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Review

Q11 Quinolones-induced hypersensitivity reactions

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ABSTRACT

Quinolones are broad spectrum antibiotics that are intensively used and can induce immediate- and delayed-type hypersensitivity reactions, either IgE or T-cell mediated, in about 2–3% of treated patients. Objective: To better understand how T cells interact with quinolones, to produce the hypersensitivity and to describe the possible prevention of the reactions. Methods: We search in PubMed for quinolones and adverse reactions naming each one of the therapeutics in use and the possible hypersensitivity reactions e.g., anaphylaxis, drug-induced delayed reactions, and hypersensitivity syndrome reactions. We also performed organ-specific hypersensitivity reactions including cutaneous reactions, hepatic reactions, and renal reactions. Results: Our data show that T cells are involved in delayed immune reactions to quinolones and that cross-reactivity among the different quinolones is frequent. The predictive tests for quinolone-induced hypersensitivity should be used in patients before they are given the medication. Conclusions: Early identification of the mechanism of toxicity, quantitative assessment using laboratory tests, analyzing risk factors for patient susceptibility to the quinolones, possible drug interactions may lead to appropriate patient selection for therapy, monitoring the injury early and discontinuation of the therapeutic agent.

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Abbreviations: ADR, adverse drug reaction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DILI, drug-induced liver injury; FDE, fixed drug eruption; HSR, hypersensitivity syndrome reaction; γ GT, gamma glutamyl transferase; IDHR, immune-mediated drug hypersensitivity reaction; IgE, immunoglobulin E; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test; MHC, major histocompatibility complex; OR, odds ratio; ORC, oral re-challenge; SCAR, severe cutaneous adverse reactions; SPT, skin prick test; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

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Q20 Introduction

Immune-mediated drug hypersensitivity reactions (IDHR) are uncommon adverse events in clinical medicine, which are restricted to a subset of vulnerable patients and pharmaceutical products. Nevertheless, such reactions represent serious consequences of therapy, and thus have a huge impact on clinical practice and public health [1]. For example, many individuals with a history of adverse drug reactions (ADR) to antibiotics receive alternative antibiotics which are sometimes less effective, often more toxic, and usually more expensive [2].

A better understanding of predisposing factors and pathophysiology, with progress in diagnostic and predictive tests, could be expected to lead to substantial benefits for afflicted patients in the provision of optimal medical care, as well as substantial savings in healthcare costs. The lack of an adequate knowledge base about IDHR similarly affects drug development programs since it is currently difficult to predict which new therapeutic compounds may elicit IDHRs before clinical trials and marketing. The mechanisms of IDHR to low molecular weight drugs generally fit one of two classifications. The first of these are reactions that occur when a drug or metabolite acts as a hapten, and the immune response is directed against the hapten or hapten–peptide conjugate. Drugs that act as haptens may be intrinsically reactive, or they may require enzymatic or non-enzymatic conversion to a reactive intermediate. It is hypothesized that the reactive compound binds to proteins, forming hapten–protein conjugates. These hapten–peptide conjugates bind to the major histocompatibility complex class I or II proteins, and then they are presented to T cells with the appropriate T cell receptor. It has been demonstrated that some haptens directly bind to major histocompatibility complex-associated peptides [3,4]. The second type of IDHR involves immune reactions in which drug administration results in an immune response to self-antigens [5]. A stimulation of the immune system produces an immune response to self-antigens. In individuals with a genetic predisposition to immune diseases, general immunostimulation may trigger early onset or exacerbation of the disease process.

The present work classifies the reactions to fluoroquinolones according to the organ system involved in the reaction. Systemic reactions include anaphylaxis, drug-induced delayed reactions, and hypersensitivity syndrome reactions (HSR). Organ-specific reactions are numerous and include cutaneous reactions, hepatic reactions, and renal reactions.

Anaphylaxis and anaphylactoid (type 1 hypersensitivity reactions)

Urticaria, angioedema and anaphylactic shock were the most common immediate ADRs associated with quinolones [6]. The incidence of serious allergic reactions was measured in terms of incidence per 10,000 first dispensations for moxifloxacin [4.3, 95% confidence interval (CI) 3.5–5.3], ciprofloxacin (5.4, 95% CI 4.4–6.5) and levofloxacin (8.7, 95% CI 7.4–10.0). In IgE-mediated reactions, cross-linking of bound IgE may be facilitated by binding to a protein. Most likely a reactive compound represents the relevant antigen.

The incidence of anaphylaxis/anaphylactoid reactions following first dispensation was low and similar among fluoroquinolones regardless of ciprofloxacin (0.1, 95% CI 0.0–0.3), moxifloxacin (0.3, 95% CI 0.1–0.5) or levofloxacin (0.5, 95% CI 0.3–0.9) use [7]. Furthermore, quinolones are the third most common class of drugs associated with HSRs. The incidence of anaphylaxis reactions to quinolones is on the rise, and it was estimated at 1.8–2.3 per 10,000,000 days of treatment [8].

The use of fluoroquinolones was a risk factor for allergic ADRs compared to other ADRs [odds ratio (OR) 2.09, 95% CI 1.85–2.36]. Moxifloxacin was the fluoroquinolone most often associated with this type of ADR among antibiotic users (OR 4.20, 95% CI 3.19–5.55) [9]. The majority of moxifloxacin HSRs were anaphylactic in nature, and moxifloxacin is generally associated with more frequent and more

severe HSRs than other quinolones [8,10,11]. Quinolone HSR occurs predominantly among atopic patients [12].

The immunogenicity of quinolones appears to be related to their structure [12]. Schmid et al. [13] review numerous ADRs that are considered to be immune-mediated, including pruritus, urticaria, angioedema and shock [13]. However, skin tests often prove unreliable in identifying patients with a propensity to develop quinolone anaphylaxis due to a large number of false negatives. A likely explanation for this is that quinolones may directly lead to the release of histamine, suggesting that HSRs to quinolones may at least partly be mediated by non-immune mechanisms (pseudo-allergy) [13]. Immediate HSR to ciprofloxacin, levofloxacin and moxifloxacin are detailed in Table 1 [14–45].

Anaphylaxis reactions are reported in a number of cases, including individuals treated with all 3 fluoroquinolones, in all age groups (2–63 years), and even gender distribution [14–22]. Manifestations of anaphylaxis were varied, including rash, pruritus and swelling, dyspnea and chest tightness, cardiovascular manifestations such as tachycardia and hypotension, and neurological manifestations such as dizziness, trembling, and impaired consciousness. Resolution of symptoms was generally observed, either spontaneously or following treatment with epinephrine, steroids or anti-histamines [14–22]. Exception was one patient who died after developing extensive bilateral brain stem signs [14].

Overall, 12 immediate-type reactions are described in patients treated with quinolones in a Spanish study [29]. There were 4 cases of anaphylactoid reaction and 13 cases of anaphylaxis reaction in a sample of 248 cases of adverse reactions reported to moxifloxacin out of a total of 2025 cases of adverse reactions reported to fluoroquinolones in the Italian Interregional Group of Pharmacovigilance. The corresponding number of cases were 4 and 4 for ciprofloxacin (out of 519 adverse reactions), and 7 and 11 for levofloxacin (out of 602 adverse reactions) [46]. Immediate-type HSRs to quinolones were found to be IgE-mediated in over 50% of cases [6]. Urticaria occurred predominantly among women ($n = 12$) than men ($n = 4$) [22–30]. A wide time to onset range between first drug exposure and appearance of urticaria is presented (2 min–2 days). Where specified, all patients show complete resolution. A case of multiple drug allergy syndrome is described in a patient with a history of generalized urticaria and bronchoconstriction on rifamycin SV and mild urticarial rashes to ciprofloxacin [47].

Anaphylactoid reactions are a type of anaphylaxis reactions that are not allergic in nature. These are also described in a number of reports. Most of the reports concern individuals treated with ciprofloxacin [31–38], with one case also reported in an individual treated with intravenous levofloxacin [39]. The reaction occurred immediately after drug exposure (15 min–3 h), with the exception of a patient who presented with symptoms after 1 day. A relatively even gender distribution is shown in the case studies review here (8 females and 6 males). All patients received the fluoroquinolones as treatment or prophylaxis for infections. The predominant manifestations of anaphylactoid reaction were rash, pruritus, dyspnea and swelling, with occasional neurological symptoms such as disorientation and headache. All patients recovered, either spontaneously or following treatment with epinephrine, steroids or anti-histamines [31–39].

Elsewhere, a case of severe IgE-mediated cutaneous and systemic reaction with generalized pruritic maculopapular rash and impairment of consciousness is described in a female treated with ciprofloxacin for urinary tract infection [40]. Photolocalized pruritic eruption induced by levofloxacin upon exposure to sunlight, contact urticaria and recall urticaria are described in three patients treated with levofloxacin [41–43]. Immediate hypersensitivity with predominantly cutaneous manifestations occurred in two male patients exposed to levofloxacin, both of which recovered [44,45].

A herpes infection diagnosed from a blister biopsy is described in an asthmatic patient who developed anaphylaxis after ingesting levofloxacin. While the initial symptoms rash and dizziness quickly improved, the patient developed dyspnea 5 days after levofloxacin

exposure [21]. Virology markers were negative in other patients in whom these were assessed [42].

Anaphylactoid reactions, anaphylaxis reactions and urticarial occurred regardless of previous tolerance to the incriminated agent, while a history of intolerance to other antibiotics was a risk factor. Additionally, most reactions were diagnosed based on their close temporal relationship with exposure to the culprit drug, as well as symptom resolution upon drug de-challenge. Neither skin testing nor basophil activation test could predict quinolone allergy [29].

Immune-mediated severe cutaneous hypersensitivity reactions

Immune-mediated ADRs other than anaphylaxis/anaphylactoid reactions are relatively rare, and included hemolytic–uremic syndrome, hemolytic anemia, thrombocytopenia, leukopenia or pancytopenia, acute interstitial nephritis, photosensitization, acute hepatitis and acute cholestatic jaundice, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), fixed drug eruption (FDE), cutaneous vasculitis, maculopapular exanthema, acute pancreatitis, serum sickness-like disease, angioimmunoblastic lymphadenopathy, acute generalized exanthematous pustulosis and eosinophilic meningitis [6].

ADRs with cutaneous presentation were the most common type of ADRs in a small sample of patients treated with fluoroquinolones [48, 49]. Specifically, the prevalence of ADRs was 0.13% in a large sample of Thai patients treated with fluoroquinolones, while the rate of cutaneous ADRs in patients ≥ 18 years of age was 0.09%, adding up to 151 cases. A history of fluoroquinolone HSR was noted in 8.6% of the sample. The rate of cutaneous ADRs differed based on the fluoroquinolone used [49]. For example, the rate of cutaneous ADRs in patients ≥ 18 years of age was 0.37% for ciprofloxacin, 0.1% for moxifloxacin and 0.06% for levofloxacin. The most common manifestation of cutaneous ADRs was maculopapular rash (39.7%). Fourteen of the 151 patients included in the study developed SJS/TEN, after a period of 1–19 days after oral ingestion of a fluoroquinolone [49]. For example, the rate of cutaneous ADRs in patients ≥ 18 years of age was 0.37% for ciprofloxacin, 0.1% for moxifloxacin and 0.06% for levofloxacin. The most common manifestation of cutaneous ADRs was maculopapular rash (39.7%). Fourteen of the 151 patients included in the study developed SJS/TEN, after a period of 1–19 days after oral ingestion of a fluoroquinolone [49].

Moxifloxacin was the most commonly incriminated drug in a sample of 69 patients with confirmed HSR to fluoroquinolone (OR 3.09, 95% CI 1.16–8.24, $p = 0.024$). The most common HSR manifestations were cutaneous (urticarial or exanthema), followed by anaphylaxis or anaphylactic shock [50]. Additionally, moxifloxacin carries a higher risk of HSRs compared to levofloxacin and ciprofloxacin (141.3 vs. 40.8 and 26.3 emergency department visits/100,000 prescriptions, respectively). This relationship was maintained when HSRs were stratified by severity (mild or moderate-to-severe) [51]. In an Italian study, moxifloxacin was associated with the highest rate of ADRs among fluoroquinolones after adjusting for drug consumption (84.6 vs. 55.3 reports/1000 inhabitants/day for levofloxacin) [52]. In a separate study, cutaneous ADRs were found to be the predominant type of ADRs associated with ciprofloxacin use, with 34.9% of all reported ADRs. The corresponding values were 13.5% for moxifloxacin and 19.9% for levofloxacin. Overall, this report shows a 0.5–3.0% incidence of cutaneous ADRs among fluoroquinolone users [48]. Ciprofloxacin was the drug most often associated with cutaneous ADRs in another study as well (33.3%), followed by levofloxacin (32.3%) and moxifloxacin (20.4%). In contrast, moxifloxacin was associated with the highest incidence of anaphylactic shock (57.1%), followed by levofloxacin (35.7%) and ciprofloxacin (7.1%) [52].

Quinolones were associated with a high risk of acute generalized exanthematous pustulosis in the EuroSCAR study (OR 33, 95% CI 8.5–127) [53]. They were also identified as one of the main classes of drugs that lead to acute generalized exanthematous pustulosis, maculopapular eruptions, photosensitivity and vasculitis in large

reviews discussing non-immediate cutaneous ADRs [54,55]. Furthermore, quinolones were also associated with bullous drug eruptions [55]. In a small report analyzing the causative agent in cases of cutaneous ADRs, quinolones were identified as a common cause of morbilliform rash and photosensitivity. As a cautionary note, the authors argue that the relatively high rate of cutaneous ADRs associated with this class of drugs might simply reflect an increased rate of prescribing quinolones [56]. Immediate cutaneous HSRs associated with ciprofloxacin, levofloxacin or moxifloxacin are detailed in Table 2 [57–84].

Acute exanthematous pustulosis occurred in several patients. They were 2 males and 1 female (63–80 years of age), of which 2 were exposed to ciprofloxacin and 1 to levofloxacin. All 3 patients experienced cutaneous manifestations and leukocytosis, with resolution of symptoms upon drug discontinuation. Skin biopsy was used for the diagnosis [57–59]. Maculopapular exanthema with cutaneous manifestations is described in two patients treated with ciprofloxacin. Both patients experienced resolution of symptoms upon ciprofloxacin de-challenge and recurrence upon re-challenge [60]. Radiation recall dermatitis associated with levofloxacin is described in a patient with a history of breast cancer treatment. Symptoms resolved upon drug de-challenge [61]. Moxifloxacin led to immune-mediated exanthema with cutaneous manifestations in a patient with a history of generalized urticaria while receiving other antibiotics [62].

