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## **Blood stream infections during chemotherapy-induced neutropenia in adult patients with acute myeloid leukemia: treatment cycle matters**

H. Syrjälä, P. Ohtonen, U. Kinnunen, R. Rätty, E. Elonen, T. Nousiainen, E. Jantunen, K. Remes, M. Itälä-Remes, R. Silvennoinen, et al.

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Title: Blood Stream Infections during Chemotherapy-Induced Neutropenia in Adult Patients with Acute Myeloid Leukemia: Treatment cycle matters

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Abstract: Purpose: To assess the frequency of bloodstream infections (BSI) during neutropenia in different cycles (C) of intensive chemotherapy treatment in acute myeloid leukemia (AML).

Methods: Register data of 327 consecutive patients aged 16-66 years having de novo AML between September 1992 and December 2001 was prospectively gathered.

Results: There were 956 treatment episodes with 456 (47.7%) positive blood cultures. BSI was monomicrobial in 327 episodes (71.7%) and polymicrobial in 129 (28.3%). The overall incidence rate (per 1000 hospital days) for BSI was 13.2, varying from 6.8 in CI after idarubicin, cytarabine and thioquanine to 15.6 in CII, 15.8 in CIII and 17.6 in CIV. The distribution of monomicrobial gram-positive BSIs was as follows: CI; 71.7%, CII; 62.8%, CIII; 53.3%, CIV; 36.6% and C I-IV together; 43.2%. The most common finding in the four different cycles was coagulase-negative staphylococci (38.3% to 30.6%). Viridans group streptococci were most commonly observed (in 20.4% of positive blood cultures) during CII after high-dose cytarabine and idarubicin treatments. The distribution of monomicrobial gram-negative BSIs was as follows: CI; 21.7%, CII; 36.3%, CIII; 45.7%, CIV; 46.9%, and CI-IV together; 37.9%.

Conclusions: It would be more reasonable to analyze chemotherapy cycle-based BSI results rather than overall results.

Response to Reviewers: Answers for the reviewers

We have changed the text in lines 207 -210 just to improve language.

Reviewer #1:

We agree with the reviewer: due to the register data we could not exclude the possibility, that two or more different micro-organisms found during a chemotherapy cycle did not represent two or more separate episodes of BSI.

"If more than one micro-organism was recovered from blood cultures of a patient during a chemotherapy cycle, the episode was defined as polymicrobial." is added to the method section in lines 115 - 116.

Reviewer #2:

We agree with the reviewer, that the cycle II is a crucial point in the data. As suggested we analyzed the cycle 2 by dividing it in two groups: those with active disease and receiving the 2nd induction (n=80) and those in remission and receiving the 1st consolidation (n=212).

|                | Active disease | Remission        | p     | (n=80) | (n=212) |
|----------------|----------------|------------------|-------|--------|---------|
| Neutropenia d  | 27(22 - 36)    | 25(19 - 31)      | NS    |        |         |
| Febrile d      | 8 (4.5 - 11)   | 6 (3 - 11)       | NS    |        |         |
| peak CRP-value | 162(123 -215)  | 159.5(110 - 202) | NS    |        |         |
| GI-tox 3&4     | 37.3 %         | 29.1 %           | 0.194 |        |         |
| CoNS           | 25 %           | 22 %             | NS    |        |         |
| VGS            | 11 %           | 20 %             | 0.119 |        |         |
| Enterococci    | 9 %            | 11 %             | NS    |        |         |
| E.coli         | 4 % 6 %        | NS               |       |        |         |
| Klebsiella     | 8 %            | 11 %             | NS    |        |         |
| Enterobacter   | 6 %            | 6 %              | NS    |        |         |
| Citrobacter    | 0              | 3 %              | NS    |        |         |
| Pseudomonas    | 4 %            | 3 %              | NS    |        |         |

We could not demonstrate any significant differences between the groups. This may partly be due to the limited number of patients (80 + 212). A more powerful study would probably demonstrate difference in amount of VGS and maybe in amount of gastrointestinal toxicity.

The following sentence has been added into the text in the results section to lines 157 - 159: "On the other hand, no difference in number of febrile or neutropenic days, in amount of grade 3 & 4 gastrointestinal toxicity, peak CRP-values, or recovery of individual microbial strains was found between those patients with active disease and those in remission in the second cycle".

The reviewer asks about the interpretation about the skin contaminants found in blood cultures. Due to the characteristics of the register data we cannot analyze more specifically these blood culture findings. Unfortunately we have to accept decisions of attending physicians.

We have changed the text about interpretation of blood cultures in the methods section: "Whether blood culture findings were true or contaminant was accepted by attending physicians." is added to the text in the line 114.

The reviewer points to the possible inability of the WHO criteria to detect gastrointestinal toxicity caused by chemotherapy. "Another explanation to our surprising findings may be that measuring toxicity by the WHO method is not sensitive enough for identifying this kind of changes in gastrointestinal tract." is added in the text into the discussion section to lines 212 - 214.

The question, whether the patients who died, did so before acquiring BSI was analyzed in cycles one and two: During the first cycle 13 patients died of whom BSI data of 11 patients were available and five had BSI. During the second cycle, eleven patients with induction treatment died, of whom eight had BSI. Taken together, the interesting idea made by the reviewer, did not seem to explain our results.

