

# Psychiatric Morbidity in Pediatric Critical Illness Survivors

## *A Comprehensive Review of the Literature*

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**Objectives:** To review the prevalence of psychiatric syndromes in pediatric critical illness survivors as well as to summarize data on vulnerabilities and pediatric intensive care unit exposures that may increase risk of developing these syndromes.

**Data Sources:** MEDLINE (1966-2009), the Cochrane Library (2009, issue 3), and PsycINFO (1967-2009) as of August 9, 2009.

**Study Selection:** Case-control, cross-sectional, prospective cohort and retrospective cohort studies as well as randomized controlled trials.

**Main Exposures:** Hospitalization for the treatment of a critical illness.

**Main Outcome Measures:** Assessments of psychiatric symptoms/disorders at least once after discharge.

**Results:** Seventeen studies were eligible. The most commonly assessed psychiatric disorders were posttraumatic stress disorder and major depression. The point prevalence of clinically significant posttraumatic stress disorder symptoms ranged from 10% to 28% (5 stud-

ies). The point prevalence of clinically significant depressive symptoms ranged from 7% to 13% (2 studies). Preillness psychiatric and/or developmental problems and parental psychopathology were associated with vulnerability to psychiatric morbidity. Neither age nor sex of a child consistently increased vulnerability to postillness psychopathology. Exposure to increased severity of medical illness and pediatric intensive care unit service-delivery characteristics (eg, invasive procedures) were predictors of psychiatric illness in some but not all studies. Early postillness psychiatric symptoms were predictors of later psychiatric morbidity.

**Conclusions:** Psychiatric morbidity appears to be a substantial problem for pediatric critical illness survivors. Future research should include more in-depth assessment of post-critical illness depressive, anxiety, and psychotic symptoms, validate existing psychiatric instruments, and clarify how vulnerability factors, pediatric intensive care unit service-delivery characteristics, and severity of critical illnesses are associated with subsequent psychopathology.

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**M**ORE THAN 200 000 children annually in the United States require admission to a pediatric intensive care unit (PICU) for the treatment of critical illnesses.<sup>1</sup> With recent advances in pediatric critical care medicine, more children are surviving critical illnesses.<sup>2</sup> Accompanying this increase in survival, research in the field has begun to focus on long-term outcomes of pediatric critical illness survivors, including physical health,<sup>3</sup> health-related quality of life,<sup>4,5</sup> and mental health.<sup>6,7</sup>

Critical illnesses and their requisite therapies expose children to extreme stressors, including pain from invasive procedures, respiratory insufficiency, delirium with potential associated psychotic experiences, and separation from their families. Critical illnesses are also, by

definition, life threatening. Therefore, psychiatric disorders, which can be triggered by exposure to extreme stressors in a vulnerable population<sup>8</sup> and are highly prevalent in children exposed to traumatic events,<sup>8</sup> are a potential concern in pediatric critical illness survivors. The recognition of psychological distress in these children is important for several reasons. Mental disorders carry an increased risk of suicide, and this risk as well as the persistence of symptoms can continue into adulthood.<sup>9,10</sup> Also, psychiatric disorders in this population may impair functioning in school, family, and social roles, lead to lags in development, and negatively affect health-related quality of life.<sup>11,12</sup>

In this article, we present the results of a review of the following: (1) the prevalence of psychiatric syndromes in children surviving critical illnesses; (2) youth

and parental vulnerabilities that may increase the risk of psychopathology; and (3) features of medical illness presentation and PICU exposures that elevate the risk for psychiatric morbidity. Our article differs from prior reviews on this topic<sup>6,7</sup> in its focus on psychiatric syndromes following critical illnesses as well as its comprehensive review of potential vulnerabilities and exposures that may increase the risk for psychiatric disorders.

## METHODS

### SEARCH STRATEGY

To identify studies eligible for review, we searched MEDLINE (1966-2009), the Cochrane Library (2009, issue 3), and PsycINFO (1967-2009) as of August 9, 2009. Our search strategy included the following terms mapped to the appropriate medical subject headings of the US National Library of Medicine and “exploded”: (*mental disorders* or *psychometrics*) and (*respiratory distress syndrome*, *adult or critical care* or *critical illness* or *intensive care units* or *sepsis* or *burns*). We also included the following terms as text words: (*depress\** or *stress* or *anxi\**) and (*respiratory distress syndrome* or *ARDS* or *acute lung injury* or *ALI*). The search was limited to English-language articles.

### STUDY SELECTION

We sequentially reviewed citations, abstracts, and full-text articles to select eligible studies. Articles were selected for review if they met the following criteria: (1) the study population comprised pediatric critical illness survivors between the ages of 2 and 19 years; and (2) psychiatric assessments occurred at any time following illness resolution. Studies of neonatal and adult intensive care unit survivors were excluded, as were abstracts, case reports, and review articles. We also excluded studies that only included transplant surgery survivors owing to concerns for the confounding of risk for psychiatric morbidity conferred by organ transplants (owing to psychiatric adverse effects of immunosuppressant medications<sup>13</sup> and the severity of chronic illness before the transplant<sup>14</sup>).