Two patients were diagnosed with cutaneous HSR. It was accompanied by hypersensitivity pneumonitis in the patient treated with moxifloxacin [63,64]. Bullous skin eruption induced by ciprofloxacin was diagnosed elsewhere [65]. Vasculitis occurred in several patients [66–73]. The majority of cases occurred in patients treated with ciprofloxacin ($n = 9$), and in one patient treated with levofloxacin. A relatively even gender distribution is present (6 females and 4 males).

Another common type of HSR associated with fluoroquinolones was fixed drug eruptions. Of 10 cases, 6 occurred with ciprofloxacin with the remaining 4 attributed to levofloxacin. A wide age range was observed (29–80 years). Symptoms generally resolved spontaneously, and recurred upon re-challenge with the culprit drug. A high likelihood of cross-reactivity to other quinolones was encountered [74–83]. Photosensitivity to UV light, characterized by cutaneous manifestations, was shown in a young girl. Symptoms did not occur in the absence of UV radiation, and resolved upon ciprofloxacin de-challenge [84].

Severe cutaneous adverse reactions

SJS and TEN are examples of rare immune-mediated ADRs associated with quinolone use [6]. An additional mechanism of quinolone-induced toxicity was introduced [85]. The parent compound of quinolones, which is chemically not reactive, can still directly bind to the MHC-peptide/T cell receptors and stimulate T cells by pharmaceutical interaction (p–i). Therefore quinolones are suspected of causing HSR by both the hapten and the p–i concepts simultaneously [85].

Moxifloxacin, ciprofloxacin and levofloxacin HSRs led to 44.0 emergency department visits per 100,000 prescriptions based on data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance system. However, moxifloxacin was associated with the highest rate of these, with 141.3 emergency department visits for an HSR per 100,000 prescriptions, followed by levofloxacin with 40.8 emergency department visits for an HSR per 100,000 prescriptions and ciprofloxacin with 26.3 emergency department visits for an HSR per 100,000 prescriptions [52]. In this report, ciprofloxacin was most often associated with moderate to severe HSRs, while moxifloxacin was most often associated with mild HSRs [52].

Quinolones were associated with a high risk of SJS/TEN in the EuroSCAR study (OR 6.9, 95% CI 1.8–27) [86]. Previously, quinolones were identified as one of classes of drugs associated with SJS/TEN in a large sample of patients in a multinational cohort. There were 11 cases observed in a sample of 245 patients (4.5%), including cases induced

Q2 Table 1

Fluoroquinolone-induced anaphylaxis–anaphylactoid (type I hypersensitivity reactions) immediate HSR.

Reference	Underlying condition and co-morbidities; drug/co-therapy	Symptoms, diagnosis and drug(s) incriminated; time to onset	Techniques to validate diagnosis; outcome
Q1 Age/gender, country			
[14] 32/F UK	Otitis media; HIV infection; history of ciprofloxacin tolerance; ciprofloxacin 500 mg twice/day	15 min after second course; anaphylaxis: dyspnea, vomiting, dizziness, epigastric pain, hypotension, and anuria	Close temporal relation Patient was unconscious with extensive bilateral brain stem signs and died.
[15] 35/F USA	Chronic granulomatous disease; IV ciprofloxacin	Anaphylaxis with itching and erythematous rash immediately after infusion	Recurrence upon ciprofloxacin de-challenge Resolution of symptoms; tolerated ciprofloxacin after desensitization
[16] 2/F USA	Polymicrobial gluteal abscesses and chronic osteomyelitis; ciprofloxacin 30 mg/kg/day	15 min after: anaphylaxis, trembling, headache, fever, flushing, tachycardia, vomiting; after 2 days: generalized maculopapular rash	SPT (–) to ciprofloxacin Intradermal test positive to ciprofloxacin Spontaneous resolution of symptoms
[17] 45/F Italy	Prophylaxis for meningococcal infection; history of ciprofloxacin tolerance; ciprofloxacin 500 mg	Anaphylaxis with pharyngeal edema, tongue swelling and generalized skin rash after 20 min	Validation not discussed Resolution of symptoms with adrenalin, anti-histamines and corticosteroids
[18] 33/M Japan	Allergic rhinitis and urticaria after eating crabmeat Oral levofloxacin, L-carbocysteine and mefenamic acid	Anaphylaxis: numbness, vertigo, sweating, shivering, itching, dyspnea, dystasia, impaired consciousness 10 min after levofloxacin	Open patch test (+) to levofloxacin Resolution of symptoms with methylprednisolone
[19] 30/F Italy	Multiple drug allergy syndrome Levofloxacin	Anaphylaxis: angioedema and relapsing urticarial	ORC (+) to levofloxacin Resolution of symptoms
[20] 26/M Japan	<i>Mycoplasma pneumoniae</i> infection Intravenous levofloxacin (500 mg/day)	Anaphylaxis chest tightness, dyspnea, wheezing, impaired consciousness	SPT (+) for levofloxacin and ofloxacin Without antibiotics improvement of symptoms, asthma worsening
[21] 58/M Korea	Fever; asthma Hepatitis viral markers negative Levofloxacin 250 mg	HSR dizziness, skin rash 2.5 h after; normal WBC 7.1×10^9 /LAST 146 U/L, ALT 698 U/L, ALP 233 U/L, γ -GTP 868 U/L, total bilirubin: 3.1 mg/dL, direct: 1.9 mg/dL	Temporal relationship to levofloxacin use ORC (+) to levofloxacin Resolution of symptoms with epinephrine, D-chlorpheniramine and methylprednisolone
[22] Spain	63/F Not mentioned Moxifloxacin	Anaphylaxis	SPT (+) to ofloxacin and moxifloxacin ORC (+) to moxifloxacin Symptoms remitted with anti-histamines
	39/F Not mentioned Ciprofloxacin	Urticaria	SPT (+) ciprofloxacin, levofloxacin, moxifloxacin; ORC (+) to moxifloxacin ORC not performed for ciprofloxacin Symptoms remitted with anti-histamines
	29/F Not mentioned Ciprofloxacin and ofloxacin	Urticaria	SPT (+) to levofloxacin, moxifloxacin; SPT (–) to ciprofloxacin, ofloxacin; ORC (+) to levofloxacin and moxifloxacin, ORC not performed for ofloxacin; ciprofloxacin well tolerated; remitted with anti-histamines
Q3	42/F Not mentioned Ciprofloxacin	Urticaria	SPT (+) to ofloxacin, levofloxacin, moxifloxacin; ORC (+) to ciprofloxacin; moxifloxacin; remitted with anti-histamines
	50/F Not mentioned Moxifloxacin	Urticaria	SPT (+) to ciprofloxacin, ofloxacin, moxifloxacin; ORC (+) to ciprofloxacin, ofloxacin, moxifloxacin Symptoms remitted with anti-histamines
	53/M Not mentioned Moxifloxacin	Urticaria	SPT (+) to ciprofloxacin; SPT (–) to moxifloxacin; ORC (+) to moxifloxacin Symptoms remitted with anti-histamines
[23] 26/F Spain	Upper respiratory tract infection No known history of ciprofloxacin allergy Ciprofloxacin 250 mg	Angioedema, generalized urticaria, and dysphonia after 2–3 min of ciprofloxacin Diagnosed with type I HSR to ciprofloxacin	SPT (+) to ciprofloxacin (non-specific as also (+) in some controls); recurrence of symptoms upon ciprofloxacin re-challenge; cross-reactivity with pipemidic acid on re-challenge; outcome not discussed
[24] 15/F USA	Cystic fibrosis History of ciprofloxacin tolerance Ciprofloxacin 500 mg twice/day	Urticaria after 2 days of ciprofloxacin treatment	Discontinuation of ciprofloxacin Resolution of symptoms
[25] 46/M Swiss	Gram-negative bacterial infection Ciprofloxacin	Generalized urticaria after each dose of ciprofloxacin	Tolerance following desensitization Recurrence upon re-challenge; SPT and intradermal tests (–) to ciprofloxacin Spontaneous resolution of symptoms

[26]	28/F Turkey	Urinary tract infection IV ciprofloxacin (400 mg 2 times/day)	Erythematous, itchy swelling after 4 days; diagnosed: urticaria, tenosynovitis	Magnetic resonance imaging Resolution of symptoms without any treatment
[27]	41/F Spain	Treated during anesthesia (induction phase) Ciprofloxacin	Erythema, rash, urticaria/angioedema; diagnosed SCAR-ciprofloxacin	Levels of serum tryptase not determined Allergic IgE-mediated mechanism confirmed Outcome not discussed
[28]	71/M Canada	Previously tolerated ciprofloxacin, levofloxacin, 1 course of moxifloxacin Moxifloxacin 400 mg/day	Nausea, dyspnea, hot flashes, generalized urticaria 30 min after 2nd dose of moxifloxacin	Intradermal tests (–) to moxifloxacin ORC (+) moxifloxacin; ORC (–) to ciprofloxacin Symptoms resolved with diphenhydramine
	44/F	Delayed reaction to ampicillin Moxifloxacin	Pruritus and headedness 30 min after 1st dose of moxifloxacin	ORC (+) to moxifloxacin; ORC (–) to ciprofloxacin; symptoms resolved
	70/F	Measles-like eruption to trimethoprim-sulfamethoxazole; moxifloxacin	Urticaria and pruritus 60 min after 1st dose of moxifloxacin	ORC: (+) to moxifloxacin Symptoms resolved
[29]	50/F Spain	Not mentioned Moxifloxacin	Urticaria	SPT (–) to moxifloxacin; ORC (+) to moxifloxacin Outcome not discussed
	83/M	Not mentioned Moxifloxacin and levofloxacin	Urticaria/angioedema	SPT (–) to moxifloxacin, levofloxacin; ORC not performed for moxifloxacin, levofloxacin Outcome not discussed
[30]	44/F Spain	Respiratory infection No history of allergy Moxifloxacin	Pruritus, generalized urticarial, angioedema and dyspnea 10 min after 1st dose of moxifloxacin	Intradermal tests (+) to moxifloxacin SPT (–) to moxifloxacin; resolution after moxifloxacin discontinuation, treatment with corticosteroids and anti-histamines Tolerance to levofloxacin Recurrence upon ciprofloxacin re-challenge Improvement of symptoms with corticosteroids
[31]	31/M USA	Chronic osteomyelitis HIV infection; IV-drug user; history of erythematous pruritic rash on ciprofloxacin Ciprofloxacin and metronidazole	Anaphylactoid reaction with total body erythroderma, pruritus, conjunctival injection, and dyspnea after 15 min of restarting ciprofloxacin	Validation not discussed Resolution of symptoms with mechanical ventilator support
	33/F	Bacterial urinary tract infection HIV infection Ciprofloxacin	Anaphylactoid reaction: difficulty swallowing, dyspnea, rash, loss of consciousness after 15 min; cyanosis, stridor	
[32]	16/M/White USA	Cystic fibrosis with pulmonary infection No history of drug allergies No history of ciprofloxacin use Ciprofloxacin	Anaphylactoid reaction with generalized itching, dyspnea, urticarial rash after 1 h	Validation not discussed Resolution of symptoms with epinephrine, diphenhydramine and steroids
	15/F/White	Cystic fibrosis deteriorating pulmonary function; allergies: penicillin, trimethoprim-sulfamethoxazole History of ciprofloxacin tolerance Ciprofloxacin 500 mg	Anaphylactoid reaction with disseminated urticarial rash, fever, headache and vomiting after 30 min	Validation not discussed Resolution of symptoms with diphenhydramine
[33]	38/M USA	<i>Salmonella</i> ; HIV infection Initial intravenous ceftriaxone followed by oral ciprofloxacin course well tolerated Ciprofloxacin 500 mg	Anaphylactoid reaction with difficulty breathing, disorientation, generalized erythematous maculopapular eruption, facial edema after 2 h after second treatment	Skin biopsy Improvement of symptoms with diphenhydramine hydrochloride
[34]	21/F/White USA	Pelvic inflammatory disease; HIV negative; allergies to penicillin, aspirin; mild intolerance to ciprofloxacin, meperidine, ranitidine Ciprofloxacin 500 mg	Anaphylactoid reaction with generalized itching, urticarial rash, shortness of breath, facial swelling, hives after 30 min; WBC ($7.1 \times 10^9/L$)	Validation not discussed Resolution of symptoms with hydrocortisone, cimetidine, diphenhydramine, epinephrine
[35]	21/M UK	Prophylaxis for meningococcal infection History of asthma Ciprofloxacin 500 mg	Anaphylactoid reaction with tight and hoarse throat, swelling of eyes after 30 min	Validation not discussed Resolution of symptoms with adrenaline and chlorpheniramine
	20/F	Prophylaxis for meningococcal infection Ciprofloxacin 500 mg	Anaphylactoid reaction with itchy rash, tight throat after 25 min	Validation not discussed Resolution of symptoms following adrenaline and chlorpheniramine
	19/F	Prophylaxis for meningococcal infection Ciprofloxacin 500 mg orally	Anaphylactoid reaction with dyspnea, tight throat, swelling of eyes, cough after 3 h	Validation not discussed Improvement of symptoms with adrenaline and chlorpheniramine
	19/M	Meningococcal infection; history of penicillin allergy Ciprofloxacin 500 mg	Anaphylactoid reaction with swelling of face and eyes after 30 min	Validation not discussed Resolution of symptoms with chlorpheniramine and hydrocortisone

(continued on next page)

Table 1 (continued)

