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Aspiration risk and respiratory complications in patients with Oesophageal Atresia

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Australia in the News

Shark 'Bigger Than 17ft Boat' Kills Woman, Perth, 5/6/2016

Crocodile swallows Australian woman during night swim, Daintree National Park, Queensland, 30/5/2016

Australian woman finds 5m Python in her house (Mission Beach, Queensland, 22/6/2016

Outline

1. Respiratory Morbidity in EA
2. What does Aspiration do to the lungs?
3. What parenchymal lung diseases are associated with aspiration?
4. Proving aspiration
5. The largest data pool: Gastroesophageal Reflux (GERD)
6. What evidence suggests that oral aspiration and GERD causes respiratory morbidity in EA?
7. Consequences of Aspiration in people with a history of EA
8. Diagnosis and Care (multi-disciplinary)

Conflicts of Interest: None.

Biases: *I think aspiration is a major cause of respiratory morbidity in EA*!

Respiratory Morbidity in EA

- 46% of EA patients have respiratory complications
- Hospitalization for respiratory complications in EA patients:
  - 38% 1st 10 years of life
  - 1.5% over 18 years of age
- Adult EA patients: persistent cough 31% (*Kovesi, Dis Esoph 2013*)
  - 24% have bronchitis at least once/year (> controls)
  - 8% have recurrent pneumonia
- Pulmonary function:
  - Restrictive defects 20-49%
  - Obstructive defects 12-54%
  - Mixed defects 0-11%
  - Bronchodilator response: 8% (*Kovesi, Chest 2004*)
- MD-diagnosed “asthma” 30%, recurrent wheeze 29% (*Gatzinsky, Acta Paed 2011*)
- > 17 cases bronchiectasis (children + adults) (*Banjar, Saud Med J 2005*)

Causes of respiratory morbidity

- Tracheomalacia – 78% EA/TEF patients
  - Persistent bacterial bronchitis associated (*Kompare, J Ped 2012; DeBoer, Ped Pulm 2016*) – reduced airway clearance
- Esophageal dysmotility, strictures – 75-100% EA patients
- Gastroesophageal Reflux (GERD) -35-58% EA patients
- Recurrent TEF – 9% EA patients
- Atopy, Asthma (*Kovesi, Dis Esoph 2013, Chest 2004*)

- As EA patients usually have many of these, which are the key causes? Can looking elsewhere help?

Aspiration

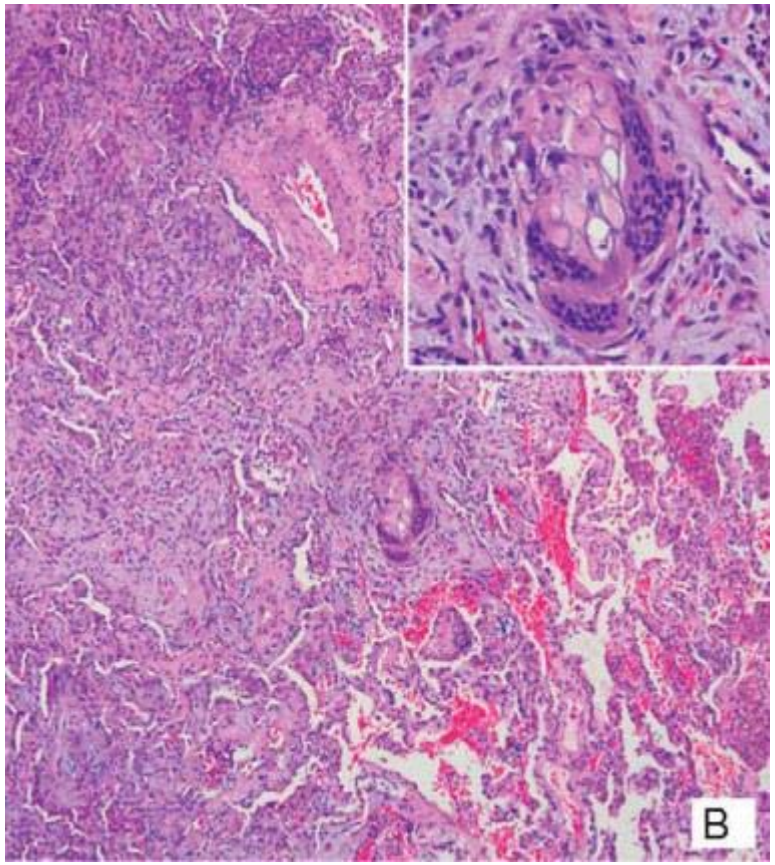
- Aspiration:
  - "inhalation of oral, gastric contents into lower respiratory tract"
  - Effect depends on origin (liquid, solid, pH, presence of bacteria), volume, chronicity
  - At least 50% healthy adults aspirate small volumes oropharyngeal secretions asleep, but cleared by airway clearance, cough, immune system, leaving no sequelae (*Marik, NEJM 2001*)