### DATA ABSTRACTION AND STUDY QUALITY

For each eligible study, we abstracted information regarding study cohorts, psychiatric measures, and potential vulnerabilities and exposures. When necessary, we contacted authors of eligible studies for additional study data.

Study quality was assessed using 5 criteria adapted from the US Preventive Services Task Force<sup>15</sup> and a previous systematic review of heterogeneous outcome data<sup>16</sup>: (1) enrollment of consecutive patients; (2) no loss to follow-up of more than 10% of study participants prior to the first psychiatric symptom assessment; (3) description of patients lost to follow-up; (4) at least 1 statistical comparison between patients lost to follow-up and those remaining in the study; and (5) adjustment for confounders by stratification, statistical adjustment, or comparison with a matched population. Quality criteria were not used in decisions regarding inclusion or exclusion of eligible studies.

## RESULTS

### STUDY CHARACTERISTICS AND QUALITY

We reviewed 8569 citations, 553 abstracts, and 58 full-text articles for inclusion. Forty-one articles were excluded for

lack of child psychiatric outcomes. Seventeen studies describing 16 unique cohorts of pediatric critical illness survivors were eligible for data abstraction. eTable 1 (<http://www.archpediatrics.com>) shows baseline descriptive data for the 17 studies ordered by follow-up assessment times. Follow-up periods ranged from immediately following hospital discharge<sup>17</sup> to up to 16 years after acute care discharge.<sup>18</sup> The studies enrolled 1067 unique patients. Seven of the studies were conducted in the United Kingdom,<sup>19-25</sup> 5 in the United States,<sup>26-30</sup> 2 in the Netherlands,<sup>18,31</sup> 1 in Canada,<sup>26</sup> 1 in India,<sup>17</sup> and 1 in Switzerland.<sup>32</sup>

Four of the studies excluded patients with a history of psychiatric disorders.<sup>21-23,31</sup> In 3 of these, patients were excluded only if they were admitted to the PICU for a suicide attempt.<sup>21,23,31</sup> In the other one, patients with any prior or ongoing psychiatric disorder were excluded.<sup>22</sup> One of the studies reported on a premorbid history of developmental problems.<sup>20</sup> Six percent of children in this study had a history of developmental problems. Another study explored prior psychiatric difficulties using the Strengths and Difficulties Questionnaire, a validated measure of general psychopathology in children completed by their parents and teachers.<sup>19</sup> Two studies reported on premorbid temperament using validated parent-report measures, the Temperament Measurement Schedule and the School-Age Temperament Inventory, in school-aged children.<sup>17,27</sup>

Only 6 of the 17 studies were of consecutive samples (eTable 2).<sup>17-21,27</sup> Most of the studies demonstrated high retention, although only 4 of the studies described the characteristics associated with participant loss<sup>18,21,30,31</sup> and only 4 of the studies compared patients lost to follow-up and those who completed the study.<sup>18,26,31,33</sup> More than half of the studies adjusted for potential confounders in analyses.<sup>18-22,25-29,31,33</sup>

### MEASURES OF PSYCHIATRIC SYMPTOMS

Eight hundred ninety-nine subjects completed at least 1 posttraumatic stress disorder (PTSD) measure, 166 completed measures of other anxiety disorders, and 224 subjects completed at least 1 depression measure. Twelve of the studies used in-person assessments with a clinician,\* 1 used an in-person computer-based assessment,<sup>30</sup> 3 used mailed questionnaires,<sup>22,25,33</sup> and 1 had a combination of in-person assessments and mailed questionnaires.<sup>18</sup> One of the studies used only questionnaires completed by parents.<sup>26</sup> The remaining studies used reports from the children themselves with or without additional parental reports. Seven studies used diagnostic interviews to ascertain psychiatric morbidity.<sup>20,22,27-30,32</sup> The remaining studies used only questionnaires to measure psychopathology (**Table 1**).

### PREVALENCE OF PSYCHIATRIC SYMPTOMS/DISORDERS

In determining the median point prevalence of questionnaire-ascertained clinically significant psychiatric symptoms, one important challenge was that several of the

\*References 17, 19-21, 23, 24, 26, 27, 29, 31, 32.

