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Interleukin-1 receptor antagonist is associated with pediatric acute respiratory distress syndrome and worse outcomes in children with acute respiratory failure

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Abstract

Objective: To test whether plasma interleukin-1 receptor antagonist (IL-1ra) or variants within the gene encoding for IL-1ra (*IL1RN*), or proteins involved in regulating IL-1β levels or IL-1β response, are associated with pediatric acute respiratory distress syndrome (PARDS) or outcomes in mechanically ventilated children with parenchymal lung disease.

Design: Prospective cohort study.

Setting: Twenty-two pediatric intensive care units participating in the multi-site clinical trial, Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE; U01 HL086622).

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Article Tweet: Plasma IL-1ra is associated with pediatric ARDS and mortality in children with acute respiratory failure requiring mechanical ventilation.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Subjects: Children 2 weeks to 17 years of age treated with invasive mechanical ventilation for acute airways and/or parenchymal lung disease.

Measurements and Main Results: 378 of 549 patients had PARDS; DNA and plasma were obtained from 523/549 and 480/549 patients, respectively. Plasma IL-1ra was highest on the day of intubation (Day 0) and decreased over the subsequent 3 days ($p<0.0001$). IL-1ra level was higher in patients with PARDS than those without PARDS ($p<0.0001$). Multivariable regression analysis of data across all days demonstrated a significant association of IL-1ra (OR= 1.30; 95% CI=1.10-1.52; $p=0.002$) and day ($p<0.05$) with PARDS, independent of age and PRISM-III score. Analysis on individual days indicated that plasma IL-1ra levels were associated with PARDS on Days 0 and 2, independent of age and PRISM-III score ($p=0.04$ and 0.003, respectively), however did not quite reach significance on Days 1 and 3 ($p=0.06$ and 0.07, respectively). IL-1ra was independently associated with mortality on Day 1 ($p=0.02$). IL-1ra also correlated with length of mechanical ventilation, measures of oxygenation and pediatric intensive care unit (PICU) length of stay. No genetic variants were associated with PARDS.

Conclusions: Plasma IL-1ra is associated with PARDS, PICU length of stay, length of mechanical ventilation, and mortality in children with acute respiratory failure requiring mechanical ventilation.

Keywords

biomarkers; acute respiratory distress syndrome; genetic variants; critical illness; pediatrics; ARDS; PARDS; SNP

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by disruption of the alveolar endothelial/epithelial permeability barrier and influx of protein rich fluid into the alveolar space (1). Other hallmarks of ARDS include dysregulation of the inflammatory response and coagulation/fibrinolysis. A number of studies have examined the association of plasma biomarkers and/or genetic variants with ARDS, or ARDS outcomes, in an attempt to better understand the pathological process and to identify markers that might be useful for diagnosis, prognostication or response to treatment. Early studies in adults demonstrated that interleukin-1 receptor antagonist (IL-1ra) is elevated in plasma and bronchoalveolar lavage fluid (BALF) in patients with ARDS and that levels may be associated with outcome (2–4). IL-1ra is a naturally occurring inhibitor of IL-1β that lacks agonist activity but competitively binds to the IL-1 receptor thereby blocking binding of IL-1β (5–8). IL-1β is an early pro-inflammatory cytokine activated in response to stressors like infection which induces the expression of other cytokines and chemokines involved in the inflammatory response. Recently analysis of three adult cohorts of patients either with ARDS, or at risk for ARDS, demonstrated that a specific variant in the gene for IL-1ra (*IL1RN*) is associated with reduced risk of ARDS and that the level of plasma IL-1ra appears to be associated with this variant (9).

Very few studies have examined the association of plasma or genetic markers with ARDS in children. While much of what has been learned in adults is likely to be applicable to

children, differences in mortality rates and response to treatment (10, 11), together with changes in the developing immune system, suggest there may be differences between children and adults that impact the development, and outcomes of, pediatric ARDS (PARDS) (1, 12). Substantial differences in immune responsiveness between adults and children are well documented. Neonates have fewer neutrophils than adults and their polymorphonuclear cells (PMNs) have a decreased chemotactic response that may persist until 1–2 years of age (12). In addition, neonatal PMNs and monocytes release less cytokine in response to lipopolysaccharide (LPS) compared to adults (13–15). In one study examining temporal cytokine profiles in both severely burned adults and children, the cytokine profiles differed significantly with adults exhibiting a more hyper-inflammatory state (16). In healthy children substantial changes in lymphocyte subsets (17, 18) and cytokine response (19–21) are also known to occur during childhood. These data suggest that there are important maturational differences between adults and children in the development, pathophysiology and outcomes of ARDS that may be reflected in plasma biomarkers. This study tests whether plasma IL-1ra or genetic variants within *IL1RN,* or genes encoding proteins involved in regulating either IL-1β levels or response, are associated with PARDS in mechanically ventilated children with parenchymal lung disease. We hypothesized that both elevated IL-1ra and specific variants would be associated with PARDS.

