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## Long-term nitrofurantoin: analysis of complication awareness, monitoring and pulmonary injury cases

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## **Abstract**

**Background:** Long-term nitrofurantoin (NF) treatment can result in pulmonary and hepatic injury. Current guidelines do not outline the type or frequency of monitoring required for detection of these injuries.

**Aims:** To assess (1) awareness of NF complications among prescribers, (2) monitoring practice and (3) to describe the pulmonary sequelae of NF-related complications.

**Methods:** (1) Electronic questionnaire to prescribers, interrogating prescribing/monitoring practices and awareness of complications; (2) Case-note review (June-July 2020) of NF monitoring among general practitioners (GPs) in our local clinical commissioning group; (3) Case review of patients diagnosed with nitrofurantoin-induced interstitial lung disease (NFILD) at our interstitial lung disease (ILD) centre (2014-2020).

**Results:** 125 prescribers of long-term NF responded to the questionnaire (82% GPs; 12% urologists). Many were unaware of the potential for liver (42%) and lung (28%) complications. 41% and 53% never monitored for these, respectively. Only 53% of urologists believed themselves responsible for arranging monitoring, whilst nearly all GPs believed this to be the prescriber's responsibility (94%). One third of all respondents considered current British National Formulary (BNF) guidelines "not at all sufficient/clear", with mean clarity scoring of 2.2/5.

Amongst NFILD patients (n=46), NF had been prescribed most often (70%) for treatment of recurrent UTI and 59% (n=27) were prescribed for >6 months. Upon withdrawal of the medication 61% displayed resolution (completely/minimal fibrosis), whilst 16% of patients had progressive lung fibrosis.

**Conclusion:** NF can cause marked or irreversible lung complications and there is currently a shortfall in awareness and monitoring. Existing monitoring guidelines should be augmented.

**Keywords:** Nitrofurantoin; General Practice; Urology; Drug-Related Side Effects and Adverse Reactions; Prescription Drug Monitoring Programs.

**How this fits in:** It is known that long-term nitrofurantoin use can induce hepatic and/or pulmonary complications and that monitoring is required for early detection. Our research highlights a shortfall in (1) awareness of nitrofurantoin-related side effects and (2) monitoring practice in the prescribing community. Hence, we suggest that awareness of potential nitrofurantoin complications be raised among GPs and urologists, that monitoring responsibilities be clarified, and that existing monitoring guidelines be augmented.

## **Introduction**

Nitrofurantoin (NF) is prescribed for treatment of acute urinary tract infections (UTIs) and prophylactically to reduce UTI recurrence.<sup>[1,2]</sup> Complications, notably hepatic and pulmonary, have been associated with short-term and long-term use and are more common in women.<sup>[3-5]</sup> Nitrofurantoin-induced interstitial lung disease (NFILD) refers to a spectrum of lung changes, from an acute hypersensitivity reaction (within 1-2 weeks) to a chronic pulmonary reaction involving fibrosis (months to years of exposure). The prevalence of severe adverse events was estimated at 0.2% (95% CI <0.01%, 1.2%) in controlled trials and from 0.02 to 1.5 events per 1,000 NF users in observational studies.<sup>[6]</sup> Although severe adverse events may be uncommon in a general population, the risk increases with longer treatment durations and the reported prevalence among individuals aged 65 years and over is 2.1%.<sup>[5]</sup> The precise mechanisms of adverse effects are not fully understood.<sup>[7-9]</sup>

Current adult British National Formulary (BNF) guidelines state: “On long-term therapy, monitor liver function and monitor for pulmonary symptoms, especially in the elderly (discontinue if deterioration in lung function)”. However, neither a method nor frequency of hepatic/pulmonary monitoring, nor a definition for “long-term” is suggested. National Institute for Health and Clinical Excellence (NICE) guidance on antimicrobial prescribing for recurrent UTI recommend review at 6 months.<sup>[10]</sup> Both NICE guidance and local clinical commissioning group (CCG) guidelines rely on referencing BNF advice.<sup>[2]</sup>

Negligence in NF monitoring has been highlighted as a significant cause of litigation according to the UK Medical Protection Society (UKMPS)<sup>[11]</sup> who advise liver function testing (LFTs) and review for respiratory symptoms at least 6-monthly, with consideration of more frequent monitoring.<sup>[11]</sup>

Improving monitoring protocols may speed recognition of complications and withdrawal of NF to lessen severity of toxicity. The current landscape of monitoring practice is unknown. This study aimed to determine: (1) the awareness of NF side effects; (2) the existing monitoring practices of NF in general practice within our local area; and (3) to describe our cohort of patients diagnosed with NFILD by multidisciplinary team (MDT) consensus at the Bristol Interstitial Lung Disease (BILD) service.