1 **Blood Stream Infections during Chemotherapy-Induced**  
2  
3 **Neutropenia in Adult Patients with Acute Myeloid Leukemia:**  
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6 **Treatment cycle matters**  
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12 5 Hannu Syrjälä,<sup>1\*</sup> Pasi Ohtonen,<sup>2#</sup> Urpo Kinnunen,<sup>3#</sup> Riikka Rätty,<sup>4</sup> Erkki Elonen,<sup>4</sup> Tapio  
13  
14 6 Nousiainen,<sup>5</sup> Esa Jantunen,<sup>5</sup> Kari Remes,<sup>6</sup> Maija Itälä-Remes,<sup>7</sup> Raija Silvennoinen<sup>7</sup> and Pirjo  
15  
16 7 Koistinen,<sup>8</sup> for the Finnish Leukemia Group.  
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19 8  
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21 9 <sup>1</sup>Department of Infection Control, and <sup>2</sup>Departments of Surgery and Anesthesiology Oulu  
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30  
31 14 and <sup>8</sup>Department of Medicine, Oulu University Hospital, Oulu, Finland.  
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34 15 # These authors have an equal distribution to the work.  
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28 **Appendix**

29

30 The other investigators and centers of the Finnish Leukemia Group collaborated in this study:

31 Liisa Volin and Tapani Ruutu, Helsinki; Timo Siitonen and Eeva-Riitta Savolainen, Oulu;

32 Vesa Lindström, Tampere; Tarja-Terttu Pelliniemi, Turku.

33

34 **ABSTRACT**

35

36 **Purpose:** To assess the frequency of bloodstream infections (BSI) during neutropenia in  
37 different cycles of intensive chemotherapy treatment in acute myeloid leukemia (AML).

38 **Methods:** Register data of 327 consecutive patients aged 16-66 years having *de novo* AML  
39 between September 1992 and December 2001 was prospectively gathered in five Finnish  
40 tertiary care leukemia centers. The patients had not received fluoroquinolone prophylaxis.  
41 Reported BSI rates were compared during neutropenia in four chemotherapy treatment cycles  
42 (C).

43 **Results:** There were 956 treatment episodes with 456 (47.7%) positive blood cultures. BSI  
44 was monomicrobial in 327 episodes (71.7%) and polymicrobial in 129 (28.3%). The overall  
45 incidence rate (per 1000 hospital days) for BSI was 13.2, varying from 6.8 in CI after  
46 idarubicin, conventional-dose cytarabine and thioquanine to 15.6 in CII, 15.8 in CIII and 17.6  
47 in CIV. The distribution of monomicrobial gram-positive BSIs was as follows: CI; 71.7%,  
48 CII; 62.8%, CIII; 53.3%, CIV; 36.6% and CI-IV together; 43.2%. The most common finding  
49 in the four different cycles was coagulase-negative staphylococci (38.3% to 30.6%). Viridans  
50 group streptococci were most commonly observed (in 20.4% of positive blood cultures)  
51 during CII after high-dose cytarabine and idarubicin treatments. The distribution of  
52 monomicrobial gram-negative BSIs was as follows: CI; 21.7%, CII; 36.3%, CIII; 45.7%,  
53 CIV; 46.9%, and CI-IV together; 37.9%. A great variation of incidence and types of  
54 microorganisms between AML chemotherapy cycles was found.

55 **Conclusions:** It would be more reasonable to analyze chemotherapy cycle-based BSI results  
56 rather than overall results.

57

58 **Key words:** acute myeloid leukemia, adult, chemotherapeutics, neutropenia, bloodstream

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## 63 INTRODUCTION

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2 64 As early as in the sixties, the importance of severe gram-negative bacterial blood stream infections (BSI) during  
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4 65 intensive chemotherapy of acute myeloid leukemia (AML) was identified [1]. In the seventies, empirical  
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6 66 treatment protocols were introduced to treat BSIs caused by gram-negative microorganism in neutropenic fever  
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8 67 patients [2]. During the next two decades, the causes of BSIs shifted from gram-negative rods to gram-positive  
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10 68 cocci [3, 4, 5, 6, 7, 8, 9]. The most important reason for this change has been explained to be due to the use of  
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12 69 antibiotic prophylaxis during periods of neutropenia in AML patients. Interestingly, the newest results suggest  
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14 70 that the proportion of gram-negative infections is once again increasing [10].

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16 71 According to the knowledge of the authors, little attention has been paid to BSI rate during  
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18 72 different chemotherapy cycles. When the febrile episodes of the so called SIGNIFICANT study [11] were later  
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20 73 evaluated, it was found that during the chemotherapy of solid tumors and lymphomas the risk of a febrile  
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22 74 episode, as a sign of possible BSI and an indication for empirical antibiotic treatment, was highest during the  
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24 75 first treatment cycle, especially in testicular and small-cell lung cancers [12]. It was also noted that if the patient  
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26 76 had a febrile episode during the first chemotherapy cycle, he or she would have an increased risk of a febrile  
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28 77 episode during the subsequent cycles [12].

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30 78 In solid tumors and lymphomas patients receive repeated cycles of the same chemotherapeutics,  
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32 79 whereas in AML different chemotherapeutics are administrated in consecutive cycles in order to achieve a  
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34 80 favorable outcome. As has been seen earlier in a small, one center study, during AML treatment with an  
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36 81 idarubicin, conventional-dose cytarabine and thioquanine schedule, the BSI rate was lower than after other  
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38 82 regimens [13] whereas high-dose cytarabine treatment was associated with a high BSI rate. The present study  
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40 83 was based on the nationwide AML-92 register data collected by the Finnish leukemia group [14], in which 327  
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42 84 AML patients with 956 chemotherapy episodes were included for the evaluation of BSI rates. None of the  
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44 85 patients had received any antibiotic prophylaxis during chemotherapy-induced neutropenia, which allowed us to  
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46 86 observe the real BSI results in four consecutive chemotherapeutic cycles.

