

Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS): A Randomized, Double-Blind, Controlled Study

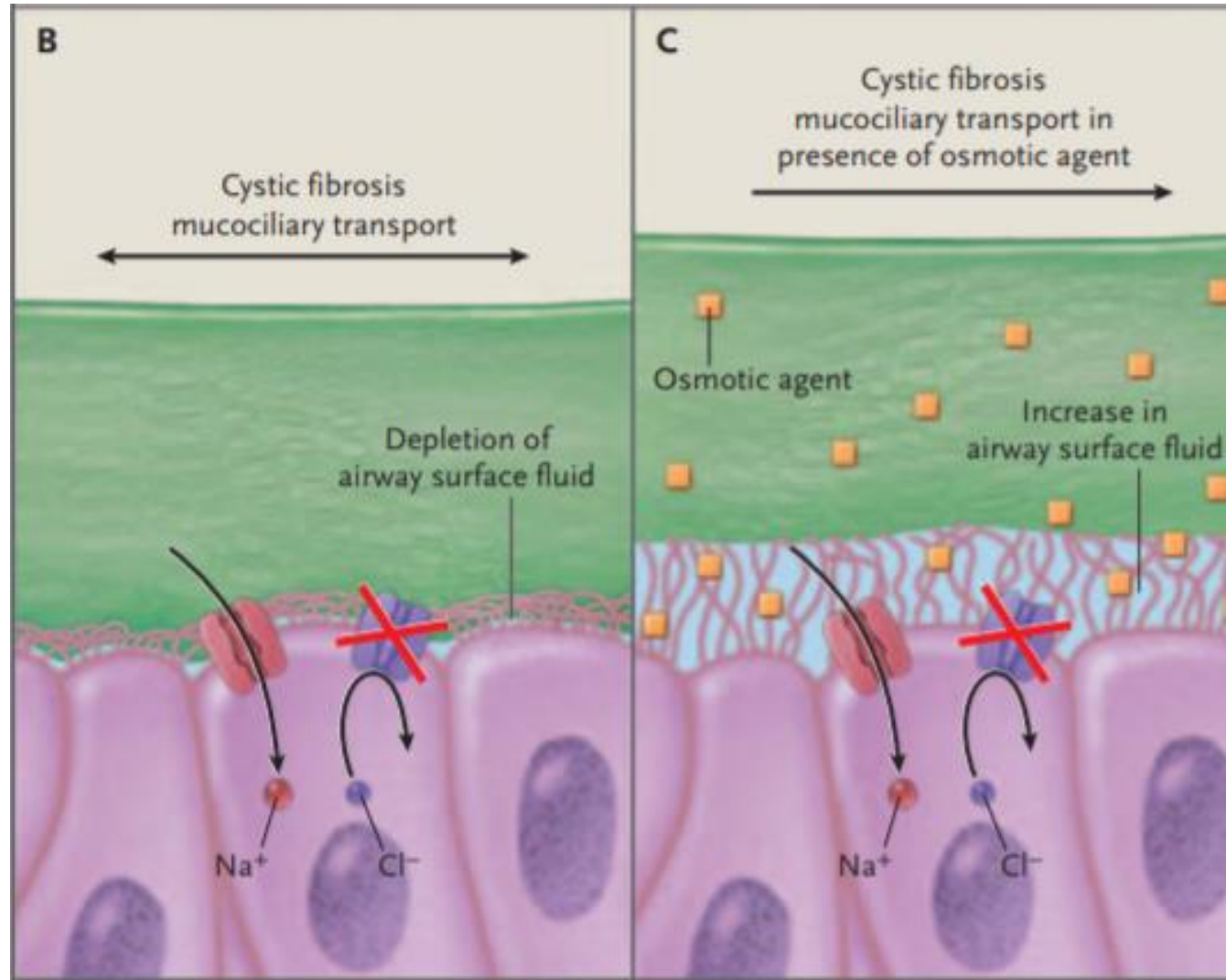
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Outline

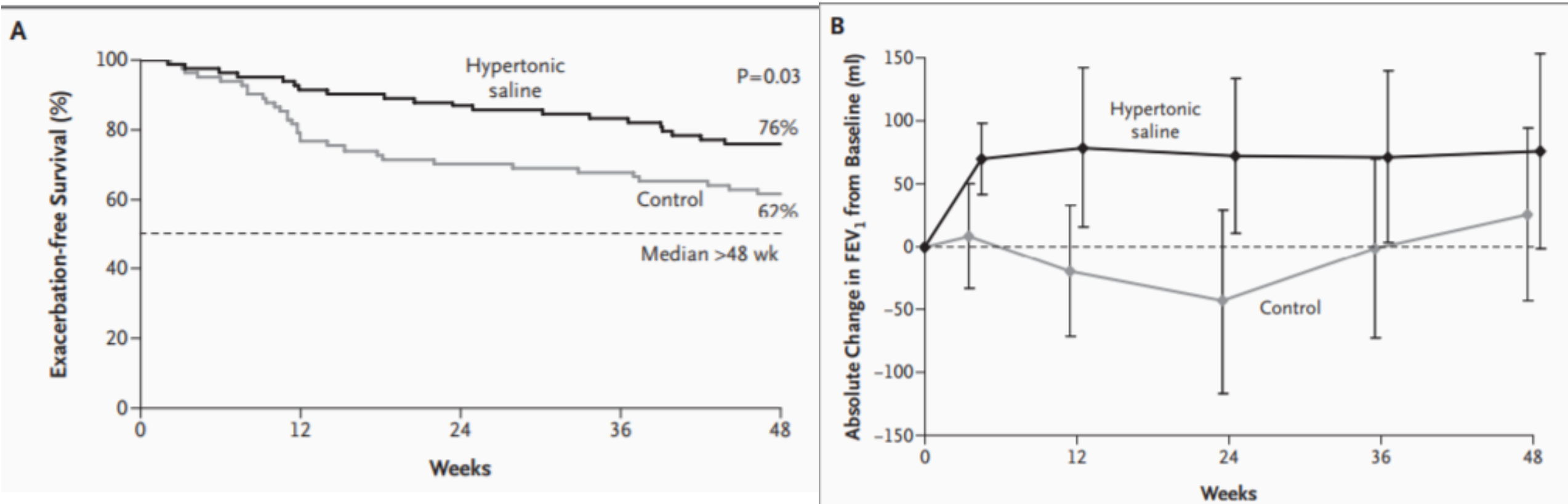
- Introduction: Evidence on inhaled hypertonic saline use
- *Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS): A Randomized, Double-Blind, Controlled Study*
- Critical appraisal
- Interactive discussion and comments

