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Research Article

Removal of pharmaceutically active compounds from hospital wastewater by ozonation pretreatment

Mahammad MANSIMLI[1], Havva ATEŞ[*2]

[1] Konya Technical University, Faculty of Engineering and Natural Science, Graduate Education Institute, Konya, Türkiye
[2]Konya Technical University, Faculty of Engineering and Natural Science, Department of Environmental Engineering, Konya, Türkiye

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ABSTRACT

Hospital wastewater includes many pharmaceutically active compounds (PhACs). Since this resulted in both PhACs distribution to the environment and development of antibiotic resistance in microorganisms, on-site treatment of hospital wastewater has gained importance. In this study, the removal of 21 PhACs consisting of 12 parent compounds and 9 main metabolites from hospital wastewater by ozonation was investigated. In this context, commonly used analgesics (Paracetamol, Diclofenac, Ibuprofen, and Naproxen, 4'-Hydroxydiclofenac, 5-Hydroxydiclofenac, 1-Hydroxyibuprofen, 2-Hydroxyibuprofen, Carboxyibuprofen, (S)-O-Desmethyl naproxen) and antibiotics (Ciprofloxacin, Sulfamethoxazole, Trimethoprim, Erythromycin, Metronidazole, Clarithromycin, Azithromycin, Clindamycin, N-Acetyl-Sulfamethoxazole, Sulfamethoxazole-β-D-Glucuronide, Clindamycin sulfoxide) were selected. PhAC analyses were performed by HPLC/MS-MS. The ozonation dose was between 0.05-5.0 mg O_3/mg COD.

In real hospital wastewater, many of the selected PhACs were detected and total analgesic and antibiotic were determined as 22.9 and 40.6 µg/L, respectively. The results showed that detected PhACs were completely removed at 1.5 mg O_3/mg COD. Sulfamethoxazole was degraded at the lowest dose of ozone (0.05mg O_3/mg COD), while Ciprofloxacin and 2-Hydroxy ibuprofen were relatively resistant to non-stoichiometric doses of ozone. The removal efficiencies of Ciprofloxacin and 2-Hydroxy ibuprofen were determined as 77% and 37%, respectively, at 0.5 mg O_3/mg COD. Additionally, COD removal was 48% at 1.5 mg O_3/mg COD. As a result, pre-oxidation of hospital wastewater can be an effective method for on-site pretreatment of PhACs.

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INTRODUCTION

The emergence of new types of drugs day by day makes inevitable their distribution into the environment. Hospital wastewater is an important point source. While the amount of water consumed in hospitals varies between 25 and 875 L/bed/day in Türkiye [1], it changed between 19 and 2258 L/bed/day worldwide [2]. Hospital wastewater is a serious problem due to its harmful effects the environment and humans through direct or indirect contact. In this context, the biggest challenge is increase of antibiotic-resistant microorganisms in aquatic environments in recent years. Hospital wastewater contains pharmaceutically active compounds (PhACs), disinfectants, drugs, radioactive elements, solvents, microorganisms, heavy

***Corresponding author.**
*E-mail address: hates@ktun.edu.tr

metals, and toxic chemicals [2]. An important proportion of pharmaceutically active compounds in WWTPs originates from hospital wastewater. In addition, studies conducted in municipal wastewater treatment plants (WWTPs) show that the antibiotic load for some antibiotics (Sulfamethoxazole, Roxithromycin, Ofloxacin, Erythromycin, and Azithromycin) was quite high and may remain at levels that may pose a risk to aquatic organisms in WWTP effluents [3, 4]. This situation highlights the need for hospital wastewater treatment to reduce both antimicrobial microorganisms and antimicrobial loads entering municipal wastewater treatment plants [5]. China and Japan, which have high rates of enteric and cancer outbreaks, have introduced on-site pre-treatment of hospital wastewater before discharge to prevent the spread of pathogens. European countries treat entirely hospital wastewater because of the risk it poses. Some countries such as France, Denmark, and Spain have conducted pilot and full-scale studies of on-site treatment of hospital wastewater [6]. In Türkiye, the occurrence of PhACs in hospital wastewater was researched [7, 8, 9]. Furthermore, the fate of PhACs was determined by treatment processes such as chemical treatment [10, 11] and biological processes [9, 12] at the laboratory scale. There is no legal regulation regarding the separate treatment of hospital wastewater from domestic wastewater and the pollutant limit values for the discharge of hospital wastewater into the sewer infrastructure in our country. Likewise, it is stated that pharmaceutical residues are not regulated at the legislative level even in many developed countries [13].