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## 50 88 MATERIALS AND METHODS

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52 89 **Background.** The study protocol and hematological results of this nationwide study population of 327  
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54 90 consecutive intensive chemotherapy-treated patients, of whom 82% experienced complete remission, has earlier  
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56 91 been published elsewhere [14].  
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92 **Study design.** The study protocol is briefly explained as follows (for a more extensive description, see ref. [14]:  
1 93 To be included the patient had to have *de novo* AML diagnosed by standard cytological criteria according to  
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3 94 French-American-British (FAB) classification [15], and be between 16 and 65 years old. The study protocol was  
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5 95 approved by the ethical committees of all five participating centers. Moreover, the National Agency for  
6  
7 96 Medicines scrutinized the protocol before the beginning of the study. All patients provided informed consent.  
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10 97           During the first induction course the chemotherapeutics used were idarubicin, conventional-dose  
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12 98 cytarabine and thioguanine. The second course, which was either first postremission or second induction course,  
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14 99 included high-dose cytarabine and idarubicin. The third course included etoposide, high-dose cytarabine and  
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16 100 mitoxantrone and the fourth course amsacrine and high-dose cytarabine. The use of supportive treatments (i.e.  
17  
18 101 growth factors, antibiotics, alimentation and blood products) were administered according to the policies of each  
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20 102 of the five hematological university centers. All patients had a central venous access. The infections were treated  
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22 103 according to generally accepted guidelines [16, 17]. The patients did not receive any antibiotic prophylaxis  
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24 104 during chemotherapy-induced neutropenia. For this study the following information was used from the  
25  
26 105 prospectively gathered register data of the AML patients recruited for the original study between September  
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28 106 1992 and December 2001: age at the time of diagnosis, sex, treatment faculty, FAB classification of AML,  
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30 107 whether or not the patient had an infection at the time of AML diagnosis and whether or not the patient had a  
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32 108 positive blood culture (in ten episodes data was missing). Moreover, the duration of hospital stays, neutropenia  
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34 109 (days when absolute neutrophil count was less than 500/ $\mu$ L), febrile days (body temperature  $\geq 38$  °C), peak C-  
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36 110 reactive protein level (mg/L) and outcome of the patients were analyzed. Furthermore, gastrointestinal toxicity  
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38 111 and the severity of infection categorized according to WHO criteria was recorded in each episode [18].  
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40 112 **Microbiological methods.** Blood was cultured at participating hospitals using automated continuous-  
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42 113 monitoring blood culture systems (CMBCS): in two centers with BacT/Alert <sup>TM</sup> (bioMérieux INDUSTRY,  
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44 114 Hazelwood, MS) and in three centers with Bactec 9240 <sup>TM</sup> (BD Diagnostics, Diagnostic Systems, Sparks, MD).  
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46 115 The microorganisms were identified by standard microbiological methods based on growth conditions and  
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48 116 appearance on solid media, fermentation of sugars and other organic compounds as well as the use of  
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50 117 commercial kits. **Whether blood culture findings were true or contaminant was accepted by attending physicians.**  
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52 118 **If more than one micro-organism was recovered from blood cultures of a patient during a chemotherapy cycle,**  
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54 119 **the episode was defined as polymicrobial.**  
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56 120 **Statistical analysis.**  
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121 The summary measurements for continuous and ordinal variables are expressed as medians with 25<sup>th</sup> and 75<sup>th</sup>  
122 percentiles unless otherwise stated. Fisher's exact test was used to analyze simple categorical data. The  
123 generalized linear mixed model approach was utilized in comparison of presence of positive BSI and toxicity in  
124 different chemotherapy cycles and the linear mixed model approach was used when comparing continuous  
125 variables (maximum CRP, duration of neutropenia, length of hospital stay and duration of fever days) between  
126 chemotherapy cycles. Both mixed-model approaches take into account that measurements are repeatedly taken  
127 from the same subjects and these within-subject measurements are not independent [19]. Furthermore, both  
128 methods use all data available, i.e., subjects with missing information are not dropped out from analyses.  
129 Incidence rates (per 1000 hospital days or 1000 neutropenic days) with 95% confidence intervals were  
130 calculated. If the number of hospital days or neutropenic days was missing it was replaced by the cycle average.  
131 Statistical analysis was performed using SPSS (SPSS, version 14.0, SPSS Inc, Chicago, IL) and SAS (version  
132 9.1.3, SAS Institute Inc., Cary, NC) statistical software.

## 133 **RESULTS**

134 The study population included 327 AML patients and their most common FAB-types were M2  
135 with 32.1%, M1 with 23.9% and M4 with 23.9%. There were 166 men and 161 women. Their median age was  
136 47.7 yrs with a range from 16 to 66 years of age. More detailed hematological results are presented elsewhere  
137 [14]. WHO grade IV infections with signs of organ failure, were observed among 22 patients in cycle I (6.7%),  
138 12 patients in cycle II (4.1%), 13 patients in cycle III (6.1%) and 9 patients in cycle IV (7.4%).

