Immune System Dysfunction Criteria in Critically Ill Children:

The PODIUM Consensus Conference

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Data Supplement

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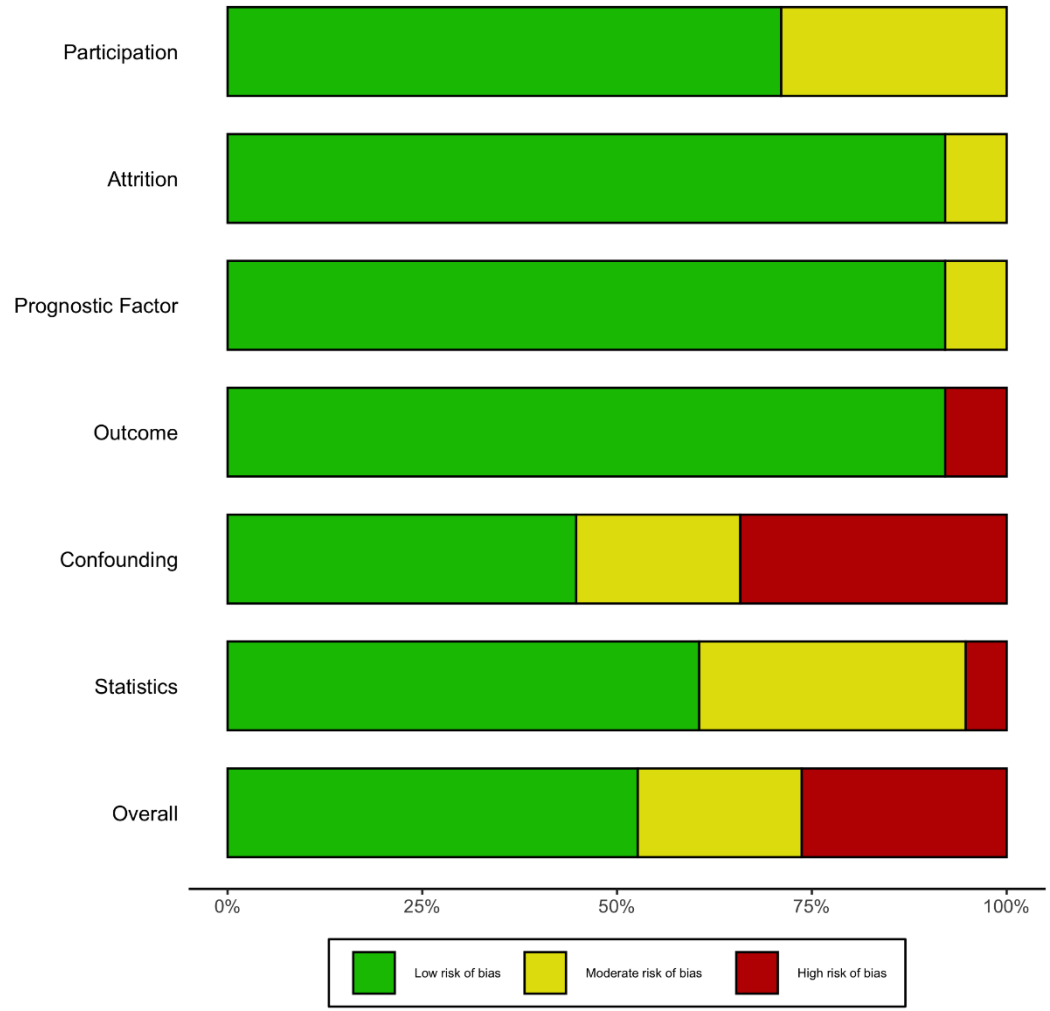

Supplemental Table 1. Studies Included in the PODIUM Immune System Dysfunction Systematic Review (n=39 studies)

Author (yr)	Funding	Study design	Location	No. of sites	Study years	Setting	Data source(s)	Sample size	Recruitment	Age categories[a]	Age details[b]
Allen (2006)	NGO	Prospective cohort	UK	1	NR	PCICU (cardiac only)	Prospective data collection	36	Consecutive	Neonates Infants Children	Median 6.5 mo [range, 9 days-24 mo]
Allen (2002)	NGO	Prospective cohort	United Kingdom	1	1999-1999	PCICU (cardiac only)	Prospective data collection	82	Convenience	Neonates Infants Children Adolescents	Median age 10 mo [range 2 days to 16 yr]
Andruszkow (2014)	NGO	Prospective cohort	Germany	1	2005-2008	PICU of unknown composition, Emergency room (ER)	Prospective data collection	59	NR/Unable to determine	Neonates Infants Children Adolescents	Mean 8.4 (4.4) yr
Boeddha (2018)	Govt.	Prospective cohort	The Netherlands	1	2012-2015	PICU (non-cardiac only)	Prospective data collection	37 PICU patients/cases and 37 healthy controls	Consecutive	Neonates Infants Children Adolescents	Median 9 yr [IQR, 5-13]
Bucuvalas (2013)	Govt.	Prospective cohort	United States, United Kingdom, Canada	17	NR	NR/Unable to determine	Prospective data collection	77	Convenience	Neonates Infants Children Adolescents	Median 9.0 yr [IQR 3.5, 16.0]
Cabrera (2009)	NR	Retrospective cohort	USA	1	2003-2005	PCICU (cardiac only)	Chart review	280	Consecutive	Neonates Infants Children	Mean 165 days (203)
Carcillo (2017)	Govt.	Prospective cohort, Observational/ descriptive study	United States	1	NR	NR/Unable to determine	Prospective data collection	100	Consecutive	Neonates Infants Children Adolescents	Mean 5.82 yr (5.69)
Christensen (2012)	Other (No external funding)	Retrospective cohort, Observational/ descriptive study	United States	1	2001-2010	Other:	Registry, Other:	29 627 to construct the lymphocyte normal ranges; 40 487 with lymphocyte counts were assessed for risks	Other (All neonates in data base, 2001-2020 with lymphocyte count)	Neonates	Gestational ages at birth ranging from 23-42 weeks
Cornell (2012)	Govt.	Prospective cohort, Observational/ descriptive study	United States	1	2005-2009	PCICU (cardiac only)	Prospective data collection	69 patients with post-op day one ex vivo mononuclear	NR/Unable to determine	Neonates Infants Children Adolescents	Median 10 mo [range 6 days-16 yr]

