Databases for Research in Pediatric Acute Respiratory Distress Syndrome

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Abstract

Problem Addressed Observational data, either previously existing or gathered specifically for research, provide exciting opportunities to understand practice variation, generate hypotheses, test the feasibility of future clinical trials, and perform comparative effectiveness research. Pediatric acute respiratory distress syndrome (PARDS) provides a prototypical example of a disease state where our science can be furthered by using observational data in the form of research databases.

Investigational Approach Literature review.

Results There are several key issues that are important to consider in the creation of PARDS databases to inform future research and answer comparative effectiveness questions. They surround (1) time-sensitive measurements mandating careful annotations of key variables, (2) explicit methodology for ventilator-related variables, (3) explicit data to calculate outcome measures, (4) granularity of data to handle dose-dependent questions, and (5) operational definitions of crucial comorbidities or other factors implicated in PARDS outcome. These areas must be explicitly handled in the ontologic framework of PARDS databases.

Conclusions In summary, there are many opportunities to use existing data to further our knowledge of PARDS. However, the aggregation of these data from previous studies, future studies, or existing electronic health care records must be done with careful consideration that the variables and data annotations are of adequate granularity and specificity to answer the questions we want to ask.

Keywords

- ▶ children
- ▶ electronic databases
- ▶ acute respiratory distress syndrome
- ▶ intensive care

Introduction

Observational data (either previously existing or gathered specifically for research) provide exciting opportunities to understand practice variation, generate hypotheses, test the feasibility of future clinical trials, and perform comparative effectiveness research.¹ A distinct advantage of observational data (particularly if it is preexisting) surrounds the ability to answer research questions with fewer resources (time and money) than what is needed for clinical trials. Furthermore, it allows us to understand the “real-world” scenario, as often

data are gathered which reflects current practice rather than controlled clinical trials. To that end, existing data may be used to conduct studies that are not amenable to a randomized trial because of lack of equipoise, relatively rare disease states (a crucial factor for pediatric critical care), or inability to standardize management.¹

Pediatric acute respiratory distress syndrome (PARDS) provides a prototypical example of a disease state where our science can be furthered by using observational data in the form of research databases. The fundamental reasons

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surround the inherent variability in management practices of PARDS, selective adoption of adult-based evidence with inappropriate consideration of pediatric-specific pathophysiology or practice, lack of a pediatric-specific definition of ARDS, and lack of consensus on even some of the most basic strategies for caring for the child with ARDS.² Some of these issues have been recently addressed by the Pediatric Acute Lung Injury Consensus Conference (PALICC), but it will likely take years before these recommendations can change clinical practice in any meaningful way.³ These factors, among others, may contribute to the lack of positive clinical trials for mechanically ventilated children or those with PARDS.^{4–7} Use of observational data from patients with PARDS may help overcome some of these limitations. Of course, key consideration must be given to data quality limitations of existing data sources, and it is crucial that the research question and data source be appropriately matched. If not, the conclusion may be misleading, particularly if key surrogate variables crucial for the research question are not available in the data source.^{8,9}

Several pediatric researchers have been able to make important contributions to the field of PARDS by using observational data.^{10–16} However, the inherent limitation to these investigations surrounds the fact that they are often single institution, with limited sample size, and reflective of the practice patterns in a relatively small number of intensive care units (ICUs). As is clear from the few multicenter observational studies in PARDS,^{17,18} among and within institutions there is incredible variation in management strategies, disease severity, mortality rates, and comorbidities.¹⁹ This makes it even more difficult to generalize single-institution findings to global PARDS practice.¹⁸

The future of PARDS research would benefit tremendously from multi-institutional databases. This will require standardization of terminology and methodology, and a clear ontologic framework to ensure that data elements from different institutions can be combined to answer questions. This review focuses on some of the issues crucial for the creation of a multicenter PARDS database that can inform future research and answer important comparative effectiveness questions. Key issues surround (1) time-sensitive measurements mandating careful annotations of key variables, (2) explicit methodology for ventilator-related variables, (3) explicit data to calculate outcome measures, (4) granularity of data to handle dose-dependent questions, and (5) operational definitions of crucial comorbidities or other factors implicated in PARDS outcome.

