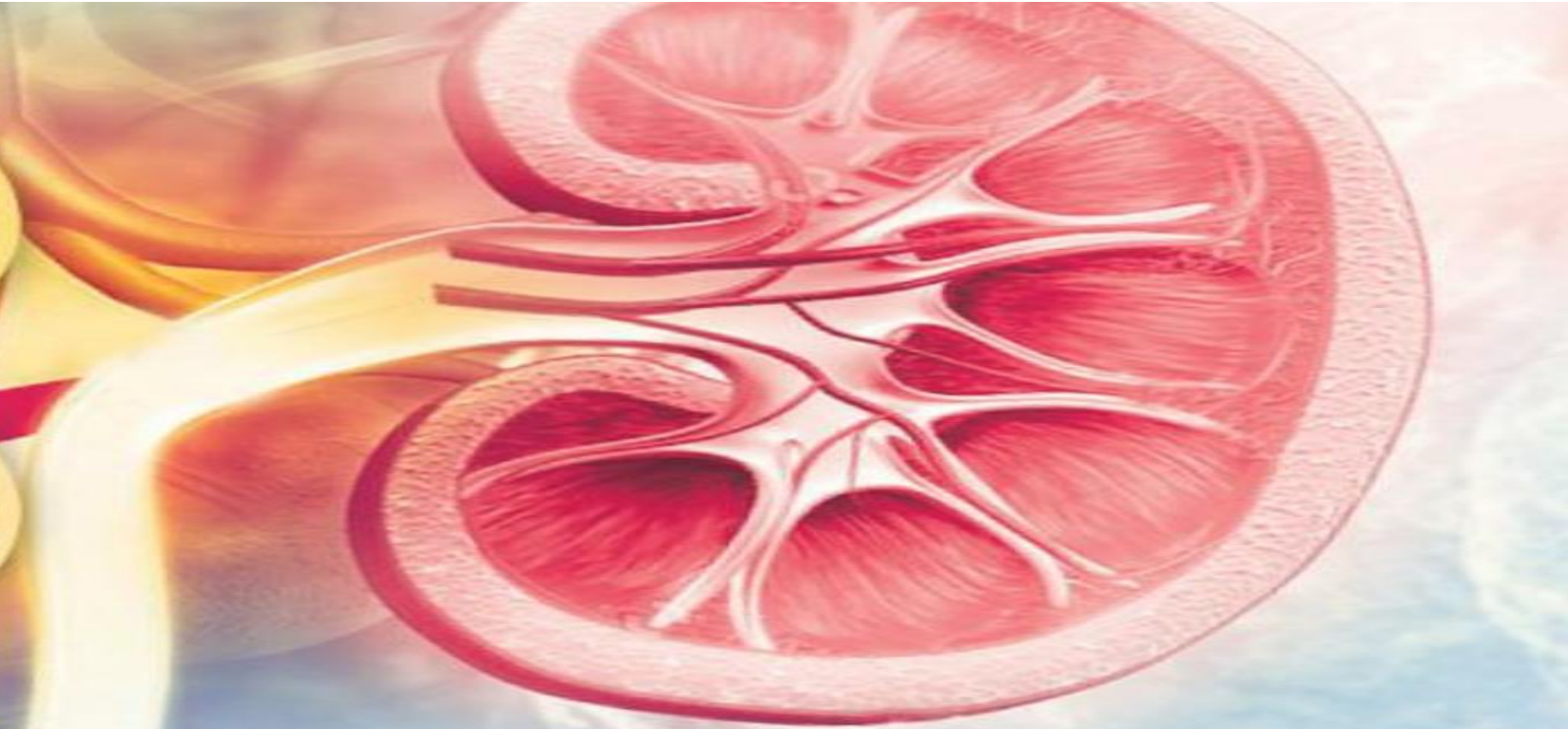
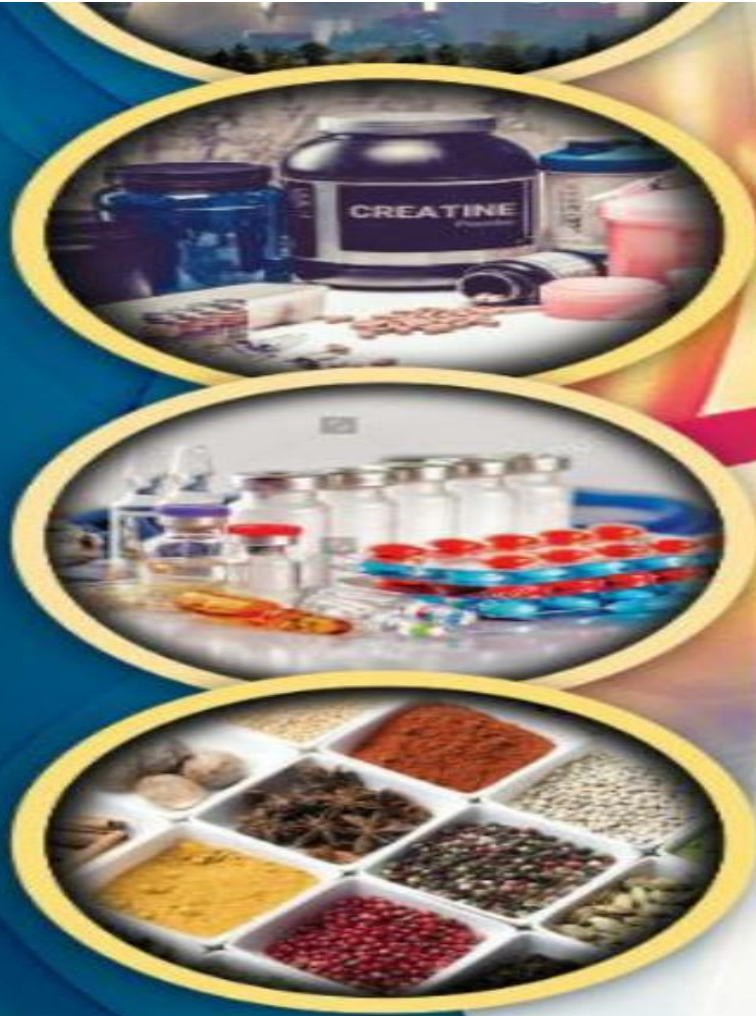


