

# De-escalation empirical antibiotic therapy improved survival for patients with severe aplastic anemia treated with antithymocyte globulin

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## Abstract

We aimed to investigate the efficacy and safety of de-escalation empirical therapy for controlling infection in patients with severe aplastic anaemia (SAA) treated with antithymocyte globulin (ATG). Eighty-seven ATG-treated SAA patients who had microbiological culture-confirmed infections from 2006 to 2015 in our center were retrospectively analyzed. The efficacy of de-escalation and non-de-escalation therapy was compared. Among all 87 patients, 63 patients were treated with de-escalation therapy and 24 patients with non-de-escalation therapy. More patients showed response to anti-infection treatment in de-escalation group than in non-de-escalation group both on day 7 (60.32% vs. 25.00%,  $P=0.003$ ) and on day 30 (79.37% vs. 58.33%,  $P=0.047$ ) since the initial antimicrobial therapy. On day 30, more patients had increased absolute neutrophil count in de-escalation group compared with non-de-escalation group (76.19% vs. 45.83%,  $P=0.007$ ), and de-escalation group had lower mortality rate (17.46% vs. 37.50%,  $P=0.047$ ) and better survival outcome ( $P=0.023$ ) on day 90. Twenty-three patients in de-escalation group and 5 patients in non-escalation group received granulocyte transfusions. Granulocyte transfusions helped to control infections in both de-escalation group ( $P=0.027$ ) and non-de-escalation group ( $P=0.042$ ) on day 7, but did not improve survival on day 90. We concluded that de-escalation antibiotics improved survival in SAA patients after ATG treatment. Early administration of broad-spectrum antibiotics pending microbiological cultures combined with a commitment to change to narrow-spectrum antibiotics should be recommended for controlling infections in SAA patients treated with ATG. Granulocyte transfusions might be an adjunctive therapy in controlling infections.

**Abbreviations:** AA = Aplastic anemia, ANC = Absolute neutrophil count, ATG = Antithymocyte globulin, CR = Complete response, CsA = Cyclosporine A, G-CSF = Granulocyte colony stimulating factor, IST = Immunosuppressive therapy, PR = Partial response, SAA = Severe aplastic anemia.

**Keywords:** anti-bacterial agents, antithymocyte globulin, aplastic anemia, granulocytes

## 1. Introduction

Aplastic anemia (AA) is a bone marrow failure syndrome, featuring pancytopenia, characterized by the reduction in hematopoietic stem and progenitor cells. Without appropriate treatment, the prognosis of severe AA (SAA) is very poor.<sup>[1–3]</sup>

Editor: Ahmet Emre Eskazan.

RF and TC contributed equally to this work.

Funding/support: This work was supported by the National Natural Science Foundation of China (Grant nos. 81570106, 81570111, 81600093, 81600088, 81400085), the Tianjin Municipal Natural Science Foundation (Grant nos. 14JCYBJC25400, 15JCYBJC24300), and Tianjin Health and Family Planning Commission (Grant nos. 15KG150).

The authors have no conflict of interest.

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Medicine (2017) 96:6(e5905)

Received: 25 September 2016 / Received in final form: 13 December 2016 /

Accepted: 27 December 2016

<http://dx.doi.org/10.1097/MD.0000000000005905>

Although the optimum treatment for SAA is hematopoietic stem cell transplantation from a human leukocyte antigen-identical sibling donor, lacking a matched donor restricts its application.<sup>[4–6]</sup> Alternatively, combined immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine A (CsA) is a standard first-line treatment for SAA.<sup>[7–10]</sup> However, neutropenia caused by SAA and the immunosuppressive effect of ATG could increase the risk of infections. So, patients are prone to infections both during and after treatment with ATG, and bacterial infections or invasive fungal diseases remain a major cause of morbidity and mortality in SAA patients.<sup>[11]</sup>

