THROMBOTIC COMPLICATIONS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.
A META-ANALYSIS OF 17 PROSPECTIVE STUDIES
COMPRISING 1,752 PEDIATRIC PATIENTS.

Short title: Thrombosis in acute lymphoblastic leukemia

Vanesa Caruso¹, Licia Iacoviello¹, Augusto Di Castelnuovo¹, Sergio Storti², Guglielmo Mariani³, Giovanni de Gaetano¹, Maria Benedetta Donati¹.
¹Laboratory of Genetic and Environmental Epidemiology, Research Laboratories, and
²Hematology-Oncology Unit, Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, ³Division of Hematology, L’Aquila University, L’Aquila, Italy.

This study was partially supported by a grant from Italian Research and Education Ministry, MIUR, No 1588

Corresponding author:
Licia Iacoviello, M.D., Ph.D.
Laboratory of Genetic and Environmental Epidemiology, Research Laboratories, Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, 86100 Campobasso, Italy
Phone: +39-874-312274 - Fax: +39-874-312710 - E-mail: licia.iacoviello@rm.unicatt.it

Word count: 3,666
Abstract

The risk of thrombosis in children with acute lymphoblastic leukemia (ALL) reportedly ranges between 1% and 37%. Epidemiologic studies have usually been hampered by small numbers, making accurate estimates of thrombosis risk in ALL patients very difficult. The aim of this study was to better estimate the frequency of this complication and to define how the disease, its treatment and the host contribute to its occurrence. We made an attempt to combine and analyze all published data on the association between pediatric ALL and thrombosis, by using a meta-analytic method. The rate of thrombosis in 1,752 children from 17 prospective studies was 5.2% (95%CI 4.2-6.4). The risk varies depending on several factors. Most of the events occurred during the induction phase of therapy. Lower doses of asparaginase (ASP) for long periods were associated with the highest incidence of thrombosis, as were anthracyclines and prednisone (instead of dexamethasone). The presence of central lines and of thrombophilic genetic abnormalities also appeared to be frequently associated to thrombosis. In conclusion, the overall thrombotic risk in ALL children was significant, and the subgroup analysis was able to identify high risk individuals, a finding that will hopefully guide future prospective studies aimed at decreasing this risk.
Introduction

ALL is more frequent in children than in adults; indeed, two thirds of all cases occur at pediatric age.\textsuperscript{1} The risk of thrombosis is increased in ALL patients \textsuperscript{2} and its occurrence may complicate the treatment course with a negative prognostic impact. Its frequency reportedly ranges between 1.1\% and 36.7\%, a quite large variation related to several factors, such as different definitions of thrombosis (symptomatic vs. asymptomatic), diagnostic methods for its detection, study design (prospective vs. retrospective) and differences in treatment protocols. \textsuperscript{2}

The pathogenesis of this increased thrombotic risk is not fully understood, but includes a combination of variables related to the disease itself, its treatment and the host. \textsuperscript{3-5}

Although many clinical and epidemiologic studies were performed in this field, the majority were either retrospective or prospective observations on small numbers of subjects. Thus, the results are contradictory and inconclusive, mainly due to lack of statistical power. However, a careful assessment of risk factors would be useful to improve the quality of treatment and to identify subgroups in which prophylactic interventions would be beneficial.

The objective of the present study was to quantitatively combine and analyze the available data, by a meta-analytic approach, to obtain accurate estimates of the thrombotic risk in pediatric patients with ALL.

Several subgroup analyses were carried out to control for possible biases arising from heterogeneous pieces of information and to sort out subpopulations at higher risk of thrombosis.
Methods

**Meta-analysis**

In the PUBMED database, all available articles were searched using the following keywords: “acute lymphoblastic leukemia/leukaemia” alone and combined with: thrombosis, “thrombotic events”, hypercoagulability, and coagulation. Subsequently, cross-references were searched for.

In addition to studies specifically designed to evaluate thrombosis occurrence in ALL patients, articles dealing with treatment protocols describing thrombosis episodes as adverse events were included, as well as papers reporting laboratory findings on hypercoagulability associated to clinical events.

