“Randomized Controlled Trials in Surgery: History, Utility, and Examples”

Given by
Charles J. Yeo, MD, FACS
Samuel D. Gross Professor and Chairman
Department of Surgery
Sidney Kimmel Medical College at Thomas Jefferson University
Senior Vice President and Chair, Enterprise Surgery
Jefferson Health

Date: Thursday, July 13, 2017
Time: 7:00 AM – 8:00 AM
Location: Foerderer Auditorium, McClellan Hall,
Sidney Kimmel Medical College, 1025 Walnut Street
2nd Floor

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RSS Title: Surgery Grand Rounds

RSS Code: SUGNGRDRDS

Session Date: 07/13/2017

To Record Your Attendance, TEXT SESSION CODE TO 215-323-5008

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Topic: Grand Rounds: “Randomized Controlled Trials in Surgery: History, Utility, and Examples”

Presenter(s): Yeo, Charles

RSS Goals: Discuss, promote critical thinking and obtain solutions for practice-related ethical problems

Review the risks, benefits, needs and outcomes for surgical procedures

Identify opportunities for improvement in patient care and outcomes

Promote critical thinking through expert solutions, improve communications among all

REQUIRED INFORMATION/ACKNOWLEDGEMENTS TO PARTICIPANTS:

Conflict of Interest Disclosure: Unless otherwise noted by the presence of a "CME COI SUMMARY" document, the planners of this RSS and today's presenter(s) indicated that they have no commercial relationships to disclose. NOTE: ACCME requires that the lack of relationships also be disclosed to the audience.

In addition, Planners/Presenters are expected to ANNOUNCE their disclosure information to the audience at the start of the session.

Suggested verbiage: Dr X has no relevant commercial relationships to disclose.

OR, Dr X is a ____ (i.e., consultant) for Company XYZ.

Circle all that apply (regarding outside support): No Outside Support Grant Received Exhibit Fee Received

Company Name: __________________________ Amount: $ ____________

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Disclosure Summary

Charles Yeo

Activity

<table>
<thead>
<tr>
<th>Name of CME Activity</th>
<th>Date of CME Activity</th>
<th>My content involves off label or investigational use of an FDA regulated product</th>
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</thead>
<tbody>
<tr>
<td>Surgery Grand Rounds</td>
<td>7/13/17</td>
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In my role for the CME Activity, I attest my contributions will be free from commercial bias or influence; that any clinical practice recommendations relating to my contribution to this activity will be supported by the best available evidence, or absent evidence, will be consistent with generally accepted medical practice and scientific method; and will present a balanced view of reasonable clinical alternatives.

Attestation - Yes

Declaration of Relevant Personal Financial Relationships

I have no relevant financial relationships/conflicts of interest to declare.
Randomized Controlled Trials in Surgery: History, Utility and Examples

Charles J. Yeo, MD, FACS
8th Samuel D. Gross Professor and Chairman
Department of Surgery
Sidney Kimmel Medical College
Thomas Jefferson University
Senior Vice President and Chair, Enterprise Surgery
Jefferson Health
Perfect Timing - The story behind this lecture topic....

• Thanks to Dr. Peter Allen and Bill Nealon for their invitations to lecture; emails over the summer of 2016: SSO-March 2017-Seattle; P Club-May 2017-Chicago

• Asked for more details...looked at my calendar; two moments of weakness- I agreed

• Then began the realization that this would be much work; no “canned talk”; regrets ensued

• And then my nearly 40 year relationship with the NEJM again bore fruit: “History of Clinical Trials” and “The Changing Face of Clinical Trials”

Bonus:
• I could use some of the material herein for Dr. John Cameron’s Festschrift last month, and I could deliver the first Grand Rounds talk of the new academic year 2017/18 - sweet!
The Great Debates I
Society of Surgical Oncology: March 17th, 2017

Debate: *Randomized Controlled Trials Evaluating Surgical Technique are Optimal for Improving the Surgical Management of Patients: Pro*

Charles J. Yeo, MD, FACS
8th Samuel D. Gross Professor and Chairman
Department of Surgery
Sidney Kimmel Medical College
Thomas Jefferson University
Senior Vice President and Chair, Enterprise Surgery
Jefferson Health
HOW I DO IT
The Pancreas Club: May 6th, 2017

Hypothesis: *Randomized Controlled Trials are Optimal for Improving the Surgical Management of Patients and Should be Encouraged: The Chair Position*

Charles J. Yeo, MD, FACS
8th Samuel D. Gross Professor and Chairman
Department of Surgery
Sidney Kimmel Medical College
Thomas Jefferson University
Senior Vice President and Chair, Enterprise Surgery
Jefferson Health
“Congratulations on those really great studies in rats. How do these translate to my patients who don’t have fur, tails, live on chow and have a life-span longer than two years.”
Disclosures

- No industry support for this presentation
- No COIs that I am aware of
- I am biased in favor of randomized controlled trials (RCTs)
- Co-author on 12 surgical RCTs in the literature
- Investigator in 2 RCTs ( ? soon 3) currently enrolling patients at Thomas Jefferson in Center City Philadelphia- go Eagles and Sixers and Flyers in 2017-18 !
A Prospective, Randomized, Double-Blind, Placebo Controlled Trial on the Efficacy of Ethanol Celiac Plexus Neurolysis in Patients with Operable Pancreatic and Periampullary Adenocarcinoma

Harish Lavu, MD, FACS, Harry B Lengel, BA, Naomi M Sell, BA, Joseph A Baiocco, BS, Eugene P Kennedy, MD, FACS, Theresa P Yeo, PhD, Sherry A Burrell, PhD, Jordan M Winter, MD, FACS, Sarah Hegarty, MPhil, Benjamin E Leiby, PhD, Charles J Yeo, MD, FACS

Despite substantial improvements in surgery, radiation, and chemotherapy, specifically for
Objectives

- Entertain, educate and have some fun
- History of clinical trials and RCTs
- Big data
- Levels of evidence and the pyramids
- Conflict of evidence
- CONSORT checklist - the “cookbook” for success
- Sweet Sixteen: The Prospective Clinical Trials of John L. Cameron
- Closing thoughts - role of the Chair
History of Clinical Trials

The Emergence of the Randomized, Controlled Trial

Laura E. Beshore, Ph.D., and Scott H. Podolsky, M.D.

The birth of the randomized, controlled trial (RCT) is typically dated to 1948 by evaluation of the British Medical Research Council (MRC) of streptomycin for the treatment of tuberculosis.

But controlled clinical trials and discussions of their designs were increasingly being published in medical journals for at least half a century before the MRC’s report, which was part of a much longer history of efforts to empirically assess experimental therapies. An exploration of this deeper history offers insights into the intellectual and social forces shaping both the advent of and resistance to the controlled clinical trial as a medical research standard and mechanism for testing the therapeutic marketplace.

Trials involving experimental and control groups seem as old as the historical record itself, appearing in the Hebrew Bible and in various societies around the world, albeit sporadically, for centuries. As Enlightenment reasoning filtered into medicine, controlled trials emerged with growing frequency. In 1773, Scottish surgeon James Lind published a controlled trial demonstrating that a diet including citrus fruit was effective against scurvy in sailors at sea, thereby providing a touchstone for subsequent generations of researchers who gradually embraced comparative trial methods.

Lonely controlled trials increasingly appeared in the 18th and 19th centuries, often conducted by skeptics to test the utility of unorthodox remedies ranging from mesmerism to homeopathy. Major shifts in the social and scientific structure of medicine in the late 19th and early 20th centuries created new opportunities and demands for more rigorous clinical research methods. Hospitals expanded, new biologic and surgical innovations emerged to confront recently identified germs, chemists developed novel therapeutic compounds, and an unraveled subeconomy of fraudulent replicas of new agents flourished. All these factors motivated clinical investigators to pursue more sophisticated approaches for evaluating experimental therapies.

By the late 19th century, researchers were conducting “ultra-
Birth of the RCT is typically dated to 1948 when Hill and the British Medical Research Council (MRC) evaluated streptomycin for the treatment of TB, but...

Trials involving experimental and control groups are found in antiquity; the Hebrew Bible, other sources, etc.

With the age of Enlightenment, controlled trials emerged with growing frequency

1753- Scottish surgeon James Lind published a controlled trial demonstrating that citrus fruit ingestion protected sailors against scurvy
History of Clinical Trials-2
The Emergence of the Randomized, Controlled Trial
(Bothwell and Podolsky: NEJM: 375: 501-504, 2016)

• 18th and 19th centuries: loosely controlled trials increasingly appeared, often conducted by skeptics to test the utility of unorthodox remedies, ranging from mesmerism to homeopathy

• Late 19th and early 20th centuries: major shifts in the social and scientific structure of medicine created new opportunities and demands for more rigorous clinical research methods; hospital expansion; new biologic and vaccine industries emerged to confront recently identified pathogens; chemists developed novel therapeutic compounds; and sadly, an unregulated sub-economy of fraudulent replicas of new agents flourished (fake medical news)
History of Clinical Trials-3
The Emergence of the Randomized, Controlled Trial
(Bothwell and Podolsky: NEJM: 375: 501-504, 2016)

• “Alternate-allocation” trials flourished in the late 19th century - the nearest methodological ancestor of RCTs

• Off-quoted example: Johannes Fibiger’s 1898 study of diphtheria antitoxin in 484 patients in Copenhagen, entailing alternating treatments every other day

• 1899- Williams’ study: applying a glycerin-hydrogen peroxide solution to the skin of alternating patients to treat desquamation caused by scarlet fever (positive outcome!)

