Acknowledgments

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Reply to Yu et al., Fung and Siu, and Lin et al.

To the Editor—Yu et al. [1] report a lower prevalence of diabetes mellitus (DM) in patients with Klebsiella pneumoniae primary liver abscess caused by K1/K2 than by non–K1/K2 strains (50%/60% vs. 86%; P = .050), thereby suggesting that poor glycemic control in diabetic patients might increase susceptibility to non–K1/K2 liver abscess, rather than K1/K2 liver abscess, as was jointly proposed by Fung and Siu [2, 3] and Lin et al. [3, 4]. Further studies are required to clarify this issue.

Contrary to the claims of Lin et al. [4], we did not assert a “low” prevalence of DM or “misrepresent the significance of DM in K. pneumoniae liver abscess” [4 (p. 1531)]. We pointed out was that, compared with the results of Fung et al. (78.4%) [5], other groups in Taiwan have consistently reported a lower prevalence of DM (64.4%–67.5%) in cases of K. pneumoniae liver abscess [6]. Regarding cases with complicated endophthalmitis, other groups have also reported a greater proportion of patients without DM (32%–42%) [7–9] than that (7%) reported by Fung et al. [5], which highlights the important fact that DM is not a prerequisite for the development of septic ocular complications from K. pneumoniae liver abscess.

Lin et al. [4] argue for expanding the definition of “severe metastatic complications.” This term, however, never appears in our article, with low mortality achieved, the main concern for K. pneumoniae liver abscess currently is catastrophic disability due to irreversible ocular and/or neurological complications [6]. Lin et al. [4] claim that “DM was verified as a significant factor for developing severe extrahepatic complications” (p. 1531) based on 2 studies that had an “overall enrollment of 354 K. pneumoniae—LA patients” in 2 studies [10, 11]. However, the first study (n = 200) [10] actually found that DM was “not related significantly to the development of endophthalmitis (P = .988),” (p. 535) and the second study (n = 225) [11] was biased by including non–K. pneumoniae cases (n = 71) in analyses for effects of DM.

We did not underestimate the virulence of K. pneumoniae genotype K2 strains in K. pneumoniae liver abscess. However, our findings did not support Fung and Siu’s assertion that K2 “should not separate from K1” [2 (p. 1530)]. As mentioned in our paper [6], their data actually showed K1 strains to be more resistant to phagocytosis than K2 strains, although the difference was statistically insignificant (P = .052) [12]. A lack of statistically significant difference does not establish equality between K1 and K2. With use of a larger sample size (100 K1 vs. 36 K2 strains) than their phagocytosis test (34 K1 vs. 15 K2 strains, from 2 geographic regions) [12], our serum assay demonstrated a significantly higher virulence for K1 than for K2 (P < .001) [6]. This suggests that K1 and K2 should be treated separately in future research, regardless of whether K2 is also a significant risk factor for septic ocular/CNS complications as is K1.

Although we have demonstrated K1 to be the most virulent cps genotype, we never stated that K1 is the only “major virulence factor” [4 (p. 1531)]. Our prior bacteriological studies have clearly showed that virulence of K. pneumoniae is multifactorial and complex [13–15].

Contrary to what Lin et al. [4] suggest,
our in vitro serum assay has the advantage of being highly clinically relevant with regard to bacterial pathogenicity for septic ocular/CNS complications, because resistance to human serum is a prerequisite for bacterial hematogenous invasion to vital organ systems. On the other hand, Mizuta et al. [16] demonstrated an extremely large variation among K. pneumoniae strains with the same serotype regarding their virulence to mice (>10^4-fold difference in LD50 among K2 strains). Therefore, conclusions derived from mice lethality tests using small numbers of K1 or K2 strains have limited generalizability.

Fung and Siu [2] misunderstood our study design and made wrong calculations regarding the numbers of cases in our studies. Their consequent arguments, including the suggestion that our analysis could be “inconclusive and uncertain,” are therefore groundless and untrue, because they ignore the fact that we had collected strains from all types of pyogenic liver abscesses since the beginning of our studies [6]. Our prior bacteriological studies on the genetic characteristics of tissue-invasive strains causing primary pyogenic liver abscess [13–15], of course, did not include strains from cases potentially secondary to intra-abdominal factors documented by physicians. On the other hand, our present clinical study examines the effects of bacterial genotypes and host factors on the occurrence of ocular/CNS complications [6], therefore requiring inclusion of all types of K. pneumoniae pyogenic liver abscesses. Their statement of an “11.25 times” increase in their liver abscess cases “due to selection criteria” is not true. We had only a total of 73 cases in 2004–2005 (36.5 cases per year; merely 2.5 times as high as the rate of 14.8 cases per year in 1997–2003). Similarly, Fung and Siu’s claims—“K2 isolates first occurred after 2002” and “a sharp increase” in K2 liver abscess [2 (p. 1530)]—are also mistaken. The percentage of K2 among all strains isolated from all types of our liver abscess cases was 17% in 1997–2001 and 22% in 2002–2005. Their another assumption, “complications...were all from cryptoegenic” liver abscess [2 (p. 1530–1)], is also incorrect. Of our 23 cases of complications, only 12 occurred from abscess culture-positive pyogenic liver abscess. Among the total 36 cases of liver abscess caused by K2 strains, 2 developed ocular/CNS complications. This yields a risk of 5.6% (2 of 36) rather than 33%. The risks of K2 (5.6%) and non-K1/K2 (4.9% [2 of 41]) strains are not statistically different (P = 1.000).

Finally, genotyping can unequivocally distinguish K1, K2, and other genotypes from each other. It can also be easily performed with standard PCR procedures.

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