								cell TNFa production			
Cui (2019)	Govt.	Case/control study (case matched)	China	1	2014-2017	PICU (non-cardiac only)	Prospective data collection	Sepsis (n=69), of which HLH (n=23) and no HLH (n=46)	Convenience	Infants Children Adolescents	Median 22 mo [IQR, 9-48]
Felmet 2005)	Govt., NGO	Prospective cohort	USA	1	1999-2000	PICU (non-cardiac only)	Prospective data collection	58 cases, 5r controls (children without multiple organ failure in the ICU)	Consecutive	Neonates Infants Children Adolescents	Mean 7.5 ry [range, 2 weeks-23 yr]
Fiore-Gartland (2017)	Govt.	Prospective cohort, Observational/ descriptive study	United States	35	2008-2016	NR/Unable to determine	Prospective data collection	171 derivation; 76 validation	NR/Unable to determine	Infants Children Adolescents	Median 6.5 yr [IQR 3.4, 10.9]
Ganda (2018)	NR	Prospective cohort, Observational/ descriptive study	Indonesia	1	2015-2016	PICU of unknown composition	Prospective data collection	70	NR/Unable to determine	Infants Children Adolescents	NR
Ganda (2018)	NR	Prospective cohort, Observational/ descriptive study	Indonesia	1	2016-2017	PICU of unknown composition	Prospective data collection	70	NR/Unable to determine	Neonates Infants Children Adolescents	Median [range] septic shock 4.25 [0.08 to 15.5 yr]; sepsis 5.08 [0.08 to 16 yr]
Genel (2010)	NR	Prospective cohort, Observational/ descriptive study	Turkey	1	2007-2008	Other:	Prospective data collection	89: 40 sepsis; 24 non-infected; 25 control	Consecutive	Neonates	Infected: n=40, 37.5 +/- 3.8 wks; non-infected: n=24, 38.3 (2.7) wks; controls: n=25, 37.7 (3.1) wks. 10 premature infants were included in the infection group
Hall (2013)	Govt.	Prospective cohort, Observational/ descriptive study	United States	15	2008-2009	PICU of unknown composition	Prospective data collection	52 with influenza; 21 control patients	Convenience	Neonates Infants Children Adolescents	Median [IQR] 7.3 [2.4-14] yrs
Hall (2007)	Govt.	Prospective cohort	USA	1	2003-2004	PICU (non-cardiac only)	Prospective data collection	30	Consecutive	Neonates Infants Children Adolescents	Median 4y [IQR, 1-11]
Hall (2011)	Govt.	Prospective cohort	USA	2	NR	PICU (non-cardiac only)	Prospective data collection	70 cases and 80 controls	Consecutive	Infants Children Adolescents	Cases, Median 5y [IQR, 1-15]; controls, 9.8y [IQR, 8-12]
Hoffman (2004)	NR	Prospective cohort, Observational/	United States	1	2000-2003	Other:,NR/Unable to determine	Prospective data collection	13	NR/Unable to determine	Children Adolescents	Median 15 yr [range 10-18]