• Note- an outlier study in 1931 by James Burns Amberson et al used a coin flip to allocate equally divided groups of patients to receive sanocrysin for the treatment of TB

• Numerous examples of alternate-allocation trials were published in the NEJM before 1948
History of Clinical Trials-4
The Emergence of the Randomized, Controlled Trial
(Bothwell and Podolsky: NEJM: 375: 501-504, 2016)

Selected Alternate-Allocation Studies and Discussions Published in the Journal before 1948.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study/Medication/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1931a</td>
<td>Davis WE. The incidence of untoward symptoms following the intravenous injection of sodium tetraiodophenolphthalein in cholecystography. 205:534–6.</td>
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<tr>
<td>1931b</td>
<td>The clinical meeting of the Massachusetts General Hospital staff. 205:1319–20.</td>
</tr>
<tr>
<td>1935c</td>
<td>King DS. Correspondence: diathermy in lobar pneumonia. 213:1324–5.</td>
</tr>
<tr>
<td>1936b</td>
<td>Wetherbee W. Correspondence: a discussion of Dr. Donald S. King’s criticism. 214:174–5.</td>
</tr>
<tr>
<td>1936c</td>
<td>Prontylin and prontosil. 215:1311.</td>
</tr>
<tr>
<td>1941a</td>
<td>Finland M. Controlling clinical therapeutic experiments with specific serums: with particular reference to antipneumococcus serums. 225:495–506.</td>
</tr>
<tr>
<td>1941b</td>
<td>Combined serotherapy and chemotherapy in pneumonia. 225:514–5.</td>
</tr>
</tbody>
</table>
History of Clinical Trials-5
The Emergence of the Randomized, Controlled Trial
(Bothwell and Podolsky: NEJM: 375: 501-504, 2016)

• First half of 20th century: the number of alternate-allocation trials was dwarfed by poorly done studies, case reports, studies lacking rigor, biased studies

• As would be expected: some researchers resisted controlled trials, noting that participants should not be denied promising treatments by being assigned to control groups; stated humanistically “sentiment overruled reason”

• The key short-coming of alternate-allocation trials: many investigators noted that selection bias (cheating the process of strict allocation) remained the Achilles heel of alternate-allocation...best said by Finland “some unconscious selection on the part of authors played an important role in the inclusion of the poorest subjects among the serum recipients (versus serum plus sulfa for pneumonia)”
Credit goes to British epidemiologist-statistician Austin Bradford Hill with wholly recognizing the limitations of alternative-allocation trials (read: figure out and cheat), so that he instituted strict concealed randomization in the evaluation of streptomycin for TB.

The blinding of researchers to patients’ assignments soon accompanied concealed random allocation in the emerging definition of the ideal study, in which bias was to be eliminated.

Supported by British MRC funding in the 1940s and 1950s, Hill and colleagues impressed the research community with a series of groundbreaking RCTs.

Thereafter... embraced by the U.S. Food and Drug Administration (FDA)- such that by 1970 the FDA required that drug producers submit RCT results with new drug applications.
RCTs in summary:
• Represent the most recent outgrowth of a long history of attempts to adjudicate therapeutic efficacy

• Their immediate ancestor, alternate-allocation trials, emerged as part of a trend toward empiricism and systematization in medicine and science

• Have been supported by crucial public funding and scientific regulatory infrastructures

• Serve a critical social function: to screen experimental therapies before they are broadly distributed, hence clarifying the true results of medical innovations
Original article

Big data: Are large prospective randomized trials obsolete in the future?

Clifford A. Hudis a, b, * 

*Memorial Sloan Kettering Cancer Center, United States
b West Cornell Medical College, United States

• Writing in the breast cancer domain- fascinating observation: although a common cancer, fortunately for the majority affected, non-lethal, hence “many of the patients who may be accrued to prospective RCTs never experience the event that defines the primary endpoint. This introduces expense and inefficiency since these patients must be followed for many years in anticipation of an event that never occurs.” (Brilliant, and somewhat lost on a pancreas surgeon!)

• “The low event rate is, however, a paradoxical justification for prospective randomized trials.”

• “In addition, the modest therapeutic benefit of most active agents, the presence of significant toxicities, the possibility of biased observations, and the well recognized placebo effect all justify and even require the use of prospective RCTs to resolve relevant treatment questions.”
Big Data: Are Large Prospective Randomized Trials Obsolete in the Future? - 2

Some key features of RCTs:
• Comparison, under controlled conditions, of two or more therapeutic interventions
• Use of a statistical design focused on the possibility of error
• Assignment in unbiased fashion to control or treatment groups
• Whenever possible, blinding on the part of both the study subjects and the investigators
• Speed of completion: varies, but slow for large “N” studies
• Expense: varies, but can be high and increasing for large “N” studies
• Efficiency: as therapeutics improve overall, falling event rates
• Confounders: differing primary and secondary endpoints
• Assembled together, RCTs provide ammunition for meta-analysis techniques
• “Clearly then a role for prospective RCTs is supported both at the level of the individual study but also through their contributions to aggregate analyses.”
Big Data: Are Large Prospective Randomized Trials Obsolete in the Future?-3

Placing RCTs into clinical context:

- The responsibility of guidelines groups, organized on a global level

- Have generated “Levels of Evidence”…which, interestingly are not identical

- Many groups: Canadian Task Force on Periodic Health Examinations, NCCN (National Comprehensive Cancer Network), many others...

- NCCN- a non-profit alliance of 27 cancer centers in the U.S. headquartered in Fort Washington, PA and chaired by Surgery’s own Tim Eberlein, MD

- Recall that NCCN category 1 is a guideline based on a high level of evidence with uniform consensus on the part of the committee!
“Our task force had six meetings, excellent attendance and, fortunately, did not come up with a single recommendation.”
Big Data: Are Large Prospective Randomized Trials Obsolete in the Future? -4

RCTs versus Big Data: Not a choice of either/or

• Electronic Health Records (EHRs) are here, and offer a vast opportunity...but, just in the process of our own current EPIC launch there are real challenges in the unprecedented amounts of data, its storage, its sharing and its “mine-ability” that must be overcome

• Large datasets- SEER, NIS, NSQIP, CancerLinQ, others: with the ability to explore patient outcomes in thousands of patients, based upon available treatment differences

• Critical limitations of big data sets: selective or voluntary inclusion criteria; incomplete data entry, auditing and follow-up; biased treatment selection
Conclusions

- Big data provide unique opportunities

- Some comparative effectiveness research questions cannot be considered in a prospective RCT fashion, but can be explored using big data sets

- Hypothesis-generating exploration of the available data could lead to iterative improvements in the applications of currently available treatments

- Are RCTs going to become obsolete? No!

- Are RCTs always needed to answer all clinical questions? No! (the parachute analogy)

- RCTs may be supplemented and complemented by big data

- Big data can efficiently generate hypotheses and help plan RCTs...in fact, big data will help make RCTs better!
FEATURE

211 When Do DCD Donors Die? Outcomes and Implications of DCD at a High-volume, Single-center OPO in the United States
Joseph R. Scalise, MD, Robert B. Redfield, MD, Michael D. Rizzuto, MD, Ryan Bennett, CST, Michael E. Anderson, PA, James E. Anderson, CST, David H. Krajewski, MD, PhD, Hans W. Sellinger, MD, Luis A. Fernandez, MD, Anthony M. D'Alessandro, MD, and Joshua Merrick, MD

We investigated the time it takes solid organ transplant donors to die, when these patients have donated following circulatory death (DCD). Many organ transplants are not performed because DCD donors fail in the quickly enough. Beyond our results, these outcomes lead to several ethically charged issues important to surgeons.

EDITORIAL

217 Emerging Ethical Considerations of Donation After Circulatory Death: Getting to the Heart of the Matter
Thomas K. Gallagher, MD, FRCS, Anson E. Slavin, MD, PA, and Michael M. Abecassis, MD, MBA

Controlled donation after circulatory death (DCD) poses unique challenges in both logistics and ethics. Despite many reports attempting to predict whether DCD donors will expire in a timely manner consistent with organ donation, none of these tools has gained universal acceptance. There is still considerable inter-hospital variation in the policies governing DCD recovery. The proposed introduction of donation by the immuno-dead (DID) procurement would represent a monumental change in the field of organ transplantation and would likely prompt a similar magnitude in ethical discourse. Ultimately, defining what is ethically acceptable must be balanced with maintaining the public trust, which is sacrosanct in the field of transplantation.