Materials and Methods

Study Design

This study, Genetic Variation and Biomarkers in Children with Acute Lung Injury (BALI; R01HL095410), was a prospective ancillary study to the multi-site clinical trial, Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE; U01 HL086622) (22). BALI was designed to examine the association of specific plasma protein and genetic biomarkers with PARDS among prospectively enrolled children with acute respiratory failure. Twenty-two of the 31 pediatric intensive care units (PICUs) participating in RESTORE volunteered to participate in this study. The study was approved by the Institutional Review Boards at all participating sites. After enrollment in RESTORE, parents or guardians were approached for consent for participation in BALI. In RESTORE, children 2 weeks to 17 years old treated with invasive mechanical ventilation for acute airways and/or parenchymal lung disease were eligible (22). Children for whom the length of mechanical ventilation was unlikely to be altered by the sedation management protocol being examined in RESTORE (*i.e.*, children who were ventilator dependent on PICU admission or those expected to be extubated within 24 h) were excluded. There were no additional inclusion or exclusion criteria for the BALI study.

Screening for RESTORE and BALI was performed concurrently. Guardians for patients were approached for consent for RESTORE within 24 h of meeting RESTORE study criteria and were approached for consent for participation in BALI as soon as possible after consenting for RESTORE (often immediately afterwards). Blood samples were taken within 24 hours of consent for BALI and again 24 and 48 hours later. The primary analyses examined the association of plasma or genetic biomarkers with the presence of PARDS. PARDS was defined using the Pediatric Acute Lung Injury Consensus Conference (23)

criteria for oxygenation index (OI) or oxygen saturation index (OSI) with the addition of the presence of bilateral infiltrates within 2 days before or 1 day after meeting OI or OSI criteria for PARDS. RESTORE and BALI were both designed when PARDS was defined using the American European Consensus Conference (AECC) definition (24). Consequently, chest radiograph data only included presence or absence of bilateral infiltrates. Individual chest radiographs were not collected as part of either study. Secondary analyses examined association of biomarkers with oxygenation defect (OI, PaO_2/FiO_2) and other relevant clinical outcomes including duration of mechanical ventilation, PICU length of stay in survivors and 90 day in-hospital mortality.

Assay of IL-1ra

Plasma IL-1ra was measured in duplicate by ELISA (#DRAOOB, R&D Systems, Inc., Minneapolis, MN). The reported limit of detection of the assay is 18.3 pg/ml; intra- and inter-assay coefficients of variations are 5.3% and 8.6%, respectively.

Genotyping

Selection of candidate genes and single nucleotide polymorphisms (SNPs) and methods for genotyping are described in the Supplement.

Statistical Analyses

Analyses related to plasma IL-1ra—Basic descriptive analyses of all demographic and key dependent variables (including frequency distributions or means, medians and standard deviations, and Pearson correlations as appropriate) were conducted on each of the four study days (0, 1, 2 and 3); differences between study days were evaluated for statistical significance using generalized estimating equations (GEE) to account for correlations within and between individuals. Development of PARDS, and secondary outcomes (death, duration of mechanical ventilation and length of PICU stay) were examined for changes over time. IL-1ra levels within each day (0-3) were investigated for association with all demographic and clinical measures (age, gender, race, ethnicity, past medical history (asthma, prematurity, seizure disorder, neurologic disorder, cancer, chromosomal abnormality), primary diagnosis (pneumonia, sepsis, bronchiolitis, asthma, aspiration), PRISM III score) using appropriate bivariate chi-square, t-tests or Wilcoxon Rank Sum Test analyses. The primary hypotheses were evaluated using binary logistic regression models for each binary outcome (PARDS, death) and Poisson regression models for the duration of mechanical ventilation and length of PICU stay outcomes. Multivariable models were developed based on the results of the bivariate analysis on association of IL-1ra with clinical and demographic variables and were adjusted for severity illness (PRISM III) and potential impact of age on IL-1ra level. As a result, for consistency across outcomes the final analyses were modeled longitudinally as a function of study day, age, PRISM III score and the log transformed IL-1ra level. All multivariable logistic regression models of binary outcomes accounted for individual clustering using GEE and adjusted for the covariates to assess changes in association with outcomes over days from Day 0 to Day 3. The explanatory measure of age was included in the final models (together with PRISM III score and IL-1ra) as fixed or time-varying covariates. We reported odds ratios with 95% confidence intervals. All statistical tests were

two-tailed, with a significance level of 0.05. All statistical analyses were performed using SAS version 9.4.