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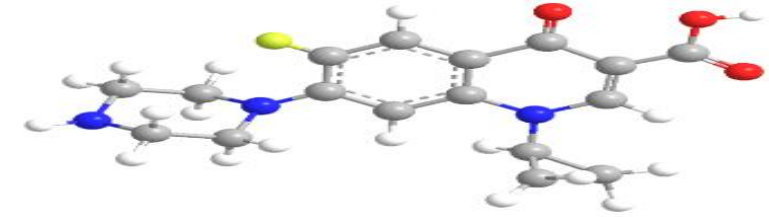
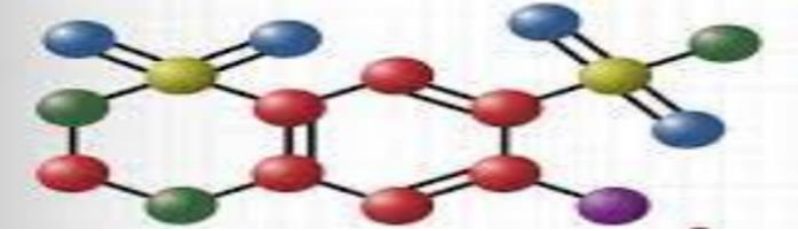


**نفر و توكسينها و كليہ**

**Kidney and Nephrotoxins**

۱۳ تا ۱۵ مهرماه ۱۴۰۱

تهران، هتل هما



# *Acute Kidney Injury Following Autoimmune Hemolytic Anemia Due to Simultaneous Use of Ciprofloxacin and Hydrochlorothiazide*

*Yaghoubi F.MD*

*TUMS , Shariati Hospital*



نفتوكسينها و كليہ

Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران

## *Introduction*

- ✓ Rare cases of autoimmune hemolytic anemia (AHA) associated with using ciprofloxacin or hydrochlorothiazide alone have been reported before.
- ✓ However, concomitant use of both drugs could lead to a severe clinical condition.
- ✓ The present study provides the case of acute kidney injury (AKI) following AHA after three days usage of ciprofloxacin and hydrochlorothiazide.



