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# Immunoglobulin prophylaxis prevents hospital admissions for fever in pediatric acute lymphoblastic leukemia: results of a multicenter randomized trial

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## Abstract

Infections lead to substantial morbidity during the treatment of acute lymphoblastic leukemia (ALL) in which the adaptive immune system is severely affected, leading to declining serum immunoglobulin levels. We performed a trial to investigate whether intravenous immunoglobulin (IVIG) prophylaxis in pediatric patients with ALL could prevent admissions for fever. This randomized controlled trial was a subtrial of the national Dutch multicenter ALL study. Patients aged 1-19 years with medium-risk ALL were randomized into two groups receiving either IVIG prophylaxis (0.7 g/kg IVIG given every 3 weeks, starting on day 22 after diagnosis) or well-defined standard of care (control group). Between October 2012 and March 2019, 91 (51%) patients were randomly assigned to IVIG prophylaxis and 86 (49%) to the control arm. In the IVIG prophylaxis group there were 206 admissions for fever *versus* 271 in the control group ( $P=0.011$ ). IVIG prophylaxis was not associated with bacteremia. However, there were significantly fewer admissions for fever with negative blood cultures in the IVIG prophylaxis group than in the control group (113 vs. 200,  $P<0.001$ ). The difference in number of admissions for fever was observed specifically during maintenance treatment (100 vs. 166,  $P<0.001$ ) resulting in fewer courses of antibiotic treatment (78 vs. 137,  $P<0.001$ ) and fewer cases of chemotherapy adaptation (72 vs. 134,  $P<0.001$ ). In conclusion, in pediatric patients with medium-risk ALL, IVIG prophylaxis was associated with significantly fewer admissions for fever with negative blood cultures during maintenance treatment, resulting in fewer courses of antibiotic treatment and fewer chemotherapy adaptations.

## Introduction

Infections are an important cause of mortality and morbidity in pediatric patients with acute lymphoblastic leukemia (ALL). In pediatric patients with hematologic malignancies, approximately 20% of deaths are related to treatment, with infection being responsible for more than half of

these deaths.<sup>1-3</sup> Alongside the mortality risk, there is substantial morbidity from fever, often leading to admissions to hospital. Moreover, infections may lead to interruption of leukemia treatment, and therefore potentially enhance the risk of relapses.<sup>4</sup>

During the treatment of ALL, the adaptive immune system is severely affected. This is manifested by persistently low

numbers of B cells, declining serum immunoglobulin (IgG) levels and low specific antibody levels.<sup>5,6</sup> Theoretically, the increased risk of infections could be partially overcome by raising the low IgG levels with supplementary intravenous immunoglobulins (IVIG).

In patients with primary immunodeficiency leading to agammaglobulinemia, prophylactic administration of IVIG has been shown to be effective in preventing infections.<sup>7</sup> In adults, it has been demonstrated that IVIG prophylaxis can reduce the number of infections in patients with lymphoproliferative diseases with hypogammaglobulinemia.<sup>8,9</sup> Currently, it is unknown whether prophylactic administration of IVIG could prevent infections during ALL treatment. Since it is an expensive treatment and its administration can lead to adverse events, the value of IVIG for infection prevention during ALL treatment needs to be established.

The trial reported here investigated the role of IVIG prophylaxis in children with newly diagnosed ALL, treated according to the DCOG ALL-11 protocol. It is the first multicenter, randomized trial investigating the effect of IVIG in patients with ALL on number of admissions for fever, blood culture results, adaptations in chemotherapy, and relapse risk.

## Methods

### Trial design

This multicenter, open-label, randomized trial was a sub-trial of the Dutch multicenter ALL study (DCOG ALL-11), described in detail in the trial register (trial registration number: EudraCT 2012-000067-25, NL3227 [clinicaltrial-register.nl]) and by Pieters *et al.*<sup>3</sup> In this IVIG subtrial, performed across six centers in the Netherlands (described in the *Online Supplementary Data*), patients were randomly assigned to IVIG prophylaxis or the control group. The trial was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their legal guardians.

### Endpoints

The primary goal was to evaluate the number of infectious episodes for which patients were admitted to hospital. As, in practice, this means an admission for fever, the primary endpoint was number of admissions for fever. Secondary endpoint, was number of therapeutic antibiotic courses, blood culture results, number of admissions to an Intensive Care Unit (ICU) because of fever, number of chemotherapy adaptations due to admission for fever, 5-year cumulative incidence of relapse, disease-free survival (with events defined as relapse, secondary malignancy or death in remission), and overall survival from the date of diagnosis.

### Patients

All patients, aged 1-19 years, in the medium-risk group of the DCOG ALL-11 trial were considered eligible for inclusion (for detailed inclusion and exclusion criteria see the *Online Supplementary Data*). Randomization was performed at the start of ALL treatment, before risk stratification in DCOG ALL-11 was done. Patients subsequently stratified according to standard- or high-risk ALL treatment then went off study.