Inhaled Hypertonic Saline



(Ratjen, *NEJM*, 2006)

Introduction- Hypertonic saline



- Age: 6 +
- Intervention: Hypertonic vs Isotonic saline X 48 weeks
- Outcomes: Reduces pulmonary exacerbations and improves FEV1

(Elkins et al., *NEJM*, 2006)

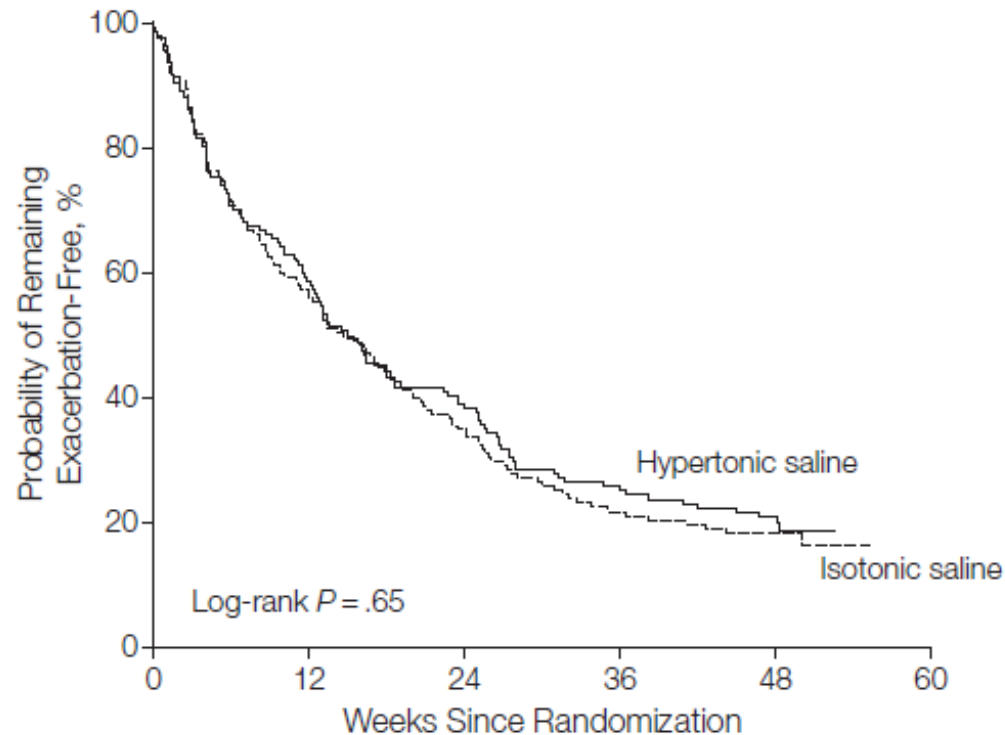
Infant CF guidelines

Chronic Pulmonary Therapies

Recommendations	Evaluation of the Evidence
39. For infants with CF under 2 years of age, dornase alfa (recombinant human DNase) may be used in symptomatic infants.	Certainty: Low Benefit: Moderate Consensus recommendation
40. For infants with CF under 2 years of age, 7 percent hypertonic saline may be used in symptomatic infants.	Certainty: Low Benefit: Moderate Consensus recommendation

Introduction- Hypertonic saline

Figure 2. Kaplan-Meier Plot of Time to First Exacerbation by Treatment Group



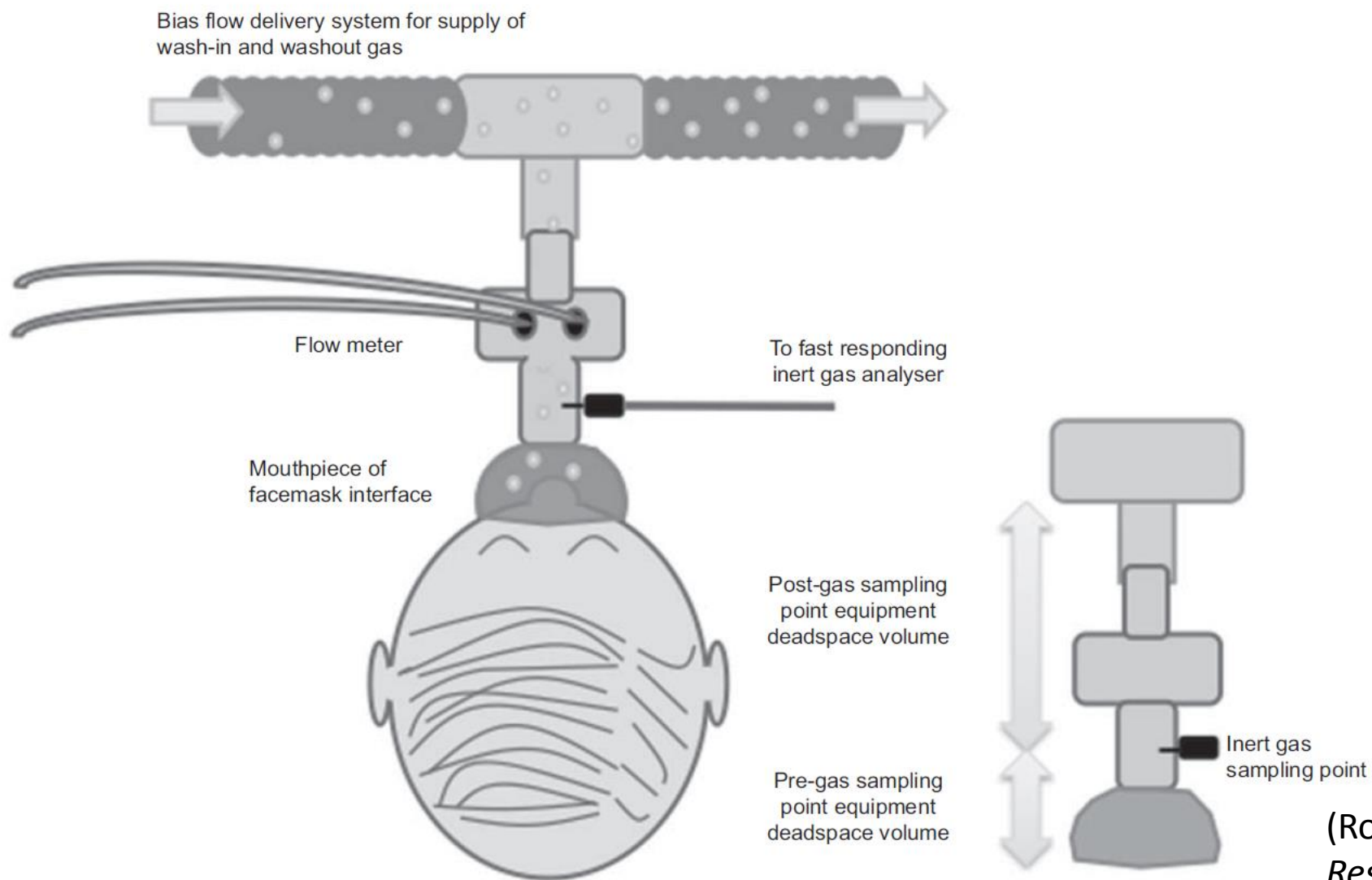
- 344 patients
- Age: 4 to 60 months
- Intervention: Hypertonic vs isotonic fluid X 48 weeks
- Outcome: No difference in pulmonary exacerbations