## Introduction

- ✓ A 42-year-old Iranian woman with no significant medical history came to a physician with a complaint of dysuria and frequency .
- ✓ On examination, the blood pressure was 140/80 mmHg, and there were no signs of fever, flank or abdominal tenderness, and costovertebral angle (CVA) tenderness. Thus, routine blood tests, urine analysis (U/A), and urine culture (U/C) were requested.
- ✓ The tests revealed :
  - ❖ Hemoglobin (Hb) 13.8 g/dL
  - ❖ Platelet count 228000
  - ❖ White blood cell (WBC) count 8500
  - ❖ Blood urea nitrogen (BUN) 12 mg/dL
  - ❖ Creatinine 0.8 mg/dL
  - ❖ U/A and U/C positive for infection.
- ✓ Then, half a pill of hydrochlorothiazide daily due to high blood pressure, and ciprofloxacin 500 mg twice a day due to dysuria and frequency, were prescribed .





## *Introduction*

✓ Three days after using the above drugs, the patient presented to the emergency department of our hospital with symptoms :

- ❖ Fatigue
- ❖ lethargy
- ❖ Nausea
- ❖ Vomiting
- ❖ Ataxia
- ❖ Oliguria
- ❖ Dark urine
- ❖ Jaundice



نفرتوکسین‌ها و کلیه

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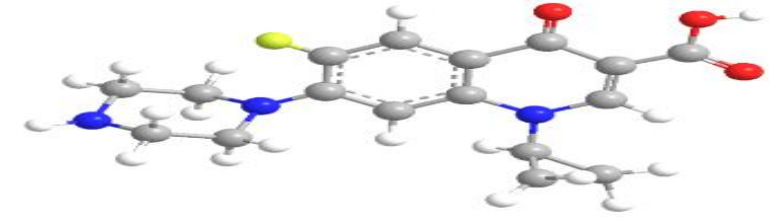
## *Introduction*

### ✓ Early laboratory findings after hospital admission :

- ❖ Hb of 7 g/dl(mcv:86)
- ❖ Platelet count 210,000
- ❖ White blood cell (WBC) count 9800
- ❖ Blood urea nitrogen (BUN) 100 mg/dL
- ❖ Creatinine 6.8 mg/dL
- ❖ Coombs test direct (4+) and indirect (2+)
- ❖ High level of lactate dehydrogenase (LDH) (820 IU/L)
- ❖ Hyperbilirubinemia (total: 3 and direct: 1.2 mg/dL).
- ❖ Erythrocyte sedimentation rate (ESR) 80 mm/hr
- ❖ C-reactive protein (CRP) 18 mg/L
- ❖ PT&PTT&INR normal
- ❖ G6PD normal
- ❖ Urine analysis showed 2+ blood, 4-6 RBC, and cola-colored urine.
- ❖ Hyperkalemia (5.2 mEq/L)
- ❖ Hyperphosphatemia (6.2 mg/dL)



## Introduction



- ✓ The secondary assessments, including ANA, Anti-dsDNA, complement components C3, C4, and CH50, c-ANCA, p-ANCA, SPEP, UPEP, Hb electrophoresis, G6PD level, CPK, amylase, lipase, alkaline phosphatase (ALP), ALT, AST, HBS-Ag, HCV, HAV, and HIV that all were normal.
  
