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# Infectious Complications Associated with the Use of Antithymocyte Globulin in Reduced Intensity Allogeneic Transplants

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## Abstract

**Purpose/Background:** Due to its mechanism, the use of antithymocyte globulin (ATG) in reduced intensity conditioning allogeneic stem cell transplant (RIC allo-SCT) therapy may increase the incidence of infection. This study analyzes the type and incidence of infectious complications in RIC allo-SCT patients conditioned with or without ATG.

**Methodology:** Electronic medical records were utilized to identify all adult patients with hematologic malignancies receiving a RIC allo-SCT between January 2001 and December 2010. Patients with aplastic anemia or deceased within 30 days of transplant were excluded. The primary outcome included the rate of infection from engraftment to one year after transplant. Secondarily, the rates of infection during the engraftment period, incidence of acute and chronic GVHD, overall survival, and disease free status at one year were investigated.

**Results:** A total of 63 patients were included. More patients receiving ATG experienced infection (81% vs. 56%, p=0.11). In the ATG group, 45.2% of patients developed multiple infections versus 18.8% without ATG (p=0.032). There was no significant difference with regard to secondary outcomes.

**Conclusion:** The overall incidence of infection as well as the incidence of viral infection alone was significantly increased in patients treated with ATG. More studies need to be conducted to determine the significance of these infections and the potential for prophylaxis or reduced immunosuppression.

**Keywords:** Antithymocyte globulin; Reduced intensity allogeneic transplant; Infection

## Background

Allogeneic stem cell transplants (allo-SCT) improve outcomes in a variety of disease states including lymphomas, leukemias, and myeloproliferative disorders [1]. Allogeneic transplants involve the intravenous infusion of hematopoietic stem cells from a compatible donor which are collected from the donor directly from the bone marrow or peripheral blood. Patients undergoing allogeneic transplants for the treatment of malignant disease receive a preparative conditioning regimen to kill as many malignant cells as possible as well as suppress the immune system to prevent graft versus host disease (GVHD) [2]. Conditioning therapies may differ depending on the type of transplant. Reduced intensity conditioning (RIC) or nonmyeloablative therapies have been associated with reduced non-relapse mortality and have provided a new option for elderly patients and those with other co-morbidities compared to the standard or myeloablative conditioning regimens. The effectiveness of allo-SCT in treating malignant disease is linked to the activity of immunoreactive cells in the graft, primarily T cells and natural killer cells [1]. This is known as the graft-versus-tumor (GVT) effect which facilitates the eradication of tumor cells in the recipient [3,4].

The addition of a T cell depleting agent, such as antithymocyte globulin (ATG), to the nonmyeloablative conditioning therapy has demonstrated a reduced incidence of GVHD and graft rejection [5]. However, the patient's immune system recovery is delayed with the use of ATG [1]. Antithymocyte globulin is a polyclonal immunoglobulin prepared by immunizing rabbits (Thymoglobulin®) or horses (Atgam®) with human thymocytes [2]. The antibodies produced destroy human leukocytes in the recipient to varying degrees depending on the various antigens that are present [5]. The main goal of ATG is to reduce the number of recipient T cells that could produce graft rejection as well as inhibit donor T cells that could induce GVHD [6]. The main adverse effect associated with its use is lymphopenia which may potentially increase the risk of infection in an already immune compromised patient.

Nonmyeloablative conditioning regimens produce significant variability in the amount of pancytopenia a patient may experience. Traditionally, following myeloablative conditioning regimens the pancytopenia may remain for days to weeks depending on the donor source. The rate at which neutrophils recover depends on the type of graft utilized. For patients receiving G-CSF-mobilized peripheral blood stem cell (PBPC) grafts, cell recovery occurs in about two weeks while bone marrow grafts take longer. Even though the degree of myelosuppression may be less in RIC regimens, the extent of lympho depletion tends to be greater. Lymphocyte recovery after allo-SCT is a prolonged process and requires several months. Traditionally, NK-cells are the first to recover, followed by CD8+ T cells and finally B cells and CD4+ T cells [1]. Infectious complications can occur during different post transplant phases. Each of these complications has been studied primarily in the myeloablative transplant setting. The first phase is the aplastic period consisting of neutropenia and toxicity associated with the conditioning regimen. During this phase, bacterial, as well

