

Proton Pump Inhibitors and Acute Interstitial Nephritis

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See CME exam on page 525.

Background & Aims: Proton pump inhibitors (PPIs) are a widely prescribed class of drugs, and their usage worldwide is increasing. Although well-tolerated, there have been case reports and a recent case series implicating these drugs in acute interstitial nephritis (AIN) and progression to acute renal failure (ARF). The aim of this study was to investigate how widespread this complication is in Australia, to identify which PPIs are implicated, and to establish whether PPI-induced AIN is a class effect. **Methods:** We undertook a retrospective case review of potential cases at 2 teaching hospitals and a review of registry data from the Therapeutic Goods Administration of Australia (TGA). Parameters sought included the drug implicated, concurrent medications, symptoms, signs, serum creatinine, and time of onset after prescription. **Results:** We identified 18 cases of biopsy-proven PPI-induced AIN causing ARF in the retrospective case review, which is the largest hospital-based case series to date. The TGA registry data identified an additional 31 cases of “biopsy proven interstitial nephritis.” An additional 10 cases of “suspected interstitial nephritis,” 20 cases of “unclassified acute renal failure,” and 26 cases of “renal impairment” were also identified. All 5 commercially available PPIs were implicated in these cases. **Conclusions:** With the ever more widespread use of this class of medications, PPI-induced AIN is likely to become more frequent. There is now evidence to incriminate all the commercially available PPIs, suggesting there is a class effect. Failure to recognize this entity might have catastrophic long-term consequences including chronic kidney disease. Increased awareness might facilitate more rapid diagnosis and management of this potentially reversible condition.

The proton pump inhibitor (PPI) class of drugs is extensively used in internal medicine and surgery and has been commercially available for approximately 20 years. These drugs are the third most frequently prescribed class of drugs in Australia (behind angiotensin-converting enzyme inhibitors and hydroxymethyl-

glutaryl-CoA reductase inhibitors).¹ Their use has increased dramatically in recent years with the introduction of additional members into the class that are superceding H₂ receptor antagonists (H₂RAs). They have several therapeutic indications including treatment of duodenal and gastric ulceration, severe reflux esophagitis, scleroderma-induced esophagitis, Zollinger-Ellison syndrome, prevention of gastric ulcers induced by nonsteroidal anti-inflammatory drugs, and enhancing antibiotic therapy in the eradication of *Helicobacter pylori* infection.^{2,3} The PPI class of drugs are well-tolerated, and reported side effects occur in less than 5% of patients, with headache, dizziness, and diarrhea the most commonly reported.⁴⁻⁹ PPIs, together with H₂RAs, comprise a large proportion of national pharmaceutical expenses in most Western countries.¹⁰

Historically acute interstitial nephritis (AIN) was predominantly associated with infections, but with the widespread use of antibiotics this etiology is seen less commonly. Medications are now responsible for the majority of cases of AIN. Studies suggest that AIN is the cause of 6%–8% of episodes of acute renal failure (ARF).^{11,12} The diagnosis of AIN seems to be most prevalent in renal biopsies in which there is unexplained renal impairment in the presence of an inactive urinary sediment, ie, lack of heavy proteinuria, significant hematuria, or presence of dysmorphic red blood cells. In this setting AIN has been reported to occur in as many as 25% of cases.¹³

Although as a class PPIs are well-tolerated, there have been case reports and a recent case series implicating these drugs in AIN progressing to ARF.¹⁴⁻³⁷ The first of these, in 1992, implicated omeprazole in the etiology of ARF caused by biopsy-proven AIN.¹⁴ In 2004, lanso-

Abbreviations used in this paper: AIN, acute interstitial nephritis; ARF, acute renal failure; CKD, chronic kidney disease; GFR, glomerular filtration rate; H₂RA, H₂ receptor antagonist(s); PPI, proton pump inhibitor(s); TGA, Therapeutics Goods Administration.