- ✓ Based on findings including hemolytic anemia with a :
  - ❖ Hb of 7 g/dl
  - ❖ Positive direct (4+) and indirect (2+) Coombs test
  - ❖ High level of LDH (820 IU/L)
  - ❖ Hyperbilirubinemia (total: 3 and direct: 1.2 mg/dL)
  - ❖ Cola-colored urine
  
- ✓ which are evidence of acute hemolysis, and the recent drug history of simultaneous use of hydrochlorothiazide and ciprofloxacin, **drug-induced acute autoimmune hemolytic anemia (DIAHA)** was diagnosed and following that Acute kidney injury (AKI) occurred



## Introduction

- ✓ Three consecutive days of 500 mg intravenous methylprednisolone, followed by 1 mg/Kg oral prednisolone was prescribed.
- ✓ Further, to control AKI, the patient underwent 4 sessions of hemodialysis, and due to the drop in hemoglobin (Hb=6.3 g/dL), she also received one unit of the packed cell under dialysis.
- ✓ Fortunately, she was discharged with Cr 1.7 mg/dL, Hb 9 g/dL, and taking 50 mg oral prednisolone a day.





## Discussion

- ✓ **Drug-induced immune hemolytic anemia (DIIHA)** is a rare and potentially fatal side effect of many drugs, with a prevalence of approximately one case per million per year
- ✓ In DIIHA, immune complexes bind to the red blood cell membrane, leading to intravascular hemolysis (immune-mediated reaction).
- ✓ DIIHA has two types, **drug-dependent, and drug-independent.**
- ✓ In the first category, antibodies cause hemolysis in the presence of drugs (drug-dependent). In this case, the drug or its metabolite binds to macromolecules on the surface of red blood cells, which act as antigens for the immune system.
- ✓ And in the second category, the presence of the drug causes the production of antibodies, but the antibodies also cause hemolysis in the absence of the drug. (drug-independent)



## Discussion

- ✓ Previously, 14 case report studies about DIIHA by ciprofloxacin or hydrochlorothiazide have been published, which were reviewed in the present study.
- ✓ **Among these 14 articles, five papers were about hydrochlorothiazide, and nine others were about ciprofloxacin.**
- ✓ Regarding five cases of hydrochlorothiazide, four were male and one female. The mean age of these people was 55 years (ranged 24 to 77 years old). All five patients developed AHA after taking hydrochlorothiazide .
- ✓ Generally, the treatment included discontinuation of hydrochlorothiazide, use of prednisone or methylprednisolone, and supportive care.
- ✓ In a study conducted in 2021, two doses of IVIG were also prescribed in addition to above.
- ✓ The prognosis of four patients was good, although one died





Cureus

Open Access Case  
Report

DOI: 10.7759/cureus.17453

## A Rare Case of Hydrochlorothiazide-Induced Hemolytic Anemia

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### Abstract

Drug-induced immune hemolytic anemia is an exceedingly rare adverse drug event. Thiazide diuretics, commonly used in the treatment of primary hypertension, have been associated with this complication. In this case report, we present a 77-year-old male who developed acute hemolytic anemia two days after starting hydrochlorothiazide in the treatment of high blood pressure.

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**Categories:** Cardiology, Internal Medicine, Hematology

**Keywords:** immune hemolytic anemia, drug-induced immune hemolytic anemia, hydrochlorothiazide, adverse drug event, immune-mediated hemolysis

The patient was started on Prednisone 1 mg/kg daily and two doses of intravenous immunoglobulin (IVIG).



نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳۰۱ مهر ۱۴۰۱ - تهران



## Fatal Intravascular Immune Hemolysis Induced by Hydrochlorothiazide

MALCOLM L. BECK, F.I.M.L.S., M.I. BIOL., JANE F. CLINE, M.D., JILL T. HARDMAN, M.A.,  
LUZ S. RACELA, M.D., AND JAMES W. DAVIS, M.D.