Reference Age/gender, country	Underlying condition and co-morbidities; drug/co-therapy	Symptoms, diagnosis and drug(s) incriminated; time to onset	Techniques to validate diagnosis; outcome
[36] 79/M USA Armenian	Pyelonephritis Intravenous ciprofloxacin 400 mg twice/day	Anaphylactoid reaction with erythema and pruritus, worsening respiratory status after 30 min	Validation not discussed Improvement with methylprednisolone, famotidine, diphenhydramine and lorazepam
[37] 15/F India	External hordeolum Ciprofloxacin	Anaphylactoid reaction with sudden loss of consciousness, pruritus, rash, shortness of breath; lip swelling	Validation not discussed; improvement of symptoms following epinephrine, hydrocortisone, diphenhydramine
[38] 25/F/White USA	Pyelonephritis No known drug allergies Ciprofloxacin 500 mg twice/day and ibuprofen	Anaphylactoid reaction angioedema, pulmonary edema, facial, lip swelling, shortness of breath the day after starting the drug	Validation not discussed Improvement of symptoms with corticosteroids and anti-histamines
[39] 49/F USA Albanian	Suspected infection Exacerbation of asthma; history of levofloxacin use for sinus infection; IV levofloxacin 500 mg/day	Anaphylactoid reaction with shortness of breath, diffuse erythema and hives immediately after levofloxacin	Validation not discussed Improvement of symptoms with diphenhydramine + methylprednisolone
[40] 24/F Brazil	Urinary tract infection IV ciprofloxacin 400 mg twice/day	Generalized pruritic maculopapular rash, after 36 h; Impairment consciousness; SCAR, systemic reaction (IgE-mediated) ciprofloxacin	SPT (+) to ciprofloxacin Recurrence symptoms upon ciprofloxacin ORC; resolution of symptoms with anti-histamines and corticosteroids
[41] 37/F China	Upper respiratory infection IV levofloxacin (4 infusions)	Recurrent swelling at the injection site beginning 2 weeks after injections; Urticaria local	Physical examination Skin biopsy Resolution of symptoms
[42] 75/F Italy	Hemorrhagic cystitis; sun exposure Levofloxacin 500 mg 2 times/day	Erythematous pruritic eruption after 10 days; Leukocytosis (WBC $11 \times 10^9/L$); photo-pruritic eruption	Discontinuation of levofloxacin Skin biopsy Resolution of symptoms
[43] 27/F Japan	Bacterial conjunctivitis Levofloxacin (0.5%) ophthalmic; beta-methasone sodium phosphate plus fradiomycin sulfate	Facial edema, pruritic rash, mild dyspnea immediately after starting; contact urticaria induced by levofloxacin	Physical examination SPT positive to levofloxacin Outcome not discussed
[44] 31/M Spain	Respiratory infection; hepatitis B and C, with complete resolution Levofloxacin 500 mg; ketorolac 10 mg	Itching, micropapular exanthema, edema, generalized erythema; HSR-levofloxacin	SPT (+) levofloxacin, ofloxacin Resolution with hydrocortisone and dexchlorpheniramine
[45] 7/M India	History of erythematous papules while on ciprofloxacin; IV levofloxacin (10 mg/kg/day)	Erythematous papules within seconds of infusion HSR-levofloxacin	Cross-reactivity between levofloxacin and ciprofloxacin Spontaneous resolution of symptoms

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; γ -GTP: γ -glutamyl transpeptidase; F: female; HSR: hypersensitivity reaction; IV – intravenous; M: male; ORC: oral re-challenge WBC: white blood cell count; SCAR: severe cutaneous reaction; SPT: skin prick test.

by ciprofloxacin, pefloxacin, ofloxacin, pipemidic acid and norfloxacin. Quinolones were associated with a high risk of SJS/TEN (OR 10, 95% CI 2.6–38) in a large retrospective analysis [87]. Fluoroquinolones were found to be one of the classes of drugs most often associated with TEN in a retrospective analysis in India [88]. Table 3a details cases of severe cutaneous adverse reactions, predominantly SJS and TEN, that occurred in individuals treated with ciprofloxacin, levofloxacin or moxifloxacin [89–118]. In Table 3b we analyzed severe adverse cutaneous reactions in patients treated with fluoroquinolones in the presence of alcohol misuse [63,90].

SJS/TEN associated with quinolones was found to occur exclusively in the first 2 months of treatment [87]. Older age is associated with a poor prognosis in patients with TEN associated with ciprofloxacin [106]. Being HIV-positive was an additional risk factor for SJS/TEN [50]. The incidence of SJS ranges from 1.2 to 6.0 per million person-years, while that of TEN ranges from 0.4 to 1.2 per million person-years [119–121].

In the Swedish Drug Information System, ciprofloxacin was associated with 3 cases of SJS, 3 cases of TEN, as well as 2 cases of erythema multiforme among 114 adverse cutaneous events reported between 1988 and 2000 as possibly being related to ciprofloxacin. Of these, 87.5% occurred in females (age range 25–74) [97]. Based on these data, Hällgren et al. [97] estimate an incidence of SJS/TEN or erythema multiforme of 0.045 per 100,000 ciprofloxacin-treated patients. Delayed HSRs to quinolones appear to be mediated by a strong T-cell immune response directed against a specific quinolone, showing that no drug metabolism is necessary for this type of ADR [122].

Drug reaction with eosinophilia and systemic symptoms (DRESS), with cutaneous manifestations, eosinophilia and hepatitis is described in 2 patients treated with ciprofloxacin, and in 2 patients who received moxifloxacin as part of anti-tuberculosis treatment. Complete resolution ensued in all patients after the culprit treatment was stopped [92–94]. Moxifloxacin-induced HSR occurred in another patient with hepatic involvement, yet eosinophilia was absent [95].

Six cases of SJS are described in patients exposed to fluoroquinolones ages 31–67 years old and outcomes were favorable in all, except for one who was also the oldest of these individuals [96–100]. On the other hand, TEN developed over a much wider age range (15–93). Of the 18 cases discussed, 9 cases were fatal, of which 6 had organ involvement. Among patients treated with ciprofloxacin who developed TEN, there were 6 males and 1 female. Six patients developed TEN after levofloxacin treatment, including 4 females and 2 males. There were 2 Indian individuals, 1 Bangladeshi individual, and 3 likely Caucasians. There were 3 females of Caucasian origins and one Asian male who developed TEN during moxifloxacin treatment [101–118].

All SJS cases occurred between 7 and 14 days after the start of treatment. Liver involvement was detected in 3 of the 5 cases of ciprofloxacin SJS, of which one presented vanishing bile duct syndrome, while the moxifloxacin SJS case was accompanied by ocular involvement. Among patients who developed SJS, fluoroquinolones were prescribed for various infections or for the prevention of infection [96–100]. Another case of vanishing bile duct syndrome accompanied by pancreatitis and pruritus is described in a patient treated with moxifloxacin [123]. Hepatic injuries were common in individuals with SJS/TEN [96–98, 104,105,115,117]. SJS with ocular involvement is reported in a patient treated with ciprofloxacin in India [124]. A case of SJS was the only serious adverse event reported in a small sample of females treated with moxifloxacin for pelvic inflammatory disease [125].

TEN is a condition most often caused by drugs. Although rare, it has a mortality rate of up to 30%, with up to 50% of affected patients failing to achieve complete resolution, most often manifesting as residual ocular lesions [119]. TEN cases occurred between 3 and 14 days in ciprofloxacin patients, 2 and 12 days in levofloxacin patients, and 3 and 7 days in moxifloxacin patients. In certain instances, TEN occurred immediately after reintroduction of ciprofloxacin in patients who have recently completed a previous treatment [102,105]. The affected BSA ranged

between 30 and 80% in cases of TEN in which this is reported, with similar rates between the three drugs. Among TEN patients, the affected organs are usually the liver and the kidneys, while respiratory distress was also reported. Their situations often have fatal outcomes, especially in the event of multiorgan failure. TEN cases without these manifestations were usually not lethal. Additionally, the presence of ocular involvement did not appear to affect the survival rate. Patients who developed TEN were prescribed fluoroquinolones for the treatment or prevention of various infections [95,100–118,123].

Co-administration of levothyroxine and ciprofloxacin, especially high doses of the former, is believed to have increased the risk of SJS in one patient by decreasing ciprofloxacin metabolism. SJS may have been caused by a marked reduction of cytochrome activity due to levothyroxine over-medication, with the patient also developing iatrogenic hyperthyroidism [99]. Co-administration of furazolidone and levofloxacin was believed to have increased the risk of TEN in a patient compared to either drug alone, as furazolidone may have induced oxidative stress that exacerbated the HSR associated with levofloxacin [114]. Two cases of severe cutaneous adverse drug reactions are reported in a couple of patients treated with lenalidomide and concomitant moxifloxacin or levofloxacin, respectively [126].

The use of etanercept was associated with rapid complete re-epithelization in a patient with TEN associated with ciprofloxacin. Resolution of TEN symptoms following treatment with this tumor necrosis factor- α antagonist suggests that this pro-inflammatory cytokine plays an important role in the pathogenesis of this condition [107].

Herpes simplex genome was isolated from aqueous taps in a patient who developed uveitis-like symptoms after moxifloxacin treatment. The patient had a history of uveitis, so the interplay between viral reactivation and moxifloxacin is unclear [127]. Digwood-Lettieri et al. [109] report the presence of herpetic lesions in the mouth of one patient who developed TEN after levofloxacin treatment. Symptoms of herpes simplex were absent in two patients diagnosed with ciprofloxacin-induced SJS [97].

Hepatic adverse drug reactions

A pharmaco-epidemiologic evaluation of hepatotoxicity associated with fluoroquinolones was prepared using a retrospective case-control study of hospital admissions data from Veterans Affairs. Fluoroquinolones were risk factors for hepatotoxicity compared to non-use of these drugs after adjusting for potential confounders (OR 1.20, 95% CI 1.04–1.38). In this study, ciprofloxacin was associated with hepatotoxicity (OR 1.29, 95% CI 1.05–1.58), while the use of levofloxacin and moxifloxacin did not increase the risk of hepatotoxicity compared to non-users of fluoroquinolones [128]. Elsewhere, levofloxacin was associated with a high risk of emergency room visits for non-infectious liver injury for current single use (OR 3.2, 95% CI 1.8–5.8) compared to non-users of antibiotics [129].

Case reports of hepatic ADRs associated with ciprofloxacin, levofloxacin and moxifloxacin use are detailed in Table 4a [130–154]. Alcohol abuse and illicit drug use were more predominant among cases than controls. However, the incidences of diabetes and current smoking were higher in controls than in cases. Alcohol abuse (6.3% among cases and 0.6% among controls) was the primary determinant of hepatotoxicity (OR 7.77, 95% CI 6.63–9.11) [128].

Cases of idiosyncratic acute liver injury are described in a population-based study among individuals with no history of liver disease (≥ 66 years). Using clarithromycin as a reference, levofloxacin (OR 2.06, 95% CI 1.14–3.73, $p = 0.046$) and moxifloxacin (OR 2.44, 95% CI 1.37–4.36, $p = 0.009$) were associated with higher odds of hospitalization for acute liver injury. A non-significant trend was observed for ciprofloxacin [155]. Orman et al. [130] discuss 12 cases of fluoroquinolone-induced liver injury considered definite, highly likely, or probable based on data from the Drug-induced Liver Injury (DILI) Network (6 ciprofloxacin, 4 moxifloxacin, 1 levofloxacin and 1

Table 2

Immediate cutaneous adverse drug reactions in individuals treated with fluoroquinolones.

Reference Q4 Age/gender, country	Underlying condition and co-morbidities Fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
[57] 80/F Swiss	Urinary tract infection Ciprofloxacin	Erythematous eruption after 5 days; fever; acute exanthematous pustulosis induced by ciprofloxacin	Ciprofloxacin stopped Physical examination; skin biopsy Spontaneous resolution of symptoms
[58] 63/M USA	Urinary tract infection Ciprofloxacin 500 mg 2 times/day	Pustular eruption on sunlight-exposed surfaces after 5 days; leukocytosis (WBC $17.3 \times 10^9/L$) Acute exanthematous pustulosis induced by ciprofloxacin + sunlight	Physical examination; skin biopsy Resolution of symptoms with prednisone
[59] 70/M Spain	Pneumonia Levofloxacin 500 mg 2 times/day	Non-follicular erythematous pustules; fever after 2 days; leukocytosis (WBC $28 \times 10^9/L$) Acute localized exanthematous pustulosis induced by levofloxacin	Skin biopsy; levofloxacin stopped — improvement Worsening of symptoms on re-challenge
[60] 15/F Swiss	Cystic fibrosis with <i>Pseudomonas</i> infection Ciprofloxacin	Pruritic maculopapular exanthema after 8 days; ciprofloxacin–maculopapular exanthema	Resolution upon ciprofloxacin de-challenge Recurrence upon re-challenge SPT (–) patch tests (–)
[60] 23/M	Cystic fibrosis with <i>Pseudomonas</i> infection Ciprofloxacin	Febrile exanthema after 1 month; ciprofloxacin–maculopapular exanthema	Resolution upon ciprofloxacin de-challenge Recurrence upon ciprofloxacin re-challenge
[61] 55/F Caucasian USA	Reconstruction with a transverse rectus abdominis myocutaneous flap in a patient with a history of breast cancer; diffuse morbilliform exanthema to amoxicillin Levofloxacin 500 mg 2 times/day	Erythematous confluent papular exanthema localized to previous radiation port after 2 days of levofloxacin; diagnosed with radiation recall dermatitis induced by levofloxacin	Levofloxacin discontinued No re-challenge Resolution of symptoms
[62] 32/F Spain	History of generalized urticaria to amoxicillin–clavulanic acid (immediate reaction) Moxifloxacin 400 mg	Non-itching micropapular exanthema several hours after starting moxifloxacin Diagnosed with immune-mediated exanthema associated with moxifloxacin	Histamine release tests positive to moxifloxacin SPT (–) moxifloxacin ORT: (+) to moxifloxacin Resolution with dexchlorpheniramine
[64] 50/F Korea	Upper respiratory infection History of drug allergy to β -lactam Antibiotics Moxifloxacin	High fever and generalized maculopapular erythematous rash after 7 days of moxifloxacin Mild thrombocytopenia AST 71 IU/L; ALT 46 IU/L Diagnosed with HSR, pneumonitis associated with moxifloxacin	Physical examination High-resolution chest computed tomography Intradermal tests positive to moxifloxacin SPT negative to moxifloxacin Complete resolution after moxifloxacin discontinuation without treatment
[65] 69/F USA	Throat soreness, fever and posterior cervical lymphadenopathy Ciprofloxacin 500 mg 2 times/day	Pruritic generalized rash after 6 days, fever and dyspnea Diagnosed with bullous skin eruption induced by ciprofloxacin	Physical examination Patient did not respond to prednisone Improvement of symptoms
[66] UK	71/F Urinary tract infection Ciprofloxacin 500 mg/day First course of ciprofloxacin was well tolerated; cephadrine 500 mg/day; Second course of ciprofloxacin was initiated	Widespread pruritic erythematous papular eruption after 4 days of ciprofloxacin during the second course; diagnosed ciprofloxacin leukocytoclastic vasculitis	Skin biopsy Time course points to ciprofloxacin as the more likely drug than cephadrine Improvement of symptoms
[67] 7/M India	79/F Chest infection Ciprofloxacin Fever Ciprofloxacin	Hemorrhagic vasculitic rash after 10 days; diagnosed with cutaneous vasculitis induced by ciprofloxacin Maculopapular, nodular purpuric rash, ulcers in 2 days; diagnosed: ciprofloxacin HSR vasculitis	Physical examination Resolution of symptoms Skin biopsy Treated with steroids Improvement of symptoms
[68] 76/M Chinese Singapore	Urinary tract infection No known history of drug allergies Ciprofloxacin 500 mg 2 times/day Previously treated with ceftriaxone and metronidazole for hepatobiliary sepsis	Pruritic rashes after 4 days of ciprofloxacin, progressing to generalized, palpable purpura leukocytosis (WBC $13.8 \times 10^9/L$) Diagnosed ciprofloxacin — vasculitis	Resolution with ciprofloxacin de-challenge Spontaneous resolution of symptoms
[69] 69/F Spain	Otitis, systemic erythematous lupus, primary anti-phospholipid syndrome Ciprofloxacin 500 mg 2 times/day First course of ciprofloxacin was well tolerated; ceftriaxone 1000 mg/day Second course of ciprofloxacin was initiated	Malaise, dizziness, disseminated pruritus, arthralgia, articular swelling and fever after 90 min during the second course Diagnosed with cutaneous vasculitis induced by ciprofloxacin	SPT (–) to ciprofloxacin and ceftriaxone Recurrence upon ciprofloxacin re-challenge Skin biopsy Spontaneous resolution of symptoms