**Table 1. Measurements of Psychiatric Symptoms/Syndromes, Ordered by Follow-up Time**

Psychiatric Condition and Source	Instrument	Follow-up, mo <sup>a</sup>	Patients at Follow-up, No.	Score <sup>a</sup>	Cutoff Score	Point Prevalence, %		
PTSD								
Muranjan et al, <sup>17</sup> 2008	IES-I IES-A ]	0	30	1.6 (2.2)	26	43		
				0.2 (0.8)		7		
Melnyk et al, <sup>26</sup> 2004	PHSI ]	1	30	0.3 (0.6)	7	...		
				0 (0)		...		
Connolly et al, <sup>27</sup> 2004 Rennick et al, <sup>33</sup> 2002	DISC CIES ]	1.4 (0.5) [1-2]	43	NA	NA	12		
				1.5		60	0.4 (0.2)	...
				6		60	0.3 (0.2)	...
				12		67	...	...
Saxe et al, <sup>28</sup> 2005	Child PTSD Reaction Index	3	72	16.8 (13.1)	...	...		
Shears et al, <sup>19</sup> 2005 <sup>b</sup>	IES	3	26	...	30	15		
Bronner et al, <sup>31</sup> 2008	CRTI ]	3	29	...	47	14		
				9		28	...	18
Colville et al, <sup>21</sup> 2008	IES-R	3 [1.8-5.7]	96	9 [0-26]	17	28		
Elison et al, <sup>22</sup> 2008	IES	4.8 (1.4)	15	27.3 (19.4), 27.5 (12.2-37.2)	...	...		
Rees et al, <sup>23</sup> 2004	CAPS-C ]	7.7 (6.9-8.6)	19	NA	NA	21 <sup>c/5<sup>d</sup></sup>		
				21		10 (6-24)	30	17
Judge et al, <sup>24</sup> 2002	IES	8.9 [3-12]	29	...	20	10		
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	0		
Vermunt et al, <sup>18</sup> 2008	PTSP	[48-192]	192	4.3	...	...		
Landolt et al, <sup>32</sup> 2009	CAPS-CA	53 (24)	43	NA	NA	19		
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	7 <sup>e</sup> /30 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	2		
Overanxious disorder								
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	30 <sup>e</sup> /33 <sup>f</sup>		
Separation anxiety disorder								
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	3		
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	0 <sup>e</sup> /7 <sup>f</sup>		
Phobic disorder								
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	13		
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	47 <sup>e</sup> /47 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	44		
Depression								
Muranjan et al, <sup>17</sup> 2008	BDS ]	0	30	6.9 (4.0)	13	13		
				1		30	5.0 (3.7)	...
Rees et al, <sup>23</sup> 2004	BDS	7.7 (6.9-8.6)	30	7.4 (4.7)	15	7		
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	0		
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	3 <sup>e</sup> /27 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	6		
Pope et al, <sup>25</sup> 2007	BDI-II	141	36	10.4 (9.7)	20	...		
Dysthymic disorder								
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	10 <sup>e</sup> /10 <sup>f</sup>		
Tic disorder								
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	6		
Psychosis								
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	3 <sup>e</sup> /6 <sup>f</sup>		
ADHD								
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	0 <sup>e</sup> /13 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	2		
Oppositional defiant disorder								
Shears et al, <sup>20</sup> 2007 <sup>b</sup>	K-SADS-IV-R	11.9 (2.3)	48	NA	NA	13		
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	23 <sup>e</sup> /23 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	0		
Conduct disorder								
Stoddard et al, <sup>29</sup> 1989	DICA-C, DICA-P	108	30	NA	NA	7 <sup>e</sup> /17 <sup>f</sup>		
Thomas et al, <sup>30</sup> 2009	C-DISC4	125	50	NA	NA	12		
Behavioral problems								
Melnyk et al, <sup>26</sup> 2004	BASC composite index ]	1	...	...	...	...		
				3		89	...	
				6		89	...	
				12		67	...	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC, Behavioral Assessment Scale for Children; BDI-II, Beck Depression Inventory, second edition; BDS, Birleson Depression Scale; CAPS-C, Clinician-Administered PTSD Scale for Children; CAPS-CA, Clinician-Administered PTSD Scale for Children and Adolescents; C-DISC4, Computerized Diagnostic Interview Schedule for Children, fourth edition; CIES, Children's Impact of Events Scale; CRTI, Children's Response to Trauma Inventory; DICA-C, Diagnostic Instrument for Children and Adolescents-Child Version; DICA-P, Diagnostic Instrument for Children and Adolescents-Parent Version; DISC, Diagnostic Interview Schedule for Children; IES, Impact of Events Scale; IES-A, IES avoidance subscale; IES-I, IES intrusion subscale; IES-R, IES-Revised; K-SADS-IV-R, Schedule for Affective Disorders and Schizophrenia for School-Age Children-IV-Revised; NA, not applicable; PHSI, Post-Hospital Stress Index for Children; PTSD, posttraumatic stress disorder; PTSP, Posttraumatic Stress Problems Scale; ellipses, not reported.

<sup>a</sup>Values are expressed as mean, (standard deviation), median, (interquartile range), or [absolute range].

<sup>b</sup>The 2 studies by Shears et al<sup>19,20</sup> reported data on the same cohort but at different follow-up times.

<sup>c</sup>Point prevalence of CAPS-C PTSD in the year following pediatric intensive care unit admission.

