Special CRS cases: AFRS, ASA triad, CF

Rodney J. Schlosser, MD
Disclosure

- Consultant: BrainLAB, Olympus, Sunovion
- Grants: NeilMed, Medtronic, Optinose, Arthrocare
- Text book

- Essentially all topical therapies are off label
Learning Objectives

• To understand the evidence for various medical and surgical treatment options for AFRS, ASA triad and CF

• To understand the impact of sinonasal inflammation upon the lower airway
Can we use EBM to take a patient from this....
....to this (ASA triad 3.5 years postop)?
A few caveats...

• Not all polyps are the same!!
  – Individual patient differences
  – Optimal Rx?
  – Cost
  – Compliance
Allergic Fungal Rhinosinusitis with Polyps!
**CRS pathophysiology**

**Mucosal Inflammation**
- Type 1 Hypersensitivity
- T-Cell mediated eosinophilia
- Leukotriene dysfunction (Aspirin sensitive)
- Local IgE mediated
- Super-antigen/bacterial by-product
- Environmental damage

- Mucosal ulceration leads to greater infection and colonization
- Intrinsic mucosal inflammation causes secondary mucociliary dysfunction through direct injury and mucus changes
- Failure of mechanical & innate immune protection. Activation of pro-inflammatory acquired immune responses
- Failure of mucus clearance leads to greater exposure to eosinophilic mucin and mucosal injury by eosinophilic mucin

**Local microbial community**
- Bacterial planktonic
- Bacterial biofilm
- Fungal
- Viral

- Infection damages cilia and their function
- Poor or absent mucociliary function fails to protect mucosa from colonization

**Muco-ciliary dysfunction**
- Direct cilia damage
- Mucus rheologic distortion
- Structural/genetic abnormalities
- Secondary to gross oedema/ostial obstruction

Harvey RJ et al, J OHNS 2009
# Systemic treatments for CRSwNP

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO abx &lt;4 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO abx &gt;12 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO antifungals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti leukotrienes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti IgE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA desensitization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Systemic treatments for CRSwNP

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<tr>
<th>Therapy</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO steroids</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>PO abx &lt;3-4 wks</td>
<td>Ib and Ib(-)</td>
<td>C</td>
</tr>
<tr>
<td>PO abx &gt;12 wks</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>PO antifungals</td>
<td>Ib (-)</td>
<td>A</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Anti leukotrienes</td>
<td>Ib(-)</td>
<td>A</td>
</tr>
<tr>
<td>Anti IgE</td>
<td>Ib and Ib(-)</td>
<td>C</td>
</tr>
<tr>
<td>ASA desensitization</td>
<td>II</td>
<td>C</td>
</tr>
</tbody>
</table>

Fokkens W et al EPOS 2012
If systemic medical therapies fail, what’s the evidence for surgery in CRSwNP?
Concepts of Endoscopic Sinus Surgery (ESS)

- Enlarge natural openings
- Preserve lining and natural structures
- Remove fungal/bacterial debris
- Aggressive topical therapies postoperatively
Concepts of ESS

Pre-op

Post-op
CRS & changing role of surgery?

Mucosal inflammation

- Remove polyps & inflammatory mucin
- Topical steroids

**Microbial community**
- Remove organisms/biofilm
- Topical antimicrobials

**Mucociliary clearance**
- Eliminate ostial obstruction
- Topical MC stimulants

Rheologic properties
- Obstructed os

**Acquired dysfunction**
- Th2 skewing
- IgE/LTs
- ASA triad
Topical therapies

- Delivery to anatomic site (target sinus)
- The proper active agent
- Impact upon lower airway??
Bewildering variety?
Prescription versions
What we don’t want to become
Topical drug considerations
Macro factors

- Surgical state
- Delivery device & volume
- Patient position
# Impact of surgery

