobulin Test (DAT) and non-reactive eluate was described in HIV-infected individuals, without clinical-laboratorial evidence of immune hemolysis. This incidence at the beginning of the infection is usually 10% increasing progressively as the disease advances reaching 85% in the final stage of infection (AIDS) [3,9].

The most probable cause of DAT positive is polyclonal hypergammaglobulinemia (resolved with serum dosage of immunoglobulins); another cause may be the presence of circulating immune complexes and IgG autoantibodies.

The differential diagnoses are ABO incompatibility, erythrocytes coated by IgA/IgM and anti-drug antibodies (Table 3) [10].

Table 3: Positive DAT differential diagnosis in HIV/AIDS

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Antecedent</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postransfusional ABO incompatibility</td>
<td>Transfusion last 3 months</td>
<td>RBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed field. Elution vs A / B RBC and IAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet, plasma, hemoderivates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elution vs RBC A / B and IAT</td>
</tr>
<tr>
<td>Clinical signs of hemolysis</td>
<td>Acute anemia, shock, hemoglobinemia, hemoglobinuria, jaundice, renal insufficiency, thrombosis, disseminated intravascular coagulation</td>
<td>Medical treatment</td>
</tr>
<tr>
<td>Laboratory indirect parameters</td>
<td>LDH, haptoglobin, reticulocytes, bilirubin</td>
<td>RBC coated by C3d, IgA or IgM</td>
</tr>
<tr>
<td>Drug-induced antibodies</td>
<td>Recent drug administration and clinical/laboratorial parameters of hemolysis</td>
<td>DAT with anti-C3d, -IgA, -IgM</td>
</tr>
</tbody>
</table>

Auto Agglutination
Frequently, the HIV-infected patients have cold antibodies (mostly without clinical significance) during the disease [11]. Rarely, these cold antibodies (IgM) may be sufficiently potent to produce spontaneous agglutination of the blood sample that can cause discrepancies with ABO and Rh typing [12].

The resolution is to try that the cold antibody does not interfere with the RBC typing. So, initially let the sample incubates at 37°C for 60 minutes and then washes RBC with physiological solution at 37°C [13,14].

If the control (albumin at 6%) invalidates the typing by spontaneous agglutination, we must use a conservative elution of RBC (heat, chloroquine, etc.) or treatment with reducing agents (2-ME, DTT).

Finally, and if the cold autoantibody is very potent (very rare), must use genotype typing with nucleic acid amplification techniques.

Serum Problems
The main functions of the immune system are to recognize microbes and control/destroy the pathogenic ones; destroy tumoral cells and protect fetal and normal cells. Integrating the immune response to bacteria (T independent) the “natural” antibodies of blood group (ABO, H, Le) mostly IgM, IgG2/IgG4 of low affinity are generated and if they do not fix complement they are usually clinically not significant (apart of ABO antibodies).

The previous exposure to pathogens carrying sequences of peptides similar to blood group antigens (T dependent) could explain the relationship between infection and detection of irregular antibodies [15] (Table 4).
As mentioned previously, there is a strong relationship between infections and development of anti-RBC autoantibodies (with or without hemolysis); the prevalence in HIV-infected patients is higher [16].

There are several proposed mechanisms, not mutually exclusive, that explain these findings [17]:

- Molecular mimicry [18]. The structural similarity between HIV and RBC structures could induce the production of autoantibodies associated with the development of autoimmune hemolytic anemia (AIHA).
- Escape to thymic deletion of auto reactive clones [17].
- Disfunction T-B which decrease of Tregs lymphocytes and increase of Th2; it may even generate polyclonal B-cell activation [19].
- Predisposition to develop drug-induced antibodies [20]. This mechanism may be the consequence of a rearrangement of the homeostasis of the immune system, which leads to exacerbate functions and express pre-existing autoreactive elements. When the immune system is exposed to polymerization (which is often in our institution), patients may develop anti-drug antibodies (via primary RBC-microbe-drug interaction).

The antibodies produced can be cold (IgM) or warm (IgG).

### Cold Autoantibodies

The pathological cold autoantibodies are defined by presenting a positive DAT by anti-C3d (negative for anti-IgG), title at 4°C > 64 and evidence of clinical hemolysis. Any cold antibody that does not meet these characteristics is generally considered non-pathological.

The clinically significant antibodies are detected by pre-heated 37°C the samples; in cases of very potent antibodies (with high thermal range), must use the cold autologous adsorption supernatant.

### Warm Autoantibodies

Different publications have documented that patients infected with HIV/AIDS have AIHA incidence of 3%; being their risk 28 times higher than the controls even in those patients treated with antiretroviral therapy, the prevalence may be the same or higher [21,22].

The clinical presentation of AIHA associated with HIV varies from a mild form, moderate to fulminant hemolysis (infrequent) [23].