(Rosenfeld et al., *JAMA* ,2012)

Evaluation of early lung disease in infants with CF

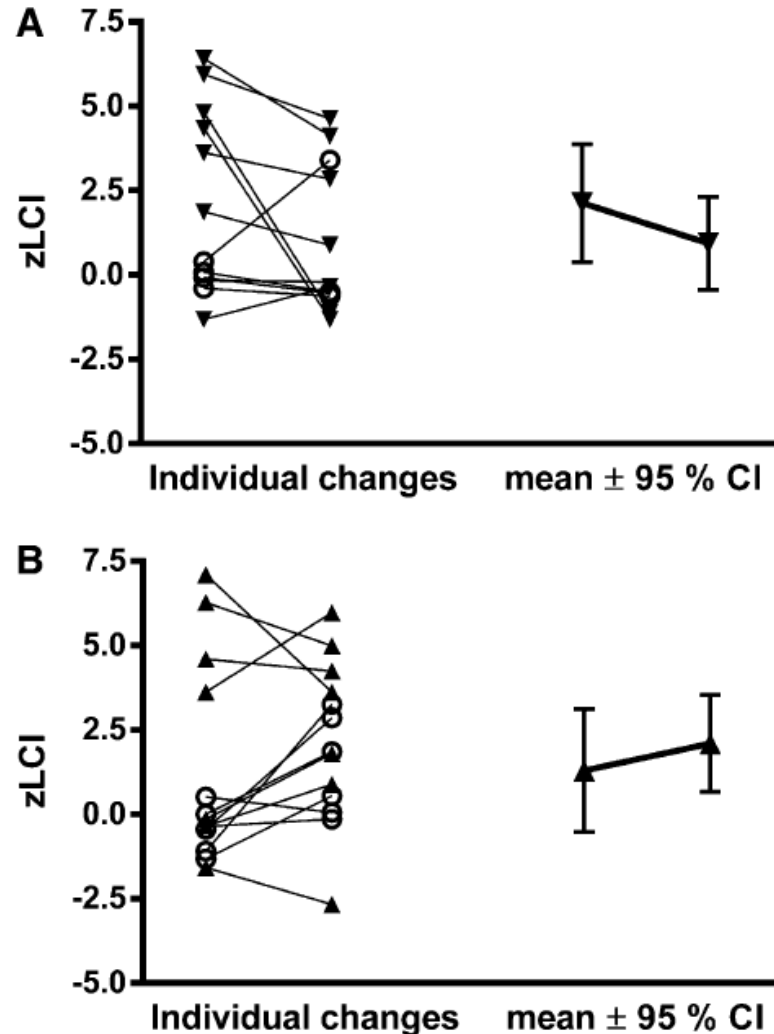
Test	Advantages	Disadvantages
Pulse oximetry	<ul style="list-style-type: none">- Widely available- Non Invasive	<ul style="list-style-type: none">- Unclear if useful in asymptomatic infants
Chest X-ray	<ul style="list-style-type: none">- Widely available- May detect early abnormalities- Minimal radiation	<ul style="list-style-type: none">- Relatively insensitive (vs CT)
CT scan	<ul style="list-style-type: none">- Identifies early signs of disease	<ul style="list-style-type: none">- Sedation- Radiation (cumulative dose)
Infant PFT	<ul style="list-style-type: none">- Sensitive to early abnormalities	<ul style="list-style-type: none">- Sedation- Expertise in the technique- Specialized equipment
MRI chest	<ul style="list-style-type: none">- Identifies early signs of disease	<ul style="list-style-type: none">- Sedation
Lung Clearance Index	<ul style="list-style-type: none">- Sensitive in early lung disease	<ul style="list-style-type: none">- Sedation- Research tool- Limited knowledge on clinically significant change

Lung clearance index (LCI)



(Robinson et al., *Eur Respir J*, 2013)

Introduction- Hypertonic saline



- 25 patients
- Age: < 6 years old (10 infants)
- Intervention: Hypertonic vs isotonic fluid X 48 weeks
- Outcome: Hypertonic saline has +ve effects on LCI

(Subbarao et al., *Am J Respir Crit Care*, 2013)

Evaluation of early lung disease in infants with CF

Test	Advantages	Disadvantages
Pulse oximetry	<ul style="list-style-type: none">- Widely available- Non Invasive	<ul style="list-style-type: none">- Unclear if useful in asymptomatic infants
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Chest MRI

- Sensitive to detect early abnormalities in lung structure and perfusion
- MRI morphology score:
 - Bronchial wall thickening/bronchiectasis
 - Mucus plugging
 - Sacculaton and abscesses
 - Consolidation
 - Pleural reaction
 - Mosaic signal intensity

Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS): A Randomized, Double-Blind, Controlled Study

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Introduction

Aim of the study: Explore feasibility, safety and initial efficacy of preventive inhalation of Hypertonic Saline in **young infants** using LCI and MRI as outcome measures.

