Treatment of Viral Bronchiolitis and the Place of Hypertonic Saline

From Basic Science to Clinical Practice

Modern – 2013 understandings

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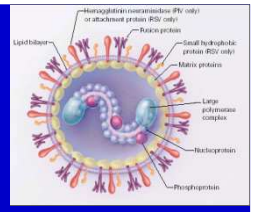
Noa – 3M 0ld baby

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.**
- **Anamnesis: Never wheezed, no family allergy/asthma**
- **CXR: Over-inflation, plate like atelectasis.**
- **PHI = Previously Healthy Infant**

Natural Course ⟺ treatments (why we fail so far)



RSV

Understanding the natural course/pathophysiology of acute viral bronchiolitis – <u>explain</u> why <u>we fail so far</u> - treating these babies

Mandelberg A, Amirav I; Pediatric Pulmonology. Jan 2010

Hall CB. N Engl J med. 2001; 344:1917-1928.
Collins PL: RSV, in :Fields Virology. 2001 1443-1485
Staat MA. Semin Resp Inf. 2002; 17:15

Natural Course PHI

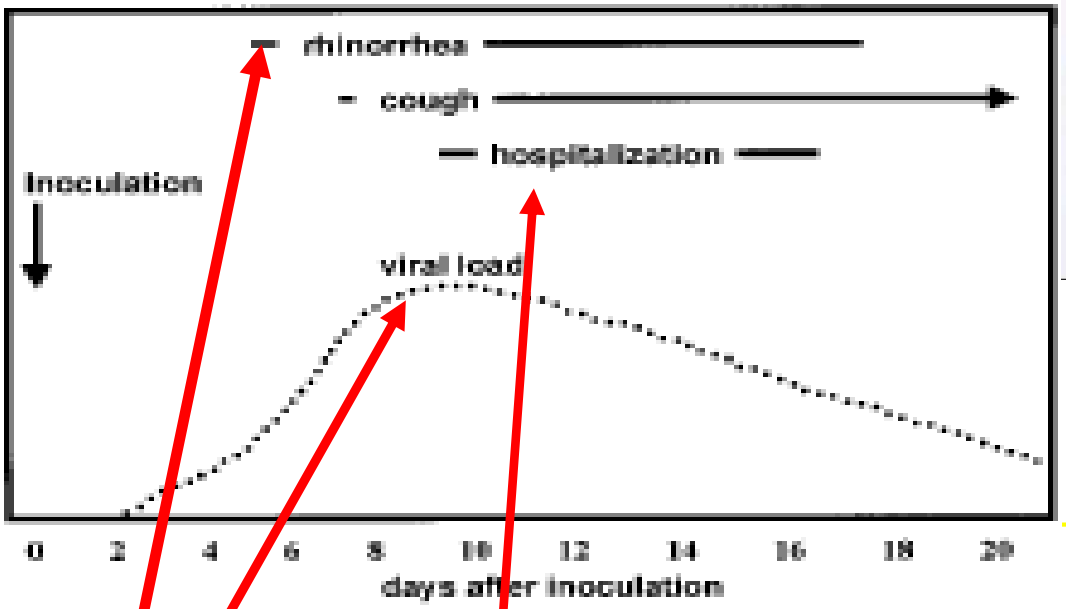
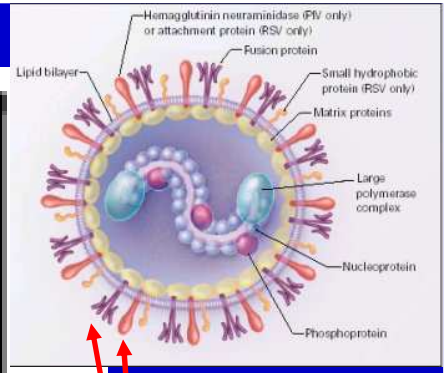


FIG. 1. Model of primary RSV infection in immunocompetent infants.



RSV

F: fusion

G: attachment

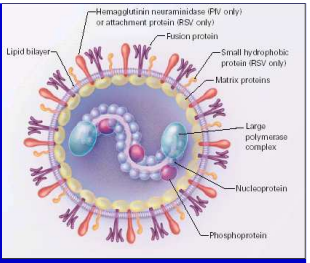
Glycoproteins

Complete restoration: 1-3 Months

- **Incubation – 5d** (to the first symptom)
- **Shedding Peak–4d in Previously Healthy Infants (PHI)**
- **Cytokines/mediators/inflammation Peak > 5d in PHI**

Hall CB. N Engl J med. 2001; 344:1917-1928. **Staat MA. Semin Resp Inf. 2002; 17:15
***Collins PL: RSV, in :Fields Virology. 2001 1443-1485

Why we fail so far



RSV

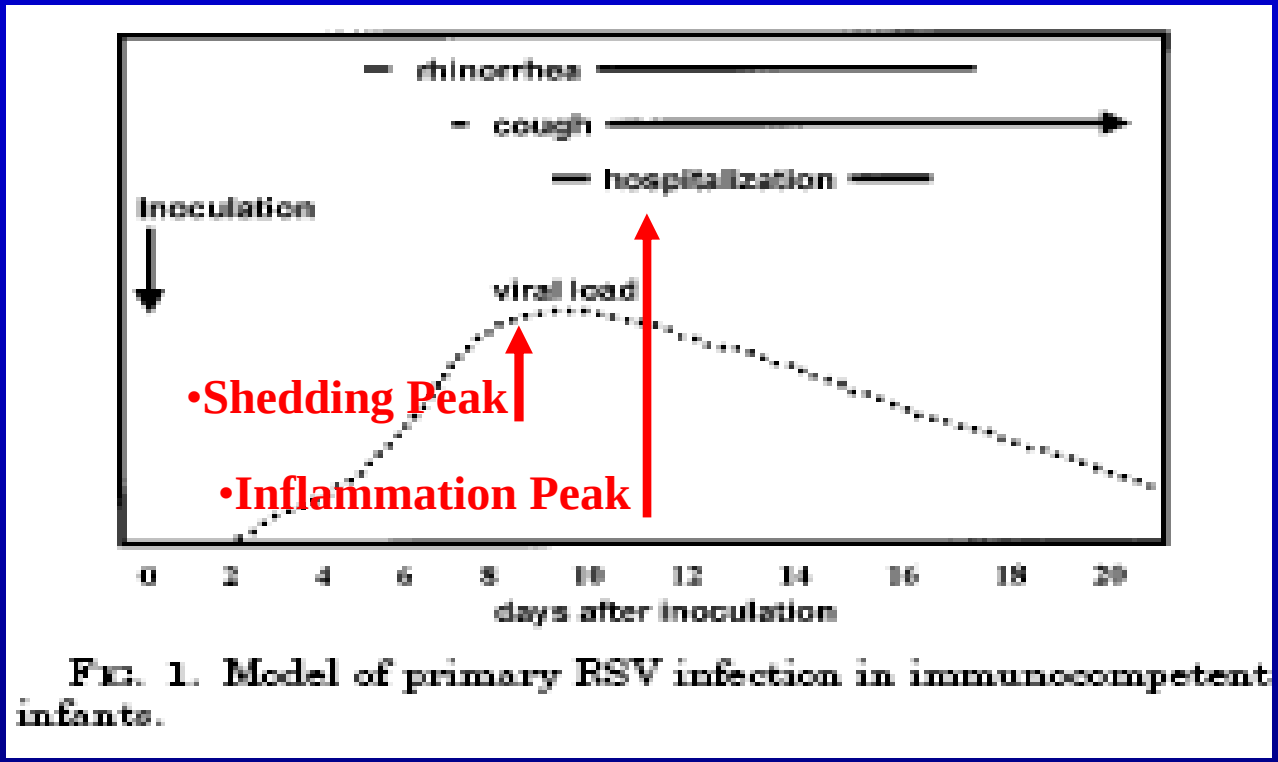


FIG. 1. Model of primary RSV infection in immunocompetent infants.

- **Anti viral agents (Ribavirin and Mono Clonal Ab) - futile in hospitalized PHI when - viral load↓ while inflammation↑ - causing all the damage.**

- **Steroids - anti-inflammatory↓, but viral shedding↑ - are unpredictable in these babies.**

Hall CB. N Engl J med. 2001; 344:1917-1928. **Staat MA. Semin Resp Inf. 2002; 17:15
***Collins PL: RSV, in :Fields Virology. 2001 1443-1485

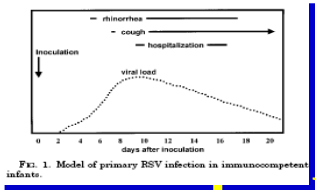
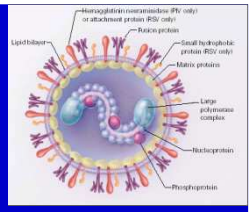


FIG. 1. Model of primary RSV infection in immunocompetent infants.

Natural Course changes

by different populations, Risk Factors / treatments



RSV

- However, the natural course differs between previously healthy infants (**PHI**) and other populations

- Some treatments which are futile in **PHI**, will be “the state of the art” in other populations.

Hall CB. N Engl J med. 2001; 344:1917-1928. **Staat MA. Semin Resp Inf. 2002; 17:15
***Collins PL: RSV, in :Fields Virology. 2001 1443-1485

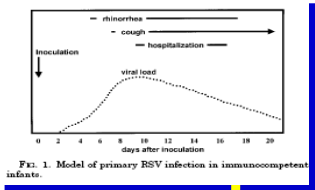
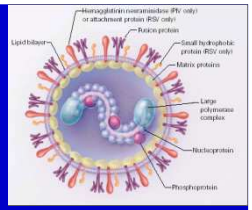


FIG. 1. Model of primary RSV infection in immunocompetent infants.

RSV



Natural Course Changes

by different populations, risk factors / treatments

- **Immunocompromised infants** (congenital, acquired or iatrogenic, BMT) **with concomitant acute viral bronchiolitis**
  - **Increased viral ↑shedding - 30-55d.**
  - **Benefit from Ribavirin and monoclonal antibodies**

- **Previously wheezing infants / or BPD / ↓TLR4…**
  - **More steroid and/or bronchodilator responsive**

- **Data on PHI in the acute phase should not be generalized to other populations.**

Tal G, Mandelberg A, et al.– J Infect Dis 2004

Hall CB. N Engl J med. 2001; 344:1917-1928.