Only English-written articles were included, if published after 1970, when ASP started to be regularly used.

“Symptomatic” thrombotic events were the end-points used for this analysis. These were defined either as “symptomatic thrombotic event”, or “symptomatic thrombosis”, “symptomatic venous thrombosis” or merely “thrombosis / thrombotic event”, but followed by description of clinical symptoms. All events were confirmed by objective methods. Studies in which the definition of events was unclear or unspecific (such as “Coagulopathy (thrombosis OR clinical bleeding)” or “Clinical or biological coagulation abnormality requiring a modification of chemotherapy or supportive care”) were excluded.

Patients included in different arms of observational comparative studies or randomized clinical trials, were considered as belonging to different “populations”.

Extracted data were: site of thrombotic event, whether it occurred during or following the induction phase of therapy, characteristics of the study population (mean age, risk stratification, ALL subtype, use of central venous catheters (CVC), prothrombotic genetic defects when studied) and treatment protocol (drugs included, type and dosage of ASP, type and moment of administration of steroids, and antithrombotic measures when applied). Approval was obtained from the Catholic University at Campobasso institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki.

**Selection of articles**

From a total of 100 articles retrieved, 67 were excluded for one of the following reasons: case reports without reference to the population at risk (12)\(^6\)\(^-\)\(^{17}\), no data about the incidence of thrombosis (20)\(^18\)\(^-\)\(^{37}\), reviews (7)\(^2\)\(^-\)\(^4\),\(^38\)\(^-\)\(^{41}\), duplicated data (4)\(^42\)\(^-\)\(^{45}\), no clear definition of the endpoints (2),\(^46\)\(^,\)\(^47\) and studies on adult patients (cut-off age from 14 to 20 years) (22).\(^48\)\(^-\)\(^{69}\)
From the PARKAA study, only symptomatic events were taken into account. The remaining 33 articles were divided as described in Table 1. Forty two populations were identified, which included 7,379 patients and 173 events. About three quarters of the subjects (74%) were included in retrospective studies. In this group, the incidence rate (IR) of thrombotic events was lower than that observed in prospective studies. As recalling of events in retrospective studies is rather erratic and prospective design constitutes the best way to observe the frequency of a phenomenon, only prospective studies were considered for subsequent analyses. However, some prospective studies reporting hypercoagulability parameters with a vague description of clinical events were also excluded.

The final model comprised 17 studies (24 populations), including 1,752 patients and 91 events. The mean age of this pooled population was 5.5 years.

**Description of the events**

Out of 91 events, 49 occurred in the central nervous system (CNS), while 39 were venous thrombosis in other sites. Twenty six cerebral events were clearly defined by the authors as being of venous origin. The remaining events were less clearly defined (Table 2.)

**Subgroups analysis**

Thrombosis rate was separately estimated for different subgroups of studies. These were created taking into account:

- **Phases of therapy**: Three distinct IRs of thrombosis were estimated. The “global” IR represents the risk of a thrombotic event during the entire duration of the treatment (from diagnosis of ALL to the end of the maintenance phase). All selected studies were considered in this estimation.

  Many studies described only the induction phase of ALL treatment, whereas a small amount evaluated only post-remission phases, such as consolidation or maintenance. These articles were pooled separately to estimate individual IRs for each of these phases (defined as “induction” and “post-induction”).

  Some authors observed the patients during the whole length of treatment but specified when the event occurred, allowing us to use their articles for the estimation of both “global” and phase-specific IRs of thrombosis.

- **Differences in treatment**: Type and dose of ASP, type of steroids, concomitant use of ASP and steroids, use of anthracyclines, and antithrombin III supplementation.

- **Year of publication of the study**.
- **Presence of genetic prothrombotic defects:** Studies evaluating the presence of genetic prothrombotic risk factors in the host were included in a separate meta-analysis in order to evaluate the risk of thrombosis in ALL patients with thrombophilia.