<table>
<thead>
<tr>
<th>Surgical State</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unoperated</td>
<td>No consistent delivery regardless of device</td>
</tr>
<tr>
<td>Balloon</td>
<td>Sphenoid ↑, Frontal, Maxillary ↓</td>
</tr>
<tr>
<td>ESS</td>
<td>Delivery increases especially with large volume</td>
</tr>
<tr>
<td>Endoscopic Lothrop or medial maxillectomy</td>
<td>Possible benefit</td>
</tr>
</tbody>
</table>

- Cadaver (n=5) and human studies (n=3)
- Conclusion: ESS optimal, critical os size 4-5 mm

Thomas III, WT et al, IFAR 2012 (submitted)
Critical os size

Brenner et al, IFAR 2012
What type of surgery is needed for postop topical therapies?

- Balloon
- MIST
- FESS
Ventilation $\neq$ access for topical treatments
Prior to successful ESS, topical therapies are ONLY nasal cavity treatments
Access for topical treatments
## Impact of device

<table>
<thead>
<tr>
<th>Device</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray/Drops</td>
<td>Little sinus distribution with either technique. Some delivery to olfactory cleft/MT that may be position dependent.</td>
</tr>
<tr>
<td>Atomizer/Nebulizer</td>
<td>Pulsating aerosols/nebs with some limited distribution to sinuses</td>
</tr>
<tr>
<td>Squeeze bottle/Neti Pot</td>
<td>Larger volumes have best distribution</td>
</tr>
</tbody>
</table>

- Cadaver (n=5) and human studies (n=15)
- **Recommend for**: Large volume devices post ESS
- **Recommend against**: Low volume devices do not consistently reach sinuses

Thomas III, WT et al, IFAR 2012 (submitted)
Sprays
Combined effects of surgery & volume

Harvey RJ et al, OHNS 2009
### Impact of position

<table>
<thead>
<tr>
<th>Position</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head upright</td>
<td>Inferior meatus with gtt</td>
</tr>
<tr>
<td>LHB (Mygind)</td>
<td>Middle meatus</td>
</tr>
<tr>
<td>LHL (Ragan)</td>
<td>Middle meatus</td>
</tr>
<tr>
<td>HDF (Mecca)</td>
<td>Increased superior distribution (Olfactory, limited ethmoid/max)</td>
</tr>
</tbody>
</table>

- Cadaver (n=3) & human (n=7) studies
- Recommend for: HDF with high volume devices
- Recommend for: LHB or LHL with drops and sprays

Thomas III, WT et al, IFAR 2012 (submitted)
Drops and LHB Position
Now that we can reach the sinuses, which active agent?

- **Mechanical**
  - Saline
  - Baby Shampoo

- **Pharmaceutical**
  - Steroids
  - Antibiotic
    - Mupirocin
    - Gentamycin / Tobramycin
    - Ampho B
  - Novel agents
    - Honey
    - Surfactants
    - Dornase Alpha
What’s the goal?

Mechanical Effects
- MCC
- Mucus rheology
- Surfactants
- Removal of Ag

Drug Delivery
- Absorption
- Distribution
## Summary of active agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Grade of evidence</th>
<th>Benefit vs Harm</th>
<th>Recommendation Level</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>B</td>
<td>Benefit</td>
<td>Recommend</td>
<td>Use saline as adjunct to other topical therapies</td>
</tr>
<tr>
<td>Standard INCS</td>
<td>A</td>
<td>Benefit</td>
<td>Strong recommendation</td>
<td>Use in CRSsNP and CRSwNP</td>
</tr>
<tr>
<td>Off label steroid</td>
<td>C</td>
<td>Equal</td>
<td>Option</td>
<td>Irrigation vs drop</td>
</tr>
</tbody>
</table>

Rudmik L, et al, IFAR 2012
Topical steroids

• Meta-analyses demonstrates benefit in both CRSwNP and CRSsNP with greatest benefit with direct sinus delivery