Most of the well-documented cases of drug-induced AIHA in patients infected with HIV/AIDS are diagnosed in our Hospital and it certainly reflects a higher level of suspicion compared to other institutions [20].

The diagnosis of AIHA in patients infected with HIV/AIDS follows the same clinical-laboratory steps of the non-infected [24]. That is, clinical evidence (acute anemia, shock, hemoglobinemia, jaundice, renal insufficiency, coagulopathy) and indirect parameters of hemolysis (increase of LDH and indirect bilirubin, decrease of haptoglobin).

Clearly the finding of positive DAT + in patients infected with HIV/AIDS (in the absence of clinical and laboratory signs of hemolysis) is not sufficient evidence for the diagnosis of AIHA.

Synthesis: The HIV infected patients may develop clinically significant alloantibodies (less frequently that HIV-negative); autoantibodies (more frequently that HIV-negative) and Drug-Induced antibodies (more frequently that HIV-negative).

### Selection of Blood to be transfused

The indication of transfusing patients infected with HIV/AIDS does not differ substantially compared with HIV-negative [25]. However, the main immunohematological problem is the positivity of pretransfusional crossmatch test (Figure 3) [10,26]. Prior to any attempt at resolution, always consider the patient’s antecedents (transfusion, pregnancy, drugs, etc.) since they can guide to the possible causes of the positive crossmatch, positive DAT and positive Indirect Antiglobulin Test (IAT).

![Figure 3: Basic resolution scheme of positive crossmatch](image)

**Figure 3: Basic resolution scheme of positive crossmatch**

Ads: Adsorption  
Autol: Autologous  
Ab: antibody  
* Clinically significant  
DD: Drug Dependent  
NIPA: No immune protein adsorption  
AIHA: autoimmune hemolytic anemia  
IAT: indirect antiglobulin test

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### Table 4: Blood group antibodies related to infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Anti-M</th>
<th>Proteus mirabilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-P</td>
<td>Proteus mirabilis</td>
<td></td>
</tr>
<tr>
<td>Anti-K</td>
<td>E. coli, Campylobacter jejuni, M. tuberculosis, E. faecalis</td>
<td></td>
</tr>
<tr>
<td>Anti-Jk</td>
<td>Micrococcus; Proteus Mirabilis</td>
<td></td>
</tr>
<tr>
<td>Anti-P</td>
<td>E. Coli, measles, mumps, chickenpox, adenovirus, Cytomegalovirus, Epstein Barr Virus, syphilis, Haemophilus influenzae, M. pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Anti-Pr</td>
<td>Viral infections</td>
<td></td>
</tr>
<tr>
<td>Anti-I</td>
<td>M. pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Anti-i</td>
<td>Epstein-Barr, Virus HIV</td>
<td></td>
</tr>
<tr>
<td>Anti-Rx</td>
<td>Viral Infection</td>
<td></td>
</tr>
</tbody>
</table>
Resolution

Hypercoagulability

Cause

CMV, HH8, HTLV

Leukoreduction and

pretransfusional heparin administration and leukoreduction only in

the thrombotic risk (due to hypercoagulable state) is solved by

detected by positive crossmatch is solved by adsorption techniques;

In summary, the immunohematological risk in HIV positive patients [36,37].

The indications to irradiation are the same as for HIV-negative

patients [29-34].

Regarding the universal irradiation of blood components to transfuse to HIV-infected patients, there is only one case of posttransfusional GVHD [35]. This is probably because posttransfusional microchimerism in HIV-infected patients is rarely detected, so the universal irradiation of blood components is not recommended. The indications to irradiation are the same as for HIV-negative patients [36,37].

In summary, the immunohematological risk in HIV positive patients detected by positive crossmatch is solved by adsorption techniques; the thrombotic risk (due to hypercoagulable state) is solved by pretransfusional heparin administration and leukoreduction only in cases of AIHA; and the presumed microbiological risk is similar to HIV-negative patients (Table 5).

Table 5: Transfusional risk in HIV positive patients

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cause</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunohematological</td>
<td>Positive crossmatch</td>
<td>Adsorption techniques</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>Hypercoagulability</td>
<td>Heparin / leukoreduction only in AIHA</td>
</tr>
<tr>
<td>Microbiological</td>
<td>CMV, HH8, HTLV</td>
<td>Leukoreduction and universal irradiation without proven benefit</td>
</tr>
</tbody>
</table>

Conclusion

The world incidence of HIV infection/AIDS is relevant; therefore, it is important to recognize the transfusional risks and problems that can be produced and how they can be solved. This publication aims to contribute to its resolution.

Acknowledgment

I express my gratitude to my medical guide Prof. Dr. Enrique Rewald (1926-2016+), a brilliant mind that Argentina did not know how to value. Special thanks to Ana Maria Ahumada FUHESA for support.

References


