Pediatric Acute Respiratory Intervention Study (PARIS) trial

P Infants <12 months old with bronchiolitis requiring supplemental oxygen
I High-flow oxygen therapy
C Standard oxygen
O_1 Escalation of care due to treatment failure
O_2 Duration of hospital stay
Duration of oxygen therapy
Rates of transfer to tertiary hospital
ICU admission
Intubation
Adverse events
D Multicenter, randomized, controlled trial

Inclusion criteria

- Infants <12 months with clinical evidence of bronchiolitis
- Supplemental oxygen required to maintain a SpO2 92-98 % (94-98% in some hospitals)

Exclusion criteria

- Critically ill infants requiring immediate respiratory support or ICU admission
- Cyanotic heart disease
- Upper airway obstruction
- Basal skull fracture
- Craniofacial malformation
- Home oxygen therapy

Methods

- Multicenter, randomized, controlled trial conducted in 17 hospitals (emergency departments and pediatric inpatient units) in Australia and New Zealand from October 2013 to August 2016
- Randomized between high-flow and standardized oxygen therapy
    - High-flow oxygen therapy: heated and humidified high-flow oxygen at a rate of 2 L/kg/min via Optiflow system; FiO2 adjusted to target SpO2 92-98 (94-98% in some institutions)
    - Standard therapy oxygen: supplemental oxygen through nasal cannula up to 2 L/min to maintain SpO2 92-98% (94-98% in some institutions)
- Primary outcome: treatment failure that resulted in escalation of care
    - Treatment failure defined by:
        - Three of the four clinical criteria present:
            - Persistent tachycardia
            - Persistent tachypnea
            - FiO2 >40% in the high flow group or >2L in the standard oxygen therapy group to maintain target oxygen saturations
            - Early-warning system triggered escalation in care
        - Clinician discretion
    - Escalation of care included an increase in respiratory support or transfer to ICU
- Secondary outcomes included:
    - Duration of hospital stay
    - Duration of oxygen therapy
    - Rates of transfer to a tertiary hospital
    - Rate of ICU admission

  - Rate of intubation
  - Rate of adverse events
- Required 582 patients per group to provide a 90% power with a type 1 error of 0.05

Results

- 1472 infants included (high-flow: 739 infants; standard: 733 infants)
- Escalation of care: NNT 9 (P<0.001) in favor of HFNC
  - High-flow: 167 infants, 12%
  - Standard: 87 infants, 23%
  - Fragility Index: 51
  - Among 167 infants that failed standard oxygen therapy, 102 (61%) has a response to high-flow oxygen therapy
- No difference in:
  - Duration of hospital stay
  - Duration of ICU stay
  - Duration of oxygen therapy
- Adverse events:
  - High-flow: pneumothorax x 1
  - Standard: pneumothorax x 1
  - Intervention not required in either care

Strengths

- Sample size
- Published trial protocol
- Generally well designed

Limitations

- Unblinded
- Escalation of care at clinician discretion
- Equivalency between intervention and control: respiratory rate higher in HFNC group

Study conclusions

- "Among infants with bronchiolitis who were treated outside an ICU, those who received high-flow oxygen therapy had significantly lower rates of escalation of care due to treatment failure than those in the group that received standard oxygen therapy."

Bottom line

- HFNC is safe in infants with bronchiolitis
- Although these finding support the efficacy of HFNC for infants with bronchiolitis, this study does not to demonstrate that early initiation of HFNC improved clinically important outcomes or disease trajectory
- A stepwise approach to oxygen therapy should continue to be utilized

Table 2. Primary Outcome in the Trial Cohort and Outcomes in Subgroups of Infants Who Received Escalation of Care.*