Methods

- Randomized 1:1, Parallel group, Double-blind, Control trial
- Intervention: 4 ml Hypertonic Saline 6% (HS) vs Isotonic Saline 0.9% (IS) twice daily for 12 months using a jet nebulizer and baby face mask
- Location: 5 CF centers in Germany (DZL)
- Inclusion criteria: Confirmed diagnosis of CF & Age < 4 months

Outcome measures

- Change in LCI
- Chest MRI score
- Anthropometric data (Weight, Height, BMI)
- Rate of pulmonary exacerbations
- Respiratory rate & oxygen saturation
- Detection of pathogens
- **Adverse & Serious Adverse Events**

Multiple-Breath Washout

- Exhalyzer D system:
 - 4% sulfur hexafluoride as tracer gas
 - Face mask
 - Child lying supine
- Sedation: Chloral hydrate (100 mg/kg body weight)
- LCI determine from acceptable wash-out curves

Chest MRI

- 1.5T MR scanner
- T1- and T2- weighted sequences
- Images assessed for morphological abnormalities by blinded independent reader
- No perfusion studies

Results – Patient flow

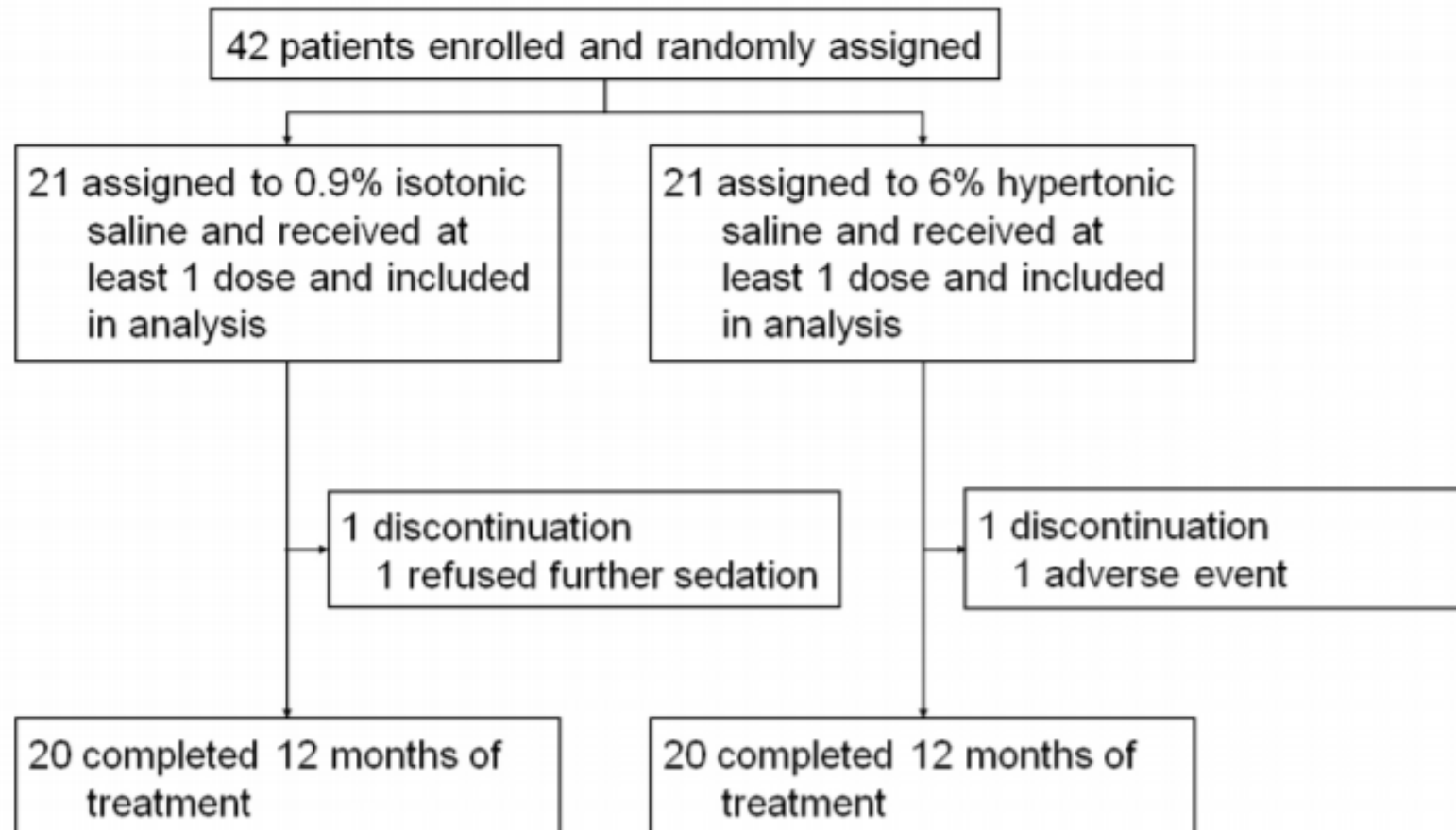


Table 1. Demographics and baseline characteristics of study population

	Isotonic saline (n=21)	Hypertonic saline (n=21)
Age, years	0.26 (0.07)	0.26 (0.08)
range, years	0.09 – 0.35	0.10 – 0.41
Sex, n (males/females)	10/11	10/11
<i>CFTR</i> genotype		
F508del/F508del	11 (52.4)	11 (52.4)
F508del/other	8 (38.1)	6 (28.6)
other/other	2 (9.5)	4 (19.0)
Pancreatic insufficient	20 (95.2)	17 (81.0)
Anthropometry		
Weight, kg	5.2 (1.1)	5.3 (1.1)
Weight z-score	-0.7 (0.9)	-0.6 (1.1)
Height, cm	59.8 (4.0)	59.8 (5.1)
Height z-score	-0.7 (1.2)	-0.6 (1.1)
BMI, kg/m ²	14.4 (1.6)	14.7 (1.6)
BMI z-score	-1.0 (1.0)	-0.8 (1.1)