## **Methods**

### ***Setting***

This study involved collaboration of the BILD service at North Bristol NHS Trust (NBT) and the Bristol, North Somerset and South Gloucestershire (BNSSG) CCG. The BILD service provides secondary and tertiary specialist ILD care to a catchment of 1.2 million in South West England.

This study was approved locally as a Clinical Effectiveness Project (Project Application Number: CE65008).

### ***Study Procedures***

#### 1) Questionnaire: Assessing Prescribing Insight

A 13-item questionnaire was electronically distributed (July 2020) to all local general practitioners (GPs) (n=675), nurses (n=145) and CCG medicine optimization pharmacists (MOPs; n=72), and South West

urologists (n=130) (Supplementary Information 1). Responses were anonymised to ensure confidentiality and encourage candid responses.

## 2) Analysis of Monitoring Practices of NF within Primary Care

Data were requested from all CCG GP practices (n=78), collated by MOPs and submitted to study organisers for analysis. Monitoring history was analysed for all patients with an active NF prescription at the time of data collection (26<sup>th</sup> June-25<sup>th</sup> July 2020) and registered at a participating GP practice. Patient demographics and extent of NF exposure (dose; duration; episodic/continuous/cyclical use) were collected from GP practice records. Data regarding relevant monitoring procedures performed at baseline and subsequently were also collated, including clinical examination, oxygen saturation, chest X-ray (CXR), spirometry and liver function tests (LFTs). Only patients with a NF prescription initiated within the preceding 2 years were included, to address contemporary practice.

## 3) Case-Note Review and Characterisation of Patients with an MDT Consensus Diagnosis of NFILD

Patients with an MDT consensus diagnosis of NFILD (September 2015-July 2020) were retrospectively identified from BILD database. From NFILD patient records, data were collated regarding basic demographics and NF exposure. Baseline (initial presentation) and final (completion of audit) lung function were documented. Spirometry measurements included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), diffusion capacity of the lungs (TLCO) and TLCO with correction for haemoglobin (KCO). Six-minute walking distance (6MWT), oxygen saturations and MRC dyspnoea scores were also compared between initial and final visits. Baseline and final high resolution computerised tomography (HRCT) imaging results were independently reviewed for changes to radiological pattern by a thoracic radiologist and a respiratory consultant. Treatment regimens including long-term/ambulatory oxygen therapy (LTOT/AOT) and steroids were interrogated.

### **Statistical Analysis**

Continuous variables were tested for normality using the D'Agostino & Pearson test. Where parametric, data were tested by paired two-tailed t-tests and presented as mean±SD (standard deviation). Where non-parametric, data were tested by Wilcoxon tests (paired) or Mann Whitney U tests (unpaired) and presented as medians with IQR. For all statistical tests,  $p \leq 0.05$  was considered statistically significant. Data were analysed using GraphPad Prism 8 for Windows, version 8.4.3 (GraphPad Software, LLC, San Diego, C.A., U.S.A.).

## **Results**

### **Questionnaire: Assessing Prescribing Insight**

Response rate among GPs and urologists respectively was 35.9% (n=242) and 31.5% (n=41). Long-term (>6 months) NF was prescribed by 39.8% (n=125) of the 314 total respondents: GPs 82.4% (n=103), urologists 12.0% (n=15).

CCG guidelines were preferred (47.2%, n=59), followed by NICE (38.4%, n=48) and local trust guidelines (10.4%, n=13). 11.2% (n=14) did not use guidelines. 65.6% (n=82) of prescriptions were for recurrent UTIs.

For treatment of recurrent UTIs, most prescribers based their antibiotic choice on culture results (52.8%, n=66). However, the first-choice treatment was NF for 28.0% (n=35) and trimethoprim for 18.4% (n=23).

