Acknowledgments

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References


Reply to Stefani et al

To the Editor—We thank Dr Stefani and colleagues for their interest in our study [1], and we reply here to their 4 comments [2]. First, the comparison of risks of invasive fungal infection between different treatments of hematological malignancies was not the scope of our study. However, patients were purposely stratified for induction, compared with consolidation chemotherapy or autologous stem cell transplantation (Mab-Campath or rituximab were not administered in any conditioning regimen). Second, the comparison of results between the 2 studies is limited from the beginning by major differences in study design. Our study was a large, multicenter, randomized trial comparing preemptive and empirical antifungal therapy, whereas the study of Maertens et al [3] was a feasibility study of preemptive antifungal therapy in 1 center. At first sight, the risk of invasive fungal infection with preemptive antifungal therapy appeared similar between the 2 studies (13 of 141 patients [9.2%; 95% confidence interval [CI], 5.0%–15.3%) in our study vs 22 of 136 patients [16.2%; 95% CI, 10.0%–24.4%] in Maertens et al [3]). However, we performed a secondary analysis of our data to estimate what might be the risk of invasive fungal infection with our preemptive antifungal therapy in the setting of the Maertens et al study [3]. In a multivariate logistic model, the duration of neutropenia was the main risk factor for invasive fungal infection; ie, each additional day of neutropenia increased the odds of invasive fungal infection by 11% (odds ratio, 1.11; 95% CI, 1.06–1.17; P < .001). The significant association between induction chemotherapy and invasive fungal infection in univariate analysis was confounded by the duration of neutropenia in multivariate analysis. Two protective factors decreased independently and significantly the risk for invasive fungal infection: empirical versus preemptive antifungal therapy (odds ratio, 0.23; 95% CI, 0.06–0.75; P = .023) and hospitalization in a laminar airflow room (odds ratio, 0.16; 95% CI, 0.03–0.63; P = .016). Other protective factors were not statistically significant, including systematic antifungal prophylaxis (P = .54) and air filtration with positive-pressure isolation (P = .34). Finally, the model predicted that significantly less invasive fungal infection (1.8%; 95% CI, 0.4%–8.1%) would have occurred if our preemptive antifungal therapy had been used in the setting of the Maertens et al [3] study (ie, mean duration of neutropenia of 21.5 days, systematic antifungal prophylaxis, and systematic hospitalization in laminar airflow room). Although the adjusted comparison of preemptive antifungal therapy between the 2 studies has more validity than a naive comparison [4], the comparison remains indirect and could not replace direct randomized evidence. In a rejoinder to the third and fourth comments of Stefani et al [2], we believe that both health benefits and costs of the many antifungal strategies should be studied in the long term, namely in a cost-effectiveness analysis [5].

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References

To the Editor—Starko [1] presented an original and creative idea to explain a continuing medical mystery, the extreme virulence of the 1918–1919 influenza pandemic. Her hypothesis, that the use of salicylates exacerbated the tendency of the infection to produce fluid in the lungs, has face validity and is supported by anecdotal evidence of widespread use of aspirin in the United States during the pandemic.

The international characteristics of the pandemic make the salicylate hypothesis difficult to sustain as the primary explanation for the unusual virulence of the 1918–1919 influenza pandemic. Her hypothesis, that the use of salicylates exacerbated the tendency of the infection to produce fluid in the lungs, has face validity and is supported by anecdotal evidence of widespread use of aspirin in the United States during the pandemic.

Thus, Starko’s intriguing hypothesis fails the test of dose-response. That is to say, in countries such as the United States, where salicylates were more available, mortality was much lower compared with regions where salicylates were less readily available. These observations are at the ecological level, and such comparisons are notoriously susceptible to confounding. However, if the salicylate hypothesis applies universally, then the ecological confounding would have to operate such that the salicylate-influenza connection is stronger in countries with less access to aspirin, which seems a priori unlikely. Indeed, the overwhelming majority of the millions of Indian peasants who were killed by the flu certainly had no access to salicylates whatsoever. If the salicylate hypothesis only works in the United States and in similar settings, then we question its validity given the worldwide scope of severe mortality in 1918–1919.

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Reply to Noymer et al

To the Editor—I understand the concern of Noymer et al [1] regarding the worldwide validity of the hypothesis that aspirin contributed to 1918 pandemic mortality [2]. However, worldwide use, as well as clinical, pathology, and physiology evidence of lung toxicity, indicate that aspirin may have played some role in mortality around the world.

I agree that aspirin is not the only risk factor for 1918 influenza mortality [2], yet the country “dose-response” test suggested fails to inform when competing risk factors are present. Potential competing factors, such as viral pathogenicity, bacterial colonization, immune response, smoking, preexisting conditions, and treatment, vary by locale; therefore, the role (etiologic fraction) of each factor is likely to vary by locale as well.

The possibility remains that the effect of aspirin on worldwide 1918 influenza mortality, if proven, may not have been trivial. Aspirin was widely used. In 1905, a British court struck down Bayer’s British patent and opened the aspirin market in the entire British Empire. In 1918, US manufacturers produced 172 million tablets [3]. During the pandemic, the Indian Surgeon General recommended gargling with diluted potassium permanganate and aspirin [4, p 89], and in Delhi, an eminent Indian surgeon “insisted that smart young doctors in Bombay were recklessly misusing it”—on the basis, he said, that it weakened the heart (old canard) and actually brought on pneumonia as a consequence” [5, p 137]. In New Zealand, 1 Maori village, impressed by aspirin, honored the local health superintendent who had provided it; a baby there was named “Aspirin” [5, p 138]. In New South Wales, Aspro was at the top of the list of fixed price wartime commodities [5, p 138]. Unfortunately, a precise reckoning of the amount of aspirin produced, distributed, and used in various countries remains elusive. Yet, importantly, even if the etiologic fraction is small, in a country with a large...