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prazole and pantoprazole were also implicated in AIN.^{11,36} PPIs featured as the most common cause of drug-induced AIN in the previous largest hospital series.¹¹

The aim of this study was to investigate how common PPI-related AIN is in Australia, to identify which PPIs are implicated, and to establish whether enough evidence is available to support the hypothesis that PPI-induced AIN is a class effect.

Methods

We performed a retrospective case review of potential cases at 2 teaching hospitals and reviewed national registry data from the Therapeutic Goods Administration of Australia (TGA) to identify cases of PPI-related AIN.

Gosford Hospital is a 452-bed teaching hospital that serves an expanding population (250,000 people in 1993 and 310,000 in 2004). Because a single nephrologist performed the renal biopsies during 1993–2003, this time period was chosen. Westmead Hospital is a 975-bed tertiary referral center that serves a population of 1.5 million people. It is the largest teaching hospital in Australia and employs 7 renal physicians.

Once cases of biopsy-proven PPI-induced AIN were identified, demographics and clinical parameters were extracted and recorded including symptoms, signs, PPI implicated, concurrent medications, serum creatinine, and estimated time of onset after prescription (where available) by review of clinical files/case notes and computer records. Case notes were carefully reviewed to ensure that the only medication change recently made was the initiation of the PPI. The diagnosis of AIN was made by independent pathologists and was retrospectively sourced for the sake of this review.

Second, registry data from the TGA of Australia were reviewed from 1991–2004.³⁸ The TGA is a unit of the Australian Government Department of Health and Ageing. It carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard, with the aim of ensuring that the Australian community has access to therapeutic advances within a reasonable time. In Australia, there is a process of voluntary self-reporting of adverse drug reactions by medical practitioners to the Adverse Drug Reactions' Advisory Committee. The analysis undertaken comprised a data search through the TGA database of medical practitioner–reported cases of drug-induced AIN; these cases were then sorted for reported cases in which PPIs were implicated. The cases of PPI-induced renal disorders were classified as: “biopsy-proven interstitial nephritis,” “suspected interstitial nephritis,” “unexplained acute renal failure,” and “renal impairment.” Cases were excluded if there was concurrent multiorgan failure because renal biopsies were rarely performed in these circumstances. The TGA registry data were sorted to exclude any hospital-based cases.

These data were reviewed, and symptoms, signs, PPI implicated, concurrent medications, serum creatinine, and time of onset after prescription were extracted and recorded.

Summary results were expressed as mean with standard deviation unless otherwise indicated. Glomerular filtration rate (GFR) was calculated by using the Cockcroft-Gault equation for each patient at baseline, time of presentation to hospital, and 3 months and 6 months after initial presentation.³⁹ After testing that the assumption of normalcy held, paired *t* test was performed to examine change in GFR. Simple linear regression was performed to identify patient factors associated with poor recovery of renal function.

Results

Of a total of 28 cases of biopsy-proven AIN identified between the 2 hospitals, 18 (64%) cases were associated with PPI use (Table 1). There were 11 cases of omeprazole-associated, 3 cases of pantoprazole-associated, 3 cases of esomeprazole-associated, and 1 case of rabeprazole-associated AIN. The median age of the patients was 74 years (interquartile range, 65–79 years). The mean duration of PPI therapy before presentation was 11 weeks. The most common presenting symptoms were nonspecific; tiredness and nausea were present in 7 (39%) and weight loss in 4 (22%) of the cases (Table 2). The most common abnormalities detected on dipstick urinalysis were pyuria in 13 (72%), proteinuria in 12 (67%), and eosinophiluria in 11 (61%) cases. The most common laboratory abnormality was a normochromic normocytic anemia that was found in 16 (89%) of the cases and an increased C-reactive protein in 14 (78%) of the cases. On renal biopsy 15 of 18 (83%) patients had evidence of eosinophils in the interstitium, which is highly suggestive of AIN. To provide some idea of how prevalent PPI-induced AIN was at one of the teaching hospitals, we sought information on the number of biopsies performed for the last 10 years (1994–2004) and identified 15 of 673 (2.2%) biopsies that were done for PPI-induced AIN.