### Procedures

Patients randomized to the IVIG prophylaxis group started IVIG prophylaxis on day 22 after diagnosis. Patients received 0.7 g/kg per infusion IVIG (Nanogam, Prothya Biosolutions), with a maximum of 50 g per infusion, every 3 weeks until week 104 of ALL treatment. Details regarding the criteria to start IVIG infusions are provided in the *Online Supplementary Data*. If an IVIG infusion had to be postponed for a period of more than 8 weeks since the preceding infusion, the patient was withdrawn from the study.

Patients in the control arm were allowed to receive IVIG treatment under strict criteria (see *Online Supplementary Data*).

Data were gathered in case report files, as described in detail in the *Online Supplementary Data*. Side effects were documented according to Common Toxicity Criteria for Adverse Events, version 4.03. Severe adverse events were defined in the DCOG ALL-11 study.

### Sample size calculation and statistical analysis

By performing Monte Carlo simulations with 10,000 replications, a sample size of 70 patients per arm was estimated to detect a reduction of admissions for fever, with a power of 80% and a one-sided test with  $\alpha=5\%$ . Details about the sample size calculation are reported in the *Online Supplementary Data*.

Analyses were performed according to the intention-to-treat principle and per-protocol principle (patients who followed the IVIG protocol for at least 1 year after diagnosis). The patients' characteristics were compared using a Pearson  $\chi^2$  test for categorical variables and a *t* test for continuous variables. Due to the presence of overdispersion, a negative binomial regression model was used to study the effect of IVIG prophylaxis on outcomes; age was included as a categorical variable in all models. The difference in duration of admission was compared using a Mann-Whitney U test. The cumulative incidence of relapse, disease-free survival and overall survival were estimated with the Kaplan-Meier methodology. A log-rank test was applied to compare differences between estimated survival curves. The total percentage of relapses was computed for each group. A two-sided *P* value  $<0.05$  was considered statistically significant. Statistical analyses were performed in SPSS version 26 and in the R software environment.<sup>10</sup> The MASS library was used to estimate the negative binomial regression model.

