Prospective Randomized Comparison of Imipenem-Cilastatin and Piperacillin-Tazobactam in Nosocomial Pneumonia or Peritonitis

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Nosocomial pneumonia and acute peritonitis may be caused by a wide array of pathogens, and combination therapy is often recommended. We have previously shown that imipenem-cilastatin monotherapy was as efficacious as the combination of imipenem-cilastatin plus netilmicin in these two settings. The efficacy of imipenem-cilastatin is now compared to that of piperacillin-tazobactam as monotherapy in patients with nosocomial pneumonia or acute peritonitis. Three hundred seventy one patients with nosocomial pneumonia or peritonitis were randomly assigned to receive either imipenem-cilastatin (0.5 g four times a day) or piperacillin-tazobactam (4.5 g three times a day). Three hundred thirteen were assessable (154 with nosocomial pneumonia and 159 with peritonitis). For nosocomial pneumonia, clinical-failure rates in the piperacillin-tazobactam group (13 of 75 [17%]) and in the imipenem-cilastatin group (23 of 79 [29%]) were similar (P = 0.09), as were the numbers of deaths due to infection (6 in the imipenem-cilastatin group [8%], 7 in the piperacillin-tazobactam group [9%]) (P = 0.78). For acute peritonitis, clinical success rates were comparable (piperacillin-tazobactam, 72 of 76 [95%]; imipenem-cilastatin, 77 of 83 [93%]). For infections due to Pseudomonas aeruginosa, 45 patients had nosocomial pneumonia (21 in the piperacillin-tazobactam group and 24 in the imipenem-cilastatin group) and 10 had peritonitis (5 in each group). In the patients with nosocomial pneumonia, clinical failure was less frequent in the piperacillin-tazobactam group (2 of 21 [10%]) than in the imipenem-cilastatin group (12 of 24 [50%]) (P = 0.004). Bacterial resistance to allocated regimen was the main cause of clinical failure (1 in the piperacillin-tazobactam group and 12 in the imipenem-cilastatin group). For the patients with peritonitis, no difference in clinical outcome was observed (five of five cured in each group). The overall frequencies of adverse events related to treatment in the two groups were similar (24 in the piperacillin-tazobactam group, 22 in the imipenem-cilastatin group). Diarrhea was significantly more frequent in the piperacillin-tazobactam group (10 of 24) than in the imipenem-cilastatin group (2 of 22). This study suggests that piperacillin-tazobactam monotherapy is at least as effective and safe as imipenem-cilastatin monotherapy in the treatment of nosocomial pneumonia or peritonitis. In P. aeruginosa pneumonia, piperacillin-tazobactam achieved a better clinical efficacy than imipenem-cilastatin, due to reduced development of microbiological resistance. Tolerance was comparable, with the exception of diarrhea, which was more frequent with piperacillin-tazobactam.

Pneumonia is the second most common type of nosocomial infection (3, 14, 15, 18). It represents 15 to 18% of nosocomial infections, translating into four to seven episodes/1,000 hospitalizations (0.6 to 1.1% of hospitalized patients) (10 to 25% of patients in intensive care units [ICU]) (13, 14). In ventilated patients, the rate of nosocomial pneumonia in medical and surgical ICU is 15/1,000 ventilator days and is increased 4- to 21-fold in comparison with nonintubated ICU patients (14). Furthermore, nosocomial pneumonia is, besides bloodstream infection, the leading cause of death from hospital-acquired infections (4, 13, 20) and also increases significantly survivors’ length of stay (13, 14). It can be caused by a wide array of pathogens including aerobic and anaerobic gram-negative and gram-positive bacteria (3, 14, 15, 29, 45). As the responsible pathogens are usually not known at the time of presentation and early and effective antibiotic therapy is correlated to survival (3, 30, 45), empirical broad-spectrum antibiotic coverage is initially recommended, either in monotherapy or in combination therapy (3, 14, 15, 30, 45).