Outcome	Standard-Therapy Group (N=733)	High-Flow Group (N=739)	Relative Risk or Mean Difference (95% CI)†	Risk Difference (95% CI)	P Value
				percentage points	
Escalation of care in overall trial cohort					
Treatment failure — no. (%)	167 (23)	87 (12)	0.52 (0.40 to 0.66)	−11 (−15 to −7)	<0.001
Interval between enrollment and escalation — days	0.67±0.83	0.72±0.82	0.05 (−0.17 to 0.26)	—	0.67
Treatment failure according to age — no./total no. (%)					0.60‡
≤3 mo	55/186 (30)	34/211 (16)	0.55 (0.36 to 0.81)	−13 (−22 to −5)	
>3 to 6 mo	34/170 (20)	22/187 (12)	0.59 (0.35 to 0.99)	−8 (−16 to −1)	
>6 mo	78/377 (21)	31/341 (9)	0.44 (0.29 to 0.66)	−12 (−17 to −7)	
Treatment failure according to on-site ICU status — no./total no. (%)					<0.001‡
No	69/247 (28)	20/270 (7)	0.27 (0.16 to 0.43)	−21 (−27 to −14)	
Yes	98/486 (20)	67/469 (14)	0.71 (0.53 to 0.95)	−6 (−11 to −1)	
Treatment failure according to premature birth status — no./total no. (%)					
Yes	38/128 (30)	27/137 (20)	0.66 (0.42 to 1.05)	−10 (−20 to 0)	0.19‡
No	129/605 (21)	60/601 (10)	0.47 (0.35 to 0.63)	−11 (−15 to −7)	
Treatment failure according to virus detected — no./total no. (%)					0.57‡
Respiratory syncytial virus	81/322 (25)	50/334 (15)	0.60 (0.43 to 0.83)	−10 (−16 to −4)	
Other	35/150 (23)	15/130 (12)	0.50 (0.27 to 0.89)	−12 (−21 to −3)	
Not tested	261	275	—	—	
Escalation of care in infants who met ≥3 of 4 criteria					
Treatment failure — no. (%)	115 (16)	53 (7)	0.46 (0.33 to 0.63)	−9 (−12 to −5)	<0.001
Interval between enrollment and escalation — days	0.64±0.64	0.73±0.80	0.09 (−0.14 to 0.32)	—	0.43
Treatment failure according to age — no./total no. (%)					0.85‡
≤3 mo	35/186 (19)	19/211 (9)	0.48 (0.27 to 0.83)	−10 (−17 to −3)	
>3 to 6 mo	29/170 (17)	15/187 (8)	0.47 (0.25 to 0.88)	−9 (−16 to −2)	
>6 mo	51/377 (14)	19/341 (6)	0.41 (0.24 to 0.70)	−8 (−12 to −4)	
Treatment failure according to on-site ICU status — no./total no. (%)					<0.001‡
No	51/247 (21)	12/270 (4)	0.22 (0.11 to 0.40)	−16 (−22 to −11)	
Yes	64/486 (13)	41/469 (9)	0.66 (0.45 to 0.98)	−4 (−8 to −1)	
Treatment failure according to premature birth status — no./total no. (%)					0.85‡
Yes	27/128 (21)	19/137 (14)	0.66 (0.37 to 1.16)	−7 (−16 to 2)	
No	88/605 (15)	34/601 (6)	0.39 (0.26 to 0.58)	−9 (−12 to −6)	

* Plus–minus values are means ±SD. Escalation of care occurred if infants met three of four prespecified clinical criteria. ICU denotes intensive care unit.
† The difference between rates is expressed as a relative risk, and the difference between outcomes that were assessed in days are shown in days.
‡ The P values for all the subgroup analyses represent the test of homogeneity across the odds ratios that were compared among subgroups.

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

Nogueria R.G. et al. *New England Journal of Medicine* 2018

P Stroke patients 6-24 hrs out with large vessel occlusion + mismatch
I Mechanical thrombectomy (MT) + standard care
C Standard care alone
O1 Utility weighted modified Rankin score
O2 Modified Rankin score
D Multicenter randomized controlled adaptive trial (blinded)

Background

- We already know that:
  - Systemic thrombolysis (ST) is beneficial for some patients until 4.5 hrs
  - ST is not as effective for large proximal clots
  - MT is more effective than ST for large proximal clots within 6 hrs
- Some data suggests MT remain beneficial past 6 hrs if clinical/infarct mismatch
  - Perfusion MRI/CT compared to clinical deficit to identify pnumbra

