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Response to Comment on "IL-15 Prevents Apoptosis, Reverses Innate and Adaptive Immune Dysfunction, and Improves Survival in Sepsis" and Comment on "IL-7 Promotes T Cell Viability, Trafficking, and Functionality and Improves Survival in Sepsis"

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Letters to the Editor

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Comment on "IL-15 Prevents Apoptosis, Reverses Innate and Adaptive Immune Dysfunction, and Improves Survival in Sepsis" and Comment on "IL-7 Promotes T Cell Viability, Trafficking, and Functionality and Improves Survival in Sepsis"

I read with interest the articles by Hotchkiss et al. on IL-15 (1) and IL-7 (2) improving survival in sepsis, based on a mouse model of cecal ligation and puncture.

We measured plasma cytokines in Malawian children with severe bacterial infection, using a multiplex assay as part of a larger study (3, 4). IL-7R signaling is known to be deficient in HIV-infected individuals and inversely associated with age (5). In total, 155 children with severe bacterial infection had IL-7 and IL-15 measured on admission. The mortality was 25%, and 52% of children were HIV infected. There were 87 males (56%), and the median age was 2.4 y (IQR 0.67–7.0). Mean plasma IL-15 and IL-7 concentrations were significantly increased in survivors compared with nonsurvivors after controlling for HIV status, age, and neutrophil count ($p = 0.017$; $p = 0.015$, respectively).

The data published in *The Journal of Immunology* (1, 2) are exciting and promise new therapies for sepsis. Data from animal models of disease contribute greatly to our understanding of disease mechanisms, but these observations ultimately need to be confirmed in vivo and ex vivo in human subjects with severe sepsis. Our study was observational and not designed to examine T cell function in detail; however, our clinical data are supportive of the hypotheses that IL-7 and IL-15 improve survival in a population with both a high incidence of HIV and a high mortality from severe sepsis. Further functional work is needed in this population to confirm our preliminary findings.

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References

1. Inoue, S., J. Unsinger, C. G. Davis, J. T. Muenzer, T. A. Ferguson, K. Chang, D. F. Osborne, A. T. Clark, C. M. Coopersmith, J. E. McDunn, and R. S. Hotchkiss. 2010. IL-15 prevents apoptosis, reverses innate and adaptive immune dysfunction, and improves survival in sepsis. *J. Immunol.* 184: 1401–1409.
2. Unsinger, J., M. McGlynn, K. R. Kasten, A. S. Hoekzema, E. Watanabe, J. T. Muenzer, J. S. McDonough, J. Tschoep, T. A. Ferguson, J. E. McDunn, et al. 2010. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. *J. Immunol.* 184: 3768–3779.
3. Carrol, E. D., L. A. Mankhambo, P. Balmer, S. Nkhoma, D. L. Banda, M. Guiver, G. Jeffers, N. Makwana, E. M. Molyneux, M. E. Molyneux, et al; Invasive Pneumococcal Disease Study Group. 2007. Chemokine responses are increased in HIV-infected Malawian children with invasive pneumococcal disease. *J. Acquir. Immune Defic. Syndr.* 44: 443–450.
4. Carrol, E. D., M. Guiver, S. Nkhoma, L. A. Mankhambo, J. Marsh, P. Balmer, D. L. Banda, G. Jeffers, S. A. White, E. M. Molyneux, et al; IPD Study Group. 2007. High pneumococcal DNA loads are associated with mortality in Malawian children with invasive pneumococcal disease. *Pediatr. Infect. Dis. J.* 26: 416–422.
5. Bazdar, D. A., M. Kalinowska, and S. F. Sieg. 2009. Interleukin-7 receptor signaling is deficient in CD4+ T cells from HIV-infected persons and is inversely associated with aging. *J. Infect. Dis.* 199: 1019–1028.

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We appreciate the comments of Dr. Carrol concerning the work in our manuscript and read with interest his findings on circulating IL-7 and IL-15 concentrations in children with severe bacterial infection, many of whom were HIV positive. Furthermore, Dr. Carrol's observations regarding increased circulating IL-7 and IL-15 in survivors versus nonsurvivors are intriguing and should be considered in light of the recent work by Crawley et al. (1), showing that soluble IL-7Rα was increased in HIV infection and that it inhibits IL-7 activity. It is possible that in certain settings quantitation of circulating IL-7 and soluble IL-7Rα will be necessary to determine the role of functional IL-7 deficiency in disease as well as to guide the use of IL-7 as a therapeutic tool (2).

Dr. Carrol also commented on performing functional studies, and in this regard, we are initiating in vitro studies to examine the effect of IL-7 in reversing the immunosuppression observed in blood incubation studies from patients with sepsis. We also agree wholeheartedly with Dr. Carrol's comments that it is time to move forward with the use of IL-7 in areas of infectious disease, including bacterial sepsis. IL-7 is currently in multiple clinical trials in patients with HIV, cancer, and hepatitis C, and in bone marrow reconstitution after whole-body irradiation (3, 4). It has been well tolerated and rarely induces the hyperinflammatory "cytokine storm" condition

that occurs with IL-2. There are risks with any new therapy; however, in our opinion, a greater risk lies in continuing on our current path in which the mortality of sepsis remains stubbornly high at 30–40% in most series (5). It is our goal to begin dose safety trials of IL-7 in patients with sepsis as soon as feasible.

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References

1. Crawley, A. M., S. Faucher, and J. B. Angel. 2010. Soluble IL-7Rα (sCD127) inhibits IL-7 activity and is increased in HIV infection. *J. Immunol.* 184: 4679–4687.
2. Mazzucchelli, R., and S. K. Durum. 2007. Interleukin-7 receptor expression: intelligent design. *Nat. Rev. Immunol.* 7: 144–154.
3. Sportès, C., F. T. Hakim, S. A. Memon, H. Zhang, K. S. Chua, M. R. Brown, T. A. Fleisher, M. C. Krumlauf, R. R. Babb, C. K. Chow, et al. 2008. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. *J. Exp. Med.* 205: 1701–1714.
4. Sereti, I., R. M. Dunham, J. Spritzler, E. Aga, M. A. Proschan, K. Medvik, C. A. Battaglia, A. L. Landay, S. Pahwa, M. A. Fischl, et al; ACTG 5214 Study Team. 2009. IL-7 administration drives T cell-cycle entry and expansion in HIV-1 infection. *Blood* 113: 6304–6314.
5. Riedemann, N. C., R. F. Guo, and P. A. Ward. 2003. The enigma of sepsis. *J. Clin. Invest.* 112: 460–467.

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