Staat MA. Semin Resp Inf. 2002; 17:15

Collins PL: RSV, in :Fields Virology. 2001 1443-1485

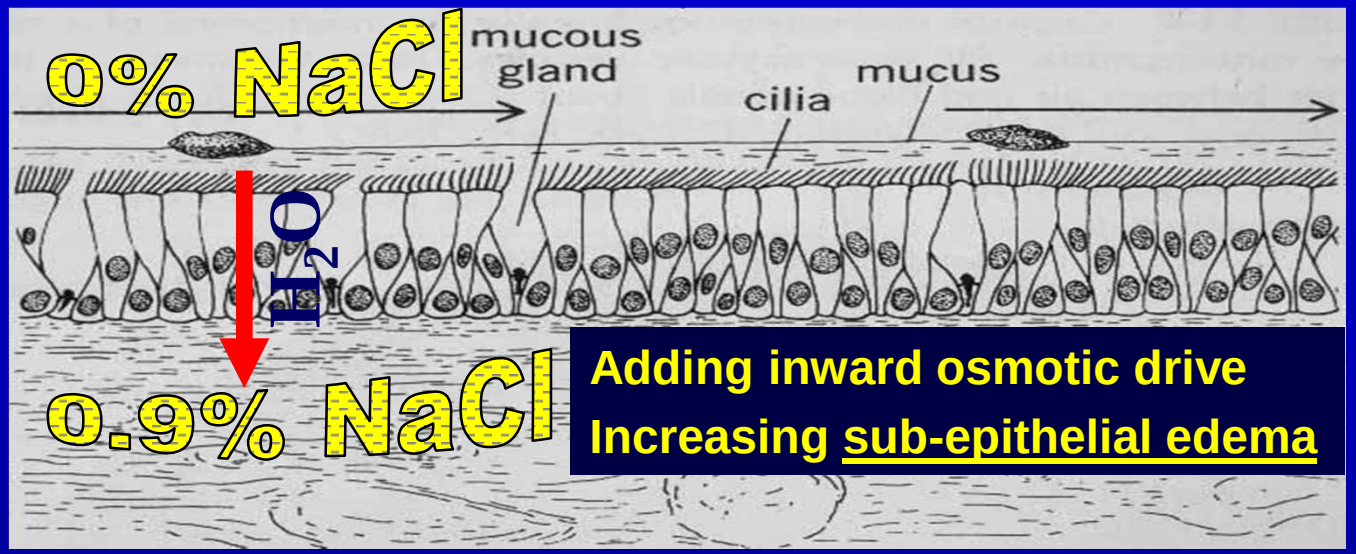
Treatment disappointments

- **Still, the mainstay of treatment for RSV - supplemental oxygen and hydration:**(*,**,*****)
- **RIBAVIRIN (inspired great hope): AAP stated: "*Ribavirin should be used"…**
  - **Based on - Smith DW. N Engl J Med. 1991; 325 : 14/14 Ventilated babies: Ribavirin V water-placebo → hospitalization↓ + ventilation↓ days.**
- **However, the ''beneficial'' effect of ribavirin could not be duplicated subsequently in PHI and only then was it appreciated that distilled water was not an appropriate placebo.**

* Hall CB. N Engl J med. 2001; 344:1917-1928. ** Darville T. Pediatrics in Review. 1998; 19:55-61
***** Schuh S. J Pediatr 2002;140:27

Treatment - disappointments

•ASL



- **AAP statement 1996: changed from "should be used" to-"Ribavirin may only be considered for children with serious underlying disorders" #PHI**

Mandelberg A, Pediatric Pulmonol. 2010

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	Should not be used routinely (individual trial may be justified)
INH steroids	Should not be used
Systemic corticosteroid	Should not be used
Leukotriene receptor antagonist	Should not be used
Monoclonal antibodies	Should not be used
Antibiotics	Should not be used
Antiviral – Ribavirin	Should not be used
Chest physiotherapy	Should not be used
Hypertonic saline	Should probably be used

Medicine used in respiratory diseases only seen in children

Hypertonic Saline in Viral Bronchiolitis and beyond – Does Hypertonic Saline "Hold Water?"

From Basic Science to Clinical Practice

Modern – 2013 understandings

A. Mandelberg

The Pediatric Pulmonary Unit.
Wolfson Medical Center, Holon, Israel

RSV-Bronchiolitis Treatment
(why we failed)

- These infants are wheezing but do not respond very well to anti-asthmatic treatment. - # Asthma 

Pathophysiology

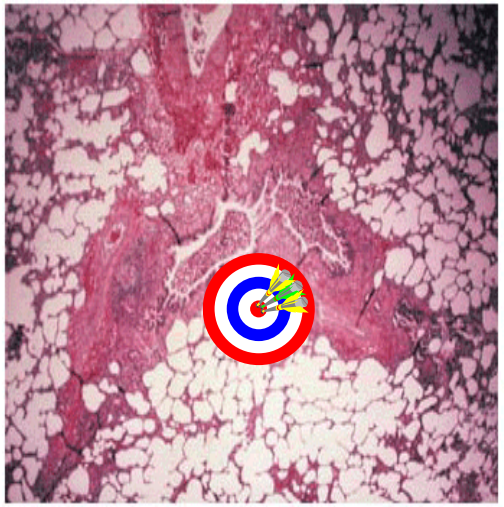
Bronchiolitis is a viral infection of the bronchiolar epithelium - subsequent: (*,)**

Profound sub-mucosal edema and mucus plugging

→

Increased secretion of mucin by exocytosis
Relative ASL Dehydration (↑mucin/water)

RSV- by ↑ATPases…absolute ASL dehydration (↑↑mucin/water↓) (***)



Bronchiolitis in an Infant with RSV (Hematoxylin and Eosin,

•Hall CB. N Engl J med. 2001; 344:1917-1928.

** Darville T. Pediatrics in Review. 1998; 19:55-61

•*** Randell SH AJRCMB 2006

Pathophysiology Oriented Treatment

- This called for a new treatment approach
- Aiming on Mucus clearance and **Hydration**
- Hypertonic saline 

Hydration is the dominant variable governing MC

- In mice model: ENaC ↑ (ASL **severe dehydration**) resulted in spontaneous **mortality of 60%** by 30 d. [Mall M, 2004; Nat Med]

- **So why CF patients "with lab evidence of severe ASL dehydration and ASL collapse" do not die so quickly?**
  - **Long periods of relative health during basal states.** [Bucher RC AJPCCM 2010]

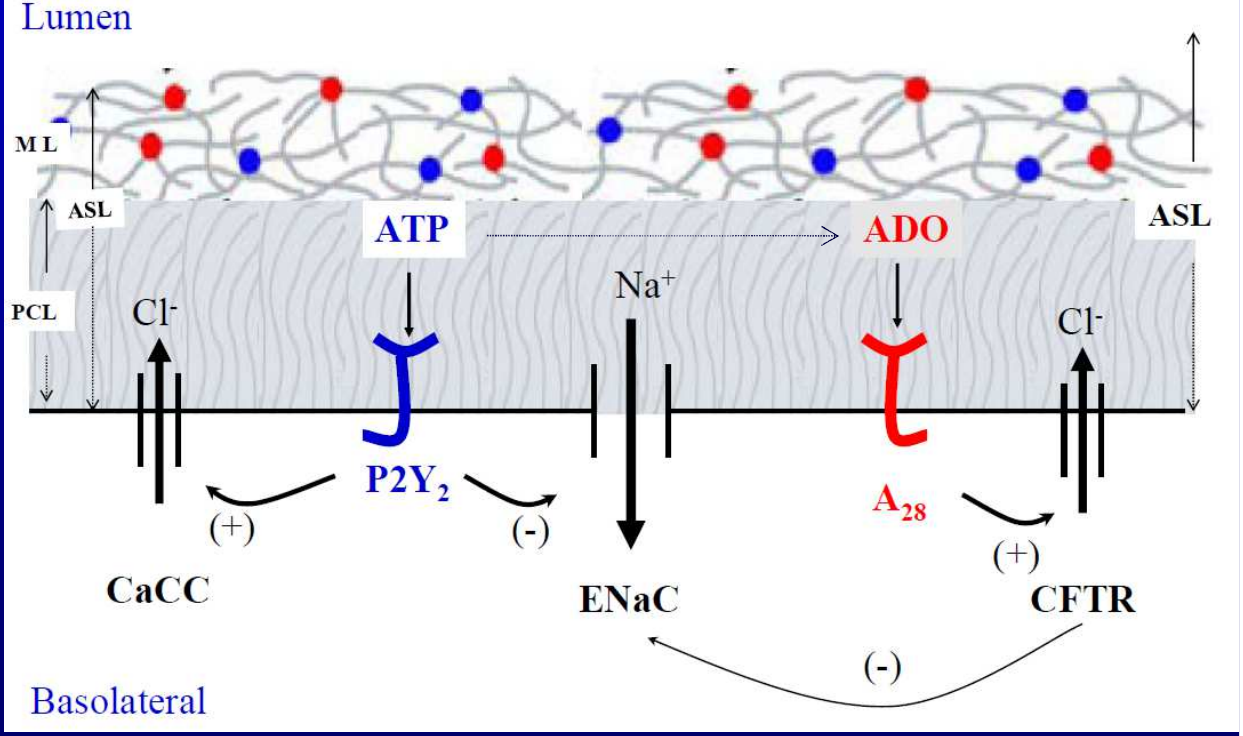
- **Back to BASIC SCIENCE**

Since airway epithelia are water permeable, water moves following Cl and Na to equalize electrolytes concentrations

- **ATP** and its metabolite **adenosine** are probably the most important regulators **hydrating** the ASL

CF cell – ↓CFTR - no response to adenosine is totally dependent on ATP.

