Autoimmune Hemolytic Anemia in Pediatric Liver or Combined Liver and Small Bowel Transplant Patients – A Case Series and Review of the Literature

Short Title: AIHA in Pediatric Solid Organ Transplantation
ABSTRACT

Background:
Autoimmune hemolytic anemia (AIHA) occurring after solid organ transplantation is an infrequently reported entity. We describe in this report 6 cases of AIHA in pediatric liver or combined liver and small bowel transplant patients.

Study Design and Methods:
We retrospectively identified and reviewed the records of pediatric liver or combined liver and small bowel transplant patients with both serological and clinical evidence of AIHA. We also performed an English language literature review for prior publications of AIHA occurring after solid organ transplantation.

Results:
We identified 6 patients presenting with severe hemolysis 9 months to 14 years after transplantation. All 6 developed warm AIHA, and two had concomitant cold agglutinins. All except one patient received various therapeutic combinations including steroids, IVIG, rituximab, plasmapheresis, native splenectomy and vincristine. Five patients achieved remission two weeks to three months following presentation. Although tacrolimus has been speculated to play a causative role in the development of AIHA after organ transplantation, our case series demonstrated slightly better outcomes despite continuing tacrolimus as compared to published cases where most patients either received significantly reduced doses of tacrolimus or were switched to a different immunosuppressant (83% vs. 76% cumulative literature remission rate).
**Conclusion:**

AIHA may occur in solid organ transplant patients at a much higher frequency than previously believed. Hemolysis is often severe and resistant to steroid treatment alone. Thus early diagnosis and institution of aggressive multi-modality treatment, including the use of rituximab, may be needed to achieve remission.

Key Words: Autoimmune hemolytic anemia, rituximab, transplantation-solid organ
INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is defined as the destruction of red blood cells (RBC) mediated by autoantibodies. Primary or idiopathic AIHA has no clear association with an underlying condition and is the most common form of this disease. In secondary AIHA, there is a clearly identifiable co-existing condition including autoimmune diseases (e.g. systemic lupus erythematosus), lymphoproliferative disorders, viral infections, stem cell or solid organ transplant, or the use of certain medications. The overall incidence of AIHA in the general population is approximately 1 in 80,000. AIHA cases are usually mediated by warm-reactive (IgG) or cold-reactive (IgM) autoantibodies. Warm AIHA (WAIHA) accounts for 70% of acquired immune hemolytic anemia cases, whereas cold AIHA or cold agglutinin syndrome (CAS) makes up only 15.6% of cases. Another 7% of patients develop mixed warm and cold AIHA (mixed AIHA).\(^1\) It is important to make the clinical distinction between WAIHA and CAS since the treatment and prognosis vary greatly.

Transplant-associated immune hemolytic anemia is known to occur in patients following stem cell transplantation. Frequently this is mediated by ABO antibodies due to major or minor incompatibility (passenger lymphocyte syndrome), leading to hemolysis with a relatively acute presentation noted within days to weeks after transplant.\(^2\) In contrast, AIHA mediated by autoantibodies can also develop in this clinical setting, but with a much lower observed frequency and occurring months to years after transplant. Reported incidences of AIHA in pediatric and adult stem cell transplant patients are 6%\(^3\) and 3 to 5%,\(^4,5\) respectively. Most published cases of AIHA presenting after stem cell transplantation occurred in patients who received T cell depleted stem cells. The mechanism of autoantibody formation has been
speculated to involve dysregulated immune reconstitution after transplant, which may lead to the polyclonal proliferation of B lymphocytes that can produce self-reacting antibodies.\textsuperscript{4-7}

Until recently, there had been only a handful of reports in the literature of AIHA in the setting of solid organ transplantation and none of these publications were sufficiently powered to report the incidence.\textsuperscript{8-14} However, the retrospective study published in 2009 by Botija et al. found that AIHA occurred at an incidence of 12.2\% in 49 pediatric intestinal transplant patients.\textsuperscript{15} Surprisingly, CAS appeared to be the most common type of AIHA, followed by WAIHA and mixed AIHA in all of these reported cases. It remains difficult to determine the true incidence of AIHA following solid organ transplantation based on current publications. However, we found it fascinating that within the last three years we have encountered 6 cases of well-documented AIHA occurring in liver or combined liver and small bowel pediatric transplant patients at our center. This may corroborate the relatively high incidence that was reported by Botija and coworkers. The details of our cases are described below.