<sup>d</sup>Point prevalence of CAPS-C PTSD at the time of the follow-up assessment.

<sup>e</sup>Point prevalence of the disorder at the time of the interview.

<sup>f</sup>Lifetime prevalence of the disorder.

included studies collected psychiatric symptom data at more than 1 time point. In these cases, we used the median value from each study in our calculation of the overall median point prevalences of disorders. Table 1 summarizes the prevalences of post-critical illness psychopathology. The most commonly assessed psychiatric syndromes were PTSD and major depression. The point prevalence of questionnaire-ascertained clinically significant PTSD symptoms in pediatric critical illness survivors ranged from 10%<sup>24</sup> to 28%,<sup>21</sup> with a median point prevalence of 16% (5 studies, n=201). The prevalence of diagnostic interview-ascertained PTSD after a critical illness was 0%<sup>20</sup> to 21%,<sup>23</sup> with a median prevalence of 13% (6 studies, n=233). The lifetime prevalence of PTSD in a cohort of 30 pediatric burn injury survivors was 30%.<sup>29</sup> The point prevalence of questionnaire-ascertained clinically significant depressive symptoms ranged from 7%<sup>23</sup> to 13%,<sup>17</sup> with a median point prevalence of 10% (2 studies, n=60). The prevalence of major depression following a critical illness as ascertained by diagnostic interview was 0%<sup>20</sup> to 6%,<sup>30</sup> with a median prevalence of 3%<sup>29</sup> (3 studies, n=128). The lifetime prevalence of major depression in 1 study was 27%.<sup>29</sup>

#### VULNERABILITY FACTORS ASSOCIATED WITH RISK FOR PSYCHIATRIC SYMPTOMS/DISORDERS

Pre-critical illness psychopathology was a potential vulnerability factor for post-PICU psychiatric morbidity in 2 studies (**Table 2**).<sup>19,27</sup> Less consistent pre-critical illness predictors of post-critical illness psychiatric disorders included a child's sex (1 of 6 studies<sup>20,21,25,31-33</sup>), younger age (1 of 8 studies<sup>17,18,20,21,28,31-33</sup>), developmental problems,<sup>20</sup> and pre-PICU maternal negative life events.<sup>20</sup> The following preillness variables were not associated with post-critical illness psychopathology in youths: family socioeconomic status,<sup>17,20,32</sup> ethnicity,<sup>20,21</sup> social deprivation (as ascertained by the Townsend Deprivation Index, a questionnaire derived from UK census data measures of familial social isolation),<sup>21</sup> birth order,<sup>20</sup> youth's level of education,<sup>17</sup> pre-PICU level of family support,<sup>27</sup> maternal education,<sup>33</sup> parental marital status,<sup>20</sup> pre-PICU temperamental difficulties,<sup>17,27</sup> or pre-PICU cognitive level.<sup>27</sup>

#### CRITICAL ILLNESS- AND TREATMENT-RELATED EXPOSURES

Exposure to invasive procedures predicted post-critical illness psychiatric morbidity in 2 of 3 studies,<sup>17,32,33</sup> PICU length of stay (LOS) predicted later psychiatric symptoms in 2 of 6 studies,<sup>17,20,21,27,31,33</sup> and severity of illness at admission predicted later psychopathology in 3 of 8 studies.<sup>17,18,20,21,28,31-33</sup> Emergency admission to the PICU,<sup>21</sup> hospital LOS in the absence of septic shock,<sup>20</sup> and no family visits during the PICU stay<sup>33</sup> also predicted post-critical illness psychiatric morbidity. Maternal presence at the time a child sustained a serious burn injury was protective against PTSD in 1 study,<sup>32</sup> and maternal participation in a program designed to enhance emotional regulation and diminish anxiety was associated with fewer behavioral problems in young PICU survivors.<sup>26</sup> The fol-

lowing critical illness- and treatment-related exposures were not associated with post-critical illness psychiatric morbidity: PICU admission diagnosis,<sup>17,31</sup> traumatic brain injury,<sup>21</sup> duration of mechanical ventilation,<sup>31</sup> hospital LOS<sup>19,32</sup> (particularly in the presence of septic shock<sup>20</sup>), sepsis or septic shock,<sup>20,21</sup> or receipt of opiates and/or benzodiazepines for 2 days or longer.<sup>21</sup>

#### POST-CRITICAL ILLNESS FACTORS

Psychiatric symptoms, memories of in-PICU psychotic/nightmare experiences, and cognitive difficulties in the days and months following a critical illness were significant prospective predictors or cross-sectional correlates of post-critical illness psychopathology.<sup>19,21,22,28,31</sup> Both child and parental retrospective perceptions of the threat to the child's life from the critical illness and the severity of illness were cross-sectional correlates of child PTSD symptoms.<sup>23</sup> Parental psychiatric symptoms were cross-sectional correlates of youths' post-critical illness PTSD symptoms in 3 studies.<sup>19,23,31</sup> The timing of the post-acute care pediatric follow-up visit was not a predictor of PTSD symptoms in 1 study,<sup>31</sup> nor was the length of follow-up in another study.<sup>32</sup>

