The Evolution of the Role of Surgery in the Treatment of Chronic Rhinosinusitis

David W. Kennedy, M.D., FACS, FRCSI

University of Pennsylvania Medical Center
Disclosures

Conflicts of interest

– Ententcare (Rhinactive) – Medical Director
– AcceptEnt (Partner, Shareholder)

• Medical Advisory Board
  – Merck
  – IntersectEnt
  – Sinuwave

• Royalties
  – Medtronic-Xomed
Goals of Presentation

• Early evolution of Endoscopic Sinus Surgery (FESS)
• Changes in thinking about sinus disease pathogenesis and impact on patients
• Technological and technique advances in the surgery
• Evolution and future of skull base surgery
Sinus Surgery: Pre-Endoscopic

• Focus on Maxillary and Frontal sinuses
• Open approaches
  – Caldwell-Luc
  – Frontal sinus osteoplasty
  – External or intranasal headlight ethmoidectomy
• Stripping of irreversibly diseased mucosa
• High failure rate
• Significant morbidity
Donald Proctor, M.D.

- 1st Chair of Anesthesiology @ Hopkins
- Professor of:
  - Anesthesiology
  - Otolaryngology
  - Environmental medicine in School of Public Health
- International expert on mucociliary clearance and nasal airflow
- Highlighted key role of ethmoid sinus
Walter Messerklinger: Endoscopic Diagnosis, 1978

Book described the endoscopic findings of pathology but not endoscopic surgery.
Introduction of FESS: 1984

- Meeting in Dubrovik
- Presented Hopkins Experience with trans-sphenoidal sinus surgery
- Met Messerklinger – starting to do surgery endoscopically
Norman Silbertrust
Karl Storz Endoscopy America Inc.
10111 W. Jefferson Blvd.
Culver City, California 90230

Dear Mr. Silbertrust:

I recently gave some papers at a nasal sinus meeting in Europe, and while there, had the opportunity to listen to and talk with Dr. Walter Messerklinger and one of his associates Dr. Heinz Stammerger. As a result of their presentations and discussions, I became convinced that the techniques of endoscopic sinus surgery which Dr. Messerklinger has advocated and practices, are indeed techniques that will in the future will replace more conventional surgical approaches to sinus disease. I had previously had the opportunity to review Dr. Messerklinger’s book on endoscopy of the nose, however, the book did not detail his surgical approaches and in the absence of this, his detailed diagnostic evaluation, described so well in the book, becomes somewhat superfluous and this I believe accounts for the fact that the publication has not been more widely popular in the United States.

As I mention, I am convinced that endoscopic sinus surgery will probably revolutionize current surgical approaches in the future. Although I am primarily an otologist—neurootologist, I have a significant interest in sinus surgery particularly as it relates to both general otolaryngology and to eustachian tube function. As Director of the Resident Training Program at The Johns Hopkins Hospital, I also have responsibility for providing the professional development of the medical students who will in the future become house staff in the department of Otolaryngology—Head and Neck Surgery.
Nasal Endoscopy and later CT Highlighted the Role of the Ostiomeatal Complex in Chronic Rhinosinusitis

- The Ostiomeatal complex originally described by Naumann, recognized by Takahashi, highlighted by the work of Messerklinger, Drettner and Proctor

- However, we recognized this was just the ‘final common pathway’ of a multifactorial disease
Subsequent Overemphasis of the Role of the Ostiomeatal Complex

• OMC and anatomic issues overemphasized
• Multifactorial nature of problem minimized
• Limited emphasis on environmental factors
• General host factors often ignored:
  – Allergy & relationship to asthma
  – Genetic factors & immunodeficiency
  – Granulomatous and autoimmune
Increased Focus on Medical Management Prior to Surgery

• Environmental control
  – Pollution
  – Smoking
  – Allergy control

• Maximal medical therapy
  – Topical steroids
  – ? Oral steroid trial
  – ? Antihistamines
  – ? Antibiotics
Patients who do not do well from FESS

- Untreated Allergies
- Continued smoking and environmental exposure
- Recurrent sinusitis due to mucosal hyper-reactivity
- Severe headaches, atypical facial pain
Refinements in Management of Chronic Rhinosinusitis Continue