[70]	80/F	Spain	Thrombophlebitis Ciprofloxacin	Skin rash soon after ciprofloxacin Renal impairment; diagnosed with cutaneous and renal vasculitis induced by ciprofloxacin	Physical examination Renal biopsy not performed Cutaneous manifestations resolved with prednisone; renal symptoms improved
[71]	50/M	Canada	Urosepsis Ampicillin and gentamicin Ciprofloxacin	Skin rash after 10 days Proteinuria; diagnosed with cutaneous and renal vasculitis induced by ciprofloxacin	Physical examination Urinalysis; renal biopsy Cutaneous manifestations resolved with prednisone; renal symptoms improved
[72]	82/F	Netherlands	Infected ischemic ulcer Ciprofloxacin 500 mg 2 times/day Clindamycin 600 mg 3 times/day	Erythema and purpura after 4 days of ciprofloxacin; diagnosed with hemorrhagic vasculitis induced by ciprofloxacin	Physical examination Temporal association with ciprofloxacin Resolution of symptoms
	71/M		Infected ischemic ulcer Ciprofloxacin 400 mg 2 times/day Clindamycin 600 mg 3 times/day	Erythema and purpura after 6 days of ciprofloxacin; diagnosed with hemorrhagic vasculitis induced by ciprofloxacin	Physical examination Aggressive infection with gangrene led to lower limb amputation
[73]	65/F	USA	Pre-existing acute pustular psoriasis Elevated WBC Levofloxacin 500 mg/day	New rash after 3 days of levofloxacin Diagnosed with leukocytoclastic vasculitis induced by levofloxacin	Levofloxacin discontinued; skin biopsy Recovery complicated by methicillin-resistant <i>Staphylococcus aureus</i> Eventual improvement of all symptoms
[74]	72/F	Spain	History of pruritic erythematous macules on multiple antibiotics Ciprofloxacin	Pruritic erythematous macules upon ORC; diagnosed with HSR induced by ciprofloxacin	SPT (–) to ciprofloxacin, norfloxacin Resolution of symptoms
[75]	35/M	Japan	Pharyngitis History of erythematous pruritic rashes with erythema on ofloxacin Ciprofloxacin 600 mg 3 times/day	Pruritic erythema after 5 days of ciprofloxacin; diagnosed with FDR induced by ciprofloxacin with ofloxacin cross-reactivity	SPT (–) to ciprofloxacin and ofloxacin ORC (+) ciprofloxacin and ofloxacin Resolution of symptoms
[76]	53/F/White	Spain	Upper airway infection Ciprofloxacin 500 mg (IV)	Intensely pruritic, confluent, macular erythematous lesions 12 h after infusion; diagnosed with FDR induced by ciprofloxacin	SPT (+) to ciprofloxacin ORC (+) to ciprofloxacin Treated with parenteral corticosteroids Resolution of symptoms
[77]	29/F	Spain	History of FDR on norfloxacin Ciprofloxacin 250 mg	Pruritic erythematous macules 2 h after 1st ciprofloxacin dose Diagnosed with FRD induced by ciprofloxacin	SPT and intradermal tests (–) to both norfloxacin and ciprofloxacin SPT (+) ciprofloxacin only on lesions Resolution of symptoms
[78]	57/F	Turkey	Respiratory tract infection History of localized reaction on ciprofloxacin Ciprofloxacin	Widespread tender, pigmented patches, scattered blisters within hours of 1st dose Diagnosed with generalized bullous FDR induced by ciprofloxacin	Physical examination Skin biopsy Resolution of symptoms following treatment with prednisolone
[79]	60/M	India	Prescribed post-operatively after cataract surgery Ciprofloxacin	Bullous eruptions over hands and erosions with crusting on lips after 1st dose; diagnosed with bullous FDR induced by ciprofloxacin	Ciprofloxacin discontinued Skin biopsy Resolution of symptoms with corticosteroids
[80]	80/F	Japan	History of FDR on levofloxacin and PL® Levofloxacin (100 mg) and PL® (acetaminophen, salicylamide, anhydrous caffeine and promethazine methylenedisalicylate)	Rash 12 h after levofloxacin plus PL®; erythematous, edematous, eroded area on lip Diagnosed with FDR induced by levofloxacin and PL®	Skin biopsy Recurrence upon ORC with levofloxacin and PL® Resolution of symptoms
[81]	54/Black F	USA	Urinary tract infection Known allergy to ciprofloxacin Levofloxacin	Generalized cutaneous eruption within hours of levofloxacin Diagnosed with levofloxacin-FDR	Physical examination Medical history Improvement of symptoms
[82]	28/F/Spain		Cystic fibrosis History of erythematous plaques on ciprofloxacin; levofloxacin 500 mg	Erythematous plaques after 1st levofloxacin dose Diagnosed levofloxacin – FDR	Cross-reactivity between levofloxacin and ciprofloxacin; resolution symptoms; patient managed with ciprofloxacin desensitization
[83]	66/F	Tunisia	Pneumonia Levofloxacin 500 mg 2 times/day Acetaminophen	Erythematous plaques 6 h after 1st levofloxacin dose New lesions after 2nd dose; Diagnosed levofloxacin – FDR	Recurrence upon exposure to levofloxacin Patch test positive to levofloxacin positive on affected area; SPT positive to ofloxacin Spontaneous resolution of symptoms
[84]	12/F	UK	Cystic fibrosis with respiratory infection Ciprofloxacin 750 mg 2 times/day	Pruritic erythematous rash after 10 days of ciprofloxacin on skin exposed to sun or fluorescent lights Diagnosed with photosensitivity (ultraviolet radiation skin damage) to ciprofloxacin	Resolution upon ciprofloxacin de-challenge Resolution of symptoms

ALT: alanine aminotransferase; AST: aspartate aminotransferase; F: female; FDR: fixed drug eruption; HSR: hypersensitivity reaction; IV – intravenous; M: male; ORC: oral re-challenge; SCAR: severe cutaneous adverse reaction; SPT: skin prick test; WBC: white blood cell count.

Table 3a

Severe cutaneous adverse drug reactions in individuals treated with fluoroquinolones.

Reference Age/gender, country	Underlying condition and Co-morbidities; fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
[89] 25/M India	Fever and diarrhea Ciprofloxacin 500 mg twice/day Paracetamol	Multiple erythematous lesions and itching after 3 days of ciprofloxacin; enlarged lymph nodes; diagnosed with erythema multiforme induced by ciprofloxacin	Resolution after ciprofloxacin de-challenge Complete resolution
[91] 40/F India	History of urinary tract infection Ciprofloxacin	Multiple erythematous lesions and conjunctival soreness after 4 days of ciprofloxacin Bullous lesions after ciprofloxacin interruption Diagnosed with erythema multiforme induced by ciprofloxacin	Resolution after ciprofloxacin de-challenge Complete resolution after treatment with prednisone
[92] 57/F Croatia	Acute left-side pyelonephritis with ipsilateral nephrolithiasis Ciprofloxacin Diclofenac and paracetamol as needed	Itching and maculopapular exanthema after 10 days of ciprofloxacin Increase in leukocyte count with eosinophilia Elevated liver enzymes with AST 71.5 IU/L, ALT 104.4 IU/L, ALP 321 IU/L and γ -GTP 119 IU/L Diagnosed with DRESS with elevated liver enzymes induced by ciprofloxacin	Resolution after ciprofloxacin de-challenge Complete resolution
[93] 24 Hispanic F USA	Urinary tract infection Ciprofloxacin	Fever, pruritic rash and edema after 2 days of ciprofloxacin Increase in leukocyte count with eosinophilia Normal levels of serum IgE Diagnosed with DRESS induced by ciprofloxacin	Resolution after ciprofloxacin de-challenge Biopsy Complete resolution
[94] 34/F Caucasian Argentina	Pulmonary tuberculosis Moxifloxacin, cycloserine, ethionamide and para-aminosalicylic acid	Cutaneous manifestations, eosinophilia and hepatitis after 60 days of treatment Diagnosed with DRESS induced by anti-tuberculosis treatment	Moxifloxacin, cycloserine, ethionamide, para-aminosalicylic; cross-reactivity with levofloxacin Favorable outcome after drug discontinuation
[94] 18/Native F Argentina	Pulmonary tuberculosis Moxifloxacin, kanamycin, pyrazinamide, ethionamide and cycloserine	Cutaneous manifestations, eosinophilia and hepatitis after 30 days of treatment Diagnosed with DRESS induced by anti-tuberculosis treatment	Moxifloxacin and pyrazinamide were involved; levofloxacin was tolerated; favorable outcome after discontinuation of drugs
[95] 52/F Korea	Pneumonia Moxifloxacin	Symptoms after 3 days of moxifloxacin AST 88 IU/L; ALT 64 IU/L; no eosinophilia Diagnosed with HSR induced by moxifloxacin	Not discussed Patient is alive.
[96] 32/Black M USA	Sore throat Ciprofloxacin daily	Skin eruptions, dyspnea, dysphagia and fever after 7 days of ciprofloxacin Tonsils were enlarged, erythematous and congested; ulcerations on the buccal mucous membranes; ALP 102 IU/L, LDH 673 IU/L, AST 47 IU/L, total bilirubin 0.7 mg/dL Diagnosed with SJS induced by ciprofloxacin	Ciprofloxacin was stopped Discharged from hospital in good condition
[97] 31/F Somalian Sweden	Prophylactic course before planned operation for chronic media otitis Levothyroxine-substituted hypothyreosis; ciprofloxacin 750 mg/day; levothyroxine	Erosions and crusts on lips and genitals, and pruritic erythematous maculopapules with hemorrhaging after 8 days of ciprofloxacin Diagnosed with SJS induced by ciprofloxacin	Physical examination Skin biopsy Improvement of symptoms upon ciprofloxacin discontinuation
[97] 33/F	Otitis media and labyrinthitis Anti-histamines for rhinoconjunctivitis Salmeterol for asthma; erythromycin, later switched to intravenous ciprofloxacin 400 mg 3 times/day	Generalized pruritic petechial rash, and erythema on lips and genitals after 12 days of ciprofloxacin Diagnosed with SJS with elevated liver enzymes induced by ciprofloxacin	Ciprofloxacin was stopped. Physical examination Skin biopsy Improvement of symptoms upon ciprofloxacin discontinuation
[98] 26/F Turkey	Acute bronchitis Ciprofloxacin 500 mg twice/day	Fever, macular erythematous eruptions, erosions on lips, buccal and genital mucous membranes after 2 weeks of ciprofloxacin; ALT 326 IU/L, γ -GTP 280 IU/L, ALP 229 IU/L, total bilirubin 4.07 mg/dL; diagnosed with SJS with vanishing bile duct syndrome induced by ciprofloxacin	Ciprofloxacin was stopped. Skin biopsy; liver biopsy Resolution of symptoms with tacrolimus and ursodeoxycholic acid, and ciprofloxacin discontinuation
[99] 66/F Greece	Acute pyelonephritis Ciprofloxacin 1000 mg/day	Fever, sinus tachycardia, generalized pruritic skin eruption (15–20% BSA), erythema in the mouth and on genitals Diagnosed with SJS induced by ciprofloxacin, enhanced by administration of levothyroxine	Physical examination Skin biopsy Complete resolution with ciprofloxacin discontinuation
[100] 67/M Canada	Flu-like symptoms Moxifloxacin	Diffuse erythematous macules after 7 days of moxifloxacin; progressed to sloughing of skin Ocular involvement Diagnosed with SJS induced by moxifloxacin	Retrospective case report Treated with corticosteroids and gatifloxacin eye drops Patient died.