#### COMMENT

Our review of psychiatric morbidity in pediatric critical illness survivors found that the point prevalence of substantial psychopathology, particularly PTSD symptoms, was high within the first year following hospitalization. To our knowledge, there are no general population estimates in children for the questionnaires discussed in this review. Nevertheless, it is interesting to note that the point prevalence of substantial PTSD symptoms in pediatric critical illness survivors is as high as or higher than that of traumatically injured children (14% at approximately 4 months<sup>34</sup>) and pediatric cancer survivors (12% of pediatric sarcoma survivors at a mean of 17 years after treatment<sup>35</sup>) using 2 of the same questionnaires, the Impact of Events Scale<sup>35</sup> and the Impact of Events Scale-Revised.<sup>34</sup> Importantly, because premorbid psychopathology may confer vulnerability to postillness psychiatric morbidity and some of the reviewed studies excluded youths with psychiatric histories, our prevalence estimates of post-critical illness psychiatric disorders are likely underestimates.

Although 14 studies examined potential vulnerabilities and exposures that could convey risk for post-critical illness psychiatric morbidity, many of the specific factors examined were unique to particular studies. Nonetheless, where similar factors were considered across multiple studies, some tentative conclusions can be made: (1) neither sex nor age appear to be consistent vulnerabilities; (2) pre-PICU psychiatric and/or developmental problems in youths are fairly consistent vulnerabilities that increase the risk of subsequent PTSD symptoms; (3) medical illness severity and PICU service-delivery characteristics such as LOS and invasive procedures may increase risk; (4) early postillness psychiatric symptoms may predict later psychiatric symptoms; and (5) parental psychiatric

**Table 2. Potential Vulnerability and/or Exposure Factors for Psychiatric Morbidity**

Source	Psychiatric Symptoms/ Disorder Scale	Measure of Association	Potential Vulnerability and/or Exposure Factors	Statistic
Muranjan et al. <sup>17</sup> 2008 (n=30)	IES-I at hospital discharge	Spearman rank test	TISS score Age, SES, education, nature of illness, illness severity, PICU LOS, premorbid temperament	$R=0.51$ , $P=.004$ $P=NS$
Melnik et al. <sup>26</sup> 2004 (n=67)	BASC composite index	$\chi^2$ test	Mother not participating in COPE program	$P<.01$
Connolly et al. <sup>27</sup> 2004 (n=43)	PTSD	Quantile regression	ICU LOS $\geq 48$ h Premorbid cognitive level Negative reactivity Approach/withdrawal Dimensions of temperament Family support	$r^2=0.19$ , $P=.001$ $P=.49$ $P=.95$ $P=.89$ $P=.83$ $P=.83$
Rennick et al. <sup>33</sup> 2002 (n=60)	CIES at 6 wk  CIES at 6 mo	Wilcoxon signed rank test Multiple regression  Multiple regression	PTSD symptoms preoperatively Child's age Invasive procedures Severity of illness LOS Maternal education Child's age Invasive procedures Severity of illness LOS Maternal education Child's sex Family visiting	$z=-2.62$ , $P=.009$ $\beta_{st}=-0.14$ , $P=NS$ $\beta_{st}=0.29$ , $P<.05$ $\beta_{st}=0.02$ , $P=NS$ $\beta_{st}=-0.08$ , $P=NS$ $\beta_{st}=-0.05$ , $P=NS$ $\beta_{st}=-0.01$ , $P=NS$ $\beta_{st}=0.0006$ , $P=NS$ $\beta_{st}=0.0004$ , $P=NS$ $\beta_{st}=-0.002$ , $P=NS$ $\beta_{st}=0.004$ , $P=NS$ $\beta_{st}=0.03$ , $P=NS$ $\beta_{st}=-0.08$ , $P<.05$
Saxe et al. <sup>28</sup> 2005 (n=72)	PTSD at 3 mo	Pearson correlation	Age TBSA burned Separation anxiety after burn Dissociation after burn PTSD symptoms 10 d after burn	$r=-0.17$ , $P=NS$ $r=0.49$ , $P<.001$ $r=0.68$ , $P<.001$ $r=0.36$ , $P<.01$ $r=0.45$ , $P<.001$
Shears et al. <sup>19</sup> 2005 (n=26) <sup>a</sup>	IES at 3 mo	Spearman rank test	Hospital LOS, d Premorbid SDQ score Follow-up SDQ score Maternal IES score	$r=0.01$ , $P=.95$ $r=0.48$ , $P=.01$ $r=0.50$ , $P=.007$ $r=0.42$ , $P=.03$
Shears et al. <sup>20</sup> 2007 (n=31) <sup>a</sup>	Psychiatric disorder in year after meningococcal disease  Psychiatric disorder at 12-mo follow-up	Multivariate logistic regression  Multivariate logistic regression	PICU admission Shock  Developmental problems Impact of maternal premorbid negative life events Hospital LOS, d GMSPS Shock $\times$ GMSPS Shock $\times$ hospital LOS, d PICU admission Shock  Developmental problems Premorbid SDQ impact score GMSPS PICU LOS, d Shock $\times$ PICU LOS, d Age, sex, social class, ethnicity, parental marital status, birth order position	$UOR=7.35$ (95% CI, 1.3 to 42.0) $UOR=4.66$ (95% CI, 1.0 to 20.9), $AOR=0.02$ (95% CI, 0.0 to 64.7), $P=.34$ $UOR=1.55$ (95% CI, 0.4 to 6.3) $AOR=1.61$ (95% CI, 1.1 to 2.4), $P=.02$  $AOR=2.53$ (95% CI, 1.1 to 5.7), $P=.03$ $AOR=0.29$ (95% CI, 0.09 to 0.9), $P=.03$ $AOR=7.61$ (95% CI, 1.4 to 42.4), $P=.02$ $AOR=0.38$ (95% CI, 0.2 to 0.9), $P=.03$ $UOR=4.8$ (95% CI, 1.0 to 23.3) $UOR=5.5$ (95% CI, 1.7 to 17.6), $AOR=9.15$ (95% CI, 0.95 to 88.2), $P=.06$  $UOR=3.4$ (95% CI, 1.2 to 9.9) $AOR=2.46$ (95% CI, 1.0 to 6.2), $P=.06$ $AOR=1.54$ (95% CI, 1.1 to 2.1), $P=.008$ $AOR=1.48$ (95% CI, 0.9 to 2.4), $P=.11$ $AOR=0.55$ (95% CI, 0.32 to 0.95), $P=.03$ $P=NS$