**MATERIALS AND METHODS**

Between April 2007 and October 2010, immunohematology work-ups (antibody screen and direct antiglobulin test (DAT)) for pediatric liver or combined liver and small bowel transplant patients were reviewed for serologic evidence of AIHA. If serologic evidence was present, clinical evidence of hemolysis was sought in each patient and response to various treatment modalities was evaluated through retrospective chart reviews.
We performed an English language literature search on Pubmed using various combinations of the search terms “liver transplant”, “small bowel transplant”, “multivisceral transplant”, “autoimmune hemolytic anemia” and “Evans syndrome”. We found 17 similar cases of transplant-associated AIHA reported in 8 publications, and an additional three case reports of transplant-associated Evans syndrome in both pediatric and adult populations.

RESULTS
We identified 7 patients with serologic evidence of warm or cold autoantibodies between April 2007 and October 2010. During this same time period, 72 pediatric liver and 32 combined liver and small bowel transplantations were performed. Six of these patients were included in our review after clinical evidence of hemolysis was verified. There were four males and two females, ranging in age from five to 24 months at the time of first transplant. Two patients required re-transplantation for acute or chronic rejection. Only one patient received an organ with minor ABO incompatibility (recipient blood type: A+; donor blood type: O+). Primary immunosuppression included tacrolimus for every patient; five patients also received either mycophenolate mofetil and/or prednisone (See Table 1).

Five of the 6 patients presented with clinically overt hemolysis between 9 to 41 months after transplant, and the remaining patient presented 14 years after the first transplant. Patients ranged in age from 15 months to 15 years of age at the time of AIHA presentation. All 6 patients developed a positive DAT for anti-IgG, ranging from microscopically positive to 3+ in reactivity strength. Warm autoantibodies were identified in all 6 patients; in 5 patients, the warm autoantibodies were present both in the plasma and eluate, in one patient they were only evident
in an eluate prepared from the patient’s RBC. Two of the 6 patients also developed a positive DAT for anti-C3d with 1+ reactivity strength. Cold autoantibodies were identified in both of these cases: one with a titer of 16 at 4°C and a thermal amplitude up to 30°C, while the other reacted up to 37°C but the titer was unknown. All 6 patients required transfusion support and had laboratory evidence of hemolysis, including low hemoglobin (nadirs between 3.7 to 6.8 g/dL), depleted haptoglobin, and elevated reticulocyte count, indirect bilirubin and lactate dehydrogenase. On peripheral smear, microspherocytes were observed in all cases. Concurrent with hemolysis, four patients demonstrated significant falls in their platelet counts from baseline all with platelet counts < 50,000/µL. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) surveillance studies were performed in all of the patients by serology or PCR. One patient developed evidence of CMV and another of EBV infection, although neither of them developed evidence of cold autoantibodies (See Table 2).