Table 1. Demographics and baseline characteristics of study population

	Isotonic saline (n=21)	Hypertonic saline (n=21)
Mode of diagnosis*		
Positive CF newborn screening	10 (47.6)	10 (47.6)
Meconium ileus/atresia small intestine	3 (14.3)	6 (28.6)
Prenatal/positive family history	2 (9.5)	4 (19.0)
Failure to thrive	4 (19.0)	1 (4.8)
Respiratory symptoms	2 (9.5)	0 (0.0)
Positive respiratory culture†		
<i>Staphylococcus aureus</i>	6 (28.6)	4 (19.0)
<i>Haemophilus influenzae</i>	0 (0.0)	0 (0.0)
<i>Pseudomonas aeruginosa</i>	0 (0.0)	0 (0.0)
<i>Streptococcus pneumoniae</i>	0 (0.0)	0 (0.0)
<i>Aspergillus species</i>	0 (0.0)	1 (4.8)
Resting respiratory rate, breaths/min	41.3 (11.5)	39.2 (10.7)
Oximetry, %	98.8 (1.1)	98.5 (1.3)
LCI	7.2 (0.7)	7.5 (0.7)
Chest MRI		
Prevalence	95.2 (20/21)	95.2 (20/21)
Morphology		
Score	8.0 (4.0 - 13.5)	3.0 (2.0 – 12.0)

Results- Absolute change LCI

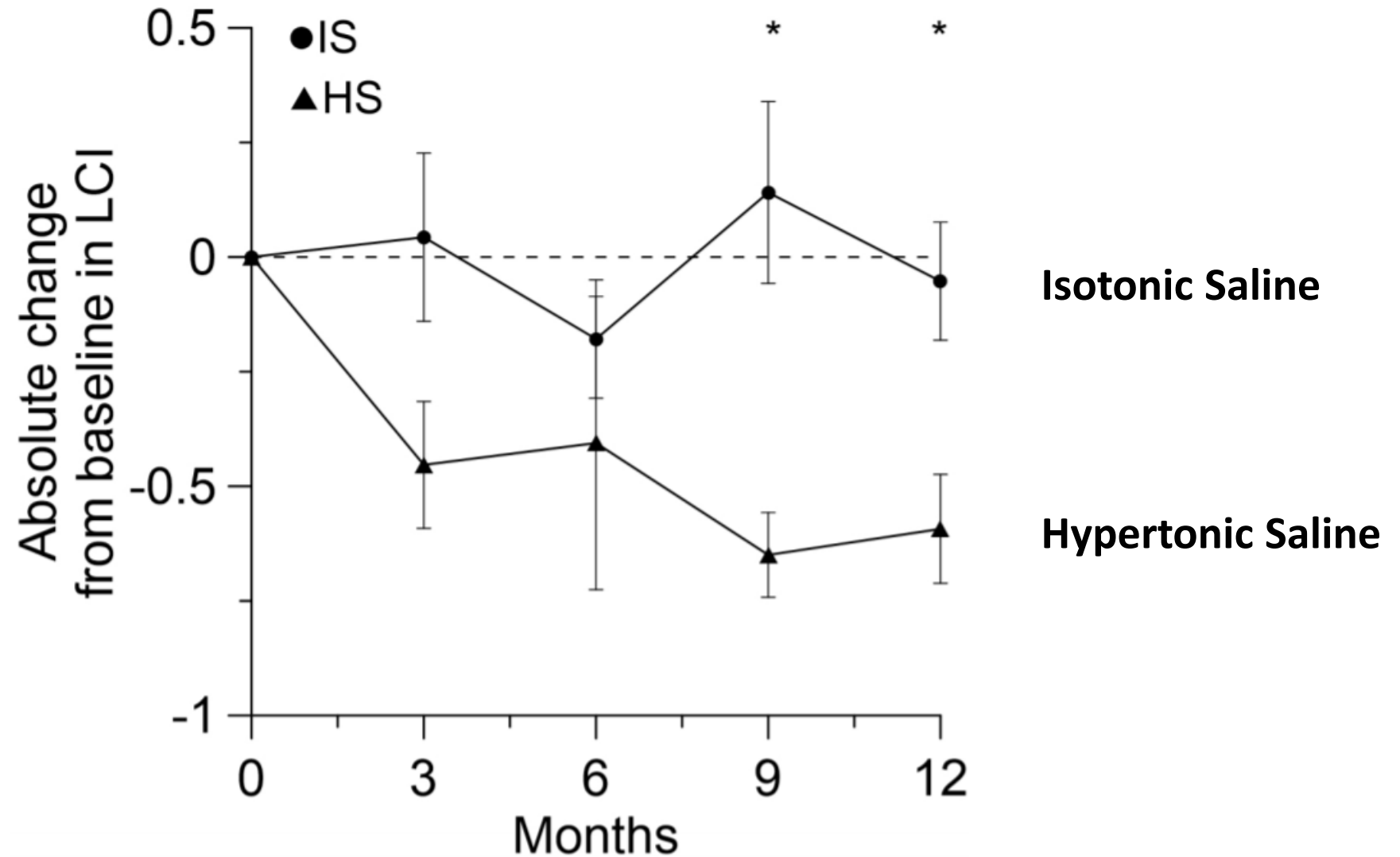


Table 2. Effects of preventive inhalation of hypertonic saline versus isotonic saline in infants with CF