Mandelberg A & Amirav I; Pediatric Pulmonol. 2010



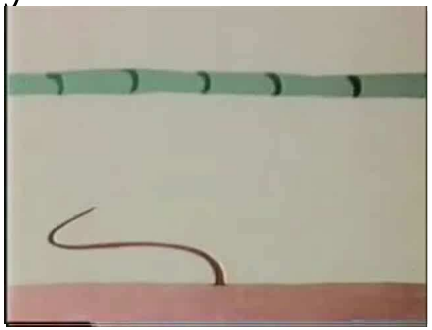
Randell SH; Am J Respir Cell Mol Biol, 2006

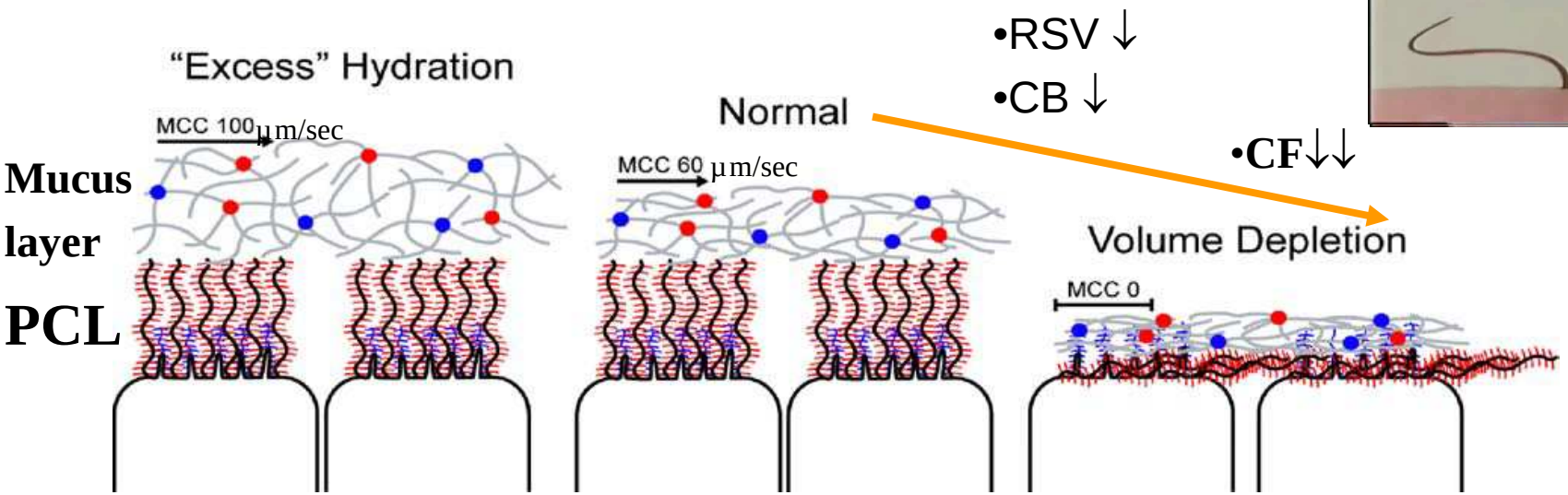
Mandelberg A & Amirav I; Pediatric Pulmonol. 2010

Rundell's model: A two separate layer structure

ASL (Airway Surface Liquid) = PCL + Mucus layer

PCL (Peri-Ciliary Liquid) = 7 micron

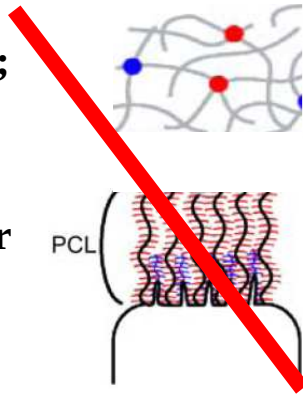




↓viscoelasticity

*collapses: PCL+Mucus Layer

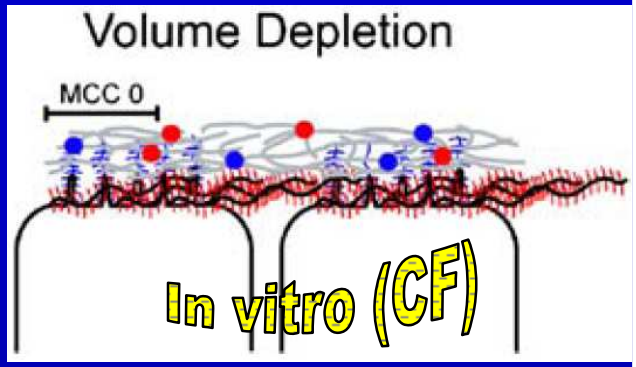
•The mucus layer acts as a <u>fluid reservoir</u>, it accepts or donates liquid to <u>maintain apposition</u> of the mucus layer inner surface with the tips of the cilia. Randell SH, 2006; AJRCMB



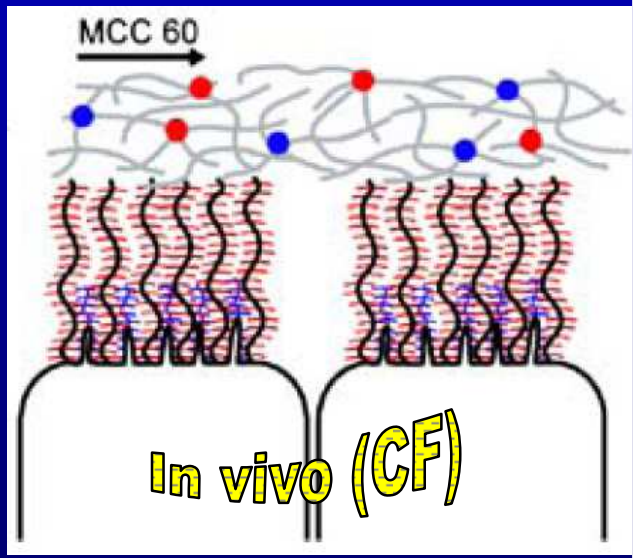
•However, in severe ASL dehydration, the ability of the mucus layer to "donate" water is <u>exhausted</u> – PCL COLLAPSE. [Tarran R, 2005;J Biol Chem]*

ASL, Old concept–New concept

- Old concept: In CF, (based on all **static** EP cultures) – complete collapse of ASL (PCL+ML) Everywhere.
- "**Why don't they die quickly**?"



- There is some wondrous compensatory mechanism - **in-vivo only.**
- Actually, **in vivo**, MCC in CF are functionally almost **normal** (at birth and in most "non-insulted" respiratory regions during life)



What is this compensatory mechanism - INVIVO only?

[Bucher RC AJPCCM 2010]

[Randell SH, 2006;Am J Respir Cell Mol Biol;35;20]

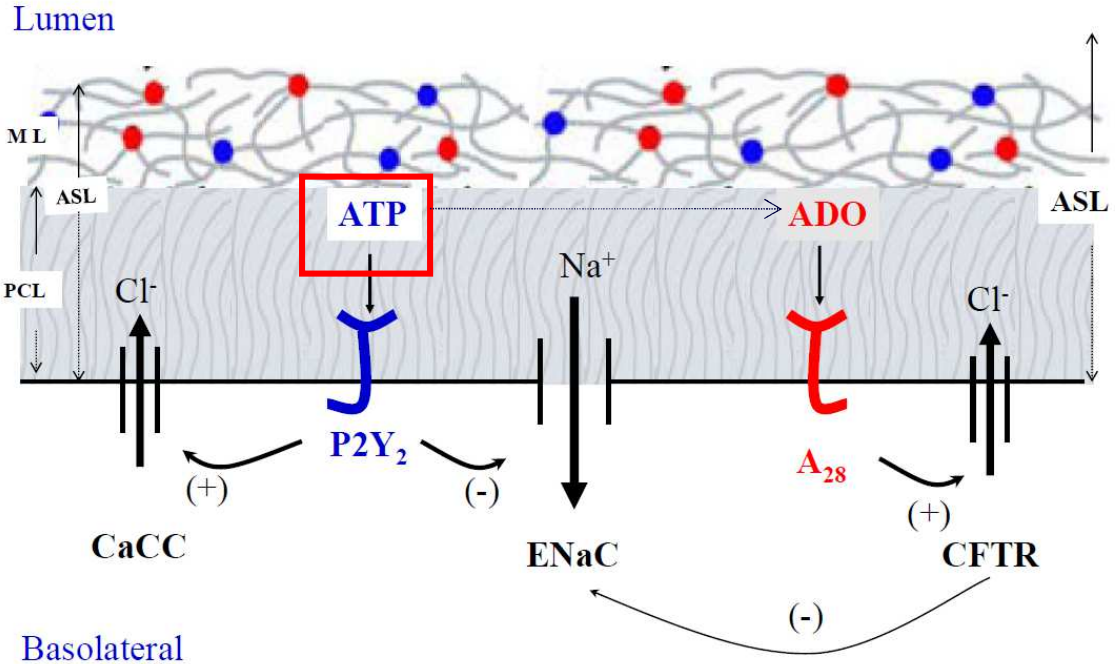
The answer is

ATP is paramount – but IN-VIVO only

- IN-VITRO - in static cell cultures - Extra-cellular ATP concentration is **negligible.**

- **However IN-VIVO** the ATP concentration **dramatically rises**

Mandelberg A & Amirav I; Pediatric Pulmonol. 2010



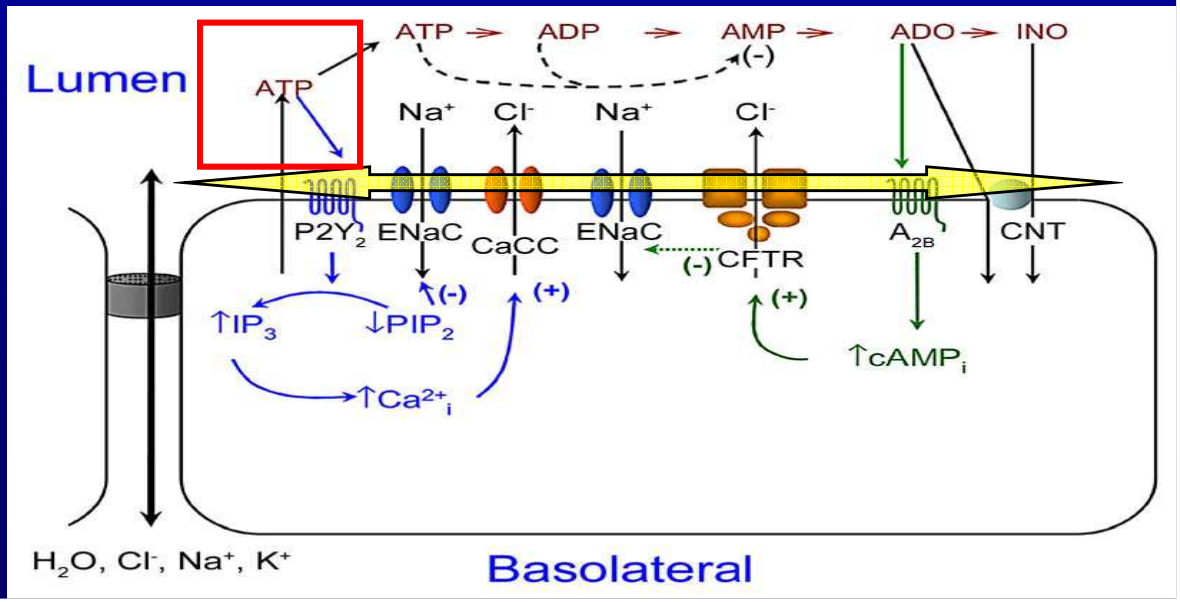
Why does ATP↑ rise INVIVO only?