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as fungal, infections are possible including *Candida* or *Aspergillus*. Additionally, herpes simplex virus (HSV) may be reactivated. The second phase is known as the neutrophil recovery period but involves major T cell dysfunction due to the use immunosuppressive therapy. Viral infections such as HSV and cytomegalovirus (CMV) present during this phase. The clinical impact is determined by the extent of GVHD. The final phase involves the recovery of B cells and CD4+ T cells. Generally patients with chronic GVHD and alternate donor allo-SCT are at greatest risk for infection involving CMV, varicella-zoster virus (VZV), and those associated with encapsulated bacteria such as *Strep pneumoniae*. In patients receiving nonmyeloablative allo-SCT, there may be differences in the types of infections acquired during each phase. Very few studies have looked at the incidence and severity of infectious complications in the RIC allogeneic SCT setting [1,3].

Mohty et al. [3] conducted a study to define the incidence and potential risk factors of infectious complications within the first six months following RIC allo-SCT and assessed its impact on clinical outcomes. All patients received a conditioning regimen consisting of fludarabine, busulfan and ATG. The clinical outcomes analyzed included time of neutrophil and platelet engraftment, time to start and severity of acute GVHD, and time to onset of CMV, bacterial, and fungal infections. The results demonstrated that ATG based RIC allo-SCT recipients experienced an increased incidence of early CMV positive antigenemia without evidence of CMV disease. Bacteremia occurred in about 25% of patients who had recovered a full neutrophil count and the incidence of fungal infections was limited [3].

It is hypothesized that the use of ATG may increase the incidence of all infections in this patient population. The purpose of this study is to evaluate the incidence of infection in patients treated with or without rabbit ATG during RIC allo-SCT.

## Patients and Methods

### Patient selection and data collection

This was a retrospective analysis of adult patients who underwent a RIC allo-SCT for a diagnosis of hematologic malignancy, between January 2001 and December 2010, at Wake Forest Baptist Medical Center. The study was approved by the institutional review board. Patients were excluded if they received a transplant for aplastic anemia or died within thirty days of transplant. The historical data was collected from a computer generated patient database as well as individual medical records.

The primary outcome evaluated the rate of infection from engraftment to one year after transplant. Bacterial, fungal, and viral infections were assessed based on positive culture data, PCR, and radiographic imaging. Viral infections analyzed included cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein Barr virus (EBV), and BK virus. Secondary outcomes included rate of infection during the engraftment period, incidence of acute and chronic GVHD, overall survival at one year, and disease-free status at one year.

Data collection consisted of patient demographics such as age, gender, diagnosis, donor type, and CMV status prior to transplant. The conditioning therapy was identified to separate patients into two cohort groups, those that received ATG versus those that did not. The date of engraftment was also collected to determine in incidence of infection before and after the engraftment period. The engraftment date was defined as the first of three consecutive days the patient had an absolute neutrophil count greater than $0.5 \times 10^2$ cells/L [7]. The incidence of graft versus host disease was also collected. Acute GVHD was defined as GVHD occurring less than 100 days after transplant and chronic GVHD was greater than 100 days after transplant [8,9]. The grading of GVHD was based on the pathology report. Survival and disease free status at one year was also analyzed at three, six, nine and 12 month time intervals. All deaths were considered when overall survival (OS) was evaluated. Event-free survival (EFS) was defined as the time from day 0 until progression of disease, relapse, or death from any cause. Deaths occurring after disease progression were categorized as relapse regardless of the remote cause of death [10-12].