• Involves multiple aspects of patient care
  – Pathogenesis and medical care
  – Patient selection for surgery
  – Imaging and identification of the anatomy
  – Anesthesia
  – Minimizing intraoperative trauma
  – Post operative debridement
  – Post operative medical therapy
• Early FESS, although it reduced the extent of surgery, often resulted in mucosal stripping with Blakesley forceps

(from Moriyama)
Through cutting forceps and later the microdebrider provided the potential for mucosal preservation.
Moriyama demonstrated long term effects of mucosal stripping, confirming prior work of Hilding and others.
Gaining 3-D Conceptualization
Image Guidance
Portable Low Dose Irradiation
Intraoperative CT

• Provides a real time image while patient still asleep

• Enables CT image guidance to be updated
More Delicate Instrumentation

- Malleable probes
- Enable ostial identification
- Improved power instrumentation
- Endoscrub – scope washer
- 3 D endoscopes
Tissue Trauma Associated with FESS has been Minimized

Mucosal Preservation

- Improved techniques
- Greater experience
- Better instrumentation
- Avoidance of tissue trauma
- No need for nasal packing
- Essentially no postoperative pain
Biodegradable Implants

- Local, Controlled Steroid Delivery
  Mometasone Furoate
- Bioabsorbable Material: PLCG
- Self-Expands to Fit Sinus Cavity
- FDA approved
- Office insertion of drug eluting stents for recurrent polyposis (60-90 day drug elution) awaiting FDA approval
- Frontal sinus stent in development
Drug-Eluting Stent Implants
Preoperative Scans
Drug-Eluting Implant (postoperative placement)
PROPEL Clinical Study Program

Pilot Study\(^1\)
- \(n=38\)
- 4 sites
- Randomized Double Blind Intra-patient Control
- Steroid-Eluting stent vs. non drug stent

ADVANCE Study\(^2\)
- \(n=50\)
- 7 sites
- Non-Randomized Single Arm
- Steroid-Eluting stents

ADVANCE II Pivotal Trial\(^3\)
- \(n=105\)
- 11 sites
- Randomized Double Blind Intra-patient Control
- Steroid-Eluting stent vs. non drug stent

Meta-Analysis\(^4\)
- \(n=143\)
- Level 1-A Data

References:
Clinically Proven to Improve Surgical Outcomes

- 3 prospective trials completed in > 200 patients
  - Pilot /pivotal prospective, multi-center, randomized, double-blind
- Improves post-op healing
- Reduces need for oral steroids

<table>
<thead>
<tr>
<th></th>
<th>Relative Reduction</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Need for Medical / Surgical Tx</td>
<td>↓ 35%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Need for Oral Steroids</td>
<td>↓ 40%</td>
<td>0.0023</td>
</tr>
<tr>
<td>Polyposis</td>
<td>↓ 46%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Drug Eluting Implants

- Penn experience to date very positive
- Reduced oral steroids and decreased debridement
- Early post-op resolution of residual asymptomatic disease translates into lower recurrence
- Potential delivery method for novel anti-inflammatory agents
Office based Long-Term Implants for Recalcitrant Polyposis

- 90 Day mometasone elution
- Dilate the obstructed cavity
- Delivers steroid directly to ethmoid cavity, where polyps frequently originate
- Alternative to revision surgery and/or oral steroids

- Variable leg lengths optimize mucosal apposition
- Greater radial force dilates the obstructed sinus
- Bioabsorbable polymer controls localized drug release

Investigational device only. Not approved for sale in U.S.
Intersect ENT Office based therapy for recalcitrant CRS

- Pilot study complete
  - n=12, 4 U.S. sites
  - Sustained reductions in patient symptom scores & endoscopic polyp volume through 6 months

- RESOLVE Pivotal trial – enrollment completed
  - n=100, 12 U.S. sites
  - Randomized Controlled Trial evaluating safety & efficacy

Investigational device. Limited by federal law to investigational use only. Not approved for sale in U.S.
Pilot Study Outcomes
n=12, 4 U.S. sites

Clinically significant reduction in patient symptom scores

> 70% Reduction in sinus obstruction @ Day 90;