Pneumonitis and Pneumonia

- Aspiration Pneumonitis (Mendelson's Syndrome)
  - Regurgitated gastric contents with reduced consciousness (anesthesia), leading to Acute Lung Injury (+/- ARDS)
  - Typically sterile (at least initially), unless gastric pH iatrogenically elevated (*Marik, NEJM 2001*)
- Aspiration Pneumonia
  - Aspiration of infected oropharyngeal secretions in patients at risk for aspiration
  - Patchy bronchopneumonia - classically dependent lobes
    - Supine: Posterior segments upper lobes & apical lower lobes
    - Sitting: basal segments lower lobes
  - Risk of necrotizing bronchopneumonia, abscess formation (*Hu, Chest 2015*)

Chronic Aspiration – Pathology (1)

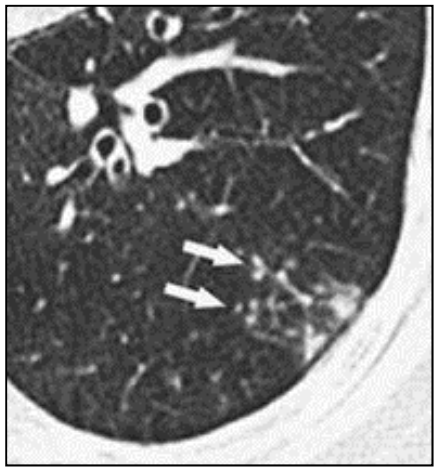
- Mukhopadhyay (*Am J Surg Path 2007*): lung biopsy 59 cases aspiration pneumonia, mean age 57 years; 32% esophageal disease, hiatus hernia.
  - 100% alveolar foreign material (vegetable matter 92%) with giant cells
  - 88%: *bronchiolitis obliterans* organizing pneumonia (intraluminal fibroblast plugs small bronchioles, alveolar ducts) – mainly associated with foreign body/suppurative granulomas, foci of bronchopneumonia
  - Few cases had interstitial foreign material with fibrosis
- Restrictive defects, low DLCO common (*Fishman, Pulm Diseases 2008*)



BOOP showing foreign-body giant cells engulfing vegetable matter within a fibrous plug

Chronic Aspiration – Pathology (2) and CT

- Cardasis (*Annals ATS 2014*): 25 cases occult aspiration, mean age 62 years; 96% had GERD, 32% hiatal hernia, 40% esophageal disease
  - CT: bronchial wall thickening, centrilobular nodules, tree-in-bud opacities; mainly lower lungs; few cases ground glass opacity, interstitial lung disease, traction bronchiectasis
  - Biopsy: poorly-formed granulomas near bronchioles with chronic inflammation, foreign body giant cells, lipoid pneumonia common
- Pereira-Silva (*J Thorac Imaging 2014*): 13 patients chronic micro-aspiration; mean age 71 years; GERD 69%, hiatus hernia 46%, esophageal dysfunction 23%
  - CT: all had centrilobular nodules & focal areas ground glass opacity - 85% in dependent lung regions; branching opacities (tree-in-bud) common; bronchiectasis 54%



Other Aspiration-Associated Lung Diseases

- Bronchiectasis
  - Caused by aspiration in 4-18% patients with non-CF bronchiectasis (especially children)
  - El-Serag (*Gastro 2001*): 1,980 neurologically-normal children with GERD, 7,920 controls
    - OR for Bronchiectasis 2.3 ($p < 0.0001$)
    - OR for Pneumonia 2.3 ($p < 0.02$)
  - Piccione (*Ped Pulm 2012*): 66 patients with bronchiectasis in an Aerodigestive Clinic; associated with severe neurologic impairment, parent report of GER (but not impedance study, fundoplication)
- *Bronchiolitis Obliterans* Syndrome post-Lung Transplant
  - Important role in worsening lung function; improves with fundoplication (*Morehead, Eur Respir Rev 2009*)
- Idiopathic Pulmonary Fibrosis
  - Possible association, especially Scleroderma patients; PPI's may slow decline in lung function (*Hu, Chest 2015*)