### Patient eligibility

Eligible patients were 18 to 60 years old with morphologically confirmed myeloid malignancy including acute myeloid leukemias, chronic myeloid leukemia, acute myeloid leukemias in second or subsequent remissions , advanced CML patients including CML in blast crisis, as well as patients of any age with intermediate or high risk MDS, and high risk myeloproliferative disorders. Exclusion criteria were hepatic dysfunction that was defined by a serum transaminase level >2.5 times the normal value, serum creatinine level >2 mg/dL or creatinine clearance <60 mL/min, major organ dysfunction that might increase the risk of the transplantation procedure, or severe psychological or medical illness. All patients and donors gave written informed consent as required by the institutional review board.

### Preparative regimen

All patients received the preparative regimen intravenous fludarabine 30 mg/m$^2$/day from day -7 until day -3 and intravenous busulfan 0.8 mg/kg every 6 hours for 8 doses from day -4 through day -3. All chemotherapy was based on actual body weight or adjusted ideal body weight if the actual body weight was ≥ 25% above the ideal body weight.

### GVHD prophylaxis

Tacrolimus in combination with methotrexate were used for GVHD prophylaxis for all patients. Tacrolimus (0.03 mg/kg/day) was begun orally on day -1, targeting serum trough levels between 5-15 ng/ml for tacrolimus until day +90 with subsequent taper through day 150-180. Methotrexate 5 mg/m$^2$ was given intravenously on day +1, +3, +6 for all patients and +11 for patient receiving unrelated donor grafts. Patients with unrelated donor grafts also received oral mycophenolate mofetil at a dose of 15 mg/kg given twice daily, from day -2 until day -60 with subsequent taper. These patients also received rabbit ATG (Thymoglobulin) 2.5 mg/kg/day from day -4 until day -1.

### Supportive care

All patients were housed in private rooms with high-efficiency particulate air filtration systems. *Pneumocystis carinii* (*P. jiroveci*) prophylaxis was instituted at the beginning of the preparatory regimen with trimethoprim/sulfamethoxazole for 4 days and reinstituted on day -42 through discontinuation of immunosuppressive drugs. Patients received prophylactic oral acyclovir 400 mg three times daily if the patient tested positive for herpes simplex virus on admission. All patients received oral fluconazole 400 mg daily from day 1 until immunosuppression was discontinued. Broad-spectrum antibiotics were started when the patient developed febrile neutropenia. Patients were screened weekly for CMV reactivation in plasma using a quantitative PCR CMV test (Amplicor, Roche Molecular Diagnostics) through day 100 post-HCT [13]. The patients were also monitored with weekly aspergillus galactomannan assay to detect early fungal infections. Platelets were transfused to maintain a platelet count 10000/L, and red

blood cells were transfused to maintain a hematocrit value 30%. The patients were monitored for regimen related toxicities and sinusoidal obstructive syndrome according to previously published criteria [14].

### Statistical analysis

Appropriate descriptive statistical analysis was conducted to determine significant differences between outcomes for those treated with or without ATG. The Students t-test was utilized for continuous data and the Fisher's Exact Test was used for categorical data. P-values less than 0.05 were considered statistically significant. For analyzing OS and EFS, the Kaplan-Meier method was used to estimate probabilities and the two-tailed log-rank test for comparing survival curves. Both SAS and R software were used for all statistical analyses.

## Results

A total of 65 patients were identified during the ten year study period. Of those, 63 patients were eligible for analysis (Figure 1). One patient was ineligible due to inappropriate diagnostic coding and one patient died within thirty days of transplant. Thirty one patients were treated with ATG and 32 did not receive ATG as a part of their conditioning therapy.

The baseline demographics were similar between study groups with regard to age, gender, disease type, and CMV status prior to transplant (Table 1). However, there was a statistically significant difference in donor type ($p<0.001$). All patients who received a matched related donor (MRD) transplant did not receive ATG. Matched unrelated donor (MUD) transplant or mismatched related donor (mMRD) transplant recipients were administered ATG during their conditioning therapy based on the treatment protocol.