Treatability of hospital wastewater in combined systems including natural-based treatment processes, activated sludge processes [14, 15], membrane bioreactors [16, 17], various filtration processes [18], chemical treatment [19, 20] and tertiary treatment [21, 22, 23] was investigated. In addition, ozonation, chlorination, and UV disinfection have been used as final treatment steps in some pilot and full-scale plants [22, 23]. These treatment methods have many advantages and disadvantages such as cost, ease of operation, sludge formation, land requirements, etc. In this context, single-stage pre-ozonation can be considered as a good option due to rapid integration for on-site treatment of PhACs. Also, it can decrease the load of organic and antibiotic-resistant microorganisms entering WWTPs.

Studies on the removal of PhACs from aquatic media using conventional [14-17], and novel treatment processes [24, 25] have been ongoing from the past to the present. However, a review study on hospital wastewater treatment stated that there were limited studies on hospital wastewater treatment, and only 10 % of the studies in the literature was on advanced oxidation processes [6].

Ozonation is widely used in water and wastewater treatment because it is a strong oxidant and reacts with many organic substances. PhACs reacted with ozone or, hydroxyl radicals formed by the decomposition of ozone. Ozone molecules are selective for certain functional groups, unlike hydroxyl radicals [26]. An important advantage of ozonation is that it enhances the degradation of PhACs when used as a pre-treatment [27]. Hospital wastewater contains compounds with high ozone affinity such as phenols, anilines, aromatics, amines, and thioethers. Therefore, they can be effectively treated even at low ozone doses (0.5 g O_3/g DOC). Independent variables affect the removal efficiencies of PhACs during ozonation. In this context, Lee et al. (2014) reported that increasing pH from 7 to 8.5 resulted in lower removal efficiencies for compounds having high ozone affinity [28]. In another study stated that ozonation following membrane bioreactor increased the removal of Norfloxacin, Ciprofloxacin, Ofloxacin, and Sulfamethoxazole from hospital wastewater [29]. Characterization of hospital wastewater can be changeable. This affects the efficiency of treatment processes. In this context, Hansen et al. (2016) investigated the effects on removal efficiency of PhACs of variable dissolved organic carbon (DOC) and pH in the pilot scale MBBR/ozonation process. Higher ozone dose was required for the same removal efficiencies at alkaline pH. Also, the needed ozone amount changed according to the structure PhACs. For instance, Sulfadiazine and Diatrizoic acid were completely removed at 0.5 mg O_3/mg DOC and 4.7 mg O_3/mg DOC, respectively [30]. Although advanced oxidation is a priority treatment process for the mineralization of PhACs, the mineralization ratio can change according to PhAC structure. A study stated that PhACs mineralized 54.7% in 1.57 g O_3/h with O_3/UV process, COD and aromatics decreased 64% and 81%, respectively [31]. In another study, removal of anti-cancer drugs in hospital wastewater with O_3/UV process was relatively low [32]. Nevertheless, ozonation has strongly recommended as a final treatment step before discharge into sensitive water environments in these studies.

Studies have generally focused on the removal of PhACs in synthetic solutions and there are limited studies on ozonation of real hospital wastewater. In addition, the parent PhACs were generally investigated in hospital wastewater in these studies. In the light of all this information, this study aimed to determine the fate of 21 PhACs (12 parent compounds and 9 main metabolites) in hospital wastewater by applying ozonation.