Significant reduction maintained out to 6 months

Lavigne F, Abstract presentation, ARS Annual meeting, 2013
Frontal Sinus Surgery: An Array of Surgical Options: 2013

- Ethmoidectomy alone
- Balloon dilation
- Draf 2 A or B (with or without trephine)
- Draf 3

More invasive
Balloon Sinuplasty

- Not just a plumbing problem
- Does not remove diseased tissue and bone
- Does not address ethmoid sinus
- Not indicated in polyposis
- Frequently used in minimal disease (?
  Amenable to medical therapy)
- Often done as office procedure
- Extremely well reimbursed
Balloon Sinuplasty

- Excellent safety record
- Useful (but expensive) as an additional tool
- Efficacy not proven (Cochrane report, EPOS)
- May become much more interesting with drug eluting stents
The Ugly side of FESS

Complications

• £€$$ – too much surgery and balloon interventions performed
• Learning curve for otolaryngologists with some major complications
• Poor management of inciting factors (smoking, allergy)
• Insufficient detail to technique and postoperative care
• Poor understanding of pathogenesis
• Scarring, late complications, nasal cripples
The Ugly: Empty Nose as a Complication of “FESS”
Why Study Bone in Chronic Rhinosinusitis?

- Frequent bone changes in diseased areas
- Localized persistent disease is common post surgery
- Localized disease frequently resolves when underlying bone removed
The Role of Bone in CRS: 2002 CT
Marked Neo-osteogenesis: 2009
Patient Bone Study (with Dr. Senior)

Materials and Methods

• 34 patients (40 specimens, 54% revisions)
• 9 controls (16 specimens)
• Tetracycline, 2 wks later demeclocycline
• Sections stained and studied semiquantitatively by light microscopy
• Quantitative examination by formal histomorphometry
• Fluorescent analysis
Bone labeled with two short courses of tetracycline two weeks apart

Tetracycline labeled bone Study
Patient Osteitis Study

Control Bone

CRS Bone
Patient Bone Study

Results

• Chronic Sinusitis Group
  – 30% No activity
  – 33% Mild Activity
  – 38% Marked Activity

• Control Group
  – 69% No activity
  – 25% Mild activity
  – 6% marked activity

• $p = 0.004$ (Mann-Whitney $u$)
Figure 1C: Bone changes on right (inoculated) side
Results

Rabbit Study #2

- Ipsilateral bone changes in 92% of animals
- Contralateral bone changes in 52% of animals
- Bilateral hyperplasia of mucosa evidenced in 60% of animals
- No apparent differences in infection rate or histological changes based on the bacterial strains utilized
- Bone involvement may be a reason why medical therapy alone often insufficient
The Role of Bone in CRS

• The bone appears to play a very active part in the disease process and changes consistent with chronic osteomyelitis.
• Bone involvement begins early in the disease process and inflammation spreads through the bone.
• The Haversian canals enlarge, become infiltrated with inflammatory cell and later undergo fibrosis.
• It is highly likely that bone inflammation part of is a significant part of the reason that the disease is difficult to resolve medically.
• No evidence of bacteria in the bone to date.
Surgery is Adjunctive to Medical Therapy

- Routine use of topical nasal steroids
- Culture directed Antibiotics
- Oral Steroids
- High volume/high dose steroid irrigations (0.5mg Budesonide or 0.6mg mometasone)
- Allergy management
- Antileukotrienes?
- Omalizumab?
- Oral Sporanox (itraconazole)??
Medical Therapy in The Patient With Difficult to Treat CRS

Nasal Irrigations

- High volume saline (preferably isotonic, buffered) with high dose topical steroid – e.g. budesonide

- Antibiotic – culture directed
  - Mupirocin (7.5 grams/liter)
  - Gentamycin (80 mgs/liter) (Wilson’s Solution)
  - Tobramycin (80 mgs/liter)
  - Ceftazidime (6 grams in 60ccs – diluted by patient to 0.6 grams in 240 ccs)

- No evidence for topical antifungal therapy at this point
Medical Therapy in The Patient With Difficult to Treat CRS