## Results

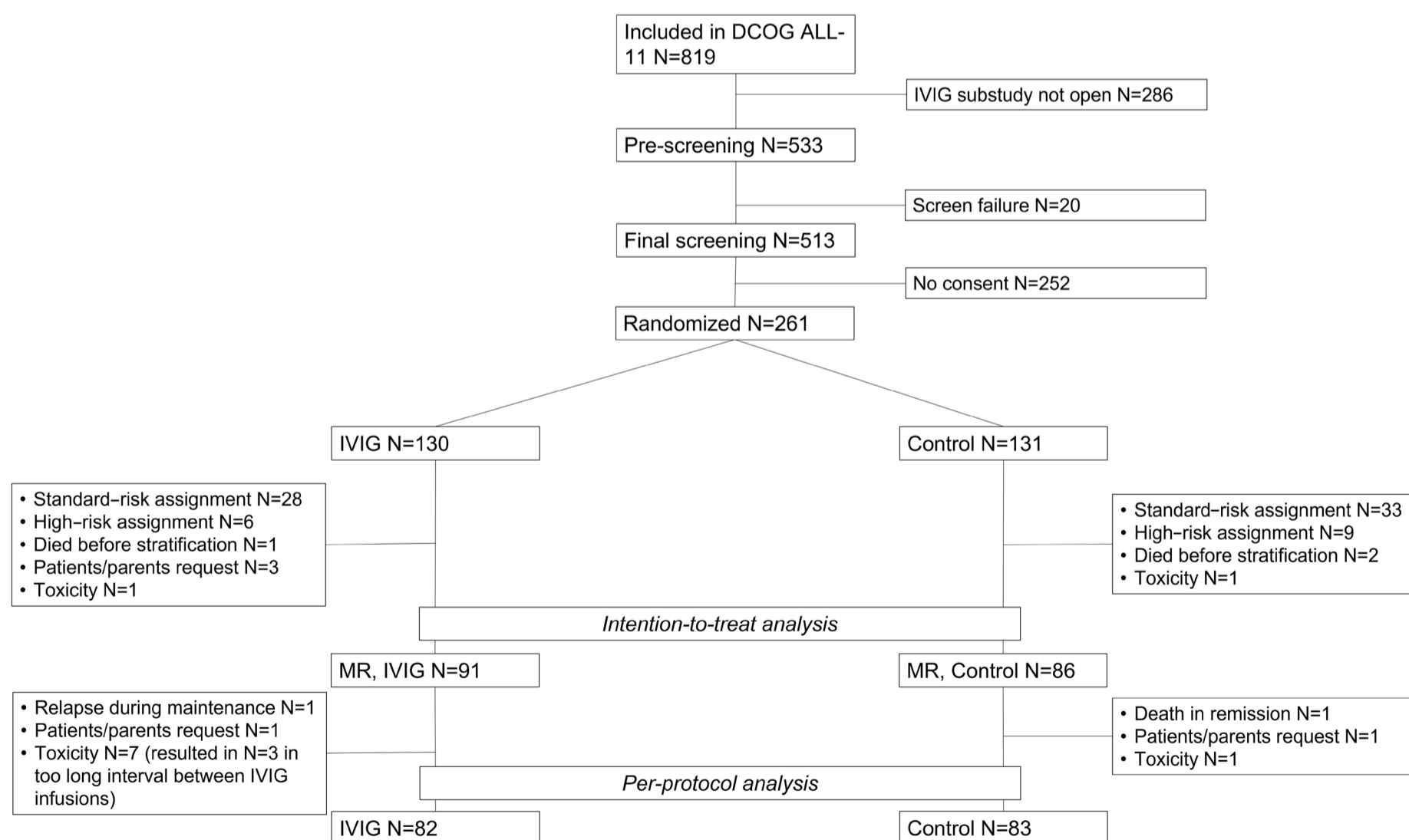
### Patients' characteristics

Patients were included from October 2012 until March 2019 in this subtrial of DCOG ALL-11. Of the 819 patients included in the DCOG ALL-11 trial, 513 were considered for randomization in this subtrial. Of these 513 patients, 252 did not consent to participation and so, ultimately, 261 patients were randomized (Figure 1). Of these randomized patients, 182 were stratified to the medium-risk group of DCOG ALL-11. Three patients in the intervention group withdrew consent after randomization, but before the actual start of IVIG prophylaxis, and two patients were not started on the IVIG trial due to toxicity during ALL induction; therefore, ultimately 177 patients (91 in the IVIG prophylaxis group and 86 in the control group) could be included in the intention-to-treat analyses. Of these 177 patients, 165 (82 in the IVIG prophylaxis group and 83 in the control group) adhered to the IVIG protocol for at least 1 year and were included in per-protocol analyses. Three patients in the IVIG prophylaxis group were withdrawn from the study because the interval between IVIG infusions was too long (Figure 1). There were no significant differences in baseline characteristics between the IVIG prophylaxis group and the control group (Table 1). Seven (4%) patients had IgG levels <4 g/L

before the start of the IVIG trial. Figure 2 shows IgG levels over time. In the control group, 69 (80%) of patients had IgG levels <4 g/L at some point during treatment and 15 (17%) patients received a total of 48 IVIG infusions. Forty-six (96%) of these infusions were during maintenance treatment. The study protocol defined under what conditions patients in the control group could receive IVIG (*Online Supplementary Data*). Unfortunately, however, for seven (47%) patients the reason for IVIG supplementation was not known, for six (40%) patients the indication was  $\geq 4$  admissions for fever, one (7%) patient received IVIG because of an ICU admission and one (7%) because of central nervous system infection.

### Safety

In total, 122 adverse events were reported in 72 patients: 76 in the IVIG prophylaxis group in 40 patients and 46 in the control group in 32 patients ( $P=0.079$ , based on negative binomial models) (*Online Supplementary Table S1*). Only four severe adverse events were considered (possibly) related to IVIG: two allergic reactions, one fever, and one acute kidney injury 2 weeks after an IVIG infusion. There were significantly more thromboses (peripheral and cerebral combined) in the IVIG prophylaxis group than in the control group (14 vs. 2, respectively,  $P=0.006$ ).



**Figure 1. CONSORT diagram.** CONSORT: Consolidated Standards of Reporting Trials; DCOG: Dutch Children Oncology Group; ALL; acute lymphoblastic leukemia; IVIG: intravenous immunoglobulin; MR: medium risk.



### Admissions for fever

In intention-to-treat analyses, we observed a total of 477 hospital admissions for fever, 206 in the IVIG prophylaxis group and 271 in the control group ( $P=0.011$ ) (Table 2; Figure 3; for estimates of effect see *Online Supplementary Table S2*). Most of the admissions were for fever in neutropenia: 127 in the IVIG prophylaxis group and 176 in the control group ( $P=0.016$ ) (Table 2; Figure 3). Patients in the youngest age quartile were more often admitted for fever than patients in the oldest quartile (304 [64%] admissions for fever in patients 1-4 years old, 21 [4%] in patients 15-18 years old) (*Online Supplementary Table S3*). Seven of 206 (3%) admissions for fever resulted in ICU admissions in the IVIG prophylaxis group and six of 271 admissions (2%) in the control group. The duration of admission was not different between the two groups, being a median of 4 days (interquartile range, 5 days) for the IVIG prophylaxis group and a median of 4 days (interquartile range, 3 days) for the control group ( $P=0.102$ ). We next studied in which treatment phase IVIG prophylaxis was most relevant. Specifically, during maintenance treatment, there were significantly fewer admissions for fever in the IVIG prophylaxis group ( $N=100$ ) than in the control group ( $N=166$ ,  $P<0.001$ ) (Table 2; Figure 3). In the maintenance phase, IVIG prophylaxis resulted in a more than 50% reduction of admissions for fever in neutropenia ( $N=51$  and  $N=108$  for the IVIG prophylaxis and control groups, respectively,  $P<0.001$ ) (Table 2; Figure 3).

