Impact of Gender on Sepsis Mortality and Severity of Illness for Prepubertal and Postpubertal Children

Anoopindar K. Ghuman, MD[1,2], Christopher J. L. Newth, MD, FRCPC[1,2], and Robinder G. Khemani, MD, MsCI[1,2]

Objective To investigate differences in sepsis mortality between prepubertal and postpubertal males and females.

Study design This was a retrospective review of the Virtual PICU Systems (VPS) database (including 74 pediatric intensive care units [PICUs]) for 2006-2008. We included prepubertal (aged 2-7 years) and postpubertal (aged 16-21 years) children with a primary diagnosis of sepsis admitted to a participating PICU.

Results Prepubertal females (n = 272; 9.9% mortality) and prepubertal males (n = 303; 10.9% mortality) had similar mortality and severity of illness (Pediatric Index of Mortality 2 risk of mortality [PIM 2 ROM]). Postpubertal females (n = 233; mortality, 5.6%) had lower mortality than postpubertal males (n = 212; mortality, 11.8%; $P = .03$). PIM 2 ROM was higher for postpubertal males than postpubertal females ($P = .02$). After controlling for hospital specific effects with multivariate modeling, in postpubertal children, female gender was independently associated with a lower initial severity of illness (PIM 2 ROM: OR, 0.77; 95% CI, 0.62-0.96; $P = .02$).

Conclusion Sepsis mortality is similar in prepubertal males and females. However, postpubertal males have a higher sepsis mortality than postpubertal females, likely related to their greater severity of illness on PICU admission. These outcome differences in postpubertal children may reflect a hormonal influence on the response to infection or differences in underlying comorbidities, source of infection, or behavior. *(J Pediatr 2013;163:835-40)*.

Studies in animals and humans have demonstrated that females and males have different immune responses.[1] In general, females are thought to have a more active baseline immune system, with a higher incidence of autoimmune diseases, a more robust response to vaccination, and some degree of protection from severe sepsis.[2,3] Evidence suggests a higher incidence of sepsis in males; however, a higher mortality from sepsis has not been demonstrated consistently.[4-13] Multiple factors may contribute to this difference in the incidence and (possibly) outcomes of sepsis, including a beneficial effect of estrogen and a harmful effect of testosterone on the immune and cardiovascular systems.

Watson et al[6] described the epidemiology of severe sepsis in US children using data from 1995. They found that infant males were more likely than females to die from sepsis, but that sepsis mortality was similar in males and females beyond infancy. They did not specifically examine prepubertal and postpubertal age groups, however. Using a large, multicenter cohort of critically ill children with sepsis, we sought to investigate a difference in mortality based on pubertal status and gender. We view this study as an initial step in identifying a possible association between sex hormones and mortality in sepsis.

Methods

We searched the Virtual PICU Systems (VPS) database of 74 national participating pediatric intensive care units (PICUs) to identify children aged 2-7 years or >16 years admitted between January 2006 and December 2008 with a primary diagnosis of sepsis or septic shock. Eligible primary diagnoses were sepsis, septic shock, toxic shock, or meningococcemia.

The largest national clinical PICU database, the VPS database (https://portal.myvps.org/participation.aspx) uses multiple strategies to optimize the accuracy of data. VPS data elements are collected prospectively for all patients admitted to each participating PICU. All PICUs submit required elements, and some PICUs submit additional optional elements. The specific

AIC	Akaike information criterion
BIC	Schwarz Bayes information criterion
CARS	Compensatory anti-inflammatory response syndrome
ll	−2 log likelihood
LOS	Length of stay
PICU	Pediatric intensive care unit
PIM 2	Pediatric Index of Mortality 2
ROM	Risk of mortality
SIRS	Systemic inflammatory response syndrome
VPS	Virtual PICU Systems

From the [1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles; and [2]Keck School of Medicine, University of Southern California, Los Angeles, CA

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elements submitted are determined based on each PICU's level of participation in VPS, not on an individual-patient basis. All VPS data are deidentified.

Children with a reported secondary diagnosis known to affect puberty (eg, adrenogenital disorder, polycystic ovaries, Turner syndrome) were excluded from the analysis. Children aged 2-7 years defined the prepubertal group, and those aged 16-21 years defined the postpubertal group. The pubertal age range was based on pubertal norms.[14-18] We chose not to include children younger than age 2 years because of the elevated testosterone levels in infant males.[19] Comorbidities were obtained from secondary diagnoses, when available, and defined as a chronic condition (with an expected disease duration longer than 12 months) in any of the following categories: cardiovascular, respiratory, neuromuscular, gastrointestinal/renal, oncologic, rheumatologic, endocrine, and other conditions. The Institutional Review Board at Children's Hospital Los Angeles approved this study.