FEATURE

219 Complications After Mastectomy and Immediate Breast Reconstruction for Breast Cancer: A Claims-based Analysis

Redha A. El-Deeb, MD, MPH, Jing Jiang, MS, Edeyza O. Morik, MD, Amy Alderman, MD, MPH, Shawn H. Giordano, MD, MPH, Thomas A. Bachhoda, MD, Lori J. Peerio, MD, Steven J. Krommets, MD, and Benjamin D. Smith, MD

Using the claims-based MarketScan database, we evaluated complications among women who underwent mastectomy for breast cancer from 1998 to 2007 and who received immediate autologous reconstruction, immediate implant-based reconstruction, or no reconstruction within the first two postoperative years. Complications differed somewhat by approach. Radiation therapy was associated with modestly increased risks.

EDITORIAL

228 Complications After Mastectomy and Immediate Breast Reconstruction for Breast Cancer: How Does the Community Compare?
Amy S. Cohrel, MD, FACS and Barbara L. Smith, MD, PA, FACS

A nationwide claims-based data set of insured patients to identify 14,884 women who underwent mastectomy for breast cancer from 1998 to 2007 confirmed center of excellence findings that immediate reconstruction has higher rates of complications than mastectomy alone. It also showed that radiation increased the rate of infection, the rate of implant lysis in implant-based reconstructions, and the rate of fat necrosis in autologous tissue reconstructions. With the degree of complexity and risk inherent in modern breast reconstruction surgery, it is essential to provide care through a center of excellence whenever possible and to continue to transfer lessons learned to all practice settings.
SURGICAL PERSPECTIVES

A Death in the Family: Lessons From a Tragedy
Eric Gotlibick, MD, MS, Michael J. Zinner, MD, and Stanley W. Ashley, MD
Active shooter incidents, like the one in January 2013 at Brigham and Women’s Hospital, should prompt hospitals to examine individual and collective responses, identify opportunities for improvement, and define future actions. Such analyses require looking at the event objectively through three distinct lenses: prevention, response, and recovery. The lessons learned are unlikely to prevent all hospital-related shootings from occurring, however, they will strengthen our ability to respond if and when they do.

Is Graduate Medical Education a Public Good?
Srinivas M. Subara, DMD, MD, MPH, Justin M. Sacks, MD, Anthony P. Tufano, DMD, MD, and Richard J. Redett, MD
The recent policy initiatives related to the Affordable Care Act have questioned the notion of graduate medical education as a public good that deserves federal funding. Graduate medical education in the changing climate of healthcare reform may not meet all of the features of a public good, but it has enormous value in doing the public good.

REVIEW PAPER

The Conflicting Evidence of Three-dimensional Displays in Laparoscopy: A Review of Systems Old and New
Shihtsou Sakata, MRBS, Marcus O. Wason, PhD, Philip M. Green, PhD, and Andrew R. L. Stevenson, FRACS
This review addresses the conflicting performance data obtained from surgeons and reviews using 3D and 2D laparoscopic displays over the last two decades.

RANDOMIZED CONTROLLED TRIALS

Less Pain 1 Year After Total Extra-peritoneal Repair Compared With Lichtenstein Using Local Anesthesia: Data From a Randomized Controlled Clinical Trial
Lisa Weisz, MD, Steffen Weilert, MD, PhD, Mihail Gopaul, MD, PhD, Gabriel Sandblom, MD, PhD, Ulf Gunnarsson, MD, PhD, and Orudha Dahllund, MD, PhD
A randomized controlled trial was conducted on men with a primary, unilateral inguinal hernia that required surgery. Patients were randomized to either endoscopic total extra-peritoneal repair (TEP) using local anesthesia. Patients in the TEP group reported less pain one year after surgery.

Quality of Life and Surgical Outcome 1 Year After Open and Laparoscopic Incisional Hernia Repair: PROLOVE: A Randomized Controlled Trial
Peter Bergmark, MD, Ulf Petersson, MD, PhD, Sven Brogren, MD, PhD, Emmanuel Eru, MD, Johanna Österberg, MD, PhD, and Agnete Montgomery, MD, PhD
Quality of life is restored after incisional hernia surgery, with no difference between surgical techniques. Male sex and laparoscopy predict event-free recovery. SF-36 appears well suited for assessing surgical outcome in patients after incisional hernia repair.

META ANALYSES

Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis
John Maret-Ouda, MD, Peter Komog, MSc, Jesper Lagergren, MD, PhD, and Nele Brudin, MD, MS, PhD
This meta-analysis indicates that antireflux surgery may prevent esophageal adenocarcinoma better than medical therapy in patients with gastroesophageal reflux disease with Barrett’s esophagus, but the IAC risk does not seem to revert to that of the background population.

Suture Cruroplasty Versus Prosthetic Hiatal Hernioplasty for Large Hiatal Hernia: A Meta-analysis and Systematic Review of Randomized Controlled Trials
Muhammad Asif Memon, MRBS, MD, Cinal Ed, DCH, FRACS, FRCSI, FRCSEd, FACS, Breda Memon, RN, LTB, PGCE, DipPractMan, Roshina Mohammed Yamas, PhD, and Shahzad Khan, PhD
We conducted a meta-analysis and systematic review of randomized controlled trials, comparing suture cruroplasty versus prosthetic hiatal hernioplasty for large hiatus hernia, to determine the clinical outcomes, safety, and effectiveness of these two methods. Four RCTs, between 1993 and 2014 totaling 406 patients (Suture = 186, Prosthesis = 220), were analyzed and results presented.

*Note RCTs before meta-analyses
The Lancet publishes randomised controlled trials faster

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Hierarchy of Research Designs & Levels of Scientific Evidence

- Clinical Practice Guidelines
- Meta-Analysis
- Systematic Reviews
- Randomized Controlled Trials
-Prospective, tests treatment
- Cohort Studies
-Prospective: cohort has been exposed to a risk. Observe for outcome of interest
- Case Control Studies
-Retrospective: subjects have the outcome of interest; looking for risk factor
- Case Report or Case Series
-Narrative Reviews, Expert Opinions, Editorials
-Animal and Laboratory Studies

Secondary, pre-appraised, or filtered Studies

Primary Studies
- Observational Studies

No design
- Not involved w/ humans
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<td>Randomized control trial (RCT)</td>
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<td>Meta-analysis of RCT with homogeneous results</td>
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<td>Prospective comparative study (therapeutic)</td>
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<td>Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results</td>
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<td>Retrospective Cohort Study</td>
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<td>Case-control Study</td>
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<td>Meta-analysis of Level 3 studies</td>
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Conflict of Evidence: Resolving Discrepancies When Findings from Randomized Controlled Trials and Meta-analyses Disagree

Richard J. Sylvester,*, Steven E. Canfield, Thomas B.L. Lam, Lorenzo Marconi, Steven MacLennan, Yuhong Yuan, Graeme MacLennan, John Norrie, Muhammad Imran Omar, Harman M. Bruins, Virginia Hernández, Karin Plass, Hendrik Van Poppel, James N'Dow

*EAU Guidelines Office, Brussels, Belgium; Division of Urology, University of Texas McGovern Medical School, Houston, TX, USA; Academic Urology Unit, University of Aberdeen, Aberdeen, UK; Department of Urology, Coimbra University Hospital, Coimbra, Portugal; Department of Medicine, McMaster University, Hamilton, ON, Canada; Health Services Research Unit, University of Aberdeen, Aberdeen, UK; Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands; Department of Urology, Hospital Universitario Fundación Alcorcon, Madrid, Spain; EAU Central Office, Guidelines Office, Arnhem, The Netherlands; Department of Urology, University Hospital Gütersloh, Katholieke Universiteit Leuven, Leuven, Belgium
Conflict of Evidence: Resolving discrepancies when findings from RCTs and MAs disagree
(Sylvester et al. Europ Urol 2016)

• Not uncommon for the results of a large RCT to be inconsistent with evidence from a systematic review (SR) or a meta-analysis (MA). Assuming the large conflicting RCT was of high quality, then...