Secondary peritonitis is another clinical setting which requires the empiric administration of antibiotics. Since this infection is usually due to polymicrobial flora, a broad coverage including anaerobes and Enterobacteriaceae is needed, as shown by Bartlett’s observation more than 25 years ago (2). Since then, a combination of clindamycin or metronidazole with an aminoglycoside has been considered standard therapy for peritonitis (17, 39). However, the development of carbapenems, broad-spectrum cephalosporins, or fluoroquinolones has afforded the possibility of restraining the use of aminoglycosides which are associated with potential nephrotoxicity and ototoxicity. Despite numerous methodological problems in several trials using patients with peritonitis, monotherapy appeared as effective as standard combinations in this setting (10, 23, 24, 32). Indeed, in a well-designed study, Solomkin et al. showed that imipenem-cilastatin was even more effective than a com-
Piperacillin is a semisynthetic ureidopenicillin with a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria and with an improved activity against *Pseudomonas aeruginosa* compared with other ureidopenicillins (6). This expanded-spectrum penicillin is nevertheless susceptible to hydrolysis by several β-lactamases (1). Tazobactam, an inhibitor derived from penicilllic acid sulfone, inhibits a wide range of commonly encountered β-lactamases of the chromosomal and plasmid-mediated types (1, 6). The combination of piperacillin and tazobactam is active in vitro against a large spectrum of bacteria including *Enterobacteriaceae, Pseudomonas*, anaerobes, and staphylococci (1, 6). Comparative and noncomparative clinical studies with or without an aminoglycoside have been conducted with patients with intra-abdominal infections (5, 23, 31, 32, 35), complicated urinary tract infections (34), *bacteremia* (7), bone and joint infections (6), gynecological infections (6, 43), empiric treatment of febrile neutropenia (11, 12, 16), and community-acquired or nosocomial pneumonia (29, 37). In all these studies, piperacillin-tazobactam has shown either a similar or a better efficacy than the comparative regimen (34, 37, 38). There was also a paucity of data comparing piperacillin-tazobactam monotherapy to other regimens in the treatment of nosocomial pneumonia. Therefore, the present study was conducted to assess the efficacy and safety of piperacillin-tazobactam in comparison to those of imipenem-cilastatin in the treatment of nosocomial pneumonia or peritonitis.

**MATERIALS AND METHODS**

**Study design.** The study was conducted from December 1993 to May 1996 in the medical and surgical wards and ICU of three Swiss hospitals: Geneva University Hospital (206 randomized patients), Lausanne University Hospital (142 randomized patients), and Sion Regional Hospital (23 randomized patients). This prospective randomized controlled trial was approved by the human-research ethics committee of each participating center. In each center, consecutive randomized patients), and Sion Regional Hospital (23 randomized patients). This prospective randomized controlled trial was approved by the human-research ethics committee of each participating center. In each center, consecutive patients who fulfilled the inclusion criteria were randomly assigned to one of the two treatment regimens by sealed numbered envelopes. The randomization was stratified according to the infection (pneumonia or peritonitis). Each study center had its own block numbers for randomization.

**Criteria for eligibility.** Patients were eligible if they were more than 16 years old and had given informed consent.

(i) **Nosocomial pneumonia.** Nosocomial pneumonia was diagnosed as a new infiltrate on chest X ray 72 h or more after admission with two or more of the following symptoms: fever ≥38°C, new onset of production of purulent sputum, significant increase in volume of purulent sputum, or peripheral leukocytosis (WBC count >10³/liter) (22). Microbiological diagnosis was attempted in all cases prior to inclusion and included cultures of sputum, nasotracheal aspirate, aspirate through orotracheal tube, bronchoscopy with bronchoalveolar lavage (BAL) and/or protected brush specimens, pleural fluid, and blood. Pneumonia was microbiologically documented if cultures of sputum or tracheal aspirate showed one or more predominant pathogens and microscopical examination showed more than 25 polymorphonuclear cells and fewer than 10 epithelial cells per low-power (×100) field (22). For BAL and protected brush specimens, we used cutoff values of 10⁶ and 10⁷ CFU/ml, respectively, as previously (8).