Genetic association analyses—The association of genetic variants with PARDS was examined using PLINK, a statistical tool set designed specifically to perform analyses related to genome wide or family based genetic association studies or population based genetic linkage analysis (25, 26). For analysis results were stratified by race and ethnicity as the frequency of genetic polymorphisms and the linkage disequilibrium patterns differ between ethnicities and races (27, 28) and such groups should be analyzed separately (29). Non-Hispanic Caucasians, Hispanic Caucasians and African Americans (52%, 20%, and 17% of the cohort, respectively) were examined as these groups included 89% of enrolled patients. The frequency of each of these subgroups in patients with successfully genotyped DNA samples (n=477) was identical both to that of the group with DNA (n=523) and the total group enrolled (n=549). Because of the relatively small number of patients principal component analysis (PCA) was performed in the whole group using the admixture informative markers listed in Table S2. Results from the PCA are shown in Figure S1. Samples were identified as outliers within each of the three major subgroups if the genomic distance of any one of the five nearest neighbors within the subgroup had a Z score less than −2.326. Outliers identified were removed from further analysis. Twelve individuals were removed from the non-Hispanic Caucasian subgroup, two from the Hispanic Caucasians and three from the African Americans leaving 234, 96, and 82 individuals, respectively. For each of the three subpopulations principal components (PCs) 1 and 2 were then used to adjust for population structure in a multivariable model of association of SNPs with PARDS which also included age, gender, past medical history of asthma, and primary diagnosis of pneumonia and sepsis. A meta-analysis of the results from the association studies for each of the 3 subpopulations was performed with the computationally efficient statistical tool designed specifically for meta-analyses of genome wide association studies, METAL (30), using β-coefficients and standard errors determined from the individual association analyses. Significance was adjusted for multiple comparisons and defined as a $p<1.25\times10^{-4}$.

Results

There were 549 patients enrolled in BALI between August of 2009 and December of 2013; DNA and plasma samples were obtained from 480 patients with an additional 43 patients for which only DNA samples were available (Figure S2). Table 1 describes the demographic and clinical characteristics of the cohort. The demographic and clinical characteristics of those with samples are nearly identical to those of the total cohort (Table S3) and are also very similar to those reported for patients enrolled in the RESTORE clinical trial (22). A total of 69% (n=378) of the patients met the criteria for PARDS and 83% (n=312) of children with PARDS met criteria on the day of intubation (Study Day 0); another 11% (n=42) met criteria on Study Day 1 and the remaining 6% met criteria on Study Days 2–5. Although 82% of the patients with plasma samples had three consecutive samples taken approximately 24 h apart, only 13% (n=62) of the patients had samples taken on Day 0, as patients' caregivers were only approached for consent for this study after patients were

enrolled in RESTORE. Consequently, for most patients, blood sampling began on Day 1 (n=209, 44%) or Day 2 (n=155, 32%).

Plasma IL-1ra was most elevated on the day of intubation (Day 0) and decreased significantly ($p<0.0001$) over the subsequent three days (Figure 1). Plasma IL-1ra correlated significantly with OI on Days 0-3 (Table 2). Similarly, plasma IL-1ra correlated with the PaO_2/FiO_2 ratio on Days 0–2 (Table 2). IL-1ra was not associated with age, gender, race, past medical history of prematurity, immunodeficiency, cancer, aspiration, pneumonia, chromosomal abnormalities or seizures. Plasma IL-1ra was lower in patients with history of asthma ($p< 0.05$) and higher in patients with sepsis ($p<0.001$). Plasma IL-1ra was associated with PRISM-III on Days 1, 2 and 3 (correlation coefficients 0.24, 0.26, 0.28, all $p< 0.001$, respectively), but was not collinear.

Association of IL-1ra with the development of PARDS

The characteristics of patients with or without PARDS at any time were similar (Table 1), except that in patients with PARDS the frequency of patients with pneumonia was greater and the frequencies of patients with the primary diagnosis of asthma or with a history of asthma were lower. In addition, the severity of illness, as measured by PRISM III score, in patients with PARDS was slightly greater than in patients without PARDS. As shown in Figure 2A, the level of plasma IL-1ra was significantly greater at intubation through Day 3 in those with PARDS compared to those without PARDS ($p<0.0001$). Multivariable regression analysis of data across all days demonstrated a significant association of IL-1ra (OR= 1.30; 95% CI=1.10–1.52; $p=0.002$) and day ($p<0.05$) on presence of PARDS, independent of age and PRISM-III score. Analysis on each day (Table 3) indicated that on Days 0 and 2, plasma IL-1ra levels were independently associated with PARDS; however the association on Days 1 and 3 did not quite reach significance ($p=0.06$ and 0.07, respectively).