[101]	Urinary tract infection Non-insulin dependent diabetes History of allergy to penicillin, co-trimoxazole and tetracycline Ciprofloxacin 500 mg twice/day	Itchy, generalized erythematous confluent rash after 7 days of ciprofloxacin; rash progressed with formation of bullous lesions which sloughed easily; purpura, conjunctival involvement, throat ulcers; progressive liver and kidney failure, pancytopenia; deteriorating consciousness Diagnosed with TEN induced by ciprofloxacin	Physical examination Laboratory analysis Patient died despite treatment with cefotaxime, netilmicin and methylprednisolone.
[102]	Drainage associated with osteomyelitis History of systemic lupus erythematosus History of rash while on previous ciprofloxacin course Ciprofloxacin 750 mg twice/day	Pruritic rash after 1st ciprofloxacin dose; rash evolved to diffuse erythematous morbilliform rash with continued use of ciprofloxacin; developed bullae, erosions and desquamation Diagnosed with TEN induced by ciprofloxacin	Physical examination Dermatological consultation Skin biopsy Patient recovered after prolonged hospitalization.
[103]	Cellulitis Ciprofloxacin	Diffuse rash and epidermal sloughing (80% BSA) after 11 days ciprofloxacin; injected conjunctivae, and lips and tongue ulcerations; AST 1455 IU/L, ALT 637 IU/L; leukopenia ($WBC 1.1 \times 10^9/L$) Diagnosed with TEN induced by ciprofloxacin	Physical examination Patient eventually died due to TEN.
[104]	Bacterially-infected venous stasis ulcers Ciprofloxacin 500 mg twice/day	Blistering on lips, conjunctivitis, and ulcers in the mouth, fever, and rash (80% BSA) 14 days of ciprofloxacin; AST 1149 IU/L and LDH 1928 IU/L; leukocytosis ($WBC 2.2 \times 10^9/L$) Diagnosed with TEN induced by ciprofloxacin	Ciprofloxacin was stopped Physical examination Skin biopsy; patients developed liver and renal failure, died due to complicated disease course
[105]	Root canal infection History of systemic lupus erythematosus Ciprofloxacin 500 mg twice/day for 5 days, followed by an additional course at the same dose	Respiratory distress and diffuse, fever and rash with epidermal sloughing after 2 doses of the second course of ciprofloxacin Desquamation of lips; anemia, leukopenia ($WBC 12.5 \times 10^9/L$), renal insufficiency, and liver failure AST 372 U/L; ALT 345 U/L Diagnosed with TEN with multi-organ involvement induced by ciprofloxacin	Skin biopsy Treated with supportive care and sulfadiazine; patient died from TEN, severe acute respiratory distress syndrome and right ventricular failure
[106]	Urinary tract infection and septicemia Ciprofloxacin	Skin lesions (60% BSA) after 3 days of ciprofloxacin Diagnosed with TEN induced by ciprofloxacin	Skin biopsy Patient died within 48 h of developing cutaneous symptoms.
[107]	Respiratory tract infection History of levofloxacin exposure Ciprofloxacin 250 mg twice/day Warfarin	Erythema, maculopapular rash, erosions of oral, nasal mucosa, flaccid blisters. Superficially denuded skin (60% BSA) Diagnosed with TEN induced by ciprofloxacin	Ciprofloxacin was stopped. Treated with etanercept with improvement Patient died within 10 days of multiorgan failure.
[108]	Urinary tract infection Ciprofloxacin	Fever, conjunctival soreness and multiple erythematous discrete confluent blanchable macules and papules after 4 days of ciprofloxacin, progressing to bullous lesions, neutropenia Leukopenia ($WBC 1.1 \times 10^9/L$); diagnosed with TEN and agranulocytosis induced by ciprofloxacin	Treated with meropenem for septicemia Full recovery
[109]	Exacerbation of chronic obstructive pulmonary disease and community-acquired pneumonia Levofloxacin 500 mg/day; long-term ranitidine, lisinopril, glipizide, isosorbide mononitrate, lorazepam and furosemide	Itching, large blistering lesions, erythematous rash and mucosal sloughing after 12 days of levofloxacin Exfoliative rash (73% BSA) Leukopenia ($WBC 18.9 \times 10^9/L$) Diagnosed with TEN induced by levofloxacin	Physical examination Levofloxacin was stopped Treated with multiple antibiotics for bacterial and viral infections Improvement of symptoms
[110]	Cough with white sputum production History of pruritic rash following ciprofloxacin Levofloxacin 500 mg/day	Pruritic rash after 3 h of levofloxacin Progression to maculopapular rash (30% BSA) Skin and mucous lesions; neurological involvement with transient loss of consciousness Diagnosed with TEN induced by levofloxacin	Skin biopsy Improvement of symptoms after levofloxacin discontinuation
[111]	Nasal polypectomy Levofloxacin 500 mg/day	Fever, large blistering lesions, erythematous rash, mucosal sloughing, and swollen edematous extremities after 9 days of levofloxacin (80% BSA) Leukopenia ($WBC 12.7 \times 10^9/L$) with neutropenia Diagnosed with TEN induced by levofloxacin	Physical examination Levofloxacin was stopped. Patient died within 3 days of admission.
[112]	Urinary tract infection History of generalized purpuric exanthema after 9 days of levofloxacin Levofloxacin 500 mg/day	Purpuric exanthema after 6 h of levofloxacin restart; progression to desquamation (40% of BSA) with conjunctivitis, skin and mucous lesions Fever, abnormal liver and kidney function Diagnosed with TEN induced by levofloxacin	Laboratory analysis Levofloxacin was stopped. Patient died with bacterial infection.
[113]	Post-operative nosocomial pneumonia Levofloxacin	Maculopapular rash after 11 days of levofloxacin Evolved to widespread vesicles, bullae (40% BSA) with skin, mucosal involvement, conjunctivitis Diagnosed with TEN induced by levofloxacin	Skin biopsy Resolution of symptoms after levofloxacin discontinuation

Q6

Table 3a (continued)

Reference Age/gender, country	Underlying condition and Co-morbidities; fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
[114] 62/M India	Fever and loose motions; levofloxacin 500 mg twice/day; furazolidone 100 mg 3 times/day; rabeprazole 20 mg/day	Skin lesions, oral ulcers and conjunctivitis after 2 days of levofloxacin (40% BSA); diagnosed with TEN induced by levofloxacin and furazolidone	Laboratory investigations Improvement after levofloxacin and furazolidone discontinuation
[115] 23/F USA	Upper respiratory illness Moxifloxacin	Morbilliform eruption and liver failure: AST 2122 U/L and ALT 1183 U/L after 3 days of moxifloxacin; erythematous morbilliform eruption (30% BSA); AST 6632 U/L, ALT 3453 U/L; total bilirubin 2.7 mg/dL; diagnosed with TEN and liver failure induced by moxifloxacin	Skin and liver biopsy Liver transplant Patient died. Acute tubular necrosis found on autopsy
[116] 45/F Caucasoid Pakistan	Treated for fever Known diabetic Moxifloxacin	Morbilliform eruption, extensive skin peeling (60% BSA) 5 days of moxifloxacin; urea 10.7 mmol/L; creatinine 75 µmol/L; ALT 87 IU/L; bilirubin and ALP elevated Diagnosed with TEN induced by moxifloxacin	Physical examination Skin biopsy Resolution of symptoms with dexamethasone and ceftriaxone
[117] 44/M Asian USA	Sinus infection History of pruritic rash with amoxicillin Moxifloxacin	Pruritic eruption after 6 days of moxifloxacin Fever, oral ulceration, lymphadenopathy; AST 1110 IU/L, ALT 1226 IU/L; diagnosed with HSR – TEN induced by moxifloxacin	Skin biopsy Improvement of symptoms
[118] 56/F Caucasian USA	Right anterior distal tibia folliculitis, cellulitis; allergy to trovafloxacin Previously tolerated ciprofloxacin and levofloxacin; moxifloxacin 400 mg twice/day	Rash after 6 days of moxifloxacin Evolved to fever, epidermal detachment and skin sloughing (significant BSA) Diagnosed with TEN induced by moxifloxacin	Physical examination Improvement of symptoms

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSA: body surface area; DRESS: drug reaction with eosinophilia and systemic symptoms; F: female; γ-GTP: γ-glutamyl transpeptidase; HSR: hypersensitivity reaction; LDH: lactate dehydrogenase; M: male; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis; SCAR: severe cutaneous reaction; WBC: white blood cell count.

Table 3b

Severe adverse cutaneous reactions in patients treated with fluoroquinolones in the presence of alcohol misuse.

Reference Age/gender, country	Underlying condition and co-morbidities Fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
[63] 17/M UK	Post-operation for cystoscopy and left ureteric stenting Previously tolerated ciprofloxacin Ciprofloxacin 250 mg 2 times/day	Skin blotches on the 2nd day, 10 min after ingesting alcohol Diagnosed SCAR induced by combination ciprofloxacin and alcohol	Close temporal relationship with alcohol ingestion Spontaneous resolution of symptoms
[90] 46/M Caucasian Greek	Chronic pelvic pain syndrome Long history of alcohol consumption without adverse events Ciprofloxacin 500 mg twice/day	Bullous erythema after alcohol ingestion during the second week of ciprofloxacin treatment Diagnosed with erythema multiforme induced by ciprofloxacin in the presence of alcohol	Resolution after ciprofloxacin de-challenge Complete resolution after alcohol abstinence

SCAR: severe cutaneous adverse reaction.

gatifloxacin). The pattern of DILI showed cholestatic injury, predominantly increased alkaline phosphatase (ALP) levels, hepatocellular injury (predominantly increased ALT levels), or mixed symptoms. This was distributed between all three drugs. Symptoms developed after a mean of 4 days of treatment, such that the time to liver injury was generally short, with abrupt onset. The population affected comprised only of adults (mean age 57, 91.7% of sample over 30 years of age). Nine patients developed the symptoms while taking the drug, while the remaining 3 did so after completing the medication course. In one case, hepatocellular DILI was accompanied by SJS [130]. Table 4b presents the role of alcohol-misuse in drug-induced hepatic injury [135,137].

Increased lipase and increased γ -glutamyl transpeptidase (γ -GT) were the most common ADRs of intravenous moxifloxacin in one study. The overall incidence of DILI was similar between moxifloxacin and comparator in a large review of phases II–IV double-blind and open-label studies performed by the manufacturer between 1996 and 2010. However, moxifloxacin was associated with a higher incidence of abnormal liver function test results. Two cases of hepatic failure occurred after moxifloxacin treatment in two individuals with a history of chronic liver disease such as hepatitis C, alcohol abuse or intravenous drug abuse [156].

One case of hepatotoxicity was identified in a sample of 9 children treated with moxifloxacin-based regimens for pulmonary tuberculosis [157].

Acute hepatitis was diagnosed in several patients (2 ciprofloxacin, 4 levofloxacin, 1 moxifloxacin) [131–137]. Similar to the population described by Orman et al. [130], all of these individuals were adults (32–99 years), and interestingly, all were male. These individuals showed hepatocellular or mixed hepatocellular and cholestatic injury patterns, with elevated ALT and AST levels, as well as elevated bilirubin levels. Death ensued in 3 patients, while progressive resolution of symptoms was observed in the remaining 6 individuals [131–137]. Çoban et al. [138] report a case of acute fulminant hepatitis progressing to fatal encephalopathy, progressive metabolic acidosis and hepatorenal syndrome in a patient treated with levofloxacin with concomitant hepatitis B infection.

Acute cholestatic hepatitis was noted in other patients (2 ciprofloxacin, 1 levofloxacin, 1 moxifloxacin; age 44–63 years) [139–142]. Aside from elevated AST and ALT levels, the primary feature in these patients was that of greatly elevated bilirubin levels, as well as elevated γ -glutamyl transpeptidase. Improvement of symptoms was observed in all patients after treatment. Cholestasis was noted in other patients as well (1 ciprofloxacin, 2 levofloxacin, 1 moxifloxacin; age 69–87 years) [143–145], while Heluwaert et al. [146] describe a patient diagnosed with jaundice after treatment with levofloxacin. Moreover, cholestatic jaundice was noted in a few additional patients (3 ciprofloxacin; ages 26–84), with symptoms including pruritus and predominantly cholestatic liver injury. Resolution ensued in all patients [147–149]. Vanishing bile duct syndrome was induced by moxifloxacin in an elderly patient [123]. Vanishing bile duct syndrome also accompanied a case of SJS [98].

Several other patients were diagnosed with DILI (1 ciprofloxacin, 1 levofloxacin, 1 moxifloxacin; ages 64–80), one of which also experienced severe ductopenia and cholestasis. Resolution of liver function test abnormalities eventually occurred in all patients [150–152]. Toxic hepatitis with fatal multiple organ failure occurred in two patients treated with levofloxacin [153,154].

Serology for hepatitis viruses or herpes viruses was negative in a patient with acute cholestatic hepatitis induced by ibuprofen and moxifloxacin [142]. Similarly, they were also negative in other patients in which they were assessed.

Renal adverse drug reactions

Ciprofloxacin nephrotoxicity includes manifestations such as allergic interstitial nephritis, acute interstitial nephritis, granulomatous interstitial nephritis, acute renal failure, and acute tubular necrosis [159]. Ninety-five cases of drug-related acute interstitial nephritis were reported over an 18 year period at a single center. Antibiotics were the cause of 49.5% of these cases, with fluoroquinolones responsible for 13.7%. Alone, ciprofloxacin was responsible for 8.4% of all cases of drug-related acute interstitial nephritis [160]. Renal ADRs in patients treated with ciprofloxacin, levofloxacin and moxifloxacin are detailed in Table 5 [161–186].

Acute renal insufficiency occurred in two patients treated with ciprofloxacin, who developed elevated serum creatinine level and blood urea nitrogen level [161]. Acute renal failure is reported in several patients treated with ciprofloxacin (4 males and 10 females; ages 18–77). Elevated serum creatinine level and/or urea nitrogen level are reported in all cases, and renal function improvement and normalization ensued following discontinuation of ciprofloxacin [162–167]. Acute renal failure with interstitial nephritis occurred in 3 other patients, all of which had favorable outcomes following discontinuation of the incriminated fluoroquinolone [166,168,169].

Other cases of acute interstitial nephritis are also reported (7 ciprofloxacin, 1 moxifloxacin; 7 males, 1 female; ages 41–79). Manifestations of these conditions included elevated creatinine levels and/or elevated blood urea nitrogen, while progressive resolution of renal symptoms occurred in all cases following discontinuation of the culprit drug [170–174]. Acute interstitial nephritis with concomitant chronic tubular damage in a patient treated with moxifloxacin also resolved following discontinuation of the incriminated drug [175].

Tubulo-interstitial nephritis was accompanied by linear tubular basement membrane deposit in one patient and by acute renal failure in two other patients, all treated with ciprofloxacin. The condition was diagnosed by renal biopsy, and all patients recovered with ciprofloxacin interruption [176–178].

Granulomatous interstitial nephritis occurred after levofloxacin treatment [179]. Allergic interstitial nephritis or vasculitis, with concomitant skin lesions, leukocytoclastic vasculitis with interstitial nephritis, are reported [180–182]. Renal manifestations also accompanied a

Table 4a

Hepatotoxicity in individuals treated with fluoroquinolones in the absence of alcohol misuse.