The severe immunodeficiency of ATG-treated SAA patients and the prevalence of multidrug-resistant pathogens have put many SAA patients at risk for poor survival consequences unless the effective therapy with broad-spectrum regimens covering the most likely pathogens is given as the initial antimicrobial treatment. De-escalation is a therapy starting with initial broad-spectrum antimicrobial agents to achieve clinical efficacy before availability of microbiological cultures, followed by narrow-spectrum agents to limit antimicrobial exposure and development of resistant organisms as soon as the causative pathogens are recognized. Contrary to de-escalation therapy, nonde-escalation therapy refers to a conventional empiric initial therapy without broad-spectrum antimicrobials. Antibiotic de-escalation has been advocated to appear safer and more successful than nonde-escalation therapy in controlling severe infections as well as reducing hospitalization costs and adverse effects from anti-

infection therapy.<sup>[12]</sup> Actually, de-escalation strategy has been supported to deal with infections in critically ill patients by many studies.<sup>[13–16]</sup> However, few studies have focused on the application of de-escalation therapy in patients with SAA, especially in SAA treated with ATG. The aim of this retrospective study was to compare the efficacy and safety of de-escalation and nonde-escalation empirical therapy for infection in patients with SAA treated with ATG.

## 2. Methods

### 2.1. Patients

Eighty-seven patients diagnosed as SAA from 2006 to 2015 in Tianjin Medical University General Hospital were enrolled in this retrospective study. All patients had received bone marrow cytogenetic examinations. SAA was defined as follows: pancytopenia with at least 2 of the following abnormalities: a neutrophil count less than  $0.5 \times 10^9/L$ , a platelet count less than  $20 \times 10^9/L$ , and a reticulocyte count less than  $20 \times 10^9/L$  with hypocellular bone marrow (less than 30% cellularity).<sup>[17]</sup> All patients received IST with rabbit anti-human ATG. After treatment with ATG, these patients had fevers and microbiological culture-confirmed infections. Patients were excluded if the results of microbiological cultures were negative. The research was in compliance of the declaration of Helsinki and the protocol was approved by the ethical committee of Tianjin Medical University General Hospital. Consent for research and publication was obtained from participants and/or their immediate family if certain participants had passed away.

### 2.2. De-escalation or nonde-escalation of antimicrobial therapy

Patients who developed a temperature greater than 38°C were treated empirically with intravenous antibiotics combined with oral anti-fungal therapy (Fluconazole) after blood cultures. Antibiotic de-escalation refers to a change of antimicrobial therapy from the broad-spectrum antimicrobials to the narrower-spectrum ones by discontinuing the antibiotics or reducing the number of antibiotics or replacing the initial antimicrobial by one with limited-spectrum coverage as soon as the susceptibility of the pathogens were obtained from the cultures (2–4 days after initial antimicrobial therapy). We defined the broad-spectrum antimicrobials as the combination of carbapenems (Imipenem or Meropenem) and antibiotics against gram-positive bacteria (Vancomycin, Teicoplanin, or Linezolid) followed by empiric intravenous anti-fungal therapy within 72 hours if fever persisted. The de-escalation regimens were adjusted according to the results of microbiological cultures. In de-escalation group, the change of regimens include discontinuation of all antimicrobials, suspension of carbapenems or anti-gram-positive bacteria or anti-fungal therapy, and replacement of carbapenems with penicillins or cephalosporins. Patients in nonde-escalation group were started with penicillins or cephalosporins. Two to 4 days later, with the availability of the microbiological cultures, the regimens were changed maintenance of initial therapy, addition of antibiotics against gram-positive organisms or anti-fungal therapy, and replacement of penicillins or cephalosporins with carbapenems.

Responses to anti-infection therapy were evaluated with microbiological (elimination of bacteria), radiographic (decrease in infiltrates or nodule size), and clinical criteria<sup>[18]</sup> on day 7 and day 30 since the initial anti-infection therapy. The clinical criteria included defervescence or body temperature decrease at least

1.5°C, hemodynamic stabilization, and improvement in symptoms such as dyspnea. A complete response (CR) was defined as improvement in all 3 criteria (microbiological, radiographic, and clinical); a partial response (PR) was defined as improvement in 1 or 2 criteria.<sup>[19,20]</sup> Response to antimicrobial therapy was defined as CR or PR.