* [Tarran R, 2005;J Biol Chem]

•Mechanotransduction: A mechanism by which cell converts mechanical stimulus into chemical activity

- SHEAR STRESS (τ =V*Q/t*I) ➡ *ATP* *(extra-cellular)*
- *[0.4-0.5 dyne/cm^2]* ~ the same in trachea, bronchi, bronchioles
- **Shear stress is parallel to the ASA**
- **Increases due to inspiratory and expiratory movements (acceleration/deceleration)**
- **Only in vivo. (Not in static tissue cultures).**

- *V* = shear force at that location
- *Q* = first moment of area
- *t* = thickness in the material perpendicular to the shear
- *I* = second moment of area of the cross section



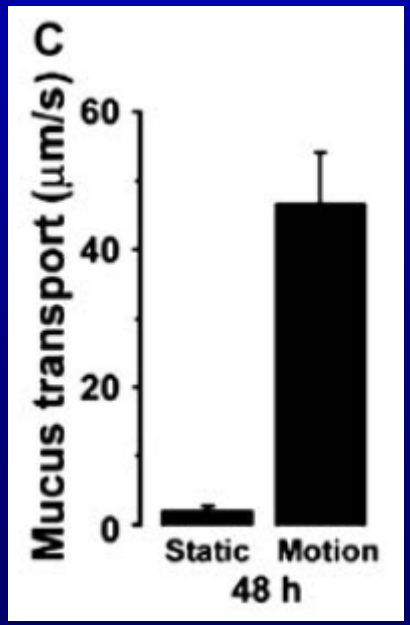
ATP = key signal during phasic motion (in vivo)

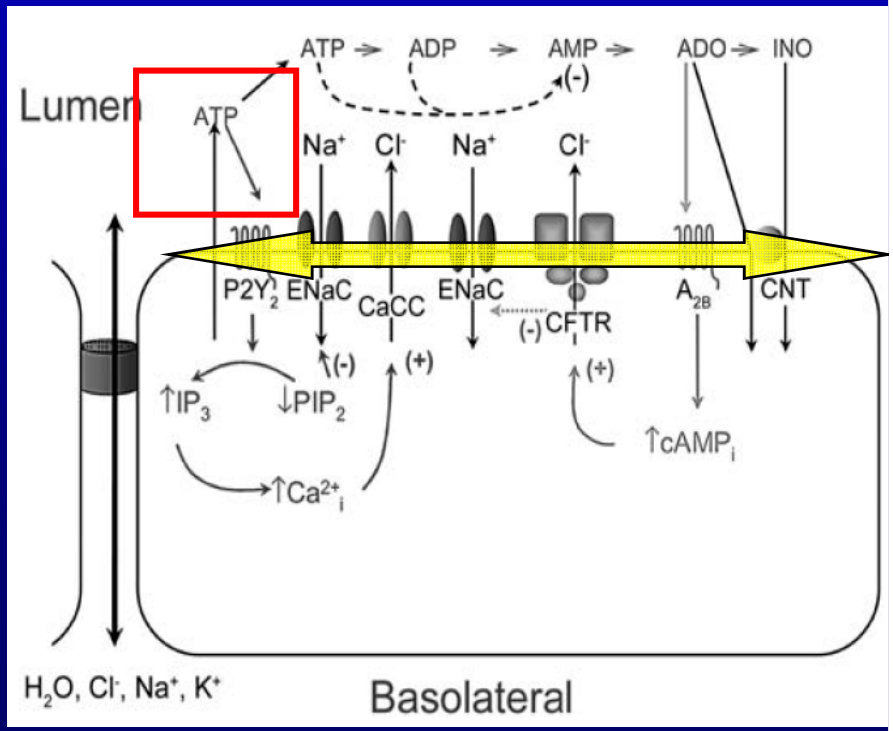
- Phasic motion of the airway wall (inflation/deflation – shear stress)-**ATP** ↑ and Adenosine ↑.- increases ASL Ht
- When **normal** human airway epithelial cells cultures were subjected to phasic shear stresses in moving heated incubators, in a rate similar to tidal breathing, the height of **ASL doubled**.

CF airway epithelial cultures

- Phasic motion

[Tarran R, 2005;J Biol Chem]



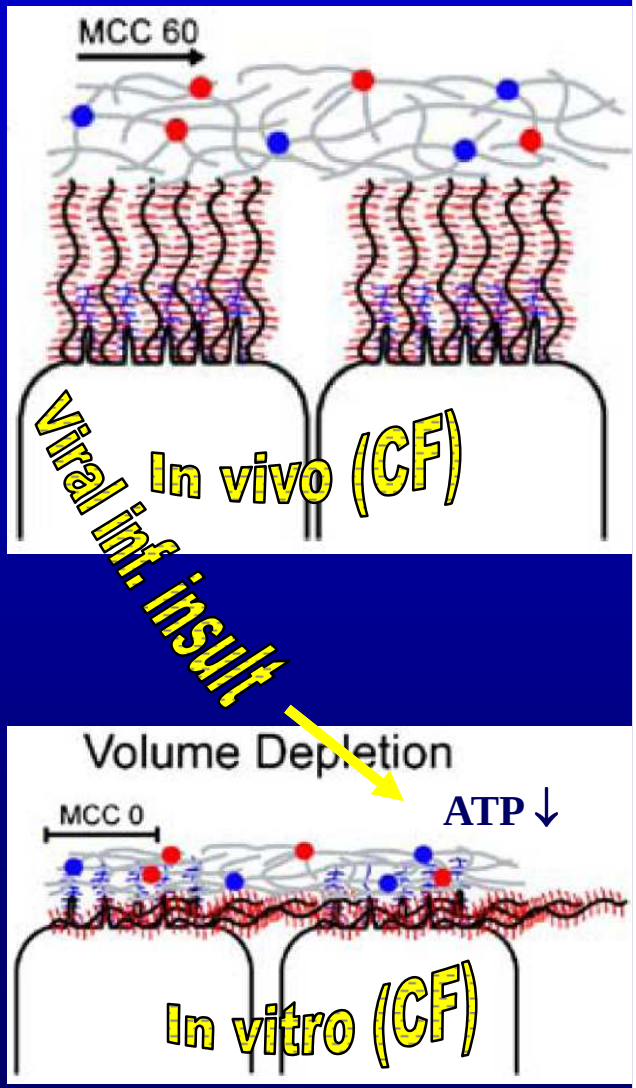


* **[Tarran R, 2005;J Biol Chem]**

ASL–VIRAL INFECTION INSULT

- Actually, **in vivo**, MCC in CF are functionally **normal** (at birth and in "non-insulted" respiratory regions during life)

- "Catastrophic" viral inf. Induce ASL dehydration and collapse



[Randell SH, 2006;Am J Respir Cell Mol Biol;35;20]

Disease exacerbations are due to intermittent catastrophic MC failures caused by VIRAL infections

- Viral infection up-regulates **ecto-ATPases, depleting extracellular ATP** – attenuating Cl secretion↓ to and increasing Na movement from↑ ASL - dehydration, MC↓.

- RSV infection in **CF epithelia** under **phasic motion** condition (simulating in vivo conditions) causes ASL collapse,
- This is true not only in **CF**. **In normal epithelia** under **phasic motion, RSV still** causes (although **less) ASL dehydration –** probably depending on the severity of the infection.