Reference	Underlying condition and co-morbidities	Presentation of symptoms, diagnosis drug(s) incriminated	Techniques to validate diagnosis outcome
Q8 Age/gender, country	Fluoroquinolone used and co-treatment		
[123] 82/M USA	Empyema; history of prostate cancer; no history of drug or alcohol abuse; previous exposure to azithromycin and ceftriaxone before starting moxifloxacin Slightly elevated liver enzymes prior to starting moxifloxacin Moxifloxacin	Acute onset jaundice and pruritus after 7 days of moxifloxacin; AST 368 IU/L, ALT 441 IU/L, ALP 821 IU/L, total bilirubin 15.3 mg/dL, direct 9.2 mg/dL; pancreatitis with lipase 2783 IU/L and amylase 1131 U/L; biopsy-immunostaining-cytokeratin 7; continued jaundice with total bilirubin 25.8 mg/dL, direct 14.5 mg/dL, AST 154 IU/L, ALT 128 IU/L, ALP 226 IU/L 10 weeks after interrupting moxifloxacin Diagnosed with vanishing bile duct syndrome induced by moxifloxacin	Physical examination Endoscopic retrograde cholangio-pancreatography Liver biopsy Improvement of pancreatitis
[130] USA	80/F Not specified Ciprofloxacin	ALT 1684 IU/L, ALP 136 IU/L, bilirubin 21.1 mg/dL after 13.3 days of ciprofloxacin; rash and eosinophilia; diagnosed with hepatocellular injury associated with ciprofloxacin	Patient died of liver failure.
	70/F	ALT 1950 IU/L, ALP 159 IU/L, bilirubin 24.6 mg/dL after 12.3 days of ciprofloxacin	Patient was hospitalized; lost to follow-up.
	45/F	Diagnosed with hepatocellular injury highly likely associated with ciprofloxacin ALT 420 IU/L, ALP 275 IU/L, bilirubin 1.5 mg/dL after 4.8 days of ciprofloxacin; diagnosed with mixed cholestatic and hepatocellular injury probably associated with ciprofloxacin	Patient recovered.
	55/M	ALT 1632 IU/L, ALP 771 IU/L, bilirubin 17.1 mg/dL after 5.2 days of ciprofloxacin; rash and fever; diagnosed with hepatocellular injury associated with ciprofloxacin	Patient was hospitalized, developed peritonitis, cholestasis while on peritoneal dialysis and died at home of unknown cause. Patient was not hospitalized.
	62/F	ALT 413 IU/L, ALP 891 IU/L, bilirubin 1.2 mg/dL after 1.6 days of ciprofloxacin HSR pneumonitis; diagnosed with cholestatic injury associated with ciprofloxacin	Patient recovered.
	36/F Not specified Ciprofloxacin	ALT 151 IU/L, ALP 1931 IU/L, bilirubin 16.5 mg/dL after 10 h; rash, fever and eosinophilia; diagnosed with cholestatic injury associated with ciprofloxacin	Patient was not hospitalized. Chronic liver injury persisted with elevated ALP and/or bilirubin.
	23/F Not specified Levofloxacin	ALT 199 IU/L, ALP 170 IU/L, bilirubin 0.8 mg/dL after 2.8 days; diagnosed with mixed cholestatic and hepatocellular injury associated with levofloxacin	Patient was hospitalized and recovered.
	45/M Not specified Moxifloxacin	ALT 1311 IU/L, ALP 379 IU/L, bilirubin 3.6 mg/dL after 11.4 days of moxifloxacin Diagnosed with SJS and hepatocellular injury definitely associated with moxifloxacin	Patient was hospitalized. Patient was lost to follow-up.
	71/M	ALT 220 IU/L, ALP 253 IU/L, bilirubin after 2.4 days of moxifloxacin 2.3 mg/dL Diagnosed with mixed cholestatic and hepatocellular injury probably associated with moxifloxacin	Patient was hospitalized. Resolution of symptoms
	46/F	ALT 395 IU/L, ALP 603 IU/L, bilirubin 33.4 mg/dL after 1.7 days of moxifloxacin Rash, fever and eosinophilia	Patient was hospitalized with persistently elevated ALP and/or bilirubin.
	64/M	Diagnosed with cholestatic injury highly likely associated with moxifloxacin ALT 823 IU/L, ALP 837 IU/L, bilirubin 1.5 mg/dL after 2 days; diagnosed with cholestatic injury associated with moxifloxacin	Patient was transplanted. Patient was hospitalized.
[131] 32/M Spain	Septic arthritis secondary to a Brodie's abscess Cloxacillin 2 g 4 times/day and ceftriaxone 1 g/day for 3 weeks, followed by ciprofloxacin 500 mg twice/day	Abdominal pain, diarrhea, fever, non-pruritic erythematous rash and malaise after 2 days of ciprofloxacin; WBC $13.8 \times 10^9/L$ with eosinophilia; AST 94 U/L, ALT 147 U/L, γ -GTP 98 U/L; LDH 552 U/L Sudden onset of jaundice, tender hepatomegaly, dyspnea, arthralgias and weakness after ciprofloxacin discontinuation, with AST 1782 U/L, ALT 2144 U/L and LDH 3631 U/L Diagnosed with acute hepatitis and multisystem failure induced by ciprofloxacin	Patient was lost to follow-up. Skin biopsy Chest radiographs Transthoracic liver biopsy Resolution of symptoms with supportive therapy and methylprednisolone
[132] Turkey	62/M Urinary tract infection Viral hepatitis excluded Ciprofloxacin 1000 mg/day	ALT 320 IU/L, AST 190 IU/L, total bilirubin 2.3 mmol/dL, γ -GTP 115 IU/L, ALP 132 IU/L after 2 days of ciprofloxacin; Diagnosed with acute hepatitis induced by ciprofloxacin	Liver biopsy Resolution of symptoms
	56/M Transurethral resection of the prostate under spinal anesthesia for prostate hyperplasia Viral hepatitis excluded Ciprofloxacin 500 mg twice/day	Pruritus and abdominal pain after 2 days of ciprofloxacin Diffuse increase on the liver echogenicity ALT 500 IU/L, AST 230 IU/L, total bilirubin 3.2 mmol/dL, γ -GTP 135 IU/L, ALP 152 IU/L Diagnosed with acute hepatitis induced by ciprofloxacin	Ultrasonography Liver biopsy not performed (elevated coagulation parameters) Resolution of symptoms
[133] 99/M Swiss	Urinary tract infection No history of alcohol abuse No chronic liver disease	Progressive jaundice, nausea and vomiting after 8 days; bilirubin 324 μ mol/L, AST 5000 IU/L, ALT 4440 IU/L, ALP 157 IU/L, γ -GTP 117 IU/L Diagnosed with acute hepatitis induced by levofloxacin	Abdomen ultrasonography Post-mortem liver biopsy Patient died of hepatic coma despite levofloxacin

	Levofloxacin 500 mg/day Cellulitis Hemodialysis patient HBsAb positive due to previous vaccination	Scleral icterus after 3 weeks of levofloxacin Confusion and drowsiness; AST 1392 U/L, ALT 857 U/L, ALP 423 U/L and bilirubin 70 µmol/L Diagnosed with acute hepatitis induced by levofloxacin AST 298, ALT 570, total bilirubin 0.7 mg/dL, after 7 days of levofloxacin Diagnosed with acute hepatitis induced by levofloxacin	interruption. Liver function tests Resolution of symptoms Patient died due to myocardial infarction following leg amputation. Abdominal ultrasound Liver biopsy Progressive resolution of symptoms Histopathologic examination Treatment included lactulose suspension and plasmaphereses Encephalopathy increased, with progressive metabolic acidosis and hepatorenal syndrome Patient died. Percutaneous liver biopsy Complete resolution
[134] 73/M Canada	Levofloxacin 250 mg/day Infectious-related hemolytic anemia; history of chronic bronchitis Levofloxacin 500 mg/day Not concomitant drug		
[136] 77/M/White Portugal	Upper respiratory infection Chronic hepatitis B infection (positive HBsAg) Levofloxacin 500 mg/day	Icteric sclera the day after finishing a 10 day course of levofloxacin, AST 1750 IU/L, ALT 937 IU/L, total bilirubin 27.8 mg/dL, direct bilirubin 6.3 mg/dL Unconsciousness compatible with grade IV hepatic encephalopathy Diagnosed with acute fulminant hepatitis failure associated with levofloxacin	
[138] 55/F Turkey			
[139] 50/M Belgium	Urinary tract infection Negative for viral hepatitis or HHVs Ciprofloxacin 250 mg twice/day	Severe pruritus, asthenia, abdominal discomfort, anorexia, diarrhea, mild fever and jaundice after 5 days of ciprofloxacin, with ALT 202 IU/L, AST 111 IU/L, ALP 314 IU/L, γ-GTP 135 IU/L; bilirubin 82 µmol/L–159 µmol/L On biopsy centrolobular cholestasis Diagnosed with cholestatic hepatitis associated with ciprofloxacin	
[140] 63/F/White Belgium	Inflammatory exacerbation of ileal Crohn's disease; no blood transfusion, alcohol abuse or family liver disease; normal liver function at baseline; negative viral hepatitis and HHVs; ciprofloxacin 500 mg/day	Jaundice and asthenia after 6 months of ciprofloxacin, with AST 660 IU/L, ALT 740 IU/L, ALP 642 IU/L, γ-GTP 3005 IU/L and total bilirubin 5.8 µmol/dL; on biopsy inflammatory infiltrate of portal tracts; diagnosed with delayed and prolonged cholestatic hepatitis with ductopenia (long-term dose-related severe hepatotoxicity) ALT 41 IU/L, AST 58 IU/L, γ-GTP 1036 IU/L, ALP 1327 IU/L after 5 days of levofloxacin Diagnosed with acute cholestatic hepatitis probably associated with levofloxacin	Liver function test Liver biopsy Normalization of liver function test results after discontinuation of ciprofloxacin
[141] 51/F Spain	Right parapneumonic pleural effusion; levofloxacin 500 mg twice/day and intravenous ceftriaxone 2 g/day	Jaundice after 4 days of moxifloxacin Total bilirubin 5.8 mg/dL, direct 4.4 mg/dL, AST 367 IU/L, ALT 862 IU/L, γ-GTP 352 IU/L, ALP 42 IU/L, LDH 323 IU/L; diagnosed with suspected acute cholestatic hepatitis induced by moxifloxacin Marked increase in ALP and γ-GTP and modest increase in ALT after 5 days of ciprofloxacin Diagnosed with cholestasis probably associated with ciprofloxacin	Laboratory parameters normalized except γ-GTP, after discontinuation of levofloxacin, with the expectation Improvement after moxifloxacin de-challenge Resolution of symptoms
[142] 44/M Spain	Maxillary sinusitis Moxifloxacin 400 mg/day for 4 days and ibuprofen 6 g over 4 days		
[143] 36/M Australia	Methicillin resistant <i>Staphylococcus aureus</i> infection and pneumonia, elevated baseline ALP and γ-GTP associated with carbamazepine and rifampicin; ciprofloxacin 750 mg twice/day		Liver function test Normalization of liver function test results after discontinuation of ciprofloxacin
[144] 87/M/White Portugal	Respiratory infection Type 2 diabetes History of ciprofloxacin toxicity Levofloxacin	Jaundice soon after starting levofloxacin ALT 85 U/L, AST 84 U/L, ALP 1129 U/L, γ-GTP 2049 U/L and total bilirubin 2.2 mg/dL Hepatomegaly Diagnosed with cholestasis induced by levofloxacin, yet hepatocellular injury could not be excluded Jaundice and itching after 5 days; AST 240 IU/L, ALT 352 IU/L, γ-GTP 1430 IU/L, total bilirubin 7.77 mg/dL, direct 7.2 mg/dL; diagnosed with cholestasis induced by levofloxacin	Abdominal ultrasound, liver biopsy Improvement of symptoms after beclomethasone, aminophylline, desloratidine and furosemide Normal aminotransferases but only partial improvement of cholestasis at 2 months
[144] 81/F/White	Respiratory infection Type 2 diabetes History of colon carcinoma Levofloxacin		Abdominal CT Liver biopsy Improvement of symptoms after ursodeoxycholic acid
[145] 69/M Spain	Respiratory infection Chronic bronchitis Moxifloxacin 400 mg/day for 5 days	Jaundice, pruritus, dark urine 3 weeks after completing moxifloxacin course; total bilirubin 28.45 mg/dL, conjugated 20.6 mg/dL, ALP 249 U/L, AST 37 U/L and ALT 58 U/L; diagnosed: cholestasis induced by moxifloxacin	Liver biopsy Resolution of symptoms
[146] 31/F France	Acute sinusitis Negative for viral hepatitis or HHVs Amoxicillin 2 g/day for 6 days Levofloxacin 500 mg/day for 5 days	Mucocutaneous jaundice 1 week after starting levofloxacin, total bilirubin 139 µmol/L, conjugated bilirubin 111 µmol/L, ALT 9.58 × N, AST 3.62 × N, ALP 1.89 × N; γ-GTP 10.52 × N; increasing bilirubin levels despite near-normalization of aminotransferase levels Diagnosed: jaundice associated with amoxicillin or levofloxacin Erythematous, pruritic rash after 6 days; Jaundiced sclera and skin, with abnormal liver function test results; diagnosed cholestatic jaundice associated with ciprofloxacin	Abdominal ultrasound Liver biopsy Disappearance of pruritus with complete and sustained normalization of liver function tests
[147] 84/F Jamaica	Urinary tract infection Ciprofloxacin		Liver function test Liver function test results normalized with intravenous fluids

(continued on next page)

Table 4a (continued)

Reference Age/gender, country	Underlying condition and co-morbidities Fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis drug(s) incriminated	Techniques to validate diagnosis outcome
[148] 47/M/White USA	Occult pyuria Negative for viral hepatitis Ciprofloxacin 500 mg twice/day	Mild jaundice and pruritis after 3rd ciprofloxacin dose; marked jaundice followed; total bilirubin 10 mg/L, direct 6.5 mg/L, ALP 163 IU/L, AST 109 IU/L; ALT 308 IU/L; no hepatomegaly or splenomegaly; diagnosed: cholestatic jaundice associated with ciprofloxacin	Liver biopsy Symptoms improved and liver test results normalized
[149] 26/M India	Acute diarrheal illness Ciprofloxacin 500 mg twice/day	Rash and jaundice after 5 days; mild hepatomegaly; AST 1055 IU/L and ALT 1700 IU/L	Abdominal examination Ultrasonography; liver biopsy
[150] 80/M USA	Acute bronchitis Local radiation treatment for hypopharyngeal cancer Normal baseline liver functions Viral hepatitis negative Amoxicillin/clavulanic acid 500 mg × 3 times/day and ciprofloxacin 500 mg twice/day	Diagnosed with cholestatic jaundice associated with ciprofloxacin Generalized maculopapular, pruritic rash after 6 days of treatment, with total bilirubin 0.8 mg/dL, AST 150 U/L, ALT 154 U/L, ALP 120 U/L Worsening liver function tests with AST 577 U/L, ALT 972 U/L, ALP 358 U/L, total bilirubin 1.9 mg/dL, direct 1.1 mg/dL and γ-GTP 638 U/L Diagnosed: hepatocellular injury associated with ciprofloxacin and/or amoxicillin/clavulanic acid	Recovery: anti-histamines, ursodiol, prednisolone Laboratory studies Normalization of liver function tests
[151] 67/F USA	Streptococcal endophthalmitis Negative for viral hepatitis IV vancomycin, ceftazidime, levofloxacin 500 mg/day Discharged on levofloxacin 500 mg/day and moxifloxacin ophthalmic solution	Jaundice after 8 weeks of levofloxacin with total bilirubin 16.3 mg/dL, direct 9.4 mg/dL, AST 273 IU/L, ALT 614 IU/L, ALP 483 U/L, Diagnosed with DILI, severe ductopenia and cholestasis associated with levofloxacin	Abdominal ultrasound Computed tomography scan Magnetic resonance; cholangio-pancreatography; liver biopsy; discharged on steroids, jaundice persisted with no liver failure; ursodiol, with slow resolution of cholestasis and hyperbilirubinemia
[152] 64/M China	Pulmonary infection in both lungs; abnormal kidney function: systemic vasculitis, necrosis; creatinine 107 μmol/L; normal liver function on admission; IV moxifloxacin 400 mg/day; feilike and cetirizine as lung protective therapy	ALT 49 U/L and AST 30 U/L after 2 days of moxifloxacin ALT 166 U/L and AST 53 U/L after 5 days No jaundice Diagnosed with drug induced liver injury associated with moxifloxacin	Moxifloxacin de-challenged Resolution of symptoms after moxifloxacin discontinuation and liver protective therapy with reduced glutathione injection and diammonium glycylrhizinate (starting day 5) Serum chemistry Patient died from multiorgan failure.
[153] 74/F USA	Acute bronchitis Negative for viral hepatitis Levofloxacin 500 mg/day	AST 4962 U/L, ALT 7071 U/L, total bilirubin 2.5 mg/dL, ALP 90 U/L after 2 days; acute respiratory distress; diagnosed: acute hepatocellular injury induced by levofloxacin	
[154] 53/F Turkey	Pulmonary infection No history of chronic alcohol intake Anti-HBsAg serology positive Levofloxacin 750 mg/day	Itching, redness and rash after 1st dose; jaundice 10 days after stopping levofloxacin; squamous lesions on skin; icteric skin and sclera; generalized edema; dyspnea; tachypnea; ALT 1222 IU/L, AST 2629 IU/L, total bilirubin 14.6 mg/dL, direct 8.2 mg/dL, LDH 2479 IU/L; urea 32 mg/dL; creatinine at 2.6 mg/dL; amylase 246 IU/L; diagnosed: levofloxacin hepatitis, multiple organ failure	Complete blood count Biochemical tests Cardiopulmonary arrest prevented liver transplant; patient died due to lack of response to cardiopulmonary resuscitation.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug-induced liver injury; F: female; HBsAg: surface antigen of the hepatitis B virus; HHV: human herpes virus; IV: intravenous; LDH: lactate dehydrogenase; M: male; SJS: Stevens–Johnson syndrome; ULN: upper limit of normal; WBC: white blood cell count; γ-GTP: γ-glutamyl transpeptidase.