**A patient receiving antihypertensive therapy developed acute intravascular hemolysis and died. Hemolysis was due to an immune process associated with antibody to thiazide. Only two other cases have been reported. Thiazide-induced hemolysis appears to be confined to those patients treated concomitantly with methyldopa. (Key words: Hemolytic anemia; Drug-induced hemolysis; Hydrochlorothiazide) Am J Clin Pathol 1984; 81: 791-794**

ANTIHYPERTENSIVE THERAPY with methyldopa causes extravascular immune hemolysis in about 0.8% of patients.<sup>9</sup> Hemolysis has not been reported in patients treated only with thiazides, although two reports of intravascular hemolysis incriminated the concurrent use of methyldopa and hydrochlorothiazide.<sup>2,7</sup> In both cases, hemolysis was a consequence of antibody produced to hydrochlorothiazide. **We now report a third case of drug-induced intravascular hemolysis associated with the concomitant use of hydrochlorothiazide and methyldopa. The patient died during the hemolytic episode.** Serologic

Received July 28, 1983; received revised manuscript and accepted for publication September 22, 1983.

Address reprint requests to Mr. Beck: Community Blood Center of Greater Kansas City, 4040 Main Street, Kansas City, Missouri 64111.

*From Community Blood Center of Greater Kansas City, University of Kansas School of Medicine, and Veterans Administration Medical Center, Kansas City, Missouri*

findings indicate that hemolysis was the result of hydrochlorothiazide antibody.

### Report of a Case

A 53-year-old black man, treated with methyldopa (Aldomet®; Merck Sharp and Dohme, West Point, PA) and hydrochlorothiazide (HydroDiuril®; Merck Sharp and Dohme) for essential hypertension for approximately 18 months, was admitted to the hospital after passing black urine. He had a two-day history of decreased appetite, weakness, headache and nausea without vomiting. He denied hematemesis, melena, hemoptysis, hematochezia, and abdominal pain, dysuria, fever, chills, sweats, joint or muscle pain, and weight loss. The dose of hydrochlorothiazide had been increased from 50 to 100 mg per day one month before. At the time of admission he was taking 1,500 mg of methyldopa and 100 mg of hydrochlorothiazide each day.

Physical examination revealed a well-nourished man in no apparent distress. Blood pressure was 180/100 mmHg, pulse 80/min and regular, respiratory rate 16, and temperature 37.5°C. Scleral icterus was present. The skin and mucous membranes were without rashes or petechiae. There was no adenopathy. Heart and lungs were normal. The liver and

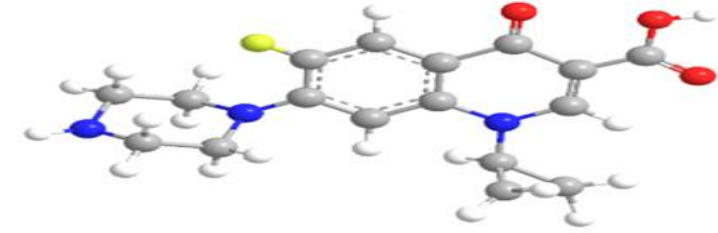
Eight hours later the patient had severe retching, midepigastic pain of sudden onset, followed closely by cardiac arrest. The hemoglobin at this time was 6.0 g/dL. Autopsy failed to reveal the cause of death. The heart weighed 650 g. There was left ventricular hypertrophy and mild coronary atherosclerosis.

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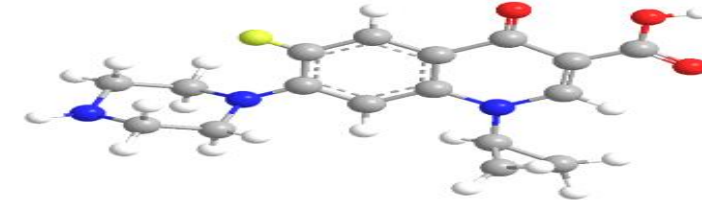
## Discussion



