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Systematic review: proton pump inhibitor-associated acute interstitial nephritis

F. SIERRA*,†, M. SUAREZ*,‡, M. REY*,‡ & M. F. VELA§

*Division of Gastroenterology and Hepatology, Fundación Santa Fe de Bogotá, Bogotá, Colombia; †Universidad de Los Andes Medical School, Bogotá, Colombia; ‡Universidad El Bosque Medical School, Bogotá, Colombia; §Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, SC, USA

Correspondence to:
Dr M. F. Vela, Division of Gastroenterology and Hepatology, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 210, Charleston, SC 29425, USA.
E-mail: velaaqui@musc.edu

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SUMMARY

Background
A number of recent case reports and case series suggest that proton pump inhibitors may cause acute interstitial nephritis.

Aim
To establish the nature of the relationship (cause or association) between proton pump inhibitor use and development of interstitial nephritis.

Methods
Data collection: Two researchers independently searched electronic databases (MEDLINE, EMBASE, GOOGLE, LILACS, COCHRANE) for articles from 1970 to 2006, including all study designs, populations and languages. Two independent reviewers assessed study quality and collected the data. Selection criteria: absence of baseline renal failure, development of interstitial nephritis after proton pump inhibitor exposure, nephritis confirmed by creatinine plus either renal biopsy or recurrence upon reinitiating proton pump inhibitor.

Results
Sixty four cases (60% females, mean age 78 years) of proton pump inhibitor-associated interstitial nephritis were found, 60 included in this review (59 confirmed by renal biopsy, one by recurrence upon reinitiating proton pump inhibitor). The most common symptoms were non-specific. The mean proton pump inhibitor treatment duration before diagnosing nephritis was 13 weeks, average recovery time was 35.5 weeks, one patient required permanent dialysis, there were no deaths.

Conclusion
Proton pump inhibitor-related interstitial nephritis is rare, idiosyncratic and difficult to predict. It requires a high level of clinical suspicion. While there is not sufficient evidence to establish a causal relationship with certainty, there does appear to be a low-prevalence association.

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BACKGROUND

Proton pump inhibitors (PPIs) are widely used around the world. In the United States in 2005 there were 95 300 000 reported prescriptions and sales totalled approximately 12.9 billion dollars, doubling the 2004 sales mark and making PPIs the second-most widely sold medication group.[1] These medications are very potent suppressors of gastric acid secretion, and are highly effective for the treatment of acid-related gastrointestinal disorders. PPIs are generally safe and well tolerated, with a side effect rate of approximately 3%. The most common side effects include headaches, dizziness, diarrhoea, constipation and cutaneous reactions.[2] At a lesser frequency, PPI use can result in hepatic dysfunction, vertigo, confusion and haematological disorders. On rare occasions PPIs may cause idiosyncratic reactions such as multiform erythema, pancreatitis, Stevens-Johnson Syndrome and interstitial nephritis.[3]

Medication-induced acute interstitial nephritis is a known cause of acute renal failure which, if diagnosed early and the inducing agent withdrawn promptly (in the first week), can have a favourable prognosis. Nevertheless, in cases where the provoking agent is not detected or if the patient is exposed to it repeatedly, the prognosis may be poor, even to the point where in some cases a renal transplant might be required.

The available studies suggest that acute interstitial nephritis accounts for 6–8% of cases of acute renal failure.[4, 5] The diagnosis of acute interstitial nephritis is most common in renal failure with inactive urinary sediment (haematuria or proteinuria); in this setting, it has been reported to occur in 27% of cases.[6] In contrast, acute interstitial nephritis occurs in 1% of renal biopsies performed for evaluation of haematuria or proteinuria.[7] While acute interstitial nephritis is most often induced by medications (this accounts for over two-thirds of cases), it can also be due to infections, tubulointerstitial nephritis and uveitis syndrome, sarcoidosis or it may be idiopathic.[8, 9] Among the most commonly implicated medications are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and PPIs.[8]

Following a recent rise in the use of PPIs, a number of individual case reports, case series and commentaries of PPI-induced acute interstitial nephritis have been reported in the literature.[9–49] This has alerted the medical community to this serious complication and has placed PPIs among the principal causes of medication-induced reversible acute renal failure.