Association of IL-1ra with other clinical outcomes in children with acute respiratory failure

Univariate analysis indicated for children with acute respiratory failure plasma IL-1ra levels on Days 0-3 were positively correlated with duration of mechanical ventilation and plasma IL-1ra levels on Days 1–3 correlated with PICU length of stay (Table S4). Multivariable analysis demonstrated that IL-1ra was associated with duration of mechanical ventilation on Days 1–3 even after adjustment for other relevant variables such as age and severity of illness ($p<0.001$, Days 1–3, Table 4). IL-1ra on Days 1–3 also remained associated with PICU length of stay in the multivariable analysis ($p=0.009$, $p<0.001$, $p=0.002$, Days 1–3, respectively, Table 5). In addition, plasma IL-1ra was elevated on all days in children with acute respiratory failure who died (Figure 2B). However, only IL-1ra on Day 1 was associated with death in both univariate ($p=0.003$) and multivariable regression analyses (Table S5), where plasma IL-1ra was associated with death independent of age and severity of illness (OR= 1.85, 95% CI=1.12 – 3.06; $p=0.02$).

Association of genetic variants with PARDS

Genetic variants in the gene for IL-1ra, *IL1RN*, as well as variants in genes whose protein products impact either IL-1β level, or response, were tested for association with PARDS. The cohort was stratified into non-Hispanic Caucasians, Hispanic Caucasians and African

Americans for analyses which were done with adjustment for population structure (as described in the Supplement). None of the variants examined showed a significant association (defined as $p<1.25\times10^{-4}$) with PARDS within any of the subgroups or when the three subgroups were combined in the meta-analysis (n=412). However, the meta-analysis did identify a SNP, rs2287047, in the gene that encodes the IL-1 receptor 1 (*IL1R1)*, for which the A allele came close to reaching a significant association with a decreased rate of PARDS using a recessive multivariable regression model including age, gender, history of asthma, and diagnosis of pneumonia or sepsis ($p=7.4\times10^{-4}$). None of the *IL1RN* SNPs were associated with level of plasma IL-1ra.

Discussion

The main findings of this study can be summarized as follows. IL-1ra levels are highest in children with acute respiratory failure requiring mechanical ventilation on the day of intubation. IL-1ra levels are associated with the development of PARDS independent of clinical and demographic factors, and Day 1 levels are independently associated with death. In addition, IL-1ra levels correlate with measures of oxygenation defect, days of mechanical ventilation and PICU length of stay. Genetic variants in either the gene for IL-1ra or in genes related to IL-1β level are not associated with development of PARDS.

In the cohort as a whole, plasma IL-1ra levels were highest on the day of intubation and dropped significantly over subsequent days. This observation suggests that therapies targeting inflammation for either prevention or mitigation of PARDS are likely to be most useful very early in the trajectory of illness, potentially in patients identified to be at risk for PARDS. IL-1ra levels are higher in patients with PARDS than in those without PARDS suggesting that those with higher IL-1ra levels have generated a more robust inflammatory response (though IL-1ra is an anti-inflammatory cytokine) and may be more susceptible to developing PARDS. The answer to this question will require a prospective study that enrolls patients from non-PICU environments before they develop PARDS, similar to the current, NIH-funded, adult Prevention & Early Treatment of Acute Lung Injury (PETAL) network (http://petalnet.org/). Examining the association of IL-1ra with PARDS is complicated by the fact that patients with a condition that causes an inflammatory response (i.e., infection, trauma, aspiration, sepsis) are at greater risk for the development of ARDS. However, better understanding this association is particularly important because a recent study examining the mortality benefit of treatment with recombinant IL-1ra from a clinical trial of adults with sepsis suggests that the response varies with plasma IL-1ra level with those with higher levels benefiting from treatment (31).

Plasma IL-1ra was significantly associated with oxygenation measures, length of mechanical ventilation, and PICU length of stay in the entire cohort (children with acute respiratory failure) on all days examined suggesting that IL-1ra levels are an indicator of severity of illness in mechanically ventilated children with acute airways or parenchymal lung disease. In addition, plasma IL-1ra on Day 1, but not Day 2 or 3, was independently associated with death. As expected the levels of IL-1ra on Days 2 and 3 while still high, are lower than that seen on Days 0 and 1, consistent with IL-1ra being triggered very early in the inflammatory cascade. This suggests that IL-1ra is only associated with death in samples taken early after

intubation presumably early in the inflammatory response. The lack of association of IL-1ra on day of intubation with death is likely due to the paucity of plasma samples on Day 0 and the low mortality in the cohort. The association we observed between IL-1ra and oxygenation measures in children with acute respiratory failure is similar to findings in one other PARDS study where IL-1ra was also reported to be associated with oxygenation measures (32). The association of IL-1ra with death in children with acute respiratory failure contrasts with findings in children with PARDS where IL-1ra was not associated with death (32). It is unclear whether this difference is due to a difference in the cohorts, that is, children with acute respiratory failure, including those with PARDS, versus a cohort of exclusively PARDS patients, or a difference in number of patients enrolled in these studies. Interestingly plasma IL-1ra has been reported to be associated with death in a small study of adult patients at risk for ARDS [3].