Many prescribers were unaware of the potential hepatotoxicity (42.4%, n=53) or pulmonary toxicity (28.0%, n=35). 52.8% (n=66) of prescribers reported that they did not measure baseline function at prescription (respiratory symptoms, oxygen saturation, respiratory examination, CXR, spirometry, LFTs). The most common baseline test/examination was LFT (32.8%, n=41), whilst 20.8% (n=26) documented baseline respiratory symptoms. A minority (<5%) checked other modalities (oxygen saturations/respiratory examination/CXR/spirometry) and some mentioned taking a history of previous lung/liver abnormalities and blood tests to assess for infection.

The questionnaire investigated frequency of follow-up monitoring. LFT was reportedly “always” monitored by 10.4% (n=13) and “lung-related examination and tests (LuRT)” “always” by 7.2% (n=9) of prescribers. The most common tendency was to “never” monitor liver (40.8%, n=51) or lung function (52.8%, n=66) (Figure 1). When prescribers did monitor, this was most commonly performed every 12 months (32.0%, n=40).

The questionnaire gauged agreement with this statement: “the prescriber of nitrofurantoin is responsible for monitoring the drug side effects/complications”. Nearly all GPs (94.2%, n=97) considered monitoring to be the responsibility of the prescriber in contrast to 53.3% (n=8) of urologists.

The questionnaire interrogated the perceived clarity and sufficiency of current guidelines for long-term NF prescription. One third of respondents (n=105) considered guidelines to be “not at all sufficient/clear” whereas 1.3% (n=4) considered them to be “perfectly sufficient/clear” (Figure 2). The mean rating of existing guidelines was 2.2/5 (SD=1.0).

### ***Analysis of Monitoring Practices of NF within Primary Care***

Data were collated from 62 of 78 GP practices in the CCG (79.4%). 503 patients used long-term NF (July 2020). Those with NF prescription initiated within the preceding 2 years are considered herein (n=265). The cohort was predominantly female (81.5%, n=216) and over 60 years old (Table 1).

Baseline monitoring (tests undertaken at prescription date  $\pm 1$  month) of any kind was absent in 73.6% (n=195) of patients; 11.7% (n=31) received only LFTs and 10.2% (n=27) only LuRT at baseline. The remaining minority (4.5%, n=12) had both LFT and LuRT at baseline.

A sub-cohort of patients (39.6%, n=105) had been on NF for 6-24 months. Of these, many received no monitoring beyond 6 months post-prescription (44.8%, n=47), had only LFT monitoring (20.0%, n=21), or had only LuRT monitoring (14.3%, n=15). Relatively few patients received both liver and lung monitoring (21.0%, n=22).

### ***Case-Note Review and Characterisation of Patients with an MDT Consensus Diagnosis of NFILD***

The BILD service database archived 16,472 MDT discussion cases of 10,500 patients (January 2014-June 2020). Of these, a consensus diagnosis of NFILD was made in 46 patients (September 2015-June 2020) (0.4% of patients).

The median age was 72.0 years (IQR 66.3-78.8, range 34-91). The majority were female (80.4%, n=37). Baseline characteristics are summarised in Table 2. The major indications for NF were as a prophylactic treatment for recurrent UTIs of unspecified cause (69.6%, n=32) and catheter-related recurrent UTIs (10.9%, n=5). Other indications included UTI and recurrent cystitis.

The duration of NF exposure preceding toxicity ranged from <1 week (acute adverse effect) to  $\geq 12$  months. Exposure duration was 6-12 months for 19.6% (n=9) and  $\geq 12$  months for 39.1% (n=18). Duration was unknown for 32.6% (n=15) of patients.

The median follow-up period by the BILD service following NF cessation was 11.0 months (IQR 6.0-23.0). From baseline to final clinic visit, spirometry showed statistically significant improvements in FVC ( $p=0.041$ ), TLCO ( $p=0.005$ ) and KCO ( $p=0.006$ ) (Figure 3).

There was no significant change in resting oxygen saturation (mean  $95.4 \pm 2.1\%$  vs  $96.1 \pm 1.7\%$ ,  $p=0.68$ ), 6MWT (median (IQR) absolute distances 280.0 m (211.3-345.5) vs 280.0 m (220.0-320.0),  $p=0.14$ ), or desaturation during 6MWT (median (IQR) 90.0% (86.8-93.0) vs 92.5% (91.0-93.0),  $p=0.34$ ) between initial visit and final visits. Notably, there was significant improvement in MRC dyspnoea score (mean  $3.3 \pm 1.2$  vs  $2.9 \pm 1.3$ ,  $p=0.011$ ).

