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Reply to "The Dual Personality of Iron Chelators: Growth Inhibitors or Promoters?"

Daniel V. Zurawski
Walter Reed Army Institute of Research, daniel.zurawski@amedd.army.mil

Anna C. Jacobs
Walter Reed Army Institute of Research

Mitchell G. Thompson
Walter Reed Army Institute of Research

Thomas J. Palys
Walter Reed Army Institute of Research

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AUTHOR REPLY

Reply to "The Dual Personality of Iron Chelators: Growth Inhibitors or Promoters?"

Daniel V. Zurawski, Anna C. Jacobs, Mitchell G. Thompson, Thomas J. Palys

Department of Wound Infections, Division of Bacterial and Rickettsial Disease, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA

In their letter, Visca et al. have shown that *P. aeruginosa* can use deferiprone as an iron "carrier," which in turn promotes bacterial growth in a low-iron M9 minimal medium (1). Since our initial publication, we have also observed that the presence of deferiprone (and some other iron chelators) at sub-MICs can promote the growth of clinical isolates of *Acinetobacter baumannii* in M9 minimal medium (our unpublished results). However, while these data are in agreement with the results published by de Léséleuc et al. with respect to deferiprone and *A. baumannii* (2), in our hands, they were also strain and chelator dependent. For example, we did not observe growth promotion with VK28 and *A. baumannii* (unpublished results). We agree with Visca et al. that the consequences of growth promoted by iron chelators at sub-MIC levels in minimal media need to be considered before clinical application. However, it is unclear how relevant these findings would be *in vivo* if a high-enough concentration of a chelator can be achieved ($\geq 1\times$ MIC). With systemic applications, these concentrations are not possible because of toxicity concerns, but for wound infections, a topical, nonsystemic application could be considered and was also highlighted in a recent review (3).

It should also be noted that our original intent was to investigate the utility of iron chelators in combination with the current standard of care with respect to war wound infections. The current standard of care to treat devastating extremity wounds suffered by U.S. military personnel includes broad-spectrum antibiotic treatment and often negative-pressure wound therapy. Other groups have shown that iron chelators in combination with antibiotics against several bacterial species *in vitro* resulted in a significant increase in bacterial killing, due in some cases to biofilm dispersal (4–7). Our approach, while similar, relied on more recently developed iron chelators (i.e., VK28 and Apo6619) (8), and we actively sought out the synergy with various conventional antibiotics. This approach has led to the discovery that, while some iron chelators have a high MIC alone against common, nosocomial bacteria (8), they also have a synergistic effect with specific antibiotics against *A. baumannii* (A. C. Jacobs, M. G. Thompson, B. W. Corey, and D. V. Zurawski, unpublished data) and other bacteria (D. V. Zurawski, U.S. patent application PCT/US12/23377). Some of these data have been presented at recent meetings (9, 10).

In light of many studies and years of research regarding iron chelators as antimicrobials, including both the failures and successes *in vitro* and *in vivo*, it is clear that many factors will contribute to their potential utility. While caution should be employed, we should still consider the prospect of using iron chelators in specific clinical settings. Clearly the choice of chelator, bacterial susceptibility, the application (i.e., systemic versus nonsystemic), and the potential of synergy, whether it be with conventional antibiotics or with other antibacterial therapies, will all need to be considered in order to optimize therapeutic potential. Given the unrelenting emergence of multidrug-resistant bacteria and the growing lack of treatment options, further research is still warranted.

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REFERENCES

1. **Visca P, Bonchi C, Minandri F, Frangipani E, Imperi F.** 2013. The dual personality of iron chelators: growth inhibitors or promoters? Antimicrob. Agents Chemother. **57**:2432–2433.
2. **de Léséleuc L, Harris G, KuoLee R, Chen W.** 2012. *In vitro* and *in vivo* biological activities of iron chelators and gallium nitrate against *Acinetobacter baumannii*. Antimicrob. Agents Chemother. **56**:5397–5400.
3. **Zhou T, Ma Y, Kong X, Hider RC.** 2012. Design of iron chelators with therapeutic application. Dalton Trans. **41**:6371–6389.
4. **Banin E, Brady KM, Greenberg EP.** 2006. Chelator-induced dispersal and killing of *Pseudomonas aeruginosa* cells in a biofilm. Appl. Environ. Microbiol. **72**:2064–2069.
5. **Neupane GP, Kim DM.** 2010. *In vitro* time-kill activities of ciprofloxacin alone and in combination with the iron chelator deferasirox against *Vibrio vulnificus*. Eur. J. Clin. Microbiol. Infect. Dis. **29**:407–410.
6. **Moreau-Marquis S, O'Toole GA, Stanton BA.** 2009. Tobramycin and FDA-approved iron chelators eliminate *Pseudomonas aeruginosa* biofilms on cystic fibrosis cells. Am. J. Respir. Cell Mol. Biol. **41**:305–313.
7. **O'May CY, Sanderson K, Roddam LF, Kirov SM, Reid DW.** 2009. Iron-binding compounds impair *Pseudomonas aeruginosa* biofilm formation, especially under anaerobic conditions. J. Med. Microbiol. **58**:765–773.
8. **Thompson MG, Corey BW, Si Y, Craft DW, Zurawski DV.** 2012. Antibacterial activities of iron chelators against common nosocomial pathogens. Antimicrob. Agents Chemother. **56**:5419–5421.
9. **Kuehn BM.** 2011. Scientists seek antibiotic adjuvants. JAMA **306**:2203–2204.
10. **Thompson MG, Corey BW, Si Y, Craft DW, Zurawski DV.** 2012. Antibacterial activities of novel iron chelators alone and in synergy against nosocomial, multidrug-resistant pathogens, p 11. 4th Biannual Gordon Conference New Antibacterial Discovery & Development, Lucca, Italy.

Address correspondence to Daniel V. Zurawski, daniel.zurawski@amedd.army.mil.

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