		descriptive study									
Ibrahiem (2016)	NR	Prospective cohort, Observational/ descriptive study	Egypt	1	2014-2014	NR/Unable to determine	Prospective data collection	57	Other (Probably convenience; no consort (flow) diagram)	Neonates Infants Children	1.5 yr [IQR: 1.0---3.0]
Jacobs (2018)	Govt.	Prospective cohort, Observational/ descriptive study	United States	1	2016-2017	PICU (non-cardiac only), Hospital floor outside the ICU	Chart review, Prospective data collection	293 patients; 400 suspected new infections	Consecutive	Infants Children Adolescents	Median 7.8 yr [IQR 3.1-13.8 yr]
Lodwick (2017)	NR	Retrospective cohort, Observational/ descriptive study	United States	1	2012-2014	Other:	Chart review, EMR query, Registry	551	Consecutive	Children Adolescents	Median [IQR] 10 [7-13]
Manzoli (2016)	NGO, Other (FAPESP, process number 2012/50173-6.)	Prospective cohort, Observational/ descriptive study	Brazil	1	2013-2015	PICU of unknown composition	Prospective data collection	30 patients with sepsis; 21 controls	Other (Perhaps consecutive; more likely convenience)	Infants Children Adolescents	Mean age (mo) survivors 99 (69.5); non-survivors, 28.5 (51.9)
Mella (2013)	Govt., NGO	Prospective cohort	USA	1	2010-2011	PICU (non-cardiac only), Hospital floor outside the ICU	Prospective data collection	ICU cases (n=20), floor cases (n=46), healthy controls (n=14)	Convenience	Neonates Infants Children	Cases, Median 2.6m [IQR, 1.6-4.45]; controls, Median 6.8m [IQR, 2.7-9.2]
Muszynski (2014)	Govt., NGO	Prospective cohort, Observational/ descriptive study	United States	1	2007-2010	PICU (non-cardiac only)	Prospective data collection, EMR query	76 critically injured children and 21 outpatient controls	NR/Unable to determine	Children Adolescents	Median [IQR] 9.9 [4.5-14.5] yr
Muszynski (2018)	Govt.	Prospective cohort	USA	1	NR	PICU (non-cardiac only)	Prospective data collection	102 cases, 35 controls	Consecutive	Neonates Infants Children Adolescents	Median 74.5m [IQR, 6-160]
Odek (2014)	NR	Retrospective cohort	Turkey	1	2002-2012	PICU of unknown composition	Chart review	51 patients; 65 admissions. Patients were included if they were admitted to PICU for a problem related their	Convenience	Infants Children Adolescents	Median age 12 mo [Range 2 mo to 18 yrs]

								primary immunodeficiency???			
Savluk (2019)	Other (Reported as none)	Prospective cohort	Turkey	1	2011-2015	PCICU (cardiac only)	Prospective data collection	53	Consecutive	Neonates	Survivors: Mean, 16.5d (1.4); non-survivors: Mean, 16.1d (1.8)
Tekin (2019)	NR	Retrospective cohort	Turkey	1	2010-2018	Emergency room (ER)	Chart review	358	Consecutive	Neonates Infants Children Adolescents	Mean, 8.96y [SD, 5.51]
Thakkar (2018)	NGO	Retrospective cohort	USA	1	NR	PICU (non-cardiac only)	Registry	138	Consecutive	Neonates Infants Children Adolescents	Summary not provided, only age categories but not for the entire cohort
Weiss (2019)	Govt., NGO	Case/control study (case matched)	USA	1	2014-2018	PICU (non-cardiac only)	Prospective data collection	167 cases (sepsis/septic shock) and 19 controls (no sepsis, no infection, no organ dysfunction)	Consecutive	Infants Children Adolescents	Median, 8.1y [IQR, 3.4-13.7]
Wong (2012)	Govt.	Prospective cohort	USA	17	NR	PICU (non-cardiac only)	Prospective data collection	220	Consecutive	Neonates Infants Children	Median, 2.2y [IQR, 0.8, 5.9]
Wong (2014)	Govt., NGO	Prospective cohort	USA	17	2009-2013	PICU (non-cardiac only)	Prospective data collection	182	Consecutive	Neonates Infants Children Adolescents	Median, 5.5 [IQR, 1.6-13]
Wong (2015)	Govt.	Prospective cohort	USA	17	NR	PICU (non-cardiac only)	Prospective data collection	241 (derivation cohort) and separate 200 (testing cohort)	Consecutive	Neonates Infants Children	Derivation cohort, Median 2.5y [IQR, 0.8-5.9]
Wong (2015)	Govt.	Prospective cohort	USA	17	2009-2013	PICU (non-cardiac only)	Prospective data collection	training (n = 374) and test (n = 93) sets	Consecutive	Neonates Infants Children Adolescents	Training set, Median 3.0y [IQR, 1.0-7.5]; test set, Median 5.6y [IQR, 1.6-9.9]
Wong (2017)	Govt.	Prospective cohort	USA	17	2009-2013	PICU (non-cardiac only)	Prospective data collection	307 derivation cohort and 77 test cohort	Consecutive	Neonates Infants Children	Median [IQR], yr, derivation cohort, survivors 2.5 [1.0-6.5]; non-survivors 1.4 [0.4-5.9]; test cohort survivors 2.0 [0.6-5.5], non-survivors 0.9 [0.2-3.6]
Xu (2013)	Govt.	Prospective cohort	China	1	2006-2012	PICU (non-cardiac only)	Prospective data collection	111	Consecutive	Infants Children Adolescents	Median 8.6y [range, 3m-15.1y]

Yehya (2018)	Govt.	Prospective cohort	USA	1	2014-2016	PICU (non-cardiac only)	Prospective data collection	152	Consecutive	Infants Children Adolescents	Median 4.2y [IQR, 1.5-10.4]
Zinter (2017)	Govt.	Prospective cohort	USA	5	2008-2015	PICU (non-cardiac only)	Prospective data collection	194	Consecutive	Infants Children Adolescents	Median 4.9y [IQR, 0.9-11.5]

Abbreviations: Govt., government; NGO, nongovernmental organization; NR, not reported; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit; IQR, interquartile range; SD, standard deviation; mo, months; yr, years