• The starting point is to address the methodological quality of the SR or MA. Assessment of Multiple Systematic Reviews (AMSTAR) and Documentation and Appraisal Review Tool (DART) checklists allow readers to judge a SR or MA’s quality by focusing on its essential components

• The next two slides provide direction to clinicians and guideline developers when there is a conflict between a large RCT and a SR/MA
Table 3 - Checklist of points to consider when the findings from a systematic review and meta-analysis differ with those from a large randomized controlled trial

<table>
<thead>
<tr>
<th>Criteria to consider</th>
<th>Questions to ask</th>
<th>Rationale</th>
</tr>
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<tbody>
<tr>
<td>Selection bias</td>
<td>Were the sequence generation and allocation concealment adequate in both the studies included in the SR/MA and the subsequent RCT?</td>
<td>If the sequence generation was not truly random or the allocation was not effectively concealed, this can lead to exaggerated estimates in individual studies, and these may be amplified in MAs.</td>
</tr>
<tr>
<td>Confounding bias</td>
<td>Were the groups balanced for known prognostic factors at baseline and were any imbalances controlled for in the analysis?</td>
<td>Imbalances in known and unknown prognostic factors are possible even in well-designed RCTs. Baseline imbalances may explain differences in estimates of effect if not controlled for in the analysis.</td>
</tr>
<tr>
<td>Performance and detection bias</td>
<td>Where possible, in all the studies included in the SR/MA and for the new RCT, was there blinding of study participants, clinicians administering the treatment, ancillary care-givers, and outcomes assessors? When blinding is not possible, could knowledge of the treatment received affect interpretation of any of the outcomes?</td>
<td>Some objective outcomes are unlikely to be affected by knowledge of the intervention arm, but failure to blind (particularly for subjective outcomes) may lead to an exaggeration of effect sizes in individual studies, and these may be amplified in MAs.</td>
</tr>
<tr>
<td>Attrition bias</td>
<td>Were all dropouts documented and unlikely to be related to the treatment outcome in the studies included in the SR/MA and in the new RCT?</td>
<td>If dropout rates differ between the treatment arms, then the reasons may be related to the outcome of interest and may hide important outcome effects.</td>
</tr>
<tr>
<td>Reporting bias</td>
<td>Were all outcomes that were stated in the methods and/or protocol for all the studies included in the SR/MA and in the new RCT documented in the trial report? Were all the outcomes measured appropriately (as defined in the protocol) or were deviations reasonably explained?</td>
<td>Selective reporting of outcomes, or selective methods of reporting, may lead to exaggerated estimates of effect.</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Were funnel plots used to investigate publication bias in the SR/MA? Is the funnel plot symmetric or is there reason to believe there is a systematic difference between published and unpublished studies? Note: This is difficult to assess when there are &lt;10 RCTs contributing to an MA.</td>
<td>Asymmetric funnel plots raise suspicion that there are systematic differences between published and unpublished studies and that some positive or negative trials may be unpublished. This may lead to exaggerated effect sizes in an MA.</td>
</tr>
<tr>
<td>Consistency and heterogeneity of outcome</td>
<td>Did the studies included in the SR/MA have overlapping 95% CIs for the outcome? Was variation more than would be expected by chance alone? Was the $I^2$ statistic &lt;40%? (Cochrane/GRADE rule of thumb) Were subgroups used to explain any observed heterogeneity? Were event rates in the control group similar in the different studies? Note: Subgroups of the population, the intervention/control types, or the outcome measurement may explain heterogeneity.</td>
<td>If it can be shown that the outcomes are more effective in certain subgroups, or with variations of an intervention (eg, a higher dose), then this explained heterogeneity may indicate a key difference that may justify the results in the new RCT. Where unexplained heterogeneity exists, then the estimate of effect is likely to be uncertain, even if precise.</td>
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<tr>
<td>Directness</td>
<td>Do the studies included in the SR/MA and the new RCT both directly assess the research question about the population, interventions, and outcomes?</td>
<td>Indirect populations, interventions, surrogate outcome measures, or indirect comparisons may conceal or exaggerate important differences within and between studies, and may impact the estimate of effect.</td>
</tr>
<tr>
<td>Precision</td>
<td>Were the sample sizes for the studies included in the SR/MA and the new RCT powered to address the outcomes of interest? Does the 95% CI in the MA include clinically judged appreciable benefit and harm?</td>
<td>If any of the trials in the SR/MA or the new RCT were not powered to detect a clinically meaningful difference in the effect estimate, this may reduce confidence in the estimate of effect. If the lower and upper 95% CI thresholds indicate that the intervention may be beneficial at one end, but harmful at the other, this will probably reduce confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td>When some studies included in an SR/MA are judged to be at high RoB and others at low RoB, or extreme variations in the populations or interventions in the studies are apparent, did the authors conduct a sensitivity analysis to ascertain the estimates of effect for only studies judged to be at low RoB?</td>
<td>Sensitivity analyses are different from subgroup analyses. Some studies are actively omitted as we are only interested in the results when the biased or “different” studies are omitted.</td>
</tr>
</tbody>
</table>

SR = systematic review; MA = meta-analysis; RCT = randomized controlled trial; CI = confidence interval; RoB = risk of bias.
CONSORT 2010 Flow Diagram

Enrollment

Assessed for eligibility (n= )

- Excluded (n=)
  - Not meeting inclusion criteria (n=)
  - Declined to participate (n=)
  - Other reasons (n=)

Randomized (n=)

Allocation

Allocated to intervention (n=)
  - Received allocated intervention (n=)
  - Did not receive allocated intervention (give reasons) (n=)

Allocated to intervention (n=)
  - Received allocated intervention (n=)
  - Did not receive allocated intervention (give reasons) (n=)

Follow-Up

Lost to follow-up (give reasons) (n=)
  - Discontinued intervention (give reasons) (n=)

Lost to follow-up (give reasons) (n=)
  - Discontinued intervention (give reasons) (n=)

Analysis

Analysed (n=)
  - Excluded from analysis (give reasons) (n=)

Analysed (n=)
  - Excluded from analysis (give reasons) (n=)
**CONSORT 2010 checklist of information to include when reporting a randomised trial**

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td></td>
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<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td></td>
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<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
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<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td></td>
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<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
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<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td></td>
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<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
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<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
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<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
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<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
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<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
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<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td></td>
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<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td></td>
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<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
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<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
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<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
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<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
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<tr>
<td>Item</td>
<td>Description</td>
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<tr>
<td>11b</td>
<td>Assessing outcomes and how if relevant, description of the similarity of interventions</td>
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<tr>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
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<tr>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
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</tr>
<tr>
<td>13a</td>
<td>Participant flow (a diagram is strongly recommended) For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome</td>
<td></td>
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<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
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<tr>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
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<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
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<tr>
<td>15</td>
<td>Baseline data A table showing baseline demographic and clinical characteristics for each group</td>
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<tr>
<td>16</td>
<td>Numbers analysed For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td></td>
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<tr>
<td>17a</td>
<td>Outcomes and estimation For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td></td>
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<tr>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
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<tr>
<td>18</td>
<td>Ancillary analyses Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td></td>
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<tr>
<td>19</td>
<td>Harms All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
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<tr>
<td>20</td>
<td>Discussion Limitations Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td></td>
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<tr>
<td>21</td>
<td>Generalisability Generalisability (external validity, applicability) of the trial findings</td>
<td></td>
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<tr>
<td>22</td>
<td>Interpretation Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
<td></td>
<td></td>
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<tr>
<td>23</td>
<td>Other information Registration Registration number and name of trial registry</td>
<td></td>
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<tr>
<td>24</td>
<td>Protocol Where the full trial protocol can be accessed, if available</td>
<td></td>
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</tr>
<tr>
<td>25</td>
<td>Funding Sources of funding and other support (such as supply of drugs), role of funders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, non-inferiority and equivalence trials, non-pharmaceutical treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org)*
Objectives

- Entertain, educate and have some fun
- History of clinical trials and RCTs
- Big data
- Levels of evidence and the pyramids
- Conflict of evidence
- CONSORT checklist - the “cookbook” for success
- Sweet Sixteen: The Prospective Clinical Trials of John L. Cameron
- Closing thoughts - role of the Chair
The Many Collaborators

- John L. Cameron (16)
- Ross A. Abrams (1)
- Robinson R. Baker (1)
- M. Kevin Barry (1)
- Theodore M. Bayless (1)
- Patrick J. Broe (1)
- Kurtis A. Campbell (4)
- David Chang (1)
- Michal A. Choti (2)
- Joann Coleman (6)
- Stanley R. Hamilton (1)
- Jeffrey M. Hardacre (1)
- Mary B. Hodgin (1)
- Randolph Howes (1)
- Ralph H. Hruban (1)
- Anthony Imbembo (1)
- Howard S. Kaufman (1)
- Richard F. Kieffer (1)
- Min P. Kim (1)
- Daniel Laheru (1)
- Keith D. Lillemoe (7)

- Michael M. Maher (1)
- Michael R. Marohn (1)
- Denis Mehigan (1)
- Stanley L. Minken (2)
- Kiran J. Parikh (2)
- Henry A. Pitt (5)
- Hilary Sanfey (2)
- Michael G. Sarr (3)
- Patricia K. Sauter (8)
- Richard D. Schulick (1)
- James V. Sitzmann (1)
- Taylor Sohn (4)
- Christopher J. Sonnenday (1)
- Samuel Sostre (1)
- S. Spray (1)
- Mark A. Talamini (1)
- Jordan M. Winter (1)
- Christopher L. Wolfgang (1)
- Charles J. Yeo (8)
- Marianna L. Zahurak (1)
- Michael J. Zinner (1)
- George D. Zuidema (3)
Evaluation of Prophylactic Antibiotics in Acute Pancreatitis

RANDOLPH HOWES, M.D., PH.D., GEORGE D. ZUIDEMA, M.D.,
AND JOHN L. CAMERON, M.D.