(continued)

symptoms are strongly associated with their children's post-critical illness psychiatric morbidity. The findings regarding age, sex, and prior psychiatric conditions are in line with those of studies of adult general intensive care unit survivors.<sup>36,37</sup> However, studies of adults have not found that severity of physical illness was associated with risk for post-intensive care unit psychopathology,<sup>36,37</sup> and there are inconsistencies regarding whether intensive care unit service-delivery characteristics such as LOS increase risk.<sup>36-38</sup>

The existing literature has several important limitations. First, only 3 small studies prospectively assessed depression and only 4 studies assessed psychiatric dis-

orders other than PTSD or major depression, leaving further questions about these important outcomes in critically ill children. Trauma-exposed youth are at increased risk for developing major depression and anxiety disorders comorbid with PTSD,<sup>39</sup> suggesting that pediatric critical illness survivors may have similar risks. Second, none of the questionnaires used to assess psychiatric symptoms in the described studies have been validated in pediatric critical illness survivors. Also, 1 of the studies found substantial difficulties with the psychometric properties of the Impact of Events Scale, leading to changes in the final questionnaire used<sup>33</sup> as well the group's endeavors to create a new questionnaire to ascertain these symp-

**Table 2. Potential Vulnerability and/or Exposure Factors for Psychiatric Morbidity (continued)**

Source	Psychiatric Symptoms/ Disorder Scale	Measure of Association	Potential Vulnerability and/or Exposure Factors	Statistic
Bronner et al. <sup>31</sup> 2008 (n=29)	CRTI at 3 mo	Spearman rank test	PICU LOS	$R=-0.12, P=NS$
			Length of MV (n=18)	$R=-0.20, P=NS$
			Reason for PICU admission	$R=-0.00, P=NS$
			PIM score	$R=0.11, P=NS$
			Follow-up time	$R=0.00, P=NS$
			Sex	$R=0.13, P=NS$
			Age	$R=0.02, P=NS$
			Mother's psychological distress score (n=25)	$R=0.48, P<.05$
			Mother's SRS-PTSD score (n=27)	$R=0.64, P<.01$
			Father's psychological distress score (n=23)	$R=0.37, P=NS$
	Father's SRS-PTSD score (n=19)	$R=0.43, P=NS$		
	CRTI at 9 mo	Spearman rank test	PICU LOS (n=28)	$R=0.25, P=NS$
			Length of MV (n=20)	$R=0.28, P=NS$
			Reason for PICU admission (n=28)	$R=0.15, P=NS$
			PIM score (n=28)	$R=0.06, P=NS$
			Follow-up time (n=28)	$R=-0.01, P=NS$
			Sex (n=28)	$R=0.17, P=NS$
			Age (n=28)	$R=0.31, P=NS$
			CRTI score at 3 mo (n=21)	$R=0.77, P<.01$
			Mother's psychological distress score (n=25)	$R=0.52, P<.01$
Mother's SRS-PTSD score (n=27)			$R=0.73, P<.01$	
Linear regression	Linear regression	Father's psychological distress score (n=21)	$R=0.70, P<.01$	
		Father's SRS-PTSD score (n=22)	$R=0.37, P=NS$	
Colville et al. <sup>21</sup> 2008 (n=96)	IES-R at 3 mo	Linear regression	Mother's SRS-PTSD score (n=27)	$\beta=1.40, t=4.09, P=.001$
			CRTI score at 3 mo (n=21)	$\beta=0.38, t=2.77, P=.02$
			Age	$\beta=-0.29$ (95% CI, -0.8 to 0.2), $P=.28$
			Male	$\beta=-1.7$ (95% CI, -4.7 to 1.2), $P=.25$
			White UK ethnicity	$\beta=0.21$ (95% CI, -2.7 to 3.2), $P=.89$
			Social deprivation (n=95)	$\beta=0.15$ (95% CI, -2.8 to 3.1), $P=.92$
			PICU LOS >2 d	$\beta=-0.52$ (95% CI, -3.5 to 2.4), $P=.73$
			Emergency department admission	$\beta=6.1$ (95% CI, 2.3 to 10), $P=.002$
			PIM score (n=94)	$\beta=0.18$ (95% CI, 0.02 to 0.3), $P=.03$
			Opiates and/or benzodiazepines $\geq 2$ d	$\beta=1.1$ (95% CI, -1.8 to 4), $P=.45$
			Sepsis	$\beta=1.4$ (95% CI, -2.8 to 5.5), $P=.51$