Time-Sensitive Measurements

As has recently been illustrated in several pediatric ARDS publications, the timing of assessment of ARDS severity may have big implications on prognostic relevance or risk stratification.^{12,13,20} There are many unanswered questions regarding what point in the illness or course of mechanical ventilation ARDS severity should be assessed. The new PARDS-specific definition put forth by the PALICC has recommended using oxygenation index (OI) or oxygen saturation

index (OSI) when OI is not available, to define PARDS severity.³ Severity stratification is important for ARDS management, as the risk-benefit profile of certain therapies and even the physiologic effect may differ substantially based on severity of disease. This is well illustrated, for example, in adult ARDS with respect to higher positive end-expiratory pressure (PEEP) strategy and prone positioning, both showing benefits in those with more severe disease, and either no benefit or harm for those with less severe disease.^{21–23} Having severe ARDS at the time of diagnosis may have different prognostic and therapeutic implications than having severe ARDS 24, 48, or 72 hours after the initial ARDS diagnosis. The initial value may be more representative of the inherent disease severity of the patient, or perhaps the quality of pre-ICU care. The later values, particularly as time persists, may reflect persistence of disease and adequacy of response (or nonresponse) to therapy. Furthermore, the timing of the diagnosis of ARDS gets further complicated by timing of presentation to medical care and any prehospital or pre-ICU therapies. Conventionally we mark the origin of ARDS when the patient meets all the given diagnostic criteria, but from biomarker studies it is clear that the inflammatory process in the lungs has likely begun well before patients meet diagnostic criteria. As such, it becomes nearly impossible to define when ARDS begins, and this process is subjective and often dependent on when therapies are implemented (i.e., mechanical ventilation, blood gas sampling, chest imaging, etc.).

Nevertheless, the issue of timing is of crucial importance for the future of PARDS research. When thinking about aggregating data from multiple institutions for research, data must be explicitly collected and annotated to understand the relationship to the time of initial diagnosis of ARDS, knowing that this, in fact, may not ultimately reflect when the disease process actually started. This becomes even more complicated now with the use of pulse oximetry-based criteria, as no longer do we need to wait until an arterial blood gas is obtained to diagnose the onset of ARDS. Given privacy laws and regulations, the timing of data will likely be referenced to a known start time of an episode (i.e., like time of ICU admission) rather than use of an actual date and time. This is relevant for not only computation of disease severity markers (i.e., such as OI, OSI, PF ratio, SF ratio),^{24,25} but also ventilator settings, markers of other organ dysfunction, markers of initial severity of illness, and therapeutic interventions (such as prone positioning, surfactant, neuromuscular blockade etc.). Moreover, the current recommendations for markers of disease severity of PARDS (OI and OSI) require that simultaneous (or near simultaneous) data are available from pulse oximetry or arterial blood gas sampling, and ventilator settings (Mean Airway Pressure [MAP] and FiO_2).²⁶ If databases are created containing the raw elements necessary to compute these composite metrics, then MAP, FiO_2 , and SpO_2 must be available simultaneously. A limitation with using existing data from electronic health records, for example, is that often these data are not charted simultaneously. That leads investigators to take several different tactics to calculate these values (i.e., requirement for

maximum time differences between charted variables, assumptions that if a parameter has not been charted recently that it has not changed, etc).^{15,27,28} This issue may become less important as more granular data are becoming available in research databases (i.e., high-frequency data of physiologic monitors and ventilators), although these highly granular data pose unique computational challenges and introduce potential inaccuracies in the data from sensor artifact, for example (i.e., pulse oximeter not connected to the patient, but data still displayed and recorded).