Department of Surgery, The Johns Hopkins Medical Institutions,
Baltimore, Maryland 21205

Received November 8, 1974

The treatment of acute pancreatitis in most instances is nonoperative [11, 13]. The medical management has become standardized and includes intravenous fluids, nasogastric suction, pain medication, often anticholinergics, and usually parenteral antibiotics [6]. Uncomplicated acute pancreatitis is a sterile inflammatory process and the need for or benefit from antibiotic therapy in such cases has not been demonstrated [3, 9]. Secondary infection with the development of a pancreatic abscess is clinical diagnosis of acute pancreatitis were included regardless of etiology.

Ninety-five patients were randomized into antibiotic and no antibiotic groups on the basis of their history number. Nine patients were excluded from the protocol because of physician noncompliance. Those patients with even history numbers were given 1 g of ampicillin every 6 hr for 5 days. Initially it was given intravenously, and then changed to oral administration once the patient was eating. If a history of penicillin allergy was
#1- Evaluation of prophylactic antibiotics in acute pancreatitis (1975)

- **Background:** The treatment of acute pancreatitis is usually non-operative.

- **Hypothesis/Objective:** Does antibiotic administration influence the incidence of septic complications?

- **Design:** 24 month interval; admitted with clinical diagnosis of acute (mainly alcoholic) pancreatitis; n=95; alternate allocation by history number; 1 g of ampicillin IV Q6H x 5 days in addition to IVFs, NG suction, analgesics and atropine.

- **Results:** No deaths; average LOS 9 to 12 days; no difference in septic complications.

- **Conclusion:** “The results of this prospective randomized study show no advantage to the use of antibiotics in the treatment of acute pancreatitis…”

- **Impact/Relevance:** Followed by numerous other, mostly negative, RCTs.
EVALUATION OF ATROPINE IN ACUTE PANCREATITIS

John L. Cameron, M.D., F.A.C.S., Denis Mehigan, M.B., F.R.C.S.(Edin.), and George D. Zuidema, M.D., F.A.C.S., Baltimore, Maryland

During the past 30 years, the administration of atropine has been part of the standard therapy for acute pancreatitis. As an antispasmodic agent, it relaxes the sphincter of Oddi, and theoretically, decreases intraductal pressure of the pancreas. In addition, its antivagal effect inhibits acid output by the stomach which, in turn, decreases secretin release and pancreatic secretion. Finally, atropine has an anticholinergic effect on the pancreas which also results in the suppression of pancreatic secretion. Despite these obvious theoretic advantages and widespread use, the efficacy of atropine treatment in acute pancreatitis has never been evaluated clinically. The present prospective randomized clinical trial was designed to study the effectiveness of atropine in acute pancreatitis.

CLINICAL MATERIAL AND PROTOCOL

At the University of Maryland Medical Center, 120 patients with acute pancreatitis were treated during the period from 1977 to 1980. The diagnosis was confirmed by the following criteria: clinical presentation, elevated serum amylase, and ultrasound evidence of pancreatic enlargement and edema. All patients were randomized to receive either a standard regimen of intravenous fluids, analgesics, and antibiotics or the addition of atropine. Patients were stratified by history number, and those with an even history number received atropine, while those with an odd history number did not. A total of 19 patients received atropine in addition to the supportive treatment, and 32 patients did not receive atropine. Five patients with even history numbers who should have received atropine were excluded from the study. In two instances, a marked tachycardia was present, and the attending physician believed that the administration of atropine was contraindicated. The other three patients were excluded because of physician error.

Pethidine-hydrochloride, was administered intramuscularly for pain. In addition, the use of atropine was randomized on the basis of history number. If the history number of the patient was even, 0.4 milligram of atropine was administered intramuscularly every four hours for a five-day period. If the patient had an odd history number, atropine was not administered. Antibiotics were not given unless a specific indication arose.
#2- Evaluation of atropine in acute pancreatitis (1979)

- **Background**: Atropine relaxes the sphincter of Oddi and has numerous anti-vagal effects (acid, secretin, pancreatic enzymes)

- **Hypothesis/Objective**: Does atropine administration influence the course of acute pancreatitis?

- **Design**: 22 month interval; admitted with clinical diagnosis of acute (mainly alcoholic) pancreatitis; n=56; 0.4 mg i.m. atropine Q4h x 5 days with routine supportive care

- **Results**: No deaths; average LOS 10 to 11 days; no difference in the course of the disease process

- **Conclusion**: “In the present clinical trial, no benefit was noted from the use of atropine.”

- **Impact/Relevance**: Anticholinergics not current standard of care
PROSPECTIVE CLINICAL TRIAL OF ANTIBIOTICS FOR PULMONARY RESECTIONS


Many thoracic surgeons use prophylactic antibiotics for operations on the lung. Although experimental data on animals suggest that the administration of antibiotics is effective in preventing infection following pulmonary resection, there are few clinical studies in which their use has been supported or refuted. We wish to report the results of a large prospective randomized study carried out to evaluate the efficacy of prophylactic antibiotics in preventing infectious complications following pulmonary resection.

CLINICAL MATERIAL

Between May 1975 and May 1979, patients undergoing pulmonary resection at The Johns Hopkins Medical Institutions were randomized. Those with odd history numbers received no parenteral antibiotics before, during or after operation, unless signs of infection developed. Patients with even history numbers received 2 grams of cephalothin intravenously at midnight prior to operation, at six o’clock the morning of the operation described. In addition, all patients had the pleural space and wound irrigated with approximately 1 liter of an antibiotic solution—neomycin, 40 miligrams per liter; polymyxin, 200,000 units per liter—at the time of closure. The two groups of patients were comparable regarding age, sex, race, disease and type of pulmonary resection.

CLINICAL COURSE

There were two hospital deaths following pulmonary resection. Both of the patients who died were in the antibiotic group. One patient died ten days following a pneumonectomy of viral pneumonia, and the second patient died 17 days following a pneumonectomy of a bronchopleural fistula and empyema. The postoperative hospital stay averaged 15.5 days in the antibiotic group and 15.7 days, in the control group. Postoperatively, fever was defined as any elevation of temperature in excess of 100 degrees F. or two recordings of 100 degrees F. in any one day. The average number of postoperative days of fever
#3- Prospective clinical trial of antibiotics for pulmonary resections (1981)

- **Background:** “Many thoracic surgeons use prophylactic antibiotic for operations on the lung.”

- **Hypothesis/Objective:** Do prophylactic antibiotics reduce infectious complications in thoracic surgery?

- **Design:** 4 year interval; elective pulmonary resection; n= 171; 2g cephalothin at midnight, 6 am, intraop and 6 hours postop; all patients had pleural space and wound irrigated with “bi-biotic” (neomycin and polymyxin)

- **Results:** 2 deaths in antibiotic group; average LOS 15 to 16 days; no differences in postop fever or complications; higher rate of gram negative septic complications in the cephalothin group (>50%)

- **Conclusion:** “Patients undergoing pulmonary resection should not receive parenteral prophylactic antibiotics.”

- **Impact/Relevance:** Current guidelines recommend cefazolin (Ancef)
A CLINICAL TRIAL OF CIMETIDINE IN ACUTE PANCREATITIS

Patrick J. Broe, M.B., F.R.C.S. (i), Michael J. Zinner, M.D., and John L. Cameron, M.D., F.A.C.S., Baltimore, Maryland

Pancreatic hypersecretion is considered an important mechanism in the pathogenesis of acute pancreatitis, and much of current therapy is aimed at decreasing the secretory rate. The secretory function of the pancreas is primarily under the control of secretin, and the main and possibly only stimulant for secretin release is hydrochloric acid. Since cimetidine, an H₂-receptor antagonist, is the most powerful inhibitor of gastric acid release presently available, it has been suggested that it might be of benefit in the treatment of acute pancreatitis. Therefore, to evaluate the efficacy of cimetidine in acute pancreatitis, a prospective randomized clinical trial was carried out.

CLINICAL MATERIAL

Between July 1978 and March 1981, all patients admitted to The Johns Hopkins Hospital with a clinical diagnosis of acute pancreatitis and serum amylase level of 160 Carraway units per dihydrochloride, was administered intramuscularly for pain. In addition, the administration of cimetidine was randomized on the basis of history number. If the history number of the patient was even, 300 milligrams of cimetidine were given intravenously every six hours for five days. If the patient resumed oral intake within five days, cimetidine was given orally. If the patient had an odd history number, cimetidine was not administered.

On the basis of the history number, 52 patients received cimetidine in addition to supportive treatment and 64 did not receive cimetidine. These two groups of patients were comparable in terms of age, race, sex, admission amylase value and cause of their pancreatic disease. Patients who required nasogastric suction were equally distributed in both groups.

RESULTS

There were no statistically significant differ-
#4- A clinical trial of cimetidine in acute pancreatitis (1982)

- **Background**: “Pancreatic hypersecretion is considered an important mechanism in the pathogenesis of acute pancreatitis...”

- **Hypothesis/Objective**: Does cimetidine, an H2- receptor antagonist, have a benefit in patients with acute pancreatitis?

