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

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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

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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

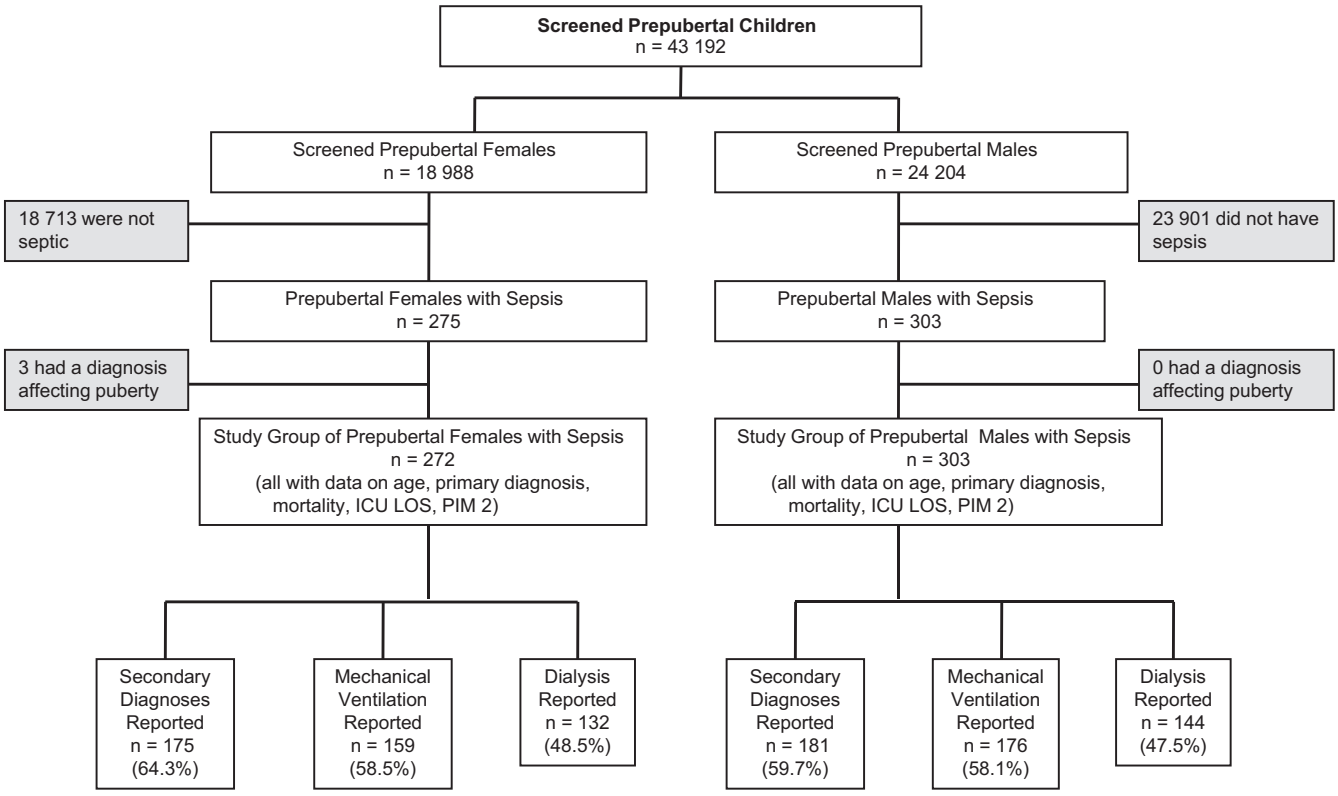

Figure 1. Flow diagram of the prepubertal study subjects and the VPS data available for analysis. *ICU*, intensive care unit.

postpubertal females and 68.8% of postpubertal males had at least 1 comorbidity. An oncologic diagnosis was the most common comorbidity (postpubertal females, 35%; postpubertal males, 39.3%).

Postpubertal males had a higher mortality than postpubertal females (11.8% vs 5.6%; $P = .03$). Stratification based on the presence of comorbidity revealed no gender-based difference in mortality, although a trend toward higher mortality was seen in postpubertal males (postpubertal females with comorbidity, 6.5%; postpubertal males with comorbidity, 12.9% [$P = .22$]; postpubertal females without comorbidity, 4.4%; postpubertal males without comorbidity, 9.5% [$P = .61$]). PICU LOS for survivors and the use of mechanical ventilation or dialysis also were not statistically significantly different between postpubertal females and postpubertal males. Postpubertal males had a higher PIM 2 ROM, however ($P = .02$) (**Table IV**).