### 2.3. Granulocyte transfusions

Granulocyte transfusions were received by patients who had the following conditions: proven or probable invasive fungal diseases or bacterial infections associated with high mortality in the experience of our center, absolute neutrophil count (ANC) was less than  $0.2 \times 10^9/L$  and expected to last for at least 10 days, and no response to appropriate antibiotic or antifungal therapy for 48 hours. All granulocyte concentrates were ABO compatible to recipients and were collected with blood cell separator (Thermo Scientific Sorvall® RC3BP™ Plus Low-speed Centrifuge) from healthy donors in Tianjin Blood Center.

### 2.4. Statistical analysis

Differences of quantitative parameters between groups were assessed using the *t* test (for data that were normally distributed) or nonparametric test (for data that were not normally distributed). Categorical variables are presented as frequencies. The mortality rate was calculated with the Kaplan–Meier method and the curves were compared using the Log-Rank test. *P* values lower than 0.05 were considered significant. The software SPSS, version 19.0 for Windows (IBM, Chicago, IL), was used for statistical analysis.

## 3. Results

### 3.1. Comparison of the baseline characteristics between patients in de-escalation and nonde-escalation group

Among the 87 patients, 52 were male and 35 were female. All patients were diagnosed as SAA and had neutropenia. The average age at onset of the disease was  $29.63 \pm 16.24$  years. Among the 87 patients, all patients received therapy of granulocyte colony-stimulating factor (G-CSF), 67 patients received therapy of CsA, and 21 patients received therapy of intravenous immunoglobulin. After fever occurred, all patients were treated with antibiotics. Among all these patients, 63 patients were treated with de-escalation therapy and 24 patients were treated with nonde-escalation therapy. Twenty-three of 63 patients in de-escalation group and 5 of 24 patients in nonde-escalation group also received granulocyte transfusions. No significant differences of the baseline clinical characteristics were found between 2 groups (Table 1).

### 3.2. Characteristics of the results of microbiological cultures

All 87 patients' infections are confirmed by microbial cultures from specific infection sites. Nine of 63 patients (14.29%) in de-escalation group and 3 of 24 (12.50%) in nonde-escalation group had more than 1 site of infection ( $P=0.829$ ). No significant differences of pathogen origins or types were found between 2 groups. In de-escalation group, 71.43% patients were infected with Gram-negative bacteria, 34.92% with Gram-positive bacteria, and 7.94% with fungi. The data were similar in nonde-escalation group (70.83%, 29.17%, and 12.50%,

**Table 1**

**Comparison of the baseline characteristics between de-escalation and nonde-escalation group.**

Characteristics	De-escalation group (N = 63)	Nonde-escalation group (N = 24)	P
Age, y	30.79 ± 15.86	26.58 ± 17.18	0.282
Male/female	37/26	15/9	0.749
Temperature, °C	38.63 ± 0.71	38.46 ± 0.65	0.322
HB, g/L	83 (34, 164)	80 (65, 154)	0.831
WBC, 10 <sup>9</sup> /L	0.50 (0.00, 4.40)	0.70 (0.01, 3.50)	0.588
ANC, 10 <sup>9</sup> /L	0.05 (0.00, 0.48)	0.09 (0.00, 0.50)	0.393
PLT, 10 <sup>9</sup> /L	23 (3, 210)	36 (3, 145)	0.134
ALT, U/L	19 (5, 237)	14 (5, 205)	0.435
Cr, μmol/L	56 (28, 153)	54 (6, 112)	0.867
CsA treatment (%)	49 (77.78%)	18 (75.00%)	0.783
IVIg treatment (%)	18 (28.57%)	3 (12.50%)	0.117
Granulocyte transfusion (%)	23 (36.51%)	5 (20.84%)	0.162

ALT = alanine aminotransferase, ANC = absolute neutrophil count, Cr = creatinine, HB = hemoglobin, IVIG = Intravenous Immune Globulin, PLT = platelet, WBC = white blood cell.

respectively) without statistical significance. Nineteen patients had multimicrobial infections (14 in de-escalation group and 5 in nonde-escalation group), involving more than 1 bacterial strain, more than 1 fungus, or combined infections of bacteria and fungi. The characteristics of the results of microbiological cultures are summarized in Table 2.