139 During the study period, there were 40 deaths (12.2%), of which 35 (87.5%) were due to  
140 infection. 12 patients died due to infection during cycle I. Five of these deaths were due to BSIs. Of the 14  
141 patients who died due to infection in cycle II, 10 were treated with the second induction treatment for active  
142 disease. 7 of them had BSI. Only 4 patients treated with consolidation treatment in cycle II died because of  
143 infection. 1 of those infections was BSI. In cycle III, five deaths were due to infections, of which three were  
144 BSIs. In cycle IV four patients died due to infection, with two BSIs among them.

145 In total there were 956 treatment episodes with 456 positive blood cultures, constituting a rate of  
146 47.7% of BSI. The overall incidence rate (per 1000 hospital days) for BSI was 13.2 (95% confidence interval  
147 12.0 to 14.5). When the cycles were compared, the median peak C-reactive protein level did not differ between  
148 the cycles, but the duration of febrile days was longest during the first cycle (Table 1). The length of hospital  
149 stay, the incidence rate for BSI per 1000 patient days or per 1000 neutropenia days were clearly higher in cycles  
150

151 II, III and IV than in cycle I (Table 1). The odds ratio for BSI (compared to cycle I) was 5.8, 5.5 and 4.8 in  
 152 cycles II, III and IV, respectively ( $P < .001$ , in all) (Table 1). Severe gastrointestinal toxicity (WHO grade III and  
 153 IV) was highest during cycle I and decreased significantly in successive cycles, the odds ratios compared to  
 154 cycle I being 0.65 at cycle II ( $P = .041$ ), 0.43 at cycle III ( $P < .001$ ) and 0.33 at cycle IV ( $P < .001$ ) (Table 1,  
 155 Figure 1).

156 During the first chemotherapy cycle, the number of BSI was slightly higher, if the patients did not have  
 157 infections at the time of AML diagnosis (25.6%) than those patients having infections (19.3%,  $P = .17$ ; Figure  
 158 2). During the second cycle, the BSI rate was still slightly higher in the patients who had already achieved  
 159 remission (64.6%) than among those who received the second induction course of chemotherapy (53.6%,  $P =$   
 160 .11; Figure 2). **On the other hand, no difference in number of febrile or neutropenic days, in amount of grade 3 &  
 161 4 gastrointestinal toxicity, peak CRP-values, or recovery of individual microbial strains was found between those  
 162 patients with active disease and those in remission in the second cycle.**

163 There was a great inter-cycle variation among positive blood cultures (from 23.3% to 61.6%) as  
 164 well as for monomicrobial BSIs (from 62.2% to 83.3%) and for polymicrobial BSIs (from 16.7% to 37.2%). In  
 165 monomicrobial BSIs, the proportion of gram-positive microorganisms decreased from cycle I (71.7%) to cycle  
 166 IV (36.6%), whereas the change was in opposite direction among gram-negatives; from 21.7% in cycle I to  
 167 46.9% in cycle IV (Table 2). The most common gram-positive microorganisms in monomicrobial BSIs were  
 168 CoNSs and viridans group streptococci; the latter was most frequently detected during cycle II. The most  
 169 common gram-negative microorganisms were *E. coli* (in cycle III and IV) and *Klebsiella* species (in cycles II  
 170 and III). Anaerobic microorganisms were seen only in cycle I and some yeasts in cycles I-III (table 2).

171 Most polymicrobial BSIs contained two microorganisms (Table 3). The most common  
 172 combination included both gram-positive and gram-negative microorganisms in each cycle (41.8% to 64.3%).  
 173 Although there was once again great variability between the cycles; the proportion of gram-negative  
 174 microorganisms was always higher than 50% (from 52.3% to 82.1%).

175 When the BSI results obtained by two different automated blood systems were compared, there  
 176 was not any statistical difference between them concerning the cycles or individual microorganisms (data not  
 177 shown).

## 179 DISCUSSION

180 Our results show that during the chemotherapy courses of adult AML patients, the BSI rate and yielded  
181 microorganisms vary greatly from cycle to cycle, probably reflecting the tendency of different  
182 chemotherapeutics to predispose patients to infections. Thus, the BSI results in AML should be evaluated based  
183 on cycles rather than on the overall results.

184 Our study has several strengths: It was a prospective multi-center study with a large  
185 homogenous study population of 327 adult *de novo* AML patients treated according to the same schedule of  
186 chemotherapeutic protocol [14]. The patients had not received any prophylactic antibiotics for neutropenia,  
187 which allowed us to study the real influence of different chemotherapeutic cycles on BSI rates during  
188 neutropenia. Our statistical approach with linear and generalized linear mixed models took into account that the  
189 same subjects were evaluated repeatedly, i.e., the measurements of the same patients are not independent. On the  
190 other hand, our register data did not include the detection day of BSI from the onset of neutropenia. The other  
191 weakness of this study was that gathered data did not include the resistance patterns of detected microorganisms  
192 or systematic information regarding the mucositis of the oral cavity of the study subjects.