Based on this background, the objective of the present study was to establish the real nature of the relationship (associative or causal) between PPI use and the development of interstitial nephritis. To achieve this objective, we performed an exhaustive search of the literature, exploring all of the studies whose principal theme was the development of interstitial nephritis following treatment with PPIs. We established no limits with respect to study design, population studied or language.

METHODS

Data source

Two researchers independently searched the following electronic databases for articles written between 1970 and 2006: MEDLINE, EMBASE, GOOGLE, LILACS and COCHRANE. In addition, a manual search was completed for graduate theses and available studies (in the reference library of the University of the Andes – Fundación Santa Fe de Bogotà), conference presentations, Internet-based communications with some of the most important authors on the topic, and the FDA. No limits were established according to the study design, the sample population or the language.

In the electronic search, the following MESH terms were used: 'proton pump inhibitor AND interstitial nephritis', 'omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole AND interstitial nephritis' (each one in separate searches), 'proton pump inhibitor AND acute renal failure', 'drugs AND interstitial nephritis', 'interstitial nephritis AND acute renal failure', 'interstitial nephritis'.

Selection of studies

We reviewed all available studies, independent of their methodological design, in which we could confirm that previous exposure to PPIs in patients without initial baseline renal failure was accompanied by the development of interstitial nephritis and acute renal failure determined by laboratory tests (creatinine and/or glomerular filtration rate) plus either renal biopsy or recurrence upon reinitiating PPI. Recovery from renal failure had to accompany the timely suspension of the inducing agent (medication). A renal biopsy was considered positive for acute interstitial

nephritis when the histology demonstrated interstitial infiltrations primarily of lymphocytes and eosinophils, along with macrophages and plasmatic cells, associated with interstitial oedema or tubulitis. The only exclusion criterion was the lack of diagnostic confirmation by renal biopsy.

Quality control and validity analysis were carried out by two independent investigators who classified the studies according to study design and associated levels of evidence.[50, 51] The search did not yield any randomized-controlled, cohort or case–control studies. Only case reports and case series with low levels of evidence and low external/internal validity were found.

Statistical analysis

Descriptive statistics (mean values and proportions) were used to summarize and describe the quantitative characteristics of the studies. A qualitative study assessment was performed based upon the classification of causal criteria for adverse effects of medications from the World Health Organization, which rates causality as certain, probable, possible, improbable and conditional of insufficient (Table 1).[52]

RESULTS

We found 64 reported cases of PPI-associated interstitial nephritis in the worldwide literature. Sixty cases met inclusion criteria. The nephritis diagnosis was confirmed by renal biopsy in 59 of the cases;[3, 4, 13, 17, 18, 21, 22, 24–27, 29, 30, 32, 35, 36, 45, 46, 48] one case demonstrated the effect upon re-administering PPIs without any other factors associated.[49] Of these 60 cases, 47 were associated with omeprazole, six cases with pantoprazole, three with esomeprazole, two with lansoprazole and two with rabeprazole. The most frequent indication was treatment of acid-peptic disorders (ulcers, gastritis and gastro-oesophageal reflux). Of the 60 cases, 24 patients (40%) were males and 36 (60%) were females. The mean age of the patients was 78 years (interquartile range: 63–89 years). The mean duration of the PPI treatment before the onset of nephritis was 13 weeks, with a minimum exposure time of 2 weeks and a maximum of 52 weeks. In 66% of the patients the exposure was <12 weeks. The most common symptoms were non-specific: nausea and emesis in 18 cases (30%) and malaise in 14 (23%); six cases (10%) were asymptomatic (Figure 1).