There were no variants in the gene for IL-1ra, including rs315952, which were associated with risk of PARDS or IL-1ra levels. This is in contrast to a previous study in adults in which the SNP rs315952 was associated with reduced risk of ARDS and higher plasma IL-1ra levels (9). This difference may be due to the smaller numbers in our study. We did observe an association between a SNP in *IL1R1,* rs2287047, and protection from PARDS in the meta-analysis including non-Hispanic Caucasians, Hispanic Caucasians and African Americans, though the p value did not reach significance ($p=7.4\times10^{-4}$). *IL1R1* encodes for the IL-1 receptor 1, which is critical for response to IL-1. rs2287047 is in a non-coding region of *IL1R1* which is involved in regulating transcription in many tissues, including lung, as indicated by the presence of epigenetic modifications involved in enhanced expression on histones in this region when evaluated using HaploReg (33). In addition, rs2287047 has been reported to be an expression quantitative trait locus (eQTL) which is associated with expression of the IL-1 receptor 1 (33, 34). Future studies will be needed to determine if this variant is associated with level of IL-1R1 and/or ARDS.

This study describes not only the inflammatory milieu in mechanically ventilated children with acute respiratory failure but also the occurrence, timing and severity of PARDS in this group of children. The occurrence of PARDS was higher than expected with 69% of the cohort meeting the criteria for PARDS. This is particularly surprising as the parent RESTORE trial intended to enroll pediatric patients with acute respiratory failure and not a sicker subset with established PARDS, and children who were ventilator dependent on PICU admission were excluded. Of the 378 children with PARDS, 83% had PARDS on the day of intubation, 11% on day 1; only 6% met criteria more than 1 day after intubation. Recently a single site retrospective study reported the median time after intubation for diagnosis for PARDS in mechanically ventilated children was 0.1–0.6 days depending upon the definition used (35). Together these findings have major implications for future biomarker study design. Specifically, by the time the degree of respiratory failure is severe enough to require mechanical ventilation over half of children may already meet the diagnosis of PARDS, which is now accommodated for by the PALICC definition of PARDS. Consequently, future studies examining association of plasma biomarkers in samples taken before diagnosis of PARDS with the development of PARDS, or studies aimed at examining specific therapies for prevention of PARDS, will need to enroll patients at risk for PARDS before they require invasive mechanical ventilation.

One of the strengths of this study is that a larger number of *at risk* children were enrolled than any other pediatric ARDS study to date and the cohort also includes a larger number of PARDS patients than any study published thus far. To our knowledge, this is the first study demonstrating an association of IL-1ra with ARDS. The only study examining plasma IL-1ra and ARDS in adults reported no association on univariate analysis, though the study enrolled only 77 patients in total including 19 with ARDS [3]. This study is also the first to examine whether plasma IL-1ra or genetic variants in either the gene for IL-1ra or in genes related to IL-1β level or action are associated with development of PARDS.

This study has some limitations. The definition for PARDS changed during the study period. Consequently for the analysis, PARDS was defined using OI or OSI criteria as suggested in the most recent recommendation for PARDS (23). However, chest radiograph interpretation was subject to the constraints of the parent study data collection, which was limited to presence of new bilateral infiltrates on each study day. Also, while the majority of patients met the criteria for PARDS on the day of intubation (Day 0), only 13% of patients had blood drawn for plasma biomarkers on Day 0. Consequently, we were unable to determine whether IL-1ra levels are significantly higher in those destined to develop PARDS before they meet the criteria for PARDS. This is noteworthy as it limited our ability to assess whether plasma IL-1ra was higher before the onset of PARDS in patients who progressed to develop PARDS. Lastly, the lack of any significant association of genetic variants with PARDS has to be interpreted with caution as the number of patients was relatively small for a genetic association study and there are no other similar cohorts of children with acute respiratory failure with and without PARDS that can be used for validation.