193 Our BSI proportion of 47.7% is higher than has been thus far reported; the figures in other  
194 studies have varied from 10% to 38.8% [11, 20, 21, 22, 23, 24, 25]. The crucial questions from the point of view  
195 of BSI frequency are study population (only leukemia patients or also patients with solid tumor and lymphomas)  
196 and whether the patients had received antibiotic prophylaxis during neutropenia. For example, in a large multi-  
197 center study with solid tumors and lymphomas, the BSI rate was 6.2% in the levofloxacin group and 7.9% in the  
198 placebo group [11]. In another multi-center study, patients having acute leukemia and a duration of neutropenia  
199 of at least 7 days, BSI rate was 20.6% in the levofloxacin group and 38.8% in the placebo group [21]. In our  
200 study, the median duration of neutropenia was more than three weeks in each cycle, which is a well-known and  
201 real risk of higher BSI rate [1]. In one of our centers, the BSI rate during neutropenia among AML patients  
202 increased from 21% to 40% when a manual blood culture system was replaced by a CMBCS [26]. Taken  
203 together, we consider that our BSI rate is realistic and moreover, our BSI incidence rate of 13.2 per 1000  
204 patient-days is rather near to the corresponding figure of 10.2 published earlier [27].

205 When the BSI results were analyzed separately in each cycle, the recovery of micro-organisms  
206 during the first chemotherapy-induced neutropenia was clearly lower than in other cycles. This phenomenon was  
207 relevant when also incidence rate per 1000 patient-days or per 1000 neutropenia-days was calculated. Our result  
208 was rather surprising, when gastrointestinal toxicity (WHO grade III and IV) was taken into account. High-  
209 dose cytarabine is well-known for its gastrointestinal toxicity. In the present data, the toxicity was highest in the

210 first cycle. It should have been lowest, because the dose of cytarabine in the first cycle was conventional rather  
211 than high, as in later cycles. As gastrointestinal toxicity was highest in the first cycle, also the recovery of  
212 micro-organisms should have been highest, but that was not the case. We can give no exact explanation for  
213 these observations, but we can speculate that leukemia *per se* may have something to do with these findings. In  
214 the first cycle all patients had active disease. Altered intestinal permeability and absorption of sugars have been  
215 demonstrated in patients with AML even without treatment [28, 29]. Another explanation to our surprising  
216 findings may be that measuring toxicity by the WHO method is not sensitive enough for identifying this kind of  
217 changes in gastrointestinal tract. On the other hand, in the present data, 63 % of deaths due to infection occurred  
218 in patients receiving induction treatment. It seems that outcome of infections is worse among AML patients with  
219 active disease than among those who have achieved remission.

220                   During the last few decades there has been a clear shift from gram-negative BSIs to gram-  
221 positive ones in neutropenic infections, which has been suggested to be due to the increased use of intravascular  
222 devices, fluoroquinolone prophylaxis and chemotherapy-induced mucositis [9]. When all cycles were analyzed  
223 together, in monomicrobial BSIs, the proportion of gram-positive microorganisms was 43.2%, and the  
224 proportion of gram-negatives was 37.9%. The corresponding figures in a recent study among patients with  
225 hematological malignancies and solid neoplasms in hospitals in the USA with neutrophils of less than 1000/ $\mu$ L  
226 were 61% and 24.9%, respectively [8]. In our series, from cycle I to cycle IV, the numbers of gram-positives  
227 decreased (from 71.7% to 36.6%) and gram-negatives increased (from 21.7% to 46.9%). The great proportion of  
228 gram-negatives in cycles III and IV was unexpected, especially because severe gastrointestinal toxicity (WHO  
229 III and IV) decreased from cycle to cycle. *E. coli* and *Klebsiella* species were the most commonly yielded gram-  
230 negatives, as has been shown in several earlier series.

231                   Of the gram-positive microorganisms, CoNSs were the most common finding also in our series  
232 in general or in the four different cycles. During the last few decades, much attention has been paid to the  
233 importance of *viridans* group streptococci as a cause of bloodstream infections during neutropenia. In several  
234 studies, it has been associated with high-dose cytarabine chemotherapy [30, 31, 32] and quinolone prophylaxis  
235 [7]. In our study, the incidence of BSIs caused by *viridans* group streptococci was highest during the second  
236 cycle with high-dose cytarabine and idarubicin and clearly lower in cycle IV, which also included high-dose  
237 cytarabine and amsacrine. Thus, the combination of chemotherapeutics and not only the high-dose cytarabine  
238 *per se* seems to be important for BSIs caused by *viridans* group streptococci.

239 It has been recently noted that the knowledge of polymicrobial infections among cancer patients  
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2 240 is sparse [33]: In trials involving neutropenic patients, the proportion of polymicrobial BSIs has varied from 8%  
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4 241 to 32% [34, 35]. Our overall figure of polymicrobial BSIs was 28.3%. However, there was once again substantial  
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6 242 inter-cycle variation. In three-fourths of the episodes, polymicrobial BSIs were caused by two microorganisms.  
7  
8 243 The most common combination included both gram-positive and gram-negative microorganisms and the second  
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10 244 most common included at least two gram-positive microorganisms together.