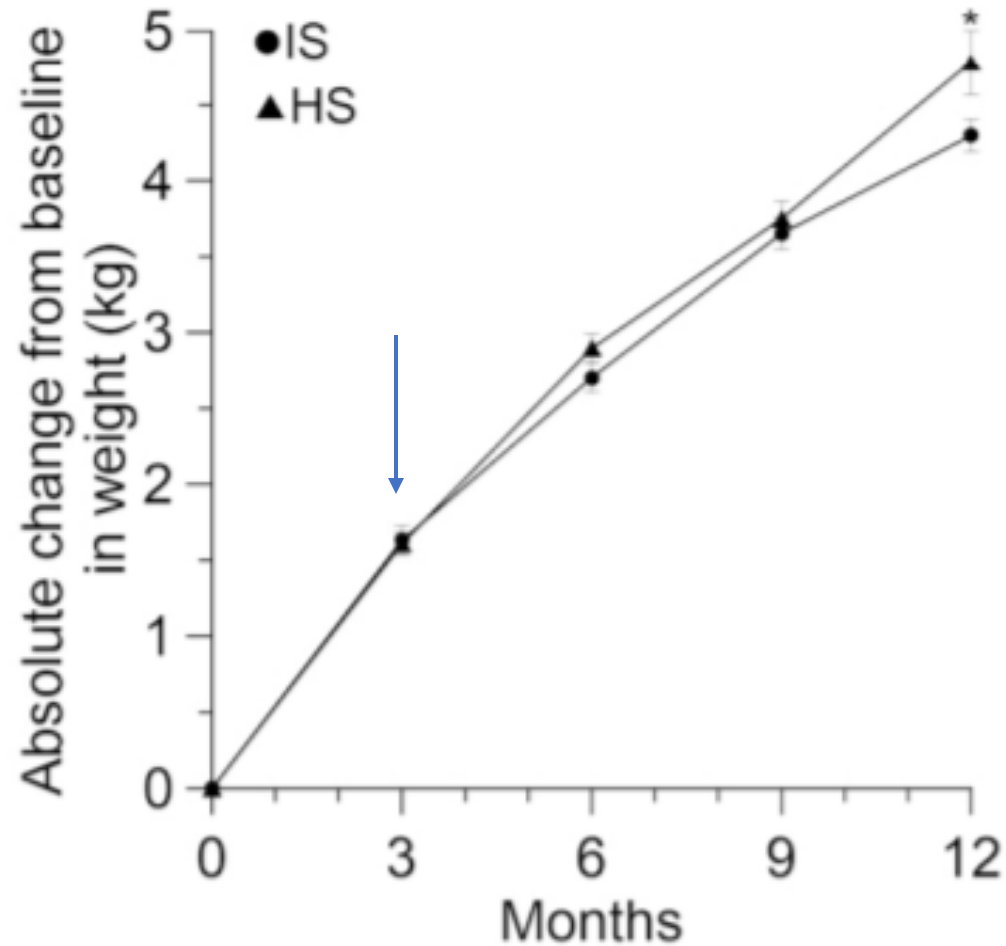
	Isotonic saline (n=20)	Hypertonic saline (n=20)	Treatment difference vs. isotonic saline
Absolute change in LCI at month 12	-0.1 (-0.5 to 0.4)	-0.6 (-1.0 to 0.2)**	-0.5 (-1.1 to 0.0)*
Absolute change in MRI morphology score at month 12	0.5 (-3.0 to 3.6)	1.9 (-0.5 to 4.3)	1.4 (-2.4 to 5.3)
Absolute change in MRI wall thickening/bronchiectasis subscore at month 12	0.8 (0.3 to 1.4)**	1.6 (0.9 to 2.3)***	0.8 (-0.1 to 1.6)
Absolute change in MRI mucus plugging subscore at month 12	0.3 (-0.6 to 1.3)	0.8 (0.0 to 1.5)*	0.5 (-0.7 to 1.6)
Absolute change in MRI consolidation subscore at month 12	-0.5 (-1.0 to 0.0)	-0.6 (-1.1 to 0.0)	-0.1 (-0.8 to 0.6)
Absolute change in MRI pleural reaction subscore at month 12	-0.2 (-0.7 to 0.3)	-0.2 (-0.6 to 0.3)	0.1 (-0.6 to 0.7)
Absolute change in MRI mosaic signal intensity subscore at month 12	0.0 (-1.8 to 1.5)	0.3 (-0.7 to 1.2)	0.3 (-1.5 to 2.0)

Table 2. Effects of preventive inhalation of hypertonic saline versus isotonic saline in infants with CF