Initial treatment of AIHA included high dose steroids alone or in combination with IVIG for all patients. In four patients, rituximab was subsequently added for persistent hemolysis despite first line treatment. Other therapies utilized included native splenectomy, plasmapheresis and vincristine. The two patients with concomitant cold agglutinins were also kept warm as part of the therapy for hemolysis. Time to first remission in five patients ranged from two weeks to three months. One of the five patients relapsed twice, but has since achieved remission. The last patient still has persistent hemolysis following three months of treatment. All patients’ primary transplant immunosuppressive regimens including tacrolimus were maintained with only minor dose adjustments during the acute episode of hemolysis in an effort to avoid organ rejection.
DISCUSSION

AIHA occurring in the setting of transplantation is not well described. In stem cell transplant, the reported incidence ranges from 3 to 5%\(^4,5\) in adult patients, and was reported to be slightly higher at 6%\(^3\) in pediatric patients. In solid organ transplant patients, the literature on AIHA until recently consisted of only single case reports or small case series. Therefore incidence of this entity was thought to be very low. However, Botija et al. recently performed the largest retrospective study to date in a cohort of 49 pediatric intestinal transplant patients and found an incidence of 12.2%.\(^15\) At our center, we observed 6 cases of well documented AIHA in pediatric liver or combined liver and small bowel transplant patients within the last three years. This suggests that the incidence of AIHA in this population may be significantly higher than previously believed. Because it is not well-described, recognition of this entity remains challenging in clinical practice, and it is likely that many such cases were unrecognized in the past. However, the true incidence cannot be established without a prospective surveillance study of the solid organ transplant patient population consisting of frequent monitoring of hemolysis laboratory parameters and serologic findings.

In our case series, we identified 6 pediatric patients following liver or combined liver and small bowel transplants with clinically evident AIHA. There were no mortalities in this patient cohort. Two patients developed severe hemolysis with hemoglobin ranging from 3.7 to 3.9 g/dL at nadir, while the four remaining patients had hemoglobin nadirs between 6.1 to 6.8 g/dL. The observed severity of anemia in our case series is consistent with published data, where most patients also had hemoglobin nadirs ranging between 2.9 to 6.7 g/dL. Only one of our patients received a minor ABO mismatched organ. This raised a concern for hemolysis due to ABO antibodies
produced by passenger lymphocytes directed against recipient RBC. Passenger lymphocyte syndrome-associated hemolysis is typically noted between five to 17 days after transplant.\textsuperscript{16} In this patient, the time to develop hemolysis occurred 11 months after transplant and there was never evidence of anti-A on this patient’s RBC. The combination of delayed hemolysis without evidence of anti-A isohemagglutinins makes passenger lymphocyte syndrome a very unlikely mechanism for hemolysis.

We identified 8 published reports of AIHA occurring in the setting of liver or small bowel transplantation (See Tables 3 & 4).\textsuperscript{8-15} In all, 17 patients were diagnosed and treated for AIHA, 13 of whom were pediatric patients and four were adults. Of the 17 reported patients, one died prior to initiation of treatment and one was treated with steroids only. The remaining 15 patients received in addition to steroids, other therapeutic modalities including IVIG, rituximab, plasmapheresis, native or graft splenectomy, alemtuzumab and cyclophosphamide. Thirteen patients achieved remission, three died (one from complications of anemia and two from infectious complications), and one continued to require low dose steroid maintenance for ongoing hemolysis.

In our case series, all 6 patients survived without significant morbidities due to hemolytic or infectious complications. Five patients reached clinical remission between two weeks to three months, three of whom had protracted clinical courses taking at least two months to reach clinical remission. Similar to previously reported cases, refractoriness to conventional steroid treatment was common, with only one of the five patients responding to steroid treatment alone. All other patients required various combinations of steroids, IVIG, rituximab, plasmapheresis,
native splenectomy and vincristine. One patient has ongoing hemolysis, despite triple therapy with steroids, IVIG and rituximab and is currently on a steroid taper. In total, four of the 6 patients received rituximab treatment and three out of the four are currently in remission.

Rituximab, a monoclonal anti-CD20, is known to exert its effect on B cells and has been reported to be beneficial in the treatment of WAIHA and CAS. The drawbacks associated with the use of rituximab include increased immunosupression, up to 6 weeks of delay in therapeutic effects on hemolysis in some patients, six months of IVIG repletion therapy and higher cost. Nevertheless, it is possible that the early use of rituximab contributed to the relatively good clinical outcome observed in our patient population.