The majority of patients exhibited some recovery of renal function by 3 months after diagnosis of AIN and withdrawal of the PPI. However, calculated GFR remained significantly reduced at both 3 months (mean reduction, 15.9 mL/min; 95% confidence interval, 7.9–23.9; $P < .001$) and 6 months (mean reduction, 11.5 mL/min; 95% confidence interval, 1.1–21.9; $P < .03$) after initial presentation when compared with baseline renal function (Figure 1).

Simple linear regression revealed no association between GFR 3 months after presentation and age ($P = .14$) or gender ($P = .99$), but it did show an association with level of hemoglobin at presentation. Those patients with a hemoglobin of <110 g/L at time of presentation with AIN had a 22 mL/min greater reduction in GFR at 3 months than those with hemoglobin >110 g/L ($P =$

Table 1. Patient PPI Dosage, Indications, Comorbidities, and Co-medications From Hospital Case Series

PPI used	Age (y)/sex	Dose (mg/day)	Indications	Prior exposure duration (wk)	Comorbidities	Other medications
Esomeprazole	63/M	NA	GERD	6	Chronic lower back pain	Amlodipine irbesartan, rofecoxib
Esomeprazole	63/F	NA	GERD	3	HTN, hypercholesterolemia	Atorvastatin, irbesartan
Esomeprazole	83/F	20	Dyspepsia	16		Amitriptyline, calcium, clopidogrel, digoxin, Disodium etidronate, iron
Omeprazole	77/M	20	Dyspepsia	4	HTN, hypothyroidism, hypoparathyroidism	<i>Aspirin</i> , felodipine, irbesartan, sertraline
Omeprazole	74/M	20	GERD	8	Gout, nephrolithiasis	<i>Naproxen</i> as required (but not in last 3 wk)
Omeprazole	78/M	40	GERD	16		Gliclazide, iron sulphate
Omeprazole	73/M	40	GERD	10	Prior thromboembolic disease	Enalapril, nifedipine, simvastatin, warfarin
Omeprazole	89/F	40	GERD	NA	HTN	Sodium bicarbonate, verapamil
Omeprazole	49/F	20	Dysphagia	4		
Omeprazole	72/F	20	GERD	24	HTN, hypercholesteremia	Atenolol, captopril, indapamide, simvastatin
Omeprazole	80/F	20	GERD	12	HTN, hypercholesteremia	Frusemide, metoprolol, rofecoxib, simvastatin
Omeprazole	65/F	20	GERD	6	HTN, hypercholesteremia	Atenolol, calcium, pravastatin, zolpidem
Omeprazole	71/M	20	GERD	8	HTN, osteoarthritis	Diltiazem, perindopril, rofecoxib, telmisartan
Omeprazole	74/F	20	GERD	8		Sertraline
Pantoprazole	77/M	80	GERD	8	HTN, IHD, chronic lower back pain	Irbesartan, nifedipine, quinine
Pantoprazole	79/F	40	Dyspepsia	12	HTN, hypothyroidism, hypoparathyroidism	Calcium, hydrochlorothiazide, irbesartan, Thyroxine
Pantoprazole	80/F	NA	GERD	16	Diabetes, atrial fibrillation, hypercholesterolemia, diverticular disease	Iron, metformin, rosiglitazone, simvastatin
Rabeprazole	62/M	40	GERD	12	HTN, IHD, transient ischemic attack, migraine, hypothyroidism	<i>Aspirin</i> , diazepam, estrogen, prochlorperazine, propranolol, simvastatin, thyroxine

NOTE. Italics indicates medications also reported as commonly causing AIN.⁴¹

GERD, gastroesophageal reflux disease; HTN, hypertension; IHD, ischemic heart disease; NA, not available.

.04). Figure 2 shows the relationship between hemoglobin at presentation and reduction in GFR at 3 months. The small number of patients precluded more complex analysis of possible predictors of poor recovery.