### 3.3. Comparison of the efficacy of de-escalation and nonde-escalation therapy

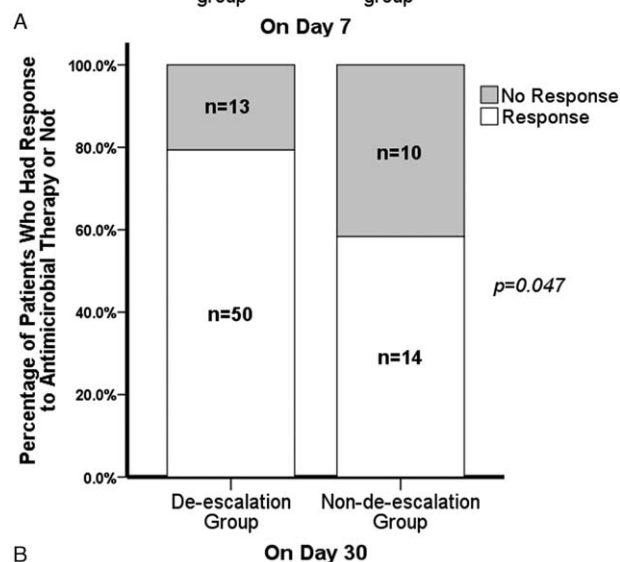
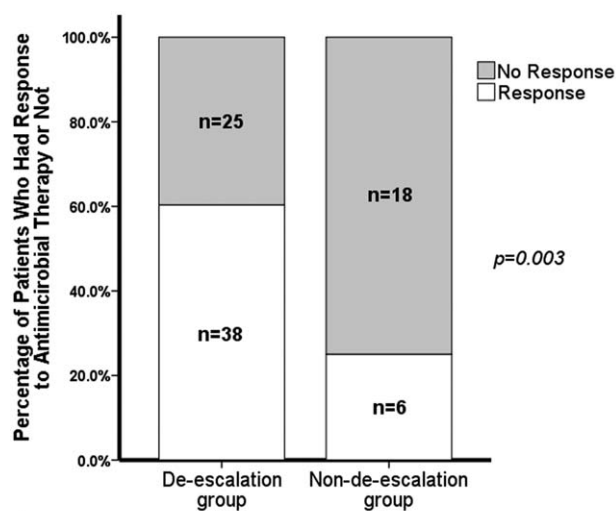
On day 7, 60.32% patients in de-escalation group, while 25.00% patients in nonde-escalation group showed response (CR + PR) ( $P = 0.003$ ) (Fig. 1A).

The treatment regimen was adjusted according the results of microbiological cultures. On the basis of the results of microbiological cultures, the carbapenems were changed to penicillins or cephalosporins for patients in de-escalation group. For patients in nonde-escalation group, penicillins or cephalosporins were changed to carbapenems on the basis of the results of microbiological cultures. After adjustment of drugs, 24 of 63 patients (38.09%) in de-escalation group changed their carbapenems to be penicillins or cephalosporins, while 18 of 24 patients (75.00%) in nonde-escalation group received carbapenems.