Finding the Route of Aspiration (1)

- Swallowing dysfunction:
  - Videofluoroscopic swallowing study or fiberoptic endoscopic evaluation
- Esophageal dysfunction
  - Upper GI, manometry
- Tracheoesophageal Fistula
  - Upper GI with pull-back study
- GERD
  - Endoscopy
  - Upper GI
  - pH probe

Finding the Route of Aspiration (2)

- GERD (continued) [2]
  - pH-Multichannel intraluminal impedance study
    - Borrelli (*Dig & Liver Dis 2010*): 21 children, mean age 4.1 years; 49% events were non-acid, 74% reached proximal esophagus; 80% episodes were liquid
      - Number reflux episodes, non-acid reflux episodes, non-acid reflux reaching proximal esophagus commoner in children with recurrent lung consolidation than asthma ($p < .01$)
    - Condino (*J Ped 2006*): 24 children with asthma & GERD, mean age 33 months;
      - 51% of events were non-acid,
      - low association with symptoms (i.e. 8% events associated with cough)

Finding the Route of Aspiration (3)

- GERD (continued) [3]
  - Nuclear scintigraphic study
    - Ravelli (*Chest 2006*): scintigraphy in 51 neurologically-normal children (median 6.5 years);
      - GER to upper 1/3 esophagus in 27%
        - # reflux episodes didn't differ in children with normal or abnormal pH studies
      - Delayed gastric emptying (> 90 minutes) 53%,
      - Aspiration on 20h delayed scan 49%
        - 75% of these had normal pH study; few had histologic esophagitis
        - Limited by $t_{½}$ ^{99m}Tc
    - Aspiration in 62% children with recurrent pneumonia & 100% patients with apnea

Proving Aspiration (1)

- Bronchoscopy showing particulate matter, or found in bronchoalveolar (BAL) lavage fluid or Lung Biopsy (Foreign bodies, foreign body granulomas)
- BAL lipid-laden macrophages or BAL lipid-laden macrophage index (LLMI)
  - 100 MQ's scored 0 (no lipid) - 4 (completely opacified) & total summed
  - Range 0 – 400; > 100 possibly associated with GERD
  - "have been associated with chronic aspiration" but sensitivity 57-100%, specificity 57-89% (*Morehead, Eur Resp Rev 2009*)
  - Borrelli (*Dig & Liver Dis 2010*): LLMI significantly higher with recurrent lung consolidation than asthma ($p < 0.05$);
    - LLMI correlated with number reflux & non-acid reflux episodes, and numbers reaching proximal esophagus ($p < 0.01$)
    - LLMI significantly correlated with number BAL neutrophils ($p<0.01$)
  - Rosen (*Ped 2008*): 50 children (mean age 6 years); LLMI not associated with pH-impedance findings, endoscopic esophagitis, clinical improvement with fundoplication
- BAL pepsin, bile acids
  - Not adequately studied (*Morehead, Eur Resp Rev 2009*)

Proving Aspiration (2) – The Future?

- Culture
  - Rosen (*J Ped 2011*): 46 children with chronic cough or wheezing, mean age 74 months; 26% had a positive BAL (mainly *Streptococcus pneumoniae, Haemophilus influenzae*)
    - +ve BAL culture predicted by amount of non-acid reflux, full-column GER on pH-impedance study, but not by pneumonia in last 6 months
- Microbiome (ribosomal 16s rRNA) ecosystem
  - Lower airways normal people have low levels oral bacteria (Prevotella, Veillonella) (*Segal, AnnalsATS 2014*)
  - Effects of aspiration not investigated
- Exhaled Breath Condensate (EBC) pH
  - Fitzpatrick (*J Allerg Clinc Immunol Pract 2014*): 110 children with asthma (in lansoprazole study); no association between EBC and esophageal pH; EBC acidity didn't change with lansoprazole; doesn't seem to be useful in GERD