(ii) **Acute peritonitis.** Acute peritonitis was assessed intraoperatively, and microbiological documentation was attempted in all cases. The only exception was sigmoid diverticulitis, which was defined as muscle guarding and rebound tenderness in the left iliac fossa or left flank with leukocytosis (WBC count, >10³/liter) or leukopenia (WBC count, <4 x 10³/liter) and fever ≥38°C. In cases where a computerized axial tomography scan was diagnostic, peritonism was sufficient for inclusion.

(iii) **Exclusion criteria.** Exclusion criteria included pregnancy or lactating state, expected survival of less than 48 h, known allergy to β-lactam antibiotics or β-lactamase inhibitors, human immunodeficiency virus infection, concomitant infection other than intra-abdominal or nosocomial pneumonia, infection with microorganisms known to be resistant to either of the study treatments, previous treatment with any appropriate antibacterial agent for the same infection, previous inclusion in the trial, and finally, serum transaminase, alkaline phosphatase, and bilirubin levels greater than or equal to three times the upper normal limit.

**Treatments.** Patients were openly assigned to one of the following two regimens: piperacillin-tazobactam at 4.5 g three times a day or imipenem-cilastatin at 500 mg four times a day. The dosage of each regimen was adjusted to renal function.

**Collection of data.** A complete history and a physical examination were performed for each patient at baseline. At each center, all patients were monitored each day by a local investigator. Clinical data was recorded on each day of treatment: vital signs, adverse events, concomitant medication, any modification of study drug dosage; for patients with nosocomial pneumonia, description of respiratory secretion, sputum production, severity of cough, rales on auscultation or dulness on percussion, mechanical ventilation, FIO₂, P/O₂, PEEP; for patients with peritonitis, oral fluid intake, diet, nausea and/or vomiting, abdominal pain, peritonism on physical examination, qualitative aspect of drainage, fluid bowel sounds, healing of surgical wound. Blood chemistry and hematology were performed at baseline, on day 3, within 2 days post treatment (early follow-up), and between 2 and 4 weeks posttreatment if appropriate (late follow-up). Microbiological samples were taken at baseline, on day 3, and on early and late follow-ups if appropriate and included blood cultures and cultures from respiratory, abdominal, or any other relevant clinical focus of infection.

**Clinical efficacy** was assessed according to published clinical guidelines (9, 42) at the end of treatment and 2 to 4 weeks after the end of treatment by a follow-up interview.

**Peritonitis.** Patients with peritonitis were considered to have been clinically cured if the initial course of therapy and the initial intervention resolved the intra-abdominal infectious process. Any further antibiotic treatment or surgery for peritonitis within 7 days after the end of treatment was considered a failure of the original treatment (42).

**Nosocomial pneumonia.** For patients with nosocomial pneumonia, cure was defined as the complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of signs and symptoms of infection (no clinical improvement), lack of improvement associated with a pathogen resistant to the allocated regimen, development of a breakthrough bacteremia or sepsis, or relapse. Patients who were not cured according to the above defined criteria were also categorized under “failure.”

A study coordinator (C.J.) discussed all patients with the local investigators and entered the data in the database with the help of a research nurse (D.A.). In addition, all patients with a diagnostic problem or a complicated clinical course as well as patients who failed therapy or were not evaluable were assessed by a blinded investigator (A.C.).

**Microbiological susceptibility tests.** Antimicrobial susceptibility tests were done by agar disc diffusion according to National Committee for Clinical Laboratory Standards guidelines. Any isolate with an inhibition zone >17 mm in diameter for piperacillin-tazobactam and ≤13 mm for imipenem was considered resistant to the antibiotic.

**Statistical analysis.** Statistics were run with the SAS software package (SAS Institute Inc., Cary, N.C.). All tests were two-tailed. A P value ≤0.05 was considered significant.