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12 245 When polymicrobial BSIs were also taken into account in our study, which included the series of  
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14 246 AML patients recruited between 1992 and 2001, the portion of gram-positive microorganisms in BSIs was even  
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16 247 higher (79.6%) than in the earlier-mentioned study from the USA: their highest figure (76%) was from the year  
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18 248 2000 [8]. The result of 50.9% of gram-negative organisms when polymicrobial BSIs were also included, is quite  
19  
20 249 similar to a recent study [36], patients were also treated without antibiotic prophylaxis. In another study the  
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22 250 proportion of gram-negatives was 52% without and 25% with antibiotic prophylaxis [23].  
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24 251 In conclusion, our AML patients had a high overall BSi rate during chemotherapy regimen-  
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26 252 induced neutropenia. However, there was great variation in BSI findings in four treatment cycles with different  
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28 253 chemotherapeutics: BSI rate was lowest in cycle I and proportions of microorganisms and polymicrobial BSIs  
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30 254 varied greatly from cycle to cycle. Therefore, in order to obtain more precise information concerning BSIs  
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32 255 during the intensive chemotherapeutic treatments of AML, the analysis of BSI results should be focused on  
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34 256 different chemotherapy cycles rather than by analyzing the overall results.  
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6  
7 261 **Conflict of Interest**

8  
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**TABLE 1. Length of hospital stay, duration of febrile episodes and neutropenia, the serum peak value of C-reactive protein, incidence rate (IR) of blood stream infections (BSI) and odds ratios (OR) for the risk of BSI and gastrointestinal toxicity in different treatment cycles (cycle I as a reference);**

|   | Cycle I <sup>a</sup> | Cycle II            | Cycle III           | Cycle IV            | P <sup>b</sup> |
|---|----------------------|---------------------|---------------------|---------------------|----------------|
| Hospital days <sup>c</sup>  | 30 (28-36)           | 37 (31-44)          | 34 (27-44)          | 31 (25-38)          | <.001          |
| IR of BSIs / 1 000 days<br>(95% CI) <sup>d</sup>                                | 6.8 (5.4 to 8.6)     | 15.6 (13.4 to 18.1) | 15.8 (13.3 to 18.8) | 17.6 (13.8 to 22.2) | -              |
| Neutrophils < 500/ $\mu$ L, days <sup>c</sup>                                   | 24 (20-28)           | 26 (19-32)          | 25 (17-37)          | 22 (18-29)          | <.001          |
| IR of BSIs/ 1 000<br>neutropenic days (95% CI) <sup>d</sup>                     | 9.2 (7.2 to 11.6)    | 23.2 (20.0 to 26.9) | 21.3 (17.8 to 25.3) | 23.6 (18.4 to 29.7) | -              |
| Temperature $\geq$ 38°C, days <sup>b</sup>                                      | 9 (5-14)             | 7 (3-11)            | 6 (3-10)            | 7 (3-9)             | <.001          |
| C-reactive protein (mg/L,<br>peak value) <sup>c</sup>                           | 164 (119-230)        | 161 (115-206)       | 158 (113-210)       | 160 (107-205)       | .30            |
| OR for BSI (95% CI) <sup>d</sup><br>P <sup>e</sup>                              | 1.0                  | 5.8 (4.1 to 8.2)    | 5.5 (3.8 to 8.0)    | 4.8 (3.1 to 7.4)    |                |
|   |                      | <.001               | <.001               | <.001               |                |
| OR for gi-toxicity, grade III<br>and IV (95% CI) <sup>d</sup><br>P <sup>e</sup> | 1.0                  | 0.65 (0.43 to 0.98) | 0.43 (0.27 to 0.70) | 0.33 (0.17 to 0.62) |                |
|   |                      | .041                | <.001               | <.001               |                |

1. <sup>a</sup> chemotherapeutics: cycle I; idarubicin, cytarabine and thioguanine, cycle II; high-dose cytarabine and idarubicin, cycle III; etoposide cytarabine and mitoxantrone, Cycle IV; amsacrine and high-dose cytarabin.

<sup>b</sup> *P*-time according to Linear mixed model.

<sup>c</sup> values are medians with 25<sup>th</sup> -75<sup>th</sup> percentiles.

<sup>d</sup> values are means with 95% confidence intervals (95%CI).

<sup>e</sup> *P*-time according to the generalized linear mixed model (7).

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**TABLE 2. Detected microorganisms during different chemotherapy cycles; the number (%) of positive blood cultures per treatment episodes in each cycle.**

|   | Cycle I<br>(n= 323) | Cycle II<br>(n=292) | Cycle III<br>(n=219) | Cycle IV<br>(n=122) | All (n=956)       |
|---|---------------------|---------------------|----------------------|---------------------|-------------------|
| <b>Blood culture positive,<br/>number (%)</b> | <b>72 (22.3)</b>    | <b>180 (61.6)</b>   | <b>133 (60.7)</b>    | <b>71 (58.2)</b>    | <b>456 (47.7)</b> |
| <b>Monomicrobial</b>                          | <b>60 (83.3)</b>    | <b>113 (62.2)</b>   | <b>105 (78.9)</b>    | <b>49 (69.0)</b>    | <b>327 (71.7)</b> |
| Gram-positive                                 | 43 (71.7)           | 71 (62.8)           | 56 (53.3)            | 26 (36.6)           | 197 (43.2)        |
| - CoNS  | 23 (38.3)           | 28 (24.8)           | 34 (32.4)            | 15 (30.6)           | 100 (30.6)        |
| - VGS   | 5 (8.3)             | 23 (20.4)           | 12 (11.4)            | 6 (12.2)            | 46 (14.1)         |
| - <i>Enterococci</i>                          | 7 (11.7)            | 9 (8.0)             | 7 (6.7)              | 4 (8.2)             | 27 (8.3)          |
| Gram-negative                                 | 13 (21.7)           | 41 (36.3)           | 48 (45.7)            | 23 (46.9)           | 124 (37.9)        |
| - <i>E. coli</i>                              | 3 (5.0)             | 7 (6.2)             | 15 (14.3)            | 12 (24.5)           | 37 (11.3)         |
| - <i>Klebsiella sp.</i>                       | 2 (3.3)             | 16 (14.2)           | 20 (19.0)            | 5 (10.2)            | 43 (13.1)         |
| - <i>Enterobacter sp.</i>                     | 1 (1.7)             | 7 (6.2)             | 6 (5.7)              | 2 (4.1)             | 16 (4.9)          |
| - <i>Pseudomonas<br/>aeruginosa</i>           | 3 (5.0)             | 7 (6.2)             | 1 (1.0)              | 3 (6.1)             | 14 (4.3)          |
| Anaerobic<br>microorganisms                   | 3 (5.0)             | -                   | -                    | -                   | 3 (0.9)           |
| Yeast   | 1 (1.7)             | 1 (0.9)             | 1 (1.0)              | -                   | 3 (0.9)           |
| <b>Polymicrobial</b>                          | <b>12 (16.7)</b>    | <b>67 (37.2)</b>    | <b>28 (21.1)</b>     | <b>22 (31.0)</b>    | <b>129 (28.3)</b> |