To investigate whether the effect of IVIG prophylaxis was influenced by a difference in follow-up time between the two groups of patients, we performed per-protocol analyses. These per-protocol analyses showed similar results: 198 hospital admissions for fever in the IVIG prophylaxis group and 265 in the control group ( $P=0.024$ ) (Table 2; Figure 3). This difference was also attributed to significantly fewer admissions for fever in the maintenance phase (99 vs. 164 in the IVIG prophylaxis group and control group, respectively;  $P=0.002$ ) (Table 2; Figure 3).

### Blood cultures, antibiotics and chemotherapy adaptation

Although the exact cause of fever was highly diverse and mostly not (microbiologically) proven, in 440 (92%) admissions for fever blood cultures were performed. In the majority of admissions for fever, the blood culture was negative (313 of 440 blood cultures, 71%). In intention-to-treat analyses, the absolute number of admissions for fever with a positive blood culture was not significantly different between the IVIG prophylaxis group ( $N=69$ ) and the control group ( $N=58$ ,  $P=0.419$ ), but detailed results regarding the exact pathogen were often not noted in the case report forms. However, IVIG prophylaxis was associated with significantly fewer admissions for fever with a negative blood culture (113 in the IVIG prophylaxis group and 200 in the control group,  $P<0.001$ ) (Table 2; Figure 3). For the admissions with a negative blood culture, many different causes of fever were reported, the

majority being fever of unknown origin or upper respiratory tract infections (147 [47%] and 86 [27%], respectively), suggesting a viral infection. When analyzing the admissions for fever during maintenance treatment separately, IVIG prophylaxis was also associated with significantly fewer admissions for fever with a negative blood culture (52 vs. 125 in the IVIG prophylaxis group and the control group, respectively,  $P<0.001$ ) (Table 2; Figure 3).

Patients in the IVIG prophylaxis group received significantly less empirical antibiotic therapy during admission for fever (165 courses) compared to the control group (212 courses,

**Table 1.** Baseline characteristics.

| Characteristics                            | IVIG group<br>N (%) | Control group<br>N (%) | P     |
|--|---------------------|------------------------|-------|
| Patients                                   | 91                  | 86                     |       |
| Gender                                     |                     |                        | 0.763 |
| Male                                       | 53 (58)             | 52 (61)                |       |
| Female                                     | 38 (42)             | 34 (40)                |       |
| Age in categories                          |                     |                        | 0.798 |
| 1-4 years                                  | 42 (46)             | 35 (41)                |       |
| 5-9 years                                  | 25 (28)             | 29 (34)                |       |
| 10-14 years                                | 14 (15)             | 14 (16)                |       |
| 15-18 years                                | 10 (11)             | 8 (9)                  |       |
| White blood cell count in categories       |                     |                        | 0.557 |
| $<25 \times 10^9/L$                        | 67 (74)             | 61 (71)                |       |
| $25-50 \times 10^9/L$                      | 10 (11)             | 7 (8)                  |       |
| $>50 \times 10^9/L$                        | 14 (15)             | 18 (21)                |       |
| Phenotype                                  |                     |                        | 0.131 |
| B-lineage                                  | 83 (91)             | 72 (84)                |       |
| T-lineage                                  | 8 (9)               | 14 (16)                |       |
| NCI risk group/lineage                     |                     |                        | 0.320 |
| B-lineage NCI standard risk                | 55 (60)             | 48 (56)                |       |
| B-lineage NCI high risk                    | 28 (31)             | 24 (28)                |       |
| T-lineage                                  | 8 (9)               | 14 (16)                |       |
| CNS status (in CSF)                        |                     |                        | NA    |
| CNS1                                       | 41 (45)             | 33 (38)                |       |
| CNS2                                       | 35 (39)             | 40 (47)                |       |
| CNS3                                       | 0 (0)               | 3 (4)                  |       |
| TLP+                                       | 9 (10)              | 7 (8)                  |       |
| TLP-                                       | 3 (3)               | 0 (0)                  |       |
| Inconclusive/not done                      | 3 (3)               | 3 (4)                  |       |
| Genetic subtype                            |                     |                        | NA    |
| <i>ETV6::RUNX1</i>                         | 21 (23)             | 19 (22)                |       |
| <i>KMT2A</i> rearranged                    | 1 (1)               | 0 (0)                  |       |
| <i>TCF3::PBX1</i>                          | 1 (1)               | 2 (2)                  |       |
| High hyperdiploid (51-65 chromosomes)      | 24 (26)             | 13 (15)                |       |
| T-other                                    | 6 (7)               | 12 (14)                |       |
| B-other                                    | 25 (28)             | 32 (37)                |       |
| Missing ploidy data                        | 13 (14)             | 8 (9)                  |       |
| IgG level at diagnosis, g/L, mean $\pm$ SD | 8.3 $\pm$ 2.4       | 9.1 $\pm$ 2.7          | 0.437 |