**Statistical analysis**

Pooled IRs were calculated using an exact method, as proposed in ref. 103. Briefly, this approach used exact maximum likelihood binomial distribution for calculating pooled rates and 95% confidence intervals; 0.5 was not added to numbers of events in studies with zero events because the method accounts for sparseness of individual studies. Homogeneity across studies was tested using the Breslow-Day test. The method provides stratum-specific estimates and test of differences across subgroups.
Results:

**Global Meta-analysis**

When considering all prospective studies, the global IR of symptomatic thrombosis was 5.2% (95%CI 4.2-6.4); homogeneity test: P = <0.0001.

The global IR of CNS and non-CNS events was 2.9% (95%CI 2.2-3.8) and 2.3% (95%CI 1.7-3.2), respectively.

**Subgroup analyses**

**Phases of therapy**

Thirteen studies reported events occurring specifically during the induction phase of ALL treatment. A total of 61 events were observed in 1,280 patients, corresponding to an IR of 4.8% (95%CI 3.7-6.0).

Twelve events occurred in later phases of treatment (consolidation and maintenance) in 609 patients (7 studies); a thrombosis IR of 2.0% (95%CI 1.1-3.3) P=0.004.

**Influence of therapy on the incidence of thrombosis during induction**

**Type of Asparaginase**

No thrombotic event was observed in the small group of patients (one study with 10 patients) treated with Erwinase-ASP (IR 0%; 95%CI 0-30) instead of E.Coli-ASP (IR 4.8%; 95%CI 3.7-6.1; P=0.49).

Separate IRs of thrombosis were estimated for studies mentioning the brand of E.Coli-ASP preparation. The population receiving E.Coli-ASP Medac® showed more events (patients: 618; events: 44; IR 8.7%, 95%CI 6.3-11.5) than the one receiving E.Coli-ASP Crasnitin® (patients: 30; events: 0; IR 0 %, 95% CI 0-10.0; P=0.14). In the studies where the preparation of E.Coli-ASP was unknown (patients: 632; events: 17), the IR of thrombosis was 2.4% (95%CI 1.5-3.7), significantly lower than that observed in the E.Coli Medac® group (P=0.0004).
**Doses of Asparaginase**

The total dose of ASP received (calculated as daily dose x days of treatment) was first evaluated. Then, daily doses and length of administration were independently used to constitute patient subgroups. (Table 3)

- No difference in thrombosis incidence was found among three groups receiving increasing total doses of ASP (20,000 to 59,000 U/m²; 60,000 to 79,000 U/m²; and ≥ 80,000 U/m²).

- Thrombotic events were significantly more numerous in the group receiving lower doses of ASP (≤ 6,000 U/m² (generally 5,000 or 6,000 U/m²)) versus ≥ 10,000 U/m² (generally 10,000 or 25,000 U/m²).

- Patients who received ASP for more than 9 days had a higher incidence of thrombosis.

Daily doses of ASP and length of therapy were combined in four groups. Although a longer administration of ASP was associated with a higher incidence of thrombosis, a lower dosage of this drug increased the risk within each group.

When evaluating only studies using E.Coli-ASP Medac®, IR of thrombosis did not change with different daily dosages of the drug.

No significant difference was observed in the incidence of thrombotic events in 1,134 patients given ASP 2-3 times weekly, as compared to 103 patients receiving the drug on consecutive days.

**Type of steroids**

In one prospective study dexamethasone was used instead of prednisone during induction. This included 56 patients in whom 3 thrombotic events were recorded (IR 2.0%; 95%CI 0.3-8.8), a rate not significantly lower than that observed in patients receiving prednisone (4.9%; 95%CI 3.8-6.3), (P=0.30).

Only 26 of 543 patients with available data about treatment in post-induction phases were treated with prednisone instead of dexamethasone. Three out of 12 events described in post-induction phases occurred in the prednisone group, accounting for a significant increase in the risk of thrombosis during this period (12.2 %; 95%CI 2.9-31.4 vs. 1.6 %; 95%CI 0.8-2.8; P=0.0004).

