Clinical Decision Support for Neonatal Mechanical Ventilation

By

Lindsey Ann Knake MD

Thesis

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Approved:

Adam Wright, Ph.D.

MHD Wael Alrifai, M.D., M.S.

Jonathan Wanderer, M.D., MPhil

L. Dupree Hatch III, M.D., M.P.H.

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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
BW	Birth weight
CDH	Congenital diaphragmatic hernia
CDS	Clinical decision support
CRIB	Clinical risk index for babies
EHR	Electronic health record
FiO_2	Fraction of inspired oxygen
GA	Gestational age
IQR	Interquartile range
kg	Kilogram
MAS	Meconium aspiration syndrome
mL	Milliliters
MV	Mechanical ventilation
NICU	Neonatal intensive care unit
PLV	Pressure-limited ventilation
RT	Respiratory therapist
US	United States
VG	Volume guarantee
VT	Tidal volume
VTV	Volume-targeted ventilation
VUMC	Vanderbilt university medical center

1.0. INTRODUCTION

Mechanical ventilation (MV) in the Neonatal Intensive Care Unit (NICU) is a necessary therapy for many neonates, but is associated increased morbidity and mortality.[1-3] In adult and pediatric populations, automated, non-physician driven ventilator weaning protocols and ventilator-based computer programs to promote lung protective strategies,[4] decrease ventilator associated pneumonias,[5] and shorten MV time have been developed.[6] However, these protocols are only validated on patients greater than 7 kilograms (kg) and, thus, are not applicable to the neonatal population.[4]

In neonates, volume-targeted ventilation (VTV) modes are associated with shorter MV courses and improved clinical outcomes.[7] Compared to pressure-limited ventilation (PLV), the use of VTV results in lower rates of death or bronchopulmonary dysplasia (BPD), pneumothorax, intraventricular hemorrhage, and fewer days of MV.[7] With recent advances in technology and biomedical informatics, computerized protocols could offer a solution to facilitate appropriate use of VTV in clinical care. We hypothesize that implementation of a clinical decision support (CDS) tool will improve the use of choosing evidence-based initial tidal volume (VT) in the NICU.

We explored this hypothesis by performing the following specific aims:

1. To quantify use of literature recommended initial VT and determine factors associated with its use in a large population of ventilated infants.
2. To develop local expert consensus recommendations for initial VT according to birth weight and admission diagnoses.

3. To evaluate if a stepwise CDS implementation can improve use of recommended initial VT settings for mechanical ventilation in the NICU.

In the first manuscript (Chapter 2) of this thesis, we describe the methods and results for Aim 1 which serves as the background section for the thesis. The second manuscript (Chapter 3) describes the methods and results for Aims 2 and 3. We then summarize the conclusions learned from completing all three aims.

2.0. Manuscript 1: Epidemiology of Tidal Volume Use During Neonatal Volume-Targeted Ventilation

Corresponding Author:
Lindsey A. Knake MD
University of Iowa Hospitals & Clinics
Department of Pediatrics, Division of Neonatology
200 Hawkins Drive
Iowa City, IA. 52242-1083
lindsey-knake@uiowa.edu

Lindsey A. Knake MD[1,2,3,4]; Mhd Wael Alrifai MD, MS[2,3,4]; Allison B. McCoy PhD[3,4]; Scott O. Guthrie MD[2,5]; Adam Wright PhD[3,4]; Christoph U. Lehmann MD[6]; L. Dupree Hatch III MD, MPH[2,7,8]

[1]Department of Pediatrics, Division of Neonatology, University of Iowa, Iowa City, IA, USA; [2]Department of Pediatrics, Division of Neonatology, Vanderbilt University Medical Center, Nashville, TN, USA; [3]Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA; [4]Vanderbilt Clinical Informatics Center, Vanderbilt University, Nashville, TN, USA; [5]Jackson-Madison County General Hospital, Jackson, TN, USA; [6]Clinical Informatics Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; [7]Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, TN, USA; [8]Critical Illness, Brain Dysfunction, and Survivorship Center, Vanderbilt University Medical Center, Nashville, TN, USA

2.1. ABSTRACT

Objective: To quantify initial VT during neonatal VTV and to characterize the agreement of initial VT with published recommendations.

Design/Setting: We performed a multi-center retrospective observational cohort study from October 2018 to September 2020 in two NICUs where VTV is the primary ventilation modality. Detailed guidelines for choosing initial VT were available in one study NICU. We generated descriptive statistics and performed a multivariable logistic regression analysis to determine factors associated with initial VT use that agreed with published recommendations.

Patients: We included infants without congenital lung anomalies who received VTV as the initial ventilation modality prior to postnatal day 14.

Results: In our study, 313 infants met study inclusion criteria and 154 (49%) infants received an initial VT of 5.0 mL/kg (median 5.0 mL/kg, IQR 5.0 – 5.1). One (0.3%) infant received an initial VT less than 3.0 mL/kg and 10 (3.2%) infants received an initial VT greater than 6.0 mL/kg. Only 45 (14%) infants received an initial VT that was congruent with published recommendations. In multivariable analysis, having a birth weight of 700 ≤1250 grams was the only factor significantly associated with an initial VT in agreement with published VT recommendations (aOR 9.4, 95% CI 1.7 – 50.4).

Conclusions: Most infants received an initial VT of approximately 5.0 mL/kg despite published recommendations. Future work should develop tools to assist clinicians in choosing evidence-based strategies during neonatal VTV.

2.2. BACKGROUND

Mechanical ventilation in the NICU is a life-saving therapy. However, MV in preterm infants is associated with increased mortality,[2] neurodevelopmental impairment,[1] structural changes in the central nervous system,[8] and BPD.[3] Despite improvements in neonatal care, BPD occurs in 40% of very low birth weight infants in the United States (US).[9]

In neonates receiving MV, VTV[7] results in improved clinical outcomes compared to PLV. Compared to PLV modes, VTV is associated with lower rates of death or BPD, pneumothorax, intraventricular hemorrhage, and fewer days of MV.[7] However, only 42% of NICUs in the US and Canada report VTV as their primary ventilation modality.[10]

One of the most important decisions neonatal clinicians must make when using VTV is to choose an initial VT that is appropriate for each infants' respiratory pathology and size. While recommendations for choosing initial VT exist,[11] a previous survey showed that initial VT often does not agree with published neonatal recommendations.[10] No studies have described initial VTs in clinical practice. The objectives of our study were to quantify initial VT used during neonatal VTV and characterize the frequency with which initial VT agreed with published recommendations for neonatal VTV use.

2.3. METHODS

Study Design, Setting, and Population: We performed a retrospective observational cohort study in the 98-bed, level IV Vanderbilt University Medical Center (VUMC) NICU and the 30-bed, level III Jackson-Madison County General Hospital NICU from October 2018 to September 2020. We collected data from October 8, 2018 to February 23, 2020 at the VUMC NICU and from March 15, 2019 to September 23, 2020 in the Jackson-Madison NICU with differences in study periods due to local infrastructure for data collection and restrictions on clinical research during the COVID-19 pandemic. We included all infants who received VTV as the initial ventilation modality prior to postnatal day 14. We excluded infants who received PLV or high frequency ventilation prior to receiving VTV and infants with congenital pulmonary airway malformations. The VUMC institutional review board approved the study with a waiver of consent.

Unit practices: In both study NICUs, non-invasive ventilation is the primary mode of respiratory support for all infants born at less than 32 weeks' gestational age (GA). For infants who receive endotracheal intubation, conventional VTV modes are the most common ventilator modalities used. During the study, both NICUs primarily used either flow-cycled or time-cycled modes with the volume guarantee feature and leak compensation on the Dräger Evita Infinity V500 ventilator (Drägerwerk AG and Co, Lübeck, Germany) activated. Both study units utilized flow sensors placed at the proximal end of the endotracheal tube. High frequency jet ventilation is generally used as the first ventilation modality for all non-vigorous infants less than 25 weeks' GA. At VUMC, unit guidelines exist to recommend initial settings based on infant weight and

diagnosis.[12] These guidelines were not present at the Jackson-Madison County General Hospital NICU during the study period.

Study Outcomes: The primary outcome for each infant was the initial VT used during the first MV course in milliliters (mL) per kilogram (kg) of birth weight (BW). We defined the initial VT as the first VT that was used for 15 or more consecutive minutes after initiating MV. Each initial VT was then classified as whether it agreed with published recommendations according to the birth weight of the infant: <700 grams (g) (5.5 – 6 mL/kg), 700 – <1250 g (4.5 – 5 mL/kg), and ≥1250 g (4 – 4.5 mL/kg).[11]

Data Sources and Additional Variables: We determined the initial VT and fraction of inspired oxygen (FiO_2) by downloading data directly from the mechanical ventilators. Patients with missing ventilator data, defined as those for whom ventilator data at the beginning of the ventilation course was not downloaded, were excluded from the study. The initial FiO_2 was defined as the recorded value on each ventilator at the same time as the initial VT. We determined the demographic and clinical characteristics of study infants including sex, race, inborn status, antenatal steroid use, postnatal day at NICU admission, BW, GA, and Clinical Risk Index for Babies (CRIB) score[13] by querying local NICU research databases manually curated by trained research nurses in each unit and electronic health records using Epic's Clarity database (Epic Systems Corporation, Verona, WI). When applicable, one study investigator (LAK) performed manual chart review to confirm outliers and capture missing data elements.