- ✓ Of nine patients who had complications after taking ciprofloxacin, six were male, and three were female.
- ✓ Their mean age was 63 years (ranged 30 to 88 years old). Two patients suffered from interstitial nephritis and hemolytic anemia simultaneously.
- ✓ The first case was a 54-year-old woman who recovered after treatment with prednisolone. Laboratory evidence showed that the patient had G6PD enzyme deficiency .
- ✓ The second case was a 79-year-old man. His hemolytic anemia was treated with ciprofloxacin cessation and taking steroids, but the acute interstitial nephritis was irreversible and progressed to end-stage renal disease .
- ✓ Two other patients had complications of thrombocytopenia and hemolytic anemia







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RENAL FAILURE  
Vol. 25, No. 4, pp. 647–651, 2003

## CASE REPORT

### Ciprofloxacin-Induced Acute Interstitial Nephritis and Autoimmune Hemolytic Anemia

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#### ABSTRACT

Ciprofloxacin has been associated with several side effects including interstitial nephritis and hemolytic anemia. The combination of both side effects is extremely rare. **In this report, we describe a case of ciprofloxacin-induced interstitial nephritis and autoimmune hemolytic anemia. Hemolytic anemia improved after stopping the drug and initiation of steroid therapy. Unfortunately, acute interstitial nephritis was irreversible and the patient developed end-stage renal disease.**

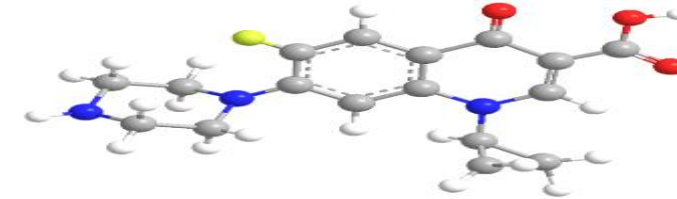
*Key Words:* Ciprofloxacin; Interstitial nephritis; Hemolytic anemia.



نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران



*Platelets*, August 2008; 19(5): 384–387

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healthcare

## CASE REPORT

### Severe thrombocytopenia and haemolytic anaemia associated with ciprofloxacin: A case report with fatal outcome

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CORRADO BLANDIZZI<sup>1</sup>, MARIO DEL TACCA<sup>1,2</sup>, & MARCO DI PAOLO<sup>3</sup>

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(Received 9 October 2007; accepted 15 February 2008)

#### Abstract

Haematological adverse reactions associated with fatal outcome are rare during treatment with ciprofloxacin. A 30-year old Caucasian man reported with abdominal pain and jaundice after 3-day administration of oral ciprofloxacin for a suspect of urinary tract infection. Clinical evaluations suggested an initial diagnosis of severe thrombocytopenia and haemolysis. The patient progressively developed petechiae and purpura on thorax and lower limbs. Despite pharmacological and supportive interventions, laboratory parameters worsened and the patient died 17 hours after admission. An accurate autopsy revealed most organs with diffuse petechial haemorrhages. No signs of bone marrow depression were found. No thrombi or signs of microangiopathies were observed in arterial vessels. Blood and urine cultures did not show any bacterial growth. This case report shows that ciprofloxacin may precipitate life-threatening thrombocytopenia and haemolytic anaemia, even in the early phases of treatment and without apparent previous exposures.

**Keywords:** *Ciprofloxacin, thrombocytopenia, adverse drug reaction, haemolytic anaemia*



## Discussion

- ✓ The evaluation of the clinical picture then suggested an initial diagnosis of thrombotic thrombocytopenic purpura (TTP).
- ✓ Accordingly, the patient was rehydrated (500 mL/3 hours), **plasma exchange was programmed and a treatment with methylprednisolone 2 g i.v. was started.**
- ✓ Owing to temporary unavailability of plasma exchange, to start **plasma infusion (1200 mL/4 hours), which is regarded as appropriate intervention for patients with TTP when plasma exchange is not readily available .**
- ✓ Moreover, considering the possibility of an immune-mediated thrombocytopenia, gamma globulins 70 g iv were administered.