**Concomitant administration of ASP and steroids**

In the two prospective studies where ASP and steroids were not given concomitantly during induction (10% of the total population), only one event was observed. The corresponding IR
of 4.2% (95%CI 1.7-8.5) was not significantly different from that calculated in the larger group of patients receiving concomitant administration of ASP and steroids (5.3%; 95%CI 4.3-6.5), P=0.55.

**Anthracyclines**

The IR was significantly lower in 495 patients from 3 studies not receiving anthracyclines as part of the induction treatment (2.7%; 95%CI 1.5-4.42.7), than in the remaining 785 patients who received daunorubicin, doxorubicin or idarubicin (6.1%; 95%CI 4.6-8.0; P=0.005).

No difference was observed in the risk of thrombosis when comparing different types of anthracyclines.

**Prophylaxis with antithrombin III**

As only one prospective study compared prophylaxis with antithrombin III against no supplementation, no analysis of this variable could be performed.

**Effect of publication period**

The IR of thrombosis was found to be significantly higher when pooling more recent versus older publications. (Figure 1)

The positive association between lower doses of ASP and thrombosis was still observed when assessing each decade separately (data not shown).

**Presence of prothrombotic genetic defects**

Prothrombotic genetic defects were investigated in 557 children (5 studies). Thirty one events were observed in 113 patients affected by at least one prothrombotic genetic risk factor (factor V G1691A mutation, prothrombin G20210A variant, TT677 methylenetetrahydrofolate reductase (MTHFR) genotype, deficiency of protein C, protein S, antithrombin, elevated lipoprotein (a)). As only one study measured antiphospholipid antibodies (APLA), this acquired prothrombotic condition was not included in the analysis.

The prevalence of genetic prothrombotic abnormalities was similar to that usually found in the general pediatric population. Pooling the 5 studies, the thrombotic risk in ALL patients with thrombophilia increased approximately 8-fold (Relative Risk (RR): 8.5 (95% CI 4.4-17.4). (Figure 2)
Discussion

Thrombosis is uncommon in children, but it may occur in some pathologic conditions, such as ALL. The prevalence and the pathogenesis of thrombosis associated to ALL are obscure. The primary disease itself can activate blood coagulation via procoagulant substances or by impairment of fibrinolytic or anticoagulant pathways. Additionally, chemotherapy and prothrombotic risk factors of the host might play a contributory role. Epidemiologic studies of pediatric thrombosis in ALL have been greatly hampered by small numbers, making estimates of thrombosis risk in this condition very difficult.

The aim of this study was to better estimate the frequency of this association by quantitatively pooling and analyzing all available data and to define how the primary disease, its treatment and the host contribute to its occurrence.

Although we tried to minimize possible biases by accurate sensitivity analyses, this meta-analysis has some limitations due to the great heterogeneity in study designs, ALL populations and treatment protocols. However, this is one of the first attempts to quantitatively combine and analyze existing data on thrombosis and ALL in a pediatric population, and may represent an important basis for generating hypotheses to be tested by future studies.

Occurrence of different thrombotic events in ALL.

The estimated occurrence of thrombosis during treatment (from diagnosis of ALL to the end of the maintenance phase) was 5.2%. This is not a trivial figure, since the estimated annual incidence of venous thrombosis in the pediatric population is about 1 per 100,000 children. Thrombotic events mainly occurred in the central nervous system and in the upper limbs, the latter being frequently associated to CVCs.

Cerebral events are critical complications of ALL treatment, while neurological manifestations can be secondary to hemorrhagic or ischemic episodes. In addition, drug-related neurological adverse events and CNS involvement of the primary disease sometimes mimic stroke syndromes. Out of the 49 CNS events described in our population, only 26 (28.6% of total) were described by the authors as “cerebral venous thrombosis”. Others were described as “cerebral thrombosis”, without mentioning whether they were arterial or venous. Other definitions, such as “cerebral infarction” and “stroke” do not allow to rule out hemorrhagic events. In fact, one of these events was only described as “stroke-like episode”. These rather vague definitions did not permit to make an accurate estimate of ischemic CNS events rate. Although cerebral venous thrombosis is a rare condition, it is frequently associated with hematological disorders.