• Safety with steroid irrigations

Snidvongs K, et al, Cochrane 2011
Welch K, et al, AJRA 2010
Steinke JW, et al, JACI 2009
Surgery improves topical steroid delivery

### A Polyp score by sinus surgery status

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Placebo Total</th>
<th>Steroid Mean</th>
<th>Steroid SD</th>
<th>Steroid Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.16.1 patients with prior sinus surgery</td>
<td>1.7</td>
<td>1.9</td>
<td>21</td>
<td>0.4</td>
<td>0.9</td>
<td>20</td>
<td>17.6%</td>
<td>0.85 [0.21, 1.49]</td>
</tr>
<tr>
<td>Dingsor 1985</td>
<td>1.38</td>
<td>1.39</td>
<td>31</td>
<td>0.5</td>
<td>0.74</td>
<td>32</td>
<td>27.5%</td>
<td>0.78 [0.27, 1.30]</td>
</tr>
<tr>
<td>Hartwig 1988</td>
<td>4</td>
<td>4.44</td>
<td>9</td>
<td>2</td>
<td>4.44</td>
<td>10</td>
<td>8.7%</td>
<td>0.43 [-0.48, 1.34]</td>
</tr>
<tr>
<td>Lund 1998</td>
<td>61</td>
<td></td>
<td></td>
<td>62</td>
<td>53.9%</td>
<td></td>
<td>0.75 [0.38, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.58$, df = 2 ($P = 0.75$); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: $Z = 3.99$ ($P &lt; 0.0001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16.2 patients without sinus surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johansson 2002</td>
<td>1.8</td>
<td>0.62</td>
<td>48</td>
<td>1.69</td>
<td>0.64</td>
<td>50</td>
<td>46.1%</td>
<td>0.17 [-0.22, 0.57]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>48</td>
<td></td>
<td></td>
<td>50</td>
<td>46.1%</td>
<td></td>
<td>0.17 [-0.22, 0.57]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.86$ ($P = 0.39$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>109</td>
<td></td>
<td>112</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.48 [0.21, 0.75]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 4.93$, df = 3 ($P = 0.18$); $I^2 = 39%$</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.51$ ($P = 0.0004$); $I^2 = 77.0%$</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2 = 4.35$, df = 1 ($P = 0.04$), $I^2 = 77.0%$</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Steroid irrigations

- N=111 post ESS pts (56% CRSwNP)
- BUD or BET (1mg qd) via squeeze bottle
- 1 year f/u improved SNOT22, endoscopy
- Most improvement in those with high eosinophilia
- UNC DBPCT no benefit
  - needs further study

Snidvongs K, et al, IFAR 2012
Safety and drug absorption?

• How much is left behind?
• What % of total irrigation solution remains?
• Discussing safety and designing future trials – what are our guidelines?
How much solution remains in the sinuses?
How much solution remains in the sinuses?

2.5±1.5%

Figure 3: The effect of the irrigation device was nonsignificant among patient groups.
Benefit to patient

97%
Safety of budesonide irrigations

• Respules (0.5mg/2ml) BID = 1 mg/day
• 3% retained volume = 30 mcg drug
• Rhinocort: 32 mcg/spray=128 mcg/day

• Current irrigations are about ¼ dose of topical spray!
• Probably doesn’t apply to drops which have higher retention
Other methods for getting steroid to the sinus cavity
Mometasone bioresorbable stent

- Meta-analysis, 2 DBRCTs, 143 pts
- Endoscopy, adhesions, oral steroid need improved
- Cost/duration of effect?