MATERIALS AND METHODS

Ozonation Process

The ozonation process used in the study is a device with a maximum capacity of 13 g/h. The process was supplied by a local firm Genozon (Türkiye). It can set in different strength of current and oxygen flow. The system consists of an oxygen concentrator and an ozone process to increase ozone production. The oxygen of the air is concentrated with the oxygen concentrator and fed to the ozone generator. Then, in the ozone generator, the diatomic oxygen molecule is converted into triatomic ozone gas and fed to 2L closed reactors. (Figure 1). The process was designed as two reactors to increase of contact of ozone with wastewater. Ozone measurement was done according to standard method. For determine the ozone used by the wastewater, waste ozone was captured in a 10% potassium iodide solution within the gas washing bottle and was titrated with potassium thiosulphate [33]. Ozonation experiments were conducted at 0.05, 0.1, 0.25, 0.5, 1.5, 3.0 and 5.0 mg O_3/mg COD doses natural pH of wastewater and room

temperature.

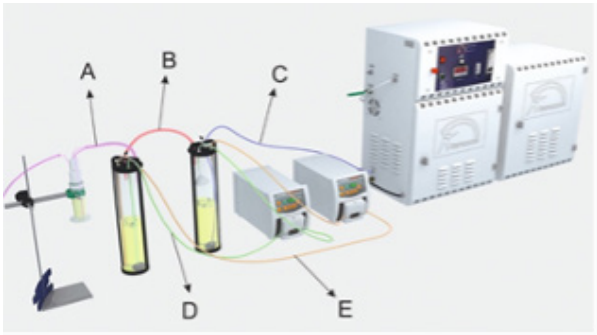

Figure 1. Ozonation process (A: inlet of waste ozone into gas washing bottle, B: foam transition between reactors, C: ozone inlet, D: the pipe that transfers ozone collected from the first reactor with funnel to the second reactor E: the pipe that ensures the continuous circulation of leachate accumulated in the second reactor) [34]

Chemicals

In this study, 21 PhACs from analgesic and antibiotic groups and their metabolites were measured. Selected analgesics were Paracetamol (PAR), Diclofenac (DCF), Ibuprofen (IBU), and Naproxen (NAP), 4'-Hydroxydiclofenac, 5-Hydroxydiclofenac, 1-Hydroxyibuprofen, 2-Hydroxyibuprofen, Carboxyibuprofen, (S)-O-desmethyl Naproxen, and antibiotics were Ciprofloxacin (CIP), Sulfamethoxazole (SMX), Trimethoprim (TMP), Erythromycin (ERY), Metronidazole, (MET) Clarithromycin (CLA), Azithromycin (AZI), Clindamycin (CLI), N-Acetyl-sulfamethoxazole, Sulfamethoxazole-β-D-glucuronide and Clindamycin sulfoxide. Mix internal standard were acquired from Dr. Ehrenstorfer GmbH (Augsburg, Germany). All standards used in this study were analytical grade and of high purity (mostly ≥98 %) and were supplied from Toronto Research Chemicals Inc. (North York, Canada). Elution solvents, water and methanol, were purchased Sigma Aldrich (Sigma-Aldrich Corporation, Germany). The other used chemicals like formic acid and ammonium formate were taken from Sigma Aldrich, too. 0.45 µm syringe type filters from Whatman, Little Chalfont, UK, HLB cartridge for solid phase extraction from Waters were purchased.

Hospital Wastewater

Used hospital wastewater was taken from the sewerage system connection of Necmettin Erbakan University hospital as two-hours composites. Oxidation experiments were made with two different samples which taken in different times. Samples analyses were immediately made for conventional parameters solid phase extraction of samples for PhACs analysis within the same day. Then, extracts were stored by HPLC-MS/MS analysis at +4 oC.

PhACs Analysis

Samples filtered with 0.45 µm syringe type filters. Solid phase extraction steps are; HLB cartridge was conditioned with 20 mL methanol and 6 mL water, sample was filtered from HLB cartridge, then was cleaned 10 mL water and was dried at 10 mL/min rate. Absorbed compounds was eluted from the cartridge with 10 mL methanol. Finally, methanol was evaporated to 1 mL through slowly nitrogen flow. Concentrated extracts were analyzed with HPLC-MS/MS (Agilent, 6460, HPLC series 1200) equipped Poroshell 120 SB-C18 (4.6 mm I.D. x 150 mm x 2.7 micron particle size) according to EPA 1694 after adding internal standard. LOQ value for all investigated PhAC and metabolites was 5 ng/L. Mobile phase flow rate and temperature 0.5 ml/min and 35 °C, respectively. Elution solvents were water consisted of 5 mM ammonium formate and 0.1% formic acid (Mobil phase A) and Methanol (Mobil phase B) and time of solvent gradient program was 28 min.