Mandatory VPS data elements used include age, gender, primary diagnosis, PICU length of stay (LOS) for survivors, PICU mortality, and Pediatric Index of Mortality (PIM) 2 score.[20] Additional optional VPS data elements include the use of mechanical ventilation or dialysis (at any time during PICU admission) and secondary diagnoses.

The primary outcome analyzed was PICU mortality. Secondary outcomes included severity of illness (PIM 2), PICU LOS for survivors, and use of mechanical ventilation or dialysis.

Outcomes were compared between prepubertal males and prepubertal females and between postpubertal males and postpubertal females for outcomes. Prepubertal males were not compared with postpubertal males, and prepubertal females were not compared with postpubertal females, owing to age-related differences in types of comorbidities and sites of infection.[6]

Statistical analyses were performed using Statistica version 10 (StatSoft, Tulsa, Oklahoma) and Stata version 10 (StataCorp, College Station, Texas). Categorical variables were analyzed using the χ^2 test with Yates correction, and continuous variables were analyzed with the t test, with appropriate transformations to satisfy assumptions of normality (log transformation for age and PICU LOS, and a logit transformation for PIM 2 risk of mortality [ROM]). Continuous variables are presented as median and IQR.

Random-effects models (ie, linear or logistic mixed models that account for possible nonindependence among observations) were used in multivariate analysis, to control for similarities between patients from the same hospital center.[21] Different models were created for prepubertal children and postpubertal children. To control for the effects of hospital center and severity of illness for the primary outcome of PICU mortality, a baseline logistic regression model was built, using hospital center as the grouping variable. Stepwise models were constructed controlling for severity of illness (PIM 2) and then gender on the outcome of mortality. The −2 log likelihood (ll), Akaike information criterion (AIC), and Schwarz Bayes information criterion (BIC) were used to compare differences between the baseline model (hospital center) and subsequent models, allowing evaluation of each stepwise variable added to the model for improved model fit and parsimony. For the secondary outcome of severity of illness, hierarchical linear regression models were constructed to evaluate independent associations between gender and PIM 2, controlling for hospital center. To satisfy assumptions of normality in the multivariate model, the logit transformation of the predicted ROM (PIM 2 ROM) was used.

Results

We screened 43 192 prepubertal and 20 276 postpubertal hospitalized children for inclusion (**Figures 1** and **2**), and enrolled 575 prepubertal children (47.3% females, 52.7% males) and 445 postpubertal children (52.3% females, 47.6% males) with a primary diagnosis of sepsis or septic shock from 68 PICUs. Overall mortality was 9.6%, with 36% of deaths occurring within 24 hours of PICU admission.

Prepubertal Children

The prepubertal males and prepubertal females were similar in terms of age and the use of dialysis and mechanical ventilation (**Table I**). For the 61.9% of prepubertal children with available information on secondary diagnoses, 70.3% of prepubertal females and 62.4% of prepubertal males had at least 1 comorbidity. An oncologic diagnosis was the most common comorbidity (prepubertal females, 37.7%; prepubertal males, 31.5%).

Mortality was similar in prepubertal females and prepubertal males (9.9% vs 10.9%; $P = .81$). Stratification based on the presence of a comorbidity produced no gender-based difference in mortality (prepubertal females with comorbidity, 13%; prepubertal males with comorbidity, 12.4% [$P = .96$]; prepubertal females without comorbidity, 7.7%; prepubertal males without comorbidity, 5.9% [$P = .98$]). PICU LOS in survivors and PIM 2 ROM did not differ significantly between prepubertal males and prepubertal females (**Table I**).

On random-effects logistic regression modeling controlling for hospital center, only PIM 2 was independently associated with mortality in prepubertal children with sepsis (OR, 1.85; 95% CI, 1.56-2.19; $P < .0001$) (**Tables II** and **III**; available at www.jpeds.com). The model fit from baseline (hospital center) improved significantly with the addition of PIM 2 ($\chi^{2\text{diff}}$, 31.02; $P < .0001$; ll, −161.34; degrees of freedom, 1; AIC, 328.67; BIC, 341.74). However, gender was not independently associated with mortality in prepubertal children, and adding gender to the baseline random-effects model (hospital center) or to the second model (hospital center + PIM 2) did not improve the model fit for the outcome of mortality. For the secondary outcome of severity of illness, after controlling for hospital specific effects, there was no significant difference in PIM 2 ROM between prepubertal males and prepubertal females ($P > .05$).

Postpubertal Children

Postpubertal females and males were similar in terms of age (**Table IV**). For the 61.1% of postpubertal children with available information on secondary diagnoses, 67.2% of