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Original article

Risks of long-term use of nitrofurantoin for urinary tract prophylaxis in the older patient

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ARTICLE INFO

ABSTRACT

Purpose: To review the current literature on reported pulmonary, liver, and nerve adverse reactions (ARs) of long-term Nitrofurantoin (NF) suppression in older patients treated for urinary tract infections (UTIs).
Materials and methods: An extensive literature search was performed on PubMed for the search terms "Nitrofurantoin," and "Nitrofurantoin and lung, pulmonary, liver, nerve or ARs". Relevant cited papers were also analyzed. Articles not in English, or related to children, or pregnant women were excluded.
Results: In 43 articles and other texts meeting the inclusion criteria from 1968 to 2014, rates of long-term NF-related pulmonary ARs compared to total NF prescriptions differed worldwide, but remained extremely small at 0.001% (USA) and 0.001% for pulmonary and hepatic ARs (France). Among all NF ARs, rates of pulmonary ARs differed across the literature from 2% (UK), 3% (Holland), 5% (Sweden), to 7% (Australia). Nerve ARs were reported as .0007% and liver ARs as .0003% of total prescriptions
Conclusions: Pulmonary, nerve, or liver ARs resulting from long-term NF prophylaxis in older patients treated for UTIs are potentially serious but extremely rare, and should not deter from the cautious use of NF in this population.

1. Introduction

The management of recurrent urinary tract infections in women tends to be challenging and can be influenced by age, renal function, the mode of recurrence—namely persistence (same bacteria) or reinfection (different bacteria), antibiotic allergies, and strain resistance to some antibiotics. Antibiotic resistance is a growing concern, especially for certain classes of antibiotics such as fluoroquinolones.

Nitrofurantoin (NF) has been the focus of much attention lately, in part due to the recommendations for its use outlined in the Beers criteria. In 2003, the first set of Beers criteria alerted the public to the dangers of NF in older adults because of the "potential for renal impairment" with a high level of severity rating.[1] In 2012, the Beers criteria update expert panel included NF on a list of drugs potentially inappropriate to use in older adults. This time the focus was on "potential for pulmonary toxicity," with a quality of evidence rated as moderate, and a strong strength of recommendation.[2] The 2012 Beers document emphasized three additional points: (1) avoid in patients with renal impairment (creatinine clearance < 60 mL/min); (2) safer alternatives are available; and (3) avoid for long-term suppression.[2]

For practitioners, these 2012 recommendations prompted additional justification to reassure concerned patients already on NF suppression. Health insurance providers also circulated notifications to physicians prescribing NF to encourage them to reconsider their decision and change to other therapies. Subsequently, the Beers 2015 recommendations were issued,[3] followed very recently by a special American Urological Association white paper on this matter to revisit the intended purpose of the Beers criteria.[4]

In this context, our goal was not to reconsider the well-established recommendations to avoid NF in older adults with renal impairment,[3] but instead to focus on the available literature data regarding NF adverse reactions (ARs), with a special emphasis on pulmonary, liver, and nerve toxicity in order to better communicate these risks to older women and to assist in their regular monitoring.

2. Materials and methods

An extensive literature search was performed on PubMed for the search terms "Nitrofurantoin," and "Nitrofurantoin and lung, pulmonary, liver, or nerves, or ARs." Relevant cited reviews were

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also analyzed. Articles not in English, or related to children or pregnant women were excluded. Four datasets were queried: ARs versus prescriptions of NF, ARs alone, retrospective and prospective studies, and tallying of case study reports in older women. As a general comment, most datasets did not provide a separate analysis of sex involvement, and thus, although not always clearly established in reports, the majority of data reviewed were for women. To determine the impact of age on pulmonary ARs, a case study subanalysis was performed in affected women using age 65 years as a traditional cut-off for older adults.

3. Results

The following results were extracted from 43 articles and other texts meeting our inclusion criteria from 1968 to 2014.