As such, we need to be explicit about timing when creating observational databases related to PARDS. In particular, we should be able to understand the longitudinal time sequence of all relevant data in relation to important clinical events such as hospital and ICU admission, initiation of noninvasive mechanical ventilation, intubation, and if possible, the time of first symptom development to understand the relationship between onset of symptoms and presentation to critical care.²⁹

Explicit Methodology for Ventilator and Monitor Variables

Perhaps the most interesting variables to consider regarding ARDS management and disease severity surround ventilator management and settings. Ventilator settings are crucial to understand the relevance of ventilator-induced lung injury, institutional practice variation, and initial and subsequent disease severity. Not having some means to control for ventilator support greatly limits any meaningful conclusions in PARDS research.^{8,9} However, variations in the way ventilator data are gathered introduces a new set of problems in PARDS research.

For example, tidal volume (V_T) is an important variable in ARDS research, brought to prominence by the ARDSnet ARMA trial.³⁰ However, there are no consistent pediatric data showing that V_T is associated with outcome in PARDS, with many observational studies.³¹ There are major differences between adult and pediatric practice, which confuse the issue of the relationship between V_T and outcome, and these issues must be dealt with when considering combining data from multiple institutions in the form of a research database.

1. V_T is the set variable in most adult ICUs, as they frequently use the square wave pattern of volume control ventilation. Pressure control is the most frequent mode used in pediatric ARDS, wherein pressure is the set variable and volume is the response variable.^{18,32} Hence, the prescription for ventilator settings is fundamentally different, as is the flow pattern. Hence, one must capture detailed information on mode of ventilation. This gets complicated when considering hybrid modes such as pressure-regulated volume control (PRVC), wherein a volume is dialed in, but an upper pressure limit is set, and volume is reduced if the pressure limit is reached. Moreover, the flow pattern is decelerating. Different ventilator manufacturers implement PRVC, for example, in different ways. Hence, we must capture data related to mode, make, set volume,

achieved volume, set pressure, and achieved pressure to best make sense of V_T data.

2. Location of V_T measurement—while the accuracy of algorithms to calculate delivered V_T back at the ventilator has improved, there may still be substantial differences based on the measurement device and location of measurement (ventilator or proximal airway), particularly for small children wherein the dead space of the ventilator tubing may be larger than their V_T .^{2,33,34} Hence, we must collect data on how and where V_T is measured to ensure that data can be combined.
3. Body weight for calculation of V_T —there is no accepted standard in pediatric critical care about which weight to use to normalize V_T measurements. Predicted body weight (PBW) is used in adult ICUs, to deal with issues of obesity. While we may be able to extrapolate using PBW for obese children, what should be done for children who are failing to thrive? Height therefore becomes a crucial variable to follow and calculate PBW, but is it inconsistently recorded in many ICUs. Furthermore, how does one measure height accurately in children with severe scoliosis? Other surrogates that may predict standing height more accurately (such as ulna length) may need to be implemented.^{2,35,36}
4. Endotracheal tube leak. While cuffed endotracheal tubes are becoming more routine in pediatric critical care, effective V_T may not be accurate with a large endotracheal tube leak. As such, both inspiratory and expiratory V_T must be gathered, allowing for selective inclusion based on a leak percentage threshold.³³

Similar issues exist for ventilator pressures, in particular peak inspiratory pressure versus plateau pressure. It is common in the literature to interchange these terms, particularly when pressure control ventilation is used. While there may be few differences between peak and plateau pressure for children with ARDS managed with the decelerating flow pattern of pressure control ventilation without significant lower airway disease, fundamentally plateau pressure requires an inspiratory hold for measurement. These maneuvers are likely not implemented routinely or consistently in pediatric critical care, and “plateau” pressure is often being mislabeled. Fundamentally, the *peak pressure* may be the relevant term in pediatric ARDS whereas *plateau pressure* is the more relevant term in adult ARDS. However, these pressures are not identical, so careful consideration must be given to which pressure is used and how it was obtained when combining data from different data sources, again with attention to mode of ventilation.