Conclusions

In summary, elevated plasma levels of IL-1ra have value as a marker of early inflammatory cascade activation in children with acute respiratory failure and there is a significant relationship of plasma IL-1ra to the development of PARDS, oxygenation measures, and long-term patient outcomes. The lack of a more consistent association of plasma IL-1ra with either death or PARDS across all days may be because IL-1ra is not a specific marker of death or PARDS, because patients are at a different time points in their trajectory of illness, or because the number of samples on Day 0 is low and the samples obtained on Days 1–3 were sampled at a time that IL-1ra levels are falling. Future studies will be needed with samples obtained before PARDS develops to answer this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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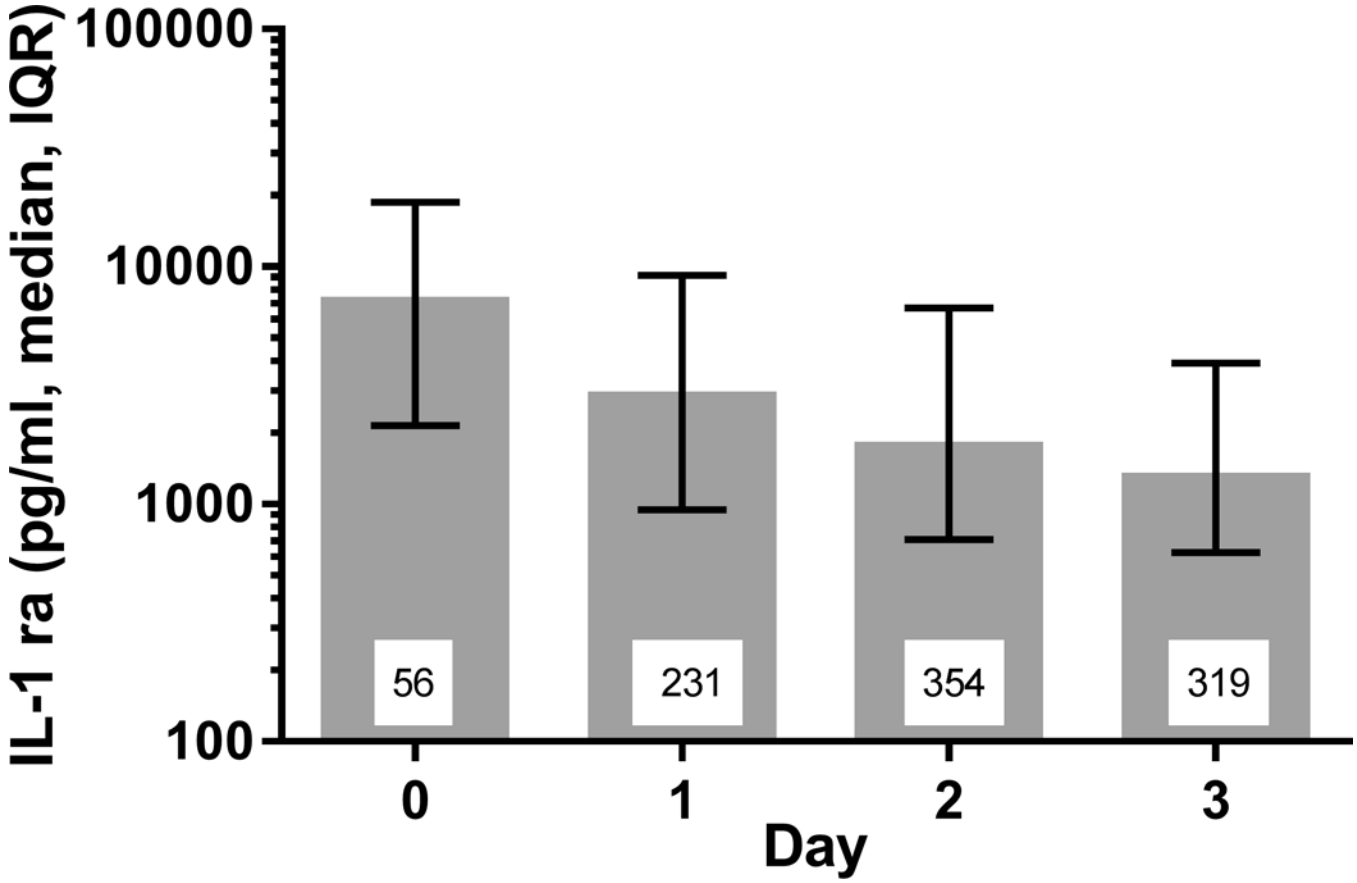

Figure 1. Plasma interleukin-1 receptor antagonist (IL-1ra) levels decrease over time in children with acute respiratory failure

Day 0 is the day of intubation. All days are significantly different from the others ($p<0.0001$) as determined by linear modeling using generalized estimating equations methods as described in Methods. The number inside each bar indicates the number of plasma samples analyzed from the indicated days.