  [Tarran R, 2005;J Biol Chem]

Disease exacerbations are due to intermittent catastrophic MC failures caused by VIRAL infections

- Rundell: Therapy to maintain ASL **hydration** is important in viral exacerbation of **all** chronic airway diseases. [Rundell 2006;AJRCMB]

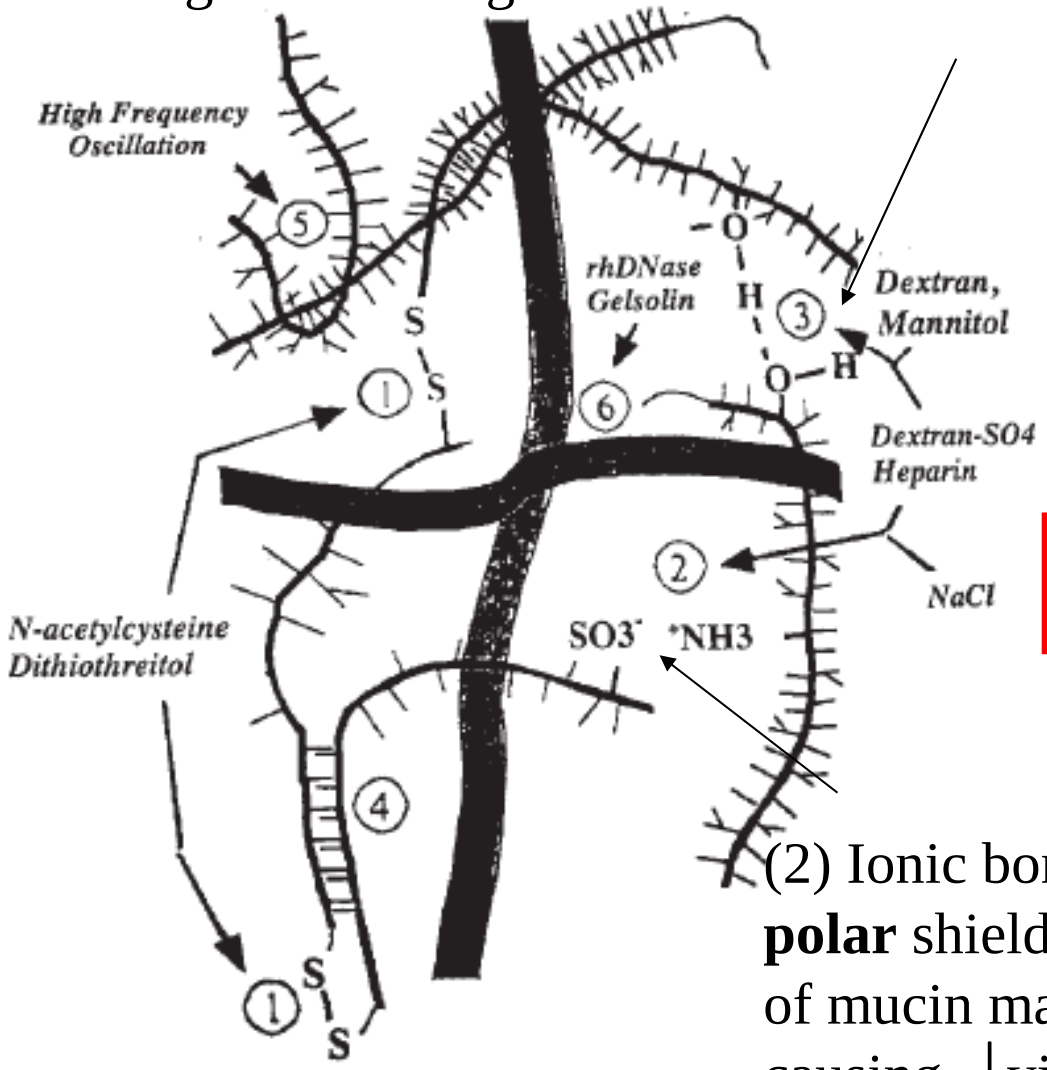
Possible mechanisms for MC ↑ of HS

1. **ASL Hydration and decreasing sub-epithelial edema by osmotic forces.**

1. מקטין בצקת בסאב מוקוזה
2. PCL = 7 מיקרון
3. שכבת מוקוס פחות יבשה

Mandelberg A, Pediatric Pulmonol. 2010

Types of bonds occurring in mucous gel



•$Na^{+}CL^{-}$

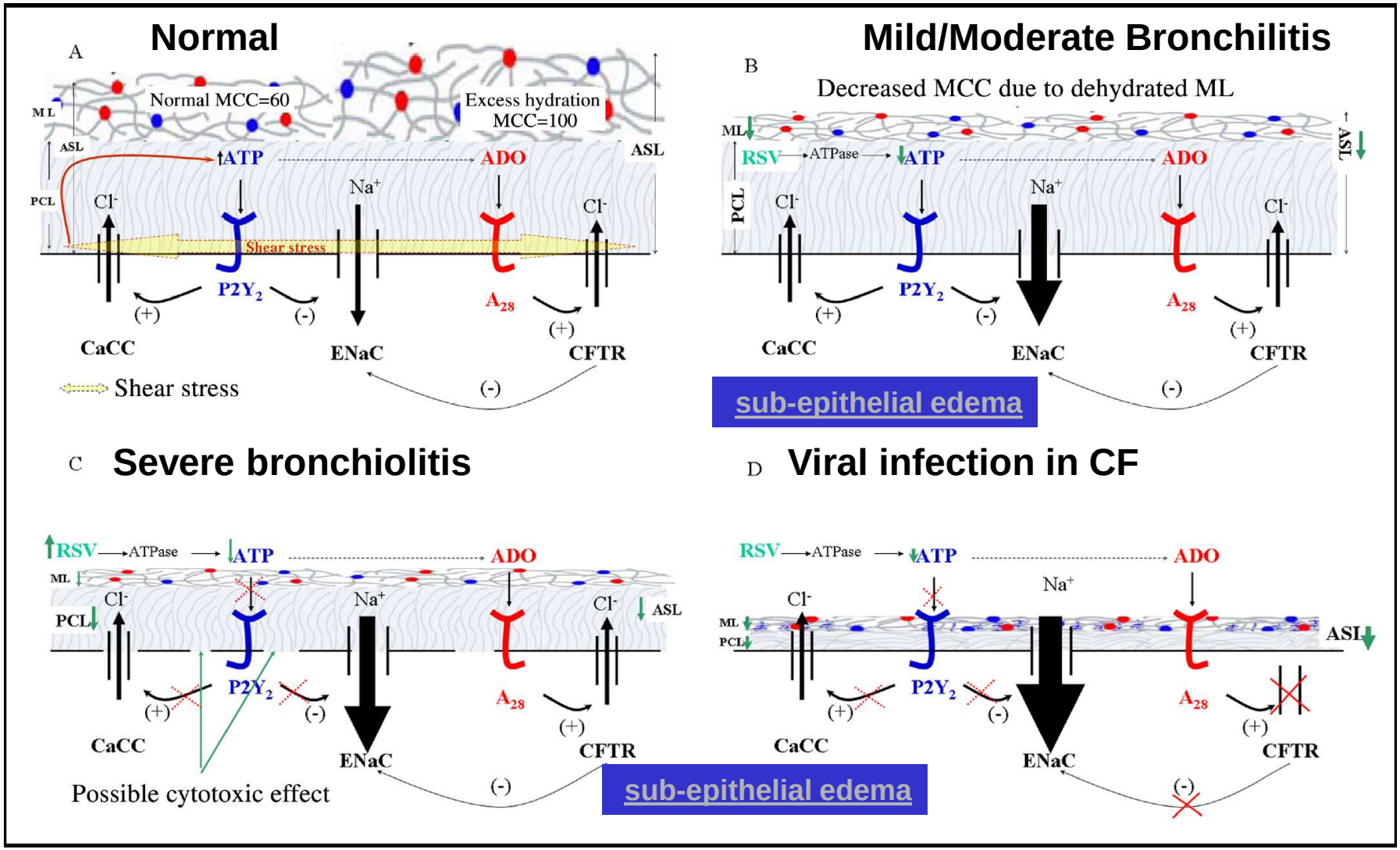
(2) Ionic bonds: **HS which is polar** shields the ionic bonds of mucin macromolecules causing ↓viscoelasticity

DAVISKAS E, J Aerosol Medicine-2006

Hypertonic Saline or High Volume Normal Saline for Viral Bronchiolitis: Mechanisms and Rationale

Pediatric Pulmonol. Jan 2010

Avigdor Mandelberg, MD[1]* and Israel Amirav, MD[2]



Clinical studies and outcomes using HS

Acute Viral Bronchiolitis

3% Hypertonic saline in RSV bronchiolitis

- **Objective:** To determine the utility of inhaled 3% hypertonic saline / epinephrine to shorten hospitalization stay and improve clinical scores in PHI hospitalized with acute viral bronchiolitis
- **Design:** Randomized, double blind, placebo-controlled trial.
  - 53 PHI - age (months): 2.9±2.1 with viral bronchiolitis
  - Received either - aerosol inhalation of 1.5 mg epinephrine / in 4mL saline–3% (treatment-group II, n=27).
  - Or aerosol inhalation of 1.5 mg epinephrine / in 4mL saline–0.9% (control-group I, n=25)
  - The above treatment was repeated 3 times every hospitalization day until discharge.

Mandelberg A et al. **CHEST** 2003; 123:481–487

RESULTS -Using 3% saline shortened-hospitalization stay by 25% * n=51

	Placebo	Treatment	
	0.9% NaCl	3% NaCl	P
	Group I (n = 24)	Group II (n = 27)	
DAYS	4±1.9	3±1.2	P<O.O5

*** $ 75,000,000 Direct Save / Year - USA**

Mandelberg A et al. **CHEST** 2003; 123:481–487

More experience – Second year + pooled meta-analysis of both years

- Second year experience: hospital stay↓ symptoms↓
- Pooled data: **N=93** (48 - epinephrine1.5mg/hypertonic saline 3% and 45 - epinephrine 1.5mg / normal saline combination). hospital stay↓ symptoms↓

Second year data	Placebo 0.9% NaCl Group I	Treatment 3% NaCl Group II	P
DAYS	3.5±1.7	2.6±1.4	P=O.O18

IMAJ 8:169-173, 2006

More experience

- **Design:** Randomized, double blind, placebo-controlled trial.
- 65 ambulatory infants
  - milder bronchiolitis.
  - 12.5±6 months old
- NaCl-3%/5mg-terbutaline (Treatment group) is more effective in decreasing symptoms as compared to NaCl-0.9%/terbutaline (Control group)