[a] Neonates (0 to 30 days), Infants (31 days to < 1 year), Children (1 year to < 12 years), Adolescents (12 years to < 18 years)

[b] Data are presented as mean (SD) or median [IQR, range]

Supplemental Table 2. Performance Characteristics for Assessment Tools and Scores for Immune System Dysfunction in Critically Ill Children (n=39 studies)

Author (yr)	Score/assessment tool	Is this a study of score/tool derivation or validation?	Inclusion criteria	Timing of score/tool assessment	Outcomes	Performance characteristics
Allen (2006)	Serum/plasma cytokine concentration, Other (IL-10 and LPS-stimulated cytokine production (IL-1ra, IL-6, IL-8, IL-10, TNF-a))	Other (Investigational)	PCICU population (only cardiac)	a) Following induction and insertion of arterial catheter; b) on release of the aortic cross-clamp; c) after the end of CPB; d) following modified ultrafiltration; e) on arrival to the cardiac intensive care unit; and f) 2, 4, 8, 14, 18, 24, and 48 hrs after admission to the ICU	Other (ICU LOS)	Other: uOR: (short vs long ICU LOS of >5d): patients in whom the whole blood response to endotoxin was maintained (TNF-a>100 pg/mL) over the first 48 hrs were more likely to have an uncomplicated short stay (uOR 4.7, 95%CI, 1-22).
Allen (2002)	Other (HLA-DR expression)	Derivation	PCICU population (only cardiac)	Lowest value within 72 hours of surgery	Other (Prolonged stay, development of sepsis, sepsis/SIRS)	AUROC: Development of sepsis/SIRS 0.85, long stay 0.75, sepsis 0.84
Andruszkow (2014)	Serum/plasma cytokine concentration	Derivation	Other (Trauma population)	Upon admission then every morning for 14 days	Mortality, Outcomes related to MODS	AUROC: IL-6 on day 2 AUC of 0.921 towards MODS
Boeddha (2018)	Other (HLA-DR expression on monocyte subsets)	Other (Investigational)	Sepsis, Other (Post-surgery and trauma)	Admission and on days 2, 3 and 4 of PICU stay	Mortality, Other (Nosocomial infection)	Other: Two-group comparisons: Patients who developed nosocomial infections (n = 13) or who died (n = 6) had lower HLA-DR expression on classical monocytes at day 2 (P = 0.002) and day 3 (P = 0.04), respectively
Bucuvalas (2013)	Serum/plasma cytokine concentration, Other (T-cell Immune Activation Markers)	Derivation	Other (Acute liver failure)	Within 48 hours of enrollment in	Mortality, Organ-specific outcomes/residual morbidity	Other: No test characteristics described
Cabrera (2009)	Lymphocyte count	Other (Investigational)	PCICU population (only cardiac)	Preoperative absolute lymphopenia (absolute lymphocyte count of less than 3000 cells/mL)	Mortality, Other (Hospital LOS, length of mechanical ventilation)	aOR: For the outcome of postoperative mortality, aOR 9.3 (95%CI, 1.8-48)
Carcillo (2017)	Other (Serum ferritin and C-reactive protein)	Derivation	Sepsis	First blood sample (for scoring) 2 days following admission	Mortality, Other (Development of immunoparalysis and/or macrophage activation syndrome (MAS))	AUROC: Mortality Youden's index (J statistic): To identify optimal thresholds for each outcome aOR: Mortality, immunoparalysis, MAS Other: Transition from one risk category to another over time was predictive of risk for mortality
Christensen (2012)	Lymphocyte count	Derivation	Other (Neonates with lymphocyte count within	Lymphocyte counts within first 72 hrs of life	Mortality, Organ-specific outcomes/residual morbidity, Other (Early onset	aOR: Early onset sepsis, intraventricular hemorrhage, retinopathy of prematurity, mortality