**Table 2**

**Comparison of the characteristics of microbiological cultures between de-escalation and nonde-escalation group.**

Characteristics	De-escalation group (N = 63)	Nonde-escalation group (N = 24)	P
Pathogens origins			
Blood	32 (50.79%)	11 (45.83%)	0.679
Sputum	25 (39.68%)	8 (33.33%)	0.585
Stool	6 (9.52%)	2 (8.33%)	0.864
Skin	2 (3.17%)	3 (12.50%)	0.095
Mouth	4 (6.35%)	1 (4.17%)	0.696
Urine	2 (3.17%)	1 (4.17%)	0.821
Nose	1 (1.59%)	1 (4.17%)	0.473
Pathogens types			
Gram-negative bacteria	45 (71.43%)	17 (70.83%)	0.956
Gram-positive bacteria	22 (34.92%)	7 (29.17%)	0.611
Fungi	5 (7.94%)	3 (12.50%)	0.510



**Figure 1.** Comparison of the efficacy of de-escalation and nonde-escalation therapy. (A) Comparison of the efficacy of de-escalation and nonde-escalation therapy on day 7. (B) Comparison of the efficacy of de-escalation and nonde-escalation therapy on day 30. Response to antimicrobial therapy was defined as complete response or partial response, evaluated by a global assessment of microbiological, clinical, and radiographic criteria.

On day 30, 79.37% patients in de-escalation group, while 58.33% patients in nonde-escalation group showed response (CR + PR) ( $P = 0.047$ ) (Fig. 1B).

No significant difference of the average defervescence time of patients who had response to therapy was found between 2 groups (days  $4.16 \pm 3.79$  vs  $4.07 \pm 3.97$ ,  $P = 0.939$ ). The patients who did not have response to therapy had persistent fever.

### 3.4. Comparison of the laboratory characteristics after treatment between patients in de-escalation and nonde-escalation group

As summarized in Table 3, after treatment, no significant difference of the levels of hemoglobin, white blood cell, ANC, and platelet was found between 2 groups. However, there were more patients whose ANC increased on day 30 in de-escalation group than that in nonde-escalation (76.19% vs 45.83%,  $P = 0.007$ ). After antimicrobial treatment, no significant difference of

**Table 3**

**Comparison of the characteristics after treatment between de-escalation and nonde-escalation group.**

Characteristics	De-escalation group (N=63)	Nonde-escalation group (N=24)	P
HB, g/L	80.5 (48, 152)	83 (54, 152)	0.690
WBC, 10 <sup>9</sup> /L	0.20 (0.00, 0.75)	0.50 (0.00, 11.00)	0.223
ANC, 10 <sup>9</sup> /L	0.00 (0.00, 6.53)	0.01 (0.00, 9.68)	0.289
ANC increased on day 30	48 (76.19%)	11 (45.83%)	0.007
PLT, 10 <sup>9</sup> /L	28 (3, 201)	36 (11, 139)	0.264
ALT, U/L	22 (7, 205)	14 (2, 240)	0.064
Cr, μmol/L	46 (20, 149)	45 (34, 98)	0.789

ALT=alanine aminotransferase, ANC=absolute neutrophil count, Cr=creatinine, HB=hemoglobin, PLT=platelet, WBC=white blood cell.

the liver function and the renal function was found between 2 groups.

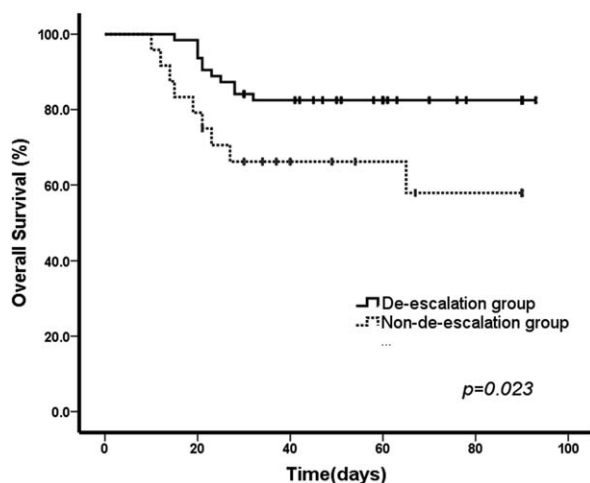
### 3.5. Comparison of the survival rate on day 90 between patients in de-escalation and nonde-escalation group

On day 90, 20 patients died including 11 patients (17.46%) in de-escalation group and 9 (37.50%) in nonde-escalation group. Compared with the patients in nonde-escalation group, patients in de-escalation group had lower mortality rate ( $P=0.047$ ). Kaplan–Meier analysis showed that patients in de-escalation group had better survival outcome than patients in nonde-escalation group ( $P=0.023$ ) (Fig. 2).