Statistical Analysis: We generated descriptive statistics to define the baseline characteristics of study infants using median and interquartile range (IQR) for continuous variables and percentages for nominal variables. Initial VT was described using median and IQR and agreement with published recommendations was reported using counts and percentages. The number of patients who received an initial VT of exactly 5.0 mL/kg was reported using counts and percentages. For initial VT, we report the total cohort and values stratified by BW. Because this was a retrospective cohort analysis, no sample size calculations were performed.

To evaluate which factors were associated with an initial VT that agreed with published recommendations, we fit a multivariable logistic regression model to the data with the congruence of initial TV with published recommendations as the dependent variable and the following a priori identified independent variables: BW, sex, inborn status, CRIB score, and initial FiO_2.

Finally, we performed a pre-specified sensitivity analysis to account for potential rounding errors by clinicians in either VT or estimated BW. For this, we classified the initial VT for each ventilation course as agreeing with published recommendations if it was within 0.3 mL/kg above or below the recommended initial VT range. This adjustment accounts for the BW specific rounding of the initial VT to a whole number that commonly occurs in practice. We then repeated our multivariable logistic regression analysis with the expanded cohort of infants' with VT in agreement with recommended

initial VT. All statistical analyses were performed using Stata/BE 17.0 (StataCorp, College Station, TX).

2.4. RESULTS

During the study period, 558 infants received MV in the study NICUs. Of these, 313/558 (56%) met study inclusion criteria (*Figure 1*). The most common reasons for exclusion from the study were missing ventilator data, first MV after 14 days postnatal age, or high frequency ventilation prior to conventional MV. The majority of study infants were inborn with median BW and GA of 2300 grams and 35 weeks, respectively (*Table 1*).

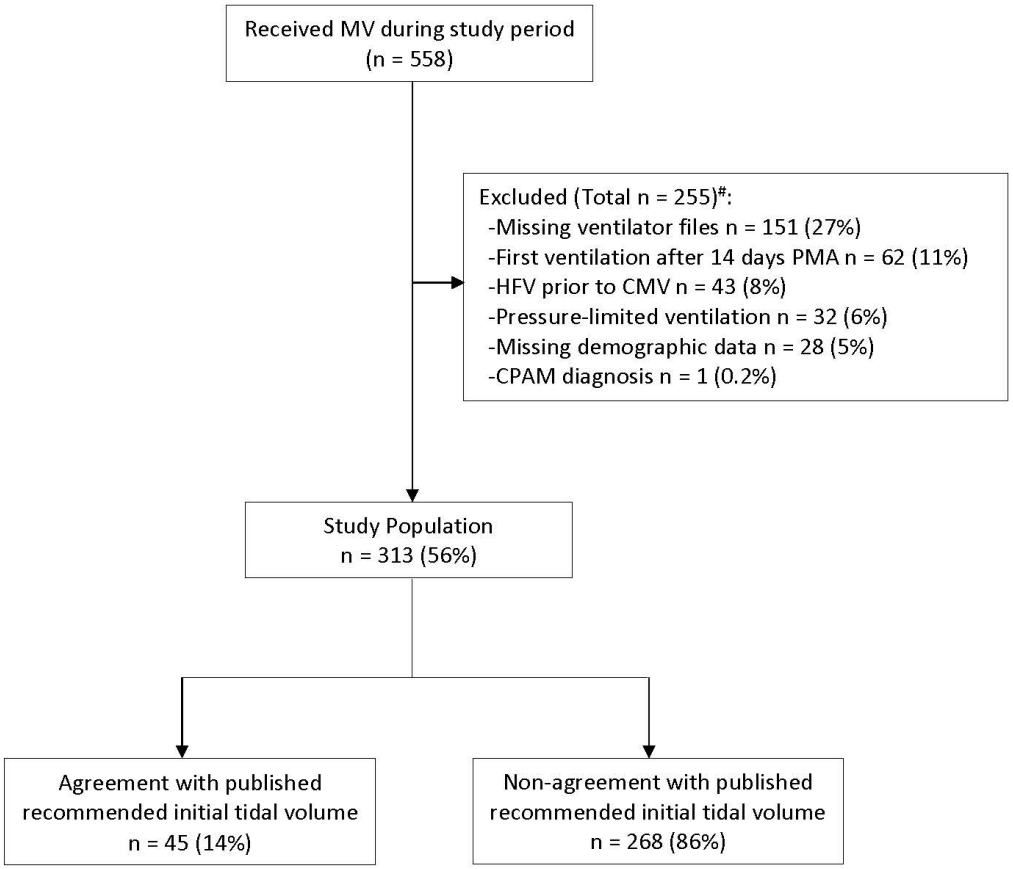

Figure 1: Flow diagram of infants included in study
Total infants excluded is less than the total of the categories as some infants were excluded for multiple reasons; PMA (postmenstrual age), HFV (high frequency ventilation), CMV (conventional mechanical ventilation), CPAM (congenital pulmonary airway malformation)

Table 1: Demographics and clinical characteristics

	Total Cohort (N = 313)	**Agreement with published recommended initial VT (N = 45)**	**Non-agreement with published recommended initial VT (N = 268)**
Male sex- n – (%)	178 (57)	24 (56)	154 (57)
Race[1]– (%)			
Caucasian	217 (74)	33 (73)	184 (69)
Black	59 (20)	7 (16)	52 (19)
Other[2]	18 (6)	2 (4)	16 (6)
Inborn – (%)	193 (62)	34 (76)	159 (59)
Any antenatal steroids[1] – (%)	130 (44)	28 (62)	102 (38)
Age at NICU admission[1] – median days [IQR]	0 [0, 1]	0 [0, 1]	0 [0, 1]
Birth weight – median grams [IQR]	2300 [1270, 3110]	1010 [880, 1220]	2423 [1545, 3185]
Birth weight categories			
<700 grams	25 (8)	3 (7)	22 (8)
700 – <1250 grams	50 (16)	31 (69)	19 (7)
≥ 1250 grams	238 (76)	11 (24)	227 (85)
Gestational age – median weeks [IQR]	35 [29, 37]	27 [26, 31]	35 [31, 38]
CRIB score[3] – median [IQR]	3 [0, 4]	2 [1, 4]	3 [0, 4]
Postnatal age at intubation – median days [IQR]	0 [0,1]	0 [0, 0]	0 [0, 1]
Initial FiO2 – median [IQR]	0.39 [0.27, 0.55]	0.39 [0.29, 0.50]	0.39 [0.27, 0.57]

VT (tidal volume), CRIB (clinical risk index for babies), FiO2 (fraction of inspired oxygen); [1]Data missing for 19 patients (6%); [2]other = Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, and patients that identified as other; [3]Data missing for 24 patients (8%)

The most common initial VT used was 5.0 mL/kg (median 5.0 mL/kg, IQR 5.0 – 5.1), with 154/313 (49%) of infants receiving an initial VT of exactly 5.0 mL/kg. This was the most common VT across the two study NICUs (50% and 37%). When stratified by BW, 5.0 mL/kg was most commonly used in larger infants: <700 g: 5/25 (20%), 700 – <1250 g: 26/50 (52%), and ≥1250: 123/238 (52%). Infants with a BW < 700g had the greatest variability in the initial VT used, though the initial VT clustered around 5.0 mL/kg in all

three BW strata (*Table 2*). All initial VTs for infants in the cohort are shown in Figure 2. Only 1/313 (0.3%) infants received an initial VT less than 3.0 mL/kg with the actual initial VT recorded at 2.9 mL/kg. The highest initial VT was 8.0 mL/kg and 10/313 (3.2%) received an initial VT greater than 6.0 mL/kg (*Figure 2*).