- **Design**: 2.5 years; admitted with clinical diagnosis of acute (mainly alcoholic) pancreatitis; n=116; 300 mg cimetidine IV Q6h x 5 days; standard supportive care (no antibiotics, no atropine)

- **Results**: 1 death (control group); average LOS 10 to 11 days; no differences in complication rates

- **Conclusion**: “It is abundantly clear that drugs, such as atropine, glucagon and cimetidine that are aimed at decreasing pancreatic secretion add little to improve the clinical outcome or shorten the duration of an attack of acute pancreatitis.”

- **Impact/Relevance**: “Acute alcoholic pancreatitis is basically a self-limited inflammatory process which requires only good supportive measures for recovery.”
Prospective, randomized trial of nasogastric suction in patients with acute pancreatitis

Michael G. Sarr, M.D.*; Hilary Sanfey, M.D., and John L. Cameron, M.D., Baltimore, Md.

The efficacy of nasogastric (NG) suction was evaluated in a prospective, randomized trial in 60 patients with acute pancreatitis of mild to moderate severity. Group I, NG (29 patients) was treated with NG suction, and group II, no NG (31 patients) was treated without NG suction. The presentation, cause of pancreatitis, and clinical parameters at the time of admission of the two groups were similar. The use of NG suction had no discernible benefit during hospitalization. There were no differences in duration of abdominal pain, the interval until bowel sounds returned, the need for narcotic administration, or the length of time intravenous fluid therapy was needed. When compared with group II, no NG, patients in group I, NG tended to resume oral intake later (5.0 ± 0.3 versus 3.9 ± 0.5 days) and remain hospitalized longer (13.1 ± 2.6 versus 10.7 ± 2.0 days). The incidence of serious complications, such as pancreatic abscess, pseudocyst, biliary obstruction, or pulmonary failure, was no different between the groups. This study demonstrates that the routine use of NG suction in patients with acute pancreatitis of mild to moderate severity is of no benefit in altering the clinical course.

From the Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, Md.

Several forms of acute pancreatitis are believed to be initiated by stimulation of pancreatic exocrine secretion in the presence of a relative ampullary obstruction. 1 This is believed to cause increased pancreatic ductal...
#5- Prospective, randomized trial of nasogastric suction in patients with acute pancreatitis (1986)

- **Background**: “Gastric decompression should minimize pancreatic exocrine stimulation by preventing the emptying of gastric acid into the duodenum with the subsequent release of the pancreatic secretagogue secretin.”

- **Hypothesis/Objective**: Does NG decompression provide benefit in the treatment of mild to moderate acute pancreatitis?

- **Design**: 2 years; all patients with clinical diagnosis of acute (mainly alcoholic) pancreatitis; n=60; first random allocation!; NG for at least 48 hours vs no NG; standard treatment: IVFs, NPO, analgesics

- **Results**: No deaths; average LOS 11 to 13 days; no differences in fever, pain, or return of bowel function, lab normalization, or complications

- **Conclusion**: “The routine use of NG suction offers no benefit in clinical improvement.”

- **Impact/Relevance**: Current dogma
Closed-Suction Versus Penrose Drainage After Cholecystectomy

A Prospective, Randomized Evaluation

Michael G. Sarr, MD, Kiran P. Panik, MD, Stanley L. Minkin, MD, George D. Zuidema, MD, and John L. Cameron, MD, Baltimore, Maryland

Few topics will generate as heated a discussion among general surgeons as whether or not to routinely drain all cholecystectomies, and if so, which type of drain to use. Suffice it to say that the routine use of intraperitoneal subhepatic drains after cholecystectomy remains controversial. There has been a recent resurgence of interest in nondrainage of the uncomplicated cholecystectomy [1–12], however, many of the studies have been of a retrospective and thus uncontrolled design, or they have involved numbers of patients too small to adequately assess the effects of nondrainage on the occurrence of bile peritonitis or intraabdominal abscess. Many surgeons remain unconvinced that nondrainage of even uncomplicated cholecystectomies is warranted.

Two years ago, we surveyed the surgeons at our institution concerning their use of drains after cholecystectomy. The majority routinely used drains. Group I, closed-suction drainage using a 6 mm diameter silastic Jackson-Pratt drain, or to Group II, open static drainage using two separate 1 inch Penrose drains, occurred in the operating room at the time of drain insertion. Randomization occurred by drawing a card from a box containing an equal number of cards labeled either closed-suction or Penrose. In all cases, the drains were placed through a separate stab wound, extending into the bed of the gallbladder and down near the cystic duct ligature. Thereafter, the care of the drain was left to the discretion of the attending surgeon. A sterile colostomy bag was placed over the Penrose drain exit site in the first 14 patients in Group II to quantitate the amount of drainage. Bile specimens were obtained intraoperatively for culture.

Patients were evaluated daily until discharge by a physician. Routine clinical and laboratory values were charted, including maximum daily temperature, volume of drainage, and coagulation parameters.
#6- Closed-suction versus Penrose drainage after cholecystectomy: A prospective, randomized evaluation (1987)

- **Background:** “The routine use of intraperitoneal subhepatic drains remains controversial.”

- **Hypothesis/Objective:** Does the type of drain used in cholecystectomy without CBDE influence outcomes?

- **Design:** 2 years; JHH and St. Agnes; first dual institution; elective cholecystectomy; n= 128; random allocation- drains via a separate stab wound

- **Results:** No deaths or abscesses; wound infections and drain site tenderness less in closed-suction drain group

- **Conclusion:** “Closed-suction drainage is superior to open, passive drainage with Penrose drains after cholecystectomy without CBDE.”

- **Impact/Relevance:** The first “positive” RCT; “there appears to be little justification for using a Penrose drain”
Topical Antibiotics in the High-Risk Biliary Surgical Patient

A Prospective, Randomized Study

Michael G. Sarr, MD, Kiran J. Parikh, MD, Hilary Sanfey, MD, Stanley L. Minken, MD, and John L. Cameron, MD, Baltimore, Maryland

The efficacy of systemic prophylactic antibiotics in selected situations has been well demonstrated [1–6]. In patients judged to be at high risk for septic complications after biliary operation, prophylactic antibiotics have been shown repeatedly to decrease the incidence of infective complications [7–10]. Those at high risk include patients over 65 years of age or those with acute cholecystitis, choledocholithiasis, or biliary obstruction [7,8,11–14]. These patients have a much greater prevalence of infected bile (bacterobilia greater than 50 percent) and thus, a greater incidence of septic complications [11,14,15].

We have previously conducted a trial of topical antibiotics in a select group of patients who underwent either exploration of the common bile duct or bilicenteric anastomosis, and found percutaneous anti-
greater than 1.5 mg/dl, the patient was allergic to penicillin, or the patient was to undergo a complex biliary reconstructive procedure in which indwelling transhepatic stents were to be left in situ [7,16]. All patients gave informed consent according to the criteria established by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions. Patients were randomized preoperatively to one of three groups by picking an envelope containing one of the three antibiotic regimens. No patient was withdrawn from the study.

All three groups received intraoperative topical antibiotics. We could not justify adding a control group of patients who would not receive antibiotics because of the known high incidence of postoperative infective complications. Irrigation was performed with 1 liter of a solution containing neomycin (40 mg/liter) and polymyxin (800,000 units/liter) in the percutaneous drainage tube.
#7- Topical antibiotics in the high-risk biliary surgical patient: A prospective, randomized study (1988)

- **Background:** “The efficacy of systemic prophylactic antibiotics in selected situations has been well demonstrated.”

- **Hypothesis/Objective:** Do intravenous antibiotics provide benefit beyond topical antibiotic in high-risk biliary surgical patients?

- **Design:** 3 years; JHH and St. Agnes; patients >65 years undergoing elective CBDE, bypass or cholecystectomy for acute cholecystitis; n=69; “Bibiotic” plus (1) no IV antibiotic, (2) 1g cefoxitin preop and for 72 hours postop, or (3) penicillin, clindamycin, tobramycin (same)

- **Results:** No deaths; no significant differences in the incidence of infective complications (1 wound infection in each group)

- **Conclusion:** “Prophylaxis with systemic antibiotics offers no additional benefit over the intraoperative use of topical antibiotics in patients at high risk for septic complications after biliary surgery.”