			first 72 hrs of life)		sepsis, intraventricular hemorrhage,retinopathy of prematurity)	
Cornell (2012)	Serum/plasma cytokine concentration, Other (Ex vivo TNFa production; serum IL-10 concentrations; histone methylation status (6 patients only))	Derivation	PCICU population (only cardiac)	Pre-op, day of surgery, post-op days 1, 3, 5	Other (Hospital acquired infections)	Se: Hospital acquired infections Sp: Hospital acquired infections PPV: Hospital acquired infections NPV: Hospital acquired infections AUROC: Hospital acquired infections
Cui (2019)	Other (sCD163 levels and mCD163 (the percentage of CD163-positive peripheral blood mononuclear cells))	Other (Investigational)	Sepsis	Within 24h after enrollment (children with presumed sepsis with fever >7d)	Mortality	Se: for the outcome of 28d mortality in children with sepsis associated HLH, sCD163 cutoff 2.001mg/L, 71.4% Sp: 100% AUROC: 0.857 (95% CI: 0.659-1.000) aOR: sCD163 for outcome of sepsis associated HLH development in children with presumed sepsis, aOR 3.091 (95%CI, 1.086-8.797)
Felmet 2005)	Other (Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia)	Other (Investigational)	Sepsis	Days 1, 3, 7, 14, and 21	Mortality, Other (Nosocomial infection)	aOR: Prolonged lymphopenia (absolute lymphocyte count < 1000 for >7 days) for outcome of nosocomial infection, aOR 5.5 (95%CI, 1.7-17), death, aOR 6.8 (95%CI, 1.3-34).
Fiore-Gartland (2017)	Serum/plasma cytokine concentration, Other (Individual and various modules of cytokines)	Other (Both derivation and validation cohorts)	Other (Critically ill children with influenza; location of care unclear)	At enrollment, mostly at the time of PICU admission	Mortality, Outcomes related to MODS, Other (Development of shock, acute lung injury/ARDS, need for mechanical ventilation, and ECLS/mortality)	aOR: Development of sock, acute lung injury/ARDS, need for mechanical ventilation, and ECLS/mortality
Ganda (2018)	Serum/plasma cytokine concentration, Other (TNFa)	Derivation	Sepsis	Presumably at admission to PICU	Other (Stated risk for development of septic shock, but likely many patients had septic shock when they were enrolled)	Se: Sepsis versus septic shock Sp: Sepsis versus septic shock PPV: Sepsis versus septic shock NPV: Sepsis versus septic shock AUROC: Sepsis versus septic shock Other: P-value comparing TNFa in patients with sepsis and septic shock was 0.05, but AUROC =100, does not make sense
Ganda (2018)	Serum/plasma cytokine concentration, Other (IL-10)	Derivation	Sepsis	Within 24 hours of PICU admission	Outcomes related to MODS, Other (Development of septic shock)	Se: Development of septic shock Sp: Development of septic shock PPV: Development of septic shock NPV: Development of septic shock AUROC: Development of septic shock
Genel (2010)	Mononuclear cell count, Other (HLH-DR expression (% and fluorescent intensity) on circulating	Derivation	Other (Neonatal intensive care unit)	First day of suspected sepsis	Mortality	Se: Mortality: 87.5% Sp: Mortality: 81.3% AUROC: Mortality: %HLA-DR expressing monocytes as a predictor of mortality was 0.89 (95% CI 0.751,.03,p=0.001) and for MFI of HLA-DR 0.80 (95% CI 0.65-0.96, p=0.008)

	mononuclear leukocytes (blinded to clinical status))					aOR: Mortality: HLA-DR expression 30% had lowered survival rate with a 30-fold higher risk of mortality (Odds ratio 30; 95% CI 3-295).
Hall (2013)	Serum/plasma cytokine concentration, Other (Primary: ex vivo LPS-stimulated monocyte TNFa production; absolute mononuclear cell count)	Derivation	Other (Children with acute respiratory failure with PCR-positive for influenza)	Single time point within 72 hrs of ICU admission (median [IQR] 31 [15-48] hrs	Mortality, Other (PICU duration of stay)	Se: Mortality as function of Ex vivo TNF production: 67% Sp: Mortality as function of Ex vivo TNF production: 100% PPV: Mortality as function of Ex vivo TNF production: 100% NPV: Mortality as function of Ex vivo TNF production: 91% AUROC: Mortality as function of Ex vivo TNF production: 0.97
Hall (2007)	Serum/plasma cytokine concentration, Other (Ex vivo lipopolysaccharide (LPS)- induced TNF- production and plasma cytokines)	Other (Investigational)	Other (Children with dysfunction of two or more organs)	Twice weekly beginning on d 3 of MODS	Mortality	Other: Two group comparisons: High mRNA levels for interleukin (IL)-10, IL-1 receptor-associated kinase (IRAK-M), and the putative inflammasome inhibitor pyrin were associated with death (p<=0.02). Plasma IL-10 levels were higher and ex vivo TNF-alpha production was lower in non-survivors (p<0.05). Among survivors, high mRNA levels for IL-10, IRAK-M, pyrin, IRAK1, or TLR4 were associated with longer durations of PICU stay and mechanical ventilation (p<=0.02)
Hall (2011)	Other (Monocyte HLA-DR expression; immunoparalysis defined by whole blood ex vivo lipopolysaccharide induced tumor necrosis factor-alpha (TNFa) response\200 pg/mL beyond day 3 of MODS)	Other (Investigational)	Other (Children with >=2 organ dysfunctions and invasive catheter)	Days 3, 7, and 14 and weekly thereafter following the development of MODS	Mortality	Other: Univariable analyses: associated with increased nosocomial infection (RR 3.3, 95% CI, 1.8-6.0, p<0.05) and mortality (RR 5.8, 95% CI, 2.1-16, p<0.05). TNFa response <200 pg/mL throughout 7 days after positive culture was associated with persistent nosocomial infection, whereas recovery above 200 pg/mL was associated with resolution of infection (p<0.05)
Hoffman (2004)	Serum/plasma cytokine concentration, Other (Serum IL-10 concentrations; monocyte HLH-DR expression)	Derivation	Other (Children undergoing living related, lobar lung transplantation)	Baseline and on post-LTdays 7, 14, 21, and 28.	Outcomes related to MODS, Other (Development of pneumonia)	Other: Recovery of baseline HLH-DR expression; recovery of baseline serum IL-10 concentration
Ibrahiem (2016)	Lymphocyte count, Other (Gamma globulin subtypes; complement components lymphocyte subsets)	Derivation	Sepsis, Other (Children with severe sepsis or septic shock)	PICU days 1 and 7	Mortality	Se: Day 1 (CD3-CD56/16+ %): 100% Sp: Day 1 (CD3-CD56/16+ %): 86% PPV: Day 1 (CD3-CD56/16+ %): 70% NPV: Day 1 (CD3-CD56/16+ %): 100% AUROC: Day 1 (CD3-CD56/16+ %): 0.950 , 95% CI 0.89-1.0
Jacobs (2018)	Serum/plasma cytokine concentration, Other (Serum IL-27 and procalcitonin)	Validation	Sepsis, Other (Immunocompromised with suspicion of infection)	Within 6 hrs of sending biosample for culture to document infection	Mortality, Other (New bacterial infection)	Se: New infection, IL-27 12% [8-19%] Sp: New infection, IL-27 94% [90-96%] PPV: New infection, IL-27 53% [35-70%] NPV: New infection, IL-27 64% [59-69%] AUROC: New infection, IL-27: 0.62 (0.5-0.68); PCT; 0.65 (0.6-0.73)
Lodwick (2017)	Lymphocyte count, Other (Leukocytosis + lymphopenia)	Derivation	Other (Children who underwent urgent or emergent appendectomy)	Day of discharge following appendectomy	Other (Development of postoperative intra-abdominal abscess following appendectomy)	AUROC: 0.76 for combined leukocytosis + lymphpenia aOR: 3.65 for leukocytosis; 4.46, for lymphpenia