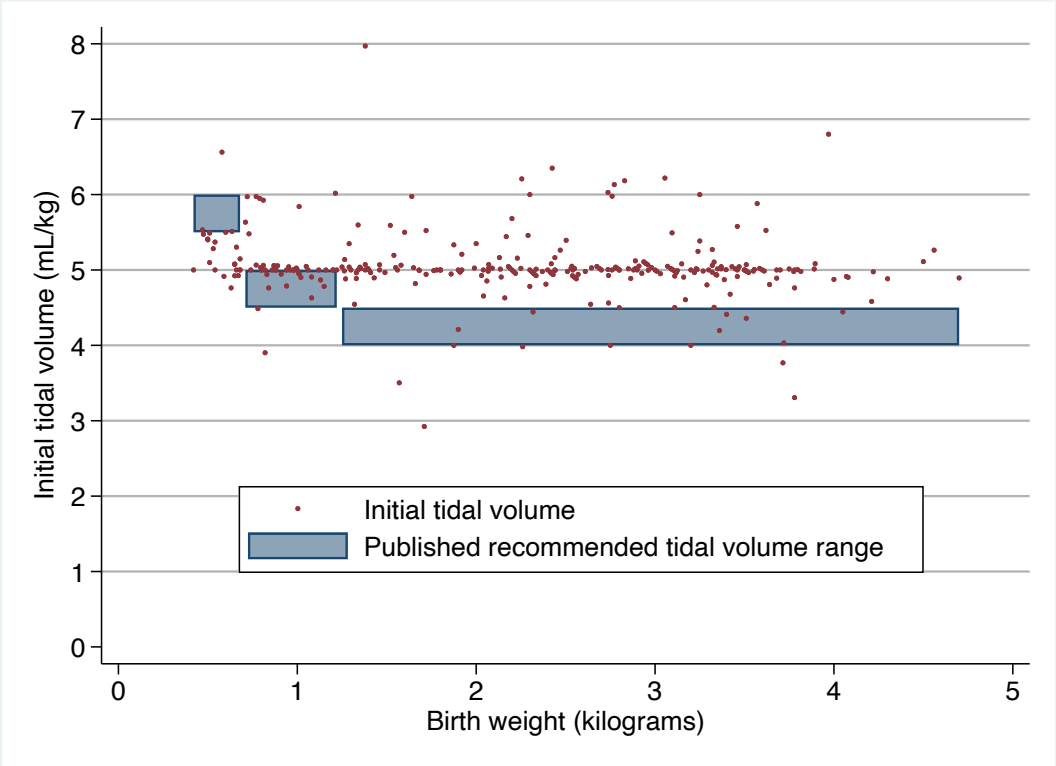

Figure 2: Initial tidal volume and recommended ranges based on birth weight.
The most common initial tidal volumes clustered around 5.0 mL/kg with 49% of infants receiving exactly 5.0 mL/kg. Only 45/313 (14%) of infants had an initial VT consistent with published recommendations (shaded areas). Infants with birth weight of 700 – <1250 g were most likely to receive VT consistent with recommendations as that category included 5.0 ml/kg in the recommended range.

Only 45/313 (14%) infants received an initial VT that was congruent with published recommendations. The percentage of infants who received an initial VT congruent with published recommendations was highest in infants with a BW of 700 – <1250 g (*Table 1*), which was also the only BW category that included 5.0 mL/kg in the recommendation. This accounts for the clinical characteristic differences seen between

those in agreement with published recommended initial VT and those with non-agreement with published recommended initial VT (*Table 1*). In multivariable logistic regression analysis, having a BW 700 – <1250 g was the only factor significantly associated with an initial VT in agreement with published recommendations (aOR 9.4, 95% CI 1.7 – 50.4) (*Table 2*).

Table 2: Factors associated with agreement with published recommended initial tidal volume

	Initial tidal volume (mL/kg) Median [IQR]	Adjusted odds ratio (95% CI)
Birth weight category		
<700 grams	5.1 [4.9, 5.4]	Reference group
700 – <1250 grams	5.0 [4.9, 5.1]	9.4 (1.7 – 50.4)
≥1250 grams	5.0 [4.9, 5.0]	0.4 (0.1 – 2.1)
Male sex	5.0 [4.9, 5.1]	0.8 (0.4 – 1.9)
Inborn	5.0 [4.9, 5.1]	1.2 (0.5 – 3.0)
CRIB score	NA	1.0 (0.8 – 1.2)
Initial FiO2	NA	1.0 (1.0 – 1.0)

CRIB (clinical risk index for babies), FiO2 (fraction of inspired oxygen)

In our sensitivity analysis using an expanded range for initial VT, the number of infants who had an initial VT congruent with published recommendations increased to 76/313 (24%, *Supplemental Table*). Consistent with our main analyses, the only factor associated with an initial VT in agreement with the published recommendations was having a BW of 700 – <1250 g (aOR 4.8, 95% CI 1.2 – 19.7).

2.5. DISCUSSION

We provide the first observational data regarding the use of initial VT during VTV in a large multicenter cohort of critically ill infants. Nearly half of infants in our cohort received an initial VT of exactly 5.0 mL/kg and the majority of infants had an initial VT clustered near 5.0 mL/kg. Though most infants received an initial VT near 5.0 mL/kg, several infants received a VT well outside recommended ranges for initial neonatal VTs. Only 14% of infants had initial VTs that were congruent with published recommendations. Having a BW 700 – <1250 g was the only factor significantly associated with having an initial VT congruent with published recommendations likely because this BW category included 5.0 mL/kg in the recommended range.

While we report the first clinical data regarding the use of initial VT during neonatal VTV, the finding that clinicians are most likely to choose an initial VT of 5.0 mL/kg, regardless of the patient size or respiratory pathology, has been reported before. In a survey of neonatologists in the United States and Canada, Gupta and Keszler presented respondents with five clinical vignettes and asked clinicians to choose the VT they would use during VTV. Similar to the clinicians in our study, the majority of survey respondents (41 – 84% depending on the vignette) chose 5.0 mL/kg as the initial VT,[10] despite studies suggesting VT should be individualized based on the patient size, instrumental dead space, and respiratory pathology.[14-22] Our study confirmed these survey results in two NICUs with nearly exclusive use of VTV.[12] At the time of our study, the VUMC NICU had unit guidelines in place for VT based on BW and respiratory

pathology while the Jackson-Madison NICU did not. Despite these differences, infants in both units received similar initial VT.

While we did not survey clinicians and respiratory therapists in our study about their reason for using 5.0 mL/kg as the initial VT in nearly all cases, multiple reasons for these findings are possible. First, the use of 5.0 mL/kg may be due to the cognitive ease of remembering this value as a starting place for VTV. Second, it is possible that clinicians may be unaware of the literature recommending an individualized approach to choosing the initial VT. Finally, it is possible that clinicians do not feel that the evidence-base for choosing appropriate initial VT for VTV is robust. Unlike in adult medicine[23], no randomized trials comparing specific VTs and evaluating long-term outcomes such as BPD or neurodevelopmental outcomes have been performed in neonates. Therefore, clinicians may feel that the optimal initial VTs are still unknown. Future research in neonatal VTV should focus on both evaluating the optimal VT to enhance long-term outcomes as well as interventions, such as clinical decision support tools, to implement the optimal VT into clinical practice.

Though the effect of different VT on long-term outcomes is not known, several short-term studies are available to guide current practice.[15 21] Nassabeh-Montazami et al showed that smaller infants require higher initial VT to achieve normal carbon dioxide levels due to increased instrumental dead space.[21] Conversely, excessive VTs must be avoided to minimize volutrauma.[24] Small initial VTs (3 mL/kg) have also been shown to increase inflammatory cytokines likely due to ineffective alveolar recruitment.[25] In our

study, we found that a small minority of infants received initial VTs of >6 mL/kg (3.2%) and of <3 mL/kg (0.3%). Though we do not know the exact reason, it is possible that these outliers were due to incorrect VT calculations because of inaccurate BW estimations or erroneous calculations at the bedside. Many ventilators require BW to be entered upon initiation of MV, opening up the future possibility of ventilator based clinical decision support or safety warnings when inappropriate VT are entered.

Our study has several limitations. First, our study is observational in nature and does not allow us to determine how much effect the choice of initial VT had on long-term clinical outcomes such as BPD and neurodevelopmental impairment. Second, though we captured a large cohort of infants, we excluded infants with diagnoses such as congenital diaphragmatic hernia or BPD. In our centers during the study period, most of the infants with congenital diaphragmatic hernia were ventilated with either PLV or high-frequency ventilation and all infants with established BPD were excluded by limiting the study to infants who were ventilated within the first two postnatal weeks. Third, we did not include the initial VT per kilogram that clinicians intended to use, only the VT that each infant received. We attempted to adjust for errors in rounding of VT or BW during our sensitivity analysis and found that even with these adjustments, most initial VT clustered around 5.0 mL/kg. Finally, our study may have limited generalizability as it was conducted in two units that primarily use VTV. While our findings likely represent the prevailing practices in most NICUs given prior survey results[10], more studies are needed in NICUs with different clinical practices.

2.6. CONCLUSIONS

In two NICUs that primarily use VTV, clinicians widely favored using an initial VT of 5.0 mL/kg for infants. Future work is needed to evaluate the optimal initial VTs for VTV and to develop tools, such as clinical decision support, to assist clinicians in choosing evidence-based strategies during neonatal VTV.

2.7. FUNDING

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2.8. WHAT IS ALREADY KNOWN ON THIS TOPIC

- Randomized controlled trials have shown that volume-targeted ventilation (VTV) leads to improved clinical outcomes compared to pressure-limited ventilation.
- Published guidelines based on short term outcome data suggest that initial tidal volumes for VTV should be chosen based on neonatal size and respiratory physiology.
- Survey data have shown that most neonatal clinicians in the US and Canada chose initial tidal volumes that are not congruent with published recommendations.

2.9. WHAT THIS STUDY ADDS

- In a multi-center retrospective observational cohort study, very few neonates received initial tidal volumes congruent with published guidelines.
- The majority of patients received an initial tidal volume of approximately 5.0 ml/kg.
- Several infants received initial tidal volumes well outside recommended ranges for neonatal volume-targeted ventilation.

