Letters to the Editor

Insufficient Evidence that Extended-Spectrum Cephalosporins Effectively Prevent Metastatic Infections Related to *Klebsiella pneumoniae*-Caused Liver Abscess

Liver abscess due to *Klebsiella pneumoniae* is a well-established entity in Taiwan (3). We read with interest the article published recently by Cheng et al. (1) in which the authors concluded that extended-spectrum cephalosporins are optimal therapy for liver abscess and effectively prevent the development of severe complications, including metastatic infections. They reasoned that this was because “extended-spectrum cephalosporins were more effective than cefazolin when an obscure metastatic infection exists in the early stage of the disease.”

There are serious flaws in the design of this study that can result in erroneous conclusions. These include (i) failure to randomize the patients, (ii) arbitrary treatment decisions made by individual physicians, (iii) arbitrary changes in regimen (cefazolin to extended-spectrum cephalosporins), (iv) insufficient data on potential delay in diagnosis, and (v) the retrospective nature of the study. For example, a few days’ delay in initiating therapy in the cefazolin group could have accounted for much of the difference. Note that 76 out of 107 (71%) of the patients were initially treated with cefazolin, but the authors report only 59 patients in the cefazolin group in their comparisons. Therefore, 17 patients received both drugs. This is not an acceptable study design for the evaluation of an interventional drug therapy. It invites bias and unforeseen confounding factors. These problems may account for the unusually high rate (37.3%) of severe complications in the cefazolin group. The usual rate of metastatic complications was 10 to 21% (1).

There is insufficient evidence for their conclusion that “use of an extended-spectrum cephalosporin instead of the cephalosporin cefazolin optimized the outcome for liver abscess due to *K. pneumoniae*.” This study does not conform to the requirements stipulated by the Centre for Evidence-Based Medicine to provide an adequate level of evidence to support treatment decisions (http://www.cebm.net/levels_of_evidence.asp#levels). Nor does it provide sufficient evidence to comply with the Infectious Diseases Society of America—U.S. Public Health Service grading system for rating recommendations in clinical guidelines (2). We therefore caution readers to remain skeptical of the conclusions drawn from this study. Prospective, randomized, clinical trials need to be done.

An average of 60 cases of *K. pneumoniae*-related liver abscesses is admitted to our medical center each year. We routinely use narrow-spectrum cephalosporins and gentamicin for treatment. Almost all of the metastatic infections were either present on admission or could be readily detected within 3 days of hospitalization. A review of 110 episodes of *K. pneumoniae*-related liver abscess seen at our hospital during a recent 2-year period revealed that the rate of metastatic infections (any site) was 14.5%. Central nervous system disease was the most common metastatic infection (meningitis, 11 out of 16 [68.8%]; endophthalmitis, 4 out of 16 [25%]). These complications were detected within 3 days in 10 out of 14 (71.4%) cases. Only one case of endophthalmitis occurred while on treatment with cefazolin and gentamicin. We rarely missed any cases of meningitis and were able to target extended-spectrum cephalosporins specifically to these patients (S. S. Lee, Y. S. Chen, H. C. Tsai,

S. R. Wann, C. H. Kao, C. C. Chi, and Y. C. Liu, unpublished data).

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Authors’ Reply

Recent recommendations provided by the Centre for Evidence-Based Medicine have been used as one of the methods to assess the significance for treatment effectiveness. Five different levels of evidence have been selected for grading the significant level of clinical studies (www.cebm.net/levels_of_evidence.asp). Prospective, randomized, and double-blinded clinical trials are suggested as the highest grade (level 1). Evaluation of drug effectiveness with a retrospective cohort study was graded at level 2. The levels of evidence are in order to generate clinically useful measures, to assess potential clinical implications, and to incorporate vital patient values into the ultimate decisions. The level of evidence reflects the confidence of different approaches in performing the clinical study. Although a retrospective study may overestimate the effectiveness of a drug, it may still provide useful information for clinical decision-making when a randomized and double-blinded clinical trial could not be performed due to various limitations. Two previous comparison studies have shown that retrospective or observational studies will also provide a good correlation with prospective studies and that the results of the observational studies were remarkably similar to those of the randomized, controlled trials (1, 3). In our study, we analyzed not only the clinical treatment outcome of development of complications, but we also evaluated all the possible risk factors that might influence the effectiveness of different regimens (2). We disagree with the comments on the flaws in the design of our study. We would like to emphasize that this is the first attempt to study the treatment of *Klebsiella pneumoniae* liver abscess, and there have been no previous publications related to this subject.

Regarding the specific criticisms, we have the following comments.

(i) Failure to randomize the patients. All our recruited patients were selected based on evidence of imaging studies confirming the presence of liver abscess, bacterial culture of pure *K. pneumoniae* in the pus drainage, and so forth (see Materials and Methods in reference 2). Since this was a retrospective study, all patients with *K. pneumoniae* liver abscess were included, and the issue of randomization is not relevant.

(ii) Arbitrary treatment decisions made by individual physicians. Since this is a retrospective study, attending physicians would make management decisions based on clinical assessment of the patient, supported by ancillary investigations. This should be the standard of care rather than a point for debate.

(iii) Arbitrary changes in regimen. Similar to the above, in a retrospective study, changes in treatment regimens by the attending physician based on clinical response is the standard of care. In the Materials and Methods section of our paper, the definition of comparison between cefazolin versus extended-spectrum cephalosporin treatment has already been clearly addressed.

(iv) Insufficient data on potential delay in diagnosis. There was no significant difference in the mean days of fever before hospitalization between patients treated with cefazolin and those with an extended-spectrum cephalosporin, as mentioned in the Results section of our paper.

(v) The retrospective nature of the study. We agree with this point and that prospective and randomized studies should be performed whenever possible.

Finally, Lee et al. have provided their own observations with reference to a manuscript that was still in preparation. At this stage, those data should be considered preliminary and incomplete, and should not be commented upon. However, it is

important to note that, similar to our conclusion, an extended-spectrum cephalosporin for metastatic infection has been recommended. An extended-spectrum cephalosporin to prevent the development of metastatic infection in the presence of other clinical risk factors, as presented in our study, seemed to be agreeable to Lee et al. Given the high rate of metastatic complication and its poor outcome, we maintain that an extended-spectrum cephalosporin instead of cefazolin optimizes the treatment outcome for *K. pneumoniae* liver abscess.

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