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Review

Antibacterial prophylaxis in pediatric patients with leukemia

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ABSTRACT

Background: Bacterial infections in pediatric patients with leukemia are associated with increased risks for morbidity and mortality. Few Recommendations have been made on the use of antibacterial prophylaxis in pediatrics with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).

Objectives: To determine the role of antibacterial prophylaxis in pediatric patients with leukemia and the most appropriate regimen that can be safely and effectively used.

Methods: Literature search was conducted independently by 3 reviewers to find studies on the safety and effectiveness of antibacterial prophylactic regimens.

Results: The search strategy resulted in 13 studies; most of them were observational studies. The available evidence recommends use of antibiotics with Gram-positive bacterial coverage in AML patients. In ALL patients, prophylaxis was used during the intensive phases of chemotherapy with ciprofloxacin being recommended most commonly.

Conclusion: Antibacterial prophylaxis mainly with coverage against Gram-positive bacteria is recommended in pediatric patients with AML. For ALL patients, prophylaxis may be considered for patients who are undergoing intensive chemotherapy phases and are at high risk for infections with ciprofloxacin being the most commonly used agent. In general more studies are needed to determine the role of antibacterial prophylaxis in pediatric patients with leukemia.

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1. Introduction

The treatment outcome of childhood leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), has improved dramatically over the past few decades (American Cancer Society, 2014; De Rooij et al., 2015). The improvement in survival rate is due to many factors including the intensive chemotherapeutic regimens used, better risk group stratification, improved hematopoietic stem cell transplantation and better

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supportive care (De Rooij et al., 2015; Abrahamsson et al., 2011). This dramatic improvement in the management of childhood leukemia is, however, accompanied by several treatment-related toxic effects, such as severe bone marrow suppression and increased risks for mortality from bacteremia or septicemia (O'Connor et al., 2014; Creutzig et al., 2004).

Use of antibacterial prophylaxis in adult patients with cancer is a well-established practice. A systematic review found that antibiotic prophylaxis in afebrile neutropenic patients significantly reduced all-cause mortality (Gafer-Gvili et al., 2012). The investigators strongly recommended antibiotic prophylaxis for patients with hematologic malignancies, preferably with quinolones. Data on the use of antibacterial prophylaxis in the pediatric population, however, are limited and controversial (Kurt et al., 2008; Johanssen et al., 2013; Inaba et al., 2014; Boztug et al., 2017)

The purpose of this review was to evaluate the current literature on the use of antibacterial prophylaxis in pediatric patients with ALL or AML, including the effectiveness and safety of the regimens.

2. Literature search

Three investigators performed the search independently and then met to discuss their search results. The PubMed, Cochrane, Sum search and Hinari databases were searched for studies published between 2000 and 2017, with the terms: *antibiotics, antibacterial, prophylaxis, prevention, infection, pediatric, children, leukemia, AML and ALL*. The references lists of the retrieved articles were searched for additional studies. Publications in language other than English, single case reports, in vitro studies and studies of patients who received bone marrow transplantation were excluded from the review.

The search strategy resulted in 13 studies (Table 1), of which three were randomized placebo-controlled trials, while the remainders were observational studies. Eight studies evaluated pediatric patients with AML, 3 studies evaluated pediatric patients with ALL, and 2 studies evaluated both patients with ALL and with AML. Patients were treated according to different chemotherapy protocols in the studies, but the chemotherapeutic agents used in the trials were similar.

3. Prophylactic regimens used in AML patients

The prophylactic regimens used in patients with AML were evaluated in 10 studies, all except one of which were observational studies, many with small sample sizes (range, 29–897 patients). Most prophylactic regimens included a Gram-positive antibacterial agent, which was usually a glycopeptide (vancomycin or teicoplanin).