These are two examples, using the most frequently considered ventilator variables. However, similar issues may exist with other important variables such as mean airway pressure, dynamic or static compliance, pulse oximetry, and capnography. Hence, initiatives to combine data must have explicit methodology and data dictionaries to ensure that the data were captured and recorded in a similar manner.

Explicit Data to Calculate Outcome Measures

Mortality is becoming harder to use as an outcome measure in PARDS research, given overall improvements in

mortality over time. Some recent estimates, particularly from randomized controlled trials, have mortality rates close to 10% for PARDS, making it impossible to adequately power an interventional study for mortality.¹³ A clinical trial that finds a 25% relative risk reduction in mortality would need more than 2,000 patients per arm to achieve statistical significance. In general, observational studies in PARDS have higher mortality, because they have fewer exclusion criteria. Combining observational datasets together may enable using mortality as an outcome measure to get higher sample sizes. Of course, which mortality becomes the next important question: ICU mortality, hospital mortality, 28-, 90-day mortality? The research question may drive the mortality variable of interest, so databases must capture several different mortality end-points, to enable the research question to match the most appropriate outcome. For example, a study examining extracorporeal membrane oxygenation (ECMO) and ARDS may have substantially different results when looking at 28- versus 90-day mortality, given that many patients with ARDS are on ECMO for weeks at a time.

Increasingly, PARDS researchers are left with surrogate outcomes such as length of stay, length of mechanical ventilation, ventilator-free days, new or progressive organ dysfunction, organ failure-free days, etc. Imprecision in measurement introduces potential for bias (i.e., length-of-stay variables subject to practice variation by providers or institutions, organ dysfunction variables subject to interpretation or incomplete data [i.e., Glasgow Coma Scale]). Moreover, there has been a recent trend to create combination variables such as ventilator-free days (i.e., days in 28 days in which a patient is alive and not on a ventilator) to reduce the sample size needed for clinical trials by combining “bad outcomes”—death and prolonged ventilation.³⁷ Limitations with these combination variables relate to potential opposite effects of the intervention (i.e., results in improved mortality but longer time on a ventilator), imprecise or variable definitions (i.e., how to handle non-invasive ventilation) that limit generalizability, and potential limited importance to the patient (i.e., not patient centered).

Given these somewhat subjective outcome measures, it becomes crucial to gather data related to confounding variables, which may affect these process variables (such as length of ventilation) and account for institutional specific variation. These relate to sedation, fluid management, inotrope or vasopressor management, transfusion strategy, neuromuscular blockade use, adjuvant therapies such as prone positioning or surfactant, etc. Furthermore, because ventilator-free days (VFDs) is becoming the new de facto outcome for many PARDS clinical trials, it is crucial that we are explicit in how we calculate this variable. There are multiple ways to handle noninvasive ventilation, for example, in the VFD calculation. Moreover, given that mortality and length of ventilation do not always move in the same direction, while we use VFDs as a primary outcome, we must also report separately mortality and LMV in survivors to understand the true treatment effect.

Granularity of Data to Handle Dose-Dependent Questions

It is clear in mechanical ventilation practice and research that a single snapshot of a patient at 8 AM does not reflect the overall state of the patient for the previous or subsequent 24 hours. The state of the patient may fluctuate throughout the 24 hours, as do the interventions. Given the complexity of critical illness, and the important interplay of therapy and disease severity and timing, most questions regarding management practices for PARDS must consider the relative “area under the curve” for which the patient is exposed to an intervention.¹⁵ For example, a patient may be receiving 6 mL/kg V_T at 8 AM, but throughout the day that value is actually fluctuating from 6 to 10 mL/kg, with a time weighted average V_T of closer to 9 mL/kg. Ventilator-induced lung injury, which we are trying to avoid with lung-protective ventilation, is incredibly dose-dependent.