Peripheral arterial thrombotic events were not reported, suggesting that the pro-thrombotic imbalance could predispose ALL patients mainly to venous thrombosis. This finding is not
surprising, as venous and arterial thrombotic diseases, while sharing some common mechanisms, differ for most risk factors.\textsuperscript{114}

\textit{Effect of ALL treatment on the occurrence of thrombosis}

Most of the thrombotic events occurred during the induction phase. This is not unexpected, as treatment is more intense during this initial phase, and, more importantly, the disease is still active at the beginning of therapy, thus yielding a large lymphoblast burden undergoing cytolysis. Patients receiving post-induction treatment have a more stable disease; as a consequence, both the intensity of the treatment and cell lysis are less pronounced.

Use of dexamethasone instead of prednisone was reportedly associated with a lower incidence of thrombotic events.\textsuperscript{73} In this meta-analysis, the population receiving prednisone during induction had more thrombotic events than those receiving dexamethasone; however, this difference was not statistically significant, probably because of the small number of patients receiving the latter steroid. In accordance, during post-induction phases, most of thrombotic events took place in the small group of patients receiving prednisone instead of dexamethasone. These findings, along with the data on the reduction in thrombosis rate when ASP and prednisone were administered separately\textsuperscript{76}, are important therapeutic issues that should be investigated in larger clinical studies.

\textit{Lower doses of ASP given for a longer period of time increase the risk of thrombosis}

ASP is an essential drug for the treatment of ALL. However, it might impair the hemostatic system by reducing the synthesis of both coagulation factors and inhibitors,\textsuperscript{3} as a consequence of asparagine depletion. It has been previously observed in laboratory studies that Erwinase-ASP and some E. Coli-ASP preparations, such as L-ASP Cranistin\textsuperscript{6}, only partially deplete the asparagine pool and are associated with less thrombotic complications, but also with a reduced antineoplastic efficacy.\textsuperscript{3, 47, 59, 83, 85} As the degree of coagulation abnormalities correlates with ASP activity,\textsuperscript{59, 83, 85} ASP-related thrombotic risk appears to be a “price” to be paid to guarantee an effective treatment to ALL patients.

In this meta-analysis, we examined whether the influence of ASP on thrombosis could differ according to different modalities of administration. In the last years, the tendency was to decrease the dose (from 10,000 to 5,000-6,000 U/m\textsuperscript{2}), to reduce the length of therapy (from 14 to 7-9 days) and to increase the interval between doses. The finding that patients receiving ASP for longer periods experienced more thrombotic events was not unexpected, but the association between lower doses of ASP and higher rates of thrombosis is a novel observation. The latter association was not found when only patients who received L-ASP Medac\textsuperscript{6} were evaluated. Unfortunately,
few studies described the type of preparation of E. Coli-ASP, and in the larger group of patients in which the brand of E. Coli-ASP was unknown, the inverse relationship between ASP dose and thrombotic events was significant.

Furthermore, the progressive increase of thrombosis risk in the last years might be partly due to more recent introduction of aggressive therapy along with lower doses of ASP. The improvement in diagnostic tools in recent years might also explain the larger number of thrombotic events detected in latest publications.

*Thrombophilia and CVCs: should we screen to prevent thrombosis?*

Contradictory results had been reported by studies checking for thrombophilia in ALL patients with thrombotic events. While some failed to show any association between genetic prothrombotic defects and increased risk of thrombosis, others found that thrombophilia represents an important additional risk factor in this population. Meta-analysis of these 5 studies showed that the presence of at least one genetic prothrombotic factor was associated with an 8-fold increase in the risk of thrombosis in children with ALL. This figure, though impressive, cannot disregard the fact that several prospective studies have suggested thrombophilia does not play a major role in the risk of thrombosis in ALL. The two largest studies were conducted by the same authors, evaluating the effect of thrombophilia on the rate of thrombosis in children treated according to different protocols. They obtained divergent results, concluding that the role of hereditary disorders of coagulation in the development of thrombosis in ALL children might depend on treatment modalities. More extensive prospective clinical studies are clearly needed to determine the impact of each single prothrombotic factor on this complication, and to guide future routine screening and prophylactic strategies.