The overall incidence of infection in the non-ATG group was 56.3% compared to 80.6% in the ATG group ($p=0.11$) (Figure 2). The number of patients with multiple positive cultures, including bacterial, viral, and fungal, as well as one positive culture were analyzed. Seven of 31 patients in the ATG group and eight of 32 patients in the non-ATG group that had positive bacterial cultures alone ($p=0.99$). Fungal infection alone was not identified in either cohort. A statistically significant increase in viral infections alone, primarily CMV, occurred in the ATG group. Five of 31 patients developed a viral infection alone ($p=0.024$) (Figure 3). Three of the five patients with only one viral infection had a positive CMV PCR, one patient developed BK viruria, and one patient developed Epstein Barr Virus (EBV).

Patients who developed multiple infections are depicted in Figure 4. A significant number of multiple infection types were identified in patients treated with ATG versus those in the non-ATG group, 45.3% and 18.8% respectively ($p=0.032$). Some of the bacterial organisms identified included Staphylococcus, Streptococcus, Enterococcus, Klebsiella, Stenotrophomonas, and Pseudomonas species. The fungal organisms identified included Candida, Apergillus, Mycobacterium, Saccharomyces, and Nocardia. The majority of the multiple infections recognized were viral and bacterial infections, 9.4% and 32.3% in the non-ATG and ATG groups respectively ($p=0.03$). In the ATG group, no patients developed fungal and bacterial infections. In the non-ATG group, 6.3% of patients developed this combination of infections ($p=0.49$). Only those patients in the ATG group had positive viral and fungal cultures, 6.5% ($p=0.24$). In the non-ATG group, 3.1% of patients developed viral, fungal, and bacterial infections and 6.5% in the ATG group ($p=0.61$). All of the multiple infections in the ATG group included a type of viral infection. Of the 32 patients in the non-ATG cohort, 14 were CMV positive prior to transplant and 18% of them developed a positive viral infection post-transplant. In the ATG group, 17 of 31 patients were CMV positive at transplant and 59% of them developed CMV infection within one year of transplant, which was statistically significant ($p=0.03$).

Infection occurring during the engraftment period was not statistically different between study groups. There were only five patients in the ATG group and two patients in the non-ATG group who developed a bacterial infection alone ($p=0.26$). No fungal or viral infections alone were identified in either group. There were 3 patients in the non-ATG group who developed multiple infections during the engraftment period and only 1 patient in the ATG cohort ($p=0.61$). Acute and chronic graft versus host disease occurred in both the ATG

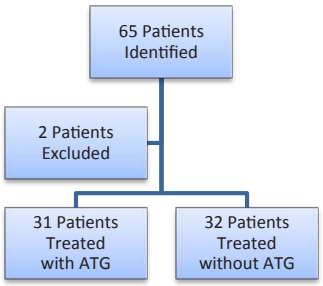


**Figure 1:** Identification of eligible subjects.

| Patients | ATG (n=31) | No ATG (n=32) | *p-value* |
|---|---|---|---|
| Mean Age, years (+/- SD) | 58.9 ± 10.0 | 61.6 ± 5.5 | 0.19 |
| Male, n (%) | 21 (67.7) | 21 (65.6) | 0.99 |
| Disease Type | | | |
| AML, n (%) | 22 (71) | 17 (53.1) | 0.2 |
| MDS, n (%) | 4 (12.9) | 9 (28.1) | 0.21 |
| CML, n (%) | 0 | 2 (6.2) | 0.49 |
| NHL, n (%) | 2 (6.5) | 1 (3.1) | 0.61 |
| Multiple Myeloma, n (%) | 1 (3.2) | 1 (3.1) | 0.99 |
| APL, n (%) | 1 (3.2) | 0 | 0.49 |
| ALL, n (%) | 1 (3.2) | 0 | 0.49 |
| CLL, n (%) | 0 | 1 (3.1) | 0.99 |
| Myelofibrosis, n (%) | 0 | 1 (3.1) | 0.99 |
| Donor Type | | | |
| MRD, n (%) | 0 | 32 (100) | <0.001 |
| MUD, n (%) | 29 (93.5) | 0 | |
| mMRD, n (%) | 2 (6.7) | 0 | |
| CMV Status | | | |
| Patient + Donor +, n (%) | 7 | 11 | 0.17 |
| Patient – Donor +, n (%) | 10 | 4 | |
| Patient – Donor -, n (%) | 7 | 12 | |
| Patient + Donor -, n (%) | 7 | 5 | |