On random-effects logistic regression modeling, controlling for hospital center, female gender was independently associated with a lower mortality in postpubertal children (OR, 0.45; 95% CI, 0.22-0.91; $P = .03$) (**Tables V** and **VI**; available at www.jpeds.com). Controlling for hospital center, gender, and severity of illness, PIM 2 was independently associated with mortality in postpubertal children (OR, 1.71; 95% CI, 1.32-2.22; $P < .0001$); however, female gender was no longer independently associated with mortality. Model fit from baseline (hospital center) improved significantly with the addition of severity of illness (PIM 2 $\chi^{2\text{diff}}$, 10.20; $P < .003$; ll, −118.77; degrees of freedom, 1; AIC, 243.55; BIC, 255.84), but gender had only a minimal impact on the model fit for the outcome of mortality. For the secondary outcome of severity of illness, after controlling for hospital effects, female gender was independently associated with a lower PIM 2 ROM in postpubertal children (OR, 0.77; 95% CI, 0.62-0.96; $P = .02$).

Discussion

We have demonstrated that prepubertal males and females admitted to PICUs with sepsis have a similar mortality and initial severity of illness. Postpubertal males with sepsis, however, have higher PICU mortality than postpubertal females, largely explained by their higher initial severity of illness in the PICU. Because PICU mortality was not significantly different in postpubertal males and postpubertal females after controlling for hospital center and severity of illness, it appears that postpubertal males and females respond equally well to PICU therapies for sepsis. The differences in mortality and severity of illness between postpubertal males and females may be explained by sex hormones, comorbidities, source or site of infection, or health-related behavioral patterns.

Severe sepsis often is characterized by an initial proinflammatory state (systemic inflammatory response syndrome

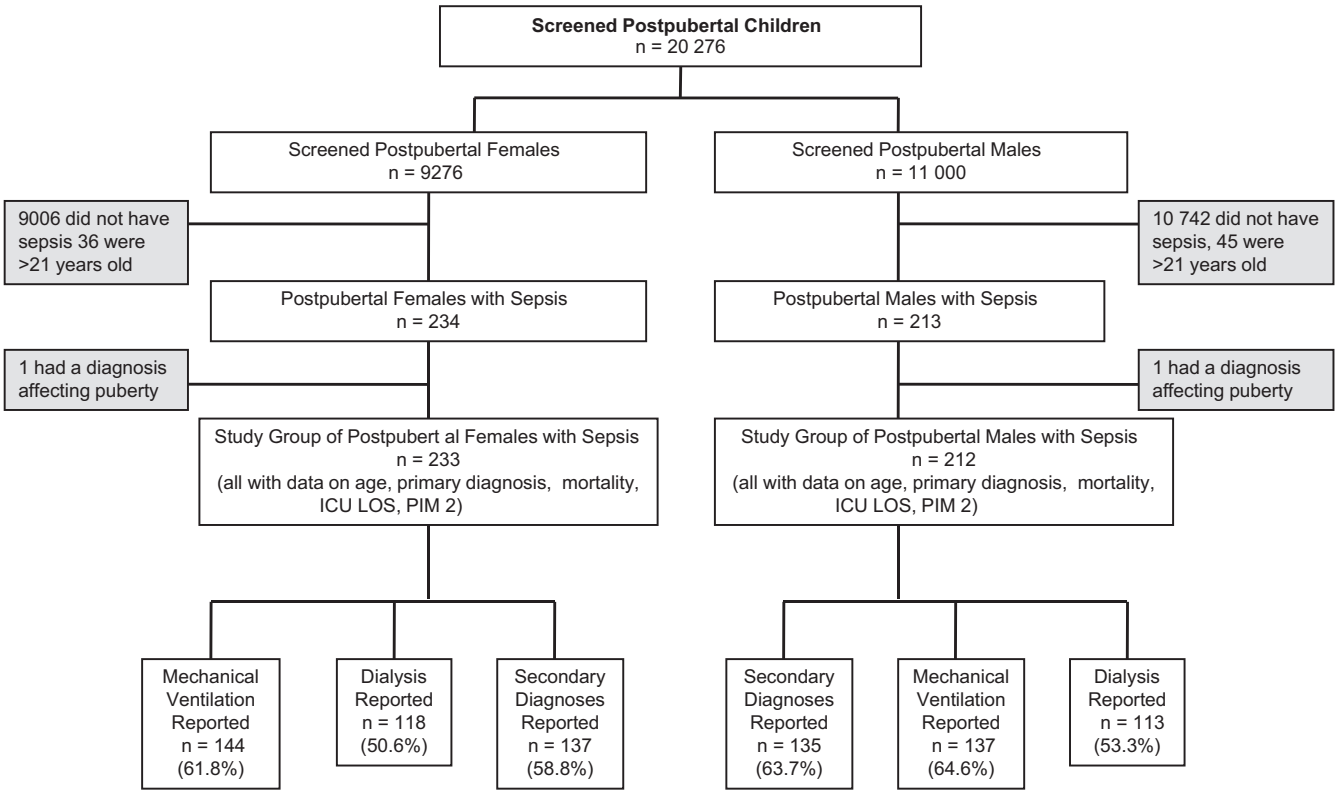

Figure 2. Flow diagram of the postpubertal study subjects and the VPS data available for analysis.