The largest study (897 patients) of AML was from the Children's Oncology Group (COG) (Sung et al., 2013). In this study, the investigators surveyed institutions that had adopted the protocol of the COG clinical trial AAML0531 to determine the effect of antibiotic prophylaxis on risk for infection and non-relapse mortality rate. The 897 eligible patients were reported from 180 institutions that responded to the survey, and the institutions that reported use of antibacterial prophylaxis were asked to name the agents used. The investigators then divided the antibacterial regimens into two groups, vancomycin/penicillin versus any other antibiotics. Among the eligible patients, 185 received antibiotic prophylaxis, 70 received vancomycin/penicillin, and 115 received another antibiotic. Vancomycin/penicillin was evaluated separately because of concern about *viridans* group streptococci in AML patients. The investigators found that antibacterial prophylaxis significantly reduced the occurrence of Gram-positive sterile site bacterial infection ($P < 0.004$) and any sterile site bacterial infection

with no statistical significance ($P < 0.058$) but did not affect the non-relapse mortality rate. They did not provide separate data on the outcomes of the two antibacterial prophylaxis regimens used.

In another retrospective study (Nolt et al., 2015), patients were treated with either the COG clinical trial AAML0531 protocol or with the modified United Kingdom Medical Research Council AML10 regimen; 29 patients were included between 2005 and 2013. The prophylactic regimen consisted of vancomycin and ceftazidime until 2010 and was then changed to cefepime as a single agent because it was expected to be less nephrotoxic and because of concern about the emergence of vancomycin-resistant enterococcus (VRE). The 29 patients received a total of 76 phases of chemotherapy. In patients who received vancomycin and ceftazidime, 28% of the phases were complicated by infectious episodes, while in patients who received cefepime as a single agent, 31% of the phases were complicated by infectious episodes, Gram-positive bacterial infections were the predominant infections. No clear trend in the number of infections with the single-drug or the multi-drug regimen emerged. The investigators concluded that preventive use of broad-spectrum antibiotics was not associated with mortality from bacteremia and that the approach was feasible and safe.

Prophylactic antibiotics administered with the St Jude AML02 protocol were evaluated in three studies (Kurt et al., 2008; Inaba et al., 2014; Al Omar et al., 2017). Kurt et al. (2008) investigated whether antibiotic prophylaxis during periods of neutropenia reduced streptococcal (*S. viridans*) sepsis and overall bacterial sepsis. They examined prophylactic regimens including oral cephalosporin, cefepime or vancomycin in combination with either cefepime, ciprofloxacin or cephalosporin. Use of oral cephalosporin as a single agent did not reduce the occurrence of septicemia as compared with no prophylaxis. In contrast, use of any vancomycin-containing regimen or cefepime reduced bacterial sepsis by 93% and 91%, respectively. The occurrence of *S. viridans* was reduced by 99% with vancomycin-containing regimens and by 100% with cefepime; however, resistant Gram-negative bacteria emerged in two patients given cefepime. Use of antibiotic prophylaxis in this study had a meaningful impact on the number of days of hospitalization; the average number of hospital days per course was 16 days with no antibiotic, 11 days with oral cephalosporin ($P = 0.1$), 7 days with cefepime ($P = 0.0039$) and 3 days with vancomycin-containing regimens ($P < 0.0001$). The authors concluded that prophylaxis with intravenous cefepime or a vancomycin regimen reduced morbidity in children with AML and resulted in dramatic decreases in the incidence of septicemia and days of hospitalization.

Inaba et al. (2014) examined the feasibility, efficacy and adverse effects of outpatient antibacterial prophylaxis in 103 children with AML. Initially, the patients received no prophylaxis or oral cephalosporin (group A); then, the protocol was amended to cefepime alone or vancomycin with either cefepime, ciprofloxacin or cephalosporin (group B). The frequency of bacteremia was significantly lower in group B (0–17%) than group A (28–79%), depending on the treatment phase. The incidence of bacteremia was not significantly different between patients who received cefepime or a vancomycin-containing regimen. Infection with *S. viridans* was significantly reduced, from 29% in group A to 1% in group B; however, 5 cases of bacteremia with VRE occurred in group B and none in group A, without related mortality. No statistically significant difference between group A and group B was found for febrile neutropenia episodes of unknown origin. The caregivers of the pediatric patients in this study were trained to administer parenteral prophylactic antibiotics; the authors found that this was feasible and reduced the frequency of documented infection but not of febrile neutropenia. Despite the emergence of VRE bacteremia, the benefits favor antibiotic prophylaxis.

Table 1
Summary data from studies with different regimens of antibacterial prophylaxis in leukemia patients.