From the TGA registry data we identified 34 cases of biopsy-proven AIN associated with PPI use (Table 3). Of these, 28 cases were associated with omeprazole, 3 cases with rabeprazole, 2 cases with esomeprazole, and 2 cases with pantoprazole. There were an additional 10 cases of suspected interstitial nephritis that were not biopsy-proven (4 cases associated with rabeprazole, 3 cases with pantoprazole, 2 cases with esomeprazole, and 1 case with omeprazole). The remaining 2 classifications from the registry data associated with PPI use were “unclassified acute renal failure” and “renal impairment” (20 and 26 cases, respectively).

Discussion

This is the first report to highlight that all 5 of the commercially available PPIs have been implicated in

causing AIN. From our hospital-based series and TGA registry data we have identified omeprazole-induced, pantoprazole-induced, esomeprazole-induced, and rabeprazole-induced AIN. The MEDLINE medical literature review we performed has also implicated lansoprazole.¹¹ Although isolated case reports have been published on omeprazole-induced AIN, there is now sufficient evidence to support our hypothesis that PPI-induced AIN is a class effect. Because of the limited number of patients in our case series, complex statistical analysis could not be undertaken. However, this study notes the association of a low hemoglobin with worse renal recovery at 3 months ($P = .04$).

In our series, 18 of 28 cases of biopsy-proven AIN were associated with PPI use (Table 1); this was the largest series of PPI-induced AIN presented to date. The most commonly implicated agent was omeprazole, followed by esomeprazole, pantoprazole, and rabeprazole. The presenting complaints were nonspecific in nature, including tiredness, nausea, and weight loss. The most

Table 2. Characteristics of Clinical Presentation of PPI-Induced AIN in Hospital Series

Age (y)/sex	Symptoms/signs	Laboratory findings/urinalysis	Estimated GFR (mL/min)				Biopsy findings	Hemoglobin (g/L)
			Baseline	Presentation	3/12	6/12		
63/M	Nausea, vomiting, weight loss, oliguria	ANE, LEU	40	4	7	6	L+++E++	90
63/F	Nausea, occasional vomiting	ANE	40	2	15	18	L+++E++	87
83/F	Unsteady, malaise	ANE, LEU, EU, HEM, PY	17	5	9	NA	L+++E+++H+	118
77/M	Confusion, lethargy, malaise, nausea, fever	ANE, ESR, LEU, EU, HEM, PRO, PY	26	6	34	40	L+++P+H+E+N+	119
74/M	Anorexia, nocturia, thirst, weight loss	CRP, ESR, LEU, EU, PRO, PY	37	19	29	34	L+P+E+	141
78/M	Hematemesis, fever	ANE, ESR, EU, PY	61	11	NA	NA	L+++E+++	82
73/M	Fatigue, lethargy	ANE, CRP, EU, GLY, PRO, PY	50	12	33	50	L+++P+	129
89/F ^a	NA	ANE, ESR, LEU	23	4	20	21		117
49/F	Fatigue, thirst	ANE, ESR, EU, GLY, PRO, PY	NA	5	22	25	L++P++E+	107
72/F	Fatigue, lethargy	ESR, EU, PRO, GLY, PY	39	9	28	25	L++P++E+	147
80/F	Fatigue, malaise	ANE, ESR	26	8	13	16	L++P++	108
65/F	Backache, lethargy, nausea	ANE, CRP, ESR, LEU, EU, HEM, PRO, PY	45	10	51	68	L++P+++H+E+	121
71/M	Nausea, metallic taste in mouth, hypertension	ANE, CRP, ESR, EU, PRO, PY	37	10	22	23	L+++P+E++	119
74/F	Nocturia	ANE, ESR, EU, PRO, PY	16	9	16	15	L+++P+N+E+	115
77/M	Anorexia, lethargy, malaise, nausea, pruritis, weight loss	ANE, ESR, LEU, EU, GLY, PRO, PY	35	12	25	28	L+++P++E+	87
79/F	Fatigue, lethargy, thirst	ANE, ESR, LEU, EU, PRO, PY	33	13	24	28	L++P+E+N+	121
80/F	Lethargy	ANE	50	10	11	10	L+E+++N+++H+	93
62/M	Frequency, nausea	ANE, CRP, ESR, PRO, EU, PRO, PY	54	23	37	44	L+++P+E+N+	129

ANE, anemia; CRP, increased C-reactive protein; ESR, raised erythrocyte sedimentation rate; EU, eosinophiluria; GLY, glycosuria; HEM, hematuria; LEU, leukocytosis; NA, not available; PRO, proteinuria; PY, pyuria; E, eosinophils in interstitium; H, red blood cell casts; L, lymphocytes in interstitium; N, neutrophils in interstitium; P, protein casts; +, few; ++, moderate; +++, plentiful.