Antibiotics

- Culture directed
- 14-21 day course, but given sparingly
- Usually in conjunction with oral steroids, surgery, or irrigations
- Augmentin
- Levaquin
- Clindamycin & Bactrim
- Clarithromycin
Medical Therapy in The Patient With Difficult to Treat CRS

**Itraconazole**

- Treatment of last resort
- Itraconazole 100-200 mgs 2x/day
  - LFT’s prior to therapy
  - Elimination of other P450 pathway drugs
  - Patient informed consent
  - LFT’s every 3-4 weeks
  - Monitor ankle edema
- IF patient responds, response seen in 3-4 weeks
  - If improvement, treat 2-3 months
Medical Therapy in The Patient With Difficult to Treat CRS

Itraconazole

- Hepatotoxic
- Cardiotoxic
- Very Expensive
- However, appears to work dramatically in a limited subset of polyp patients (including some ASA Sensitive patients)
- Mode of action uncertain (potent antiangiogenesis)
- Patient selection for therapy not defined
- No controlled trials
Local Postoperative Care

Day 1 or 2, and weekly until healed

- Suction maxillary and frontal sinuses
- Remove crusts
- Divide adhesions
- Remove residual/recurrent mucosal disease
- Remove osteitic bone
- Endoscopic appearance, not symptoms guides medical therapy
Future Potential for Wound Healing Nasal Irrigation?

- PHI currently used in skin ulcers (Tegaderm Matrix wound dressings)
- Rabbit Model
- Identical lesions created in maxillary sinuses
- Both maxillary sinuses irrigated twice daily for 2 weeks
- One side saline, opposite side modified PHI
Hematoxylin & Eosin

1. Normal Saline vs RhinActive
Type IV β Tubulin

1. Normal Saline vs RhinActive
**Postoperative Irrigation with Ionogens: Results for Mucosal Ciliary Recovery at 2 weeks**

<table>
<thead>
<tr>
<th></th>
<th>0 %</th>
<th>&lt; 30 %</th>
<th>30 - 60 %</th>
<th>&gt; 60%</th>
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<tbody>
<tr>
<td><strong>Hematoxylin &amp; Eosin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>53</td>
<td>46</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td>Rhinactive</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>175</td>
</tr>
<tr>
<td><strong>β Tubulin Type IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>53</td>
<td>46</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Rhinactive g/Br</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>186</td>
</tr>
</tbody>
</table>
Postoperative Care

- Surgery is largely adjunctive to the medical therapy
- Endoscopic follow up and debridement is required because
  - Persistent disease is frequently asymptomatic
  - Persistent disease is frequently localized
  - Scarring is natural sequella of inflammation and trauma
Medical Therapy in The Patient With Difficult to Treat CRS

**Treatment Goals**

- Not just symptom resolution
- Endoscopic resolution of Disease
- Stable mucosa
- Gradual resolution of mucosal hyper-reactivity
- Slow withdrawal of medical therapy (oral steroids 1st)
- Avoidance of long term recurrence
Rhinosinusitis
Objective vs. Subjective Outcomes
Kennedy Study

- 126 patients
- 56 enrolled prospectively
- 70 enrolled retrospectively (consecutive follow-up)
- 120 evaluated by questionnaire and endoscopically at mean f/u 18 months post surgery
Objective vs. Subjective Outcomes

Kennedy Study

- 240 fields of information collected/patient
- Questionnaires re-mailed to patients at 7.8 years mean post surgery
Rhinosinusitis

Kennedy Study

- 71% prior nasal/sinus surgery
- 49% at least one prior ethmoidectomy
- Maximum number of procedures - 13
Subjective Results by Extent of Perioperative Disease

<table>
<thead>
<tr>
<th></th>
<th>Non Polyposis (n=49)</th>
<th>Middle Meatal Polyposis (n=37)</th>
<th>Diffuse Polyposis (n=34)</th>
<th>Total (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked improvement</td>
<td>40 (81.6%)</td>
<td>33 (89.2%)</td>
<td>29 (85.4%)</td>
<td>102</td>
</tr>
<tr>
<td>Mild improvement</td>
<td>7 (14.3%)</td>
<td>4 (10.8%)</td>
<td>4 (11.7%)</td>
<td>15</td>
</tr>
<tr>
<td>No improvement or</td>
<td>2 (4.1%)</td>
<td>0</td>
<td>1 (2.9%)</td>
<td>3</td>
</tr>
<tr>
<td>worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Overall Endoscopic Postoperative Findings in the Operated Cavities