Proportions and means in baseline characteristics and outcome were compared between treatments by using Fisher’s exact test, two-sample t test with pooled variance, or Wilcoxon test, as appropriate. In considering outcomes, relative risks (RRs) with 95% confidence intervals (95% CIs) were used to measure the size of the effect of the tested regimen (piperacillin-tazobactam) versus the reference regimen (imipenem-cilastatin).

Adjusted analyses were run when necessary. The Mantel-Haenszel stratified test was used to measure adjusted relative risks for an outcome while controlling for a potential confounding factor with a binomial distribution. Multivariate logistic regression was used to get adjusted odds ratios when several potential confounding factors were identified for a group or subgroup, whether they were discrete or continuous.

**RESULTS**

Three hundred seventy-one patients were randomized, of whom 58 were not evaluable for response because of violation of entry criteria (37 patients), less than 48 h of therapy (13 patients), addition of another antibiotic without adequate reason (4 patients), early stop of resuscitation (3 patients), or early toxicity (1 patient). Twenty-two of these patients were receiving imipenem-cilastatin, and 36 were receiving piperacillin-tazobactam. Among the 313 remaining patients, 154 had nosocomial pneumonia and 159 had acute peritonitis.

**Nosocomial pneumonia.** Among the 154 evaluable patients in the pneumonia group, 75 received piperacillin-tazobactam and 79 received imipenem-cilastatin. Baseline characteristics were equally distributed between the two treatments, with the exception of bacteremic infections, which were more common
in the imipenem-cilastatin group (10 of 79 versus 3 of 75 [P = 0.08]) (Table 1).

Nosocomial pneumonia was microbiologically documented in 124 of 154 patients (81%), 58 of 75 (77%) in the piperacillin-tazobactam group and 66 of 79 (83%) in the imipenem-cilastatin group (P = 0.42) (Table 2). The samples leading to microbiological diagnosis were (i) sputum or tracheal aspirate (41 for piperacillin-tazobactam versus 43 for imipenem-cilastatin), (ii) BAL or protected brush (14 versus 13), and (iii) blood (3 versus 10) (Table 2). In 60% (75 of 124) of cases of microbiologically documented pneumonia, a unique pathogen was recovered. In this subgroup, gram-negative bacilli were predominant (63 of 75 [84%]) and P. aeruginosa was the most frequently isolated pathogen (28 of 63 [44%]). Staphylococcus aureus and Streptococcus pneumoniae were the only two gram-positive organisms isolated in the monobacterial pneumonia subgroup and represented together only 16% (12 of 75). Mixed infections were observed in 40% of microbiologically documented cases of pneumonia (49 of 124). Again, in this subgroup P. aeruginosa was the most frequently found pathogen (isolated in 17 of 49 patients [35%]) (Table 2).

TABLE 1. Patient characteristics at baselinea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Piperacillin-tazobactam (%)</td>
</tr>
<tr>
<td>Nosocomial pneumonia Total</td>
<td>75 (64.2)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.1 ± 16.9</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>68.4 ± 13.9</td>
</tr>
<tr>
<td>APACHE II at randomization</td>
<td>14.6 ± 6.8</td>
</tr>
<tr>
<td>Male/female</td>
<td>58/17</td>
</tr>
<tr>
<td>No. of comorbidities:</td>
<td></td>
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<tr>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>1–2</td>
<td>35 (46.7)</td>
</tr>
<tr>
<td>3–4</td>
<td>30 (40.0)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>PEEP</td>
<td>6.4 ± 2.2</td>
</tr>
<tr>
<td>pO2/FiO2</td>
<td>143.7 ± 75.3</td>
</tr>
</tbody>
</table>