			TBI	$\beta=1.8$ (95% CI, -1.2 to 4.8), $P=.24$
			Factual memory	$\beta=-0.48$ (95% CI, -3.5 to 2.5), $P=.76$ ; $\Delta\beta=1.3$ (95% CI, -1.7 to 4.3), $P=.39$
			Delusional memory	$\beta=3.0$ (95% CI, -0.05 to 6.1), $P=.05$ ; $\Delta\beta=3.0$ (95% CI, 0.06 to 5.9), $P=.04$
			Mann-Whitney U test	Mann-Whitney U test
CANTAB pattern recognition memory score	$R=-0.57, P=.03$			
Elison et al. <sup>22</sup> 2008 (n=14)	IES	Spearman rank test	Child-perceived severity of illness	$R=0.40, P=.009$
Rees et al. <sup>23</sup> 2004 (n=21)	IES	Spearman rank test	Child-perceived life threat	$R=0.36, P=.002$
			Parent-perceived severity of illness	$R=0.30, P=.01$
			Parent-perceived life threat	$R=0.40, P=.004$
			Parental IES score	$R=0.40, P=.006$

(continued)

toms.<sup>40</sup> Third, all of the studies enrolled preschool- and elementary school-aged children, and there are concerns regarding the validity of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)<sup>41</sup> PTSD diagnostic criteria in these age groups.<sup>42,43</sup> Fourth, none of the studies separated subjects by developmental stage (eg, prepubescent, adolescent), so we could not assess this factor as a vulnerability to post-critical illness psychopathology. There is evidence to suggest that trauma-exposed adolescents are at greater risk for subsequent psychopathology than younger children.<sup>39</sup> Moreover, it is unclear whether the psychiatric morbidity that these children experience is primarily a result of premorbid factors, the critical illness itself, or the subsequent treatment. Owing to these methodological limitations, confidence regarding the precision and validity of this review's findings should be tempered.

Additional research is needed to understand vulnerabilities and exposures that may increase the risk of psychiatric morbidity in pediatric critical illness survivors. No reviewed studies assessed the impact of prior exposure to trauma as a predictor of psychopathology following a critical illness. Studies of adult traumatic injury survivors have found that increased prior trauma exposure is a potent predictor of PTSD following an injury.<sup>44,45</sup> A similar association in pediatric critical illness survivors would be important to establish. Also, researchers have found an increased risk of psychiatric symptoms in adolescents with serious medical conditions.<sup>46</sup> Therefore, a potential intermediate conveying risk for post-critical illness psychopathology may be a child's preexisting medical illness severity. Potential proxies for preexisting medical illness severity to ascertain include the presence of multiple comorbid conditions,<sup>47</sup> previous medical hos-

**Table 2. Potential Vulnerability and/or Exposure Factors for Psychiatric Morbidity (continued)**

Source	Psychiatric Symptoms/ Disorder Scale	Measure of Association	Potential Vulnerability and/or Exposure Factors	Statistic
Vermunt et al, <sup>18</sup> 2008 (n=192)	PTSD	Linear regression	PRISM score	$P=NS$
			Age when mother was informant	$\beta=-0.36, P<.05$
			Age when father was informant	$\beta=-0.43, P<.05$
Landolt et al, <sup>32</sup> 2009 (n=43)	PTSD	Spearman rank test	Age at injury	$R=-0.08, P=NS$
			Age at assessment	$R=-0.06, P=NS$
			Female	$R=-0.10, P=NS$
			SES	$R=-0.02, P=NS$
			Fire injury	$R=0.02, P=NS$
			Mother present at accident	$R=-0.35, P<.05$
			Burn size	$R=0.11, P=NS$
			Face burned	$R=-0.15, P=NS$
			Hospital LOS, d	$R=0.13, P=NS$
			No. of skin graft procedures	$R=0.07, P=NS$
			Length of follow-up	$R=-0.04, P=NS$
Pope et al, <sup>25</sup> 2007 (n=36)	BDI-II	Analysis of variance	Female	$F_{1,75}=8.85, P=.004$