3.0. Manuscript 2: Clinical decision support for neonatal mechanical ventilation

Corresponding Author:
Lindsey A. Knake MD
University of Iowa Hospitals & Clinics
Department of Pediatrics, Division of Neonatology
200 Hawkins Drive
Iowa City, IA. 52242-1083
lindsey-knake@uiowa.edu

Lindsey A. Knake MD[1,2,3,4]; Mhd Wael Alrifai MD, MS[2,3,4]; Allison B. McCoy PhD[3,4]; Jonathan Wanderer MD, MPhil[3,4,5]; Kevin B. Johnson MD, MS[2,3,4]; Christoph U. Lehmann MD[6]; Adam Wright PhD[3,4]; L. Dupree Hatch III MD, MPH[2,7,8]

[1]Department of Pediatrics, Division of Neonatology, University of Iowa, Iowa City, IA, USA; [2]Department of Pediatrics, Division of Neonatology, Vanderbilt University Medical Center, Nashville, TN, USA; [3]Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA; [4]Vanderbilt Clinical Informatics Center, Vanderbilt University, Nashville, TN, USA; [5]Department of Anesthesiology Vanderbilt University Medical Center, Nashville, TN, USA; [6]Clinical Informatics Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; [7]Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, TN, USA; [8]Critical Illness, Brain Dysfunction, and Survivorship Center, Vanderbilt University Medical Center, Nashville, TN, USA

3.1. ABSTRACT

Objective: To develop local agreement on initial VT recommendations and implement CDS in the electronic health record (EHR) to improve the congruence of initial VTs with the published consensus guidelines.

Design: We administered a three-round modified Delphi survey to clinicians and respiratory therapists (RTs) to review the current literature surrounding initial VT recommendations. A rules-based CDS system was designed and implemented into the EHR. We then performed a time series analysis to evaluate pre-CDS intervention (October 2018 – September 2020) and post-CDS intervention (September 2020 to June 2021) with the primary outcome being initial VT concordant with published CDS recommendations. Patients ventilated at less than 14 postnatal days of age were included in the study. Bivariate analysis was perfomed using chi-squared and multivariate analysis was performed using segmented multivariable logistic regression adjusting for time on study, time since intervention, and BW.

Results: During the Delphi survey, 19/21 participants completed all three rounds and consensus agreement was reached on all clinical scenarios except meconium aspiration syndrome (MAS). During the post-CDS intervention period, the CDS was presented to 78 providers on 201 unique patients with 112/201 patients meeting study inclusion criteria. In the pre-CDS intervention cohort, 59/422 patients (14%) were concordant with recommended initial VTs and the post-CDS intervention cohort had 21/112 (19%) concordant (p=0.21). After adjusting for temporal trends, CDS implementation was associated with slightly increased odds of receiving recommended

initial VT over the study period (aOR 1.12 for each 2-week post-implementation period, 95% CI 1.03 – 1.22).

Conclusions: We found no clinically significant improvement in increased compliance with initial VT recommendations after the CDS implementation.

3.2. BACKGROUND

Clinical decision support systems are computer based information systems used to integrate clinical and patient information to provide support for clinical decision-making.[26] Clinical decision support systems have been implemented for neonatal care to reduce parenteral nutrition[27] and drug doing errors,[26] improve appropriate protein dosing in preterm neonates,[28] and reduce errors in prescribing continuous drug infusions.[29] Clinical decision support systems may be implemented in open loop or closed loop systems.[30] An open loop system recommends therapeutic changes but requires providers to agree or reject the recommendation.[26] A closed loop system allows the computer or ventilator to implement the recommended change without caregiver input or supervision. As technology advances, closed loop systems may become standard of care because of the complexity of the critical care environment and the needs for quality, safety, and reproducibility.[4,31] Short-term clinical studies have shown that computerized closed loop FiO_2 control on neonatal ventilators may achieve better oxygenation control while limiting excess oxygen exposure.[32] However, because of the inherent risks of closed loop systems, open loop communication systems are generally implemented initially to allow vetting, exhaustive testing, and monitoring of the CDS recommendations.

While CDS systems for MV has been developed and tested in the adult and pediatric populations,[33] we are unaware of CDS systems for neonatal MV. We have previously shown (Chapter 2) that clinicians have poor compliance with choosing an initial VT congruent with published recommended initial VTs. Our objectives were to achieve local

consensus agreement on initial VT recommendations and to design and implement an open loop CDS into the EHR to improve the congruence of initial VTs with the published local consensus guidelines.

3.3. METHODS

Vanderbilt's Institution Review Board approved all aspects of this study with a waiver of consent.

Develop Guideline Consensus: We invited 21 neonatologists, RTs, neonatal nurse practitioners, and neonatal fellows all with a special interest in neonatal mechanical ventilation to review existing literature on neonatal mechanical ventilation and achieve consensus on recommendations to be included in a CDS tool. Using a modified Delphi procedure,[34] we administered an online questionnaire using the Research Electronic Data Capture (REDCap) program[35 36] that provided a summary of the relevant literature regarding initial VT for different patient populations. This group then rated their agreement with each proposed VT recommendation on a 1 – 9 Likert scale. The Delphi procedure lasted 3 rounds with each round being open for two weeks to allow adequate time for responses. In rounds 2 and 3, the participants were presented with their previous responses and the median response of the entire Delphi panel. Participants then had an opportunity to adjust their responses in subsequent rounds. After round 3, all VT recommendations that met criteria for agreement using the UCLA/RAND criteria[34] were included in our initial VT recommendations. We defined agreement as a panel median score between 7 – 9 on the Likert scale and no evidence of disagreement among members which was defined as one third or more of members giving a score of 1 – 3 on the Likert scale (*Figure 3*).

Strongly Disagree	Disagree	Moderately Disagree	Mildly Disagree	Undecided	Mildly Agree	Moderately Agree	Agree	Strongly Agree
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)

Figure 3: Likert Scale
Scale that was used during the modified Delphi Survey

Clinical Decision Support Design and Implementation: After we identified consensus initial VT guidelines, we designed and developed the CDS logic required to implement the CDS into our local EHR, Epic (Epic Systems Corporation, Verona, WI). Figure 4 displays the algorithm we used to implement the CDS.

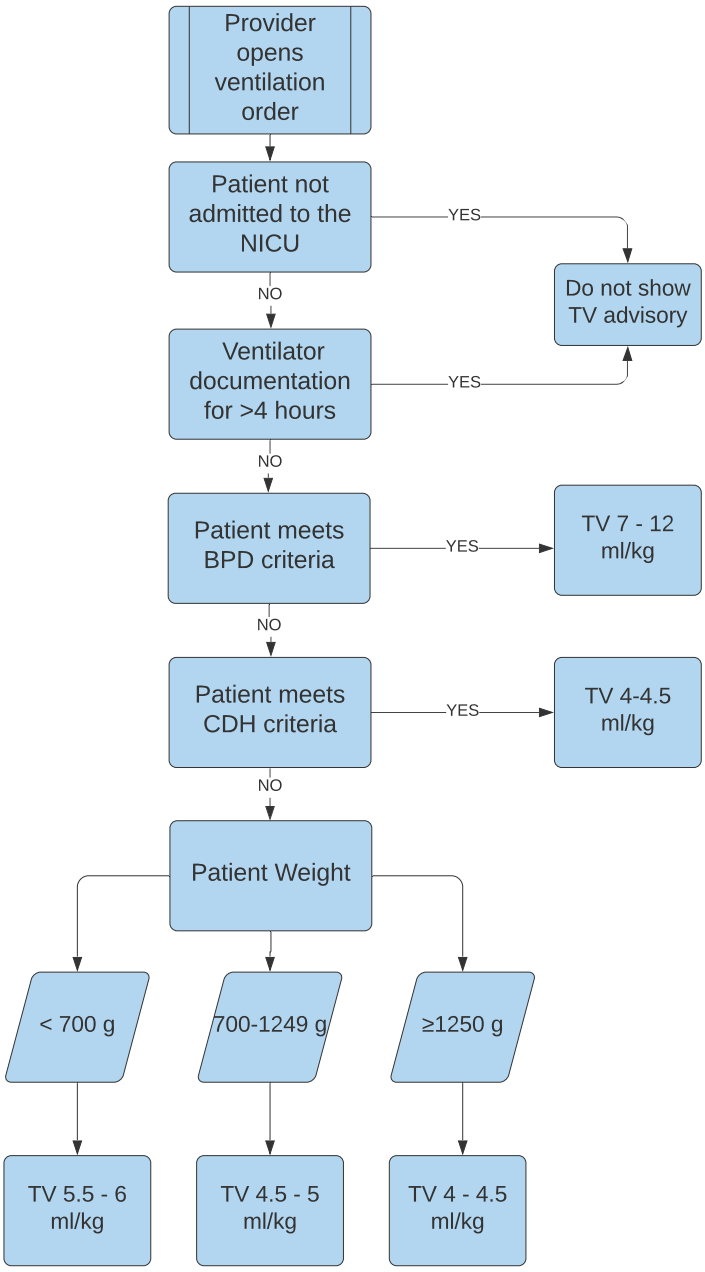


Figure 4: CDS algorithm
Flow chart displaying the logic built into the EHR to create the CDS