Interestingly, many of the patients in the previously reported cases were diagnosed with CAS (7/17 patients). This is different from our experience since all 6 of our patients developed WAIHA, including two with concomitant cold agglutinins, and none developed CAS alone. CAS is usually diagnosed in the clinical setting of a patient presenting with signs and symptoms of hemolysis and acrocyanosis. They will usually have significantly elevated cold agglutinin titers of greater than 1,000 at 4°C. Thermal amplitude is considered to be a better indicator of a clinically significant cold agglutinin since most healthy individuals may have cold autoantibodies, but they do not react above room temperature. Further reading revealed that these previously published reports often did not provide detailed serologic results, and most made the assumption that the cold autoantibodies found were clinically significant even though titers at 4°C were less than 64 or not performed. Furthermore, the thermal amplitude test was either not performed or poorly documented in these reports. It should be noted that Petz and Garratty found strongly reactive concomitant cold agglutinins in 35% of patients with WAIHA, which when
appropriately tested, usually displayed normal titers at 4º C and restricted thermal amplitude, indicating the lack of clinical significance of such cold agglutinins.\textsuperscript{1} Similarly, the cold agglutinins in those previously reported post-solid organ transplant AIHA cases may not be in themselves pathogenic either. However, the pathogenic, warm autoantibodies might have been missed. Three of the patients in these reports appeared to have developed mixed AIHA.\textsuperscript{12,15} We also observed this relatively rare form of immune hemolysis in two of our patients. One developed a cold agglutinin with a titer of 16 at 4ºC that was reactive up to 30ºC; and the other patient’s cold agglutinin titer was unknown, however, it was reactive up to 37ºC. The first patient responded excellently to steroid therapy alone while being kept warm and reached remission in two weeks, but the other patient relapsed twice and required steroids, IVIG and rituximab triple therapy for a month before achieving remission.

Evans syndrome (ES) is a rare autoimmune disorder defined by the combination of immune thrombocytopenia and AIHA. Interestingly, there are three case reports in the literature of ES presenting after liver transplant (See Tables 3 & 4).\textsuperscript{17-19} In our case series, four of the 6 patients developed concurrent severe thrombocytopenia with platelet counts falling below 50,000/µL, and one required multiple platelet transfusions for active bleeding. Although none of them was given the formal diagnosis of ES, the temporal relationship between AIHA and the onset of severe thrombocytopenia raises the possibility that some of these cases represented ES. Although there have been only three such reported cases in both the pediatric and adult liver transplant population, our observation suggests ES may be much more common than previously thought.
Since the early 1990’s, tacrolimus has been an integral part of the primary immunosuppressive regimen in wide use for liver transplant patients. Consequently the role of tacrolimus as the causative agent in the relatively rare entity of AIHA following transplantation is difficult to assess. Calcineurin inhibitors such as tacrolimus have been postulated to cause an imbalance in the T and B cell immunity, leading to a more pronounced B cell response and formation of autoantibodies. This theory bears similarity to the mechanism of pathogenesis proposed for the observed relatively higher incidence of AIHA in patients who receive T cell depleted stem cells transplants. Furthermore, there are differences reported in the absorption, bioavailability, distribution and metabolism of tacrolimus in pediatric versus adult patients. This raises the possibility that these biological differences may underlie the observed higher incidence of AIHA in pediatric patients as compared to their adult counterparts.