Han JK, et al, IFAR 2012
## Summary of active agents

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<th>Protocol</th>
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</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>B</td>
<td>Equal</td>
<td>Option vs recommend against</td>
<td>Variable, high volumes appear to be better</td>
</tr>
<tr>
<td>Antifungal</td>
<td>A-</td>
<td>Harm</td>
<td>Recommend against</td>
<td></td>
</tr>
<tr>
<td>Alternative agents</td>
<td>C</td>
<td>N/A</td>
<td>N/A</td>
<td>Surfactants, honey, xylitol</td>
</tr>
</tbody>
</table>

Rudmik L, et al., IFAR 2012
Does any of this sinus stuff apply to the lower airway?
Effects of INCS upon asthma in AR patients

• 18 studies, 2162 patients
• 3 subgroups
  – INCS vs placebo spray
  – INCS plus oral ICS vs oral ICS alone
  – Nasal inhalation vs nasal placebo
• Asthma QoL, FEV1, medication scores

Lohia S, Schlosser RJ, etal, Allergy 2013 (in press)
INCS improves asthma sx, FEV1, rescue meds

**INCS spray vs Placebo**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours experimental</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agondi 2008</td>
<td>3.77 ± 0.56</td>
<td>3.12 ± 0.97</td>
<td>14 4.1% 0.65 [0.07, 1.23]</td>
</tr>
<tr>
<td>Corren 1992</td>
<td>3.22 ± 2.6879</td>
<td>3.36 ± 2.2062</td>
<td>8 0.3% -0.14 [-2.40, 2.12]</td>
</tr>
<tr>
<td>Henriksen 1984</td>
<td>8.5 ± 0.798</td>
<td>7.9 ± 1.7555</td>
<td>17 1.6% 0.60 [-0.32, 1.52]</td>
</tr>
<tr>
<td>Sandrini 2003</td>
<td>18 ± 10.4293</td>
<td>19 ± 5.9905</td>
<td>9 0.0% -1.00 [-9.66, 7.66]</td>
</tr>
<tr>
<td>Stelmach 2005</td>
<td>2.2 ± 1.89</td>
<td>1.23 ± 2.55</td>
<td>19 0.7% 0.97 [-0.46, 2.40]</td>
</tr>
<tr>
<td>Watson 1993</td>
<td>2.4 ± 0.2</td>
<td>2 ± 0.2</td>
<td>21 93.3% 0.40 [0.28, 0.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>90 ± 100%</td>
<td>88 ± 100%</td>
<td>0.42 [0.30, 0.53]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 1.77, df = 5 (P = 0.88); I^2 = 0$

Test for overall effect: $Z = 6.97 (P < 0.00001)$

**INCS spray with oral ICS vs oral ICS**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours experimental</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katal 2010</td>
<td>37.1 ± 41.0122</td>
<td>36.5 ± 38.6523</td>
<td>166 1.7% 0.60 [-7.58, 8.78]</td>
</tr>
<tr>
<td>Nathan 2005</td>
<td>20.6 ± 52.1776</td>
<td>23.6 ± 53.1085</td>
<td>259 1.4% -3.00 [-12.15, 6.15]</td>
</tr>
<tr>
<td>Stelmach 2005</td>
<td>2.57 ± 1.79</td>
<td>2.79 ± 1.53</td>
<td>17 96.9% -0.22 [-1.30, 0.86]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>469 ± 100%</td>
<td>442 ± 100%</td>
<td>-0.24 [-1.31, 0.82]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.39, df = 2 (P = 0.82); I^2 = 0$

Test for overall effect: $Z = 0.45 (P = 0.65)$

**Nasal inhalation vs nasal placebo**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedersen 1998</td>
<td>2.67 ± 0.31</td>
<td>2.08 ± 0.42</td>
<td>12 49.9% 0.59 [0.29, 0.89]</td>
</tr>
<tr>
<td>Pedersen 1998a</td>
<td>3.27 ± 0.24</td>
<td>1.09 ± 0.42</td>
<td>12 50.1% 2.18 [1.91, 2.45]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24 ± 100.0%</td>
<td>24 ± 100.0%</td>
<td>1.39 [-0.17, 2.94]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.24; \chi^2 = 59.90, df = 1 (P < 0.00001); I^2 = 98$