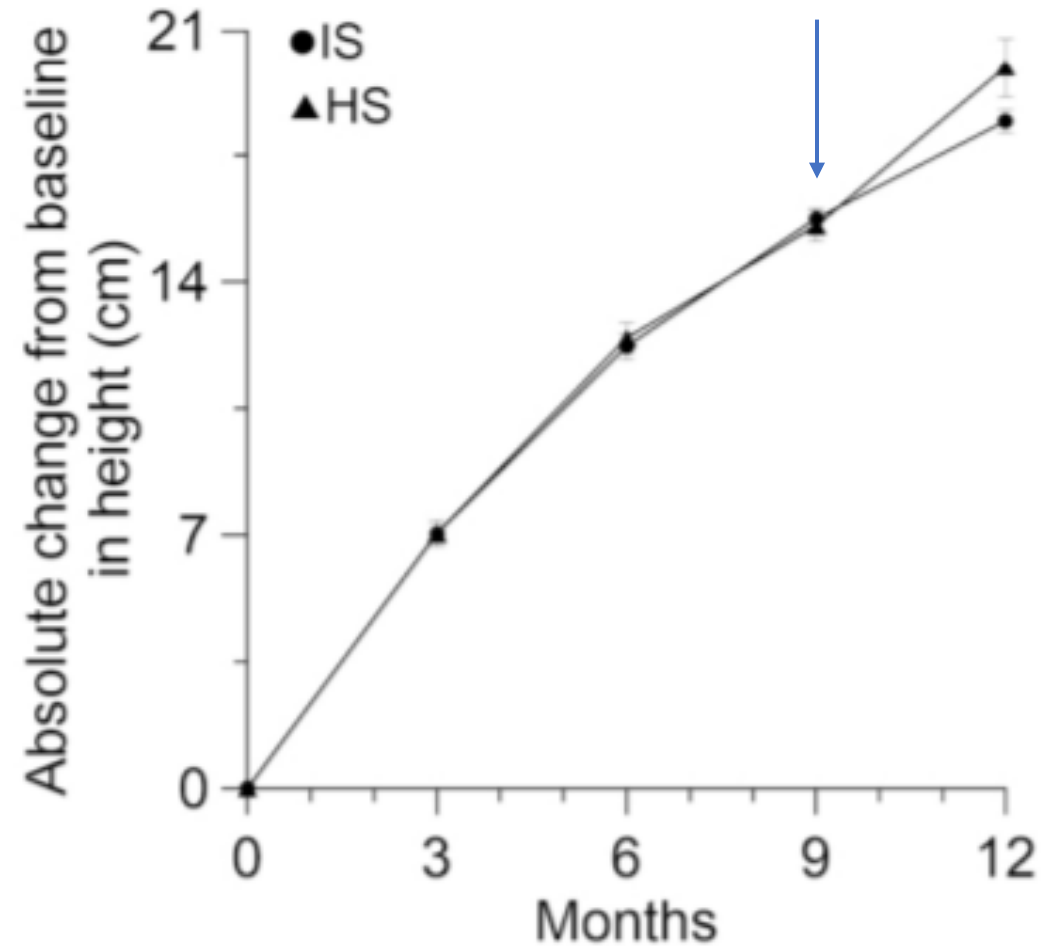
	Isotonic saline (n=20)	Hypertonic saline (n=20)	Treatment difference vs. isotonic saline
Absolute change in weight (kg) through month 12	4.3 (4.0 to 4.7)***	4.8 (4.1 to 5.5)***	0.5 (-0.3 to 1.2)*
Absolute change in weight z-score through month 12	-0.1 (-0.4 to 0.2)	0.3 (-0.4 to 0.9)	0.3 (-0.3 to 0.1)
Absolute change in height (cm) through month 12	18.5 (17.4 to 19.5)***	20.0 (17.3 to 22.6)***	1.5 (-1.3 to 4.3)
Absolute change in height z-score through month 12	0.3 (-0.1 to 0.6)	0.9 (-0.3 to 2.1)	0.6 (-0.6 to 1.8)
Absolute change in BMI (kg/m ²) through month 12	1.1 (0.3 to 1.9)**	1.2 (0.5 to 1.9)**	0.2 (-0.9 to 1.2)
Absolute change in BMI z-score through month 12	0.2 (-0.5 to 0.8)	0.3 (-0.2 to 0.8)	0.1 (-0.7 to 0.9)
Absolute change in resting respiratory rate (breaths/min) at month 12	-9.9 (-15.7 to -3.9)***	-10.3 (-16.6 to -4.0)**	-0.4 (-8.5 to 7.7)
Absolute change in oximetry (%) at month 12	-1.6 (-2.4 to -0.9)***	-1.3 (-2.3 to -0.2)*	0.4 (-0.9 to 1.7)

Results- Anthropometric measurements

A

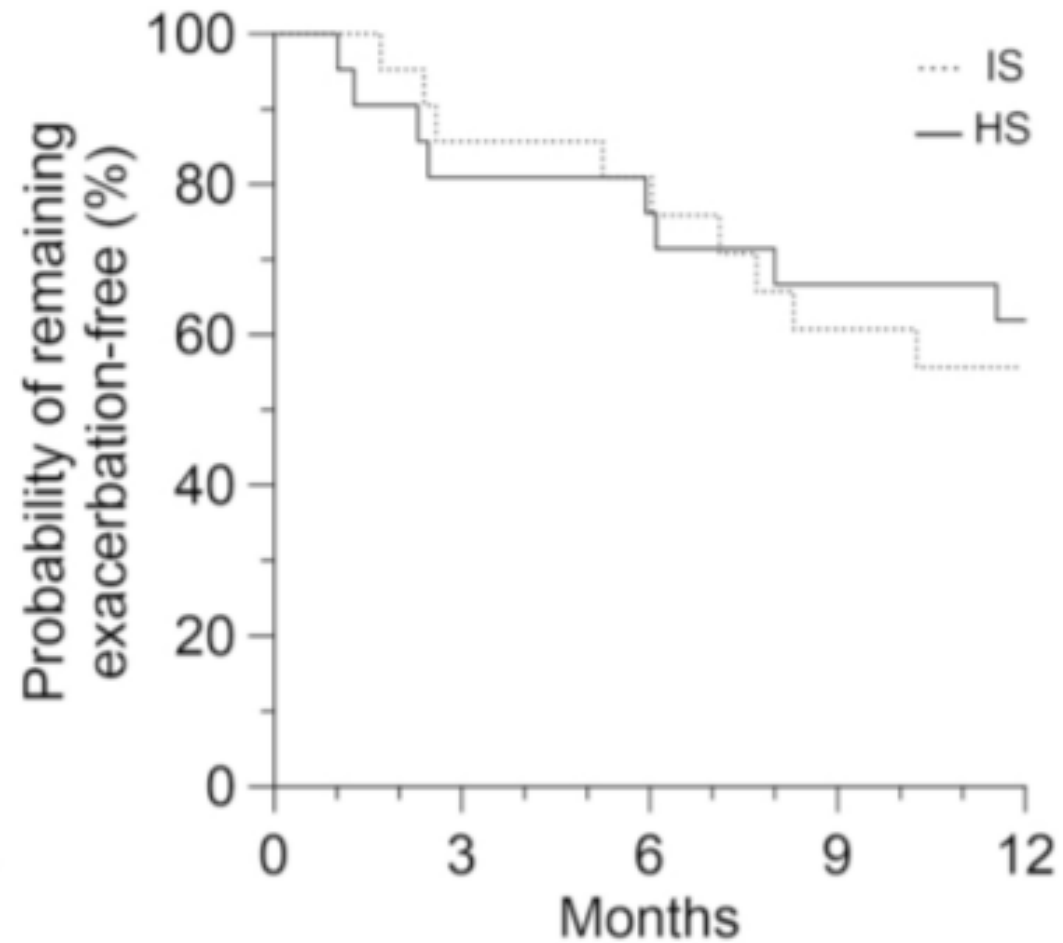


B



Results- Pulmonary exacerbations

D



Results- Microbiology

- Low prevalence and acquisition of upper airway infection with
 - *Staphylococcus aureus*
 - *Haemophilus influenzae*
 - *Pseudomonas aeruginosa*
 - *Streptococcus pneumoniae*
 - *Aspergillus* species
- No difference in between groups.