3.1. Lung toxicity and avoidance of NF for long-term suppression

This result section includes data primarily on lung toxicity as it is the most commonly involved organ. The data are presented in four sections including: ARs, retrospective and prospective series, and case series (Appendix 1).

3.1.1. Spectrum of pulmonary adverse reactions
Pulmonary ARs are typically divided into acute and chronic reactions. The acute reactions are more common and the development of one does not appear to increase one's risk for the other reaction.[5,6] Acute pulmonary reactions appear within days of starting the medication.[7] Patients typically report respiratory and constitutional symptoms. Rash and eosinophilia are also common. If the drug is stopped complete resolution is the norm; however, if not, the reactions can become severe and progress to acute respiratory distress syndrome.[8] Rechallenge virtually always causes a relapse and is not recommended.

In contrast, the chronic ARs appear months to years after drug initiation. Persistent cough and dyspnea are the primary symptoms.[9] A large variety of interstitial lung disease patterns have been reported including nonspecific interstitial pneumonia, desquamative interstitial pneumonia, organizing pneumonia, and eosinophilic pneumonia.[10] Drug cessation is necessary for all and corticosteroids may be of value for severe disease or disease that progresses despite removal of the NF. Residual disease is common despite the above measures.

3.1.2. AR reporting compared to total NF prescriptions
Two large scale studies compared the number of reported chronic ARs of NF to the total number of prescriptions of NF. The first large dataset (1953—1984) was reported by D'Arcy[11] based on adverse reports to the drug manufacturer, Norwich Eaton Pharmaceuticals, Norwich, New York, USA, in which the rates of reported ARs in a study encompassing 121,430,000 courses of treatment were tallied.[10] Pulmonary reactions were reported in 0.0002% courses of treatment, liver reactions in 0.0003% of courses, neuropathy in 0.0007% of courses, and blood dyscrasias in 0.0004% of courses, totaling 0.001% in chronic, severe complications.[11] Notably, of all the chronic side effects, pulmonary reactions were the least frequent, despite being the reason stated in the Beers 2012 criteria for warning against NF. Another study analyzing NF prescriptions in France in 2010 compiled 261,000 prescriptions of NF, with an estimated 1500—2500 prescriptions for treatment > 4 months.[12] They estimated that chronic pulmonary or hepatic reactions occur in one out of every 517—862 prescriptions, or 2.9 cases/y. Meanwhile, the French Committee on Drug Monitoring reported "severe ARs," mainly pulmonary or hepatic for NF, with a

frequency of 1/20,551 NF prescriptions (0.0049%).[13] This frequency increased with treatment duration: from 1 case/24,800 for short-term prescriptions (1 month) to 1 case/7666 for long-term prescriptions (>1 month). These two studies indicated that reactions to chronic NF remained very low when compared with the amount of prescriptions of NF.

3.1.3. AR reporting
In 1982, Penn and Griffin[14] compared ARs between the UK (reported from the Committee on Safety of Medicines), Sweden (from Holmberg et al[5]), and Holland (from the Netherlands Drug Registration Authority), noting that AR reporting varied between countries as seen in Table 1. From those data, pulmonary chronic effects of NF ranged from 2.0% to 5.3% of adverse reports. Furthermore, even within a country, AR reporting varied between years. For instance, from 1964 to 1980 in the UK, AR reporting declined from 1.77% to 0.11%, but increased from 1.5% in 1965—1969 to 7.9% in 1970—1974 in Sweden. In this same Swedish study from 1966 to 1976, Holmberg et al[5] analyzed 921 patients with ARs, 42 of which were on therapy for >1 year. Of those 42 patients (mean age 68 years), 23 experienced a pulmonary AR to NF. They also noted that risk of ARs increased with age, and that women were more at risk compared with men.