This simple rules-based algorithm was built into the EHR as a refreshable report displayed within the ventilator order by two of the authors who are physician builders (LAK and MWA). It displayed for all infants admitted to the NICU during the first four

hours a patient was mechanically ventilated since the goal was to provide only recommendations for the initial VT. Prior to implementing the CDS into the EHR, we received feedback from clinician experts, CDS analysts, and end-users. The CDS was implemented for clinicians placing orders on September 23rd, 2020. (*Figure 5*)

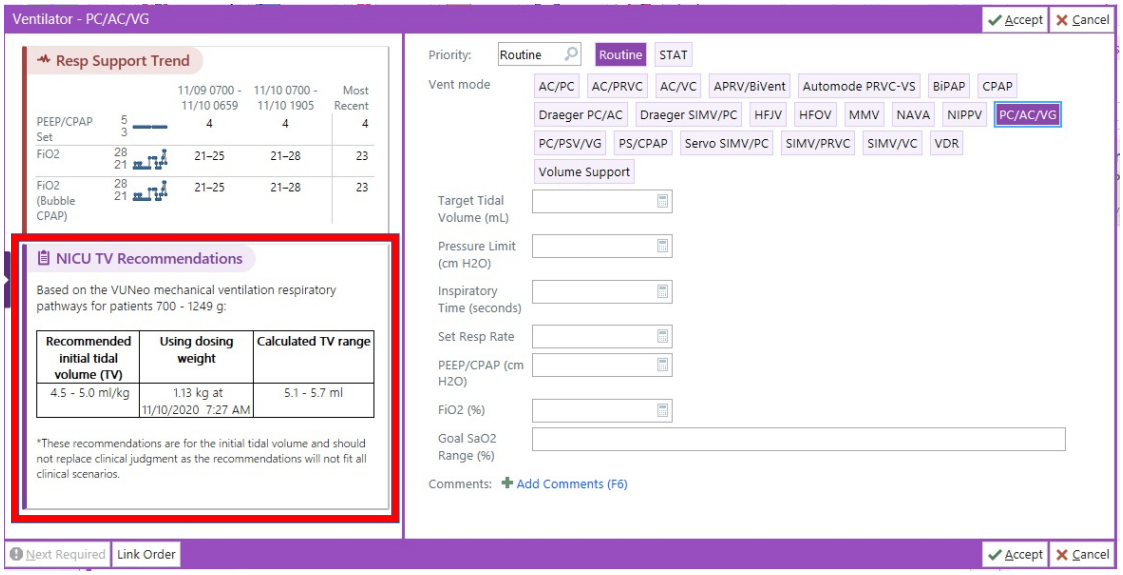


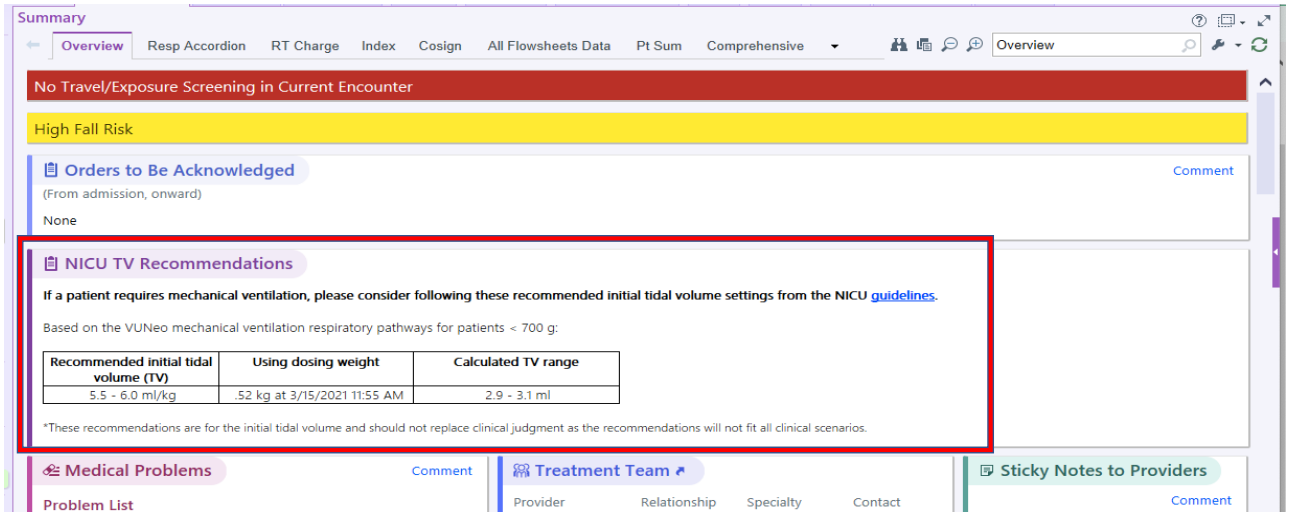
Figure 5: CDS implemented into the EHR
Figure of the ventilator order in our EHR. The red box outlines the CDS that was developed and implemented

Additionally on September 30th, 2020 a silent clinical decision support alert using the same criteria as Figure 4 was implemented. This clinical decision support alert was designed to monitor how often the CDS was being displayed in the clinical orders and who was receiving the alerts. One author (LAK) performed periodic audit checks to ensure the CDS and clinical decision support alerts were functioning appropriately.

Neonatal RTs are frequently involved in choosing the initial VT for VTV. Due to this, we decided *a priori* to sequentially release a CDS tool into the RT work flow on April 7th, 2021. This was implemented on their home screen summary page and in the side bar

tab. Prior to implementation we received end-user feedback and different users preferred different work flows, thus, it was implemented in two locations to accommodate multiple work flows (*Figure 6*). The CDS for RTs was displayed for the first four hours of life for any baby who was ventilated from birth and during the first two weeks of life if the baby hadn't been mechanically ventilated during that time. After both CDS implementations, education was provided to the respective groups via email and presentations to answer questions and cultivate awareness of the CDS.

A.



B.

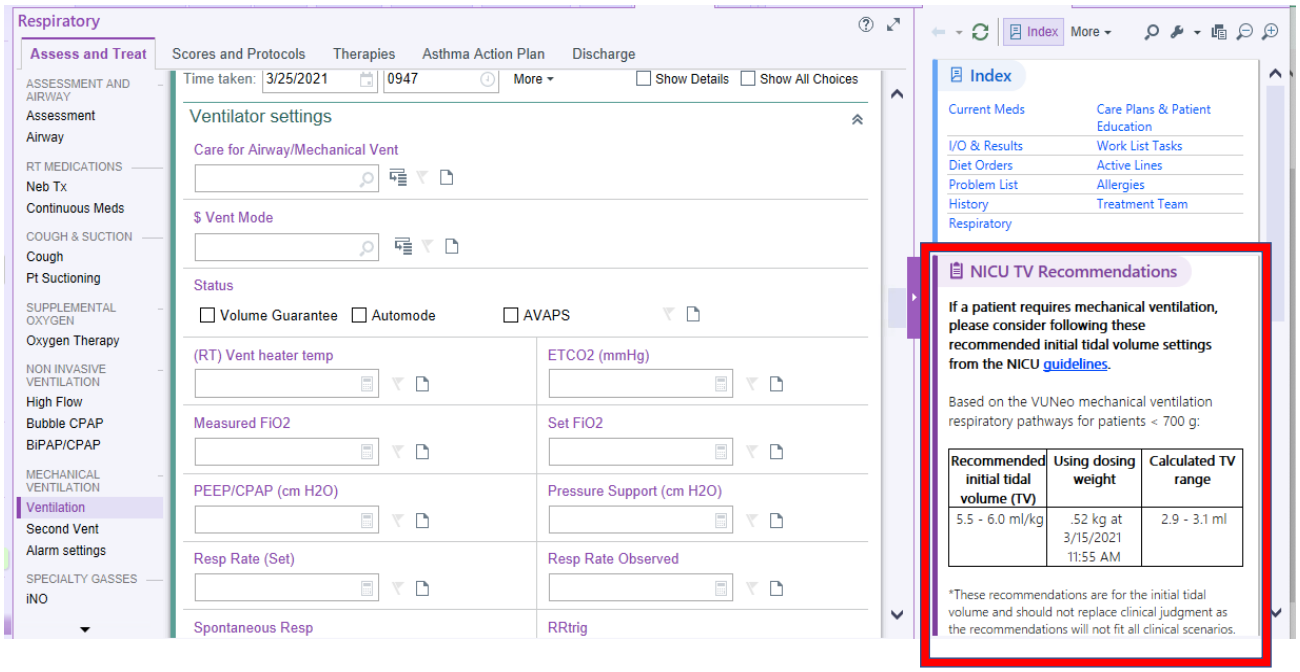


Figure 6: CDS implemented into the RT workflow
5A shows the CDS in the RT summary navigator and 5B show the CDS displayed on the side bar tab which can be viewed while updating vent orders.

After CDS implementation, a contextual inquiry was performed by one invstigator (LAK) from May 2021 to June 2021 to interview end users on usability and feedback of the

CDS. The end users who were interviewed included RTs, neonatal nurse practitioners, pediatrics residents, and physician assistants.

Study Design and Study population: We used a prospective interrupted time series design to evaluate CDS interventions. Primary outcome was defined as the initial VT congruent with published recommendations. Data collected from October 2018 to September 2020 served as our historical control and we continued prospectively caputuring data until June 2021.