Reference no.	Type of study	Patients and treatment	Prophylactic regimen	Results
Boztug et al. (2017)	Retrospective	– Diagnosis: AML – No. of patients: 50 – Protocol: AML-BFM 2004 Creutzig et al. (2010)	Teicoplanin or vancomycin with/without ciprofloxacin or piperacillin/tazobactam	Streptococcus viridans sepsis: – Prophylaxis group: 0% – No prophylaxis group: 15% p < 0.0001 Febrile neutropenia: – Prophylaxis group: 44% – No prophylaxis group: 82% p < 0.0001
Sung et al. (2013)	Multicenter survey	– Diagnosis: AML – No. of patients: 897 – Protocol: COG trial AML0531 Gamis et al. (2013)	Penicillin or vancomycin Other prophylactic regimens	Sterile site bacterial infection: – incidence rate ratio: 0.85 (95% CI 0.72–1.01) P = 0.058 (prophylaxis versus no prophylaxis) Gram-positive sterile site infection: – incidence rate ratio: 0.71 (95% CI, 0.57–0.90) P = 0.04 (prophylaxis versus no prophylaxis) Number of chemotherapy phases with infectious episodes (vancomycin and ceftazidime group): 29% Number of chemotherapy phases with infectious episodes (cefepime group): 31%
Nolt et al. (2015)	Retrospective	– Diagnosis: AML – No. of patients: 29 – Protocol: COG trial AML0531 or the modified UK MRC AML10 regimen Gibson et al. (2005)	Until 2010: vancomycin and ceftazidime. After 2010: cefepime	
Kurt et al. (2008)	Randomized double blind study	– Diagnosis: ALL – No. of patients: 110 – Protocol: Wijaya Kusuma-ALL 2000 Widjajanto et al. (2012)	Ciprofloxacin.	Prophylaxis group: – Induction failure rate: 31% – Risk of experiencing fever: 50% – Clinical sepsis rate: 50% – No prophylaxis group: – Induction failure rate: 25% – Risk of experiencing fever: 33% – Clinical sepsis rate: 39%
Inaba et al., (2014)	Retrospective	– Diagnosis: AML – No. of patients: 103 – Protocol: St. Jude AML02 protocol Rubnitz et al. (2012)	Group A: no prophylaxis or oral cephalosporin Group B: cefepime or vancomycin plus either oral cephalosporin or ciprofloxacin or cefepime.	Clinically or microbiologically documented infections: Group A: 40–90% Group B: 11–29% P < 0.0001
Al Omar et al. (2017)	Retrospective	– Diagnosis: AML – No. of patients: 78 – Protocol: St. Jude AML02 protocol Rubnitz et al. (2012)	(1) Oral cephalosporin (2) cefepime (3) vancomycin plus either Ciprofloxacin or cephalosporin or cefepime	Odds of bacterial sepsis or streptococcal viridans sepsis (compared to no prophylaxis): (1) oral cephalosporin: P = 0.81, P = 0.9 (2) cefepime: P < 0.0001 (3) vancomycin plus either
Felsenstein et al. (2015)	Retrospective	– Diagnosis: ALL, AML – No. of patients: 113 ALL patients, 36 AML patients. – Protocol: for ALL patients: Taiwan pediatric oncology group ALL-2002 protocol Liang et al. (2009), for AML patients: Taiwan pediatric oncology group AML-97A protocol Liang et al. (2006)	Ciprofloxacin	Ciprofloxacin or cephalosporin or cefepime: P < 0.0001, P < 0.0001 Blood stream infections: Prophylaxis group: 10 episodes. No prophylaxis group: 44 episodes. P < 0.01
Yeh et al. (2014)	Retrospective	– Diagnosis: AML – No. of patients: 50 – Protocol: St. Jude AML02 protocol Rubnitz et al. (2012)	Ciprofloxacin.	Number of episodes of bacterial infections: – 73 episodes of bacteremia: 62% Gram-positive bacterial infections, 33% Gram-negative bacterial infections.
Yousef et al. (2004)	Multicenter, randomized double blind placebo-controlled trial	– Diagnosis: acute leukemia – No. of patients: 88 with acute leukemia (total number 173) – Protocol: NA	Amoxicillin/clavulanate	Failure free survival rate: – Prophylaxis group: 28% – No prophylaxis group: 45% P = 0.014