Two other studies focused solely on pulmonary ARs. The first study was performed by Holmberg and Boman[6] from 1966 to 1976 in Sweden, in which reports to the Swedish Adverse Drug Reaction Committee were analyzed. Out of 447 pulmonary AR reports, 49 were due to chronic NF intake, 41 of whom were on therapy for 10 months to >65 months. Approximately three quarters of the patients required hospitalization because of an adverse pulmonary reaction. The median age of the women on long-term therapy was 58 years, suggesting that younger women are equally susceptible to the chronic side effects of NF as older women are.

The second study from Australia focused on adverse outcome reporting without comparison to the amount of prescriptions. By 2004, the Australian Adverse Drug Reactions Advisory Committee received a total of 576 adverse reports.[15] Of these 142 were pulmonary ARs, 40 of which were chronic NF-induced pulmonary AR reports. Older women (median > 70 years) were the predominantly affected demographic group.[15] These authors and others have postulated this may reflect usage of NF.[15,16] Time of onset of the AR ranged from 8 months to 16 years. Of the 40 patients with chronic pulmonary toxicity, 12 patients recovered and two patients died. The remainder had persistent lung damage. This study illustrated the unpredictable onset and rarity of pulmonary damage.

3.1.4. Retrospective studies
Two large retrospective studies focused on pulmonary ARs. In the first retrospective study from 1989, Jick et al[17] identified 742 long-time users and 16,101 patients with first courses of treatment of NF, and compared their hospitalization rates. In the group of long-time users, only one man aged 65 years was hospitalized for dyspnea (one women aged 89 years was hospitalized for possible

Table 1
Percent of reported adverse reactions across the UK, Sweden, and Holland (total adverse reports).

Reaction	UK (155)	Sweden (921)	Holland (unknown)
Pulmonary reaction (%)	2	5.30	3.40
Liver damage (%)	3.90	Not available	9.10
Peripheral neuropathy (%)	14.10	2.20	9.10

Note. From "Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland," by Penn and Griffin, 1982, *British Medical Journal (Clinical Research Edition)*, 284, p. 1440—2. Copyright 1982, *BMJ Publishing Group Ltd.* Adapted with permission.

NF-induced pulmonary AR), and acute pulmonary toxicity occurred three times (women aged 46 years, 49 years, and 75 years). This rate of 0.27% of patients on long-term NF therapy suffering from a pulmonary complication is extremely low. Although women are noted throughout literature to be more susceptible to NF complications, only one woman from this study had a long-term complication. This is remarkable given that the majority of NF prescriptions were for women. A second retrospective study from 1997 to 2002 by the Mayo Clinic identified 18 patients with chronic pulmonary ARs (17 women, six previous smokers) aged 47–90 years (median 72) who used NF prophylactically.[18] These patients were receiving a median dosage of 100 mg NF, and their median onset of symptoms was 23 months, with a median of 4 months of symptoms before diagnosis. One patient died of pneumonia complications 5 months later, and one patient did not improve even after 5-years post-NF discontinuation. The remainder improved but half required corticosteroid therapy. Residual abnormalities persisted in 14 patients and only three had complete resolution. This is a significant rate of morbidity and mortality within a group already known to have NF-induced pulmonary problems, but appears very small when compared with all the patients placed on NF prophylaxis. Interestingly, resolution of pulmonary ARs were found to correlate neither with length of NF usage nor with duration of pulmonary symptoms.

3.1.5. Prospective studies

Finally, in one unique prospective study from 1975 to 1992, Brumfitt and Hamilton-Miller[19] charted the rates of NF ARs in 219 female patients aged 9–89 years who had planned to be on 1 year of NF therapy at various dosages (average of 9.9 months). Although 46% of patients reported a reaction with NF at an average of 9.9 months, only one patient reported a serious complication (peripheral neuropathy), and older patients (>65 years) were as likely to have an AR as younger patients.