GERD and Asthma - Mechanisms

- *Over 1,600 publications in PubMed on GERD & Asthma*
- Potential mechanisms of asthma causing GERD
  - Cough, negative pressure counteracts LES (especially if hiatal hernia)
- Potential mechanisms of GER causing asthma
  - Reflex - Stimulation of vagal nerves in esophagus; some end in same region of nucleus of the solitary tract where respiratory sensory nerves terminate.
    - Amarasiri (*BMC Pulm Med 2013*): esophageal infusion acid reduces FEV_1, PEF, increases parasympathetic activity in 40 adult asthmatics, regardless of GER on pH probe
    - Ferrari (*Scand J Gastro 2007*): 29 adults with asthma treated with omeprazole x 12 days
      - No effect on methacholine challenge (regardless of presence of GER on pH probe)
      - Significant reduction in cough sensitivity to capsaicin challenge in patients with pH probe evidence of reflux, and with proximal acid exposure, # of refluxes, and De Meester Score
    - Number esophageal reflux episodes associated with Methacholine challenge, but not FEV1 (*Havemann, Gut 2007*)
  - Micro-aspiration - causing bronchoconstriction, airway inflammation
    - Non-acid GER may stimulate protective airway reflexes less

The Association between GERD and Asthma (1)

- Thakkar (*Ped 2010*): systematic review 20 articles, 5,706 patients
  - 22.8% of children with asthma diagnosed with GERD, 68% asthma patients studied had abnormal pH probe, 49% patients studied had abnormal proximal pH
  - Prevalence asthma in children with GERD 13% versus 7% in controls
- Havemann (*Gut 2007*): systematic review 28 studies
  - Prevalence GERD (Montreal Definition) 58% in adults with asthma, vs. 38% controls, OR 5.5;
  - Prevalence abnormal esophageal pH 51% (not associated with asthma medication use, symptoms of GERD, but associated with Hs asthma 1 study)
  - OR asthma in patients with GERD 2.7

The Association between GERD and Asthma (2)

- DiMango (*AJRCCM 2009*): esomeprazole in 304 adults with poor asthma control
  - abnormal distal or proximal esophageal pH associated with oral steroid use,
  - proximal reflux associated with worse quality of life;
  - neither associated with FEV_1, asthma control, methacholine challenge
- Kwiechien (*J Asthma 2011*): in 66 children with asthma, mean age 10 years; night asthma symptoms associated with longer time spent at night with esophageal pH < 4

The Effects of Treating GERD on Asthma (1)

- Gibson (*Cochrane Review 2002*): 12 studies & 396 patients (mainly adult); no consistent effect on am or pm peak flow, asthma symptoms
- Kiljander (*AJRCCM 2010*): RCT esomeprazole 40 mg daily or BID in 828 adults with asthma & +ve GERD score for 26 weeks
  - small improvement in FEV_1 (~0.1L) & quality of life;
  - no effect on peak flow, exacerbations, symptoms
- Littner (*Chest 2005*): RCT lansoprazole 30 mg BID for 24 weeks in 207 adults with asthma + GERD symptoms
  - No change in lung function, symptoms
  - Significantly more moderate-severe exacerbations (needing prednisone) with plabeo, OR 2.9
  - Improved quality of life

The Effects of Treating GERD on Asthma (2)

- Am Lung Assoc (*NEJM 2009*): RCT esomeprazole 40 mg daily for 6 months in 402 adults with no GER symptoms (40% had abnormal pH probe);
  - no effect on symptoms, lung function, methacholine challenge, steroid use – regardless of pH probe findings
- Holbrook (*JAMA 2012*): RCT lansoprazole 15-30 mg daily for 6 months in 306 children with asthma without GER symptoms, mean age 11; ½ had pH probe (abnormal in 43%):
  - no effect on quality of life, pulmonary function, methacholine challenge, exacerbations – including in 49 children with abnormal pH probe
- Rothenberg (*J Ped Surg 2012*): 235 children with asthma on prednisone underwent laparoscopic Nissen fundoplication; 90% reduced or stopped steroids, 90% with night symptoms improved, FEV1 improved 26% (n=56)

- Summary: some efficacy PPI in asthmatics with symptomatic GERD (but inconsistent between studies); no effect in asymptomatic patients
- However – PPI's don't treat non-acid GER