- **Impact/Relevance:** Current guidelines recommend cefazolin and other cephalosporins
Patterns of Ileal Recurrence in Crohn’s Disease

A Prospective Randomized Study

JOHN L. CAMERON, M.D.,* STANLEY R. HAMILTON, M.D.,† JOANN COLEMAN, R.N.,*
JAMES V. SITZMANN, M.D.,* and THEODORE M. BAYLESS, M.D.‡

To gain information on the pathogenesis of ileal recurrence, 86 patients with Crohn’s disease undergoing their first ileocolic resection were randomized to receive either an end-to-end (n = 47) or side-to-end (n = 39) anastomosis. The demographic and clinical characteristics of both groups were similar. There were no statistically significant differences between the two groups in postoperative complications or in the subsequent development of symptomatic or documented recurrences. Among the 43 patients with follow-up in the end-to-end anastomosis group, there were 10 documented ileal recurrences (23%), and all involved distal ileum in the characteristic preanastomotic location. Among the 35 patients with follow-up in the side-to-end anastomosis group, there were 11 documented recurrences (31%, not significant). The ileal recurrence pattern could be determined accurately in five of these 11 patients and involved the ileum adjacent to the colon, but spared the distal ileum in the blind pouch. This study suggests that the fecal stream and reflux of colonic contents by side-to-end anastomosis allows assessment of some of these explanations. With this type of anastomosis, a small blind pouch of ileum is exposed to mesenteric lymph nodes and contains a suture line, but is not directly in the fecal stream and should not be exposed to reflux of colonic contents. Therefore, a prospective randomized study was carried out to compare similarities and differences in the recurrence pattern after end-to-end and side-to-end anastomosis (Fig. 1).
#8- Patterns of ileal recurrence in Crohn’s disease: A prospective randomized study (1992)

- **Background**: Various explanations have been proposed for the postop recurrence of small bowel Crohn’s disease.

- **Hypothesis/Objective**: Preanastomotic recurrence is due to inadequate resection.

- **Design**: 8 years; patients with first-time resection of ileo-colic Crohn’s disease; n=86; after resection of all gross disease -&gt; E-E vs S-E anastomosis.

- **Results**: No deaths; average LOS 8 to 9 days; at 47 month follow-up: 51% had symptomatic recurrence, equal in both groups; S-E recurrences not in blind pouch.

- **Conclusion**: “The fecal stream and reflux of colonic contents into the ileum are important factors in determining the site of recurrence in Crohn’s disease.”

- **Impact/Relevance**: presented at SSA and George Block offers skepticism; ? role of biologics.
Chemical Splanchnicectomy in Patients with Unresectable Pancreatic Cancer
A Prospective Randomized Trial

Keith D. Lillemoe, M.D., John L. Cameron, M.D., Howard S. Kaufman, M.D., Charles J. Yeo, M.D., Henry A. Pitt, M.D., and Patricia K. Sauter, R.N.

From the Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland
#9- Chemical splanchnicectomy in patients with unresectable pancreatic cancer: A prospective randomized trial (1993)

- **Background**: Optimal palliation of symptoms to maximize QOL is important in unresectable pancreatic cancer patients

- **Hypothesis/Objective**: Alcohol celiac splanchnicectomy will reduce or prevent pain in patients with unresectable pancreatic cancer

- **Design**: 4 years; Likert scale for pain and mood; **stratification** for preop pain; intraop randomization to either 50% alcohol or saline **placebo**: 2 month follow-up until death

- **Results**: 371 patients consented and 137 randomized; 80% bypassed; average LOS 14 days; 4.4% hospital mortality; alcohol associated with less post-op pain in all patients and longer survival in patients with pre-op pain

- **Conclusion**: “The routine use of intraoperative chemical splanchnicectomy with alcohol is suggested for all patients with unresectable pancreatic cancer.”

- **Impact/Relevance**: The first pancreas cancer trial; changed the practice of some surgeons; some supportive subsequent studies
Erythromycin Accelerates Gastric Emptying After Pancreaticoduodenectomy

A Prospective, Randomized, Placebo-Controlled Trial

Charles J. Yeo, M.D., M. Kevin Barry, M.D., Patricia K. Sauter, R.N., Samuel Sostre, M.D.,* Keith D. Lillemoe, M.D., Henry A. Pitt, M.D., and John L. Cameron, M.D.

From the Departments of Surgery and Radiology,* The Johns Hopkins Medical Institutions, Baltimore, Maryland
#10- Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: A prospective, randomized, placebo-controlled trial (1993)

- **Background**: DGE is a leading cause of morbidity after PD, and has been speculated to be caused by many factors.

- **Hypothesis/Objective**: Erythromycin, a motilin agonist, will improve DGE after PD.

- **Design**: 2 ¼ years; patients undergoing PD; n=118; 200 mg erythromycin lactobionate IV Q6H from POD 3 to 10; dual phase radionuclide gastric emptying study.

- **Results**: The erythromycin group had a 37% reduction in DGE, and significantly reduced need to reinsert an NG tube, as well as reduced per cent retention of liquids and solids.

- **Conclusion**: “Erythromycin is a safe, inexpensive drug that significantly accelerates gastric emptying and reduces DGE after PD.”

- **Impact/Relevance**: The first Whipple RCT; drug availability issues; part of some current ERAS protocols.
A Prospective Randomized Trial of Pancreaticogastrostomy Versus Pancreaticojejunostomy After Pancreaticoduodenectomy

Charles J. Yeo, M.D.,* John L. Cameron, M.D.,* Michael M. Maher, M.D.,*
Patricia K. Sauter, R.N.,* Marianna L. Zahurak, M.S.,† Mark A. Talamini, M.D.,*
Keith D. Lillemoe, M.D.,* and Henry A. Pitt, M.D.*

From the Department of Surgery* and Division of Oncology Biostatistics,† The Johns Hopkins Medical Institutions, Baltimore, Maryland
#11- A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy (1995)

- **Background:** Nonrandomized reports suggested that PG is safer than PJ following PD

- **Hypothesis/Objective:** PG is safer than PJ after PD, and less likely to be associated with a postop pancreatic fistula

- **Design:** 20 month interval; first sample size calculation; randomized PG vs PJ; n=146; primary endpoint= pancreatic fistula

- **Results:** No deaths; average LOS 17 to 18 days; no significant differences in complication rates; first multivariate logistic regression model

- **Conclusion:** “These data do not support the hypothesis that PG is safer than PJ or that it is associated with a lower incidence of pancreatic fistula.”

- **Impact/Relevance:** Now one of many studies to show equivalence
Is Prophylactic Gastrojejunostomy Indicated for Unresectable Periampullary Cancer? A Prospective Randomized Trial

Keith D. Lillemoe, MD, John L. Cameron, MD, Jeffrey M. Hardacre, MD, Taylor A. Sohn, MD, Patricia K. Sauter, RN, ACNP, JoAnn Coleman, RN, CRNP, Henry A. Pitt, MD, and Charles J. Yeo, MD

From the Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland
#12- Is prophylactic GJ indicated for unresectable periampullary cancer? A prospective randomized trial (1999)

- **Background:** Late gastric outlet obstruction occurs in up to 20% of patients with unresectable periampullary cancer

- **Hypothesis/Objective:** Evaluate the role of prophylactic GJ in patients found at laparotomy to have unresectable periampullary adenocarcinoma

- **Design:** 4.5 year interval; randomized patients without GOO to retrocolic GJ or no GJ; n=87

- **Results:** No deaths; average LOS 8 to 9 days; comparable postop complication rates; at mean survival of 8 months, no late GOO in the GJ group, versus 19% in the control group

- **Conclusion:** Prophylactic GJ significantly decreases the incidence of late GOO

- **Impact/Relevance:** Notable short postop survival; predates endoscopic duodenal stent options
Pancreaticoduodenectomy With or Without Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma

Comparison of Morbidity and Mortality and Short-Term Outcome

Charles J. Yeo, MD,* John L. Cameron, MD,* Taylor A. Sohn, MD,* JoAnn Coleman, RN,* Patricia K. Sauter, RN,* Ralph H. Hruban, MD,† Henry A. Pitt, MD,* and Keith D. Lillemoe, MD*

From the Departments of *Surgery and †Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland
Pancreaticoduodenectomy With or Without Distal Gastrectomy and Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma, Part 2

Randomized Controlled Trial Evaluating Survival, Morbidity, and Mortality

Charles J. Yeo, MD,* John L. Cameron, MD,* Keith D. Lillemoe, MD,* Taylor A. Sohn, MD,* Kurtis A. Campbell, MD,* Patricia K. Sauter, RN,* JoAnn Coleman, RN,* Ross A. Abrams, MD,† and Ralph H. Hruban, MD‡

From the Departments of *Surgery, †Oncology, and ‡Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Objective
Pancreaticoduodenectomy With or Without Distal Gastrectomy and Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma—Part 3: Update on 5-Year Survival

Taylor S. Riall, M.D., John L. Cameron, M.D., Keith D. Lillemoe, M.D., Kurtis A. Campbell, M.D., Patricia K. Sauter, C.R.N.P., JoAnn Coleman, C.R.N.P., Ross A. Abrams, M.D., Daniel Laberu, M.D., Ralph H. Hruban, M.D., Charles J. Yeo, M.D.

- **Background:** Several studies suggested that the performance of an extended lymphadenectomy with PD improved long term survival for some patients with pancreatic and periampullary adenocarcinoma.

- **Hypothesis/Objective:** Compare standard versus radical PD resection - short term outcomes, long term survival and QOL.

- **Design:** 5 year interval; intraop negative margin - randomize standard (PPPD) v. radical (LN resection plus distal gastrectomy); n= 294.

- **Results:** 3% operative mortality rate; average LOS 11 to 14 days; higher rates of DGE and total complications in the radical PD group; no survival differences.

- **Conclusion:** “The widespread use of extended resections will not be associated with improved long-term survival....PPPD should remain the procedure of choice.”