Castanola and Boni (2003)	Prospective observational	<ul style="list-style-type: none"> - Diagnosis: ALL - No. of patients: 69 - Protocol: - XI (MRC UKALL XI) Gibson et al. (2005) 	Ciprofloxacin.	Rate of hospitalization: <ul style="list-style-type: none"> - Prophylaxis group: 58% - No prophylaxis group: 90% P < 0.001 Rate of proven bacteremia: <ul style="list-style-type: none"> - Prophylaxis group: 9% - No prophylaxis group: 22% P = 0.028
Feng et al. (2014)	Randomized double blind placebo-controlled trial	<ul style="list-style-type: none"> - Diagnosis: ALL - Number of patients: 71 - Protocol: NA 	Ciprofloxacin.	Ciprofloxacin can prevent fever in neutropenic patients with ALL during the induction phase of chemotherapy with good tolerance and no serious side effects. Due to the selective pressure of intestinal flora resistance to ciprofloxacin, the long-term effectiveness needs further investigation.
Widjajanto et al. (2013)	Retrospective	<ul style="list-style-type: none"> - Diagnosis: AML - No. of patients: 45 - Protocol: frontline regimen by the children oncology group, regimen for relapse treatment. 	Ciprofloxacin.	Incidence of bacteremia: <ul style="list-style-type: none"> - Prophylaxis group: 36% - No prophylaxis group: 32%
Laoprasopwattana et al. (2013)	Prospective observational	<ul style="list-style-type: none"> - Diagnosis: AML - No. of patients: 38 - Protocol: NOPHO 2004 Hasle et al. (2012) 	Vancomycin plus cefepime. Piperacillin/tazobactam	Duration of hospital stay: <ul style="list-style-type: none"> - Prophylaxis group: 22 days - No prophylaxis group: 29 days P < 0.001 Rate of lung infection: <ul style="list-style-type: none"> - Prophylaxis group: 39% - No prophylaxis group: 80% P < 0.001

AML: acute myeloid leukemia.
 BFM: Berlin-Frankfurt-Munster.
 COG: children oncology group.
 UK MRC: United Kingdom medical research council.
 ALL: acute lymphoblastic leukemia.
 NA: not available.

The most recent study with the St Jude AML02 protocol was that of Al Omar et al. (2017), who used ciprofloxacin as a single prophylactic antibiotic in 50 AML patients between 2010 and 2015. Of these patients, 84% had at least one episode of bacterial infection. Gram-positive bacterial infections represented 62% of all episodes of bacteremia, coagulase-negative staphylococcus and *viridans* streptococci being the most commonly isolated bacteria.

Two other studies examined use of ciprofloxacin as a single antibacterial agent. One (Felsenstein et al., 2015) found that ciprofloxacin neither altered the incidence of overall bacteremia nor changed the pattern of fever or use of supportive care in 35 patients with de novo AML and 10 patients with relapsed AML. The other study (Yeh et al., 2014) is the only one that supports use of ciprofloxacin as a single agent in AML patients. The authors examined 24 patients treated with the protocol of the Taiwan Pediatric Oncology Group and found 25 episodes of bloodstream bacterial infections with no prophylaxis and 5 episodes with use of ciprofloxacin ($P < 0.01$).

Our search retrieved only one prospective study of AML patients, who received antibacterial prophylaxis according to the NOPHO 2004 protocol (Feng et al., 2014). Of the 38 patients included, 18 received either a combination of vancomycin and cefepime or piperacillin/tazobactam as a single agent; the comparison group of 20 patients received no antibacterial prophylaxis. Patients in the prophylactic group had fever less frequently than the control group ($P < 0.001$), a shorter duration of hospitalization ($P < 0.001$), and a lower rate of lung infections ($P < 0.001$). No statistically significant difference was observed between the two prophylactic regimens.

