

The relationship between latitude and allergic gastroenteritis hospital admissions in New Zealand infants



Recent epidemiological studies suggest that non-IgE-mediated childhood food allergic disorders, such as eosinophilic esophagitis, celiac disease, and allergic gastroenteritis (AG), may be increasing in parallel with previously observed increases in childhood immunoglobulin (IgE)-mediated food allergy (FA) and food-induced anaphylaxis (FIA).^{1–4} The term AG encompasses food protein-induced enterocolitis syndrome (FPIES), eosinophilic enteritis and colitis, food protein-induced enteropathy, food hypersensitivity enteritis and colitis, but not eosinophilic esophagitis. Given evidence linking latitude/sun exposure/vitamin D status to the pathogenesis of IgE-mediated FA/FIA, we sought to explore whether a similar relationship existed between latitude and rates of non-IgE-mediated FA such as AG.

We examined geographical variation in New Zealand (NZ) International Classification of Disease (ICD-10⁵) classified hospital admission rates (expressed as per 10⁵ population) between July 2000 and June 2018 for AG (K52.2), food-induced anaphylaxis (FIA; T78), all-cause anaphylaxis (sum of T78, T78.2 [unspecified], T80.5 [blood products], and T88.6 [medication]) in infants aged younger than 12 months. Sting anaphylaxis was excluded, because it was not possible to distinguish anaphylaxis from nonallergic venom reactions using ICD codes. Infective gastroenteritis admissions (A0 to A9) and all cause (total) admissions were examined as comparators. More detailed codes for AG such as FPIES (K52.21) were unavailable. Average disease-specific admission rates were calculated for each geographic region of NZ (territorial local authority, TLA), then attributed to the latitude of the geographical center of population (population centroid) of the corresponding TLA. Admission rates were compared with the pooled population demographic data for each TLA, using 2013 census data. Data were obtained from the NZ Ministry of Health and Statistics, New Zealand. Poisson regression (SAS version 9.4) was performed to examine the outcome of the number of admissions for each coded disease of interest, with latitude and other demographic factors as predictors, using the logarithm of the population aged younger than 12 months as the offset variable. Univariable (unadjusted) models included latitude as the only predictor, whereas multivariable (adjusted) models also examined ethnicity, proportion English speakers, and indicators of education and affluence. The Human Research and Ethics committee of Calvary Bruce/Calvary John James Private Hospitals approved the study (HREC ID 54-2016).

Over the study period, there were 334,333 all-cause (total) admissions: 156 due to AG, 378 all-cause anaphylaxis admissions (of which 351 [93%] were attributed to food), and 14,595 infectious gastroenteritis admissions. Those admitted with AG and FIA were predominantly male (69% and 67%, respectively) compared with those with infective gastroenteritis (53%) or all-cause admissions (58%). On both univariable and multivariable regression analysis, significant associations were seen between latitude and hospital admission rates for AG, all-cause anaphylaxis, FIA, and infectious gastroenteritis, with higher rates in southern (further from the equator) compared with northern New Zealand ($P < .001$). By contrast, no relationship was found between all-cause admissions and latitude in an adjusted model (Table 1). By multivariable

Poisson regression, latitudinal associations were most marked for AG hospital admission rates; for each 10-degree increase in latitude south, admission rates increased 10.9-fold (CI: 2.8–42; $P = .0005$), all-cause anaphylaxis admission rates increased 3.7-fold (CI: 1.5–8; $P = .0033$), FIA increased 4.0-fold (CI: 1.6–9.7; $P = .003$), and infective gastroenteritis 2.5-fold (CI: 2.5–2.9; $P < .0001$) (Table 1). By contrast, all-cause admission rates were lower in southern compared with northern latitudes (unadjusted analysis) but were not associated with latitude in the adjusted model (fold change 1.02; CI: 0.99–1.05; $P = .30$). Adjusting for ethnicity or indices of socioeconomic status did not attenuate the finding. Financial barriers were unlikely to have distorted the data; hospital care is provided without charge in the public sector. The strength of our study was the ability to access government-derived data for all hospital admissions in New Zealand, albeit without access to individual medical files.

In the first exploration of the relationship between latitude and rates of non-IgE-mediated AG within a single country, we report a significant latitudinal gradient in AG-related hospital admission rates in New Zealand. The higher rates in southern New Zealand (farther from the equator) could not be accounted for by regional differences in ethnicity or multiple indices of socioeconomic status. The trends were unlikely to be related to regional differences in health-seeking behaviors, given that similar patterns were not observed for all-cause admissions. The similar north–south gradient in FIA hospital admission rates mirrors similar latitudinal trends in IgE-mediated FA in other countries (as reviewed⁶). We also found unexpectedly higher admission rates for infectious gastroenteritis in southern New Zealand. Given the relationship between latitude and vitamin D status (including in New Zealand⁷), vitamin D also might play a role in protecting against infectious gastroenteritis, consistent with previous observations of an association between vitamin D deficiency and increased risk of infective gastroenteritis in children.⁸

As with similar studies reliant on hospital-derived admissions data, possibly variations in diagnostic accuracy, coding errors, access to hospital services, or an inability to distinguish between single and multiple admissions for the same patient may have influenced admission rates. Even if such factors were operative, however, they are unlikely to account for the north–south pattern of AG and FIA admissions that was absent in all-cause admissions.