The study population and data sources were previously described in Chapter 2. We additionally included subjects from VUMC if they met study inclusion criteria from October 2018 to June 2021. We did not include patients from Jackson Madison County General Hospital in this analysis. Our pre-CDS intervention cohort included infants who were mechanically ventilated from October 8, 2018 – September 23, 2020 and the post-CDS intervention cohort include all infants mechanically ventilated from September 24, 2020 to June 17, 2021.

Statistical Analysis: We generated descriptive statistics to define the baseline characteristics of study infants using median and interquartile range (IQR) for continuous variables and percentages for nominal variables.

We evaluated our pre-CDS and post-CDS interventions as a bivariate analysis using chi-squared test and we evaluated our interrupted time series data using segmented

regression to model temporal trends across our study periods. A multivariable logistic regression analysis was performed controlling for time as a linear variable and allowing a slope change after implementation of the CDS intervention. We additionally controlled for BW category since this variable was previously found (Chapter 2) to be associated with concordance with recommended initial VT. For the regression analysis, time was modeled as a continuous variable with resulting odds ratios describing the total change in odds over 2-week periods. All statistical analyses were performed using Stata/BE 17.0 (StataCorp, College Station, TX).

3.4. RESULTS

Delphi Results: Of 21 participates invited to complete the survey, 19 / 21 (90%) completed all three rounds. Ten attending neonatologists, five RTs, three neonatal nurse practitioners, and two neonatal fellows participated in the survey from April 20, 2020 to June 2, 2020. Table 3 displays the panel results at the end of the third round using the compiled median likert score from all participant (*Figure 3*).

Table 3: Final Round Modified Delphi Results

Clinical Scenario	**Likert Score – Median [IQR]**
Preterm with BW <700g, VT 5.5 – 6 ml/kg	8 [7,8]
Preterm with BW 700 – 1250g, VT 4.5 – 5 ml/kg	8 [7,8]
Preterm with BW ≥ 1250g, VT 4.0 – 4.5 ml/kg	7 [6,8]
Late preterm or term, with BW ≥ 1250g, VT 4.0 – 4.5 ml/kg	7 [6,8]
Late preterm or term with CDH, VT 4.0 – 4.5 ml/kg	7 [7,8]
Obstructive MAS on CXR, VT 5.5 – 6 ml/kg	6 [5,7]
MAS with “whiteout” CXR, VT 4.5 – 5 ml/kg	7 [6.8]
Infant with established severe BPD, VT 7 – 12 ml/kg	8 [7,8]

BW (birth weight), VT (tidal volume), CDH (congenital diaphragmatic hernia), MAS (meconium aspiration syndrome), CXR (chest X-ray), BPD (bronchopulmonary dysplasia)

During the Delphi, the obstructive MAS recommendation did not meet agreement criteria so neither of the MAS recommendations were included in our final published guidelines. Table 4 displays the updated Vanderbilt NICU Respiratory Care Pathways and Initial VT Recommendations that were published on July 15th, 2020. Full guidelines are available in Appendix 3.

Table 4: Published Respiratory Care Guidelines

Diagnosis	Recommended Initial Mode (VG modes)	Recommended Initial VT (ml/kg)	Set PIP limit after X-ray confirmation (cm H_2O)	Recommend i-time or max i-time (sec)
Preterm birth weight:				
BW < 700g	PC-AC	5.5 – 6.0	25 – 30 (limit at 20 – 25)	0.3
BW 700 – 1249g	PC-PSV	4.5 – 5.0	25 – 30 (limit at 20 – 25)	Max limit 0.6
BW ≥ 1250g	PC-PSV	4.0 – 4.5	25 – 30 (limit at 20 – 25)	Max limit 0.6
Term, late preterm	PC-PSV	4.0 – 4.5	30 – 35 (limit at 25 – 30)	Max limit 0.6
CDH	PC-PSV	4.0 – 4.5	25 – 30 (limit at 20 – 25)	Max limit 0.6
Established severe BPD	PC-AC	7.0 – 12.0	30 – 35 (limit at 25 – 30)	0.5 – 1.0 (1:2 I:E ratio)

VG (volume guarantee), VT (tidal volume), BW (birth weight), CDH (congenital diaphragmatic hernia), BPD (bronchopulmonary dysplasia)

Clinical Decision Support: From September 30th, 2020 to June 16th, 2021, 435 clinical decision support alerts were triggered averaging 2.4 alerts per day and 1.1 unique patients per day with CDS recommendations displayed in their ventilation order. A total of 201 patients had the CDS displayed during the study period with 78 unique providers notified. The most common provider types to receive alerts were neonatal nurse practitioners (56%), resident physicians (15%), fellows (12%), physician assistants (11%), and staff physicians (6%).

Time Series Analysis: Of the 201 patients who received our CDS recommendations, 112 met study inclusion criteria. The pre-CDS cohort had a median BW of 2319 g (IQR 1250 – 3125) and the post-CDS cohort had a median BW of 2430 g (IQR 1310 – 3080).

During the pre-CDS period, 59/422 patients (14%) received an initial VTs concordant with published recommedations and during the post-CDS period 21/112 (19%) received an initial VTs concordant with published recommedations (Table 5, p = 0.21). The median initial VT used was 5.0 mL/kg in both the pre-CDS (median 5.0 mL/kg IQR 4.9 – 5.1) and post-CDS cohorts (median 5.0 mL/kg IQR 4.9 – 5.1).

Table 5: Bivariate results showing inital VT concordant with recommendations pre and post-CDS implementation

	Pre-CDS	Post-CDS
VT Concordant	59	21
VT Non-concordant	363	91

p= 0.21

After adjusting for temporal trends, implementation of our CDS was associated with a slightly increased odds of congruence with recommended initial VT (aOR 1.12 for each 2-week change in time, 95% CI 1.03 – 1.22). Birth weight category of 700 – <1250g also remained significantly associated with an initial VT congruent with published recommendations (aOR 4.69, 95% CI 1.7 – 12.96). Trends in use of recommended initial VT are displayed in Figure 7.

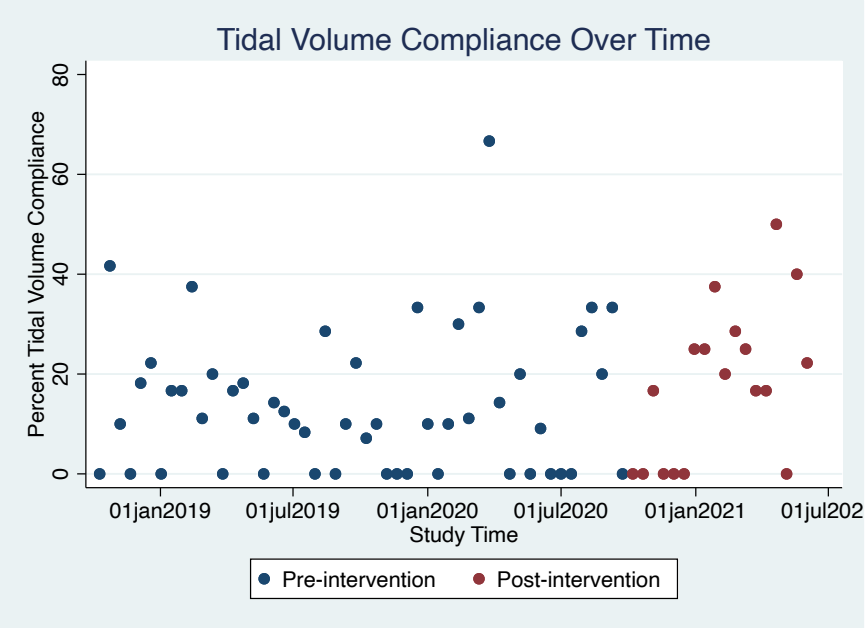


Figure 7: Two-week Initial Tidal Volume Trend
Each dot represents the percentage of VT concordant with recommendations over the two week time interval.

Contextual Inquiry Survey: Seven participants were interviewed within a few hours of placing a new patient on the ventilator and potentially interacting with the CDS which included three RTs, two residents, one NNP, and one physician assistant. The majority of them responded that the fellow or RT chose the initial VT and it was chosen before opening the EHR. Many of them did not use the CDS when choosing the initial VT. The majority agreed with the CDS recommendation but did not notice it or remember to use it when placing the patient on the ventilator. The residents and nurse practitioners recommended that a pop-up notification or pre-populated order may have improved their recognition of the CDS recommendations. RTs would have preferred colored or highlighted recommendations where they document in the flowsheets or a physical reminder placed on the ventilator.

3.5. DISCUSSION

We have implemented and tested the first CDS system for neonatal MV using stepwise CDS implementation in the EHR to recommend initial VT for neonatal clinicians. We were able to generate consensus recommendations using a modified Delphi approach. However, after implementation of our CDS we did not achieve a clinically significant improvement of initial VTs concordant with published recommendations. The contextual inquiry survey suggested that it wasn't because clinicians or RTs were opposed to the recommendations, but rather the recommendations did not fit into their clinical work flow.