Because tacrolimus was suspected to have contributed to the development or possibly exacerbate the clinical course of AIHA, the treating physicians in most of the previously reported cases chose to significantly reduce the dose of tacrolimus, or switch to another immunosuppressive agent. However, in our cohort, all patients were maintained on tacrolimus with only minor dose adjustments to stay within the therapeutic range while they were treated for AIHA. Compared to the previously reported cases in which tacrolimus was discontinued or given at a significantly reduced dose, our patients had slightly better outcomes despite continuing tacrolimus treatment, with five of the 6 patients (83% versus the 76% cumulative remission rate reported in the literature) reaching remission. Therefore, our findings suggest that maintaining tacrolimus during an acute hemolytic episode may be an acceptable alternative. This is an important finding because tacrolimus reduction or withdrawal shortly after transplantation, especially in small
bowel transplant recipients, is potentially very harmful given the increased chances for organ rejection.

In summary, AIHA occurring in solid organ transplant patients is not well-understood and the exact incidence is not yet known. Early clinical suspicion and diagnosis will facilitate prompt and effective therapy to minimize complications related to hemolysis or treatment associated infection. In the majority of published studies and our own experience, most patients were resistant to conventional steroid treatment for AIHA. It appears that early institution of aggressive multi-drug treatment regimens, especially the use of rituximab, may be needed to achieve remission.

ACKNOWLEDGEMENT

The authors wish to thank the staff at the UCLA Transfusion Medicine Service for providing excellent support. We would also like to acknowledge Rebecca Davis for providing invaluable immunohematology assistance, Alyssa Ziman M.D. for her critical review of the manuscript and Christopher Fink M.D. for his clinical expertise.
REFERENCES


<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Initial diagnosis</th>
<th>Age at transplant</th>
<th>Graft Type</th>
<th>Primary immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Gastroschisis</td>
<td>11 months &amp; 14 months</td>
<td>OLT + SBT x2</td>
<td>T/S/MMF</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Gastrochisis</td>
<td>20 months</td>
<td>OLT + SBT</td>
<td>T/MMF</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Biliary atresia</td>
<td>5 months</td>
<td>OLT</td>
<td>T/S</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Biliary atresia</td>
<td>1 year &amp; 15 years</td>
<td>OLT x 2</td>
<td>T</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Intestinal atresia</td>
<td>10 months</td>
<td>OLT + SBT</td>
<td>T/MMF</td>
</tr>
<tr>
<td>*6</td>
<td>F</td>
<td>Citrulinemia</td>
<td>6 months</td>
<td>OLT</td>
<td>T/S</td>
</tr>
</tbody>
</table>

* This patient received a liver with minor ABO incompatibility (recipient: A+ / donor: O+)
M: male
F: female
T: tacrolimus
S: steroid
MMF: mycophenolate mofetil
OLT: orthotopic liver transplant
OLT + SBT: combined small bowel and liver transplant
All donor splenectomies were performed during transplant
Table 2. Immunohematology findings, clinical characteristics and outcomes

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age at time of AIHA diagnosis</th>
<th>DAT (direct antiglobulin test)</th>
<th>Antibodies identified</th>
<th>Interval between transplant and onset of hemolysis</th>
<th>Time to remission following treatment for hemolysis</th>
<th>Nadir hemoglobin level (g/dL)</th>
<th>Concurrent severe thrombocytopenia (&lt;50,000/µL)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5 years</td>
<td>1+</td>
<td>WAA &amp; CAA (4°C titer: 16; reactive up to 30°C)</td>
<td>29 months</td>
<td>2 weeks</td>
<td>6.6</td>
<td>Yes</td>
<td>S/Keep warm</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>4.5 years</td>
<td>3+</td>
<td>Negative</td>
<td>WAA</td>
<td>32 months</td>
<td>3.7</td>
<td>Yes</td>
<td>S/IVIG/R/PE/native splenectomy</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td>15 months</td>
<td>3+</td>
<td>Negative</td>
<td>WAA</td>
<td>9 months</td>
<td>6.1</td>
<td>No</td>
<td>S/IVIG/R/V</td>
<td>Remission</td>
</tr>
<tr>
<td>4</td>
<td>15 years</td>
<td>3+</td>
<td>Negative</td>
<td>WAA</td>
<td>14 years</td>
<td>6.1</td>
<td>Yes</td>
<td>S/IVIG/PE/native splenectomy</td>
<td>Remission</td>
</tr>
<tr>
<td>5</td>
<td>5.5 years</td>
<td>Microscopically positive</td>
<td>Negative</td>
<td>WAA*</td>
<td>41 months</td>
<td>Ongoing</td>
<td>No</td>
<td>S/IVIG/R</td>
<td>Ongoing treatment</td>
</tr>
<tr>
<td>6</td>
<td>17 months</td>
<td>1+</td>
<td>WAA &amp; CAA (Titer at 4°C unknown, reactive up to 37°C)</td>
<td>11 months</td>
<td>1 month</td>
<td>3.9</td>
<td>Yes</td>
<td>S/IVIG/R/ keep warm</td>
<td>2 relapses, currently in remission</td>
</tr>
</tbody>
</table>