The contribution of CVCs to thrombosis in pediatric patients with ALL could not be thoroughly investigated in this meta-analysis, as only few studies reported the proportion of patients bearing a CVC. However, the fact that more than one quarter of symptomatic events were catheter-related thrombosis (Table 2) suggests CVCs to be an important local risk factor for site-specific venous thrombosis.

Susceptibility of ALL patients to bleeding is an important concern in respect to potential implementation of prophylactic strategies in patients with a combination of thrombotic risk factors. Only 11 of the prospective studies included in this meta-analysis gave data about hemorrhagic complications, allowing to calculate a pooled IR of 2 %. Therefore, bleeding seems to be less common than thrombotic complications in ALL children, but a prospective observational study should assess the complex hemostatic disturbances affecting ALL subjects.
In conclusion, the induction treatment of ALL appears to predispose pediatric patients to thrombotic complications due to a combination of factors linked to the disease itself, to its treatment, to the genetic background of the host and to some acquired conditions. The difficulty to eliminate all possible confounders in this meta-analysis does not allow to definitely state that lower doses of ASP increase the risk of thrombosis. Detailed information on the kinetics of ASP in children is lacking; therefore our finding could encourage studies aimed at determining whether ASP therapy could be improved in ALL pediatric patients, by a careful individualized risk-efficacy approach. Data on the reduction in thrombotic events rate when ASP and prednisone were administered separately and when dexamethasone instead of prednisone is given are significant and should be supported by larger clinical studies. In the meantime, systematic screening for prothrombotic risk factors should be encouraged in the setting of well-designed prospective clinical studies, as a strategy to identify those patients at higher risk of thrombosis, in whom prophylactic approaches presently lacking could be developed.

**Acknowledgements**

We are grateful to Professor Jozef Vermylen, Catholic University, Leuven, for his critical review of the manuscript.
Legend to the Figures

Figure 1. IRs of clinical thrombotic events in different subgroups of studies.

Figure 2. Relative Risk of thrombotic events in ALL children with at least one pro-thrombotic genetic defect.
Table 1. Classification of 33 selected studies according to their main objectives and prospective or retrospective design.

<table>
<thead>
<tr>
<th>Groups of studies</th>
<th>Number of Studies</th>
<th>Populations</th>
<th>Patients</th>
<th>Events</th>
<th>IR for thrombosis (%) (95% CI)</th>
<th>Homogeneity test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>71-80</td>
<td>11</td>
<td>1232</td>
<td>5.6 (4.3-7.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B1</td>
<td>1 81</td>
<td>81</td>
<td>13</td>
<td>520</td>
<td>3.9 (2.3-5.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>B2</td>
<td>6 70, 82-86</td>
<td>86</td>
<td>13</td>
<td>520</td>
<td>3.9 (2.3-5.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>C</td>
<td>9 87-95</td>
<td>9</td>
<td>126</td>
<td>0</td>
<td>0 (0-0.3)</td>
<td>NA</td>
</tr>
<tr>
<td>D</td>
<td>7 96-102</td>
<td>9</td>
<td>5501</td>
<td>82</td>
<td>1.5 (1.2-1.8)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

In bold, studies included in the Final Prospective Model.

**A**: Prospective studies designed for evaluating clinical thrombotic events.

**B1**: Prospective studies describing outcomes of therapeutic protocols, with reference to thrombotic events as complications.

**B2**: Prospective comparative studies or open randomized clinical trials comparing different doses or preparations of ASP (3), EC vs. Erwinase ASP (2), or prophylaxis with antithrombin III vs. no prophylaxis (1).

**C**: Prospective studies designed for the evaluation of laboratory parameters of hypercoagulability which describe clinical thrombotic complications as additional information.