Methods

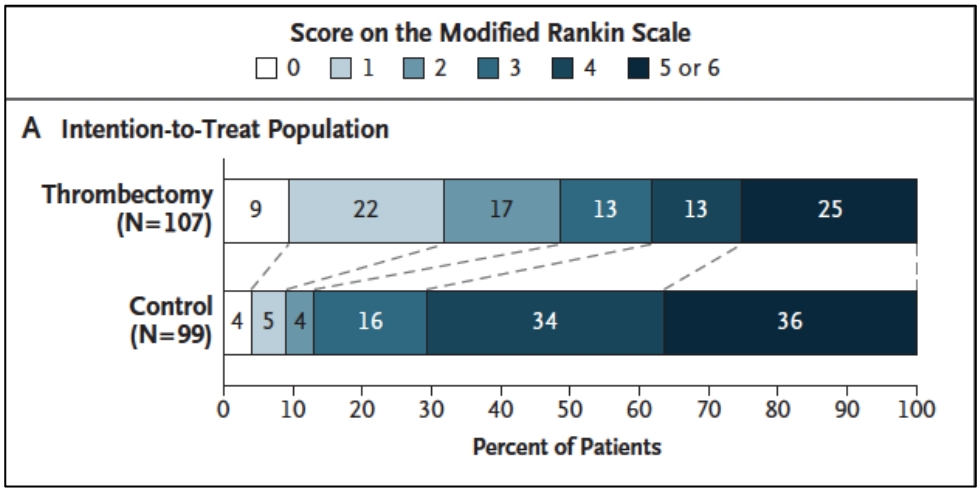
- Multi-national multi-center RCT with adaptive design across 26 centers (2014-17)
  - Adaptive design: stop-point not pre-specified
- Standard care included systemic thrombolysis as indicated
- MT with Trevo device (Stryker Neurovascular)
- Co-primary endpoints:
  - Utility weighted modified Rankin *(huh?)* at 90 days: Authors made up a score based on a weighted average of modified Rankin from patient-centered and clinician centered studies
  - Modified Rankin at 90 days: score <3 = functional independence
- Secondary endpoints:
  - Early response, infarct volume, reperfusion markers
- Lots of very complicated statistics
  - Bayesian adaptive enrichment design with interim analyses testing for futility, enrichment, and trial success

Inclusion

- Ischemic stroke patients > 18 years
- ICA or proximal MCA occlusion on CT angio or MRI
- Mismatch in clinical deficit vs. imaged infarct volume
  - Clinical deficit measured using NIHSS
- 6-24 hrs from last seen well
- Pre-stroke modified Rankin 0 or 1
- Less than one third of MCA territory infarcted

Results

- 206 randomized (107 thrombectomy 99 control)
- Groups balanced at baseline
- Primary endpoints:
    - Utility weighted modified Rankin: 5.5 (MT) vs 3.3 (control)
    - Modified Rankin < 3: 49% (MT) vs. 13% (control)



- Secondary endpoints:
    - Higher rates of reperfusion based on imaging/angio and rapid clinical improvement within 7-10 days
- Safety:
    - No difference in mortality, ICH, rapid deterioration, procedural complications

Study Conclusions

- Mechanical thrombectomy improves outcomes in large anterior cerebral vessel infarcts 6 to 24 hours after being seen well if there is a deficit/infarct mismatch

Appraisal

- How valid are these complex trial designs and statistical analyses?
- Heavy manufacturer funding and involvement suggests bias
- How many patients had to be screened to find the 206 who fit criteria?
- Do we have the resources in our stroke system to extend the time window to 24hrs? At what cost?

Overall

- Together with the DIFUSE-3 trial (up to 16 hr window) there seems to be another paradigm shift in stroke care. Will our system be able to accommodate the need?

Is Tachycardia at discharge from the pediatric emergency department a cause for concern? A nonconcurrent cohort study.

Wilson PM, Florin TA, Huang G, *et al*. 2017

P Patients < 19-year-old seen and discharged from pediatric emergency departments or urgent care centers
I Discharge tachycardia (last recorded pulse ≥ 99th percentile)
C Normal heart rate for age at time of discharge
O_1 Unscheduled ED or urgent care revisit within 72 hours of discharge
O_2 Clinically important interventions received and disposition at revisit
Diagnosis associated with index visit and revisit
Prevalence of discharge tachycardia at the index visit
Pain, fever, and medications associated with discharge tachycardia
Temporal relationship of final documented heart rate at discharge
D Observational, retrospective cohort study

Background

- Pediatric early warning systems (PEWS): early detection and appropriate escalation of care for hospitalized children with abnormal vital signs
- Tachycardia in the pediatric emergency department is common
    - Can reflect both benign states (fear, anxiety, pain) and potentially devastating conditions (sepsis, shock, cardiac dysfunction)
    - In non-pediatric emergency departments, tachycardia has been associated with clinical deterioration following discharge

Inclusion criteria

- Children less than 19 years old treated and discharged from emergency departments or urgent care centers

Exclusion criteria

- No heart rate recorded

Methods

- Observational, retrospective cohort study conducted at Cincinnati Children's Hospital Medical Center from January 1 to December 31, 2013
- Data extracted from EMR (EPIC)
- Primary outcome:
    - Unscheduled revisit to ED or urgent care center within 72 hours of discharge (also included direct admissions to hospital)
- Secondary outcome:
    - Clinically important interventions:
        - Specific respiratory or cardiovascular support
        - Administration of particular medications + admission
        - Performance of particular procedures
    - Diagnosis associated with index visit and revisit
    - Prevalence of discharge tachycardia at the index visit
    - Pain, fever, and medications associated with discharge tachycardia
    - Temporal relationship of final documented heart rate at discharge
- Results reported as adjusted RR with 95% confidence intervals