Table 4b

Hepatotoxicity in individuals treated with fluoroquinolones in the presence of alcohol misuse.

Reference	Underlying condition and co-morbidities, Fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis drug(s) incriminated	Techniques to validate diagnosis outcome
[135] 63/M/White Spain	Atypical pneumonia due to acute <i>Micobacterium pneumoniae</i> ; pharyngo-laryngeal squamous cell carcinoma No known liver disease despite history of alcohol consumption; virology negative for hepatitis and HHV; ALT 302 U/L, AST 220 U/L, γ -GTP 78 U/L, LDH 615 U/L, normal ALP and total bilirubin on admission Sequential treatment with levofloxacin 500 mg twice/day (days 1–4), doxycycline 100 mg twice/day (days 5–10) and naproxen 500 mg 3 times/day (days 7–9)	Asthenia, jaundice and dark urine on day 10, with ALT 1577 U/L, AST 1754 U/L, ALP 189 U/L, total bilirubin 68.4 μ mol/L, direct bilirubin 59.8 μ mol/L Progressed to coagulopathy, encephalopathy, renal failure and severe hyperbilirubinemia Diagnosed with acute hepatitis possibly related to any of levofloxacin, doxycycline and naproxen	Liver biopsy Patient was not accepted for liver transplant and died.
[137] 58/M Spain	Acute bronchitis; chronic alcohol intake (>40 g/day); smoking No history of liver disease Moxifloxacin 400 mg/day for 5 days	Jaundice 5 days after completing moxifloxacin; leukocytosis (WBC 15.5×10^9 /L; 88% neutrophils) AST 3185 IU/L, ALT 2589 IU/L, γ -GTP 107 IU/L, ALP 94 IU/L, total bilirubin 27.0 mg/dL, conjugated bilirubin 14.0 mg/dL and LDH 822 IU/L; hepatomegaly and unstructured poli-lobular contours; diagnosed with acute hepatitis induced by moxifloxacin on chronic ALD	Abdominal ultrasound Magnetic resonance imaging Treatment with prednisone Condition worsened with grade II hepatic encephalopathy Patient died.

ALD: alcohol-induced liver disease ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug-induced liver injury; F: female; HHV: human herpes virus; IV: intravenous; LDH: lactate dehydrogenase; M: male; SJS: Stevens–Johnson syndrome; ULN: upper limit of normal; WBC: white blood cell count; γ -GTP: γ -glutamyl transpeptidase.

couple of cases of cutaneous vasculitis [70,71]. Ciprofloxacin crystal nephropathy is also discussed [183–186].

Laboratory assays

The quinolones represent a class of broadly used antibiotics with extensive indications for infections caused by many bacterial pathogens. Nevertheless, like other antibiotics, they can cause immune mediated adverse side-effects, not only IgE-mediated but also T cell-mediated. The evidences outlined above suggest that numerous delayed HSRs to quinolones are associated with a strong T cell immune response against the relevant quinolone.

The laboratory test to show anaphylactic quinolones-IgE mediated reaction was described by Manfredi et al. [12]. However, the study of Manfredi et al. suggests that the IgE antibodies can only bind to the drug bound to a solid phase if positions C2 to C6 of the quinolone are accessible [12]. As a result, IgE tests in sera were negative in cinoxacin-hypersensitive patients, but positive when they were tested for the presence of IgE to other quinolones, which bind via the side chain at position 7 to the carrier molecule.

To predict delayed HSRs two laboratory methods are available. Both methods are based on the extraction of patient's lymphocytes.

1– Lymphocyte transformation test (LTT) was used to establish moxifloxacin-induced delayed hypersensitivity. Primary blood mononuclear cells (PBMCs) of the patient were cultured with different concentrations of moxifloxacin for 7 days and [^{3} H]-thymidine incorporation was measured [122].

2– Lymphocyte toxicity assay (LTA). Genetically susceptible individuals carry defects in drug detoxifying pathways, such that a greater amount of a reactive drug metabolite is produced than that which can be detoxified. The LTA is an in vitro laboratory tool that can be used to diagnose and predict clinical HSRs. Because data suggested that lymphocytes lacked the ability to significantly generate reactive metabolites but possessed a full range of detoxifying capabilities, increased in vitro cytotoxicity, in the presence of a complete bioactivating system, was believed to indicate a reduced ability to detoxify these reactive species. We hypothesized then that increased cell death signified an increased susceptibility to HSRs as a direct result of defects in detoxification capabilities. Recurrent findings wherein in vivo (in humans) HSRs correlate with the susceptibility of patients' PBMCs to metabolism-dependent in vitro

cytotoxicity support this hypothesis The LTA makes use of lymphocytes isolated from patient blood. Lymphocytes are chosen as surrogate target cells as they possess the patient's genotype and will phenotypically express the patient's drug detoxifying deficiencies [187]. LTA was employed to determine ciprofloxacin and moxifloxacin-induced HSRs. Lymphocytes of patients that presented hypersensitivity to the specific quinolones and of individuals that took the same drug and did not have a reaction to it, have been exposed to the drug in the presence or absence of a microsomal system for 24 h. At the end of the period toxicity was measured [187]. We validated the LTA for assessing HSRs caused by several drugs including anti-epileptics, sulfonamides, anti-virals, non-steroidal anti-inflammatory drugs, platelet inhibitors [187–197]. Because each microplate well acts as its own control, it has the unique advantage of incorporating any autolysis that may occur, while eliminating slight variations in cell number as well as dye binding. The test can help enhance the accuracy of the causality assessment of the likely agent and in screening for “cross-reacting” drugs. In HSRs caused by anti-epileptics, antibiotics, or platelet inhibitors the LTA test can help in choosing alternative safer therapies for the patient or even their relatives. In vitro testing using the LTA has shown that there is a familial occurrence of hypersensitivity to sulfonamides and anti-epileptic drugs, with a autosomal pattern of inheritance that suggested that the patient's siblings' risk of reacting to an aromatic anti-epileptic drug may be as high as one in four [187]. In addition, these data support the hypothesized need for a balance between bioactivation and detoxification processes and suggest that the ability of in vitro cytotoxicity to assess detoxification capabilities may allow its use as a biomarker for HSRs. Furthermore, the reported incidence of HS reactions to TMP–SMX is dramatically higher in the HIV-infected population than in any other population studied [188]. In the tables we reported the possible risk factor of the individuals that presented HSRs to quinilones. These risk factors include viral infections with hepatitis viruses, HIV, HHV6 as well as interactions with drugs of use and misuse. There is not a specific ethnic population that is predisposed to quinilone HSRs.

In vivo patch (epicutaneous) test

The patch tests for quinilones can be performed, as described [198], on the upper back of the patients at 6–8 weeks after complete healing of

Table 5
Renal adverse drug reactions in individuals treated with fluoroquinolones.

Reference	Underlying condition and co-morbidities	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
Q10 Age/gender, country	Fluoroquinolone used and co-treatment		
[161] USA	23/F/White Pulmonary <i>Mycobacterium avium</i> intracellular complex infection Cystic fibrosis; initially normal creatinine and urea; rifabutin, ethambutol, ciprofloxacin 750 mg twice/day Previous isoniazid, pyridoxine, ethambutol, clarithromycin ciprofloxacin	Elevated creatinine 5.1 mg/dL and urea level 44 mg/dL after 3 weeks of treatment Diagnosed: acute renal insufficiency associated with ciprofloxacin	Laboratory testing Normalization of serum creatinine and blood urea nitrogen level following ciprofloxacin interruption
	16/F/White Sinusitis Cystic fibrosis Ciprofloxacin 750 mg twice/day	Elevated serum creatinine level at 3.2 mg/dL and blood urea nitrogen level at 29 mg/dL after 10 days of ciprofloxacin Diagnosed with acute renal insufficiency associated with ciprofloxacin	Laboratory testing Normalization of serum creatinine and blood urea nitrogen level following ciprofloxacin interruption
	[162] 31/F USA Upper respiratory tract infection Ciprofloxacin 250 mg twice/day	Fever, pyuria, acute renal failure after 3 days of ciprofloxacin, creatinine 220 μ mol/L, urea level at 7.8 mmol/L Leukocytosis WBC 26.3×10^9 /L Proteinuria; creatinine peaked at 700 μ mol/L; diagnosed: non-oliguric acute renal failure ciprofloxacin-induced Diffuse erythema multiforme after 6 days of ciprofloxacin; creatinine 390 μ mol/L; leukopenia WBC 1.4×10^9 /L Diagnosed: oliguric acute renal failure with rash associated with ciprofloxacin	Urinalysis Renal ultrasound scan Percutaneous renal biopsy Decrease of serum creatinine level following prednisone
	73/F Urinary tract infection Adenocarcinoma Ciprofloxacin 500 mg twice/day	Diffuse erythema multiforme after 6 days of ciprofloxacin; creatinine 390 μ mol/L; leukopenia WBC 1.4×10^9 /L Diagnosed: oliguric acute renal failure with rash associated with ciprofloxacin	Urinalysis Decrease of serum creatinine level and resolution of rash
[163] USA	67/M Urinary tract infection; metastatic prostate cancer; bilateral nephrostomy tubes in place; no nephrotoxic reaction during previous norfloxacin and ciprofloxacin exposure Ciprofloxacin 500 mg twice/day	Creatinine level peaked at 540 μ mol/L Diagnosed: non-oliguric acute renal failure associated with ciprofloxacin	Laboratory analysis Improvement of creatinine level following ciprofloxacin interruption
	67/M Urinary tract infection Diffuse large-cell lymphoma Ciprofloxacin 750 mg 3 times/day	Elevated creatinine 548 μ mol/L and proteinuria after 4 days of ciprofloxacin Diagnosed: oliguric acute renal failure induced by ciprofloxacin	Renal ultrasound Renal function improve and normalized after ciprofloxacin interruption
	60/F Neutropenia and fever after chemotherapy; metastatic malignant melanoma; ciprofloxacin 750 mg 3 times/day; clindamycin 600 mg 3 times/day	Elevated serum creatinine level at 451 μ mol/L after 3 days of treatment Diagnosed: anuric acute renal failure associated with ciprofloxacin	Gallium scan; normalization of creatinine level following ciprofloxacin interruption and hemodialysis
	73/M Neutropenia, fever after chemotherapy; malignant fibrohistiocytoma; ciprofloxacin 750 mg 3 times/day and clindamycin 600 mg 3 times/day for 5 days	Elevated serum creatinine level at 186 μ mol/L 10 days after starting treatment Diagnosed with non-oliguric acute renal failure associated with ciprofloxacin	Routine follow-up Normalization of serum creatinine level following ciprofloxacin interruption
	69/F Neutropenia, fever after chemotherapy Metastatic breast cancer Ciprofloxacin 750 mg 3 times/day; 7 days metronidazole 500 mg 3 times/day	Creatinine 1193 μ mol/L 2 weeks after starting treatment Diagnosed: oliguric acute renal failure associated with ciprofloxacin	Routine follow-up Normalization of serum creatinine level following ciprofloxacin interruption
	62/F Neutropenia, fever after chemotherapy Retroperitoneal sarcoma Ciprofloxacin 750 mg 3 times/day and clindamycin 600 mg 3 times/day	Creatinine 645 μ mol/L; urea 18.6 mmol/L after 6 days of treatment Diagnosed with non-oliguric acute renal failure associated with ciprofloxacin	Laboratory work-up Normalization of serum creatinine and urea following ciprofloxacin interruption
[164] 38/M Spain	Cavitary pneumonia; transfusion-associated AIDS and hepatitis C virus infection History of opportunistic infections Baseline creatinine 96 μ mol/L Ciprofloxacin 200 mg twice/day	Elevated serum creatinine level at 575 μ mol/L after 4 days of ciprofloxacin Diagnosed with acute renal failure associated with ciprofloxacin	Laboratory analysis Progressive resolution of symptoms after discontinuing ciprofloxacin Neutropenia ensued and patient died
[165] Hong Kong	69/F <i>Mycobacterium avium</i> intracellular complex lung infection; T-cell lymphoma Previous renal biopsy showed glomerulo-sclerosis, interstitial fibrosis and tubular atrophy; baseline serum urea $1.2 \times$ ULN; creatinine $1.1 \times$ ULN; Ciprofloxacin 500 mg twice/day, clarithromycin 500 mg twice/day and clofazimine 100 mg/day	Serum urea $4 \times$ ULN and serum creatinine $6.8 \times$ ULN after 10 days of treatment; profuse pyuria and hematuria; urinalysis at baseline showed presence of protein and microscopic hematuria Diagnosed: no-noliguric acute renal failure associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms after discontinuing ciprofloxacin
	74/F Pulmonary tuberculosis; renal impairment likely due to diabetic nephropathy (urea $2.5 \times$ ULN; creatine $1.3 \times$ ULN) and chronic pyelonephritis; drug-induced cholestatic hepatitis while taking rifampicin and isoniazid Ciprofloxacin 500 mg/day; isoniazid 300 mg/day	Serum urea $5 \times$ ULN and serum creatinine $2 \times$ ULN after 10 days of treatment Worsening of pyuria and hematuria Diagnosed with acute renal failure associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms after discontinuing ciprofloxacin Septicemia ensued and patient died