RESULTS AND DISCUSSIONS

Total analgesic and antibiotic concentrations were 22.9 and 40.6 µg/L, respectively. Additionally, the PhACs detected in hospital wastewater collected on different days were not similar (Table 1). A review study stated that the average concentration of analgesics in hospital wastewater was higher in North America than in Asia and Europe. However, the average concentration of antibiotics was high in Asia. Average concentrations of analgesics and antibiotics ranged from 10 to 100 µg/L [2]. It was reported that the most frequently detected antibiotics were CIP, SMX, and TMP in hospital effluents [36]. In this study, CIP, SMX, and TMP were detected in hospital wastewater samples. In a study conducted in Türkiye, Gönder and al. (2021) reported that SMX and 4N-Acetyl-Sulfamethoxazole and Naproxen were detected in high concentrations in both summer and winter [8].

The COD value of the hospital wastewater was 767.1±232 mg/L. Ozone amounts were determined taking into consideration the measured COD. Table 1 shows PhACs change in different ozone doses. PAR was completely removed in 15 min under an O_3 flow rate of 13 g/h. Additionally, it was removed 82% in the lowest ozone dose. In studies on ozonation of PAR, it was determined that PAR was removed more easily in acidic or alkaline pH. For instance, Andreozzi et al. (2003) reported that it was completely removed in acidic and neutral pH in aqueous solution containing 4.9–5.3 mM PAR [37]. However, removal was completed in a shorter time in acidic pH. In another study, TOC was reduced (20 mg/L) by only 18% at pH 7.2 and 60 min contact time at 1 g/h ozone dose. This shows that the mineralization of PAR was quite low with ozonation [38]. Degradation and COD removal were determined as 69% and 35% at pH 2.0, 94% and 39% at natural pH, and 96% and 65% at pH 10.0 for 60 min contact in 0.5 g/h ozone dose of 50 mg/L PAR [39]. Ozonation is an effective method of treating DCF from drinking water and wastewater, however, a 10:1 molar ratio of ozone to DCF is important for the formation of non-hazardous by-products in an aqueous solution [40]. In this study, DCF was removed at a dose of 1.5 mg O_3/mg COD. While 15% of IBU was excreted from the body in its original form, the ratio for hydroxyIBU form was 26% [41]. The main biotransformation products of IBU were also 2-hydroxyIBU and 1-[4-(2-methylpropyl)phenyl]ethan-1-ol (MPPE) [42]. Therefore, in addition to IBU, derivatives can also be detected in wastewater. In this study, both IBU and 2-hydroxyIBU from

selected by-products were detected in hospital wastewater at 2103 and 5512 ng/L, respectively. 2-hydroxyIBU was resistant to ozone doses between 0.05 and 0.5 mg O_3/mg COD. The removal efficiency of 2-hydroxyIBU was only 38%. However, both parent and by-product were removed at 1.5 mg O_3/mg COD (Table 1). Olak-Kucharczyk et al. [43] determined that IBU and its important by-products like 2-hydroxyIBU, 4EBA, and MPPE were easily removed by ozonation, similar to this study. NAP and their degradation by-product (S)-O-desmethyl NAP were detected in similar concentrations, and they removed >99% at an ozone dose of 1.5 mg O_3/mg COD. SMX and N-acetyl-SMX were easily removed at the lowest dose (0.05 mg O_3 / mg COD). Alharbi et al. [44] researched the removal and formation of thirteen transformation products during the ozonation of SMX. The study results show that SMX and its by-products were easily removed as in our study. On the other hand, Dantas et al. [45] stated that although SMX was degraded in 15 min at a ozone dose of 0.4 g/L, only 10% of SMX was mineralized. CLA was removed at 1.5 mg O_3/mg COD dose. ERY and CLI were not detected in hospital wastewater samples. This may be related to the fact that these antibiotics are not used in hospitalized patients. CIP was resistant to oxidation under stoichiometric ozone dose (0.05-0.5 mg O_3/mg COD) like PCT. Since both compounds have an aromatic structure, this can be related to their molecular structures. The mineralization of CIP by ozonation is generally less than that observed for so-called persistent organic pollutants containing aromatic rings and oxygenated groups [46]. In this context, the removal efficiency of CIP was <77% between 0.05-0.5 mg O_3/mg COD dose. TMP was easily removed in 0.25 mg O_3/mg COD dose. MET, CLA, and AZI were detected as 9989, 1453, and 1003 ng/L and were completely removed at 1.5 mg O_3/mg COD. AZI is an antibiotic that was detected in high concentrations [2] on the contrary found in this study. These antibiotics were not evaluated in lower oxidant doses, because they were not detected in the first sample of hospital wastewater. Although hospital wastewater has many matrices, similar results were obtained to those obtained for aqueous solutions in previous studies. Studies on the ozonation of hospital wastewater are given in Table 2. Many of these studies reported that PhACs were generally removed effectively.

