ministration of adequate therapy with greater hospital mortality [4–6]. In a study of SAB, Lodise et al [7] found that delayed treatment was an independent predictor of infection-related mortality. Schramm et al [8] examined 549 patients with sterile site infections due to methicillin-resistant *Staphylococcus aureus* (474 with SAB) and also showed that not administering adequate antibiotic therapy within 24 h of developing infection increased the risk of hospital mortality, by both univariate and multivariate analyses.

Although, the current study of SAB failed to demonstrate an association between adequate therapy and outcome, physicians should be careful not to minimize the clinical importance of getting antibiotic therapy "right" as soon as possible. This would appear to be most important for the sickest patients, including those with septic shock and neutropenia [9, 10]. Therefore, it seems logical to develop local strategies aimed at optimizing treatment practices for patients with serious infections, including SAB. Such strategies should include the administration of adequate antibiotic therapy administered in a timely manner.

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References

1. Ammerlaan H, Seifert H, HarbathS, et al. Adequacy of antimicrobial treatment and outcome of *Staphylococcus* aureus bacteremia in 9 western European countries. Clin Infect Dis **2009**; 49:997–1005.
2. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–1596.
3. Barochia AV, Vitberg D, Xizhong C, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med (in press).
4. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother **2005**; 49:3640–3645.
5. Labelle AJ, Micek ST, Roubinian N, et al. Treatment-related risk factors for hospital mortality in *Candida* bloodstream infections. Crit Care Med **2008**; 36:2967–2972.
6. Garey KW, Rege M, Pai MP. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multicenter study. Clin Infect Dis **2006**; 43:25–31.
7. Lodise TP, McKinnon PS, Swiderski L, et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin Infect Dis **2003**; 36: 1418–1423.
8. Schramm GE, Johnson JA, Doherty JA, et al. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit Care Med **2006**; 34:2069–**2074**.
9. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. Antimicrob Agents Chemother **2008**; 52:3188–3194.
10. Thiel SW, Asghar MF, Micek ST, et al. Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis. Crit Care Med **2009**; 37:819–824.

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Reply to Kollef

To the Editor.—Dr. Kollef [1] raises a concern related to the definition of adequate therapy as used in our study [2]. Patients were classified as receiving adequate therapy despite treatment delays of up to 2 days (1 day with severe sepsis and septic shock) after the onset of *Staphylococcus aureus* bacteremia, whereas several investigators have demonstrated, in retrospective studies, associations between the timing of adequate antimicrobial therapy and outcome.

In our study, delay of adequate antimicrobial therapy was not associated with increased mortality, which contradicts with some [3–6] but not all studies [7–9]. Data on hour of prescription were lacking in our database; however, the association between inadequate therapy and mortality was not stronger when taking 1 day as the cutoff for all cases of bacteremia.

The obvious intuitive association between inadequate treatment and mortality may be obscured by several factors. First, the definitions of inadequate therapy are inherently arbitrary and vary among studies [10, 11]. We used the recommendations provided by McGregor et al [10] to define appropriate treatment as validly as possible.

Second, because such studies are observational, removing confounding factors is a challenge. In observational studies, significant differences that exist between treatment groups may not be adjusted sufficiently using commonly used multivariable techniques. As an example, we consider a study of critically ill patients with bacteremia, in which therapy was defined as inadequate if administered antimicrobials were ineffective against the causative pathogen at the time of identification of the microorganism and its antibiotic susceptibility [12]. The estimated "adjusted" effect of inadequate antimicrobial treatment of bloodstream infection, compared to adequate therapy, on hospital mortality had an odds ratio of 6.9, after including the following factors: use of vasopressors, age, organ dysfunction, and severity of illness, in a multivariable logistic regression model.

A major limitation of such an analysis is that the model only includes confounders based on statistical significance with respect to mortality (determined by a stepwise variable selection approach, with a P value of .05 as the limit for acceptance or removal of terms), which may inappropriately exclude important confounding factors that adjust for differences between treatment groups, such as time in the hospital prior to bloodstream infection, prior use of antimicrobials, and serum albumin level. Presumably, these differences were factors that influenced the probability that treatment was inadequate, or they were proxies for such factors. Not including

these factors in the model may contribute to an exaggerated estimate of an effect [12]. Therefore, we added a propensity score as an additional covariate to determine whether measured differences between the inadequate and adequate treatment groups contributed to residual confounding [7, 11].

