Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis (Online data supplement)

Sachin Yende
Gina D'Angelo
John A. Kellum
Lisa Weissfeld
Jonathan Fine
Robert D. Welch
Lan Kong
Melinda Carter
Derek C. Angus
for the GenIMS Investigators

METHODS

Subjects and design

Inclusion criteria were subjects older than 18 years and who met clinical and radiologic criteria for CAP, described by Fine et al (E1). Exclusion criteria were: transfer from another hospital; discharge from a hospital within the prior ten days; episode of pneumonia within the past 30 days; chronic mechanical ventilation dependency, cystic fibrosis; active pulmonary tuberculosis; positive HIV antibody titer; alcoholism with evidence of end-organ damage; admission for palliative care; prior enrollment in the study; incarceration, and; pregnancy.

Clinical and outcome variables

We gathered detailed baseline and sequential clinical information by structured subject or proxy interviews, bedside assessment by study nurses, and from medical records. Pre-hospitalization chronic health conditions were ascertained using the Charlson comorbidity index (E2). Severity of illness was assessed using APACHE III and the Pneumonia Severity Index (PSI) (E1, E3). We defined severe sepsis as pneumonia with acute organ dysfunction following the 2001 International Consensus Criteria (E4). We defined acute organ dysfunction as a new Sequential Organ Failure Assessment (SOFA) score of $\geq$ 3 in any of six organ systems, based on the recent international Sepsis Occurrence in the Acutely ill Patient (SOAP) study (E5). We assessed vital signs at hospital discharge to assess whether subjects met criteria for clinical stability at hospital discharge, as described by Halm et al (E6).

Laboratory procedures

We obtained blood in the GenIMS cohort for cytokine assays daily for the first week and once weekly thereafter, while subjects remained in hospital. For this study we analyzed only the last cytokine measurement. Once discharged, no further blood sampling was performed. Each blood sample was drawn into pyrogen-free vials containing heparin. Plasma was separated by centrifugation, divided into four 1.5 mL tubes, frozen at –80°C, and batched and shipped on dry ice.

Statistical analyses

We first conducted univariate comparisons of sociodemographic and prior health for those who survived or died at 90 days and one year to ascertain early and late predictors of mortality. For univariate analyses, we using Chi-square and Fisher's exact test for discrete data and Wilcoxon rank-sum test for continuous data. We constructed Tobit models to compare cytokine concentrations to account for data that were truncated because they were below detection thresholds (38% and 81% of subjects for IL-6 and IL-10) (E7). We used survival models to estimate hazard ratios (HR) for circulating cytokine concentrations and death over one year. We used Gray's model because the hazards failed Cox's proportionality assumption (E8), implementing an index approach for censored covariates. The Gray's model estimates hazard ratios at each of ten consecutive time points and thus provides a detailed description of the change in hazard ratios over one year. We estimated adjusted and unadjusted hazard ratios by entering IL-6 and IL-10 in the model independently and concurrently. The

final model included adjustment for age, race, gender, and Charlson and APACHE III scores.

For cause-specific mortality, we used a Tobit model to compare cytokine concentrations at discharge for different causes of death. We used Putter's competing risk model (E9) to assess associations between cytokines and cause-specific mortality because the associations between cytokines and different causes of death are dependent and these risks compete with one another until a subject dies due to a specific cause of death.

We conducted three sensitivity analyses. We restricted the analyses to the subset with a cytokine measurement within 48 hours of hospital discharge to examine the association in individuals in whom cytokines were drawn only on the day of and the day prior to discharge. Since the association between cytokines and long-term mortality could be confounded by severity of illness, we restricted the analysis to the subset that did not develop any new organ dysfunction during the hospital course. Finally, we restricted the analyses to the subset discharged home because these subjects were most likely to have recovered from the acute illness. All analyses were performed assuming significance at $p<0.05$ and using R version 2.3.1 and Stata version 7.0.

References

E1. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med* 1997;336:243-50.

E2. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.

E3. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, . The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-1636.

E4. Levy MM, Fink M, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250-1256.

E5. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group

on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-710.

E6. Halm EA, Teirstein AS. Management of Community-Acquired Pneumonia. *N Engl J Med* 2002;347:2039-2045.

E7. Epstein MP, Lin X, Boehnke M. A tobit variance-component method for linkage analysis of censored trait data. *Am J Hum Genet* 2003;72:611-620.

E8. Kasal J, Jovanovic Z, Clermont G, Weissfeld LA, Kaplan V, Watson RS, Angus DC. Comparison of Cox and Gray's survival models in severe sepsis. *Crit Care Med* 2004;32:700-707.

E9. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26:2389-2430.

Table E1. -- Causes of death stratified by pre-existing chronic health conditions in subjects who died over one year after hospital discharge

Pre-existing health conditions*	Causes of death, n (%)				
	Cardiovascular	Infection	Cancer	Chronic respiratory disease	Renal
Cardiovascular disease†					
Prior cardiovascular disease (n=120)	51 (42.5)	11 (9.2)	21 (17.5)	15 (12.5)	7 (5.8)
No prior cardiovascular disease (n=152)	33 (21.7)	22 (14.5)	45 (29.6)	27 (17.8)	8 (5.3)
Cancer					
Prior cancer (n=42)	4 (9.5)	3 (7.2)	30 (71.4)	0	1 (2.4)
No prior cancer (n=217)	76 (35)	30 (13.8)	33 (15.2)	38 (17.5)	14 (6.5)
Renal failure					
With prior renal disease (n=25)	15 (60)	2 (8)	3 (12)	1 (4)	3 (12)
No prior renal disease (n=234)	65 (27.8)	31 (13.3)	60 (25.6)	37 (15.8)	12 (5.1)

*Data regarding pre-exisitng health status was missing for 28, 41, and 41 subjects for cardiovascular disease, cancer, and renal failure, respectively.

†Cardiovascular disease included history of coronary artery disease, myocardial infarction, coronary artery stent placement, or coronary artery bypass graft surgery.