Associations: Aspiration & EA Respiratory Morbidity

- In 68 type C EA, respiratory complications including recurrent pneumonia associated with GERD 74%, recurrent TEF 13%, esophageal stricture 10% (*Delius, Surgery 1992*)
- Recurrent TEF associated with cough, recurrent pneumonia (*Ghandour, J Ped Child Health 1990*)
- In 20 EA children, bronchitis, pneumonia associated with dysphagia (*Couriel, Acta Paed Scand 1982*)
- In 334 EA patients, persistent respiratory symptoms associated with allergies, family history allergy (*Chetcuti, Arch Dis Child 1993*)
- 2/3 children with EA and wheezing had history of atopy (*Couriel*)
- Allergies are common:
  - Allergic rhinitis 15%, +ve allergy tests 54% children (*Malmstrom*)
  - Allergies 42%, +ve allergy tests 37%, high IgE 20% adults
    - Associated with current respiratory symptoms (*Sistonen*)

Effect of GERD in EA (1)

- Robertson (*Ped Pulm 1995*): +ve Methacholine challenge in 48% of 18 EA patients, not associated with symptoms atopy
  - Frequency +ve methacholine challenge similar to controls
- Peetsold (*Ped Pulm 2011*): lower FEV_1 associated with prior anti-reflux surgery, but not restrictive PFT or exercise capacity
- Malmstrom (*J Ped 2008*): in 23 adolescent EA patients:
  - +ve histamine challenge (78%) not associated with fundoplication, esophageal symptoms, # pneumonias, allergy tests, MD diagnosis of asthma
  - Airway reticular basement membrane thickening not associated with GI symptoms, atopy, esophageal biopsies, atopy, histamine challenge, FE_{NO}
  - Restrictive defect not associated with fundoplication, current esophageal symptoms
- Legrand (*Arch Dis Child 2012*): PFT's in 57 EA children not associated with GER (symptoms or objective test), fundoplication

Effect of GERD in EA (2)

- Obstructive defects associated with history of GERD (but not results of 2h pH probe), choking spells during infancy, pneumonia 1st 4 years of life (*LeSoeuf, J Ped Surg 1987; Agrawal, Arch Dis Child 1999; Chetcuti, Thorax 1992*)
- Sistonen (*Eur Resp J 2010*): +ve histamine challenge (41%) in 101 adult patients associated with atopy, elevated IgE; not with esophageal metaplasia
  - Restrictive defects associated with GERD-related esophageal metaplasia
  - Elevated FE_{NO} not associated with atopy

Bronchiectasis and EA

- DeBoer (*Ped Pulm 2016*): 17% rate bronchiectasis (CT) in 15 clinic patients & 23% in 15 patients (*Cartabuke, Gastro Rep 2015*); Robertson: 4% rate by CXR
- Bronchiectasis generally associated with massive aspiration:
  - gastric, colonic interposition, selected referral population (*Banjar, Saud Med 2005*),
  - longstanding GERD (*Jayasekera, J Ped Surg 2012*),
  - massive pouch secretions, Trisomy 21 (*Kang, J Allerg Clin Immunol 2007*),
  - undiagnosed TEF (*Behnia, Intern Med 2001*) or broncho-esophageal fistula (*Dogan, Resp 1999 Azoulay, J Thor Cardiovasc Surg 1992*)

Summary

- In general population, bronchiectasis clearly associated with GERD, BOOP with aspiration; relationship between GERD and Asthma unclear

- In EA, atopy, GERD inconsistently associated with low FEV_1, restrictive defects
  - *Could some restrictive defect be related to BOOP?*
- In EA, airway reactivity inconsistently associated with atopy but not shown to be associated with GERD
- Confounded by:
  - Method of diagnosing aspiration (biopsy, pH probe, acid versus non-acid reflux, need for surgery, LLMI)
  - effects of *past* GERD,
  - previous fundoplication
- Bronchiectasis likely associated with massive, chronic aspiration in EA

Follow-up

- Clear need for long-term follow-up, ideally by multi-disciplinary expert teams (*De Boer, Ped Pulm 2016; Bjornson, Paed Child Health 2006*)
- Respiratory follow-up should include:
  - Serial pulmonary function testing (spirometry, lung volumes, +/- bronchodilator response) (*Delacourt, JPGN 2011; Beucher, Ped Pulm 2013*)
  - CT chest if bronchiectasis suspected
  - CXR, exercise testing when clinically indicated
- Investigate for aspiration, tracheomalacia when respiratory morbidity detected