### 3.6. Influence of granulocyte transfusions on the efficacy of de-escalation therapy and nonde-escalation therapy

Previous studies reported that granulocyte transfusions could be an adjunctive therapy for treating severe infections of patients with SAA,<sup>[19,20]</sup> so the influences of granulocyte transfusions on de-escalation and nonde-escalation therapy were investigated.

In 28 patients who received granulocyte transfusions, 23 were in the de-escalation group and 5 were in the nonde-escalation group. As summarized in Table 4, no significant difference of the baseline clinical characteristics was found between patients with and without granulocyte transfusions both in de-escalation and



**Figure 2.** Comparison of the outcomes between patients in de-escalation and nonde-escalation group.

nonde-escalation group. After antimicrobial treatment, no significant difference of the blood cell counts, liver function, and the renal function was found between patients with and without granulocyte transfusions in de-escalation and nonde-escalation groups.

In de-escalation group, more patients with granulocyte transfusions showed response (CR+PR) than patients without granulocyte transfusions (78.26% vs 50.00%,  $P=0.027$ ) on day 7, while no significant difference of the response on day 30 was found between patients with and without granulocyte transfusions (91.30% vs 72.50%,  $P=0.076$ ). In nonde-escalation group, more patients with granulocyte transfusions showed response (CR+PR) than patients without granulocyte transfusions on day 7 (60.00% vs 15.79%,  $P=0.042$ ) and on day 30 (100.00% vs 47.37%,  $P=0.034$ ) (Fig. 3).

No difference of the mortality between patients with and without granulocyte transfusions was found either in the de-escalation group (8.70% vs 22.50%,  $P=0.165$ ) or in the nonde-escalation group (0.00% vs 5.26%,  $P=0.600$ ).

### 3.7. Comparison of the mortality in patients receiving granulocyte transfusions between de-escalation and nonde-escalation group

Among 23 patients who received granulocyte transfusions in de-escalation group, 2 patients died (8.70%) within 90 days of follow-up, while no one died in 5 patients who received granulocyte transfusions in nonde-escalation group (0.00%). There was no difference of the mortality rate in patients receiving granulocyte transfusions between de-escalation and nonde-escalation group ( $P=0.494$ ).

## 4. Discussion

ATG is a powerful immunosuppressive agent active not only against T lymphocytes but also against B lymphocytes, natural killer cells, and monocytes.<sup>[21]</sup> Due to the highly immunosuppressive nature of ATG, it is important to give antibiotics immediately to all febrile SAA patients treated with ATG. However, identification of infections is not very easy for these patients. On one hand, not all fevers developing early after ATG treatment are of septic origin; on the other hand, some patients with infections do not present positive microbiological cultures.<sup>[22]</sup> To guarantee that all febrile patients in the current study had infections, only patients with positive microbiological cultures were enrolled.

Antimicrobials are a key component of a comprehensive management strategy against severe infections, which are one of the worldwide leading causes of deaths for patients with severe immunodeficiency. Therefore, choosing an appropriate optimal initial coverage of the pathogens pending the results of cultures is a major factor associated with survival.<sup>[11,23,24]</sup> De-escalation strategy consists of switching from a broad-spectrum empiric antimicrobial therapy to a narrower-spectrum after a systematic reassessment after treatment initiation.<sup>[25]</sup> However, there are very few specific reports about the application of de-escalation therapy in patients with SAA. In the current study, de-escalation therapy was more effective than nonde-escalation on both day 7 and day 30. Besides, the survival rate on day 90 in de-escalation group was also higher than that in nonde-escalation group. It should be noticed that after acquiring the results of microbiological culture, only 38.09% patients in de-escalation group needed to change the carbapenems to be penicillins or cephalosporins.