3.1.6. AR case studies related to pulmonary damage

The case study literature yielded 17 case reports from 1968 to 2014 that detailed pulmonary ARs related to chronic use of NF in older women ($N = 25$). Patient data from these reports are provided in Appendix 1. The age results of this compilation are detailed in Figure 1. Treatment duration ranged from 9 months to 7 years,

cessation of NF after symptom onset ranged from 2 weeks to >4 years, and dosage also varied from 50 mg to 300 mg. Once NF was discontinued and corrective treatment implemented, this review of case studies indicated that these pulmonary ARs tended to be at least partially reversible. One patient died possibly as a result of isoniazid, while another had a right bundle branch block, with a total of three deaths in this cohort.[20,21]

3.2. Liver toxicity

Hepatic damage due to NF varies widely, from granulomatous lesions, cirrhosis, liver necrosis, to chronic active hepatitis.[22] Overall incidence for hepatic damage attributed to both long- and short-term NF has been reported to be 0.02–0.035%, and may be due to immunoallergic idiosyncrasy.[22] The diagnosis of NF-induced hepatic reactions is a diagnosis of exclusion, which is substantiated upon resolution of symptoms once NF has been discontinued.[22] The only way to confirm NF related hepatic reactions is by rechallenge, which is contraindicated given its potential for adverse outcomes.[23]

To add to the complexity of reactions to chronic NF use, liver and pulmonary reactions may present together.[24] Thus, if a patient presents with multiple systemic symptoms, NF toxicity should still be considered.

3.2.1. AR reporting

One retrospective study by Stricker et al[25] from the Netherlands analyzed 52 reports of NF-induced hepatic ARs to the Netherlands Center for Monitoring Adverse Reactions from 1963 to 1987. Thirteen (12 women) reports were due to "chronic" effects. Thirty-eight reports were likely due to NF, of which 13 were due to chronic effects, and 85% were for patients aged > 65 years. Also, the incidence for adverse hepatic reactions (chronic and acute) for women aged > 64 years was 47%, with 18.4% of prescriptions going to that same age group. This study does indicate that older women are more likely to suffer from an adverse liver reaction when exposed to NF for a long time.

3.2.2. Case reports

Individual case reports of hepatic effects due to chronic NF were not compiled due to the comprehensive case study analysis recently published by Sakaan et al.[23] The dataset from this paper was
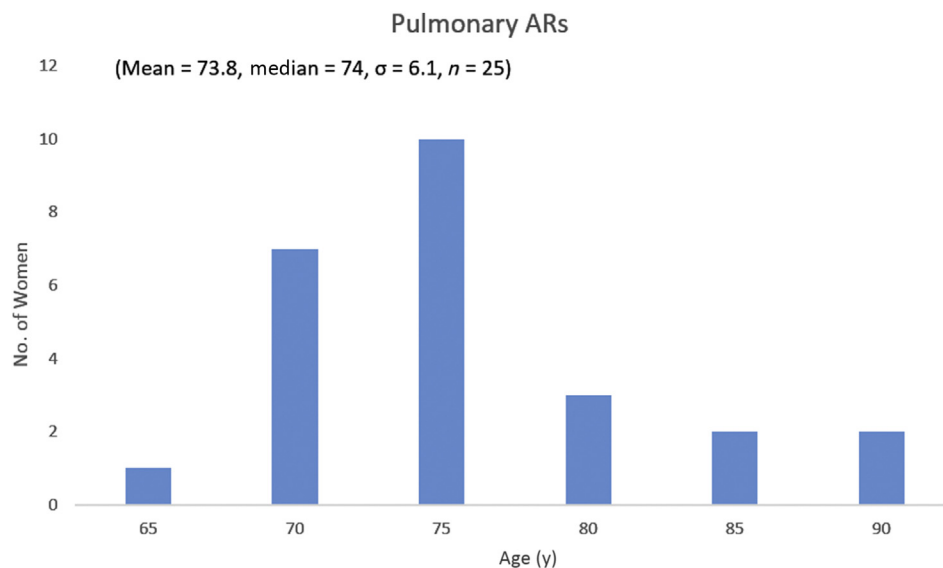

Figure 1. Compilation of published case studies pulmonary adverse reactions (ARs) related to long-term use of nitrofurantoin ($N = 17$, representing 26 patients) in women aged > 65 years.

screened for older women on long-term (> 3 months) therapy with NF and analyzed. Seventeen out of 33 patients (51.5%) were aged < 65 years when they had a chronic liver reaction to NF. From these data, older and younger women appeared to be equally at risk for liver toxicity with chronic NF intake. Most patients' symptoms (jaundice, hepatomegaly, malaise) resolved after discontinuing NF, and in some cases, with the addition of cortisol treatment. However one patient (aged 33 years) needed a liver transplant and seven died, of whom two were children and the others were 47–59 years of age.