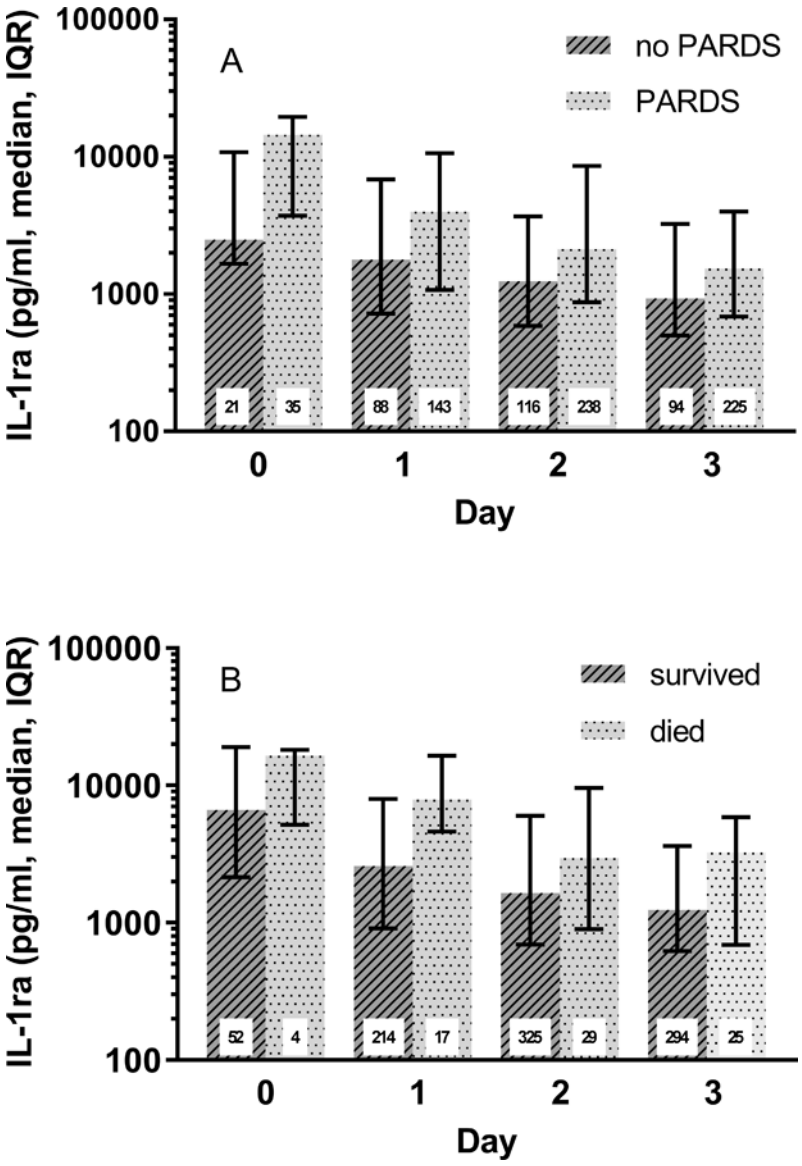

Figure 2. Plasma interleukin-1 receptor antagonist (IL-1ra) is higher in children with PARDS or in non-survivors

A) Plasma IL-1ra in children with or without pediatric acute respiratory distress syndrome (PARDS). If a child met the criteria for PARDS on the indicated day or any day before that they were considered to have PARDS. $p<0.0001$ using generalized estimating equations methods as described in Methods. B) Comparison of plasma IL-1ra in children who died or survived. Day 0 is the day of intubation. The number inside each bar indicates the number of plasma samples analyzed from the indicated days.

Table 1.

Characteristics of Patients with and without Pediatric Acute Respiratory Distress Syndrome (PARDS)

Characteristics	All (n=549)	No PARDS (n=171)	PARDS (n=378)	p[a]
	n (%)	n (%)		
Female	251 (46)	84 (49)	167 (44)	0.28
Non-Hispanic White	287 (52)	84 (49)	203 (54)	0.26
Intervention site	324 (60)	105 (61)	219 (58)	0.46
Primary diagnosis				
Pneumonia	203 (37)	52 (30)	151 (40)	0.03
Bronchiolitis	107 (20)	37 (22)	70 (19)	0.39
Acute respiratory failure related to sepsis	104 (19)	26 (15)	78 (21)	0.13
Asthma or reactive airway disease	56 (10)	27 (16)	29 (8)	0.004
Aspiration pneumonia	34 (6)	14 (8)	20 (5)	0.19
Other	45 (8)	15 (9)	30 (8)	0.74
Medical history of:				
Prematurity	72 (13)	19 (11)	53 (14)	0.35
Asthma	89 (16)	36 (21)	53 (14)	0.04
Seizure disorder	56 (10)	17 (10)	39 (10)	0.89
Neurologic disorder	45 (8)	16 (9)	29 (8)	0.51
Cancer	37 (7)	12 (7)	25 (7)	0.86
Chromosomal abnormality	39 (7)	8 (5)	31 (8)	0.14
Died	47 (9)	19 (11)	28 (7)	0.15
PRISM III	8 (4-13)	8 (3-12)	9 (4-14)	0.03
Age (y), median (IQR)	3.8 (0.6-11.0)	3.0 (0.5-10.9)	4.0 (0.7-11.1)	0.39