**Table 4**

**Comparison of the baseline characteristics between patients with and without granulocyte transfusions in de-escalation and nonde-escalation therapy group.**

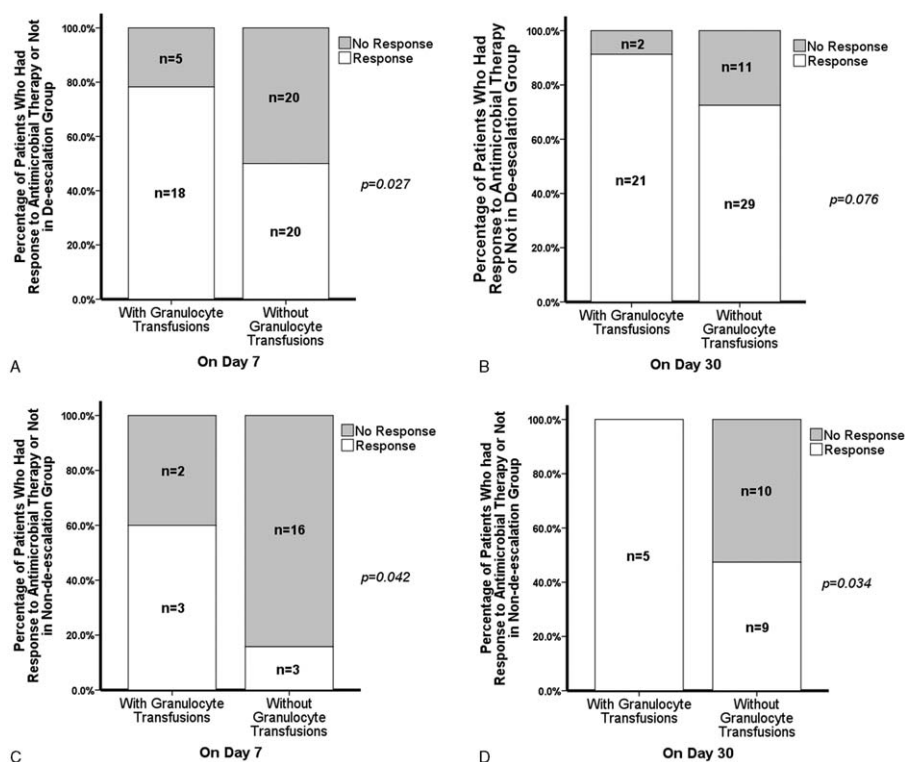
Characteristics	De-escalation therapy			Nonde-escalation therapy		
	With granulocyte transfusions (N=23)	Without granulocyte transfusions (N=40)	P	With granulocyte transfusions (N=5)	Without granulocyte transfusions (N=19)	P
Age, y	31.52 ± 17.05	30.38 ± 15.34	0.785	26.20 ± 15.45	26.68 ± 18.00	0.957
Male/female	15/8	22/18	0.428	3/2	12/7	0.897
Temperature, °C	38.78 ± 0.76	38.54 ± 0.67	0.207	38.52 ± 0.73	38.43 ± 0.65	0.830
Baseline HB, g/L	83 (34, 164)	83 (56, 154)	0.563	74 (65, 134)	83 (66, 154)	0.722
Baseline WBC, 10 <sup>9</sup> /L	0.52 (0.06, 4.40)	0.50 (0.00, 4.40)	0.597	0.55 (0.04, 2.00)	0.70 (0.01, 3.50)	0.413
Baseline ANC, 10 <sup>9</sup> /L	0.04 (0.00, 0.48)	0.05 (0.00, 0.48)	0.994	0.20 (0.04, 0.45)	0.01 (0.00, 0.50)	0.499
Baseline PLT, 10 <sup>9</sup> /L	22 (3, 100)	29 (3, 210)	0.508	49 (24, 145)	36 (3, 121)	0.317
Baseline ALT, U/L	30 (8, 237)	16.5 (5, 121)	0.063	19 (5, 65)	14 (5, 205)	0.547
Baseline Cr, μmol/L	56 (30, 118)	56 (28, 153)	0.913	70 (44, 96)	51 (6, 112)	0.424