3.3. Nerve toxicity

Peripheral neuropathy is one of the chronic adverse reactions of long-term NF use. No retrospective studies focusing on nerve adverse reactions to chronic NF therapy were found.

3.3.1. Case reports

The last case report analysis on NF-induced polyneuropathy was performed by Toole and Parrish[26] in 1973. They reviewed 137 cases of NF-induced polyneuropathy, 100 of which were followed-up long term, and 10 of which had treatments longer than 90 days. Of those 100 patients, 34% made a complete recovery, 45% a partial recovery, 13% showed no improvement, and 8% died. Recovery usually occurred within a few days to several months after NF was discontinued. However, these data include patients both on long- and short-term NF, and the age data were not provided.

Most case studies were reported in the 1960s to the 1980s, and this review presents available recent reports. Tan et al[27] chronicled two women, aged 59 years and 53 years, who were on long-term NF suppression and suffered general dysesthesias and pelvic pain, respectively. The first woman remained symptomatic 3 years after discontinuation of NF, and the second woman's symptoms improved. Yiannikas et al[28] reported on a 71-year-old woman on NF therapy for almost 1 year who developed paresthesia of her hands and feet along with decreased deep tendon reflexes. None of these three patients discussed had other causes of neuropathy such as diabetes.

4. Discussion

In this review, we carefully studied all adverse events reported with NF so that the practicing physician can be aware of the available literature on this topic when discussing risks of long-term NF exposure with his/her older patients. Several observations were made for lung toxicity including the importance of early recognition of persistent cough and dyspnea with subsequent discontinuation of NF. Recovery from pulmonary ARs depends on the type of pulmonary reaction, how soon NF was discontinued after the presentation of symptoms, and the degree of symptom severity. As a result, this review suffers from under-reporting of all NF-related ARs. However, even if only one out of every 100 pulmonary ARs is reported, the rate of pulmonary ARs would still be very low. Only a registry could keep track of these events in a longitudinal study. Such an effort may be necessary to better delineate the real risks of using NF in a long-term chronic fashion.

The rates of liver and nerve toxicity are even less frequent than lung toxicity. Nonetheless, it is appropriate for the physician to monitor their patients on long-term NF prophylaxis, and consider "regular monitoring" with inquiries on peripheral neuropathy symptoms and possible liver function tests.[29]

The combined worldwide experience with chronic NF therapy remains modest at best in establishing the rates of ARs for older patients. There is sufficient information to call attention to ARs, but it appears that large-scale and long-term prospective studies are still needed. For the practicing urologist, NF remains a good treatment option in the acute setting of urinary tract infection with an adequate renal function. It is important to be acquainted with the Beers criteria[4] and exercise caution and proper monitoring[29] in the long-term use of NF for antibiotic suppression in the individualized care of older adults.

5. Conclusion

The currently reported rates of pulmonary, hepatic, and nerve ARs related to the long-term use of NF remain very small. Although pulmonary, nerve, or liver ARs resulting from long-term NF prophylaxis in older patients treated for urinary tract infections are potentially serious, they should not deter from the cautious use of NF in this population.

Conflicts of interest

The authors have nothing to disclose.

Appendix 1

Pulmonary AR case studies related to chronic use of nitrofurantoin in older women.