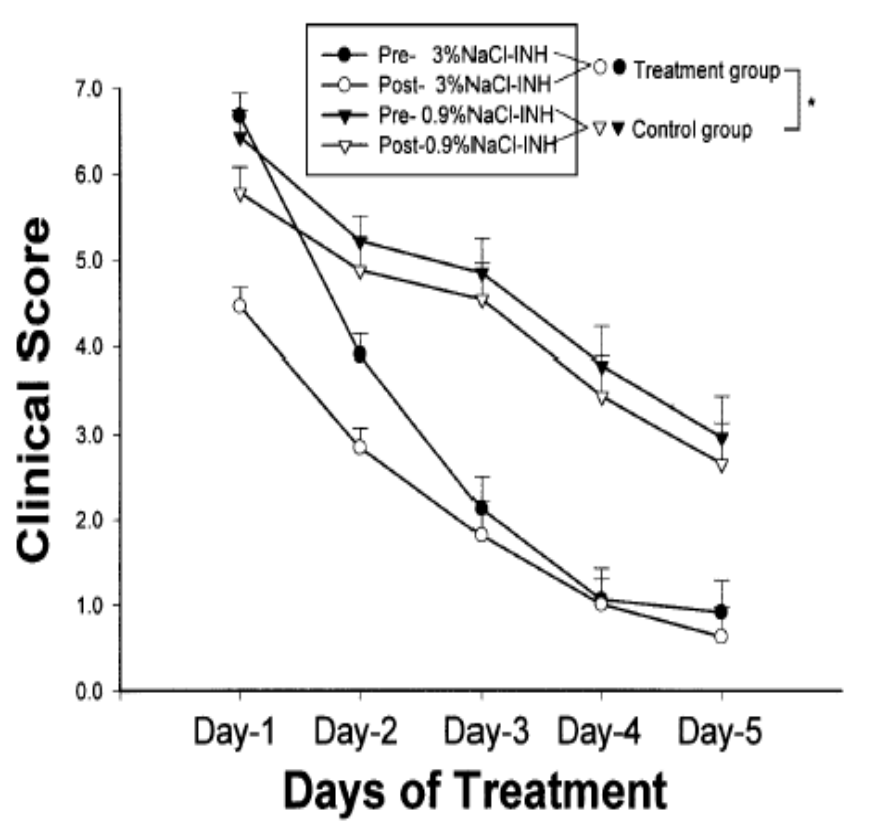


FIGURE 1. After the baseline measurement on the first day, the CS score differed significantly between the two groups: terbutaline/3% NaCl (treatment group) vs terbutaline/0.9% NaCl (control group). *$p < 0.005$. INH = inhalation.

Sarrell EM, Tal G, Witzling M, Somekh E, Houri S, Cohen HA, Mandelberg A. **CHEST 2002**

Nebulized Hypertonic Saline in the Treatment of Viral Bronchiolitis in Infants

Brian A. Kuzik, MD, MSc, FRCP(C), Samim A. Al Qadhi, MD, MBChB, Steven Kent, BSc(med), MD, FRCP(C), Michael P. Flavin, MB, MRCP(UK), FRCP(C), Wilma Hopman, MA, Simon Hotte, MD, and Sarah Gander, MD

Design: A prospective, randomized, double-blinded, controlled, multicenter trial (**3 centers – 3 Years** 2003-2006 study).

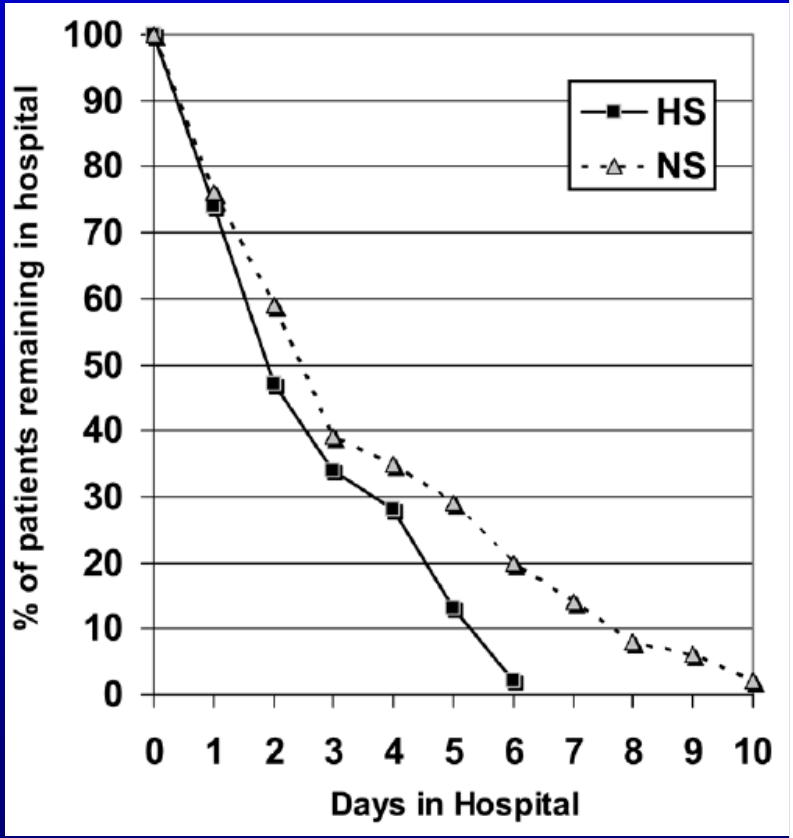
Nebulized **3% HS** (treatment group) or **0.9% NS** (control) - 9 INH / Day

Principal outcome : Length of stay (LOS)

Results: **26% reduction in LOS** to 2.6±1.9 days, compared with 3.5±2.9 days in the NS group (*P*=0.5)

The treatment was well tolerated, with no adverse effects

Conclusions: The use of nebulized 3% HS is a safe, inexpensive, and effective.



(J Pediatr 2007;151:266-70)

Cochrane Review - "The bible"

Nebulized hypertonic saline solution for acute bronchiolitis in infants

- First published in **2008**, Issue 4
- Last published in **2013**, Issue 7 - (adding more studies to a new full meta-analysis)
- **no change to conclusions**.

Cochrane Review 2013

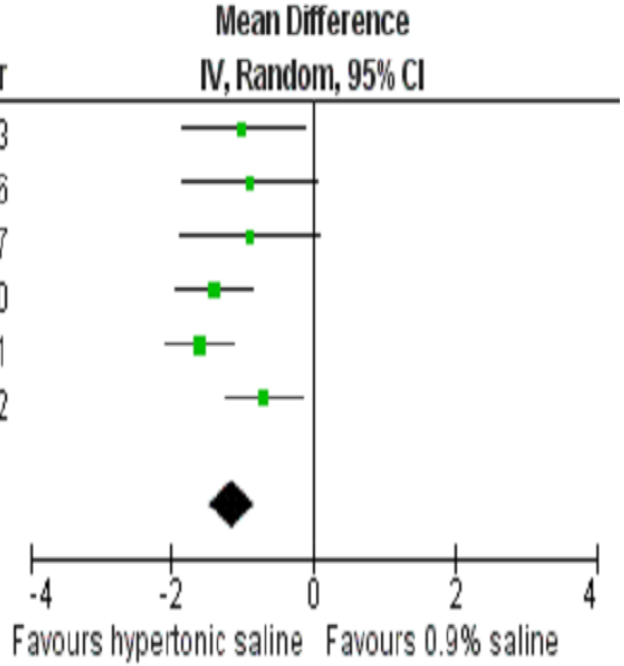
Nebulized hypertonic saline solution for acute bronchiolitis in infants

Figure 2. Hypertonic saline versus 0.9% saline: length of hospital stay (days)

Study or Subgroup	Hypertonic saline Mean	SD	Total	0.9% saline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mandelberg 2003	3	1.2	27	4	1.9	25	11.5%	-1.00 [-1.87, -0.13]	2003
Tal 2006	2.6	1.4	21	3.5	1.7	20	9.9%	-0.90 [-1.86, 0.06]	2006
Kuzik 2007	2.6	1.9	47	3.5	2.9	49	9.5%	-0.90 [-1.88, 0.08]	2007
Luo 2010	6	1.2	50	7.4	1.5	43	21.6%	-1.40 [-1.96, -0.84]	2010
Luo 2011	4.8	1.2	57	6.4	1.4	55	25.6%	-1.60 [-2.08, -1.12]	2011
Giudice 2012	4.9	1.3	52	5.6	1.6	54	21.8%	-0.70 [-1.25, -0.15]	2012
Total (95% CI)			**254**			**246**	**100.0%**	**-1.15 [-1.49, -0.82]**	

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 7.18$, $df = 5$ ($P = 0.21$); $I^2 = 30\%$

Test for overall effect: $Z = 6.83$ ($P < 0.00001$)