[SIRS]), followed by a compensatory period of anti-inflammation (compensatory anti-inflammatory response syndrome [CARS]). Prolonged SIRS or a pronounced CARS state is thought to cause much of the morbidity and mortality from severe sepsis. Lymphocytes, neutrophils, macrophages, natural killer cells, and endothelial cells all display receptors for sex hormones.[2] The function of these receptors may account for the notable differences in phagocytosis, cytokine production, and cardiovascular function between males and females.[1,2,8,22-26] In general, females have a stronger humoral immune response than males, with higher baseline immunoglobulin levels and greater immunoglobulin production after vaccination.[2] Although testosterone is generally considered an immunosuppressant, some studies have reported higher levels of proinflammatory cytokines in men.[2,23,25]

The immune response to sepsis is a complex process that occurs in stages. Although there is substantial evidence suggesting that sex hormones play a role in modulating this response, the net influence on either SIRS or CARS is yet unclear and may differ from patient to patient depending on numerous other factors.

Animal research suggests that sex hormone therapy in sepsis can influence outcome. Estrogen administration improves the response to sepsis in male mice, and testosterone administration is associated with worse outcomes in female mice.[24,27,28] In a study of male mice with sepsis, administration of a selective estrogen receptor agonist was associated with improved survival.[29] Although estrogen and testosterone receptors are potential future therapeutic targets in sepsis, the specific immune response to estrogen or testosterone in humans awaits further elucidation.

SIRS-induced shock with cardiovascular collapse resulting in multiorgan failure is a common cause of sepsis mortality.[7,30,31] Adult studies of traumatic shock have shown lower lactate levels (even with higher injury severity scores) and less organ failure in women than men.[32,33] In septic shock, the rate of renal dysfunction is lower in women.[34] Differences

Table I. Characteristics of prepubertal children with sepsis

	Females (n = 272)	Males (n = 303)	*P* value
Age, months, median (IQR)	55.0 (37.5-74.2)	51.3 (33.5-75.3)	.47*
Mechanical ventilation, n (%)†	60 (37.7)	55 (31.3)	.26‡
Dialysis, n (%)§	7 (5.3)	6 (4.2)	.87‡
PICU LOS, days, median (IQR)	2.85 (1.28-6.46)	2.52 (1.41-5.94)	.89*
PIM 2 ROM, median (IQR)	0.014 (0.010-0.053)	0.016 (0.010-0.058)	.24*
Mortality, n (%)	27 (9.9)	33 (10.9)	.81‡

**t* test based on the appropriate variable transformation to satisfy assumptions of normality.
†Mechanical ventilation data were available for 159 prepubertal females and 176 prepubertal males.
‡χ^2 test.
§Dialysis data were available for 132 prepubertal females and 144 prepubertal males.

Table IV. Characteristics of postpubertal children with sepsis

	Females (n = 233)	Males (n = 212)	*P* value
Age, months, median (IQR)	211.3 (201.8-230.2)	210.4 (201.7-230.3)	.77*
Mechanical ventilation, n (%)†	35 (24.3)	45 (32.8)	.15‡
Dialysis, n (%)§	14 (11.8)	10 (8.8)	.59‡
PICU LOS, days, median (IQR)	2.50 (1.37-5.67)	2.90 (1.30-6.35)	.66*
PIM 2 ROM, median (IQR)	0.013 (0.009-0.041)	0.013 (0.010-0.050)	.02*
Mortality, n (%)	13 (5.6)	25 (11.8)	.03‡

*t test based on the appropriate variable transformation to satisfy assumptions of normality.
†Mechanical ventilation data were available for 144 postpubertal females and 137 postpubertal males.
‡χ^2 test.
§Dialysis data were available for 118 postpubertal females and 113 postpubertal males.

in cardiovascular responses, possibly related to endothelial cell sex hormone receptors, may lead to the lower rate of hemodynamic instability and lower severity of illness on presentation in females.

