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Long-Acting Opioid Use Reporting

TO THE EDITOR—I read with interest the recent article by Wiese et al in *Clinical Infectious Diseases* [1]. The authors conducted a retrospective cohort study of Tennessee Medicaid-enrolled adults initiating long-acting opioids. During 61 240 episodes of immunosuppressive opioid use and 22 811 episodes of nonimmunosuppressive opioid use, they identified 1906 serious infections. Importantly, nonimmunosuppressive opioid use was associated with a lower rate of serious infection than immunosuppressive opioid use (adjusted incidence rate ratio, 0.78 [95% confidence interval, .66–.91]).

Of note, patients could contribute >1 observation period to the analysis. Hence, the 84 051 total episodes of long-acting opioid use occurred in only 69 128 patients (ie, 14 923 episodes occurred in patients who had already contributed an episode). This is important because observations from the same patient are more likely to be correlated than observations from different patients [2]. However, the authors do not mention how many of the serious infections in their dataset were

repeat events. Moreover, it is unclear whether their Poisson models account for the correlation between repeated measures. Such models typically include a random-effects term to account for unobserved effects shared by all members of a cluster [3]. Without this adjustment, the confidence intervals reported by the authors may not be accurate, thereby bringing into question their conclusions.

I suggest Wiese et al report how many repeat infections occurred in their dataset and clarify whether repeated measures have been appropriately accounted for in their analysis.

Note

Potential conflicts of interest. D. B. reports an Early Career Fellowship (award number APP1140503) from the Australian National Health and Medical Research Council, and a 2016 fellowship from Gilead, outside the submitted work. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Boettiger

TO THE EDITOR—We appreciate the comments by Boettiger [1] in response to our recent article describing the association

between the use of prescribed long-acting opioid analgesics and the risk of serious infections [2].

Among the 69 128 patients who contributed 84 051 episodes of new long-acting opioid use, only 13.9% (n = 9632) of patients had 2 distinct episodes of follow-up. Even fewer patients (3.4%) had >2 distinct episodes (maximum of 9 episodes). No substantial difference in the number of repeat episodes was observed by exposure opioid type, likely due to our strict requirement that patients have no long-acting opioid use in the prior 6 months and no evidence of a recent hospitalization for any reason within 30 days prior to cohort reentry. Furthermore, as outlined in the article, our comparisons focused on periods of current long-acting opioid use, such that only 1217 infections were included in the primary analysis (see Table 2 in our article) [2]. Of these, only 12 (1.0%) infections represented a repeat infection during a separate episode for the same patient. No patient contributed >2 infections in the primary analysis.

We agree that it is important to consider potential correlations between episodes, which could occur between multiple episodes from the same patient. Such correlations reduce the study's effective sample size, requiring wider confidence intervals than those provided by analysis methods that ignore the correlation. One valid approach that accounts for correlation is including a patient-level random effect in the analysis model, as suggested by Boettiger. Another valid approach is to use a robust standard error calculation that acknowledges the correlation at the patient level. This is the approach used in the manuscript.

In summary, the large number of unique patients and nonrepeat infections in our study ensured high precision in our estimated effects regardless of within-patient correlation, and more importantly, our reported analyses did account for the potential correlation between episodes.

Notes

Potential conflicts of interest. C. G. G. has received consulting fees from Pfizer and Merck, and received research support from Sanofi-Pasteur, the Campbell Alliance, the Centers for Disease Control and Prevention, the National Institutes of Health, the US Food and Drug Administration, and the Agency for Health Care Research and Quality. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Microscopic Screening of Sputum Samples Should not be Used when Testing for *Legionella* Species

TO THE EDITOR—The systematic review by Ogawa et al [1] highlights the high specificity of the sputum Gram stain of good-quality samples for detecting bacterial pathogens, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*. It has become standard practice in microbiology laboratories for sputum samples to undergo microscopic screening for quality before proceeding to culture [2]. Whilst this is a reasonable approach for most pathogens, it has been noted that

patients with Legionnaires' disease frequently do not produce purulent sputum and that standard sputum screening protocols should not be applied when testing for *Legionella* species [3, 4]. These observations were made over 20 years ago, before the widespread use of polymerase chain reaction (PCR), and only on sputum samples that were culture-positive for *Legionella pneumophila*.

In order to provide more contemporary data on this subject, we conducted a review of the Gram stain microscopy findings from 224 sputum samples processed at Canterbury Health Laboratories, Christchurch, New Zealand, between 1 January 2013 and 31 January 2019 that were positive for any *Legionella* species by culture and/or PCR, using methods described previously [5]. Table 1 shows the Gram stain microscopy findings for these samples, grouped according to the various combinations of microscopic findings. As is typical for our region [6], *Legionella longbeachae* was the predominant species, identified in 158 (71%) of PCR-positive and 47 (65%) of culture-positive samples. Most other samples were positive for *L. pneumophila* (29 [13%] of PCR-positive samples and 17 [24%] of culture-positive samples).

Regardless of the screening criteria used, a large proportion of *Legionella*-positive samples would have been rejected if microscopic screening had been used prior to testing, thereby potentially missing opportunities to diagnose Legionnaires' disease. For example, if the commonly used criteria of Murray and Washington [7] (ie, processing only samples with <10 squamous epithelial cells [SECs] and >25 polymorphonuclear neutrophils [PMNs] per low-power field) were applied, 75% of PCR-positive samples and 64% of culture-positive samples would have been rejected. In contrast, if processing only occurred in samples with <10 SECs per low-power field (regardless of the number of PMNs), 41% and 29% of samples, respectively, would have been rejected.

Table 1. Microscopic Findings of Sputum Smears by *Legionella* Culture and Polymerase Chain Reaction Results

Number (Per Low Power Field) of:		PCR Positive, n = 224	Culture Positive, n = 72
SEC	Leucocytes		
>25	<10	12	3
>25	10–25	6	4
>25	>25	24	4
10–25	<25	22	2
10–25	>25	26	6
<10	>25	57	26
<25	<25	98	28
>10	...	91	21
...	<25	124	37

Abbreviations: PCR, polymerase chain reaction; SEC, squamous epithelial cells.

Our results confirm previous observations and show similar findings for PCR testing and for species other than *L. pneumophila*. When testing for Legionnaires' disease by culture and/or PCR, all sputum samples should be tested, regardless of the Gram stain microscopy findings. Otherwise, a large proportion of cases of Legionnaires' disease will be missed.

We agree with the conclusions in this systematic review [1] regarding the further work required in evaluating sputum Gram stain in conjunction with point-of-care tests, but would add that molecular diagnostic testing should be included.

Note

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