IVIG: intravenous immunoglobulin prophylaxis; NCI: National Cancer Institute; CNS: central nervous system; CSF: cerebrospinal fluid; NA: not applicable; TLP: traumatic lumbar puncture; SD: standard deviation.

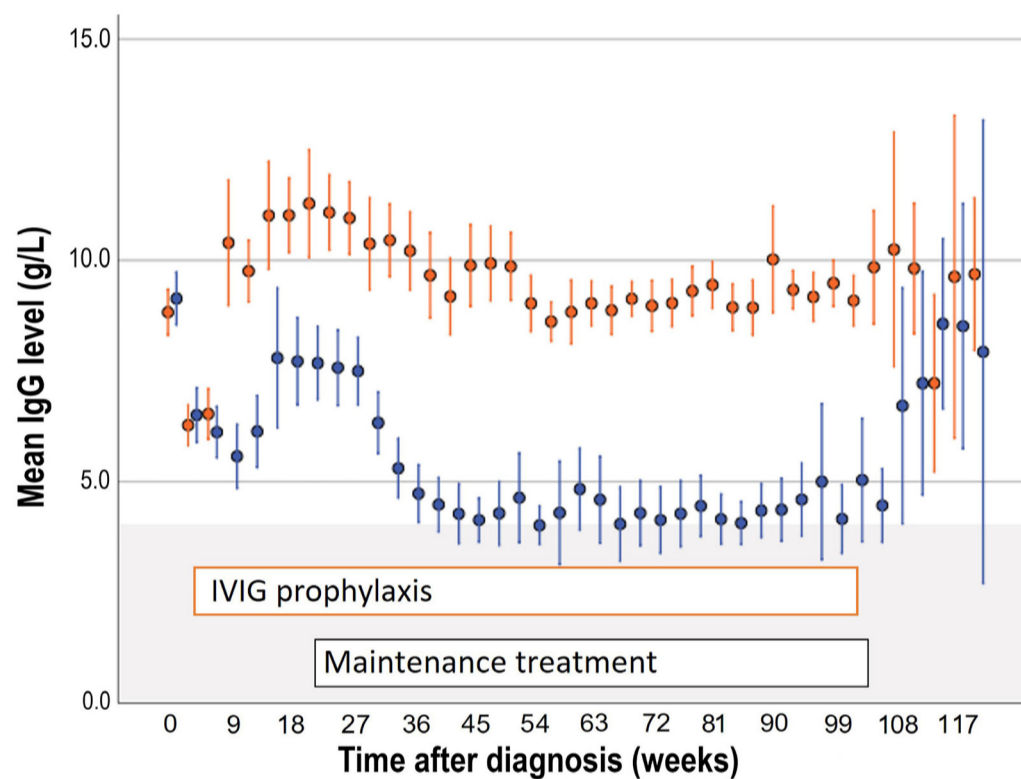
$P=0.030$ ) (Table 2; Figure 3). The difference was more pronounced during maintenance treatment (78 vs. 137 in the IVIG prophylaxis and control groups, respectively;  $P<0.001$ ) (Table 2; Figure 3).

The number of adaptations of chemotherapy after admission for fever was significantly smaller in the IVIG prophylaxis group than in the control group, during maintenance treatment (72 vs. 134, respectively,  $P<0.001$ ) (Table 2; Figure 3). In per-protocol analyses, IVIG prophylaxis was associated with significantly fewer admissions for fever with negative blood cultures as well (108 vs. 198 in the IVIG prophylaxis and control groups, respectively;  $P<0.001$ ) (Table 2; Figure

3), especially in the maintenance phase (52 vs. 125, respectively,  $P<0.001$ ) (Table 2; Figure 3). IVIG prophylaxis resulted in significantly less empirical antibiotic therapy (78 vs. 136 courses in the IVIG prophylaxis and control groups, respectively;  $P<0.001$ ) (Table 2; Figure 3), and fewer adaptations of chemotherapy (72 vs. 132, respectively;  $P<0.001$ ) (Table 2; Figure 3) in the maintenance phase.