The mean COD and BOD values of hospital wastewater were 767.1 mg/L and 248 mg/L. COD and BOD were removed 48% and 73%, respectively, at 1.5 mg O_3/mg COD. However, removal efficiencies of COD and BOD did not increase linearly with increasing ozonation time (3.0 mg O_3/mg COD and 5.0 mg O_3/mg COD). Additionally, the BOD/COD ratio decreased from 0.41 to 0.2. It can be explained that ozone primarily reacts easily with degradable organics.

CONCLUSION

PhACs are biologically persistent and toxic. Detection frequency increases in aquatic environment with their increasing use day by day. Interference to non-point PhACs sources is difficult. Thus, point sources must be managed well for human and environmental health. Especially hospital wastewater has high potential in terms of both PhACs and antibiotic resistance microorganism. Ozonation has disinfection and oxidation effects and can be easily adapted to treatment steps. In this context, the fate of selected 21 PhACs was evaluated pre-ozonation of hospital wastewater. The obtained results show that 21 PhACs and metabolites were almost completely removed during pre-ozonation of hospital wastewater. Especially, 1.5 mg O_3/mg COD ozone dose were efficient in removal of investigated PhACs and metabolites. Although PAR had the highest concentration with 333.7 μg/L, it was removed 82.4 % even at the lowest ozone dose. SMX was completely removed in this condition.

Table 1. Fate of PhACs concentration in different ozone doses (ng/L)

		Ozone Dose (mg O_3 / mgCOD)							
PhACs	**HW-S1**	**0.05**	**0.1**	**0.25**	**0.5**	**HW-S2**	**1.5**	**3.0**	**5.0**
Paracetamol	333675	58581	51104	9877	21250	6961	<5	<5	<5
Diclofenac	<5	<5	<5	<5	<5	1891	<5	<5	<5
4'-Hydroxydiclofenac	<5	<5	<5	<5	<5	<5	<5	<5	<5
5-Hydroxydiclofenac	<5	<5	<5	<5	<5	<5	<5	<5	<5
Ibuprofen	<5	<5	<5	<5	<5	2103	<5	<5	<5
1-Hydroxyibuprofen	<5	<5	<5	<5	<5	<5	<5	<5	<5
2-Hydroxyibuprofen	1204	1223	1347	1153	752	5512	<5	<5	<5
Carboxyibuprofen	<5	<5	<5	<5	<5	<5	<5	<5	<5
Naproxen	<5	<5	<5	<5	<5	3226	<5	<5	<5
(S)-O-Desmethyl Naproxen	<5	<5	<5	<5	<5	3210	<5	<5	<5
Ciprofloxacin	31100	31099	26455	15541	6969	18521	<5	<5	<5
Sulfamethoxazole	14919	<5	<5	<5	<5	3572	<5	<5	<5
N-acetyl-sulfamethoxazole	<5	<5	<5	<5	<5	4560	<5	<5	<5
Sulfamethoxazole-β-D-glucuronide	<5	<5	<5	<5	<5	<5	<5	<5	<5
Trimethoprim	626	606	531	<5	<5	1196	<5	<5	<5
Erythromycin	<5	<5	<5	<5	<5	<5	<5	<5	<5
Metronidazole	<5	<5	<5	<5	<5	9989	<5	<5	<5
Clarithromycin	<5	<5	<5	<5	<5	1453	<5	<5	<5
Azithromycin	<5	<5	<5	<5	<5	1302	<5	<5	<5
Clindamycin	<5	<5	<5	<5	<5	<5	<5	<5	<5
Clindamycin Sulfoxide	<5	<5	<5	<5	<5	<5	<5	<5	<5

HW-S1: hospital wastewater sample 1, HW-S2: hospital wastewater sample 2.