**D**: Retrospective studies
Table 2. Sites of thrombosis.

<table>
<thead>
<tr>
<th>Site of thrombosis (N=91)</th>
<th>Number of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>49 (53.8)</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>26 (28.6)</td>
</tr>
<tr>
<td>Cerebral thrombosis (non-specified)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>9 (9.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (9.9)</td>
</tr>
<tr>
<td>Non CNS venous thrombosis</td>
<td>39 (42.8)</td>
</tr>
<tr>
<td>Non-specified DVT</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>DVT-lower limbs</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>DVT-upper limbs + CVC-associated thrombosis</td>
<td>25 (27.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Right atrium</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Portal thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Superficial thrombosis</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Non-specified site of thrombosis</td>
<td>3 (3.3)</td>
</tr>
</tbody>
</table>
Table 3. IR of thrombosis according to different doses of L-Asparaginase.

<table>
<thead>
<tr>
<th></th>
<th>Populations</th>
<th>N</th>
<th>Events</th>
<th>IR (%)</th>
<th>Heterogeneity across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95%IC)</td>
<td></td>
</tr>
<tr>
<td><strong>Total dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20,000 to 59,000 U/m²</td>
<td>7</td>
<td>202</td>
<td>8</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.8-7.5)</td>
<td></td>
</tr>
<tr>
<td>60,000 to 79,000 U/m²</td>
<td>2</td>
<td>760</td>
<td>41</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3.9-7.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>≥ 80,000 U/m²</td>
<td>8</td>
<td>318</td>
<td>12</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.0-6.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Daily dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6,000 U/m²</td>
<td>7</td>
<td>476</td>
<td>38</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(5.7-10.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 10,000 U/m²</td>
<td>10</td>
<td>804</td>
<td>23</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.9-4.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Total days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9 days</td>
<td>14</td>
<td>945</td>
<td>29</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.1-4.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 9 days</td>
<td>3</td>
<td>335</td>
<td>32</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6.6-13.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Interaction between ASP daily dose and length of therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9 days, ≤ 6000 U/m²</td>
<td>4</td>
<td>141</td>
<td>6</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.7-8.8)</td>
<td></td>
</tr>
<tr>
<td>&lt; 9 days, ≥ 10000 U/m²</td>
<td>10</td>
<td>804</td>
<td>23</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.8-4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 9 days, ≤ 6000 U/m²</td>
<td>3</td>
<td>335</td>
<td>32</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6.6-13.3)</td>
<td></td>
</tr>
<tr>
<td>≥ 9 days, ≥ 10000 U/m²</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
References


103. Martin DO and Austin H. Exact estimates for a rate ratio. Epidemiology. 1996;7:29-33


Figure 1

**Phases of therapy**

*Induction*

*Post-induction*

**ASP daily dose**

\[ \leq 6000 \text{ U/m}^2 \]

\[ \geq 10000 \text{ U/m}^2 \]

**Length of ASP therapy**

\[ < 9 \text{ days} \]

\[ \geq 9 \text{ days} \]

\[ < 9 \text{ days}, \leq 6000 \text{ U/m}^2 \]

\[ < 9 \text{ days}, \geq 10000 \text{ U/m}^2 \]

\[ \geq 9 \text{ days}, \leq 6000 \text{ U/m}^2 \]

**Use of anthracyclines**

Yes

No

**Type of steroids**

*Prednisone*

*Dexamethasone*

**Year of publication**

\[ \leq 1989 \]

1990-1999

\[ \geq 2000 \]

IR of clinical venous thrombosis (%)

0 3 6 9 12
Figure 2

- Wermes C, et al\textsuperscript{71}, N=73
- Elhasid, et al\textsuperscript{75}, N=27
- Mitchell LG, et al\textsuperscript{70}, N=60
- Nowak-Gottl U, et al\textsuperscript{42}, N=289
- Mauz-Korholz C, et al\textsuperscript{43}, N=108

All: 8.5 (4.4-17.4)

RR of thrombosis
Thrombotic complications in childhood acute lymphoblastic leukemia. A meta-analysis of 17 prospective studies comprising 1,752 pediatric patients

Vanesa Caruso, Licia Iacoviello, Augusto Di Castelnuovo, Sergio Storti, Guglielmo Mariani, Giovanni de Gaetano and Maria B Donati