Results

- 149740 visits evaluated (76,552 patients receiving care at the urban ED, 39,852 at the suburban ED, and 33,336 at the urgent care centers)
    - 1,023 children did not have a documented HR and excluded
    - 126,774 visits and 85,709 unique patients met inclusion criteria
    - Discharge tachycardia in 8.3% (n=10470)
        - More likely to be aged 12-36 months, have an associated fever or treated with inhaled respiratory medications
- Unscheduled revisits within 72 hours of discharge:
    - 3.4% (n=4,294) of patients had an unscheduled revisit within 72 hours of discharge
        - 4.8% (n=502) were tachycardic at discharge vs. 3.3% (n=3790) were not tachycardic at discharge
        - Adjusted RR 1.3 (95% CI: 1.2-1.5)
- Secondary outcomes
    - Increased need for
        - Oxygen: RR 1.8
        - Respiratory drugs and admission: RR 2.0
        - Antibiotics and admission: RR 1.5
        - IV with admission: RR 1.4
    - Did not have increased
        - Rate of admission: admission from ED RR 1.1 (95% CI 0.9 to 1.3); direct admission to the hospital RR 0.6 (95% CI 0.3 to 1.3)
        - Clinically important interventions at revisit
- Other observations:
    - Tachycardia was associated with fever and puffers but not pain
    - Tachycardia often measured > 30 minutes prior to discharge (only 15.1% had a heart rate measured with in 30 minutes of discharge)
- Sensitivity analysis performed on
    - Patients with HR recorded within 30 minutes of discharge: adjusted RR 1.5 (95% CI 1.2-1.8)
    - Patients seen only in ED: RR 1.3 (95% CI 1.1-1.4)

Strengths

- Large sample size
- Low risk of bias
- Equivalent groups

Limitations

- Chart review
- Retrospective
- Revisits to sites or providers not included in the study were not captured
- Decision to intervene at second visit highly variable and subjective

Author's conclusion

- *"Discharge tachycardia is associated with an increased risk of revisit. It is likely that tachycardia at discharge is not a critical factor associated with impending physiologic deterioration."*

Take-home point

- Many children discharged home with tachycardia
    - More likely to return to the department and receive treatment
    - No significant deterioration requiring lifesaving intervention

- Therefore, it is likely safe to discharge children with isolated tachycardia home as long as clear instructions regarding return are provided

EBM Topic: OR vs RR

1. OR and the RR are both used to express an association between exposure and outcome.

Traditionally used in horse racing betting
See hypothetical example from Gordis, 5th edition
- Say, the expected probability that a horse will win the race is 60%

$$\text{Odds} = \frac{60\%}{1 - 60\%} = \frac{60\%}{40\%} = 1.5$$

(or 3:2, as usually expressed at the racetrack)

	Disease	No disease
Exposed	a	b
Not exposed	c	d

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

$$OR = ad / bc$$

2. RR isn't appropriate for a case control study. The denominator is chosen by the investigator (cases/controls). In a cohort study you can calculate RR or OR (RR is better).

$$\text{Odds Ratio} = \frac{\text{Odds of a history of exposure in the Cases}}{\text{Odds of a history of exposure in the Controls}}$$

$$\text{Odds Ratio} = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{a \times d}{b \times c}$$

Turns out same as in a cohort study.

$$\text{Odds Ratio} = \frac{\text{Odds of disease in the Exposed group}}{\text{Odds of disease in the Non-Exposed group}}$$

$$\text{Odds Ratio} = \frac{a}{b} \Big/ \frac{c}{d} = \frac{a \times d}{b \times c}$$

3. Under some conditions the OR in a case-control design approximates RR that you would have got with a cohort design:

When the Risk of Disease is Low:

	Disease	No disease
Exposed	a	b
Not exposed	c	d

$a + b \cong b$

$c + d \cong d$

Disease risk is low: 100 / 10,000 = 1%

Exposure	Develop Disease: Yes	No	
Yes	200	9800	10,000
No	100	9900	10,000

$$\text{Relative Risk} = \frac{200 / 10{,}000}{100 / 10{,}000} = 2.00$$

OR≈RR

$$\text{Odds Ratio} = \frac{200 \times 9{,}900}{9{,}800 \times 100} = 2.01$$

Prevalence of pulmonary embolism in patients presenting to the Emergency Department with syncope