Table 2. Studies on removal of PhACs by ozonation in literature

Ozone dose	Working pH	Reaction time, min	Hospital wastewater characterization	PhACs	Temperature	Catalyst/ Chemical	Removal efficiencies	Ref.
100 mg O_3/L	pH: 3.70 and 10.85	120	COD: 450 mg/L	Amoxicillin, Ciprofloxacin	20 ± 2°C	H_2O_2	Amoxicillin: %99, Ciprofloxacin %96 in alkaline conditions	[47]
4 mg O_3/L	pH: 3-9	5		Amoxicillin, Ciprofloxacin and Acetaminophen	Room temp.		Amoxicillin: 98%, Ciprofloxacin: 99%, Acetaminophen: %98.5 at pH 9	[48]
10 mg O_3/L	pH: 7.8	10	COD: 642 mg/L, total phosphor: 7 mg/L	Ciprofloxacin and Ofloxacin	25 ± 1°C		Ciprofloxacin: 66% and Ofloxacin: 84%	[49]
43.9 g/ m3	pH: 8.89	10-20	COD: 256 mg O_3/L	17 anticancer drugs	20 °C	H_2O_2	Except for cyclophosphamide all compounds were removed 100%	[50]
0.25,0.5,1 and 1.5 g O_3/g COD	pH: 7 and 8.5	30	pH: 8.1-8.5	56 PhAC	22 ± 2°C	H_2O_2	92% and 100% for pH 7 and 8.5 at ≥0.5 g O_3/g COD	[28]
1.57g O_3/h	O_3 and O_3/UV: pH 11 and 8.6; O_3/Fe^{+2} and O_3/FE^{2+}/UV: pH 3	120	BOD: 140 mg/L, COD: 448 mg/L, pH:8.6, Nitrogen as NH3: 35.6 mg/L	Azithromycin, Ciprofloxacin, Trimethoprim, Penicillin, Naficillin, Ketoprofen, Phenylbutazon, Prednisolone, Prednison, Betamethasone, Propyphenazoe, Atenolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Propranolol	Room temperature	Fe^{+2}, UV	99.5% except for Betamethasone, aromatics: 81%, COD: 64%	[31]

Ozone dose	Working pH	Reaction time, min	Hospital wastewater characterization	PhACs	Temperature	Catalyst/ Chemical	Removal efficiencies	Ref.
0.5 - 5.3 mg O_3/ mg DOC	pH: 5-8	60	pH: 5-9, COD: 6-20 mg/L	33 PhAC	15 °C		90%	[30]
10 mg O_3/L	pH: 9	60	pH: 7, COD:420 mg/L, nitrate: 6.7 mh/L, phosphate: 13.9 mg/L	Daunorubicin	20 ± 2 °C	UV	Daunorubicin, Doxorubicin and Epirubicin were removed 97.3%, 88.3%, 99% at pH 9. Irinotecan was removed 45.6 % at pH 9, 63.8% at pH 5.	[32]
20 mg O_3/L	pH: 5-9	30-60	pH: 8.1, BOD:387±197, COD: 807± 325 mg/L	Ciprofloxacin	20 °C	UV, H_2O_2	Totally degraded at pH 9	[51]
0.05-5.0 mg O_3/ mg COD	pH: 6.8 and 7.2	0.5-45	BOD:248 mg/L, COD: 767.1	21 PhACs	Room temperature		All PhACs were completely removed at 1.5 mg O_3/ mg COD	This study

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DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

USE OF AI FOR WRITING ASSISTANCE

Not declared.

ETHICS

There are no ethical issues with the publication of this manuscript.

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