^aOnly case not biopsy-proven.

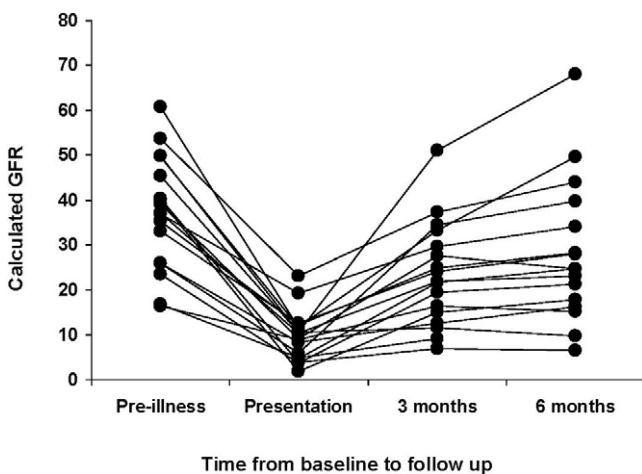


Figure 1. GFR calculated by using Cockcroft-Gault equation highlighting the change from pre-illness to 6 months after presentation.

common laboratory abnormalities were pyuria, eosinophiluria, and proteinuria.

The major limitation of this review is the retrospective nature of the contemporaneous relationship between PPI use and the subsequent development of AIN. However,

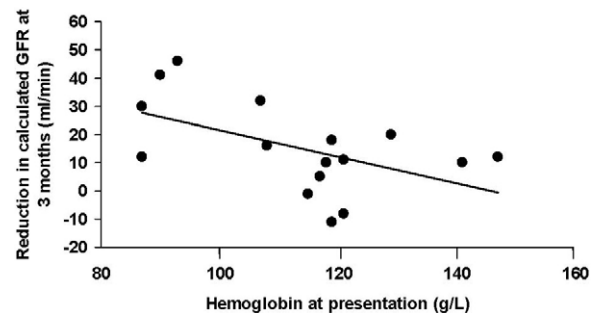


Figure 2. Relationship between hemoglobin at presentation and reduction in GFR at 3 months after presentation.