Manzoli (2016)	Other (Delta PBMC HLR-DR expression (Days 3-5 versus 2-3 days after 1st sample))	Derivation	Sepsis, Other (Diagnosis of severe sepsis or septic shock)	PICU day 3-5 and then 2-4 days later	Mortality, Other (Multiple other outcomes; uncertain which were identified a prior)	Se: 85.7 (95% CI 42.1-99.6) Sp: 65 (95% CI 40.7-99.6) PPV: 46.1 (95% CI 19.2-74.8) NPV: 92.8 (95% CI 66.1-99.8)
Mella (2013)	Serum/plasma cytokine concentration, Other (Plasma IL-6, IL-8, IL-10 and TNF-alpha; cytokin production capacity (with LPS stimulation))	Other (Investigational)	Other (RSV bronchiolitis)	Within 24h of admission	Other (PICU LOS, hospital LOS)	aOR: Children with impaired TNF-α production capacity (<1000 pg/mL) had almost 6-fold higher odds of being in the hospital >2 days (aOR, 5.82 [95% CI, 1.42-23.85]; P = .014), and worse disease severity as evidenced by a CDSS >10 (aOR, 20.27 [3.63-113.28]; P = .001)
Muszynski (2014)	Serum/plasma cytokine concentration, Other (Ex vivo production of TNFa by mononuclear cells (Ex vivo TNFa <520 pg/mL))	Derivation	General PICU population (only non-cardiac), Other (Trauma and burn injury)	Enrolled on first week day following PICU admission. Serial blood samples on Mon, Wed, and Fri until PICU discharge	Other (Development of nosocomial infection within 14 days)	Se: 82% [95% CI: 67-92%] Sp: 86% [95% CI: 42-100%] PPV: 97% [95% CI: 86-100%] NPV: 43% [95% CI: 18-71%] aOR: 10.85 [3.0. 39.3]
Muszynski (2018)	Other (Innate immune function was quantified by whole blood ex vivo LPS-induced TNF-a production capacity. Adaptive immune function was quantified by ex vivo phytohemagglutinin-induced IFN-g production capacity)	Other (Investigational)	Sepsis	Within 48 hours of sepsis onset	Outcomes related to MODS	Other: aRR: early innate immune suppression remained independently associated with increased MODS days (aRR, 1.2; 95% CI, 1.03-1.5) and organ dysfunction days (aRR, 1.2; 95% CI, 1.1-1.3
Odek (2014)	Other (PRISM, PELOD, need for mechanical ventilation, renal replacement therapy, vasoactive-inotropic support, and PICU duration of stay)	Derivation	General PICU population (mixed cardiac and non-cardiac), Other (Children with primary immunodeficiency)	Variables assessed during PICU admission	Mortality	Other: Descriptive statistics comparing 38 children who survived with 27 children who died
Savluk (2019)	Other (Neutorphil-lymphocyte ratio)	Other (Investigational)	PCICU population (only cardiac)	Preoperative	Mortality	Se: For the outcome of in-hospital mortality, NLR cutoff 2.57, 78% Sp: For the outcome of in-hospital mortality, NLR cutoff 2.57, 65% AUROC: For the outcome of in-hospital mortality: 0.74 (95% CI 0.63-0.95; p = 0.001)
Tekin (2019)	Other (Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR))	Validation	Other (Trauma)	Arrival to the ED	Mortality	Se: For the outcome of in-hospital mortality, NLR cutoff 2.77, 70%; PLR cutoff 61.83, 90% Sp: For the outcome of in-hospital mortality, NLR cutoff 2.77, 77%; PLR cutoff 61.83, 85% AUROC: For the outcome of in-hospital mortality, NLR 0.764 (0.636-0.891); PLR 0.928 (0.871-0.985)