Table 1. Classification of causal criteria for adverse effects of medications[52]

Classification	Criteria
Certain	Clinical event which includes abnormalities in the laboratory that occurs in a coherent temporal relation to the administration of the drug, and that cannot be explained by concurrent illness, drugs or other chemicals
	The response to withdrawal of the medication can be clinically demonstrated
	That the phenomenon be pharmacologically demonstrable, using the re-administration of the medication if necessary
Probable	Clinical event that includes abnormalities in the laboratory that occurs within a 'reasonable' time period after the administration of the drug, and for which it 'would be improbable' to explain by concurrent illness, drugs or other chemicals
	In clinical follow-ups there is a reasonable response upon withdrawal of the medication
	It is not necessary to re-administer the drug
Possible	Clinical event including abnormalities in the laboratory, occurring within a reasonable time period upon administering the medication, but which can be explained by illness, other medications or concomitantly used chemicals
	Information about suspending the drug is hidden or is unclear
Improbable	Clinical event including abnormalities in the laboratory, within a reasonable time period upon administering the drug, but for which a causal relation is improbable due to the fact that other drugs, chemicals or illness can provide a causal explanation
Conditional	Clinical event including abnormalities in the laboratory, reported as an adverse reaction to the drug but for which more essential data are necessary to make an appropriate evaluation or for which additional data are beginning to be evaluated
Insufficient	The report suggests an adverse reaction that cannot be judged because the information is insufficient or cannot be verified or corroborated

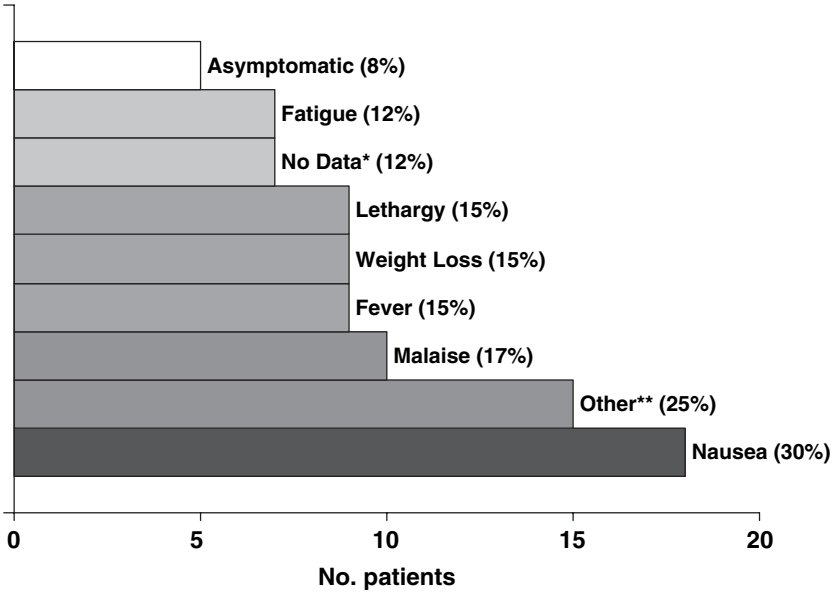

Figure 1. Presenting symptoms in 60 cases of proton pump inhibitor-associated acute interstitial nephritis. * Data regarding symptomatology unavailable for these cases: ** Other symptoms included anorexia, polyuria and diaphoresis.

The most common urine analysis abnormalities were: pyuria (considered as >5 leucocytes/field in non-centrifuged urine or >10 cells/field in centrifuged urine) in 36 cases (61%), proteinuria in 18 cases (30%), eosinophiluria in 13 cases (21%) and haematuria in 10 cases (17%). There were 17 cases (28%) for which urine analysis was not reported. The most common laboratory abnormality was normocytic normochromic anaemia, reported in 22 cases (37%).

Of the 60 cases included in the review, 59 were confirmed by histology. A biopsy was considered to be positive for acute interstitial nephritis when the histology demonstrated interstitial infiltrations, principally of lymphocytes and eosinophiles, along with macrophages and plasmatic cells, associated with interstitial oedema or tubulitis. Histological findings were distributed as follows: lymphocytic infiltration in 59 cases (100%); eosinophilic infiltration in 47 cases (80%).

The associated comorbidities that could impair renal function were: arterial hypertension (51%); hypercholesterolaemia (10%); coronary illness (8%); diabetes mellitus (5%); neoplasia (5%) and nephrolithiasis (2%). Of the 60 patients in the sample, 34 (56%) were taking one or more medications that could potentially cause interstitial nephritis in addition to a PPI, 18 (31%) were taking other medications not known to cause interstitial nephritis and eight (13%) were taking a PPI without any other medications (Figure 2a). Of the 34 patients taking one or more medications that could be associated with acute interstitial nephritis, 15 (44%) were on thiazide or loop diuretics, nine (26%) on angiotensin receptor blockers (ARB), six (18%) on angiotensin-converting enzyme inhibitors (ACE-I), five (15%) on NSAIDs and four (12%) on antibiotics (Figure 2b).