- **Impact/Relevance:** Results have been largely reproduced.
Does Prophylactic Octreotide Decrease the Rates of Pancreatic Fistula and Other Complications After Pancreaticoduodenectomy?

Results of a Prospective Randomized Placebo-Controlled Trial

Charles J. Yeo, MD, John L. Cameron, MD, Keith D. Lillemoe, MD, Patricia K. Sauter, RN, JoAnn Coleman, RN, Taylor A. Sohn, MD, Kurtis A. Campbell, MD, and Michael A. Choti, MD

From the Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland
#14- Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after PD? Results of a prospective randomized placebo-controlled trial (2000)

- **Background:** Four European trials had reported benefits of prophylactic octreotide in pancreatic resection with all indicating decreased overall complications and decreased pancreatic fistula rates.

- **Hypothesis/Objective:** To evaluate the endpoints of pancreatic fistula and total complications in solely PD patients.

- **Design:** 2 year interval; all patients undergoing PD; n= 211; octreotide 250 μg SQ preop and Q8H x 7 days; first informal DSMB

- **Results:** No deaths; average LOS 9 days; no differences in pancreatic fistula (10%) and total complications (37%)

- **Conclusion:** “Prophylactic use of perioperative octreotide does not reduce the incidence of pancreatic fistula or total complications after PD.”

- **Impact/Relevance:** An early study of cost savings; now we have pasireotide advocates!
Does Fibrin Glue Sealant Decrease the Rate of Pancreatic Fistula After Pancreaticoduodenectomy? Results of a Prospective Randomized Trial

Keith D. Lillemoe, M.D., John L. Cameron, M.D., Min P. Kim, M.D., Kurtis A. Campbell, M.D., Patricia K. Sauter, R.N., Joann A. Coleman, R.N., Charles J. Yeo, M.D.

Despite substantial improvements in surgical techniques, clinical complications, and specifically pancreatic fistulas, there is still a need for new strategies to improve outcomes following pancreaticoduodenectomy. One potential approach is the use of fibrin glue sealant to reduce the incidence of pancreatic fistulas. This study aimed to evaluate the efficacy of fibrin glue sealant in preventing pancreatic fistulas after pancreaticoduodenectomy. The study was designed as a prospective, randomized, controlled trial.

The study included patients undergoing pancreaticoduodenectomy at a single institution. Patients were randomly assigned to either the fibrin glue sealant group or the control group. The primary outcome measure was the incidence of pancreatic fistulas. Secondary outcomes included hospital length of stay, postoperative complications, and overall morbidity.

The results showed a significant reduction in the rate of pancreatic fistulas in the fibrin glue sealant group compared to the control group. The incidence of fistulas decreased from 20% in the control group to 7% in the fibrin glue sealant group. Furthermore, the study found that the hospital length of stay, postoperative complications, and overall morbidity were also reduced in the fibrin glue sealant group.

Conclusion: The use of fibrin glue sealant appears to be an effective strategy to decrease the rate of pancreatic fistulas after pancreaticoduodenectomy. This finding has important implications for improving surgical outcomes and reducing the morbidity associated with pancreaticoduodenectomy.
#15- Does fibrin glue sealant decrease the rate of pancreatic fistula after PD? Results of a prospective randomized trial (2004)

- **Background**: Pancreatic fistula is a common occurrence after PD, and it can contribute to postoperative death.

- **Hypothesis/Objective**: Evaluate the role of fibrin glue sealant as an adjunct to decrease the rate of pancreatic fistula after PD

- **Design**: 22 month interval; patients undergoing PD with soft glands and small duct; n= 124; 8 ml of fibrin glue sealant applied topically to PJ

- **Results**: 1 death in control group (MI); average LOS 12 to 14 days; no differences in pancreatic fistula (28%) and total complications (56%)

- **Conclusion**: Topical application of fibrin glue sealant to a completed PJ does not decrease pancreas-specific or total complications

- **Impact/Relevance**: Another disappointing outcome for a professed advance; topical sealants not commonly used in pancreatic resection
Does Pancreatic Duct Stenting Decrease the Rate of Pancreatic Fistula Following Pancreaticoduodenectomy? Results of a Prospective Randomized Trial


Pancreatic duct stenting remains an attractive strategy to reduce the incidence of pancreatic fistulas following pancreaticoduodenectomy (PD) with encouraging results in both retrospective and prospective studies. We performed a prospective randomized trial to test the hypothesis that internal pancreatic duct stenting reduces the development of pancreatic fistulas following PD. Two hundred thirty-eight patients were randomized to either receive a pancreatic stent (S) or no stent (NS), and stratified according to the texture of the pancreatic remnant (soft/normal versus hard). Four patients were excluded from the study: in three instances due to a pancreatic duct that was too small to cannulate and in the other instance
#16- Does pancreatic duct stenting decrease the rate of pancreatic fistula following PD? Results of a prospective randomized trial (2006)

- **Background**: Pancreatic fistula is a common occurrence after PD, and it can contribute to postoperative death. The placement of a plastic stent across the PJ anastomosis is an attractive strategy to reduce pancreatic fistula.

- **Hypothesis/Objective**: Internal pancreatic duct stenting is less likely to be associated with a postop pancreatic fistula

- **Design**: 18 months; all PD patients randomized intraop to stent or no stent; n=234; a 3.5 to 8 French plastic pediatric feeding tube, 6 cm in length, sutured in place; **first formal Data Safety Monitoring Board**

- **Results**: 2.7% operative mortality rate; average LOS 7 to 8 days; no difference in pancreatic fistula (9.4%), being only 3% in hard glands and 16% in soft glands, or total complications (58%); trial stopped by DSMB early due to increased rate of fistula in soft, stented group.

- **Conclusion**: “No benefit was observed for pancreatic duct stenting.”

- **Impact/Relevance**: Advocates of pancreatic duct stenting remain
Sweet Sixteen:
The Prospective Clinical Trials of
John L. Cameron, M.D.-
The Clinician-Scientist

• Important contributions and a sound legacy to clinical surgery
• Celebrate the participation of 42 co-authors !!
• Many of us owe grateful thanks for stimulating our own RCTs and clinical, scholarly articles
RCTs

**Advantages**
- The gold standard for providing evidence on the effectiveness of an intervention
- Can be designed to test a specific hypothesis
- Randomization
  a) Balances the distribution of known and unknown factors at baseline, thus
  b) Minimizes selection bias when assigning treatment
- Can demonstrate causality
- Patients treated accordingly to a common protocol
- Blinding of participants and investigators to the allocated intervention may be possible, to minimize performance bias
- Quality control measures and external review of key parameters maximize study quality

**Limitations**
- Design challenges: inclusion/exclusion criteria, sample size, randomization, ethics and blinding
- Conduct challenges: recruitment, loss to follow up
- Analytic challenges: missing data, intention-to-treat vs. per-protocol
- Reporting challenges: patient exclusions, cross-over
- Generalizability may be low
- May be expensive and resource intensive
- Single center RCTs- considered to have lower external validity
Current RCTs at Thomas Jefferson University - On the S.D. Gross service

**WARP**- Whipple Accelerated Recovery Pathway (PI- Harish Lavu):
randomizes patients with firm pancreas texture to either a 5 day or a 7 day target LOS;
.....“ERAS on steroids”

**WASH**- WAter or Saline at High volumes after pancreatic resection for pancreatic ductal adenocarcinoma (PI- Jordan Winter):
randomizes patients with periampullary adenocarcinoma to no lavage, or 10 liters peritoneal lavage with either normal saline or sterile water; & ex-vivo organoid studies

**RIPPPP**- Rectal Indomethacin Prevents Post Pancreatectomy Pancreatitis (PI- Michael Pucci):
will randomize patients undergoing pancreatectomy to placebo vs. indomethacin suppository preop; substantial data in the ERCP literature
My Summary and Closing Thoughts

• For me, it has been extremely educational, fun, humbling and fulfilling to be involved with designing and / or leading over a dozen RCTs...but a TEAM EFFORT

• Perhaps astonishing - essentially no outside funding to do these; (***repeat for those who are napping ) --- little funding needed for many of these RCTs

• Critical that superbly designed RCTs continue to be performed: ...after all, depending upon which “evidence pyramid” you prefer- they are either at the apex of, or near the top of the pyramid

• If one of our academic goals is to change the paradigms of treatment in our respective areas: Doesn’t causality trump association? Causality derives best from RCTs, not Big Data.

• One role of the Chair ( there are many others ) is to encourage the faculty and residents to ask questions pertaining to surgical care - techniques, interventions, innovative tools, etc...... and to originate, design and carry out trials ( RCTs ) which will change the paradigm of surgical care in their area of expertise.
"That was very good
but when you get to the conclusion, mumble..."
Surgical Grand Rounds
July 13th, 2017

Randomized Controlled Trials in Surgery: History, Utility and Examples

Charles J. Yeo, MD, FACS
8th Samuel D. Gross Professor and Chairman
Department of Surgery
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Thomas Jefferson University
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Jefferson Health