Author	Age (y)	Length of use, dosage	Pulmonary reaction	Symptoms	Death	Treatment	Recovery
Sakata et al[1], 2014	69	2.5 y, 100 mg every other d	Crackles, interstitial infiltrates, ground glass opacities, giant cell granulomas	2 wk dyspnea and fatigue	No	Discontinued, home oxygen	Back to baseline at 3 y follow-up
Ghimire and Nepal[2], 2013	71	Not noted	Not noted	Dyspnea, anemic	No	Discontinued	Yes, glucose-6-phosphate dehydrogenase deficiency
Mullerpattan et al[3], 2013	67	1 y prior and 1 mo, not noted	Interstitial pneumonia with bilateral reticular shadows, ground glass opacities, bilateral crackles	Rapid onset of dyspnea, tachypnea	Yes	Discontinued, IV methylprednisone 500 mg for 3 d, pirfenidone and N-acetyl-cysteine	Deteriorated for 1 mo until respiratory failure
Madani and Mann[4], 2012	88	4 y, not noted	Interstitial lung disease	6 mo of productive cough and dyspnea, crepitation, fibrosis on CT	No	Discontinued, prednisone	Yes
Hardak et al[5], 2010	85	1 y, not Noted	Diffuse reticular infiltrates, ground glass opacities	3 mo fever, dyspnea, dry cough, crackles	No	Discontinued	Resolution

(continued)