Test for overall effect: $Z = 1.74 (P = 0.08)$

**Overall**

| Total (95% CI)    | 583 ± 100% | 554 ± 100% | 0.69 [0.04, 1.35] |

Heterogeneity: $\tau^2 = 0.70; \chi^2 = 140.38, df = 10 (P < 0.00001); I^2 = 93$

Test for overall effect: $Z = 2.08 (P = 0.04)$
Meta-analysis: Impact of ESS upon asthma

- N=21 studies, 812 patients, mean f/u 26 mos
- NSD in FEV1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% pts improved</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall asthma control</td>
<td>78%</td>
<td>72 – 82%</td>
</tr>
<tr>
<td>Frequency asthma attacks</td>
<td>85%</td>
<td>75-92%</td>
</tr>
<tr>
<td># hospitalizations</td>
<td>64%</td>
<td>53-75%</td>
</tr>
<tr>
<td>PO steroids</td>
<td>73%</td>
<td>67-78%</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>28%</td>
<td>23-35%</td>
</tr>
<tr>
<td>Bronchodilator use</td>
<td>36%</td>
<td>29-44%</td>
</tr>
</tbody>
</table>

Vashishta R, Schlosser RJ, etal, IFAR 2013 (submitted)
All CRSwNP treated similarly: Big hole ESS, steroid irrigations

AFRS 13 months  
s/p 3rd ESS

ASA triad 8 months  
s/p 5th ESS
CF sinusitis… another can of worms

- Small sinuses
- Thick mucus
- Definite bacterial issues
  - Staph, Pseudomonas
- Nutrition/vitamin D?
- Compliance
ESS in CF patients

- Improves sinonasal symptoms, endoscopy and hospitalizations up to 1 year
- No impact upon PFTs

Virgin F, et al AJRA 2012
Systematic review and MA: ESS in CF

- 19 studies, 586 pts
- ESS improves sinonasal QoL
- No improvement in PFTs
- Conflicting data on hospitalizations, abx used, endoscopy scores

Macdonald KI etal, Rhinology 2012
Local immune response in asthma (and CRSwNP)

Akdis C, Nat Med 2012
Experimental Method

Af (or other insult) x 24 hrs

Control, CRSsNP, CRSwNP, AFRS

HSNECs

Wash HSNECs
Remove insult
Incubate 24 hrs
Collect conditioned media

Mediators?
PGE₂, GM-CSF
CCL2/20

Control APC maturation/migration
Ag uptake/T cell skewing
Surface markers: CD80/86/209/40
Cytokine production

Th2 skewing
↑IL-4, 5, 13

B cell/plasma cell
↑IgE
DC maturation (CD80/86 similar) to CD209

Mulligan JK, et al. IFAR 2011
HSNECs secrete factors which lead to DC skewing and subsequent impact upon T cells

Mulligan JK, et al IFAR 2011
Local delivery factors

Getting it to the proper sinus

Penetrating gel and sol layers of mucus

Trans-cellular or paracellular

Figure 2.

Bleier BS et al, Oto Clin N Amer 2010
In vitro modeling of drug delivery

Bleier BS et al, J Pharm Pharmacol 2012
Disease specific response

(a) IL-6 suppression

Control | CRSwNP
---|---
Dex 0.001 mg/ml | *P < 0.05*
Dex 1 mg/ml | *P < 0.05*

(b) IL-8 suppression

Control | CRSwNP
---|---
Dex 0.001 mg/ml | *P < 0.05*
Dex 1 mg/ml | *P < 0.05*

(c) Reduction in cytokine secretion

IL-6 | IL-8
---|---
Control | CRSwNP
---|---
*P < 0.05* | *P < 0.05*

Bleier BS et al, J Pharm Pharmacol 2012
CRS treatments

- Approach based upon pathophysiology and evidence
- Topical therapies likely to make a major impact
- Evidence supports large volume delivery of saline and steroids in post operative patients
- Other agents (antibiotics, antifungals, other) have limited evidence to support their use
- May improve lower airway disease