### Relapse, disease-free survival and overall survival

There were seven relapses in the IVIG prophylaxis group and six in the control group. The 5-year relapse incidence was 8.4% (3.1%) and 7.5% (3.3%) for the IVIG prophylaxis and control



**Figure 2. IgG levels in the intravenous immunoglobulin prophylaxis and control groups.** Mean IgG levels and 95% confidence intervals were higher in the IVIG prophylaxis group (in orange) than in the control group (in blue), as displayed over 3-week intervals. IgG levels for the control group were censored after IVIG supplementation. The gray area indicates IgG levels  $\leq 4$  g/L, a commonly used cutoff for supplementation. The numbers of IgG level measurements per group at various time-points are shown below the graph.

● **IVIG prophylaxis** 87 36 56 51 39 53 40 52 43 53 44 50 13 7  
 ● **Control** 81 30 42 39 39 36 23 31 23 30 18 21 7 7

**Table 2.** Comparison of outcomes in the intravenous immunoglobulin prophylaxis and control groups, overall and during maintenance treatment separately.

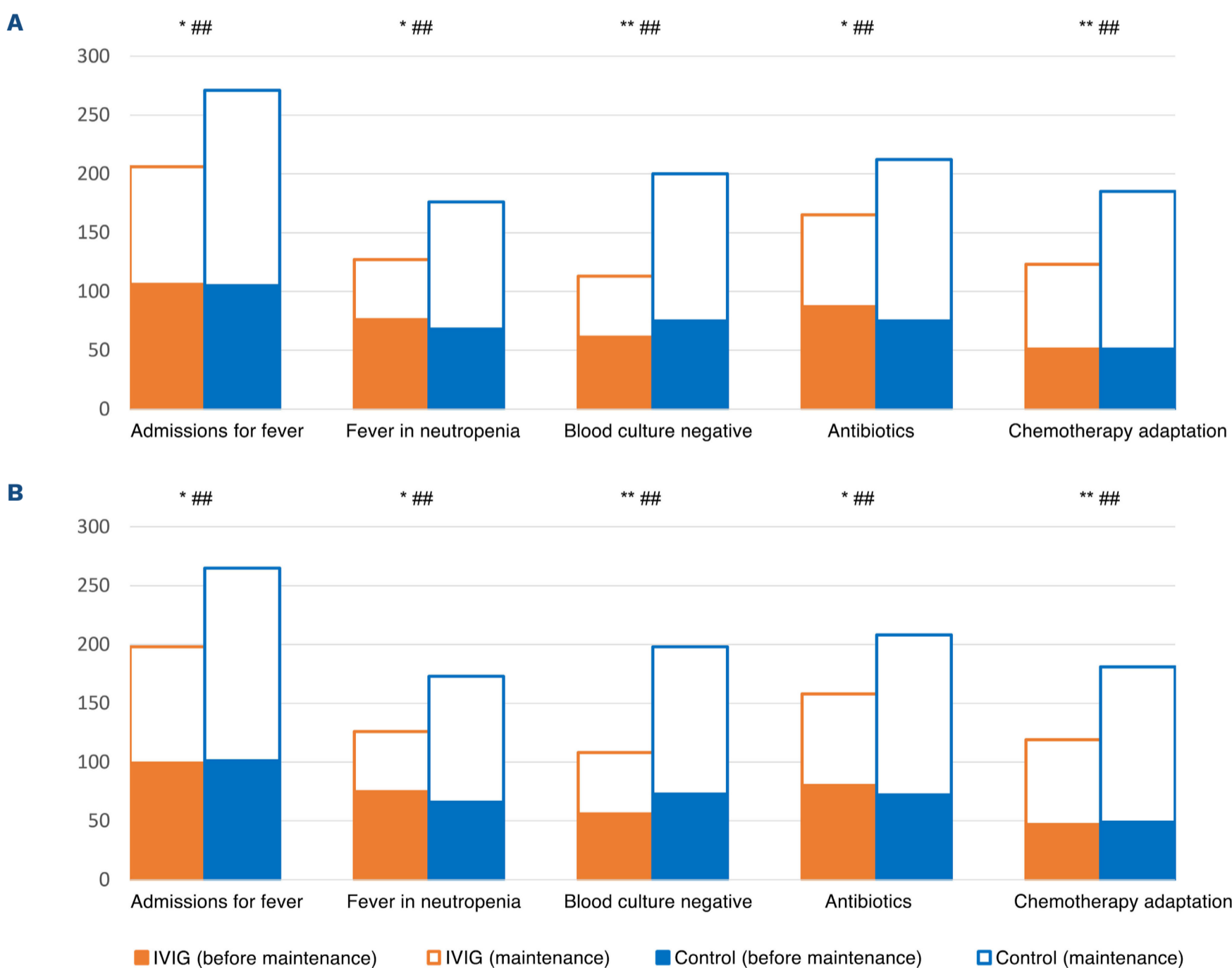
| Outcome, number of episodes  | Overall |         |        | Maintenance phase |         |        |
|------------------------------|---------|---------|--------|-------------------|---------|--------|
|                              | IVIG    | Control | P      | IVIG              | Control | P      |
| Intention-to-treat analyses  |         |         |        |                   |         |        |
| Admissions for fever         | 206     | 271     | 0.011  | 100               | 166     | <0.001 |
| Fever in neutropenia         | 127     | 176     | 0.016  | 51                | 108     | <0.001 |
| Negative blood cultures      | 113     | 200     | <0.001 | 52                | 125     | <0.001 |
| Empirical antibiotic therapy | 165     | 212     | 0.030  | 78                | 137     | <0.001 |
| Adaptation in chemotherapy   | 123     | 185     | 0.003  | 72                | 134     | <0.001 |
| Per-protocol analyses        |         |         |        |                   |         |        |
| Admissions for fever         | 198     | 265     | 0.024  | 99                | 164     | 0.002  |
| Fever in neutropenia         | 126     | 173     | 0.040  | 51                | 107     | <0.001 |
| Negative blood cultures      | 108     | 198     | <0.001 | 52                | 125     | <0.001 |
| Empirical antibiotic therapy | 158     | 208     | 0.029  | 78                | 136     | <0.001 |
| Adaptation in chemotherapy   | 119     | 181     | 0.005  | 72                | 132     | <0.001 |