Table 3. Treatment-emergent adverse events

	Isotonic saline (n=21)		Hypertonic saline (n=21)	
	Affected infants	Occurred events	Affected infants	Occurred events
All adverse events	21 (100)	240 (100)	21 (100)	219 (100)
All adverse events with incidence > 5% in any treatment group:				
Infection of upper respiratory tract without fever	17 (81.0)	52 (21.7)	16 (76.2)	41 (18.7)
Rhinorrhea	10 (47.6)	17 (7.1)	17 (81.0)	31 (14.2)
Cough	12 (57.1)	34 (14.2)	14 (66.7)	25 (11.4)
Infection of upper and lower respiratory tract without fever	7 (33.3)	9 (3.8)	9 (42.9)	13 (5.9)
Infection of upper respiratory tract with fever	8 (38.1)	13 (5.4)	7 (33.3)	9 (4.1)
Infection of upper and lower respiratory tract with fever	7 (33.3)	8 (3.3)	6 (28.6)	10 (4.6)
Abdominal distension / flatulence	4 (19.0)	4 (1.7)	8 (38.1)	8 (3.7)
Fever	6 (28.6)	7 (2.9)	5 (23.8)	10 (4.6)
Diarrhea	6 (28.6)	7 (2.9)	5 (23.8)	9 (4.1)
Infection of lower respiratory tract without fever	6 (28.6)	7 (2.9)	3 (14.3)	10 (4.6)

Table 3. Treatment-emergent adverse events

	Isotonic saline (n=21)		Hypertonic saline (n=21)	
	Affected infants	Occurred events	Affected infants	Occurred events
Conjunctivitis	5 (23.8)	9 (3.8)	2 (9.5)	3 (1.4)
Gastroenteritis	3 (14.3)	4 (1.7)	4 (19.0)	7 (3.2)
Otitis media	4 (19.0)	7 (2.9)	3 (14.3)	3 (1.4)
Obstructive bronchitis	4 (19.0)	9 (3.8)	1 (4.8)	1 (0.5)
Abdominal pain	3 (14.3)	5 (2.1)	2 (9.5)	2 (0.9)
Constipation	3 (14.3)	4 (1.7)	2 (9.5)	3 (1.4)
Dyspnea	2 (9.5)	4 (1.7)	3 (14.3)	3 (1.4)
First detection of <i>P. aeruginosa</i>	2 (9.5)	2 (0.8)	3 (14.3)	3 (1.4)
Nasal congestion	2 (9.5)	2 (0.8)	3 (14.3)	3 (1.4)
Candida nappy rash	1 (4.8)	1 (0.4)	3 (14.3)	3 (1.4)
Exanthema subitum	2 (9.5)	2 (0.8)	2 (9.5)	2 (0.9)
Iron deficiency anemia	3 (14.3)	3 (1.3)	1 (4.8)	1 (0.5)
Salt loss syndrome	2 (9.5)	3 (1.3)	1 (4.8)	1 (0.5)
Urticaria	2 (9.5)	2 (0.8)	1 (4.8)	1 (0.5)
Bronchopulmonary secretion	1 (4.8)	1 (0.4)	2 (9.5)	2 (0.9)








Results- Summary

- Infants treated with inhaled HS:
 - Rapid and sustained decrease in mean LCI
 - Increased absolute weight
- No difference in pulmonary exacerbation rates, RR & O₂ saturation
- No difference in pulmonary pathogens

Discussion- Adherence to therapy

- Adherence high and comparable in both groups according to the medication diary completed by the parents
- Low dropout rates

Discussion- Trajectories of LCI

	Healthy infants	AREST CF (2015)	Subbarao (2013)	PRESIS (2018)
		If never infected  By 0.5 units	Hypertonic 	Hypertonic 
		If hx of infection 	Isotonic 	Isotonic 

Discussion- MRI findings

- No change
- Authors speculate lack of perfusion study makes the measurement more coarse and not detect small differences

Critical appraisal

Strengths

- Age range substantial lower than what has been previously studied in RCTs
- Well blinded and randomized

Limitations

- Isotonic Saline is an active comparator
- MRI score might not be sensitive enough to detect early disease
- Small study (n=42)
- No compared medication list available

Points for discussion

- Applicability:
 - Does this study apply to your patient population?
 - How many of you start hypertonic saline routinely in asymptomatic infants?
 - Would this article change your practice?

References

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Standard statistical analysis

- SPSS 22.0 and SAS 9.4 with standard statistical analysis.
- For categorical data: Chi-square test or Fisher's exact test
- Continuous data: Unpaired Student t-test or one-way ANOVA with least significant difference-Bonferroni post-hoc test or Wilcoxon signed-rank test.
- Anthropometry: Hierarchical linear mixed regression model.

Additional slide: ISIS 2012

Table 2. Comparison of Pulmonary Exacerbation Rates and Related End Points

End Point	Hypertonic Saline	Isotonic Saline	Hypertonic Saline to Isotonic Saline Ratio (95% CI)	
			Unadjusted	Adjusted ^a
Pulmonary exacerbations rate, events/person-year (95% CI) ^b	2.3 (2.0-2.5)	2.3 (2.1-2.6)	0.97 (0.83-1.13)	0.98 (0.84-1.15)
Total No. of treatment days for a pulmonary exacerbation, mean (95% CI) ^c	60 (49-70)	52 (63-71)	1.13 (0.91-1.40)	1.11 (0.89-1.37)
First pulmonary exacerbation, hypertonic saline/isotonic saline, HR (95% CI)			0.94 (0.74-1.21)	0.94 (0.73-1.22)