## Table 1. Reported cases of AHA induced by ciprofloxacin

Case Year	Sex/Age (years)	Underlying disease	Concomitant medication	Duration*	Complications	Treatment	Response
1 1995	F/65	Degenerative osteoarthritis	Diclofenac	9 weeks	AHA	Discontinue ciprofloxacin & diclofenac, supportive care, prednisolone	Good
2 1997	M/42	CLL	Methylprednisolone	4 days	AHA, Thrombocytopenia	Treatment was changed to an oral combination of ampicillin and sulbactam	Good
3 1999	F/54	RA, Total knee replacement	methotrexate, NSAID, Atenolol, Ranitidine,	2 days	AHA Interstitial nephritis	Discontinue ciprofloxacin, supportive care  Prednisolone, ranitidine, phosphate binders	Good
4 2002	M/53	ALL	Doxorubicin  Vincristine,  L-asparaginas, prednisone	2 days	HUS	Discontinue ciprofloxacin, plasma exchange, hemodialysis	Good
5 2002	M/79	HTN, tuberculous pleurisy, right pneumectomy for a giant tuberculoma.	Felodipine, lormetazepam	5 days	AILD	First methylprednisolone, then systemic chemotherapy	Good
6 2003	M/79	-	-	unknown	AHA interstitial nephritis	Discontinue ciprofloxacin, steroid, supportive treatment, hemodialysis	AHA improve, AIN was irreversible
7 2008	M/30	-	-	3 days	AHA thrombocytopenia	Supportive treatment  Plasma exchange, plasma infusion methylprednisolone, gamma globulins, tranexamic acid	Poor
8 2009	M/76	Emphysema, hypercholesterolemia, HTN	ticarcillin/clavulanic acid  Unfractionated heparin	4 days	DITP	Discontinue ciprofloxacin	Good
9 2010	F/88	Colorectal cancer, HTN, G6PD, Mediterranean deficiency	Capecitabine, irinotecan, bisoprolol, lercanidipine, irbesartan	2 days	Intravascular hemolysis secondary to G6PD, Mediterranean deficiency	Supportive care, discontinue ciprofloxacin, replaced with piperacillin tazobactam	Good

\* Duration of drug consumption before AHA



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## Table 2. Reported cases of AHA induced by hydrochlorothiazide

Table 2. Reported cases of AHA induced by hydrochlorothiazide							
Case Year	Sex/Age (years)	Underlying disease	Concomitant medication	Duration*	Complications	Treatment	Response
1 1976	M/67	HTN	Methyldopa	4 years	3 episodes of AHA	Discontinue HCTZ & Methyldopa, Supportive care	Good
2 1981	M/24	HTN	Methyldopa	18months	AHA, Renal failure	Supportive care methylprednisolone, hemodialysis	Good
3 1984	M/53	Essential HTN	Methyldopa	18months (Dose increase one month ago)	AHA	prednisone	Poor
4 1988	F/53	HTN	Methyldopa	10 days	AHA	Discontinue HCTZ & Methyldopa, Supportive care	Good
5 2021	M/77	CAD, HTN, CABG, Hyperlipidemia	-	2 days	DIAHA	Discontinue HCTZ Prednisone, Supportive care, Two doses of IVIG	Good



نفرتوکسین‌ها و کلیه

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## Conclusion

- ✓ Fluoroquinolones, which are broad-spectrum antibiotics, can autoimmune hemolytic anemia (AHA) cause isolated thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and bone marrow failure .
- ✓ Further, Hydrochlorothiazide and other thiazide diuretics are associated with DIIHA.
- ✓ Rare cases of autoimmune hemolytic anemia (AHA) associated with using ciprofloxacin or hydrochlorothiazide alone have been reported before.
- ✓ However, concomitant use of both drugs could lead to a severe clinical condition.





*Thanks for your attention*