Another glycopeptide antibiotic, teicoplanin, administered at a dose of 15–20 mg/kg intravenously on alternate days was evaluated in a study of 50 patients (Boztug et al., 2017). *Viridans* sepsis was not detected in any phase of chemotherapy, whereas 12 cases were seen with no antibiotic ($P < 0.0001$). In addition, there were fewer episodes of febrile neutropenia in the prophylaxis group (44%) than in those with no prophylaxis (82%) ($P < 0.0001$). As in the other studies, the investigators found that use of glycopeptide antibiotics was safe and feasible, resulting in a dramatic reduction in *S. viridans* bacteria-associated sepsis and a decreased incidence of febrile neutropenia.

4. Prophylactic regimens used in ALL patients

Three studies investigated antibacterial prophylaxis in pediatric patients with ALL (Widjajanto et al., 2013; Laoprasopwattana et al., 2013; Yousef et al., 2004), in all of which the only agent used was ciprofloxacin. In a double-blinded, placebo-controlled trial (Widjajanto et al., 2013), patients aged 0–14 years in the induction phase of the WK-ALL-2000 protocol were randomly assigned to either ciprofloxacin or placebo. Of the 110 patients included, 58 received ciprofloxacin and 52 received placebo. Patients who received ciprofloxacin had a lower nadir of the absolute neutrophil count ($P < 0.01$), and a higher mortality rate (19% versus 6%) ($P = 0.05$). Therefore, the investigators warned against use of ciprofloxacin prophylaxis during the induction phase in ALL patients.

In another randomized placebo controlled trial (Laoprasopwattana et al., 2013), however, patients who received ciprofloxacin had fewer neutropenic fever episodes (50%) than patients in the placebo group (73%) ($P = 0.046$), with good tolerance and no serious side-effects. This study was limited by small number of patients and had a power of only 53% to detect a difference between the two groups.

The third study was a pilot study on ALL patients treated with the MRC UKALL XI protocol (Yousef et al., 2004). Patients received

ciprofloxacin following each delayed intensification course of chemotherapy and were compared with controls. The investigators found that patients who received ciprofloxacin had a lower rate of hospitalization, with a median hospital stay of 6 days versus 10 days for the controls ($P < 0.001$); a lower rate of admission to an intensive care unit, from 12% to 1.5% ($P = 0.02$); and a lower rate of overall bacteremia, from 22% to 9% ($P = 0.028$). In addition, no Gram-negative bacterial infections were reported in the ciprofloxacin group.

The study described above with use of the Taiwan Pediatric Oncology Group protocol (Yeh et al., 2014) also included 62 patients with ALL. The investigators observed 5 episodes of bloodstream bacterial infection in those receiving ciprofloxacin prophylaxis and 19 episodes in those with no prophylaxis ($P = 0.02$). Another study of both ALL and AML patients was a randomized, double-blinded, placebo-controlled, multicenter study (Castanola and Boni, 2003), which is the only one in which amoxicillin/clavulanate was given as prophylaxis to pediatric cancer patients. Although the study did not have enough power (88 patients) to demonstrate a clinically significant effect, use of amoxicillin/clavulanate was associated with detectable reductions in the occurrence of fever and infection in neutropenic children with acute leukemia.

5. Discussion

The optimal prophylactic regimen for pediatric leukemia patients is not clearly defined. Most of the studies of administration of prophylactic regimens were small retrospective observational studies; only three were randomized, double-blinded, placebo-controlled trials. The outcomes measured among the studies were not consistent, varying from the rate of bacterial infections, sepsis, rate of febrile neutropenia or length of hospital stay. Despite the limitations of the currently available literature, however, administration of antibacterial agents to AML patients appears to be effective and safe; in ALL patients, this does not appear to be a standard of care in all protocols.