Thakkar (2018)	Other (White blood cell count, neutrophil percentage, and lymphocyte percentage)	Other (Investigational)	Other (Burn >=10% TBSA)	72h or more post-injury	Other (Infection)	aOR: Abnormal lymphocyte percentage on or after 72h postinjury: aOR 7.2 (95%CI, 2.1-24.5)
Weiss (2019)	Other (Mitochondrial respiration and content within circulating peripheral blood mononuclear cells)	Other (Investigational)	Sepsis	Days 1-2, 3-5, and 8-14 after sepsis recognition or once for controls	Outcomes related to MODS	AUROC: Persistently low spare respiratory capacity was predictive of residual organ dysfunction on day 14 (AUC, 0.72; 95% CI, 0.61-0.84)
Wong (2012)	Other (PERSEVERE biomarker-based risk stratification tool)	Derivation	Sepsis	First 24h of ICU admission	Mortality	Se: For in-hospital mortality, derivation cohort, 91% (95% CI 70 - 98), test cohort, 89% (64 - 98), combined cohorts, 93% (79 - 98) Sp: For in-hospital mortality, derivation cohort, 86% (80 - 90), test cohort, 64% (55 - 73), combined cohorts, 74% (69 - 79) PPV: For in-hospital mortality, derivation cohort, 43% (29 - 58), combined cohorts, 32% (24 - 41) NPV: For in-hospital mortality, derivation cohort, 99% (95 - 100), combined cohorts, 99% (96 - 100)
Wong (2014)	Other (PERSEVERE (C-C chemokine ligand 3 (CCL3), interleukin 8 (IL8), heat shock protein 70 kDa 1B (HSPA1B), granzyme B (GZMB), and matrix metallopeptidase 8 (MMP8)))	Validation	Sepsis	First 24h of presentation	Mortality	Se: for the outcome of 28-day mortality, 83% (62-95) Sp: 75% (68-82) PPV: 34% (22-47) NPV: 97% (91-99) LRL PLR: (2.4-4.7); NLR: 0.2 (0.1-0.5) AUROC: 0.811 (0.704-0.917)
Wong (2015)	Other (Serum biomarkers: elastase 2 (ELA2), fibroblast growth factor 13 (FGF13), matrix metalloproteinase 8 (MMP8), olfactomedin 4 (OLFM4), and proteinase 3 (PRTN3))	Derivation	Sepsis	Within 24 hours of initial presentation to the PICU with septic shock	Organ-specific outcomes/residual morbidity	Se: For the outcome of septic AKI: derivation cohort, 93 (75-99); test cohort, 85 (61-96) Sp: Derivation cohort, 88 (83-92); test cohort, 77 (70-83) PPV: Derivation cohort, 51 (37-65); test cohort, 29 (18-43) NPV: Derivation cohort, 99 (96-100); test cohort, 98 (93-99)t, LR: PLR: Derivation cohort, 7.9 (5.4-11.6); test cohort, 3.7 (2.7-5.2); NLR: Derivation cohort, 0.08 (0.02-0.3); test cohort, 0.2 (0.07-0.6) AUROC: Derivation cohort, 0.95 (0.91-0.99); test cohort, 0.83 (0.72-0.95)
Wong (2015)	Other (tPERSEVERE (temporal PERSEVERE))	Derivation	Sepsis	Biomarker changes from days 1 to 3 of septic shock.	Other (Complicated course (defined as persistence of two or more organ failures at day seven of septic shock or 28-day mortality))	Se: Training set: 93% (86-97); test set: 88% (69-97) Sp: Training set: 60% (54-66); test set: 64% (51-75) PPV: Training set: 48% (41-55); test set: 49% (34-64) NPV: Training set: 96% (92-98); test set: 93% (82-99) LR: PLR: Training set: 2.35 (2.01-2.74); test set: 2.47 (1.74-3.50); NLR: training set: 0.11 (0.05-0.23); test set: 0.18 (0.06-0.53) AUROC: Training set: 0.83 (0.79-0.87); test set: 0.84 (0.75-0.92)
Wong (2017)	Other (PERSEVERE-XP)	Derivation	General PICU population (mixed cardiac and non-cardiac)	Within 24 hours of a septic shock diagnosis	Mortality	Se: for the outcome of 28-day mortality, and combined derivation and test cohorts: 95% (80-99) Sp: 81% (76-85) PPV: 35% (26-45) NPV: 99% (97-100) PLR: 5.0 (4.0-6.3)