**Table 1:** Baseline demographics.

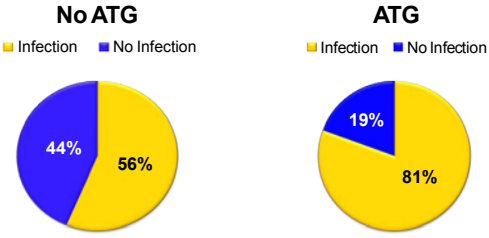


**Figure 2:** Overall Incidence of Infection.

and non-ATG cohorts without a statistically significant difference in incidence (Table 2). The majority of patients developed either grade one or grade two GVHD.

The Kaplin-Meier curves in Figure 5 depict the proportion of patients surviving and the proportion of patients who were disease free after transplant. At one year, survival for the ATG group was 46%, and 53% for the non-ATG group (p=0.46). The percentage of patients with relapse was 32% in the ATG group and 33% in the non-ATG group (p=0.98).

## Discussion and Conclusion

This study attempted to point out the incidence of infectious complications associated with the use of rabbit antithymocyte globulin as a part of the RIC therapy in patients undergoing allogeneic stem cell transplants. The incidence of GVHD was also analyzed to determine if there is a role for decreased immunosuppression in these patients based on the rate of infection. Only one study to date has investigated the incidence of infection in reduced intensity conditioning allogeneic transplant recipients. However, the purpose of the study conducted by Mohty, et al. was to define the incidence and potential risk factors of early infectious complications within the first six months following RIC allo-SCT from identical siblings. Our study followed patients one year from transplant with extended follow up. We did not limit to HLA-identical sibling allogeneic transplants. Strength of our study is that we had similar number of patient receiving transplants from sibling as well as unrelated donors. Our sibling transplants did not receive ATG and only recipients of unrelated donor grafts and mismatched donor grafts received ATG.

Overall, the baseline characteristics were similar between study groups with one exception, the patients treated with ATG were recipients of mismatched related donor transplants or matched unrelated transplants. The results of this study show a correlation between the use of ATG and the increased risk of infection. Overall, there was an increased rate of infection in the cohort receiving ATG.