In most of the studies of AML pediatric patients, broad-spectrum intravenous antibiotics were administered because of the high risks for bacterial infections and related complications such as bacteremia and septicemia associated with AML treatment protocols. Gram-positive bacterial infections, mainly with heterogeneous *S. viridans*, were the most common in AML patients (Creutzig et al., 2004; Kurt et al., 2008; Johanssen et al., 2013). In the studies of Kurt et al. (2008) and Inaba et al. (2014), infectious episodes were compared with and without administration of broad-spectrum antibiotics mainly containing vancomycin; the authors found a high rate of documented bacterial infections, especially Gram-positive bacteria and *S. viridans*, when no prophylaxis was used. The high rate of Gram-positive isolates is due to factors such as the use of high-dose cytosine arabinoside therapy in all AML protocols and the high incidence of oral mucositis (Creutzig et al., 2004). Both studies were limited by their retrospective design and potential confounding factors. Use of teicoplanin, a glycopeptide with Gram-positive bacterial coverage, was evaluated as an alternative to vancomycin in outpatient clinics, with a significant reduction in the number of Gram-positive bacterial infections and febrile neutropenia episodes (Boztug et al., 2017). In addition, teicoplanin has fewer adverse effects and requires less frequent administration than vancomycin (Svetitsky et al., 2009); however, in this study, the number of patients who received teicoplanin instead of vancomycin was not specified, and patients who received vancomycin and teicoplanin were considered as one group and analyzed together.

Use of cefepime as a single antibacterial agent or in combination with vancomycin in AML patients was associated with a

reduced incidence of septicemia and fewer days of hospitalization (Inaba et al., 2014). Therefore, cefepime may be warranted when VRE bacterial emergence is a concern.

Several studies have recommended use of fluoroquinolones for adult patients, and a systematic review of studies on antibiotic prophylaxis in afebrile neutropenic patients after chemotherapy (Gafer-Gvili et al., 2012) showed the most significant reduction in mortality in trials with quinolones. Our search for studies of antibacterial prophylaxis in children showed, however, that use of ciprofloxacin as single antibacterial prophylaxis in AML patients was associated with a high rate of infections, mainly with Gram-positive bacteria (Kurt et al., 2008; Inaba et al., 2014; Al Omar et al., 2017). Other studies have also reported that prolonged use of fluoroquinolones is a major risk factor for Gram-positive bacterial infection, especially with heterogeneous *S. viridans* (Al Omar et al., 2017; Razonable et al., 2002); the retrieved studies were retrospective and included small numbers of patients. In only one study (Yeh et al., 2014), use of ciprofloxacin was associated with a reduced rate of bloodstream infections and febrile neutropenia; the bacteria isolated most commonly were *S. viridans* and *Escherichia coli*-extended spectrum beta-lactamase.

Despite the recommendation to administer broad-spectrum antibiotics such as vancomycin as prophylaxis in AML patients, a few studies showed that use of vancomycin may be a risk factor for the emergence of VRE (Kurt et al., 2008; Inaba et al., 2014; Yoon et al., 2011). In one study (Yoon et al., 2011), the investigators showed that vancomycin use may prolong the duration of VRE colonization among patients in intensive care. Nevertheless, the benefits of using antibacterial coverage against Gram-positive bacteria may outweigh the risks. Further studies are needed to confirm the association between use of vancomycin for prophylaxis and the emergence of VRE.

Fewer studies have been reported on pediatric patients with ALL. The effects of antibacterial prophylaxis were investigated mainly during intensive chemotherapy phases such as the induction or the delayed intensification phases and ciprofloxacin was the only agent investigated. In a randomized double blinded placebo-controlled study (Laoprasopwattana et al., 2013), ciprofloxacin reduced the incidence of fever in neutropenic patients during the induction phase of chemotherapy, with no serious side-effects. A pilot study (Yousef et al., 2004) showed that use of ciprofloxacin during intensive phases of chemotherapy was associated with reduced rates of hospitalization, febrile neutropenia and bacterial infections. As emergence of Gram-negative bacteria resistant to fluoroquinolones has been reported in patients who received ciprofloxacin (Widjajanto et al., 2013; Kern et al., 2005), ciprofloxacin should be used cautiously, especially in the long term.

A randomized controlled trial showed a lower nadir of neutrophil count and higher mortality in ALL patients in the induction phase who received ciprofloxacin on a reduced intensity protocol; however, the results were not statistically significant. Investigators recommended that this agent not be used (Widjajanto et al., 2013).

In conclusion, antibacterial prophylaxis mainly with antibiotics that cover Gram-positive bacteria is recommended in pediatric patients with AML. For ALL patients, more studies are required to determine the role of antibacterial prophylaxis; however, prophylaxis may be considered for patients who are undergoing intensive chemotherapy phases and are at high risk for infections, ciprofloxacin being the most commonly used agent.

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