Author	Age (y)	Length of use, dosage	Pulmonary reaction	Symptoms	Death	Treatment	Recovery
	74	3 y, not noted	FEV_1 = 58%, FVC = 68%, diffuse reticular infiltrates	3 y dyspnea, dry cough, fatigue, crackles	No	Discontinued	Resolution
	72	6 mo, not noted	Diffuse reticular infiltrates	6 mo, dyspnea, dry cough, fatigue	No	Discontinued	Resolution
	75	3 y, not noted	FEV_1 = 44%, FVC = 37%, diffuse reticular infiltrates, peripheral fibrosis, pleural effusion	1 y, dyspnea, decreased breath sounds	No	Steroids, discontinued	Fibrosis
	86	2 y, not noted	FEV_1 = 44%, FVC = 55%, diffuse reticular infiltrates	6 mo, dry cough, dyspnea, crackles	No	Discontinued	Resolution
	75	5 y, not noted	FEV_1 = 67%, FVC = 69%, D_LCO = 37%, ground glass opacities	1 y, dyspnea, crackles	No	Steroids, discontinued	Partial resolution
	70	14 mo, not noted	Ground glass opacities	2 mo, dry cough, dyspnea, malaise, crackles	No	Steroids, discontinued	Resolution
Martins et al[6], 2008	74	3 y, not noted	Subpleural interstitial thickening, chronic eosinophilic pneumonia	Chronic cough, 20 mo ago x-ray showed fibrosis, crackling rales	No	Oral and inhaled corticosteroids, later NF discontinued	No significant improvement on imaging, dyspnea and rales resolved after 15 mo
Bhullar et al[7], 2007	71	3 y, 100 mg every other d	Patchy airspace disease, calcified hilar lymphadenopathy, restrictive pattern	3 y intensifying dyspnea, cough	No	Discontinued	1 wk subjective improvement, 5 mo FVC normal, 7 mo clear on radiographs
Lin and Bhally[8], 2007	67	5 y, 50 mg/d	Reduced FEV_1 and FVC, bilateral ground glass opacity	8 wk nonproductive cough, 2 wk progressive dyspnea, crackles, hypoxia	No	Discontinued, prednisone 40 mg	Prolonged hospital course, 2 mo symptoms and chest x-ray improved
Hargett, et al[9], 2006	77	9 mo, not noted	Cellular interstitial infiltrates and scattered MGC consistent with GIP	6 mo dyspnea	No	Discontinued, prednisone	2 mo, return to normal
Bidad and Harries-Jones[10], 2004	76	14 mo, not noted	Interstitial and reticular shadowing, FEV_1/FVC = 91%, like pulm fibrosis or pneumonitis	6 wk tachypnea, tachycardic, crackles	No	Discontinued, prednisolone	2 wk, less breathlessness; later reduced shadowing, parenchymal abnormalities
Fawcett and Ibrahim[11], 2001	82	4 y, 50 mg/d	Reduced FEV_1 and FVC, mosaic perfusion, patchy ground glass opacities, biopsy suggestive of BOOP	2 y productive cough, increasing breathlessness	No	Discontinued, prednisone 30 mg/d reduced over 6 wk	8 mo return to baseline, FEV_1 and FVC improved, improved basal reticular shadowing
Sheehan et al[12], 2000	75	3 y, not noted	Widespread reticular pattern, ground glass changes, parenchymal distortion	2 y increasing dyspnea, crackles	No	Distincontinued, oral methylprednisolone	6 wk, return to normal
Robinson[13], 1983	71	10 mo, 300 mg/d	Bilateral reticular shadowing, reduced D_LCO	Dyspnea, nonproductive cough, bilateral crepitations, sensorimotor neuropathy	No	Discontinued	2 y, no improvement in pulmonary symptoms
Willcox et al[14], 1982	65	4 y, not noted	Small lung fields, bilateral shadowing on x-ray, restrictive disease	1 y progressive dyspnea, dry cough, bilateral crackles, poor chest expansion	No	Discontinued, prednisone 40 mg/d withdrawn gradually over a mo	1 mo, chest x-ray clearer, improvement in pulmonary fxn tests, cough subsided, crackles almost gone
Oxenhandler[15], 1977	67	4 y, not noted	Bilateral fibrosis, vasculitis of pulmonary veins	Unproductive cough, 1 mo later hospitalized for dyspnea, 7 mo later fibrosis, 1 mo later fever, malaise, dyspnea	Yes, due to INH	5 d prednisone, 10 d prednisone, last hospital visit discontinued NF, with 20 mg/d prednisone and 300 mg/d INH	Unexplained fever 2 mo after INH started, died
Kursh et al[16], 1975	78	Intermittent few y, not noted	Bilateral pleural effusions, bilateral diffuse pulmonary infiltrate, pulmonary fibrosis	2 mo severe dyspnea; later fever, productive cough, egophony and rales	Yes	Hospitalized twice, was intubated the second time, NF discontinued 3 d prior to death	In hospital, developed incomplete right bundle branch block, died
	68	>6 y, 50 mg/d	Chronic interstitial pneumonitis and fibrosis, bilateral diffuse process at bases of lungs, restrictive disease	> 4 y of cough, dyspnea	No	Dexamethasone 0.75mg 2×/d, later NF discontinued	6 wk, less dyspnea, patient improved, pulmonary symptoms present 6 y later
Rosenow et al[17], 1968	75	Intermittent for approx. 7 y, 50 mg 4×/d for 2–3 wk, 5×/y	Restrictive ventilation, impaired CO diffusion, chronic interstitial pneumonitis, focal interstitial fibrosis	7 wk, cough, dyspnea. Cyanosis, bilateral decreased chest expansion crackling, rales, T wave changes	No	Discontinued, 0.25 mg/d digitoxin, 5mg 4×/d prednisone	5 wk, symptomatic improvement, CO diffusion still impaired
	66	15 mo, not noted	Diffuse bilateral interstitial process, restrictive pulmonary fxn and impaired CO diffusion	5 mo progressive nonproductive cough, dyspnea, chest pain, bilateral crackling rales	No	Discontinued, 10 mg 4×/d prednisone, 7 mo smaller dose of prednisone	4 wk, clearing of diffuse process, 8 mo, no imaging abnormality, CO diffusion increased

BOOP = bronchiolitis obliterans organizing pneumonia; CO = carbon monoxide; CT = computed tomography; D_LCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume of 1 second; FVC = forced vital capacity; fxn = function; GIP = giant cell interstitial pneumonia; INH = isoniazid; IV = intravenous, MGC = multinucleated giant cells; NF = nitrofurantoin; PFT = pulmonary function tests; TLC = total lung capacity.

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