1.5 year (mean) Follow-up

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Well Healed*</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>68 (77.3%)</td>
<td>20 (22.7%)</td>
</tr>
<tr>
<td>Middle meatal polyps</td>
<td>41 (57.7%)</td>
<td>30 (42.3%)</td>
</tr>
<tr>
<td>Diffuse polyps</td>
<td>16 (23.5%)</td>
<td>52 (76.5%)</td>
</tr>
<tr>
<td>Totals</td>
<td>125 (55.1%)</td>
<td>102 (44.9%)</td>
</tr>
</tbody>
</table>
Rhinosinusitis

Results

At 18 months post-surgery:
- Subjective improvement was independent of disease stage
- Endoscopic findings were highly dependent on disease stage
Sinusitis Study

Conclusions

• Early symptomatic improvement, same or better in diffuse disease
• Symptomatic improvement does not correlate well to resolution of disease
• Asymptomatic persistent disease common in diffuse sinonasal polyposis
• Objective outcome correlates closely with preoperative extent of disease
• Smoking is a contraindication to elective FESS
• Disease should be staged radiographically
FESS: Long Term Results

- Overall Symptom Improvement
  - 71% 7.8 years
  - 68% 1.5 years

- (p=0.605, Mann-Whitney U Test)

- 18% Of this pre-selected group of patients (75% prior surgery, up to 13 surgeries prior to study) had undergone revision surgery in the 7.8 year follow up period
FESS: Long Term Results

Percent of Patient Reporting Improvement

- Headache/Pressure: 92.2%
- Nasal discharge: 93.4%
- Nasal congestion: 97.1%
- Sense of smell: 80%
- Recurrent infections: 92%
FESS: Long Term Results

Medication Uses

- Antibiotics
  - 82% less antibiotics

- Patients on oral steroids at time of surgery
  - 69% of patients had decreased requirement at 1.5 yrs
  - 75% of patients had decreased requirement at 7.8 yrs
FESS: LONG TERM RESULTS

Asthma

27/30 (90%) pts. reported improvement in severity

Number of attacks:
Less 20/27 pts. (74.1%)
Unchanged 4/27 pts. (14.8%)
More 3/27 pts. (11.1%)
FESS: LONG TERM RESULTS

Asthma

Symptom score improvement
61% at 7.8 years
49% at 1.5 years

Medication Usage
49% decreased inhaler usage
(average decrease 71.4%)
65% decreased oral steroids
(average decline 66%)
To use endoscopic evaluation and treatment to manage persistent, asymptomatic disease, adjust medical management and avoid symptomatic recurrence.
Local Therapy

- Demonstrates significant promise
- Should help to improve healing
- May be the future when combined with balloon dilatation/minimalistic surgery
Evolution Endoscopic Surgical Techniques Outside of CRS

- Improved surgical techniques and instrumentation
- Reliable closure of Skull base defects
- Endoscopic Pituitary surgery (initiated 1988)
- Endoscopic orbital surgery (initiated 1987, published 1990)
- Endoscopic oncologic surgery (initiated 1989)
The Expanding Role of Endoscopic Techniques: Skull Base and Intracranial Surgery

Factors

• Ability to close skull base defects - (91-95% success)
• Increased familiarity
• Image guidance
• Intraoperative low dose CT
• Endoscrub
• Tissue debriders
• Suction-irrigation drills
• More focused adjunctive therapy
Robotic Skull Base Surgery

• Potentially very exciting
• Ability to cauterize and operate in currently inaccessible areas
• Absence of tremor
• Improved closure
Endoscopic sinus surgery in 2014 – What has changed?

Summary

- Better understanding of pathogenesis
- Improved understanding of surgery indications in CRS
- Improved instrumentation and surgical techniques
- Viable extended endoscopic techniques for frontal sinus surgery
- Recognition of persistent asymptomatic disease
- Critical nature of postoperative medical management
- Extension endoscopic oncologic skull base