Fizell et al. *Americal Journal of EM* 2018

P Adult patients presenting with syncope
I none
C none
O1 Diagnosis of PE
D Retrospective cross-sectional

Background
- An Italian NEJM article in 2016 found that 17% of patients admitted with first time syncope had a PE
- This would suggest that all syncope patients should be worked up for PE
- Many disagreed with the findings suggesting that:
    - The PEs may have been incidental findings
    - The selection criteria were highly selective
- The question remains: which syncope patients should be risk stratified for PE (clinical variables and d-dimer)

Methods
- Retrospective review of pre-existing data from University of Utah (2010-15)
- Data was prospectively collected for all patients presenting with syncope:
    - Baseline characteristics
    - Outcomes of ED testing
    - Inpatient evaluation
    - 30-day follow-up (telephone and chart review)
- University of Utah has an observation unit where syncope patients get telemetry, echo, and referral to outpatient Holter
- Outcomes: CT or V/Q diagnosis of PE in ED, hospital, or within 30 days

Inclusion
- Data collection performed by undergraduate research assistants
- Potential patients identified based on chief complaint at triage (not sure which ones)
- Then asked, “have you passed out within the past 24 hrs?’

Results
- 778 patients screened, 348 included
- 54% were SOB, 49% had CP, 17% had calf swelling/pain
- Overall rate of PE = 1.4%
    - Two patients diagnosed in the ED
    - None diagnosed as inpatient
    - Three self-reported PE on phone interview
- Telephone contact rate = 68%
- No PE’s identified on chart review

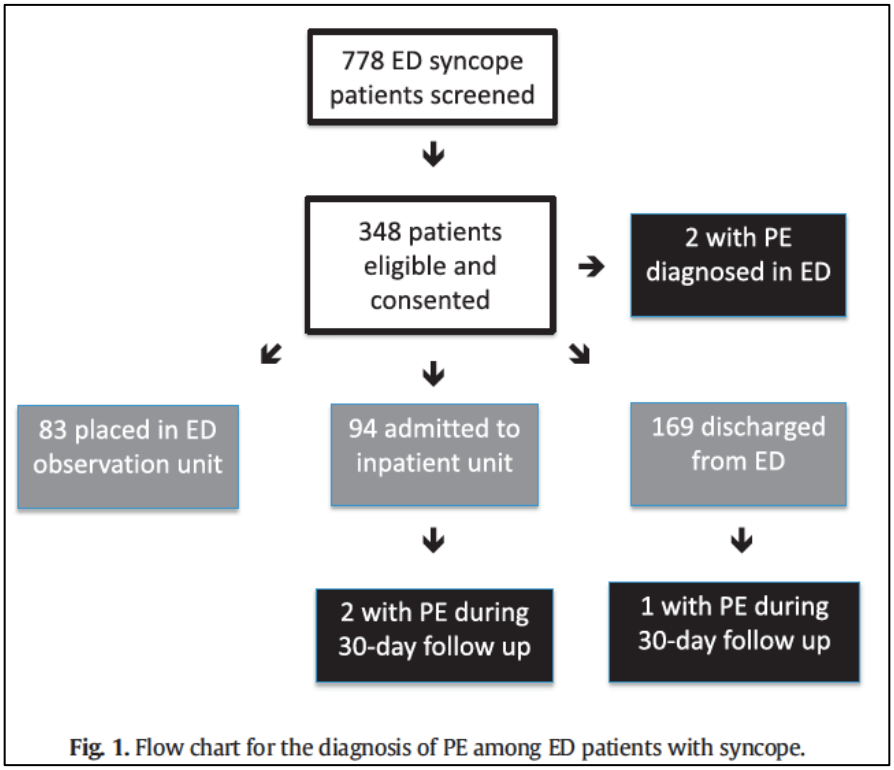


Fig. 1. Flow chart for the diagnosis of PE among ED patients with syncope.

Study Conclusions

The prevalence of PE in ED patients with syncope is perhaps 1.4% and therefore routine workup for PE is not warranted

Appraisal

- Seems generalizable to the ED patient population
    - However, inclusion criteria (i.e. definition of syncope patient) may be invalid or unreliable given non-MD screening interview
- Underestimation could result from losses to follow-up (EMR data or phone contact)
- Use of secondary data limits interpretation

Overall

The lack of standardized inclusion criteria *and* PE definition across studies underpins current disagreement amongst authors. A prospective trial is underway, which may help a bit. PE presenting as syncope is still as tricky as ever.