* WAA is present only in the eluate  
S: steroids  
R: rituximab  
PE: plasmapheresis  
V: vincristine  
WAA: warm autoantibody  
CAA: cold autoantibody
<table>
<thead>
<tr>
<th>Type of publication</th>
<th>Age or Age range at time of AIHA diagnosis</th>
<th>Gender</th>
<th>Type of transplant</th>
<th>Primary Immunosuppression</th>
<th>Type of autoimmune condition</th>
<th>Time to develop hemolysis after transplant</th>
<th>Time to remission following treatment for hemolysis</th>
<th>Nadir hemoglobin level (g/dL)</th>
<th>Treatment</th>
<th>Primary Immunosuppression modification</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Case series (6)</td>
<td>NP</td>
<td>M (4)</td>
<td>Liver; liver/small bowel; multivisceral</td>
<td>T/S/B/A/TM</td>
<td>WAIHA (3); CAS (1); Mixed AIHA (2)</td>
<td>1-21 months (average 10 months)</td>
<td>NP</td>
<td>NP</td>
<td>S/IVIG/R/PE/A/graf splenectomy/keep warm</td>
<td>Tacrolimus switched to sirolimus (4)</td>
<td>Remission (5); Died of infection (1)</td>
<td>Botija8</td>
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<tr>
<td>Case report</td>
<td>16 months</td>
<td>M</td>
<td>Liver</td>
<td>T</td>
<td>Warm acting IgG and IgM AIHA</td>
<td>8 months</td>
<td>10 weeks</td>
<td>3.9</td>
<td>S/IVIG/R</td>
<td>Tacrolimus switched to cyclosporine</td>
<td>Remission</td>
<td>Schappi8</td>
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<tr>
<td>Case series (3)</td>
<td>13 months; 2 year 5 months; 4 year 1 month</td>
<td>F (3)</td>
<td>Liver</td>
<td>T</td>
<td>CAS (3)</td>
<td>6-26 months</td>
<td>3 weeks-1 month</td>
<td>3.6-5.3</td>
<td>S/PE/keep warm</td>
<td>Tacrolimus switched to cyclosporine</td>
<td>Remission</td>
<td>Wong7</td>
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<tr>
<td>Case report</td>
<td>3 years</td>
<td>F</td>
<td>Multivisceral</td>
<td>T</td>
<td>CAS</td>
<td>18 months</td>
<td>7 months</td>
<td>5.8</td>
<td>S/R/C/ exchange blood transfusion</td>
<td>Tacrolimus dose reduced</td>
<td>Remission</td>
<td>Brunner10</td>
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<td>9 years</td>
<td>F</td>
<td>Liver</td>
<td>T/S</td>
<td>CAS</td>
<td>4 months</td>
<td>NP</td>
<td>3</td>
<td>S/keep warm</td>
<td>Tacrolimus switched to cyclosporine</td>
<td>Remission</td>
<td>Kitamura11</td>
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<tr>
<td>Case report</td>
<td>7 years</td>
<td>M</td>
<td>Liver</td>
<td>T</td>
<td>Mixed AIHA</td>
<td>6 years</td>
<td>NA</td>
<td>2.9</td>
<td>None – patient died prior to initiation of treatment</td>
<td>None</td>
<td>Died of complications of anemia</td>
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<td>Case report</td>
<td>8 years</td>
<td>M</td>
<td>Liver</td>
<td>T/MMF</td>
<td>Evans syndrome</td>
<td>22 months</td>
<td>20 months</td>
<td>5.2</td>
<td>S/IVIG/R/C/F/nati ve splenectomy</td>
<td>Tacrolimus switched to cyclosporine</td>
<td>Remission</td>
<td>Domenech7</td>
</tr>
<tr>
<td>Case report</td>
<td>5 months</td>
<td>M</td>
<td>Liver</td>
<td>T</td>
<td>Evans syndrome</td>
<td>3 months</td>
<td>1 month</td>
<td>5.4</td>
<td>S/IVIG</td>
<td>Tacrolimus dose reduced</td>
<td>Remission</td>
<td>Yokoyama8</td>
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M: male  F: female  
PE: plasmapheresis  F: fludarabine  AIHA: autoimmune hemolytic anemia  WAIHA: warm autoimmune hemolytic anemia
| CAS: cold agglutinin syndrome | Mixed AIHA: mixed warm & cold autoimmune hemolytic anemia | NP: not provided | NA: not applicable |
Table 4. Literature review of reported cases of autoimmune hemolytic anemia or Evans syndrome in adult solid organ transplant patients (liver, liver/small bowel, multivisceral)