Renal function was measured during follow-up tests of creatinine levels. The mean initial creatinine level was 1.2 mg/dL, with a mean elevation related to the onset of nephritis of 6.0 mg/dL. There was a mean subsequent recovery of 2.1 mg/dL in an average follow-up time of 35.5 weeks (interquartile range: 24–52 weeks). In all cases, PPIs were withdrawn following the diagnosis of interstitial nephritis (in three cases they had been withdrawn within 2–3 weeks of initiation). In 13% of the cases other associated medications were withdrawn. Corticoids were prescribed for treatment of nephritis in 20 cases (34%). Three patients required dialysis treatment in the initial phases, but only one ended up on permanent dialysis. There were four cases of documented decreased renal function upon re-administration of PPIs.[24, 32, 35, 48] There were no reports of death due to acute renal failure in the sample.

Based on qualitative study assessment, the relationship between PPIs and interstitial nephritis could be classified as certain in 12 cases, probable in nine, possible in 37, conditional in one and insufficient in one (Table 2). Details of cases with a certain or probable association are shown in Table 3.

DISCUSSION

Acute interstitial nephritis is responsible for approximately 15% of acute renal failure cases.

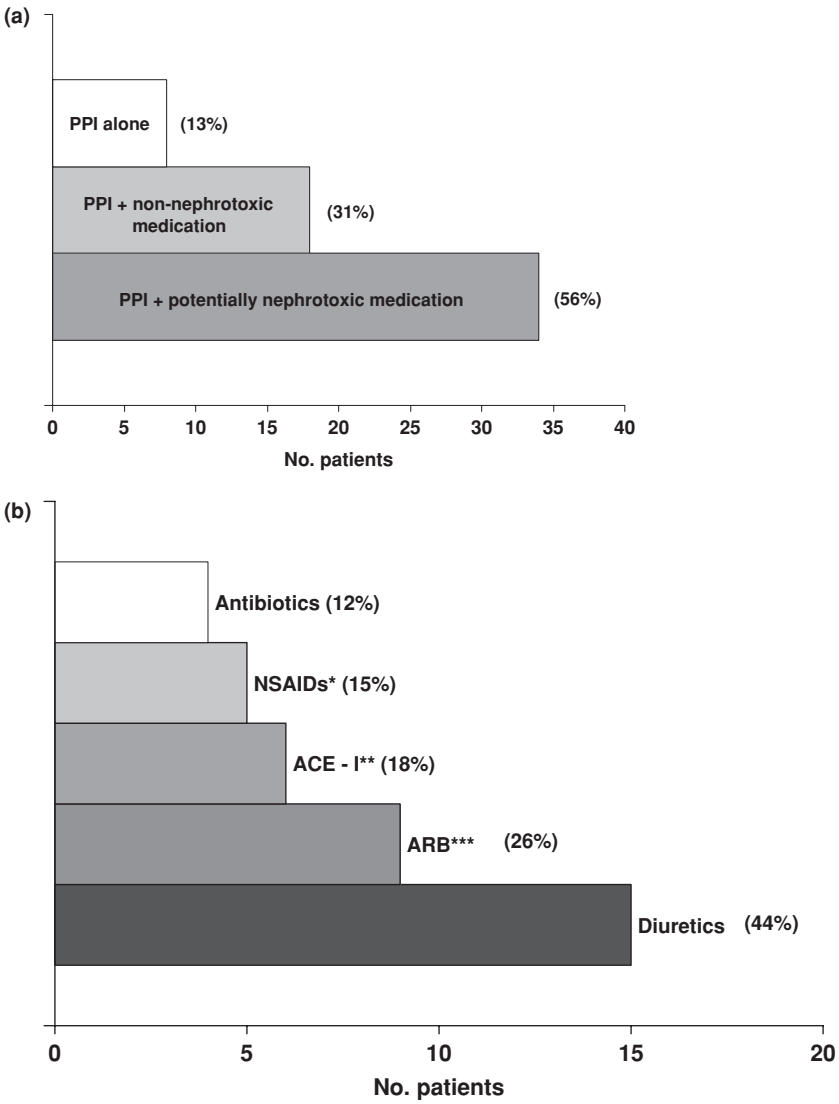

Figure 2. (a) Concomitant medications in 60 patients who developed acute interstitial nephritis following exposure to a proton pump inhibitor (PPI). (b) Concomitant medications in 34 patients who developed acute interstitial nephritis following exposure to a PPI along with one or more drugs capable of causing acute interstitial nephritis.