The patterns of fibrosis at baseline HRCT included cellular non-specific interstitial pneumonia (NSIP) (13.0%, n=6), fibrotic NSIP (17.4%, n=8), organising pneumonia (OP) (10.9%, n=5), fibrotic OP (2.2%, n=1) and hypersensitivity pneumonitis (13.0%, n=6), with an overlap of features in the remaining 20 patients.

Follow-up HRCT were available in 44 patients, at a median interval of 10.5 months (IQR 5.0-22.0). Interval radiological changes (Figure 4) in most cases showed complete resolution/minimal fibrosis (61.4%, n=27). Some showed progression of fibrosis over the follow-up period (15.9%, n=7). The remainder of patients showed no change (22.7%, n=10).

HRCT radiological outcomes were not statistically significantly between corticosteroid-treated patients and those who had not received corticosteroids (n=29, n=15,  $p=0.83$ ), although the cohorts were small.

Of the 46 patients, four consequently required LTOT and five required AOT.

## **Discussion**

### ***Summary***

This study has found low awareness of complications and suboptimal monitoring associated with long-term NF treatment, evident from both prescriber self-reporting and patient records. We advocate augmentation of current guidelines with a model monitoring plan. The pulmonary outcomes of NFILD patients serve as a warning of some potential consequences of low awareness/monitoring, even before exploring hepatic impacts.

Inadequate monitoring delays drug cessation and increases toxicity.<sup>[6]</sup> The questionnaire revealed low rates of active baseline testing, required to recognize any abnormalities in future monitoring results. However, in practice, many patients may have received “passive” baseline testing associated with routine health checks.



By our definition of baseline monitoring, we showed that monitoring in practice may be lower than self-reported monitoring. Follow-up monitoring is also low; large proportions of prescribers reported that they “never” monitor liver or lung complications and only a minority “always” monitor these.

The questionnaire also uncovered a discrepancy in perceived responsibilities between primary and secondary care professionals. Some primary care respondents expect secondary professionals to perform baseline tests. Furthermore, almost all GPs, compared to approximately half of urologists, considered monitoring to be the prescriber’s responsibility. Effective communication between primary and secondary care is vital to ensure high quality healthcare. Breakdown of this communication can result in reduced quality of care.<sup>[12]</sup>

### ***Strengths and Limitations***

This study engaged all parties involved in prescribing and monitoring of NF. The questionnaire had an adequate response rate from a large sample population but remains susceptible to response bias. Despite this, among respondents, the results are concerning and suggest a general low awareness and/or perceived significance of the problem. All LFTs in data collection were considered as undertaken for monitoring purposes. It is not possible to attribute this with certainty; many LFTs are likely to be coincidental given the cohort’s advanced age and comorbidities. Hence, deliberate hepatic monitoring was likely overestimated. It should also be acknowledged that GPs often rely on existing clinical information/results in decision-making about baseline safety for prescribing.

We recognise that the sample of NFILD patients was relatively small. Nonetheless, the primary focus of this study was monitoring, not sequelae of complications. There are further limitations with retrospective study that include missing data. The COVID-19 pandemic may have affected the final four months of the investigation window, possibly impacting follow-up, treatment routines or respiratory outcomes for some patients.

### ***Comparison with Existing Literature***

Although complications of NF have long been recognised,<sup>[13,14]</sup> there is a dearth of studies on awareness/monitoring for NF complications. Audits examining other medications with known potential pulmonary side-effects show a similar monitoring shortfall.<sup>[15–18]</sup>

Other large NF-related studies have shown similar pulmonary complications.<sup>[7,14,19–21]</sup> Demographics of these larger cohorts also matched this cohort in age distribution and sex ratio.<sup>[4,5,22]</sup>