	77/M	Pulmonary tuberculosis; drug-induced hepatitis to anti-tuberculosis agents (ALT $2.5 \times$ ULN at baseline); ciprofloxacin 500 mg/day; isoniazid 300 mg/day	Serum urea $3 \times$ ULN; creatinine $1.5 \times$ ULN after 8 days of treatment Diagnosed: acute renal failure associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms after discontinuing ciprofloxacin
[166] USA	56/F	Prophylaxis on the day of stem cell reinfusion; multiple myeloma High-dose chemotherapy; ciprofloxacin 750 mg/day; rifampin 300 mg twice/day	Creatinine 3.3 mg/dL after 10 days of treatment and peaked at 4.5 mg/dL Diagnosed with oliguric acute renal failure associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms with solumedrol
	53/M	Prophylaxis on the day of stem cell reinfusion; breast cancer; high-dose chemotherapy; ciprofloxacin 750 mg/day, rifampin 300 mg twice/day; acyclovir 400 mg 3 times/day	Creatinine 1.5 mg/dL after 8 days of treatment and increased to 4.8 mg/dL Diagnosed with acute renal failure (nephritis) associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms after discontinuing ciprofloxacin
[167] 18/F Germany		Exacerbation of lung disease; cystic fibrosis Ciprofloxacin 750 mg 3 times/day for 3 weeks; nitrofurantoin 5 mg/kg/day for 1 week	Creatinine 12.8 mg/dL and blood urea 165 mg/dL 1 week after finishing ciprofloxacin course Diagnosed with acute renal failure associated with ciprofloxacin	Urinalysis Renal ultrasound Renal biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin Percutaneous renal biopsy Normalization of serum creatinine level with prednisone
[168] 11/M UK		Typhoid fever Ciprofloxacin and cefuroxime	Creatinine levels 1183 μ mol/L; urea 37 mmol/L after 2 weeks of ciprofloxacin Diagnosed: ciprofloxacin – acute renal failure (interstitial nephritis)	
[169] 44/M Germany		<i>Legionella</i> pneumonia and aortic valve endocarditis Moxifloxacin, meropenem and vancomycin	Mild maculopapular rash and edema after 4 weeks of moxifloxacin Creatinine 1.6 mg/dL; urea 40.6 mg/dL at presentation; creatinine 7.1 mg/dL and urea 196.8 mg/dL 9 days later Diagnosed: maculopapular rash and acute renal failure (interstitial nephritis) associated with moxifloxacin	Skin biopsy Renal biopsy Progressive resolution of symptoms with systemic glucocorticoids
[170] 73/F USA		Bronchitis Non-small cell lung cancer Ciprofloxacin 500 mg twice/day	Creatinine 9.1 mg/dL; urea 110 mg/dL after 8 days of ciprofloxacin Diagnosed: non-oliguric renal failure (acute interstitial nephritis) associated with ciprofloxacin	Renal ultrasound and biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin and treatment with prednisolone
[171] 47/M USA		Infection Ciprofloxacin 500 mg twice/day	Flank pain, decreased urine output and eosinophilia after 1st dose of ciprofloxacin; creatinine 2.4 mg/dL; urea 41 mg/dL after 4th dose of ciprofloxacin Diagnosed: acute interstitial nephritis associated with ciprofloxacin	Urinalysis Progressive resolution of symptoms after discontinuing ciprofloxacin
[172] 79/M/White Singapore		Urinary tract infection Intravenous ciprofloxacin 500 mg twice/day	Maculopapular rash after ciprofloxacin Jaundice; LDH 676 U/L, total bilirubin 5.0 mg/dL, indirect 3.8 mg/dL Leukocytosis (WBC 13.5×10^9 /L) Creatinine 3.0 mg/dL, urea 79 mg/dL, increased to 9.8 mg/dL and 171 mg/dL Diagnosed: oligoanuric acute interstitial nephritis associated with ciprofloxacin and autoimmune hemolytic anemia	Urinalysis Laboratory analysis Renal biopsy Progressive resolution of symptoms with prednisone Patient remained dialysis dependent.
[173] UK	55/M	Urinary tract infection Ciprofloxacin 500 mg twice/day	Creatinine 237 μ mol/L after 12 days of ciprofloxacin; diagnosed: ciprofloxacin – acute interstitial nephritis	Renal biopsy Progressive resolution after discontinuing ciprofloxacin
	71/M	<i>E. coli</i> septicemia Ciprofloxacin 250 mg twice/day	Creatinine 883 μ mol/L after 3 weeks of ciprofloxacin Diagnosed: acute interstitial nephritis associated with ciprofloxacin	Renal biopsy Progressive resolution of symptoms with prednisolone Patient died of empyema.
	41/M	Suspected urinary infection History of biopsy-proven IgA nephropathy Ciprofloxacin 500 mg twice/day	Creatinine 613 μ mol/L after 3 days of ciprofloxacin; Diagnosed: acute interstitial nephritis associated with ciprofloxacin	Laboratory analysis Progressive resolution of symptoms with prednisolone
	73/M	Acute bronchitis Ciprofloxacin 500 mg twice/day	Creatinine 1391 μ mol/L after 2 days of ciprofloxacin; Diagnosed: acute interstitial nephritis associated with ciprofloxacin	Renal biopsy Progressive resolution of symptoms with prednisolone
[174] 65/M Germany		Pneumonia Pneumectomy for non-small cell lung cancer Moxifloxacin 400 mg/day for 2 weeks	Worsening oliguria 4 days after completing moxifloxacin course Creatinine 1204 μ mol/L Leukocytosis (WBC 14.0×10^9 /L) Diagnosed: acute interstitial nephritis associated with moxifloxacin	Renal biopsy Progressive resolution of symptoms with prednisolone

(continued on next page)

Table 5 (continued)

Reference Age/gender, country	Underlying condition and co-morbidities Fluoroquinolone used and co-treatment	Presentation of symptoms, diagnosis and drug(s) incriminated	Techniques to validate diagnosis outcome
[175] 68/F Germany	Fever and dry cough Moxifloxacin 400 mg/day for 10 days	Nocturia 10 days after finishing moxifloxacin course; creatinine 2.9 mg/dL; urea 27 mg/dL; proteinuria Proximal renal tubular acidosis and Fanconi syndrome Diagnosed: acute interstitial nephritis with concomitant chronic tubular damage associated with moxifloxacin	Urinalysis Renal biopsy Histopathology Progressive resolution of symptoms with prednisolone
[176] 64/F USA	<i>Staphylococcus aureus</i> cavitary pneumonia Ciprofloxacin 750 mg twice/day	Creatinine 8.2 mg/dL, urea 79 mg/dL after 11 days of ciprofloxacin; diagnosed: tubulo-interstitial nephritis, renal failure ciprofloxacin-associated	Percutaneous renal biopsy Progressive resolution of symptoms with prednisone
[177] 70/F Sweden	Fever and angitis Small-cell anaplastic pulmonary carcinoma Ciprofloxacin 750 mg twice/day	Creatinine 729 µmol/L after 8 days of ciprofloxacin; diagnosed: tubulo-interstitial nephritis with linear tubular basement membrane deposit associated with ciprofloxacin	Renal biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin
[178] 54/F UK	Urinary tract infection Normal baseline kidney function Ciprofloxacin 500 mg twice/day	Creatinine 315 µmol/L after 8 days of ciprofloxacin; renal function deteriorated: creatinine 445 µmol/L; urea 38 mmol/L; oliguria; intravascular hemolysis; diagnosed: tubulointerstitial nephritis with acute renal failure associated with ciprofloxacin	Renal biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin and treatment with prednisolone
[179] 47/F USA	Presumed cellulitis No known prior renal disease Levofloxacin 250 mg/day Previous treatment with amoxicillin-clavulanic acid	Creatinine 141.44 µmol/L and blood urea 9.3 mmol/L after 1st levofloxacin dose, increased to 397.8 µmol/L and 25.7 mmol/L; mildly elevated AST and ALT; diagnosed: granulomatous interstitial nephritis associated with levofloxacin	Renal ultrasound scan Renal biopsy Liver biopsy Progressive resolution of symptoms after discontinuing levofloxacin and treatment with prednisone
[180] 73/M/White Italy	Urinary frequency; urgency with dysuria Non-small cell lung cancer Levofloxacin	Palpable purpura and erythematous skin lesions after 3 days of levofloxacin Decreased urine output Creatinine 6.4 mg/dL; urea 190 mg/dL Diagnosed: nephrotoxicity (likely allergic interstitial nephritis or vasculitis) associated with levofloxacin	Urinalysis Progressive resolution of symptoms with prednisone and furosemide
[181] 80/M USA	Wound infection and purulent pericarditis Vancomycin, ciprofloxacin and rifampin	Creatinine 3.5 mg/dL after 6 weeks of ciprofloxacin; creatinine increased to 4.4 mg/dL, urea 49 mg/dL Diagnosed: renal vasculitis associated with ciprofloxacin	Renal biopsy Resolution of symptoms with prednisone
[182] 80/F Israel	Bilateral pneumonia Negative for viral hepatitis, HIV, HHVs Tazobactam–piperacilline and azithromycine, followed by levofloxacin 500 mg/day	Petechiae and purpura after 5 days of levofloxacin; creatinine 3.3 mg/dL and blood urea 120 mg/dL; diagnosed: levofloxacin–leukocytoclastic vasculitis and interstitial nephritis	Physical examination Urinalysis Resolution of symptoms with prednisone
[183] 58/F France	Pyelonephritis Ciprofloxacin 500 mg twice/day	Dark urine and oliguria after 2nd ciprofloxacin dose; creatinine 478 µmol/L, urea 16.6 mmol/L and creatinine clearance 13.1 mL/min Leukocytosis (WBC 13.0 × 10 ⁹ /L) without eosinophilia Creatinine peaked at 805 µmol/L Diagnosed: oligoanuric acute renal failure with tubular lesions (ciprofloxacin salt deposition)	Urinalysis Renal ultrasound Renal biopsy Infrared microscopy Progressive resolution of symptoms with prednisolone and furosemide
[184] 90/F USA	<i>Proteus</i> sp. in tracheal aspirate Ciprofloxacin 750 mg twice/day	Creatinine 1.6 mg/dL with oliguria after 8 days of ciprofloxacin; creatinine peaked at 3.8 mg/dL; diagnosed: ciprofloxacin crystal nephropathy	Serum analysis Resolution of symptoms after discontinuing ciprofloxacin
[185] I T A L y	74/M Malaise and diarrhea Ciprofloxacin 750 mg/day Low-dose angiotensin-converting enzyme inhibitor	Creatinine 1.4 mg/dL after 4 days of ciprofloxacin, peaked at 7 mg/dL; urine pH 5.5 Diagnosed: reversible acute renal failure due to ciprofloxacin crystal nephropathy	Renal biopsy Resolution of symptoms after discontinuing ciprofloxacin
	78/F Acute bronchitis Ciprofloxacin 750 mg twice/day Low-dose angiotensin-converting enzyme inhibitor	Decreased urine output after 3 days of ciprofloxacin, with creatinine 3.4 mg/dL Urine pH 4.5; diagnosed: reversible acute renal failure due to ciprofloxacin crystal nephropathy	Renal biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin
[186] 16/F Tunisia	Urinary tract infection Ciprofloxacin 500 mg twice/day	Creatinine 900 µmol/L, urea 33 mmol/L after 5 days of ciprofloxacin; urine pH 6.0; diagnosed: ciprofloxacin crystal nephropathy	Percutaneous kidney biopsy Progressive resolution of symptoms after discontinuing ciprofloxacin

ALT: alanine aminotransferase; F: female; LDH: lactate dehydrogenase; M: male; ULN: upper limit of normal; WBC: white blood cell count.

the cutaneous adverse drug reaction. The authors took the commercialized form of the drugs diluted to 10 or 25% in white petrolatum and applied using plasters. The patch test reactions can be evaluated at 20 min, 24 and 48 h. However there are many false positive and false negative to the reaction. False negative epicutaneous patch tests with quinolones have been reported previously in cases of confirmed quinolone sensitivity [198–201].

Oral provocation tests

Oral provocation tests should be used only after all AEDs have been tried and shown to be unsuccessful. Caution is recommended when there is a vague history of an adverse drug reaction, since re-challenge may turn a previously minor reaction into a serious HSR. Drug re-challenge is not performed if serious reactions, such as severe HSRs, DILI, SJS or TEN, have previously occurred [202,203]. The benefit of subsequent medication use, outweighs the known potential risks that may occur. Re-challenging a sensitized individual to a drug is one of the most convincing ways to verify a person's HSR reaction. This approach has also been used in pre-clinical safety testing of biotechnology products (e.g., recombinant proteins, monoclonal antibodies) to determine if animals may have generated reagenic antibodies that could induce anaphylaxis. However, to use this approach in humans is unethical.

Conclusions

Unexpected, indirect, idiosyncratic adverse reactions, affect directly a patient's life. Team work is necessary to prevent reactions. Collaboration between clinicians, pharmacists and a special laboratory medicine professional might impact on clinical practice in the treatment of hypersensitivity syndrome to quinolones and their prevention. Since the patients are the beneficiaries of the therapy, further collaboration between the health professional team and the patients is advisable. Moreover, the treating physician, health insurance companies, regulatory agencies and the pharmaceutical industry, are also interested to prevent these adverse reactions. Unexpected side effects caused by one drug might lead to withdrawal of this drug from the market. Indeed, serious adverse drug effects in patients led to the withdrawal or restriction of quinolones such as temafloxacin, grepafloxacin, trovafloxacin, and sparfloxacin. The re-challenge of the patient to the culprit drug is not an option. Using laboratory tests could provide a better guidance for the prescription of a certain drug as suggested by the above described immunogenetic tests.

Conflict of interest

The authors declare that there are no conflicts of interest.

Uncited reference

[158]

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