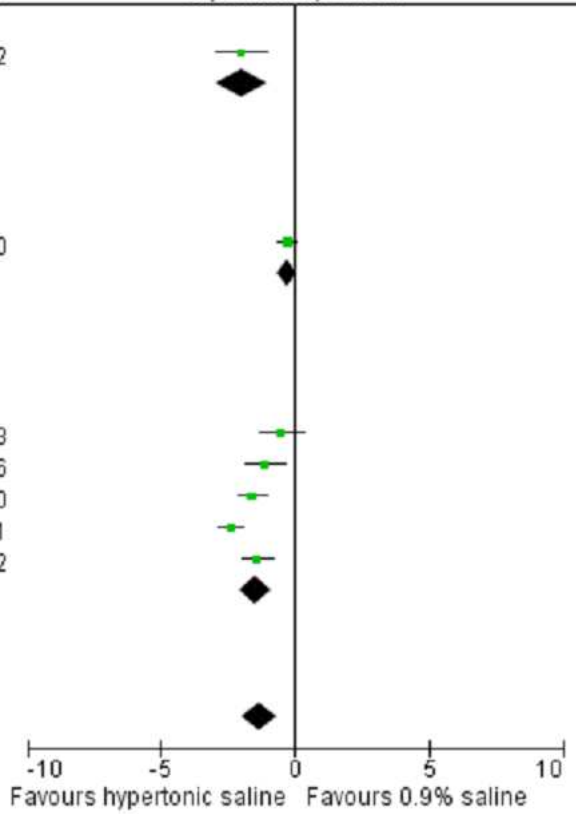


Cochrane Review 2013

Nebulized hypertonic saline solution for acute bronchiolitis in infants

Figure 5. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 2

Study or Subgroup	Hypertonic saline Mean	SD	Total	0.9% saline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.4.1 Outpatients									
Sarrell 2002	2.77	1.4	33	4.77	2.31	32	12.6%	-2.00 [-2.93, -1.07]	2002
Subtotal (95% CI)			**33**			**32**	**12.6%**	**-2.00 [-2.93, -1.07]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 4.21 (P < 0.0001)									
1.4.2 Emergency department patients									
Al-Ansari 2010	3.85	1.16	115	4.12	1.11	56	15.7%	-0.27 [-0.63, 0.09]	2010
Subtotal (95% CI)			**115**			**56**	**15.7%**	**-0.27 [-0.63, 0.09]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.47 (P = 0.14)									
1.4.3 Inpatients									
Mandelberg 2003	6.41	1.4	24	6.92	1.62	25	13.1%	-0.51 [-1.36, 0.34]	2003
Tal 2006	5.35	1.3	20	6.45	1	20	13.9%	-1.10 [-1.82, -0.38]	2006
Luo 2010	2.2	1.1	50	3.8	1.5	43	14.9%	-1.60 [-2.14, -1.06]	2010
Luo 2011	3.5	1.1	57	5.9	1.5	55	15.2%	-2.40 [-2.89, -1.91]	2011
Giudice 2012	6.8	1.4	52	8.2	1.7	54	14.6%	-1.40 [-1.99, -0.81]	2012
Subtotal (95% CI)			**203**			**197**	**71.7%**	**-1.45 [-2.06, -0.85]**	
Heterogeneity: Tau² = 0.36; Chi² = 18.94, df = 4 (P = 0.0008); I² = 79%									
Test for overall effect: Z = 4.74 (P < 0.00001)									
Total (95% CI)			**351**			**285**	**100.0%**	**-1.32 [-2.00, -0.64]**	
Heterogeneity: Tau² = 0.73; Chi² = 56.79, df = 6 (P < 0.00001); I² = 89%									
Test for overall effect: Z = 3.81 (P = 0.0001)									
Test for subgroup differences: Chi² = 18.98, df = 2 (P < 0.0001), I² = 89.5%									



Cochrane Review 2013

Nebulized hypertonic saline solution for acute bronchiolitis in infants

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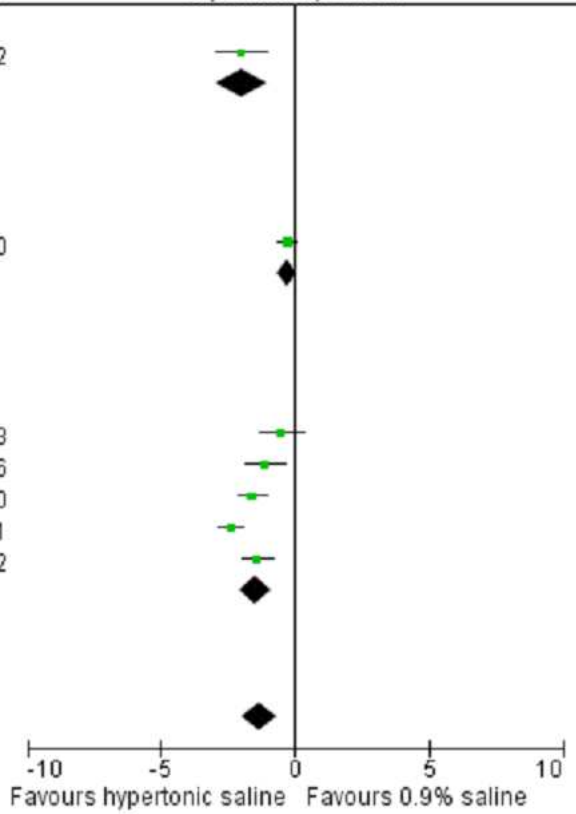

Cochrane Review - "The bible"

Nebulized hypertonic saline solution for acute bronchiolitis in infants

- First published in **2008**, Issue 4
- Last published in **2013**, Issue 7 - **no change to conclusions**.

Authors' conclusions

Current evidence suggests nebulised 3% saline may significantly reduce the length of hospital stay among infants hospitalised with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.

PLAIN LANGUAGE SUMMARY

The establishment of a therapeutic role for hypertonic saline solution may provide a cheap and effective therapy for these patients.

We included 11 randomised trials involving 1090 infants with mild to moderate bronchiolitis. All but one of the 11 trials are considered as high-quality studies with low risk of error (i.e. bias) in their conclusions. Meta-analysis suggests that nebulised hypertonic saline could lead to a reduction of 1.2 days in the mean length of hospital stay among infants hospitalised for non-severe acute bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations. No significant short-term effects (at 30 to 120 minutes) of one to three doses of nebulised hypertonic saline were observed among emergency department patients. However, more trials are needed to address this question. There were no significant adverse effects noted with the use of nebulised hypertonic saline when administered along with bronchodilators.

Given the clinically relevant benefit and good safety profile, nebulised hypertonic saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis.

נייר עמדה (2012)

- נייר עמדה מטעם האיגוד הישראלי לרפואת ילדים, האיגוד הישראלי לרפואת ריאות ילדים והאיגוד הישראלי לאירוזולים ברפואה.

- ממליצים על טיפול עם מלח היפרטוני 3% או 5% (עם בטה אגוניסטים) בחולים מאושפזים ובחולים אמבולטורים עם ברונכיוליטיס ויראלי.

- בחולים מאושפזים מקצר אשפוזים ובחולים אמבולטורים משפר סימפטומים – CS.

Beyond

Does Hypertonic Saline

Further "Hold Water?" in Older "asthmatic" children

New "hot" data

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hypertonic Saline and Acute Wheezing in Preschool Children

Dorit Ater, Hanita Shai, Bat-El Bar, Nir Fireman, Diana Tasher, Ilan Dalal, Ami Ballin and Avigdor Mandelberg

Pediatrics; originally published online May 21, 2012;
DOI: 10.1542/peds.2011-3376

WHAT'S KNOWN ON THIS SUBJECT: Most acute wheezing episodes in preschool children are associated with rhinovirus, which decreases extracellular adenosine triphosphate levels, leading to airway surface liquid dehydration and submucosal edema, which cause failure of mucus clearance. These children respond poorly to available treatments.

WHAT THIS STUDY ADDS: Hypertonic saline inhalation, a pro–airway surface liquid hydration therapy, significantly decreases both length of stay by 33% (1 day) and the absolute risk of hospitalization by 30% in preschool children presenting with acute wheezing episode to the emergency department.

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Oral Dexamethasone for Bronchiolitis: A Randomized Trial

Khalid Alansari, Mahmoud Sakran, Bruce L. Davidson, Khalid Ibrahim, Mahmoud Alrefai and Ibrahim Zakaria

Pediatrics 2013;132;e810; originally published online September 16, 2013;

WHAT IS KNOWN ON THIS SUBJECT: Some infants presenting with bronchiolitis are later diagnosed with asthma. Corticosteroid treatment of all infants with bronchiolitis is not clearly efficacious.

WHAT THIS STUDY ADDS: We used infant eczema or asthma history in a first-degree relative to select patients with bronchiolitis for dexamethasone or placebo blinded treatment. Dexamethasone treatment of 5 days led to significantly earlier readiness for discharge from infirmary treatment.

- **Asthma predictive index positive = Selective population**

PEDIATRICS®
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Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial

AUTHORS: Mina M. Chowdhury, MB, ChB,[a] Sheila A. McKenzie, FRCP,[b] Christopher C. Pearson, FRACP,[c] Siobhan Carr, FRCPCH,[b] Caroline Pao, MRCP,[b] Arvind R. Shah, FRCPCH,[c] Elizabeth Reus, MSc,[a] Joseph Eliahoo, PhD,[e] Fabiana Gordon, PhD,[e] Hubert Bland, MB, ChB,[f] and Parviz Habibi, PhD, FRCP, FRCPCH[a]

WHAT'S KNOWN ON THIS SUBJECT: Bronchiolitis, a leading cause of infant hospitalization, has few proven treatments. A few small studies have reported the beneficial effects of a mixture of 21% oxygen + 79% helium (Heliox). The 2010 Cochrane Review concluded that additional large randomized controlled trials were needed to determine the therapeutic role of Heliox in bronchiolitis.

WHAT THIS STUDY ADDS: The Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE) trial is the largest multicenter randomized controlled trial to date to investigate the efficacy of Heliox in acute bronchiolitis. The delivery method for Heliox therapy was found to be crucial to its efficacy.

CONCLUSIONS: Heliox therapy does not reduce LoT unless given via a tight-fitting facemask or CPAP. Nasal cannula heliox therapy is ineffective.

Pediatrics 2013;131:661–669

The NEW ENGLAND JOURNAL of MEDICINE

Epinephrine and Dexamethasone in Children with Bronchiolitis

Amy C. Plint

N Engl J Med 2009;360:2079-89.

800 infants – Pediatric Emergency Dep.

Outcome – hospitalization rate within 7 D

Placebo N=200	26.4%	NS
Dexamethazone–1mg/kg and 0.6mg/kg-5 days	25.6%	NS
Epinephrine 1:1000 - 3cc	23.7%	NS
Dexamethazone + Epinephrine	17.1%	p=0.07

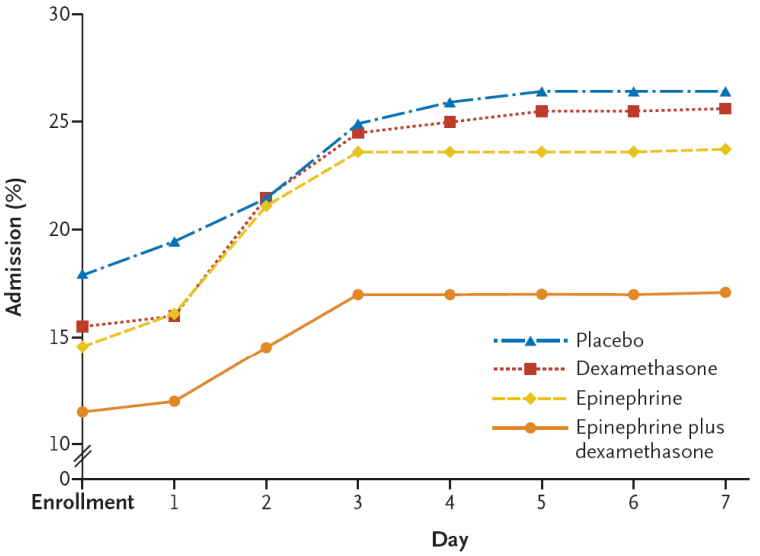


Figure 3. Cumulative Admissions during the First 7 Days after the Initial Emergency Department Visit, According to Study Group.