Abbreviations:  $\beta$ , linear regression coefficient in multivariable model adjusted for specified confounders; AOR, adjusted odds ratio;  $\beta$ , linear regression coefficient in multivariable model;  $\beta_{st}$ , standardized linear regression coefficient in multivariable model; BASC, Behavioral Assessment Scale for Children; BDI-II, Beck Depression Inventory, second edition; CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, confidence interval; CIES, Children's Impact of Events Scale; COPE, Creating Opportunities for Parent Empowerment; CRTI, Children's Response to Trauma Inventory; GMSPS, Glasgow Meningococcal Septicemia Prognostic Score; ICU, intensive care unit; IES, Impact of Events Scale; IES-I, IES intrusion subscale; IES-R, IES-Revised; LOS, length of stay; MV, mechanical ventilation; NS, not significant; PICU, pediatric intensive care unit; PIM, Pediatric Index of Mortality; PRISM, Pediatric Risk of Mortality; PTSD, posttraumatic stress disorder; SDQ, Strengths and Difficulties Questionnaire; SES, socioeconomic status; SRS-PTSD, Self-Rating Scale for Posttraumatic Stress Disorder; TBI, traumatic brain injury; TBSA, total body surface area; TISS, Therapeutic Intervention Scoring System; UOR, unadjusted odds ratio.

<sup>a</sup>The 2 studies by Shears et al<sup>19,20</sup> reported data on the same cohort but at different follow-up times.

pitalizations, and/or the number of prior emergency department visits. Furthermore, prospective studies of the effects of parental psychopathology on the psychiatric outcomes of their children following a critical illness are needed to clarify the nature of the associations found here and to identify potential avenues for intervention. If outcomes of childhood critical illnesses are worsened by parental psychiatric symptoms, then parents of children with post-critical illness psychiatric disorders should also be screened for psychopathology following their child's hospitalization. Parents of youths diagnosed with major depression have been found to have a high prevalence of psychopathology themselves,<sup>48</sup> and treatment of parental psychiatric disorders may improve the mental health outcomes of their children.<sup>49</sup> Studies screening parents of traumatically injured children for alcohol use disorders<sup>50</sup> and screening parents of depressed adolescents for major depression<sup>51</sup> have shown that such screening programs not only are feasible but also have identified potential areas for intervention that may improve the health of both the children and their parents.

As interest in the outcomes of pediatric critical illness survivors is increasing, we make several recommendations for future studies of psychiatric morbidity in these patients. First, studies assessing post-critical illness psychopathology should prospectively evaluate the prevalence of and risk factors for depressive, anxiety, and psychotic symptoms. Second, studies should use diagnostic interviews to validate commonly used questionnaires and diagnostic criteria in children surviving critical illnesses. Third, studies prospectively examining psychiatric and functional morbidities in critical illness survivors younger than 2 years are needed. Studies of burned youth that included children as young as 1 year found that even very young children

may also be at increased risk for psychiatric symptoms following a serious illness.<sup>52,53</sup> Fourth, future studies should assess child developmental stage, use valid and reliable measures of temperament, prior trauma exposure, family psychiatric history, and youth lifetime psychiatric and medical history as potential vulnerabilities to post-critical illness psychopathology, and incorporate these factors into a comprehensive model including PICU factors (eg, invasive procedures, pain, delirium, illness severity) and posthospitalization factors (eg, parental psychopathology). Ultimately, such studies can lead to implementation of screening mechanisms that use validated instruments to target at-risk youth prior to acute care discharge, facilitating appropriate interventions and referrals before the development of substantial psychiatric morbidity.

In conclusion, pediatric critical illness survivors appear to have substantial psychiatric morbidity. Although further research is needed to more fully define factors that may increase the risk of post-critical illness psychopathology, we can preliminarily conclude that a child's age and/or sex are not vulnerabilities, preillness psychiatric and/or developmental problems are probable vulnerabilities, severity of illness and PICU service-delivery characteristics may be exposures that elevate risk, and early post-critical illness psychiatric symptoms as well as parental psychiatric symptoms are strong correlates of subsequent youth psychiatric morbidity. In the meantime, clinicians should recognize that psychiatric illnesses are common in pediatric critical illness survivors, requiring collaboration between pediatric intensivists, surgeons, pediatricians, child psychiatrists, pediatric psychologists, and social workers in a multidisciplinary team to ensure prompt, comprehensive evaluation and treatment.

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