A small proportion of NFILD patients demonstrated progressive fibrosis despite cessation. Current literature has raised concerns about irreversible pulmonary sequelae of NF use<sup>[8,20,22–24]</sup>, although concurrent ILD diagnosis unrelated to NF cannot be excluded. Most of our cohort were exposed to NF for >6 months before complications. Comparing radiological outcomes and duration of exposure presented evidence of a positive correlation between duration and chronic impacts, consistent with Holmberg and colleagues’ findings; 47% of their cohort with chronic respiratory disease developed this following at least 12 months of NF.<sup>[3]</sup>

### ***Implications for Practice***

Progressive ILD is a significant outcome from long-term NF administration, as well as being a medicolegal prescribing risk. This warrants improvements in baseline assessment and monitoring of NF patients. Development of education and explicit guidelines on the risks of NF complications could address the low prescriber awareness highlighted in this study and improve compliance. We urge GPs, when prescribing NF, to be wary of its hepatic and pulmonary risks.

Most questionnaire respondents used CCG and NICE guidelines for monitoring and rated current guidelines poorly (2.2/5). BNF guidelines state that prescribers should "monitor liver function and monitor pulmonary symptoms" but there is no reference to baseline testing, nor a suggested monitoring plan. Such guidelines should be augmented, emphasising risks and detailing monitoring plans.

Novel guidance may include but is not limited to:

1. Clear verbal and written information for patients defining potential side-effects of NF, documenting this provision;
2. Need for baseline oxygen saturations, MRC dyspnoea score, respiratory examination, ideally CXR in last 6 months, and LFT and creatinine clearance in last 12 months;
3. Need for regular follow-up monitoring: respiratory symptoms, oxygen saturations, MRC dyspnoea score, respiratory examination and LFT, ideally at 3-monthly periods during dosing;
4. Rapid cessation if toxicity is suspected;
5. Rapid accessibility to local hepatology and respiratory services;
6. Review of automated warning/monitoring signals on electronic prescribing platforms.

We have deliberately excluded spirometry given the challenge of delivering this in the current pandemic. This guidance may be sufficient to detect medication-related toxicity. We recognize that this guidance may represent an increased burden on GPs. Before any guidance is finalized, a cost-effectiveness analysis could be undertaken, potentially including a modelling study to ascertain the optimal set of monitoring items, hence determining the most effective way to mitigate risk whilst recognizing feasibility.

A further safeguard is improvement of communication pathways between GPs and urologists, so that all parties are aware that the prescriber is responsible for monitoring. Novel guidance could clarify such recommended communication.

The majority of BILD patients were exposed to NF for >6 months before complications. There is need for further research into causative durations but limiting use to 6 months and/or cycling it with a different antibiotic may prove protective.<sup>[25]</sup> Beyond 6 months, clinicians should reconsider the prescription in light of its risks.

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None

#### **Competing interests**

The authors have declared no competing interest

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## **Tables and figures**

Table 1. Age distribution of the 503 patients prescribed long-term (>6 months) NF at GP practices (n=78) within the BNSSG CCG.

Table 2. Baseline characteristics of BILD patients with NF-induced interstitial lung disease (NFILD).

Figure 1. Frequency with which long-term prescribers of NF self-reported initiating a monitoring programme for patients using NF.

Figure 2. Reported quality rating of current prescription guidelines for NF, across all respondents of the questionnaire.

Figure 3. Spirometry test result changes over interval of BILD clinic treatment for NFILD. FVC increased by median 5.00% (95% CI -0.79, +15.18). FEV1 increased by mean 2.93% (95% CI -4.86, +10.72). TLCO increased by mean 7.70% (95% CI +2.49, +12.91). KCO increased by mean 7.10% (95% CI +2.27, +11.94). FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLCO = diffusion capacity of the lungs; KCO = TLCO correction for haemoglobin, \* statistically different from baseline value (p<0.05).

Figure 4. Interval radiological outcomes of NFILD patients followed up in the BILD clinic.

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Table 1. Age distribution of the 503 patients prescribed long-term (>6 months) NF at GP practices (n=78) within the BNSSG CCG.

Age range (years)	%
0-20	3.0
21-40	18.1
41-60	25.3
61-80	38.1
≥ 81	15.5

Table 2. Baseline characteristics of BILD patients with NF-induced interstitial lung disease (NFILD).