Table 3. PPI and Comorbidities of Biopsy-Proven AIN Cases From the TGA Registry

PPI	Age (y)/sex	Dosage (mg/day)	Other medications
Esomeprazole	65/M	20	Gliclazide, metformin
Esomeprazole	62/F	40	Atorvastatin, irbesartan
Omeprazole	77/F	20	Enalapril, estrogen, <i>indomethacin</i>
Omeprazole	76/F	40	Carbidopa/levodopa, digoxin, diltiazem, glyceryl trinitrate, indapamide, lisinopril, spironolactone
Omeprazole	51/M	20	Iron
Omeprazole	74/F	20	Cephalexin, metoclopramide, temazepam
Omeprazole	47/F	40	Ranitidine, <i>piroxicam</i> , tiaprofenic acid
Omeprazole	75/F	20	<i>Aspirin</i> , calcium, fosinopril
Omeprazole	61/F	40	Estrogen, folic acid, fluorouracil, progesterone
Omeprazole	72/M	40	Amoxicillin, cisapride, metronidazole
Omeprazole	50/F	40	Estrogen, medroxyprogesterone
Omeprazole	71/M	20	<i>Allopurinol</i> , <i>aspirin</i> , diltiazem, dothiepin, enalapril, <i>frusemide</i>
Omeprazole	70/F	20	
Omeprazole	66/M	20	Paroxetine, verapamil
Omeprazole	56/F	20	Celecoxib, estrogen, methotrexate, rofecoxib
Omeprazole	65/F	20	Calcium, felodipine, salbutamol, telmisartan
Omeprazole	77/F	40	<i>Aspirin</i> , irbesartan, simvastatin, thyroxine, verapamil
Omeprazole	86/F	20	Atenolol
Omeprazole	51/M	20	Warfarin
Omeprazole	65/F	20	
Omeprazole	60/M	NA	Calcium, leflunomide, prednisolone
Omeprazole	NA	20	Docusate sodium, insulin, iron, temazepam, timolol, verapamil
Omeprazole	71/F	NA	<i>Aspirin</i> , thyroxine
Omeprazole	67/F	40	Methotrexate, prednisolone
Omeprazole	73/M	20	Clomipramine, fluticasone
Omeprazole	78/M	NA	<i>Aspirin</i> , atorvastatin, paroxetine, perindopril
Omeprazole	63/F	NA	<i>Aspirin</i> , bendrofluazide, doxepin, oxazepam, prednisolone
Omeprazole	71/F	20	Amitriptyline, diazepam
Omeprazole	57/M	40	
Pantoprazole, Omeprazole	62/M	40	Nystatin
Pantoprazole	76/M	40	<i>Aspirin</i> , atorvastatin, felodipine, prochlorperazine, tiludronate
Rabeprazole	35/F	40	Metoclopramide
Rabeprazole	NA	NA	
Rabeprazole	76/M	NA	<i>Aspirin</i> , atorvastatin, diltiazem

NOTE. Italics indicates medications also reported as commonly causing AIN.⁴¹

NA, not available.

the number of cases supports an association between the two, and all members of the PPI class have been implicated. We are confident the diagnosis in all the cases we present from our hospital series is indeed AIN. It is not possible to differentiate PPI-induced AIN from AIN caused by other medications on histologic grounds. In all our cases the only medication changed or introduced before the diagnosis of AIN was reached was a PPI (Table 1). We believe the close temporal relationship between the onset of AIN and the introduction of a PPI establishes causality. Confounders such as gastrointestinal bleeding or dehydration did not cause the ARF, because these tend to cause ischemic acute tubular necrosis with different histologic features. The presence of eosinophils on biopsy is characteristic of AIN and was evident in 83% (15/18) of our cases.

Our observations were derived from hospital data, registry data, and a MEDLINE review of the medical

literature published in English. From the hospital data and MEDLINE review there is a high degree of certainty that the implicated PPI was the actual cause of the AIN. The TGA registry data are more tenuous, given that some patients were simultaneously taking medications previously implicated in causing drug-induced AIN. The data were obtained from a combined search of the registry for adverse drug reactions suspected to be associated with PPIs as well as a search for all-cause AIN. This identified not only cases of AIN in which a PPI was the sole medication but also cases in which the PPI was prescribed in combination with other drugs that might potentially have contributed to the AIN. To aid in the interpretation of the registry data, the proximity of when the offending PPI was commenced relative to other medications was recorded wherever possible (data not shown). In almost all cases there was a close temporal relationship between the initiation of the PPI and the

diagnosis of AIN. We suspect that the majority of cases in both the categories “unexplained acute renal failure” and “renal impairment” were caused by PPI-induced AIN but were not classified as such because of lack of awareness of this complication at the time of reporting. It is worth noting that the TGA data represent an underestimate of the true prevalence of this complication because reporting to the registry is voluntary, and an unspecified proportion of cases remain unreported. None of our hospital-based cases have been duplicated in the TGA registry data.

A MEDLINE, Embase, and PubMed review on this topic uncovered 34 published case series/reports in the English-language medical literature (Table 4). The most common agent implicated was omeprazole (30 cases), followed by lansoprazole (2 cases) and pantoprazole (2 cases). Where clinical data were reported, the most common symptoms and signs were fever (44%), anorexia/weight loss (44%), fatigue/lethargy (40%), nausea/vomiting (27%), malaise (16%), and rash (8%). Patients were asymptomatic in only 12% of the cases. The most common laboratory features/urinalysis findings were pyuria (84%), proteinuria (60%), hematuria (56%), anemia (44%), eosinophilia (36%), eosinophiluria (20%), and leukocytosis (16%). The average serum creatinine on presentation was 5.27 mg/dL (466 μ mol/L) and on resolution was 1.46 mg/dL (129 μ mol/L). From our series and from the MEDLINE review, nonspecific symptoms predominated as the presenting complaints in PPI-induced AIN. The findings on urinalysis from the literature review are comparable to our case series.