Third, outcome depends on the population studied. Several studies have highlighted specific populations with bacteremia that may be vulnerable to inappropriate antimicrobial therapy: patients in intensive care units [12], patients with septic shock [13], patients with nosocomial bacteremia [5], or patients with neutropenia [7]. In contrast, studies that included more heterogeneous patient populations have found a lack of association [9]. Our study included a heterogeneous patient population, including patients with or without severe sepsis, patients with methicillin-susceptible *S. aureus* bacteremia, patients with methicillin-resistant *S. aureus* bacteremia, and patients with community-acquired or hospital-acquired primary and secondary bacteremia. The study was underpowered to detect an association between antimicrobial therapy and mortality within specific subgroups of patients with bacteremia.

Fourth, many studies only report single-center results, often from US tertiary care centers [5, 6], in contrast to our study, which reported the results of 60 randomly selected teaching and nonteaching hospitals in Europe. Finally, outcome depends on the microorganism studied. Mortality associated with gram-negative bacteremia or candidemia cannot be compared with *S. aureus* bacteremia [14].

Yet, as explicitly stated in our study, we are not advocating that physicians stop relying on the importance of immediate administration of appropriate antimicrobial therapy for patients with potentially life-threatening infections. On the other hand, in a setting with a low prevalence of methicillin-resistant *S. aureus* bacteremia, it may be justified not to switch from empirical β-lactam therapy to vancomycin in a clinically stable patient who is not having severe sepsis or septic shock if the microbiology laboratory reports gram-positive cocci in clusters in the Gram stain of a positive blood culture. Our findings suggest that the view on what is usually considered appropriate or inappropriate therapy may not be fully correct, as elegantly stated in the accompanying editorial [15].

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References

1. Kollef MH. Should we be debating the importance of timely adequate antimicrobial therapy? Clin Infect Dis 2010; 50:617–8 (in this issue).
2. Ammerlaan H, Seifert H, Harbarth S, et al. Adequacy of antimicrobial treatment and outcome of *Staphylococcus aureus* bacteremia in 9 western European countries. Clin Infect Dis **2009**; 49(7):997–1005.
3. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) **2003**; 82(5):322–332.
4. Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. Crit Care Med **2004**; 32(4):992–997.
5. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin Infect Dis **2003**; 36(11):1418–1423.
6. Schramm GE, Johnson JA, Doherty JA, Micek ST, Kollef MH. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit Care Med **2006**; 34(8): 2069–**2074**.
7. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. Antimicrob Agents Chemother **2008**; 52(9):3188–3194.
8. Kim SH, Park WB, Lee KD, et al. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother **2004**; 54(2):489–497.
9. Scarsi KK, Feinglass JM, Scheetz MH, Postelnick MJ, Bolon MK, Noskin GA. Impact of inactive empiric antimicrobial therapy on inpatient mortality and length of stay. Antimicrob Agents Chemother **2006**; 50(10): 3355–3360.
10. McGregor JC, Rich SE, Harris AD, et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis **2007**; 45(3):329–337.
11. Harbarth S, Nobre V, Pittet D. Does antibiotic selection impact patient outcome? Clin Infect Dis **2007**; 44(1):87–93.
12. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **2000**; 118(1):146–155.
13. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34(6):1589–1596.
14. Wisplinghoff H, Bischoff T, Tallent SM, Seifert

H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39(3):309–317.
15. Moellering RC Jr. What is inadequate antibacterial therapy? Clin Infect Dis **2009**; 49(7): 1006–1008.