Male:female ratio	9:37
Age (years)	71.76 ± 1.62
<b>Lung Function</b>	
FVC (L)	2.30 ± 0.11
FEV1 (L)	1.82 ± 0.07
Ratio (%)	79.8 ± 1.43
TLCO (mmol/min/KPa)	4.10 ± 0.23
KCO (mmol/(min/kPa/L)	1.27 ± 0.08
<b>Six Minute Walk Test</b>	
Distance walked (m)	270.3 ± 22.8
Minimum desaturation (%)	89.5 ± 0.87
MRC dyspnoea score	3.3 ± 0.17

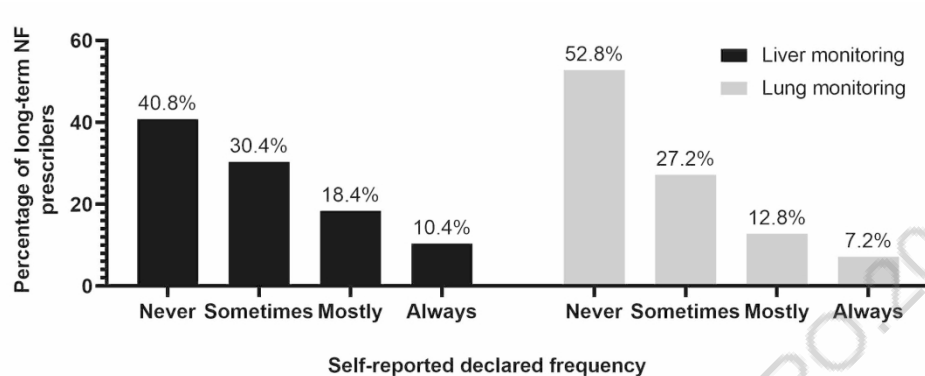


Figure 1. Frequency with which long-term prescribers of NF self-reported initiating a monitoring programme for patients using NF.

205x80mm (300 x 300 DPI)

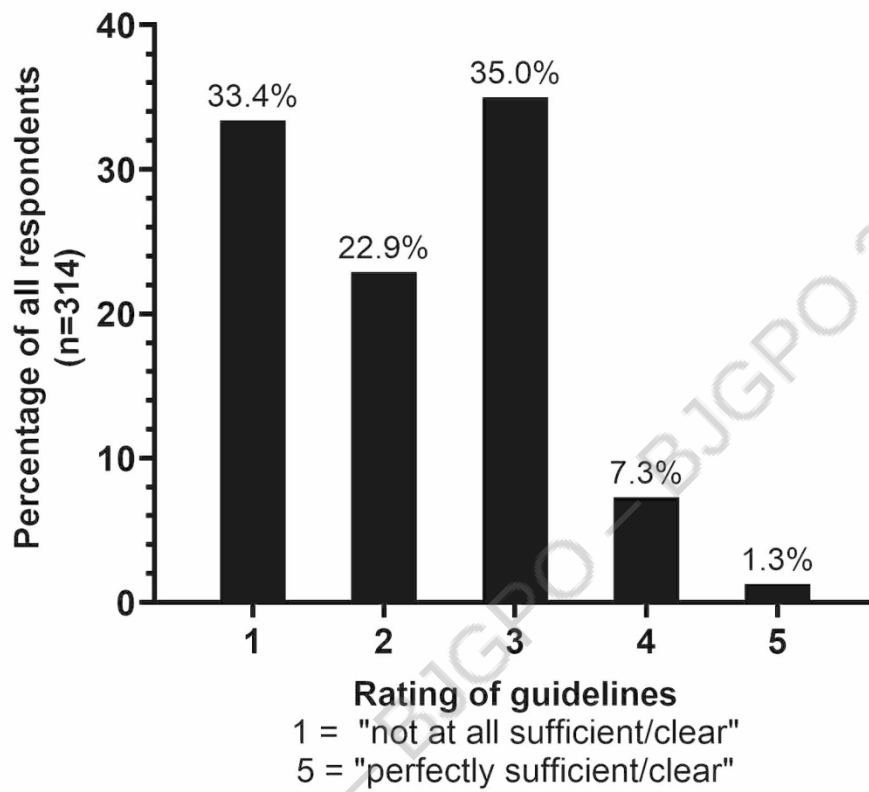


Figure 2. Reported quality rating of current prescription guidelines for NF, across all respondents of the questionnaire.