TABLE 2. Documentation and microbiology of nosocomial pneumonia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Piperacillin-tazobactam (n = 75) [%]</td>
</tr>
<tr>
<td>Clinical documentation</td>
<td>17 [23]</td>
</tr>
<tr>
<td>Microbiological documentation</td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>18</td>
</tr>
<tr>
<td>Tracheal aspirate</td>
<td>23</td>
</tr>
<tr>
<td>BAL</td>
<td>11</td>
</tr>
<tr>
<td>Protected brush</td>
<td>3</td>
</tr>
<tr>
<td>Blood</td>
<td>3</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>29</td>
</tr>
<tr>
<td>E. coli</td>
<td>16</td>
</tr>
<tr>
<td>Enterobacter sp.</td>
<td>2</td>
</tr>
<tr>
<td>Klebsella sp.</td>
<td>2</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>4</td>
</tr>
<tr>
<td>S. aureus</td>
<td>2</td>
</tr>
<tr>
<td>Mixed</td>
<td>25</td>
</tr>
<tr>
<td>P. aeruginosa + other</td>
<td>5</td>
</tr>
</tbody>
</table>
Infections due to *P. aeruginosa*. Since pneumonia due to *P. aeruginosa* is associated with a worse prognosis (4, 17–20, 25, 36, 42), a subgroup analysis was done on the 55 patients with infections due to *P. aeruginosa* (Table 4). Forty-five patients had nosocomial pneumonia (21 were treated with piperacillin-tazobactam and 24 were treated with imipenem-cilastatin); 10 had peritonitis (5 in each group). The baseline characteristics of the patients with nosocomial pneumonia were different in terms of sex (male/female ratio, 16/5 in the piperacillin-tazobactam group versus 11/13 in the imipenem-cilastatin group ($P = 0.07$)), number of polymicrobial infections (piperacillin-tazobactam, 5 of 21; imipenem-cilastatin, 13 of 24 ($P = 0.07$)), and APACHE II score (piperacillin-tazobactam, 10.9; imipenem-cilastatin, 14.3 ($P = 0.06$)). Clinical failures were observed more often in patients treated with imipenem-cilastatin (12 of 24 [50%]) than in patients treated with piperacillin-tazobactam (2 of 21 [10%]) ($P = 0.004$). They were mainly due to the development of resistance (six to imipenem-cilastatin, one to piperacillin-tazobactam) or initial resistance (one to imipenem-cilastatin, none to piperacillin-tazobactam) to the allocated regimen. In a crude analysis, the RR for clinical failure comparing piperacillin-tazobactam to imipenem-cilastatin was 0.19 (95% CI, 0.05 to 0.76) ($P = 0.004$) (Table 4). A multivariate logistic regression model was built to control for

![Table 3. Outcomes in patients according to type of infection](image)

![Table 4. Outcomes of infections due to *P. aeruginosa* (alone or in combination with other organisms) according to treatment regimen](image)
suggests that piperacillin-tazobactam monotherapy is at least as effective as imipenem-cilastatin, which is commonly used in the treatment of nosocomial pneumonia and peritonitis. Despite randomization, the two groups were somewhat imbalanced regarding bacteremia at baseline. Since this parameter is negatively related to prognosis (3, 14, 44), a stratified analysis was run to adjust for this potential confounding factor. The result confirmed the equivalence of the two treatments regarding clinical efficacy. Although analysis of subgroups may be questionable for methodological reasons because the benefit of randomization may be lost, we believe that those results are worth presenting. Indeed, potential confounding factors were first identified in the subgroup of patients with pneumonia due to \textit{P. aeruginosa}, and an adjusted analysis (logistic regression) was run, confirming the crude analysis.