						LR: NLR: 0.07 (0.02-0.36) AUROC: 0.91 (0.87-0.95)
Xu (2013)	Serum/plasma cytokine concentration, Other (Pediatric Multiple Cytokine Score (PMCS) integrated: IL-6, IL-10, TNF-alpha and IFN-gamma)	Other (Investigational)	Sepsis	Initial onset of septic shock	Mortality	AUROC: PMCS 0.83 (0.71-0.94)
Yehya (2018)	Other (PARDSEVERE (4 biomarkers included in PERSEVERE, plus age, platelets, infectious versus noninfectious ARDS etiology, presence or absence of an immunocompromising condition, and initial and 24-hour PaO2/FiO2 and OI))	Derivation	Other (Pediatric ARDS)	Within 24 hours of ARDS onset	Mortality	Se: for the outcome of PICU mortality, derivation (n=122) 1 (0.78-1); test (n=30) 0.83 (0.36-0.99) Sp: derivation (n=122) 0.65 (0.55-0.74); test (n=30) 0.71 (0.49-0.87) PPV: derivation (n=122) 0.33 (0.21-0.48); test (n=30) 0.42 (0.16-0.71) NPV: derivation (n=122) 1 (0.93-1); test (n=30) 0.94 (0.71-1) LR: PLR: derivation (n=122) 2.9 (2.2-3.8); test (n=30) 2.9 (1.4-5.9); NLR: derivation (n=122) NA; test (n=30) 0.2 (0-1.4) AUROC: derivation (n=122) 0.85 (0.78-0.92); test (n=30) 0.82 (0.62-1)
Zinter (2017)	Serum/plasma cytokine concentration, Other (OI plus: interferon-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6 IL-7, IL-8, IL-10, IL-12, IL-15, IL-17, IL-18, IL-23, MIP-1α, MIP-1β, TNF-α, and TNFR2; biomarkers of endothelial injury (Ang-2, vWF, and sTM))	Other (Investigational)	Other (Pediatric ARDS)	Within 24 hours of onset of ARDS	Mortality	AUROC: For mortality or severe morbidity: OI 0.70 (95% CI, 0.62-0.77); OI, IL-8, and TNF-R2 0.77 (95% CI, 0.70-0.83); OI, IL-6, IL-8, IL-10, TNF-R2, and hematopoietic cellular transplantation (HCT) history 0.79 (95% CI, 0.72-0.86)

Abbreviations: Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUROC, area under the receiver operating characteristics curve; aOR, adjusted odds ratio; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit

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Research Priorities

The non-cellular elements of the immune response have been the subject of frequent investigation in critically ill children. High serum levels of inflammatory biomarkers including C-reactive protein, ferritin, and soluble CD163 have been associated with the presence of infection and other inflammatory disorders including hemophagocytic lymphohistiocytosis, and may have a role in predicting mortality in septic children.[1, 2] High levels of cytokines and chemokines have also been consistently associated with morbidity and mortality from pediatric critical illness. Elevated serum levels of pro-inflammatory mediators such as interleukin (IL)-6, IL-8, soluble IL-2 receptor, interferon-γ-inducible protein (IP)10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α have all been associated with increased nosocomial infection and/or mortality risks in children with sepsis,[3-8] critical influenza,[9-11] acute respiratory distress syndrome (ARDS),[12] liver failure,[13] and/or trauma.[14-16] Multiple studies have also associated high serum levels of anti-inflammatory cytokines with adverse outcomes from pediatric critical illness, often concurrent with elevations in levels of pro-inflammatory mediators. Evidence of this "cytokine storm" include elevations of serum IL-10 levels in children who go on to develop nosocomial infection or death after sepsis,[17-19] trauma,[14] lung transplantation.[20] and cardiopulmonary bypass.[21, 22] These biomarkers represent a small fraction of the total number of pro- and anti-inflammatory mediators whose systemic levels have been associated with adverse outcomes from adult and pediatric critical illness.

Rather than focusing on single serum protein mediators, Wong et al developed and validated a panel of biomarkers including C-C chemokine ligand 3, IL-8, heat shock protein 70 kDa 1B, granzyme B, and matrix metallopeptidase 8 in septic children.[23, 24] This panel, when measured in the first 24 hours of pediatric septic shock, was able to reliably estimate mortality

probability in a multi-center, heterogeneous cohort. It is currently unclear if this panel can predict outcomes in the wider pediatric ICU setting with it may have utility in children with ARDS.[25] Cytokine and chemokine levels were not included in the current definitions of immune system dysfunction because 1) they are not yet available for measurement in the clinical laboratory, 2) the validation of thresholds for individual mediators that reliably identify children at risk for adverse outcomes across diagnoses has proven to be challenging, and 3) elevations in serum protein levels do not necessarily imply dysfunction of leukocytes. Elevations in serum cytokine levels, while predictive of outcomes, may be representative of initial severity of illness and tissue injury rather than solely diagnostic of immune system dysfunction.

Transcriptomic studies, by contrast, have identified patterns of mRNA expression by leukocytes from critically ill children. Wong et al was able to demonstrate segregation of children with septic shock into discrete endotypes through mRNA profiling of whole blood.[26] Reduced expression of a panel of gene products associated with lymphocyte signaling was associated with increased risks of mortality and prolonged organ dysfunction. Weiss et al recently reported an association between persistent impairment of mitochondrial function in peripheral blood mononuclear cells and persistence of organ dysfunction in septic children.[27] While being more specific to leukocyte function, these assays are not yet available for clinical use. While many biomarkers of the inflammatory response are not specific to the immune system, it is likely that proteomic profiling,[28, 29] transcriptomic profiling,[30] or a combination of both[31, 32] may allow us to identify children with immune system dysfunction in the pediatric ICU.

Although absolute cellular numbers are included in these definitions of immune dysfunction, the composition of subtypes of leukocytes as well as changes in the composition of circulating leukocytes over time may have utility in predicting outcomes from pediatric critical

illness. Gaining more insight, for example, into the significance of the neutrophil/lymphocyte ratio[33, 34] and developing high-throughput phenotyping procedures that can rapidly differentiate leukocyte subtypes[35] would further enhance our understanding of immune dysfunction in pediatric critical illness.

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