Although our data suggest the possibility of hormonal differences as a reason for the higher mortality in postpubertal males compared with postpubertal females, there are other possible explanations as well. X-linked genetic differences between the genders may be a factor, although it unlikely plays a large role, given the similar mortality in prepubertal children. Children with comorbidities, particularly oncologic diseases, are at increased risk for mortality including from sepsis and represent a large percentage of pediatric hospital and PICU admissions.[11,12,35-40] The relationships among gender, comorbidity type, and mortality merit further investigation. Unfortunately, given the limited information on secondary diagnoses and the resultant diminished power within each comorbidity subgroup, we were unable to fully investigate the influence of comorbidities on mortality in this study. Our multivariate analysis controlled for severity of illness; however, current pediatric severity of illness scores might not completely characterize the contribution of chronic conditions to ROM.[40] We chose not to investigate whether the survival benefit is related to the absence of testosterone or to the presence of estrogen (by comparing the mortality difference between prepubertal males and postpubertal males and between prepubertal females and postpubertal females), owing to an inability to control for the age-related differences in underlying disease prevalence, site of infection, and comorbidities, as noted by Watson et al[6] in their study of children with severe sepsis. Accordingly, the higher sepsis mortality in postpubertal males compared with postpubertal females also may be related to differences in underlying specific comorbidities, source or site of infection, or interventions that we were unable to characterize.

Moreover, there are important differences in the health-related behavioral patterns of postpubertal males and postpubertal females. Adolescent males are less likely than adolescent females to seek medical attention as an outpatient, and adult males take a longer time to seek attention for myocardial infarction than adult females.[41,42] Postpubertal males coming to medical attention for sepsis later after symptom onset would clearly affect their severity of illness at presentation, and thus outcomes.

This study has several limitations, largely related to the available dataset. Large retrospective population studies in children often are constrained by limited collected data, and prospective research with similar enrollment numbers is generally impractical. The clinicians caring for the children diagnosed sepsis, and although guidelines for the diagnosis of pediatric sepsis and septic shock were published before the start of this study, there is no formal standardization for diagnosis entry in the VPS database.[43] Limited secondary diagnosis information did not allow us to fully characterize comorbidities. In addition, we were limited to defining pubertal status by age, not through the more accurate methods of assessing hormone levels or physical examination.

Confirming and further characterizing the mortality difference between postpubertal males and females will be important for further investigations and interventions aimed at improving outcomes after shock. It is unlikely that direct hormone therapy will have a place in the treatment of septic shock any time soon, owing to multiple potential problems, including the adverse side effects of hormone therapy and the difficulty identifying which hormones to give and which specific patient population may benefit from specific hormones. On the other hand, further evidence demonstrating different outcomes in postpubertal males and females with septic shock may lead to studies that target subpopulations with unique risk factors for mortality from septic shock, possibly contributing to the development of individualized treatment strategies and additional intervention possibilities. ■

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Table II. Random-effects models in prepubertal children with sepsis

	AIC	BIC	ll	Δll (χ^2)	df	*P* value (χ^2)
Model 1: Hospital center	388.712	397.420	−192.356	-	2	-
Model 2: Hospital center + PIM 2	328.674	341.737	−161.337	31.019*	1	<.0001
Model 3: Hospital center + PIM 2 + gender	330.610	348.027	−161.305	0.032†	1	1
Model 4: Hospital center + gender	390.567	403.630	−192.284	0.072*	1	1

df, degrees of freedom.
*Δll from model 1.
†Δll from model 2.

Table V. Random-effects models in postpubertal children with sepsis

Model	AIC	BIC	ll	Δll (χ^2)	df	*P* value (χ^2)
Model 1: Hospital center	261.946	270.142	−128.973	-	2	-
Model 2: Hospital center + PIM 2	243.546	255.840	−118.773	10.200*	1	.003
Model 3: Hospital center + PIM 2 + gender	242.513	258.905	−117.257	1.517†	1	.44
Model 4: Hospital center + gender	258.828	271.122	−126.414	2.559*	1	.22

*Δll from model 1.
†Δll from model 2.

Table III. Multivariate regression for the outcomes of mortality and severity of illness (PIM 2) in prepubertal children with sepsis

Outcome	OR (95% CI)	*P* value
Mortality		
Model 1		
Hospital center	0.12 (0.08-0.18)	.0001
Female gender	0.90 (0.53-1.54)	.74
Model 2		
Hospital center	0.71 (0.40-1.26)	.24
PIM 2	1.85 (1.56-2.19)	.0001
Female gender	1.08 (0.60-1.95)	.80
Severity of illness (PIM 2)		
Hospital center	0.04 (0.03-0.05)	.0001
Female gender	0.86 (0.67-1.10)	.24

Table VI. Multivariate regression for the outcomes of mortality and severity of illness (PIM 2) in postpubertal children with sepsis

Outcome	OR (95% CI)	*P* value
Mortality		
Model 1		
Hospital center	0.28 (0.10-0.81)	.02
Female gender	0.45 (0.22-0.91)	.03
Model 2		
Hospital center	0.76 (0.30-1.94)	.57
PIM 2	1.71 (1.32-2.22)	.0001
Female gender	0.53 (0.25-1.10)	.09
Severity of illness (PIM 2)		
Hospital center	0.03 (0.02-0.03)	.0001
Female gender	0.77 (0.62-0.96)	.02