**NOTE.** CoNS, coagulase-negative staphylococci; VGS, viridans group streptococci. Among gram-positives and gram-negatives, only three most common microbes are mentioned, and among gram-negatives also the presence of *Pseudomonas*.

**TABLE 3. Characterization of microorganisms of polymicrobial bloodstream infections in different chemotherapy cycles**

| <b>Blood stream infections</b>    | <b>Cycle I<br/>(n=12)</b> | <b>Cycle II<br/>(n=67)</b> | <b>Cycle III<br/>(n=28)</b> | <b>Cycle IV<br/>(n=22)</b> | <b>All (n=129)</b> |
|-----------------------------------|---------------------------|----------------------------|-----------------------------|----------------------------|--------------------|
| Number of microorganisms          |                           |                            |                             |                            |                    |
| - Two                             | 8 (66.7)                  | 49 (73.1)                  | 24 (85.7)                   | 16 (72.7)                  | 97 (75.2)          |
| - More than two                   | 4 (33.3)                  | 18 (26.9)                  | 4 (14.3)                    | 6 (27.3)                   | 32 (24.8)          |
| Combinations of microorganisms    |                           |                            |                             |                            |                    |
| - Gram-positives only             | 5 (41.7)                  | 27 (40.3)                  | 5 (17.9)                    | 3 (13.6)                   | 40 (31.0)          |
| - Gram-positive and anaerobic     | -                         | 4 (6.0)                    | -                           | -                          | 4 (3.1)            |
| - Gram-positive and yeast         | -                         | 1 (1.5)                    | -                           | 2 (9.1)                    | 3 (2.3)            |
| - Gram-positive and gram-negative | 6 (50.0)                  | 28 (41.8)                  | 18 (64.3)                   | 11 (50.0)                  | 63 (48.8)          |
| - Gram-negatives only             | 1 (8.3)                   | 4 (6.0)                    | 3 (10.7)                    | 5 (22.7)                   | 13 (10.1)          |
| - Gram-negative and yeast         | -                         | 3 (4.5)                    | 2 (7.1)                     | 1 (4.5)                    | 6 (4.7)            |



## Figure legends

**FIGURE 1.** Positive blood culture findings (%) during four chemotherapy cycles among adult acute myeloid leukemia patients. Gram-positive, gram-negative and other micro-organisms (yeast, anaerobes and polymicrobial). Gastrointestinal toxicity grade III and IV according to the WHO. The difference between positive blood cultures in cycle I vs. the other three,  $P < 001$  each (multilevel generalized linear model). Cycle I; idarubicin, cytarabine and thioguanine, cycle II; high-dose cytarabine and idarubicin, cycle III; etoposide, cytarabine and mitoxantrone and cycle IV; amsacrine and high-dose cytarabine.

**FIGURE 2.** Comparison of positive blood culture findings in cycle I between patients having (Inf +) or not having infection (inf -) at the time of diagnosis of AML ( $P = .17$ ), and in cycle II the comparison between those patients having achieved remission (rem +) and those still having an active disease (rem -,  $P = .11$ , Fisher's Exact Test, two-tailed).