<table>
<thead>
<tr>
<th>Type of publication</th>
<th>Age or age range at time of AIHA diagnosis</th>
<th>Gender</th>
<th>Type of transplant</th>
<th>Primary Immunosuppression</th>
<th>Type of autoimmune condition</th>
<th>Time to develop hemolysis after transplant</th>
<th>Time to remission following treatment for hemolysis</th>
<th>Nadir hemoglobin level (g/dL)</th>
<th>Treatment</th>
<th>Primary Immunosuppression modification</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Case report</td>
<td>NP</td>
<td>M</td>
<td>Liver</td>
<td>T/S/MMF</td>
<td>CAS</td>
<td>12 months</td>
<td>7 months</td>
<td>6</td>
<td>S/IVIG/R</td>
<td>Tacrolimus dose reduced</td>
<td>Remission</td>
<td>Guitard13</td>
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<tr>
<td>Case series (3)</td>
<td>59, 59 and 66 years</td>
<td>M (2)</td>
<td>F (1)</td>
<td>T/MMF</td>
<td>DAT positive AIHA: IgG (1); IgG &amp; C3d (1); DAT negative AIHA (1)</td>
<td>3-6 years</td>
<td>NP</td>
<td>4.7-6.7 (schistocytes seen in one patient)</td>
<td>S/IVIG/R</td>
<td>Mycophenolate mofetil discontinued (1)</td>
<td>Remission (1); Low dose steroid maintenance (1); Died of infection (1)</td>
<td>Retana14</td>
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<tr>
<td>Case report</td>
<td>38 years</td>
<td>M</td>
<td>Liver</td>
<td>T (discontinued due to recurrent sepsis)/S</td>
<td>Evans syndrome</td>
<td>7 months</td>
<td>NP</td>
<td>8 Platelet nadir: 3,000/µL</td>
<td>S/IVIG</td>
<td>None</td>
<td>Died of infection</td>
<td>Au19</td>
</tr>
</tbody>
</table>

T: tacrolimus  
S: steroid  
MMF: mycophenolate mofetil  
R: rituximab  
DAT: direct antiglobulin test  
AIHA: autoimmune hemolytic anemia  
CAS: cold agglutinin syndrome  
NP: not provided