In the previous largest hospital-based case series, PPI drugs were identified as the largest cause of drug-induced AIN.¹¹ Of a total of 14 cases of drug-induced AIN, PPI usage featured in 8. Our study together with this case series argues against the widely held belief that the most common causes of drug-induced AIN are the penicillins, nonsteroidal anti-inflammatory drugs, or loop diuretics.⁴⁰

PPI-induced AIN is an idiosyncratic reaction; hence it is very difficult to stipulate which patients might be at risk of developing the condition. From our case series the majority of the affected patients were elderly (median, 74 years), and it might well be these patients are at a higher risk, but why remains unknown. The exact pathogenesis of PPI-induced AIN remains to be elucidated; however, it is thought to be triggered by a hypersensitivity immune reaction to the drug or one of its metabolites. One hypothesis suggests metabolites of these drugs act as

haptens (mimicking renal antigens), planted antigens, or deposit as circulating immune complexes. The presence of both CD4 and CD8 T lymphocytes in the inflammatory infiltrate suggests T-cell-mediated hypersensitivity reactions and cytotoxic T-cell injury mechanisms are involved.⁴¹ Findings such as fever, rash, arthralgias, and eosinophilia observed in the classic methicillin-induced AIN provide evidence for a hypersensitivity phenomenon. Although T cells are implicated in the pathogenesis, there is also evidence in the literature from experimental animal models to implicate a role for the humoral immune system.⁴² Further studies are required to evaluate precisely how PPIs cause AIN.

Treatment of this condition has not been subject to the rigors of a randomized controlled trial, particularly looking at the benefits of corticosteroids. Because of the low frequency of this entity, it would require a multicenter study to establish such a benefit. This is unlikely to occur without a concerted effort from a national nephrologic society. Patients in our hospital-based series with biopsy-proven PPI-induced AIN all received prednisone 50–75 mg/day titrated to weight and subsequently weaned to zero during a period of 8–12 weeks.

The recognition and diagnosis of AIN are vitally important because the condition is potentially reversible. Most patients diagnosed with AIN recover renal function; however, some patients retain a degree of renal impairment, and some even progress to end-stage chronic kidney disease (CKD).¹² Notably, it was not possible to correlate the degree of histopathologic changes (cellular infiltrate or chronicity of interstitial fibrosis) with subsequent prediction of recovery of renal function.

As the use of PPIs increases, medical practitioners and pharmacists need to appreciate the potential for PPIs to cause AIN. This review demonstrates that in Australia, PPIs are the predominant cause of renal failure due to AIN. All the commercially available PPIs have been implicated, suggesting this to be a class effect. Awareness of this iatrogenic complication and timely withdrawal of the offending drug might prevent the more catastrophic consequences of this entity. Future studies will be required to ascertain whether there are any epidemiologic factors in patients that can predispose them to AIN. Because of the relative minority of patients prescribed PPIs who develop AIN, a concerted multicenter trial might be required to evaluate future therapeutic interventions.