P values are based on negative binomial models including age of the patient; IVIG: intravenous immunoglobulin prophylaxis.

groups, respectively (*Online Supplementary Figure S1*). One patient in the IVIG prophylaxis group died in remission 45 months after diagnosis, due to a complication of stem cell transplantation; of note, this patient stopped the IVIG trial within 3 months after diagnosis because the interval between IVIG infusions was too long due to toxicity. Two patients in the control group died, one of bacteremia 9.5 months after diagnosis and one after relapse 54 months after diagnosis. IVIG prophylaxis did not significantly affect either 5-year disease-free survival, which was 90.3% (3.3%) and 91.4% (3.4%) for the IVIG prophylaxis and control groups, respectively) (*Online Supplementary Figure S1*) or overall survival, which was 98.7% (1.3%) and 98.8% (1.2%) for the IVIG prophylaxis and control groups, respectively (*Online Supplementary Figure S1*).

## Discussion

This is the first randomized trial investigating IVIG prophylaxis in pediatric ALL patients. Although IVIG prophylaxis did not result in the targeted 50% reduction of admissions for fever overall, it did result in significantly fewer admissions for fever with a negative blood culture, less empirical antibiotic therapy, and fewer adaptations of chemotherapy during maintenance treatment. Once patients were admitted for fever, IVIG prophylaxis did not affect the duration of admission and there was no effect on ICU admissions. Although IVIG prophylaxis resulted in less adaptation of chemotherapy, it did not have any significant impact on relapse, disease-free survival or overall survival. However, the number of relapses was small in this cohort.



**Figure 3. Admissions for fever and fever in neutropenia, cases with negative blood cultures, empirical antibiotic therapy, and chemotherapy adaptations in the intravenous immunoglobulin prophylaxis and control groups.** (A) Intention-to-treat analyses. (B) Per-protocol analyses. The Y axis shows the number of episodes in the intravenous immunoglobulin prophylaxis group (in orange) and the control group (in blue). Filled bars represent episodes before maintenance treatment of acute lymphoblastic leukemia (ALL), open bars represent episodes during maintenance treatment. P values are based on negative binomial models including age of the patient. \*P<0.05, \*\*P<0.01 for analyses during the entire ALL treatment; #P<0.05, ##P<0.01 for analyses during the maintenance phase of ALL treatment separately. IVIG: intravenous immunoglobulin prophylaxis.



A recent retrospective study in pediatric patients with ALL during maintenance therapy, with a small number of patients (63 patients receiving some IgG monitoring/supplementation), did not show a significant impact of IVIG supplementation on febrile episodes.<sup>11</sup> These data are hard to compare to our study, due to the retrospective character and the small size of that study.

