Reply to Wang

TO THE EDITOR—We read with interest Dr Wang’s comment on our recent paper [1, 2]. As we already commented in our earlier response to the comments by Drs Tleyjeh and Baddour [3, 4], we share concern regarding the nonsignificant higher adjusted risk of death among patients with early valve replacement during infective endocarditis. The results should be interpreted cautiously given the limitations of the study and possible hidden confounders. Indeed, as Dr Wang suggested, increasing the number of patients would give P values <.05. However, by increasing the number of patients, we can almost always, at some point, obtain statistical significance. Usually, in such cases treatment effect decreases. Despite this, the observed difference warns that we should be cautious in suggesting surgical treatment immediately after stroke, but if indications are clearly present, recent stroke should not be a hindrance to intervention.

We also, as we wrote in the paper, regret that some important parameters were not included in the analysis because data on the severity of disease and neurological outcome, as well as on structured causes of death, were not collected. Unfortunately, we cannot provide an answer to the question on the causes of death as Dr Wang suggested. We hope that the ICE PLUS study will give more information on this subject.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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.

Bruno Barsic
School of Medicine, University of Zagreb, Hospital for Infectious Diseases, Zagreb, Croatia

References


Correspondence: Bruno Barsic, University of Zagreb, School of Medicine, Hospital for Infectious Diseases, Zagreb, Croatia (bruno.barsic@bfm.hr).

Clinical Infectious Diseases 2013;57(11):1663

© The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cit567

Lowering of Third Generation Cephalosporin Breakpoints

TO THE EDITOR—Like Drs Tamma and Powers [1], I have concerns about the pharmacokinetic-pharmacodynamic (PK/PD) data used by the Clinical and Laboratory Standards Institute (CLSI) to justify revisions to cephalosporin breakpoints and also to eliminate the requirement to test for extended-spectrum β-lactamases (ESBLs) for therapeutic purposes. The background and rationale article by Dudley et al [2] indicates that the pivotal PK/PD data driving these decisions were those of Andes and Craig [3]. If so, the decisions were made on the basis of vague and incomplete data that lacked scientific rigor. The data should not have been considered relevant to diagnostic and therapeutic considerations for patients infected with ESBL producers. My concerns about the data are as follows:

1. The data were from studies presented at 3 meetings (Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC] 1995, ICAAC 2003, and Infectious Diseases Society of America 2003). Only the abstracts remain. There are no published data available to evaluate.
2. There are no descriptions of methodology for the studies, making it impossible to determine their appropriateness, the quality of the data, or the accuracy of the conclusions.
3. It is unknown how many isolates were tested or how many were Escherichia coli, Klebsiella species, Enterobacter species, and Serratia species, or how many of each were ESBL-producing and how many produced other β-lactamases.
4. It is unknown how minimum inhibitory concentrations (MICs) were determined.
5. It is unknown how ESBLs were confirmed (especially important with Enterobacter and Serratia species), or how the various β-lactamases were characterized, or how many of each ESBL type were in each organism group.
6. It is unknown if the studies used the same or different methods or if they included any of the same isolates.
7. AmpCs and ESBLs interact similarly with cephalosporins. If a large number of AmpC producers was included in the non-ESBL group of isolates, one would expect to see similar cephalosporin MICs and similar therapeutic outcomes for the 2 groups. It would have been more meaningful to divide the isolates into 3 groups: ESBL producers, AmpC producers, and isolates without either ESBLs or AmpCs. Then the results for the ESBL and AmpC producers could have been compared to the non-ESBL producers to determine if either ESBLs or AmpCs made a difference. This was not done.

These issues make it impossible to determine the validity of either the data or...
the conclusions. It is unclear how the data could have been considered sufficiently credible to prove that ESBLs do not matter and that laboratories only need to report MICs, a position that conflicts with therapeutic outcome data and expert opinion [4–10]. With this hypothesis unproven, the subsequent Monte Carlo simulation analysis to optimize dosing and set breakpoints was invalid and just an example of the “garbage in, garbage out” phenomenon that occurs when invalid data are used in computer simulations.

Finally, the biggest concern is the failure of the CLSI to discern the weakness of the data, suggesting a flawed breakpoint-setting process that warrants correction.

Notes

Acknowledgments. I thank my wife, Gina Thomson, for her support and suggestions for this correspondence.

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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.

References


Correspondence: Kenneth S. Thomson, BAgSc, MSc, PhD, (kstaac@creighton.edu).

Clinical Infectious Diseases 2013;57(11):1663–4
© The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/cit569

Kenneth S. Thomson
Department of Medical Microbiology and Immunology, Creighton University School of Medicine, Omaha, Nebraska