The same is true when considering prone positioning, for example. It is clear that the duration of prone positioning is a crucial variable, with most studies targeting duration between 16 and 20 hours for optimal effect.^{4,22,38} Hence, simply collecting information about the presence or absence of a given therapy, or a single point in time, will potentially lead to imprecise or incorrect conclusions about the relationship between a variable of interest and outcome. As such, the granularity of the data gathered must be sufficient to answer the specific research question. The now-near ubiquitous nature of electronic medical records will facilitate gathering these more granular data, and increasingly there are researchers outside of medicine interested in these problems and big data questions. There have been countless examples of successful collaborations between intensivists, engineers, and computer scientists, which have resulted not only in interesting publications but in informatics-based solutions to critical care problems.^{39–45} This has the potential to translate into smarter solutions for patient monitoring, predictive analytics to prevent complications or suggest therapies that may be beneficial for an individual patient, and personalized medicine approaches based simply on existing data. The analytic techniques are complicated given that most ICU data are inconsistently sampled, repeated time series analysis, which mandate specific mathematical techniques.⁴¹ However, it is precisely these problems that computer scientists are looking to tackle, with clinical partners. Hence, we should not shy away from attempting to capture “all the data,” as there are researchers waiting to push the envelope with new analytic techniques to answer important clinical questions.

Operational Definitions of Crucial Comorbidities or Other Factors Implicated in the Outcome of PARDS

What is clear from the past 30 years of PARDS research is that the factors driving outcome are multifactorial. Preexisting comorbidities, causes of lung injury, or other “confounding factors” may be the biggest drivers of death for PARDS.⁴⁶ Two critically ill children with similar etiology and initial severity

of PARDS may have markedly different outcomes based on the presence or absence of preexisting pulmonary disease (i.e., chronic lung disease) or immunodeficiency, for example.^{7,18} Chronic illness is a major consideration in pediatric critical care, with recent estimates that greater than 50% of all pediatric ICU (PICU) patients have complex chronic conditions on admission to the PICU, which are associated with higher severity of illness adjusted mortality.⁴⁷ Preexisting comorbidities make it more difficult to test the potential efficacy of new therapeutic interventions because the effect of an intervention on mortality may be less.^{11,15,16} While death from ARDS in both adults and children occurs frequently from multiple organ failure, and not refractory hypoxemia, the hypoxemia metrics likely capture the severity of the initial insult as well as the inflammatory response seen in ARDS. This common response may be ultimately what explains the development of multiple organ dysfunction, which leads to death in both adult and pediatric ARDS. The presence of preexisting comorbidities modifies this response, as a less severe insult in a child with immunodeficiency may be more likely to result in death than the same insult in a previously healthy individual. Furthermore, the presence of multiple comorbidities amid chronic illness confounds the potential benefits of therapeutic interventions in which even reversal of the acute pathophysiology with a therapy does not reverse the progressive organ dysfunction because previous insults to those organs prevent recovery.

As such, our research databases for PARDS must contain robust information regarding comorbidities and disease etiologies, as these may be the most important factors implicated in outcome for the patient. Unfortunately, there are few agreed-upon standards for some of these “comorbidities,” and the imprecision in assignment of these “diagnoses” may further complicate the question. For example, an ex-34-week premature infant who is on 0.25 L of oxygen at baseline may be very different than an ex-24-week infant who is on home mechanical ventilation. Both would be labeled as having chronic lung disease, but the information about home therapy is probably the most crucial way to stratify the severity of the preexisting illness. The later patient, for example, would not be stratified into mild, moderate, and severe ARDS using the recent PALICC recommendations for ARDS severity, whereas the first child would be appropriate to stratify in this manner.³ Hence, these types of data must be available in PARDS databases.

In summary, there are many opportunities to use existing data to further our knowledge of PARDS. However, the aggregation of these data from previous studies, future studies, or existing electronic health care records must be done carefully to ensure that we can answer the questions we want to ask. In particular, we must pay close attention to the time-sensitive nature of measurements mandating careful annotations of key variables, have explicit methodology for ventilator-related variables, gather explicit data to calculate outcome measures, cater the granularity of data to handle dose-dependent questions, and ensure that we have operational definitions of crucial comorbidities or other factors implicated in PARDS outcome. These are crucial factors to

ensure successful applications of research databases in PARDS.

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