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Fatal Respiratory Events Caused by Zanamivir Nebulization

To the Editor—A 25-year-old pregnant woman (26 weeks gestation) was referred from a private hospital in August 2009 because of severe hypoxia secondary to influenza A (H1N1) pneumonia proven by reverse-transcription polymerase chain reaction test. Her symptoms commenced with one week of fever, followed by intense cough and dyspnea requiring mechanical ventilation. Chest radiograph showed bilateral alveolar opacification involving three-fourths of the entire lung fields. Oral oseltamivir, nebulized zanamivir, and intravenous dexamethasone were initiated promptly. The patient was ventilated by Nellcor-Puritan-Bennett-840 ventilator in pressure-controlled mode. At the best positive end–expiratory pressure (PEEP) of 14 cm H_2O, the plateau pressure was 27 cm H_2O and the arterial oxygen partial pressure–to–fraction of inspired oxygen concentration ratio (PaO_2/FiO_2) was 64. On the second day, we observed inexplicably low exhaled tidal volumes. Replacement of the ventilator, under the same settings, immediately recovered an additional 100 ml of exhaled tidal volume. The patient was in stable condition afterward with a pulse oxygen saturation (SpO_2) of 88%–92% until midnight of the fourth hospital day, when the on-call physician was notified of a sudden ventilator malfunction. The nurse in charge stated that the incident happened while nebulizing zanamivir and was preceded by a few alarms that needed machine reset. While the patient was waiting for a new (third) ventilator, her SpO_2 dropped to 65%. This SpO_2, however, rose slowly and reached 90% in 24 hours. At this circumstance, blockade in the expiratory filter was suspected. To prevent damage to the reusable filter, we placed a disposable filter (CareStar, DrägerMedical) at the point proximal to the main filter. At midnight of the fifth hospital day, the problem recurred. This time, rapid removal of the disposable filter led to immediate resumption of ventilator function. Examination of the removed filter demonstrated inside-blockade caused by sticky material. Following this second episode of ventilator malfunction, patient became severely hypoxemic (SpO_2, 71%–78%) and developed bilateral pneumothoraces. Despite all aggressive measures, her oxygenation failed to improve and the patient expired on the eighth hospital day.

Diagnosis and treatment of influenza A (H1N1) pneumonia in this patient was late, which resulted in severe acute respiratory distress syndrome. Because sedatives and muscle relaxants routinely used in managing critical patients might cause impaired gastrointestinal function, the absorption of oral oseltamivir becomes unpredictable. Alternative administration of inhaled zanamivir, although safe and effective [1, 2], is also a practical problem in intubated patients. Endotracheal nebulization of zanamivir at double doses (20 mg in saline) is therefore widely practiced in Thailand during this influenza pandemic. We suspect that this incident of filter blockade was caused by the 20 mg lactose in each blister of zanamivir [3]. A simulation was performed by connecting the ventilator to a test lung and a pressure manometer. From the sixth dose of zanamivir nebulization, we observed significant retardation of expiratory flow with 1.5–2 cm H_2O elevation of PEEP and airway pressure. Severe ventilator occlusion occurred transiently during the eighth dose and became persistent at the ninth dose of nebulization—during which the ventilator automatically opened its safety valve and switched to a low respiratory rate, a low airway pressure, and a zero PEEP ventilation. Further ventilator reset failed to recover its previous function. We conclude that expiratory filter obstruction caused by nebulized zanamivir resulted in severe hypoxemia and pneumothoraces that led to fatality in this patient. The fatal respiratory events were immediately reported to GlaxoSmithKline, and steps were taken by GlaxoSmithKline and the United States Food and Drug Administration, with subsequent notification to healthcare professionals and hospital risk managers [4].

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References

1. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med **2005**; 353:1363–1373.
2. Tanaka T, Nakajima K, Murashima A, Garcia-Bournissen G, Koren G, Ito S. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. CMAJ **2009**; 181:55–58.
3. US GlaxoSmithKline. Relenza prescribing information. **2008**. Available at: http://us.gsk.com/products/assets/us_relenza.pdf. Accessed 6 January 2010.
4. US Food and Drug Administration. MedWatch The FDA Safety Information and Adverse Event Reporting Program. Relenza (zanamivir) inhalation powder. Updated **2009**. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm186081.htm. Accessed 9 October 2009.

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