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Reply to Luppi et al

To the Editor—We thank Dr Luppi and his colleagues for their comments about the mechanisms of ibrutinib contributing to the risk for invasive fungal disease (IFD) [1]. Our manuscript [2] listed the host factors defined as characteristics of individuals clearly predisposed to an IFD. Due to space limitations, we provided no discussion of the mechanism by which such factors contributed to predisposition to IFD.

Our characterization of ibrutinib as a "recognized B-cell immunosuppressant" was not intended to imply that B-cell suppression was the explanation for its association with IFD but rather its primary therapeutic use. The inhibition of Bruton tyrosine kinase (BTK) has become a crucial element in the treatment of indolent B-cell malignancies. Ibrutinib, an irreversible inhibitor of BTK, is now approved for the treatment of chronic lymphocytic leukemia [3], mantle cell lymphoma [4], marginal zone lymphoma [5], small lymphocytic lymphoma [6], and Waldenström macroglobulinemia [7]. BTK has been widely characterized as a critical mediator of B-cell receptor signaling that regulates B-cell survival, activation, differentiation, and interaction with the environment [8]. Hence, BTK is also essential in the development and functioning of adaptive immunity. However, from a host factor's perspective, the B-cell immunosuppressant activity of ibrutinib is the common denominator for all of these approved therapeutic indications. BTK also plays a major role in innate immunity (1) in Toll-like receptor–mediated recognition of infectious agents; (2) in maturation, recruitment, and function of innate immune cells, including neutrophils, monocytes, macrophages, and T cells; and (3) in regulating $NLRP_3$ inflammasome activation [9].

We agree that ibrutinib has multiple effects on immunity other than B-cell activity, including activity against T cells, macrophages, and multiple inflammatory pathways, which makes it an effective second therapy for graft-vs-host disease after failure of one or more lines of systemic therapy [10].

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of their respective institutions.

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Tetanus and Diphtheria Boosters

Slifka et al [1] show that the incidence of diphtheria and tetanus is similar in countries that do or do not recommend regular boosters to their populations, implying that boosters are unnecessary. Their data are important but should not