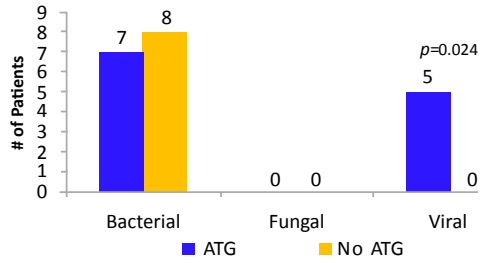


**Figure 3:** Patients with single infection episode.

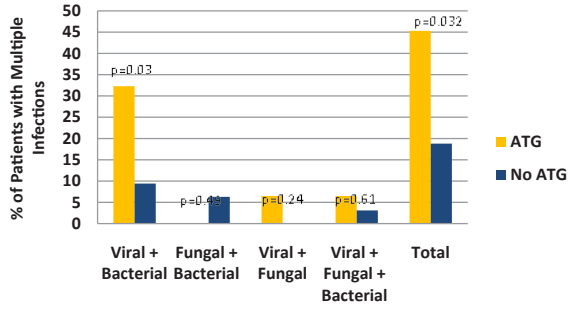


**Figure 4:** Patients with multiple infections.

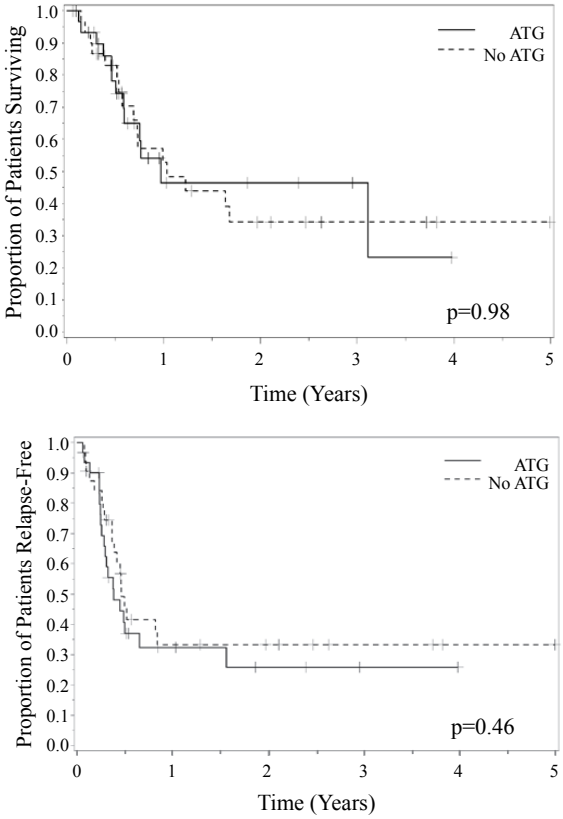


**Figure 5:** Disease-Free Status and Survival Outcomes.

| Secondary Outcomes | ATG (n=31) | No ATG (n=32) | *p*=value |
|---|---|---|---|
| **Acute GVHD, n (%)** | 6 (19.4) | 7 (21.9) | 0.99 |
| Grade 1 | 2 | 5 | 0.43 |
| Grade 2 | 2 | 0 | 0.24 |
| Grade 3 | 2 | 1 | 0.61 |
| Grade 4 | 0 | 1 | 0.99 |
| **Chronic GVHD, n (%)** | 5 (16.1) | 6 (18.8) | 0.99 |
| Grade 1 | 3 | 4 | 0.99 |
| Grade 2 | 2 | 1 | 0.61 |
| Grade 3 | 0 | 1 | 0.99 |
| Grade 4 | 0 | 0 | 1 |

**Table 2:** Graft Versus Host Disease (GVHD).

Even though it was not a statistically significant difference the clinical significance may be important. In particular, the incidence of multiple infections as well as viral infections alone was significantly increased in the ATG group. Interestingly, the incidence of GVHD did not significantly differ between the two study populations. This result raises the question regarding the use of ATG producing higher risk of infection without additional GVHD prevention.

This study was not without limitations. This was a single-center retrospective cohort study. A small sample size was included. However, the study population encompassed all RIC allo-SCT patients treated at the institution since January 2001. Due to the fact that this was a retrospective chart review analysis, it has its own limitations regarding accuracy of documentation for the data outcomes. It is difficult to consider that the ATG is the only factor involved in the incidence of infection in the ATG cohort due to additional use of mycophenolate mofetil. But still there may be some correlation since the patients

who developed infections did not have significant neutropenia or myelosuppression related to use of mycophenolate mofetil.

The other interesting aspect of the study is that viral infections and particularly polymicrobial infections were increased in the patient who received ATG. Fungal infections, on the contrary, were not dramatically increased. This may suggest that ATG leads to selective immunosuppression of subset of T lymphocytes involved in viral immunity. Impact of this excess immunosuppression on incidence of GVHD and relapse are other important questions which need to be answered in future studies.

The results of this study demonstrate the potential increased incidence of infection in those patients treated with ATG in the setting of RIC allo-SCT. With the increase of infection rates, it is reasonable to consider decreasing the dose of ATG administered, decreasing the amount of immunosuppression utilized, or increasing the amount of monitoring that is conducted in this population. Due to the lack of data, more studies need to be performed to determine the appropriate action required to limit the potential harm associated with complicated infections related to the use of a lympho depleting agent such as anti-thymocyte globulin [15].

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