Enrollment data represent all patients admitted at their initial visit to the emergency department, and data for day 1 represent patients admitted within 24 hours of this visit.

Dexamethazone Cumulative dose = 4mg/kg/6days

9% (N=18) preventive hospitalization

Cochrane Review 2013

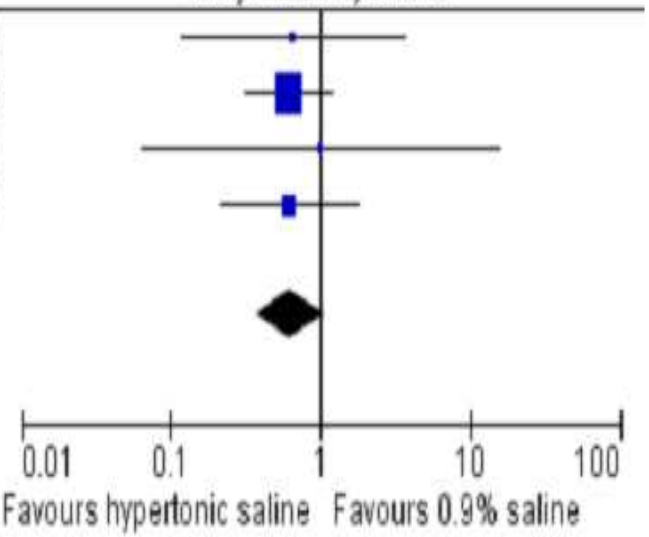
Nebulized hypertonic saline solution for acute bronchiolitis in infants

Figure 3. Hypertonic saline versus 0.9% saline: rate of hospitalisation.

Study or Subgroup	Hypertonic saline Events	Total	0.9% saline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Sarrell 2002	2	33	3	32	9.3%	0.65 [0.12, 3.62]	2002
Grewal 2009	8	23	13	23	62.4%	0.62 [0.32, 1.20]	2009
Anil 2010	1	75	1	74	3.6%	0.99 [0.06, 15.48]	2010
Ipek 2011	5	60	8	60	24.6%	0.63 [0.22, 1.80]	2011
Total (95% CI)		**191**		**189**	**100.0%**	**0.63 [0.37, 1.07]**	
Total events	16		25				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 3 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 1.72$ ($P = 0.09$)



37% reduction in hospitalization. However p=0.9

Noa – 3M 0ld baby

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.**
- **Anamnesis: Premature-28W 1500gr, ventilated for 5 days, needed oxygen for 50 days. Family-no atopy**
- **CXR: Over-inflation, plate like atelectasis.**
- **= Previously BPD (=CLD of NB)**

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	
INH steroids	
Systemic corticosteroid	
Leukotriene receptor antagonist	
Monoclonal antibodies	
Antibiotics	
Antiviral – Ribavirin	
Chest physiotherapy	
Hypertonic saline	

Medicine used in respiratory diseases only seen in children

Noa – 3M 0ld baby

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.**
- **Anamnesis: Post BMT 3 2 weeks ago. Family-no atopy.**
- **CXR: Over-inflation, plate like atelectasis.**
- **= Immune deficient baby**

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	
INH steroids	
Systemic corticosteroid	
Leukotriene receptor antagonist	
Monoclonal antibodies	
Antibiotics	
Antiviral – Ribavirin	
Chest physiotherapy	
Hypertonic saline	

Medicine used in respiratory diseases only seen in children

Dafna – 7M 0ld baby

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.**
- **Anamnesis: Previously recurrent wheezing.**
  Family-mother-asthma+allergy.
- **CXR: Over-inflation, plate like atelectasis.**
- **= Previously Infantile asthma**

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	
INH steroids	
Systemic corticosteroid	
Leukotriene receptor antagonist	
Monoclonal antibodies	
Antibiotics	
Antiviral – Ribavirin	
Chest physiotherapy	
Hypertonic saline	

Medicine used in respiratory diseases only seen in children

Shiri – 7M 0ld baby

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: No Dyspnea, wheezing, mild rales, 40 BPM, no retractions.**
- **Anamnesis: Mother says “wheezing from birth, less at night. Family-no atopy.**
- **CXR: Over-inflation, plate like atelectasis.**
- **= Persistent wheezing**

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	
INH steroids	
Systemic corticosteroid	
Leukotriene receptor antagonist	
Monoclonal antibodies	
Antibiotics	
Antiviral – Ribavirin	
Chest physiotherapy	
Hypertonic saline	

Medicine used in respiratory diseases only seen in children

Yosi – 2.5Y 0ld boy

- **Presenting: Fever, rhinitis, cough for 2 days**
- **Exam: Dyspnea, wheezing,, 60 BPM, retractions.**
- **Anamnesis: Never wheezed, no family allergy/asthma**
- **CXR: Over-inflation, plate like atelectasis.**
- **= Viral triggered wheezing**

ERS TASK FORCE

W. Lenney Eur Respir J 2009; 34: 531–551

TABLE 3 Treatment of acute viral bronchiolitis

Recommendations

Bronchodilators	
INH steroids	
Systemic corticosteroid	
Leukotriene receptor antagonist	
Monoclonal antibodies	
Antibiotics	
Antiviral – Ribavirin	
Chest physiotherapy	
Hypertonic saline	

Medicine used in respiratory diseases only seen in children

Hypertonic Saline in Viral Bronchiolitis and beyond – Does Hypertonic Saline "Hold Water?"

From Basic Science to Clinical Practice

Modern – 2013 understandings

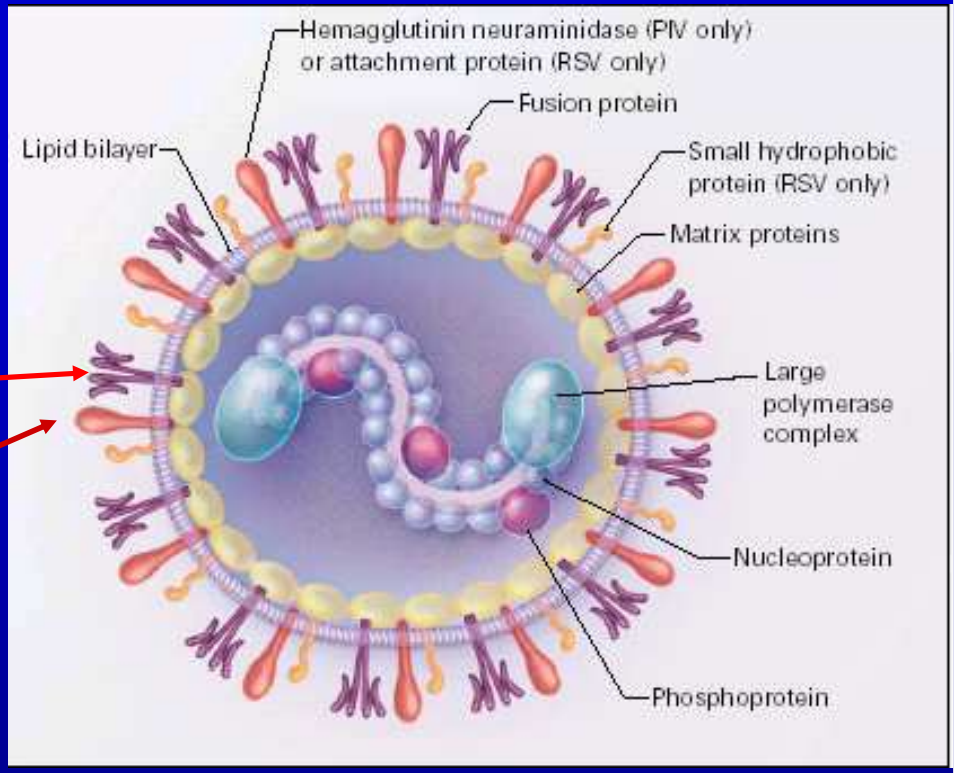
A. Mandelberg

The Pediatric Pulmonary Unit.
Wolfson Medical Center, Holon, Israel

Viruses (n - increase with molecular diagnosis)

- Respiratory syncytial virus (RSV) is the most common approxymately – 80%
- Rhinovirus
- Parainfluenza virus
- Human metapneumovirus
- Influenza virus
- Adenovirus
- Coronavirus
- Human bocavirus
- Using molecular diagnostics, more than one virus may occur in up to one-third of young children hospitalized with bronchiolitis
-

- **family: paramixoviridae, enveloped, ss-RNA,**
- **two surface glycoproteins:**
  - **F: fusion, conserved**
    - **T1 response**
  - **G: attachment,**
    - **T2 response**
  - **strains A and B**



Hall CB. N Engl J med. 2001; 344:1917-1928. **Staat MA. Semin Resp Inf. 2002; 17:15
***Collins PL: RSV, in :Fields Virology. 2001 1443-1485

RSV burden

- **Virtually all children become infected with RSV within two years after birth, (*,****)**
  - **50%- infected twice (****)**
- **0.5-2% require hospitalization (*,**,****)**
  - **2/3 of the cost of annual RSV epidemics result of hospitalization (*)**
  - **N↑ In Infants < 1 y: annual hospitalization/1000 ↑ 2.4-fold, from 12.9 in 1980 to 31.2 in 1996 (***)**
- **In 1985 - 100,000 children were hospitalized with RSV infection in USA = $300 million. (*).**

•*Hall CB. N Engl J med. 2001; 344:1917-1928. **National Center of Infectious Diseases 2002
•*** Shay DK. JAMA 1999; 282:1440 ****Collins PL: RSV, in :Fields Virology. 2001 1443-1485

RSV burden - Risk factors

- **1% of PHI are hospitalized = largest "risk group" (up to 75% of hospitalized babies)**
  - **Calls for genetic/immunological markers**

- **Age < 6 weeks**
- **Premature infants**
- **BPD / CLD, CF**
- **Congenital Heart Disease**
- **Immunosuppressive disease / therapy**
- **Underlying conditions:**
  - **Cong anomaly, CP, metabolic Disease**

* Hall CB. N Engl J med. 2001; 344:1917-1928. **Staat MA. Semin Resp Inf. 2002; 17:15