Hypersensitivity or adverse reactions to medications, although idiosyncratic and potentially reversible, is the most common cause. Animal pathophysiological studies suggest that the medication and its metabolites can act as haptens, mimicking certain renal antigens or depositing themselves in the renal interstice as immune complexes, creating an inflammatory reaction which is responsible for the renal damage. Among the medications most commonly involved are betalactamics, sulphonamides, diuretics, angiotensin converting enzyme inhibitors and non-steroidal anti-inflammatory agents. Although they are generally safe and widely tolerated, in the last few years, PPIs have been implicated as causal agents in cases of interstitial nephritis. The first case was reported in 1992 involving omeprazole.[49] Later documented cases report this adverse effect for the five types of PPIs in current use: omeprazole, pantoprazole, esomeprazole, lansoprazole and rabeprazole.

The existing literature does not contain a global report on the annual prescription of PPIs, but data from the US show that these are the second most sold medications after HMG CoA reductase inhibitors, with 144 458 formulas prescribed and a total sales volume of 12.9 billion USD in 2005.[1] In Australia, PPIs are the third most frequently prescribed medications after angiotensin II inhibitors and statins.[11] One of the largest case series in our sample was reported in Auckland, New Zealand.[17] Surveys from that country reveal that approximately 750 000 units of PPIs are prescribed per month.[3] All of these reports underscore a very high usage of PPIs worldwide.

Table 2. Causal relationship between PPIs and acute interstitial nephritis based on the World Health Organization classification[52] (see Table 1 for details of classification)

Classification	Number of cases
Certain	12
Probable	9
Possible	37
Improbable	0
Conditional	1
Insufficient	1

Our review has some limitations. Studies with high level of evidence (such as randomized trials) addressing the research question could not be found. All of the information found came from observational case reports and case series that cannot control for confounding factors, both known and unknown. These studies have low internal validity and provide insufficient evidence strength to establish causality (level of evidence 3–4 with type D recommendation),[50] and then may be subject to bias (publication, selection and methodological biases). Additionally, the studies exhibit variability in population, intervention and measurements of results, making comparisons difficult. In some cases, due to the retrospective nature of the

Table 3. Cases of PPI-induced acute interstitial nephritis with a certain or probable association based on the World Health Organization classification[52] (see Table 1 for details of classification)

WHO classification	Reference	Age (years)	Gender	Time to onset (weeks)	Comorbidities	Other drug exposures	Time to recovery (weeks)
Certain	3	79	M	3	Gastritis		52
Certain	3	78	M	2	Dyspepsia	Simvastatin	16
Certain	12	89	F	not available	HTN	Verapamil	24
Certain	12	49	F	4			24
Certain	22	63	F	8			24
Certain	4	77	F	36			156
Certain	4	57	M	2			120
Certain	27	74	M	12			12
Certain	32	77	F	8	Malaria	Cefuroxime	6
Certain	35	70	F	2	HTN, gastritis	Lisinopril	4
Certain	48	86	F	8	Pneumonia	Erithromycin	3
Certain	49	74	F	24	HTN	Amiloride, HCTZ	2
Probable	3	86	F	1.5	A fib	Sotalol	Not specified
Probable	3	74	M	24		Ibuprofen, amoxicillin/clavulanate	96
Probable	3	77	F	28	HTN, PUD	Candesartan, felodipine, metoprolol	12
Probable	3	80	M	8	Myelodysplasia, polymyalgia, CAD	Prednisona, metoprolol	16
Probable	12	65	F	6	HTN, hypercholesterolaemia	Atenolol, calcium, zolpidem, pravastatine	24
Probable	12	80	F	16	DM, A fib, hypercholesterolaemia	Iron, metformin, rosiglitazone, simvastatin	Not specified
Probable	29	31	F	8	HTN, history of pre-eclampsia	Nifedipine	2
Probable	30	73	M	12	BPH	Tamsulosin, norfloxacin	16
Probable	46	75	M	2	Prostate adenocarcinoma, oesophageal ulcer		2