IVIG prophylaxis likely prevented viral infections in our cohort of patients. There was no difference in the number of positive blood cultures, but there was a significant decrease in admissions for fever with a negative blood culture in the IVIG prophylaxis group. Most admissions for fever with a negative blood culture were attributed to fever of unknown origin and upper respiratory tract infections, indicative of a reduction in viral infections by IVIG prophylaxis, in line with previous observations in adult patients with lymphoproliferative diseases.<sup>9</sup>

IVIG prophylaxis was well tolerated and not associated with severe side effects, in line with previous observations,<sup>12</sup> although there was a trend for more severe adverse events in the IVIG prophylaxis group. The study was not set up to analyze specific severe adverse events separately; however, IVIG prophylaxis was significantly associated with an increased risk of thrombosis. The causal mechanism of thrombosis is difficult to define as, for example, patients also received asparaginase and glucocorticoids, and had central venous catheters (of note, in the DCOG ALL-11 protocol patients received vincristine and dexamethasone pulses throughout maintenance). In our country, it is common practice for patients to keep their central venous catheter throughout maintenance treatment. Our data did not include information on other risk factors for thrombosis such as factor V Leiden and activated protein C resistance. Ten out of 16 (62.5%) thromboses occurred prior to maintenance treatment, suggesting that other risk factors played a role in the development of thrombosis. Potentially, awareness of thrombosis was biased towards the IVIG group. Nonetheless, thrombosis is a potential side effect of IVIG, which should be kept in mind when prescribing IVIG prophylaxis.

It is worth noting that 15 (17%) patients in the control group received one or more IVIG infusions (under strict conditions). The control group was, therefore, formed of patients receiving standard of care and the effect of IVIG prophylaxis might have been more pronounced had the group receiving the intervention been compared against a true control group of patients who did not receive any IVIG.

The fact that the study was not blinded may theoretically have led to a bias in admitting patients in the control group to hospital more often. However, the majority of admissions were for fever in neutropenia, which is a strict indication for admission. In addition, there was no difference in duration of admission for fever between the two groups, suggesting that once admitted, patients were equally ill in both groups. We, therefore, believe that this potential bias due to non-blinding has not influenced our data considerably.

A drawback of our study is that it was designed with a randomization early within the DCOG ALL-11 protocol, before a large number of patients had developed hypogammaglobulinemia. In our study, only seven (4%) patients had IgG levels <4 g/L before the start of the IVIG trial, which is a commonly used cutoff for supplementation.<sup>13</sup> Based on these seven patients, we cannot determine whether patients with hypogammaglobulinemia at diagnosis would benefit most from IVIG prophylaxis. However, in this trial, IVIG prophylaxis prevented admissions for fever specifically during maintenance treatment, which is also the period of lowest IgG levels (Figure 2).<sup>5</sup> Potentially, measuring IgG levels during maintenance treatment could be helpful in determining which patients would benefit from IVIG prophylaxis.

The medium-risk group of the DCOG ALL-11 study is the largest risk group and included 70% of all patients. Only medium-risk patients were included in our IVIG prophylaxis subtrial. Although a downside of our study is that almost half of the eligible patients did not consent to the trial, we believe the data are generalizable to the entire medium-risk group, as overall and disease-free survival rates are comparable.<sup>3</sup> The advantage of only including medium-risk patients in the study is that this resulted in a homogeneous group of patients in whom the effect of IVIG prophylaxis could be well studied. A limitation, however, is that this is not a subset of patients with the highest risk of (viral) infections. Ultimately, it would be useful to determine whether IVIG prophylaxis can prevent infections in patients with a high viral infection risk, for example younger patients, patients with trisomy 21, patients within families with young children, patients with an intensive (high-risk) treatment schedule, treatment during winter months and patients who have developed multiple infections previously. Moreover, it would be interesting to study the effect of IVIG prophylaxis in patients receiving newer, more targeted B-ALL therapies resulting in B-cell aplasia and consequently hypogammaglobulinemia, such as chimeric antigen receptor T cells and blinatumomab. Setting up a study only randomizing these patients with a high risk of viral infections would, however, require an extremely long recruitment period.

To conclude, in pediatric patients with medium-risk ALL, IVIG prophylaxis leads to a significant reduction of admissions for fever with negative blood cultures during maintenance treatment, and leads to a decrease in the use of empirical antibiotic therapy and chemotherapy adaptations. As IVIG prophylaxis likely prevents viral infections, our data do not support routine use of IVIG prophylaxis for every ALL patient. However, a subset of patients with a high risk of viral infections might benefit from IVIG prophylaxis, with fewer admissions for fever, in maintenance treatment. When prescribing IVIG prophylaxis, clinicians should bear in mind a potential risk of thrombosis.

#### Disclosures

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### Contributions

KAT analyzed the data and prepared the manuscript. HAGK gathered data and analyzed the data. PWS and HS gathered data. MF analyzed the data. CCB, IMS, WJET, MAV, and CMZ enrolled patients and collected data. CMT, RP, and MB designed the study and interpreted data. All authors reviewed, revised, and provided final approval of the manuscript.

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### Data-sharing statement

Datasets supporting the results of the completed study, containing unidentifiable data, will be made available after the publication of the final study results, within 3 months from an initial request, to researchers who provide a methodologically sound proposal. The data will be provided in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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