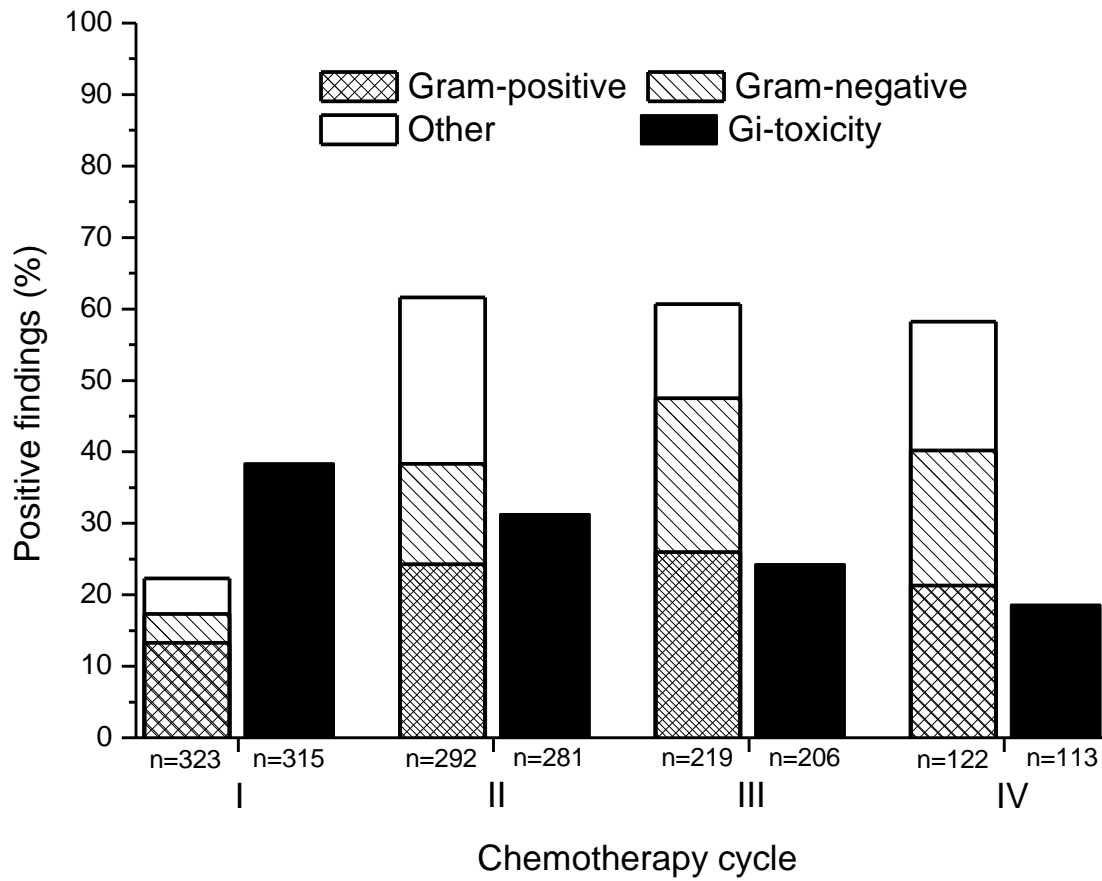


Figure 1.

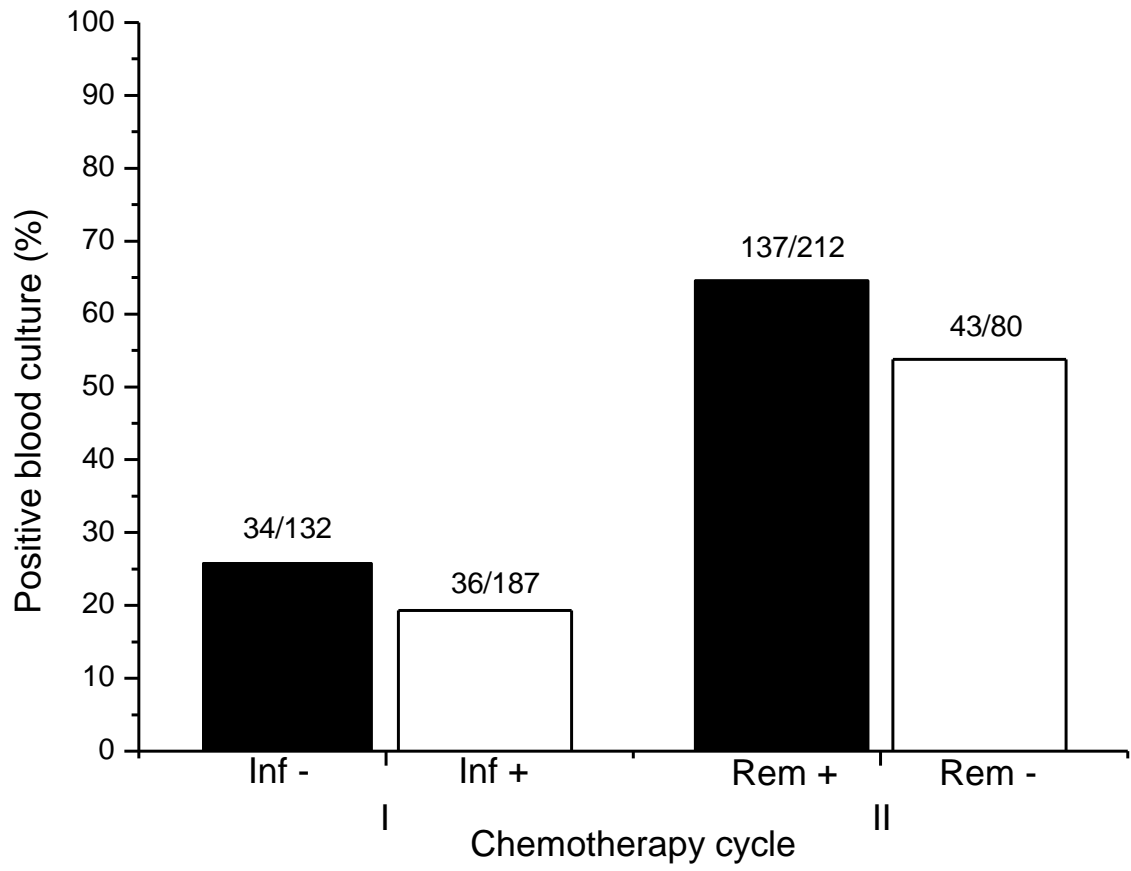


Figure 2.

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