HTN, hypertension; A fib, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; BPH, benign prostatic hypertrophy; HCTZ, hydrochlorothiazide.

reports, the temporal relation between nephritis and the use of PPIs made it difficult to establish causality and determine whether the interstitial nephritis was due to another medication.[13, 24, 25, 35, 45] In other reports, there were a number of confounding factors that could neither be measured nor controlled.[3, 4] The administration and subsequent discontinuation of various medications that could provoke interstitial nephritis in conjunction with PPIs could alter our conclusions, given that interstitial nephritis is an idiosyncratic reaction that is independent of the dosage and the time of exposure to the agent. In some reports, not all of the necessary variables to confirm a causal relationship were documented. Additionally, considering that our sample was a collection of cases, the inherent heterogeneity could have altered the results. Such heterogeneity implies that for each case the effect was measured in a different manner, after exposure to different types of PPIs, with different environmental exposures, and with the potential for biological variation. Overall, 64 cases published in the last 15 years were identified; 60 of these met inclusion criteria and were used in the final analysis. The relationship between PPIs and interstitial nephritis could be classified as certain in 12 cases, probable in nine, possible in 37, conditional in one and insufficient in one (Table 2).

Despite the limitations that we outline above, several conclusions can be made based upon careful consideration of the available data.

Proton pump inhibitor-induced interstitial nephritis appears to be rare. Of note, the numerator of this relation (the number of cases) could be biased by the lack of reports. However, so might the denominator because of the widespread use of PPIs that implies a low prevalence of this particular complication. The fact that the same effect was reported for the five proton inhibitors suggests a possible effect of medication class rather than of each individual agent.[13] PPI-induced interstitial nephritis is an idiosyncratic reaction of hypersensitivity to the medication or its metabolites and is not related to the time of exposure or the dosage, making it difficult if not impossible to identify the risk factors for its occurrence.

With regard to the population characteristics, interstitial nephritis appeared in a larger proportion of females (M:F = 1:1.5) and it was more frequent in older patients who are more susceptible to adverse effects, given multiple comorbidities and polypharmacy. Additionally, in older patients the renal interstice is more vulnerable to damage due to compromised peritubular blood flow, which permits a larger exposure time between the medication and the interstice.[3] More than half of the sample of patients were on other medications capable of causing acute interstitial nephritis or had comorbidities known to be risk factors for the development of renal failure.

The initial symptoms were non-specific (mainly nausea and emesis followed by general discomfort and fever). The classically described presentation of medication-induced interstitial nephritis, characterized by fever, joint pain and cutaneous eruptions was infrequent. It is worth noting that the most common symptoms for this disorder were often identical to the ones for which PPIs are prescribed. As such, doctors must be alerted to any possible association, considering the importance of renal functioning (creatinine, urine analysis), before making a decision regarding the medication (whether to increase dosage and/or change to another proton inhibitor).

Proton pump inhibitor-induced interstitial nephritis has a good prognosis. A complete and rapid recovery generally occurred upon withdrawal of the medication, although in some patients (one-third) corticoids were prescribed. This is still a controversial therapy. Only three patients required dialysis,[3, 17, 22] possibly due to delays in the discontinuation of the medication after the diagnosis of acute renal failure. Of these, only one patient required permanent dialysis.

Overall, based on this review it would appear that PPI-associated interstitial nephritis is a rare, idiosyncratic and difficult to predict phenomenon. As such, we hope that gastroenterologists, nephrologists and any doctors involved in the care of patients who take PPIs are all alert to the symptoms that may suggest interstitial nephritis in the first weeks following the initiation PPI therapy, so that an early and opportune diagnosis can be made. This requires a high level of clinical suspicion and careful management. While there is no sufficient evidence to establish with certainty a causal relationship, there does appear to be a low-prevalence association between the use of PPIs and the development of interstitial nephritis and associated acute renal failure.

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