152x128mm (300 x 300 DPI)

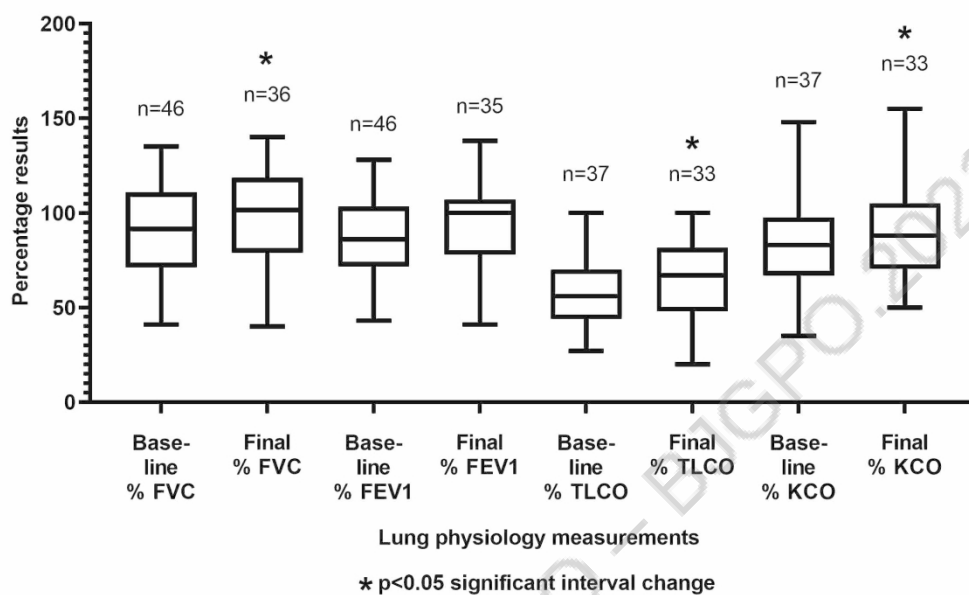


Figure 3. Spirometry test result changes over interval of BILD clinic treatment for NFILD. FVC increased by median 5.00% (95% CI -0.79, +15.18). FEV1 increased by mean 2.93% (95% CI -4.86, +10.72). TLCO increased by mean 7.70% (95% CI +2.49, +12.91). KCO increased by mean 7.10% (95% CI +2.27, +11.94). FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLCO = diffusion capacity of the lungs; KCO = TLCO correction for haemoglobin, \* statistically different from baseline value (p<0.05).

197x127mm (300 x 300 DPI)



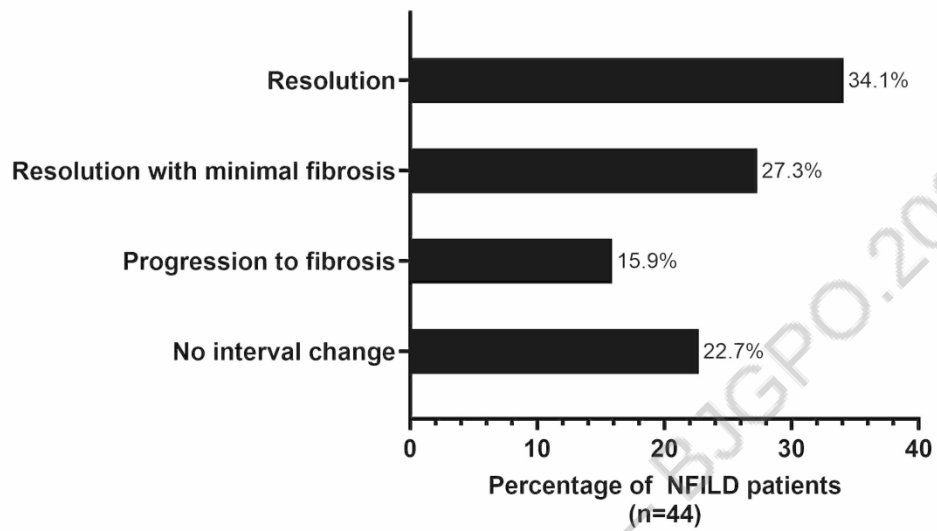


Figure 4. Interval radiological outcomes of NFILD patients followed up in the BILD clinic.

196x113mm (300 x 300 DPI)