While CDS systems are a novel implementation for neonatal MV, there are already a number of computerized interventions available in both the adult and pediatric populations that have shown fewer days of MV and fewer days admitted to the intensive care unit.[33 37] In pediatric intensive care units, computerized systems recommending adjustments to MV have shown increased compliance rates after incorporating feedback from end users.[38] However, most of these systems have been either external systems that have not been incorporated into the EHR or algorithms built into the ventilator.[39] There are ongoing stepped-wedge studies evaluating EHR-based implementation strategies prescribing low VT in adults.[40] There are consensus guidelines in both the adult and pediatric literature for evidenced based weaning protocols, however, there is still little consensus on weaning practices for neonatal ventilation.[41 42] Thus, we chose to implement CDS for initial VT recommendations since there are published literature recommendations and we were able to achieve a local

consensus agreement around those recommendations. However, implementing CDS into the hospital workflow proved to be challenging.

Prior to implementing our CDS we evaluated the five rights of CDS[43] and designed an implementation that we believed had satisfied all of those rights. We knew we would be working within a multi-disciplinary team so we decided a priori to implement CDS for the clinicians and subsequently for the RTs. However, our CDS implementation was limited by the capability of the EHR to only notify clinicians at the time they are placing the order. Because this study took place in a large academic center, the clinicians placing the orders may not be the clinicians making the decision on what initial VT to implement. Also, we knew that implementing the CDS in the EHR would not include any CDS directly on the ventilator itself which is many times where the MV settings are directly entered before the patient has a birth weight or medical record number in the EHR. We specifically chose not to create the CDS as a pop-up alert or closed-loop system since we knew there would be clinical scenarios like transfers from outside hospital that our recommendations may not apply. We hypothesize that increased compliance with our recommendations would likely have been achieved by creating a pop-up notification or incorporating CDS directly on the ventilators.

This study has multiple strengths including the modified Delphi procedure that allowed us to ensure we had local clinician consensus prior to implementation. We also used stepwise CDS with implementation for clinicians and then the RTs in the second phase of our study to try to incorporate the different workflows of our large multidisciplinary

team. While the interrupted time series design of our study allowed us to account for changes over time during the study period, it also requires us to assume linearity for our multivariable logistic regression model which may not be entirely valid. Without the use of a randomized controlled trial, we were unable to account for all possible variables that may have affected the choice of initial VTs during the study period. Additional limitations to this study included our limited amount of post-intervention follow up time compared to the longer period of historical data we had available. If we had a longer post-intervention follow up time period, we could have tested additional CDS interventions. The silent clinical decision support alert we created to track the CDS that was displayed during the placement of the order was unable to track the CDS for the RTs that was implemented in the second phase of our CDS. Thus, we are unaware of the total number of RTs that were exposed to the CDS during the study period.

3.6. CONCLUSIONS

After implementing stepwise CDS for clinicians and RTs that were based on published local consensus guidelines, we did not achieve clinically significant improvement in concordance with initial VT recommendations over the 9-month post-CDS intervention study period. Due to the complexities of implementing CDS into a multi-disciplinary workflow, future implementation of CDS for MV may require rigorous implementation science methods including pilot studies with iterative adjustments made to the CDS design, multi-disciplinary educational sessions, and work flow analyses. Future work should also be performed to explore partnering with industry sponsors to include CDS modules on the ventilators themselves.

4.0. Summary

We were able to complete all three aims of this thesis to evaluate our hypothesis that implementation of a CDS tool will improve the use of choosing evidence-based initial VTs in the NICU. In our first manuscript we showed that baseline compliance of initial VT use was low with most infants receiving 5.0 mL/kg regardless of BW. This displayed that implementing CDS around initial VT into the EHR provided the opportunity to significantly improve the compliance rate of initial VT in the NICU. Prior to designing and implementing our CDS we performed a modified Delphi procedure to achieve local consensus agreement on the VT recommendations. We were able to achieve consensus on all clinical scenarios other than MAS, thus, we excluded that from our published guidelines and CDS.

We successfully implemented stepwise CDS first into the clinician's workflow and then the RT's workflow. We additionally built and created a silent clinical decision support alert that was able to monitor how often our CDS was being displayed in the ventilator order and which types of providers were receiving the VT recommendations. While our interrupted time series analysis showed a slight improvement in compliance overtime it was not a clinically significant improvement. Because of the limited improvement with our CDS, we performed a small contextual inquiry survey a few hours after the participants had an opportunity to interact with the CDS. Survey responders were not opposed to the recommendations that we displayed but rather did not notice the CDS during their clinical workflow.

With the interrupted time series design of our study, additional CDS interventions such as a clinical decision support alert or a personalized compliance dashboards could have been implemented into the EHR to try to improve initial VT compliance and bring awareness to the recommendations. However, provider clinical decision support alerts have historically had low acceptance rates and it may not fix all the underlying workflow issue.[44-46] Frequently, there is not a linear clinical work flow especially for a multidisciplinary team where multiple team members may be contributing to the initial VT recommendations. The clinical workflows are also very different for emergent intubations where there is little time to open the EHR and look at the recommendations vs planned intubations where there may be ample time for a discussion and review of the CDS recommendations.

Future implementations of CDS to improve neonatal MV in different institutions should include multidisciplinary focus groups to gain a strong understanding of the workflow in the unit with plans for CDS to be implemented in multiple places in the workflow as there is likely not one implementation strategy that is best for everyone. Qualitative methods and implementation science strategies may need to be employed to achieve buy-in for the recommended changes. Depending on the cultural practices around MV in the unit, educational sessions may be required prior to implementation to ensure the clinical personal are aware of the protocol changes and planned CDS. Pilot studies with iterative CDS adjustments should be performed to allow the opportunity to improve the CDS if there are additional areas in the clinical workflow that need to be targeted.

Ultimately, CDS in the EHR may not be the most efficient place to catch the end-user's attention. The mechanical ventilator may be the most appropriate location to incorporate CDS for MV to cut out the barrier of any external CDS recommending how to set up the ventilator. Adult medicine is beginning to pilot closed-loop automation for anesthesia care.[47] Thus, considering collaboration with ventilator manufacturing companies may be required to implement the most effective form of CDS directly into the ventilator. However, future work is still needed to validate the safety of machines to automatically adjust the mechanical ventilators with sufficient checks and balances in place to prevent harm to the patient. As technology continues to advance and the demands of medical personal continue to increase, a CDS system that can automatically adjust the patient's ventilation needs in real time will likely become the fastest and most efficient way to adjust a patient's mechanical ventilation.

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Appendix 1: Student Role in Manuscripts

Dr. Knake was involved in the original design and creation of the thesis hypothesis and aims of the study. She personally extracted and analyzed the ventilator data to complete the first manuscript and she performed her own statical analysis in both manuscripts with supervision from her mentors. She wrote the literature review and survey questions for the Delphi survey and participated in the organization and roll out of the survey. She developed and built all the CDS tools implemented for this project and regularly audited them to ensure their accuracy. She created all the figures and tables in both manuscripts and wrote the initial drafts of both manuscripts with edits and revisions from her committee members.

Appendix 2: Supplemental Figures

Supplement: Sensitivity analysis of factors associated with recommended initial tidal volume

	Agreement with published recommended initial VT N (%) Total N = 45	Agreement with published recommended initial VT ± 0.3 ml/kg N (%) Total N = 76	Adjusted odds ratio (95% CI)
Birth weight category			
<700 grams	3 (7)	10 (13)	Reference group
700 – <1250 grams	31 (69)	41 (54)	4.8 (1.2 – 19.7)
≥1250 grams	11 (24)	25 (33)	0.1 (0.03 – 0.5)
Male sex	24 (53)	38 (50)	0.7 (0.3 – 1.3)
Inborn	11 (24)	23 (30)	0.8 (0.4 – 1.7)
CRIB score	NA	NA	1.0 (0.8 – 1.1)
Initial FiO2	NA	NA	1.0 (0.9 – 1.0)

VT (tidal volume), CRIB (clinical risk index for babies), FiO2 (fraction of inspired oxygen)

Appendix 3: Vanderbilt NICU Respiratory Care Pathways and Initial Tidal Volume (TV) Recommendations

Purpose:

The purposes of the NICU Respiratory Care Pathways are to provide evidence-based recommendations for the use of mechanical ventilation based upon a patient's pathophysiology. By standardizing the respiratory care provided, we intend to create a shared mental model amongst all team members about the pathology necessitating mechanical ventilation and the goals of ventilation.

Rationale:

Observational evidence suggests that standardized respiratory care improves overall short- and long-term respiratory outcomes in the NICU. [48 49] Currently substantial practice variation exists in the Vanderbilt NICUs regarding the initiation, escalation, weaning and discontinuation of mechanical ventilation. This variation in practice makes it difficult to standardize the respiratory care that is provided. These pathways will use the available evidence and local expert consensus created using a Delphi procedure[34] to standardize ventilator care.