The emergence of \textit{P. aeruginosa} resistant to imipenem-cilastatin has been reported in several trials. The development of resistance to imipenem-cilastatin in \textit{P. aeruginosa} is related to the loss of a specific porin (OprR2). Our previous study showed that imipenem-cilastatin resistance was not prevented by the addition of netilimcin (10). In two studies comparing imipenem-cilastatin to either ceftazidime (33) or ciprofloxacin (21), imipenem-cilastatin was less effective than ceftazidime or ciprofloxacin in the \textit{P. aeruginosa} pneumonia subgroup. In both studies, the development of resistance to imipenem-cilastatin in \textit{P. aeruginosa} strains explained the lower efficacy of imipenem-cilastatin. We now report that piperacillin-tazobactam is superior to imipenem-cilastatin in preventing the emergence of \textit{P. aeruginosa} resistance. Piperacillin is highly active against \textit{P. aeruginosa} (1, 6, 38). When piperacillin resistance develops in \textit{P. aeruginosa}, it is mostly due to a chromosomal \textbeta-lactamase. Tazobactam is active against Richmond and Sykes class II to V \textbeta-lactamases and against extended-spectrum \textbeta-lactamases but has only species-specific activity against chromosomal class Ic \textbeta-lactamases. In particular, tazobactam is usually not active against \textit{P. aeruginosa} chromosomal \textbeta-lactamases and thus does not reverse piperacillin resistance in \textit{P. aeruginosa} strains resistant to piperacillin. On the other hand, tazobactam has no inducing capacities on chromosomal class I \textbeta-lactamases (6) and therefore exerts only a minimal selective pressure in favor of species producing this class of \textbeta-lactamase. Thus, it is clear that the improved efficacy of piperacillin-tazobactam over that of imipenem-cilastatin for \textit{P. aeruginosa} pneumonia can be expected only in clinical centers in which \textit{P. aeruginosa} resistance to piperacillin is low, as is the case in the three centers involved in the present study.

In acute peritonitis, piperacillin-tazobactam was equivalent to imipenem-cilastatin in our study. Both drugs achieved excellent cure rates, in excess of 90% (95 and 93%, respectively). The clinical cure rate for piperacillin-tazobactam was comparable to that (91%) in the study by Brismar et al. which also compared piperacillin-tazobactam to imipenem-cilastatin in intra-abdominal infections (5). However, while the clinical cure for imipenem-cilastatin was only 69% in the latter study, it reached 93% in our study. This improved efficacy of imipenem-cilastatin for peritonitis was probably related to the daily dosage of imipenem-cilastatin used in the present study (0.5 g four times a day instead of three times a day in the study by Brismar et al.). In the study by Brismar et al. most of the difference in clinical failures between the two groups was due to more frequent development of intra-abdominal abscesses and surgical-wound infection in the imipenem-cilastatin group.

In the present study we observed equal distributions of clinical failures in the two treatment groups, i.e., only one case of intra-abdominal abscess in the piperacillin-tazobactam group and none in the imipenem-cilastatin group, while surgical-wound infections were equally distributed between the two treatment groups.
groups. Most importantly, the present study confirms previous trials demonstrating that a combination treatment with aminoglycoside in intra-abdominal infections can be replaced by less toxic monotherapies.

Both treatments were well tolerated, with comparable amounts of adverse reactions, with the exception of diarrhea, which was more frequent in the piperacillin-tazobactam-treated patients. It is worth noting that this difference had already been observed in a study comparing piperacillin-tazobactam to clindamycin and gentamicin in women with pelvic infections, where diarrhea was significantly more frequent in patients treated with piperacillin-tazobactam (43).

In conclusion, piperacillin-tazobactam monotherapy is at least as effective and safe as imipenem-cilastatin in the treatment of nosocomial pneumonia and peritonitis. In P. aeruginosa nosocomial pneumonia, piperacillin-tazobactam was associated with an improved efficacy over that of imipenem-cilastatin. The observed failures were mainly due to the development of microbiological resistance to imipenem-cilastatin. The observed failures were mainly due to the development of microbiological resistance to imipenem-cilastatin. Finally, adverse events and superinfections were equally distributed between the two treatment groups with the exception of diarrhea, which was more frequent with piperacillin-tazobactam.

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REFERENCES

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Inhibition of Human Hepatitis B Virus Replication by AT-61, a Phenylpropenamide Derivative, Alone and in Combination with (−)β-1-2′,3′-Dideoxy-3′-Thiacytidine

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Efficacy of the Carbocyclic 2′-Deoxyguanosine Nucleoside BMS-200475 in the Woodchuck Model of Hepatitis B Virus Infection

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