[a] p value determined by Chi-square or Mann-Whitney test. PRISM= pediatric risk of mortality, y= year, IQR= interquartile range.

Table 2.

Plasma Interleukin-1 Receptor Antagonist Levels are Correlated with Indices of Oxygenation in Patients with Acute Respiratory Failure

Day	N	Oxygenation Index Correlation Coefficient	p	PaO_2/FiO_2 Correlation Coefficient	p
0	41	0.36	0.02	−0.32	0.04
1	171	0.31	<0.0001	−0.21	<0.005
2	249	0.27	< 0.0001	−0.16	0.01
3	215	0.18	0.008	−0.12	0.07

N indicates the number of plasma samples analyzed from the indicated day with oxygenation index or PaO_2/FiO_2 available on that day.

Table 3.

Multivariable Analysis of Association of Interleukin-1 Receptor Antagonist (IL-1ra) with Pediatric Acute Respiratory Distress Syndrome

Variable	Odds Ratio	95% Confidence Interval	p
Day 0			
Age	0.96	0.87-1.06	0.43
PRISM III	1.04	0.96-1.12	0.38
IL-1ra	1.79	1.03-3.11	0.04
Day 1			
Age	1.01	0.96-1.06	0.68
PRISM III	1.02	0.99-1.06	0.23
IL-1ra	1.23	0.99-1.53	0.06
Day 2			
Age	1.00	0.96-1.04	0.92
PRISM III	1.01	0.98-1.05	0.42
IL-1ra	1.33	1.10-1.60	0.003
Day 3			
Age	1.00	0.96-1.04	0.85
PRISM III	1.02	0.99-1.06	0.27
IL-1ra	1.23	0.99-1.53	0.07

N for Days 0-3 is 56, 231, 354, and 319, respectively. PRISM= pediatric risk of mortality

Table 4.

Multivariable Analysis of Association of Interleukin-1 Receptor Antagonist (IL-1ra) with Duration of Mechanical Ventilation in Children with Acute Respiratory Failure

Variable	Correlation Coefficient	95% Confidence Interval	p
Day 0			
Age	−0.06	−0.10—0.01	0.01
PRISM III	0.01	−0.02 – 0.05	0.45
IL-1ra	0.24	−0.09–0.57	0.15
Day 1			
Age	0.01	−0.01–0.03	0.17
PRISM III	0.01	−0.01–0.03	0.24
IL-1ra	0.18	0.08–0.28	<0.001
Day 2			
Age	0.02	0.01–0.03	0.007
PRISM III	0.01	−0.001–0.02	0.10
IL-1ra	0.15	0.09–0.21	<0.001
Day 3			
Age	0.02	0.004–0.03	0.01
PRISM III	0.01	−0.001–0.02	0.08
IL-1ra	0.13	0.07–0.20	< 0.001

N for Days 0-3 is 56, 231, 354, and 319, respectively. PRISM= pediatric risk of mortality.

Table 5.

Multivariable Analysis of Association of Interleukin-1 Receptor Antagonist (IL-1ra) with PICU Length of Stay in Survivors

Variable	Correlation Coefficient	95% Confidence Interval	p
Day 0			
Age	−0.62	−1.03—0.22	0.003
PRISM III	0.20	−0.31–0.71	0.43
IL-1ra	0.59	−2.31–3.48	0.69
Day 1			
Age	0.14	−0.19–0.48	0.41
PRISM III	0.12	−0.16–0.41	0.39
IL-1ra	2.26	0.63–3.89	0.007
Day 2			
Age	0.25	−0.01–0.50	0.06
PRISM III	0.09	−0.13–0.31	0.42
IL-1ra	2.17	0.88–3.46	<0.001
Day 3			
Age	0.29	0.02–0.56	0.04
PRISM III	0.10	−0.13–0.33	0.41
IL-1ra	2.59	1.05–4.13	0.001

N for Days 0-3 is 52, 214, 325, and 294, respectively. PICU= pediatric intensive care unit, PRISM= pediatric risk of mortality