Our interest in undertaking this study arose from our previous ecological studies examining geographic differences in proxy markers for FA and anaphylaxis (prescription rates for infant hypoallergenic formula and epinephrine autoinjectors and hospital anaphylaxis admission rates) and season of birth influences on the same proxy markers (as reviewed⁶). Taken together, these studies provided preliminary evidence for a possible role for sun exposure or vitamin D status as 1 potential contributing factor to the pathogenesis of IgE-mediated FA. The biological plausibility of vitamin D's role in the development of IgE and non-IgE-mediated food allergic disorders is underpinned by the known pleiotropic effects of vitamin D on the developing immune system as recently reviewed by Poole et al.⁹ Although association is not equivalent to causation, our data provide a rational basis for further studies examining sun exposure and vitamin D status as 1 of several potential factors contributing to the pathogenesis of non-IgE-mediated food allergic disorders such as FPIES and other AG-related disorders.¹⁰

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Table 1Association Between Latitude (per 10 Degrees) and Hospital Admissions by Cause, in Unadjusted and Adjusted Models^a

Cause of admission	n	Unadjusted			Adjusted ^b		
		RR	95%CI	P	RR	95%CI	P
Allergic gastroenteritis	156	3.68	2.27–5.96	<.0001	10.88	2.92–42.05	<.0001
All-cause anaphylaxis	378	2.48	1.81–3.42	<.0001	3.65	1.54–8.66	<.001
Food anaphylaxis	351	2.36	1.69–3.29	<.0001	3.96	1.61–9.73	<.001
Infectious gastroenteritis	14,595	2.07	1.97–2.19	<.0001	2.53	2.23–2.86	<.0001
All causes ^c	334,333	0.74	0.73–0.75	<.0001	1.02	0.99–1.05	.31

RR, rate ratio from Poisson regression model, with 95% confidence interval and P value.

^aUnivariable models examined each predictor individually, whereas multivariable models use all predictors.^bAll multivariable models adjusted for % Maori, % English speaking, % employed, % without qualifications, % tobacco smoking, % internet access, % home ownership, and median individual and household income (per NZ \$10,000).^cAll-cause admission includes all hospitalizations (ie, vast majority of causes are not shown in table).

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Rapid desensitization of hydroxychloroquine



Hydroxychloroquine is an antimalarial agent with immunosuppressive and cytotoxic properties that is considered safe and effective in pregnant patients with a history of mild lupus nephritis (LN).^{1,2} Hypersensitivity to hydroxychloroquine usually manifests as maculopapular exanthems within 2 to 33 days and rarely as eosinophilia or other systemic symptoms.³ Several prolonged desensitization protocols, ranging from 4 to 36 days, have been proposed to manage prior histories of hydroxychloroquine hypersensitivity.^{3–7} We report the first successful rapid desensitization to hydroxychloroquine in a female patient of reproductive age with a history of LN and hypersensitivity to hydroxychloroquine.

A 24-year-old woman with a history of LN had recently discontinued azathioprine and pregabalin treatment for teratogenic and pregnancy safety reasons before conception and thus was seeking hydroxychloroquine desensitization because of her history of hydroxychloroquine-associated delayed hypersensitivity. After starting hydroxychloroquine therapy for her LN diagnosis 8 years ago, the patient had developed urticaria on the chest and neck within several days. The hydroxychloroquine treatment was discontinued after 6 months because of pruritus and worsening urticaria that spread to the face, abdomen, and lower extremities but did not progress to vesicles. After no success with topical corticosteroids, diphenhydramine alleviated the pruritus until full resolution of symptoms within a month after discontinuation of hydroxychloroquine use. Eight years after this hydroxychloroquine-

associated delayed hypersensitivity reaction, an expedited, 5-hour desensitization to hydroxychloroquine was scheduled in an office setting (Table 1). Mild gastrointestinal reflux had been present before the desensitization and was reported after the first few doses. Urticaria and pruritus manifested on the neck and arms immediately after administration of the fourth dose. Because there are no well-established tests to determine the nature of this reaction, we are unable to say whether this was immediate or delayed hypersensitivity. The urticaria resolved within a half hour with 50 mg of diphenhydramine. The third and fourth doses were repeated without adverse effects. The protocol was continued, with minor lip burning reported between the sixth and seventh doses. No other adverse responses manifested.

The 100-mg dose was repeated for the final step of the desensitization protocol and maintained as a daily medication. Mild skin dryness and lip burning resolved within several weeks. The patient reported no adverse events after several months of follow-up. This is the first reported desensitization to hydroxychloroquine performed in less than 24 hours with minimal adverse responses.

Hydroxychloroquine is a commonly prescribed aminoquinoline antimalarial used to treat dermatologic, ophthalmologic, hematologic, cardiovascular, gastrointestinal, and, most often, rheumatic autoimmune diseases, such as systemic lupus erythematosus (SLE).^{3,6} Hydroxychloroquine is preferred over other aminoquinoline antimalarials, such as chloroquine, because of less association with renal toxic effects.⁹ Hydroxychloroquine decreases lysosomal acidification, disrupts endosomal maturation, interferes with phagocytosis, inhibits nucleic acid binding to Toll-like receptors,