Table 4. Patient Characteristics From the Literature Review

Authors	Age (y)/ sex	Prior exposure duration (wk)	PPI	Symptoms/signs	Serum creatinine mg/dL ($\mu\text{mol/L}$)				Biopsy- proven
					Baseline	Presentation	Peak	Resolution ^a	
Ruffenach et al, ³ 1992	74/F	36	Omeprazole	Anorexia, fatigue, malaise	1.02 (90)	6.11 (540)		1.28 (113)	No
Kuiper, ⁵ 1993	58/F	10	Omeprazole	Pruritic rash	1.50 (133)	20 (168)	3.20 (283)	1.50 (133)	No
Christensen et al, ⁶ 1993	86/F	8	Omeprazole	Fever/rash		9.71 (858)			Yes
Assouad et al, ⁷ 1994	75/M	3	Omeprazole	Asymptomatic	1.20 (106)	3.0 (265)	4.8 (424)	1.9 (168)	Yes
Gronich et al, ⁸ 1994	65/F	NA	Omeprazole	Fever					
Jones et al, ⁹ 1994	76/F	12	Omeprazole	Anorexia, lethargy	1.81 (160)	4.98 (440)		1.92 (170)	Yes
Lewis et al, ¹⁰ 1994	77/F	42	Omeprazole	Nausea, malaise/ weight loss, fever	0.94 (83)	5.18 (458)		1.36 (120)	Yes
Singer et al, ¹¹ 1994	65/M	16	Omeprazole	Anorexia/weight loss, fever		3.40 (301)	4.84 (428)	1.63 (144)	Yes
Aust Adverse Drug React Bull, ¹² 1995	51/M	12	Omeprazole	Fatigue, rigors		2.15 (190)			Yes
Fleury et al, ¹³ 1995	69/M	8	Omeprazole	Weight loss/oliguria					
O'Donnell, ¹⁴ 1996	69/M	2	Omeprazole	Headache, lethargy, nocturia		2.43 (215)		1.24 (110)	No
Badev et al, ¹⁵ 1997	70/F	2	Omeprazole	Anorexia, nausea, vomiting		9.73 (860)		1.92 (170)	Yes
d' Amamo et al, ¹⁶ 1997	71/M	16	Omeprazole	Fever, night sweats		8.71 (770)		1.92 (170)	Yes
	72/F	1	Omeprazole	Anorexia, fatigue/ flank tenderness	1.41 (125)	2.60 (230)	4.97 (439)	1.27 (112)	No
Yip et al, ¹⁷ 1997	50/F	8	Omeprazole	Lethargy, nausea, vomiting	1.05 (93)		4.98 (440)	1.05 (93)	Yes
Landray et al, ¹⁸ 1998	77/F	8	Omeprazole	malaise, nausea, weight loss/fever	1.39 (123)	2.29 (202)	7.74 (684)	1.6 (141)	Yes
Montseny et al, ¹⁹ 1998	69/M	12	Omeprazole	Asymptomatic	0.93 (82)	1.58 (140)	3.51 (310)	1.06 (94)	Yes
Myers et al, ²⁴ 1999	36/F	12	Omeprazole	Nausea, vomiting, weight loss		5.87 (519)	10.54 (932)	1.26 (111)	Yes
Geetha, ²⁰ 1999	78/F	2	Omeprazole	Fever	1.13 (100)	4.41 (390)	6.22 (550)	2.04 (180)	No
Shuster, ²¹ 2000	70/F	3	Omeprazole	Fatigue/fever		4.41 (390)	5.88 (520)		No
Post et al, ²² 2000	73/M	16	Omeprazole	Dry mouth, malaise/fever	1.1 (97)	5.87 (519)	6.86 (606)	1.19 (105)	Yes
Wall et al, ²³ 2000	31/F	13	Omeprazole	Asymptomatic	1.58 (140)	5.44 (481)		1.6 (141)	Yes
Delve et al, ²⁵ 2003	66/F	12	Omeprazole	Anorexia, fatigue, night sweat, weight loss/fever	1.24 (110)	3.29 (291)		1.36 (120)	Yes
	73/F	8	Omeprazole	Dehydration, nausea, lethargy, vomiting, weight loss	1.02 (90)	8.6 (760)		1.92 (170)	Yes
Ra et al, ²⁶ 2004	77/F	8	Pantoprazole	Fatigue/fever	1.31 (100)	3.39 (300)	7.24 (640)	2.04 (180)	Yes
Moore et al, ²⁷ 2004	23/M	6	Pantoprazole	Nausea, vomiting		17.85 (1578)		1.6 (141)	Yes

NA, not available.

^aFollow-up varied in reported cases (range, 1 wk–6 mo).

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