ALT=alanine aminotransferase, ANC=absolute neutrophil count, Cr=creatinine, HB=hemoglobin, PLT=platelet, WBC=white blood cell.

Thus, early administration of broad-spectrum antibiotics should be a strategy advocated for controlling infections in SAA patients treated with ATG.

Patients with SAA have primarily a decrease in the blood counts resulting in severe and prolonged neutropenia and increased susceptibility to bacterial or fungal infection. Previous studies have demonstrated that the morbidity of infection was correlated with the severity and duration of neutropenia.<sup>[26]</sup> All of our patients had neutropenia before the treatment of ATG. Interestingly, although no significant difference of the levels of

ANC was found between patients in de-escalation and nonde-escalation group after treatment, there were more patients whose ANC increased in de-escalation group than those in nonde-escalation. As the antibiotics could not increase the ANC, we thought 2 possible explanations should be considered. First, the infections were controlled more quickly in de-escalation group than in nonde-escalation group, which might be beneficial for ATG to give play to its therapeutic role. Second, penicillins and cephalosporins might be more prone to cause granulocytopenia than carbapenems.



**Figure 3.** Influence of granulocyte transfusions on the efficacy of antimicrobial therapy. (A) Comparison of the efficacy between patients with granulocyte transfusions and without granulocyte transfusions in de-escalation group on day 7. (B) Comparison of the efficacy between patients with granulocyte transfusions and without granulocyte transfusions in de-escalation group on day 30. (C) Comparison of the efficacy between patients with granulocyte transfusions and without granulocyte transfusions in nonde-escalation group on day 7. (D) Comparison of the efficacy between patients with granulocyte transfusions and without granulocyte transfusions in nonde-escalation group on day 30. Response to antimicrobial therapy was defined as complete response or partial response, evaluated by a global assessment of microbiological, clinical, and radiographic criteria.

Previous studies reported that granulocyte transfusions could be an adjunctive therapy for treating severe infections of patients with SAA.<sup>[19]</sup> Quillen et al<sup>[20]</sup> analyzed granulocyte transfusions in SAA patients with severe infections in National Institutes of Health in the past 11 years and found that granulocyte transfusions could help to increase the survival rate. Wang et al<sup>[19]</sup> retrospectively analyzed 56 patients and observed that granulocyte transfusions combining with G-CSF to treat severe infections in SAA patients had better responses. In the current study, we observed that granulocyte transfusions could improve the efficacy in de-escalation group at the early stage of infection. It is noteworthy that the levels of ANC in de-escalation group were not increased further by granulocyte transfusions. This should be explained that the life of granulocyte is very short and the granulocyte transfused into patients exerts its effect immediately and is consumed promptly.

This study has some limitations. First, it is a retrospective study and treatment regimens that might influence the evaluation of the patients' outcome were not controlled strictly. Second, patients who had infections but had no microbiological proof were not included in the study, so selection bias could not be excluded. Third, no data regarding infection relapse rates and the occurrence of drug-resistant bacteria were gathered to demonstrate the safety of the de-escalation strategy. Further prospective studies might be needed to validate the results of the current study further.

In conclusion, early administration of broad-spectrum antibiotics combined with a commitment to change to narrow-spectrum according to the result of microbiological culture is a strategy advocated for controlling infections in SAA patients treated with ATG. Granulocyte transfusions might be an adjunctive therapy at the early stage of infection.

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