Table 1: Evidence Based Initial Ventilator Recommendations

Diagnosis	Recommended Initial Mode (VG modes)	Recommended Initial TV (ml/kg)	Set PIP limit after X-ray confirmation (cm H_2O)	Recommend i-time or max i-time (sec)
Preterm birth weight:				
BW < 700g	PC-AC	5.5 – 6.0 [14 21 50]	25 – 30 (limit at 20 – 25)	0.3
BW 700 – 1249g	PC-PSV	4.5 – 5.0 [11 25]	25 – 30 (limit at 20 – 25)	Max limit 0.6
BW ≥ 1250g	PC-PSV	4.0 – 4.5 [15]	25 – 30 (limit at 20 – 25)	Max limit 0.6
Term, late preterm	PC-PSV	4.0 – 4.5 [11]	30 – 35 (limit at 25 – 30)	Max limit 0.6
CDH	PC-PSV	4.0 – 4.5 [16 22]	25 – 30 (limit at 20 – 25)	Max limit 0.6
Established severe BPD	PC-AC	7.0 – 12.0 [19 20]	30 – 35 (limit at 25 – 30)	0.5 – 1.0 (1:2 I:E ratio)

Caveats:

- These recommendations do not replace clinical judgment and will not fit all clinical scenarios.
- These settings should be altered if the medical providers and the respiratory therapists (RTs) deem more appropriate settings.
- An individual patient's pathology and physiology may change frequently and abruptly, and the use of these pathways should not be rigid.
- Constant consideration and multi-disciplinary discussion about the continuing need for mechanical ventilation and the goals of mechanical ventilation therapy is critically important in tailoring therapy to the individual needs of each infant.
- Respiratory care in the NICU is a dynamic field and these pathways will be updated with new evidence as this becomes available.
    - Recurring assessment yearly or with new evidence
        - Next scheduled assessment of guidelines- May 2021

Special Considerations:

- Most of the pathways recommend a volume-targeted ventilation (VTV) mode with the evidence for these recommendations cited below.

- Use of a VTV mode can safely be accomplished with our current ventilators (Dräger Evita® Infinity® V500), which employ a flow sensor at the proximal end of the endotracheal tube.
- VTV modes can be used immediately after placing an endotracheal tube (and before obtaining a chest x-ray to confirm endotracheal tube position) provided that the correct tidal volume is set and an appropriate pressure limit is entered. This will theoretically limit lung injury due to both barotrauma and volutrauma.
- Dräger Evita® Infinity® V500 ventilators are able to compensate for most endotracheal tube leaks (<80%). Should an endotracheal tube leak be greater than 80%, consideration should be given to: 1) attempting extubation should this be clinically appropriate, 2) exchanging the endotracheal tube for a larger size, or 3) using a pressure limited ventilation mode. Tidal volume will not be reliably known with the latter option.

Default settings:

Settings to be entered if conversation is unable to occur between RT and provider

a. Mode: PC-PSV with volume guarantee[51]
b. Initial set tidal volume: see **Table 1**
c. Pressure limit:
    i. Set at 23 cm H_2O (to limit at 18 cm H_2O) until CXR to confirm endotracheal tube placement
    ii. Then set limit based on recommendations in **Table 1**
d. Inspiratory time max: 0.6 seconds
e. PEEP: 5 cm H_2O.
f. Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute

Diagnosis-based Respiratory Care Pathways

1) Prematurity/Respiratory Distress Syndrome (RDS)- <700 grams

a) Initiation of ventilator support [52-56]
   i) Mode: PC-AC with volume guarantee (alternatively PC-PSV with volume guarantee)
   ii) Initial tidal volume: 5.5-6 cc/kg [14 21 50]
      (1) Infants <700g may require tidal volumes 5.5-6 cc/kg due to relatively large instrumental deadspace [14 21 50]
   iii) Pressure limit:
      (1) Initial: Set at 23 cm H_2O (to limit at 18 cm H_2O).
      (2) After CXR confirmation: Set at 25-30 cm H_2O (to limit at 20-25 cm H_2O)
   iv) Inspiratory time: 0.3 seconds
   v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR, and oxygen requirement
   vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute
   vii) Additional considerations: If the infant meets criteria, consider surfactant administration as soon as possible after intubation.

2) Prematurity/Respiratory Distress Syndrome (RDS)- 700-1249 grams

a) Initiation of ventilator support [52-56]
   i) Mode: PC-PSV with volume guarantee (alternatively PC-AC with volume guarantee)
   ii) Initial tidal volume: 4.5-5 cc/kg [11 25]
   iii) Pressure limit:
      (1) Initial: Set at 23 cm H_2O (to limit at 18 cm H_2O).
      (2) After CXR confirmation: Set at 25-30 cm H_2O (to limit at 20-25 cm H_2O)
   iv) Inspiratory time max: 0.6 seconds
   v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR, and oxygen requirement
   vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute
   vii) Additional considerations: If the infant meets criteria, consider surfactant administration as soon as possible after intubation.

3) Prematurity/Respiratory Distress Syndrome (RDS)- ≥1250 grams

a) Initiation of ventilator support [52-56]
   i) Mode: PC-PSV with volume guarantee (alternatively PC-AC with volume guarantee)
   ii) Initial tidal volume: 4-4.5 cc/kg [15]
   iii) Pressure limit:
      (1) Initial: Set at 23 cm H_2O (to limit at 18 cm H_2O).
      (2) After CXR confirmation: Set at 25-30 cm H_2O (to limit at 20-25 cm H_2O)
   iv) Inspiratory time max: 0.6 seconds
   v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR, and oxygen requirement
   vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute
   vii) Additional considerations: If the infant meets criteria, consider surfactant administration as soon as possible after intubation.

4) Term RDS/Pneumonia/Meconium aspiration syndrome with poor aeration on CXR

a) Initiation of ventilator support [57]
   i) Mode: PC-PSV with volume guarantee
   ii) Initial tidal volume: 4-4.5 cc/kg [11]

iii) Pressure limit:
(1) Initial: Set at 25 cm H_2O (To limit at 20 cm H_2O)
(2) After CXR confirmation: Set at 30- 35 cm H_2O (To limit at 25 - 30 cm H_2O)
iv) Inspiratory time max: 0.6 seconds
v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR and oxygen requirement
vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute
vii) Additional considerations: If the infant meets criteria, consider surfactant administration as soon as possible after intubation.

5) Late Preterm/Term Infant with Congenital Diaphragmatic Hernia (CDH)

a) See Congenital Diaphragmatic Hernia protocol for further details.
b) Initiation of conventional mechanical ventilation settings if LHR > 1.3 [16 22 58]
i) Mode: PC-PSV with volume guarantee (alternatively PC-AC with volume guarantee)
ii) Initial tidal volume: 4-4.5 cc/kg [16 22]
iii) Pressure limit:
(1) Initial: Set at 23 cm H_2O (to limit at 18 cm H_2O).
(2) After CXR confirmation: Set at 25-30 cm H_2O (to limit at 20-25 cm H_2O)
(3) If unable to ventilate at a set pressure limit of 30 (to have a maximum PIP of 25) switch to HFOV
iv) Inspiratory time max: 0.6 (Inspiratory time of 0.3 if in time-cycled mode)
v) PEEP: 4-5 cm H_2O
vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-60 breaths per minute

6) Established severe bronchopulmonary dysplasia (BPD)

a) Initiation of ventilator support [59-61]
i) Mode: PC-AC with volume guarantee
ii) Set tidal volume: 7-12 cc/kg [19 20]
iii) Pressure limit:
(1) Initial: Set at 30 cm H_2O (To limit at 25 cm H_2O)
(2) After CXR confirmation: Set at 30-35 cm H_2O (To limit at 25-30 cm H_2O). May require higher pressure limit depending upon the severity of the lung disease.
iv) Inspiratory time: Consider longer I-times (0.5-1). Adjust in concert with rate to allow at least 1:2 or 1:3 I:E ratio
v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR and oxygen requirement
vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 30-40 breaths per minute depending on set tidal volume.
vii) Additional considerations: The chronologic age at which a chronically ventilated preterm infant should be considered to have lung pathophysiology that requires a larger tidal volume strategy is not known. Evidence suggests that these changes may occur after only 2-3 weeks of mechanical ventilation.[62]

7) Post-operative/post-procedural/neurologic disease/apnea

a) Initiation of ventilator support
i) Mode: PC-PSV with volume guarantee
ii) Set initial tidal volume: Follow Table 1 recommendations based on weight
iii) Pressure limit:
(1) Initial: Set at 25 cm H_2O (To limit at 20 cm H_2O)
(2) After CXR confirmation: Set at 30-35 cm H_2O (To limit at 25-30 cm H_2O)

iv) Inspiratory time max: 0.6 seconds
v) PEEP: 5-6 cm H_2O. Adjust based on clinical exam, CXR and oxygen requirement
vi) Respiratory rate: High enough to ensure minute ventilation of 200-300 cc/kg/min. Approximately 40-50 breaths per minute

8) Special Circumstances

a) Mechanical ventilation for pulmonary over-circulation in infants with ductal dependent congenital heart disease
   i) Use Term RDS pathway.
   ii) Target lower minute ventilation to manage over-circulation. See Ductal Dependent Congenital Heart Disease protocol for further details.
b) Pulmonary hypoplasia
   i) Consider using primary high frequency ventilation mode
c) Pulmonary air leak syndrome (Pulmonary interstitial emphysema [PIE], pneumothorax, bronchopleural fistula, tracheoesophageal fistula)
   i) Consider high frequency ventilation mode