Equipoise, Innovation and the Role for Comparative Studies

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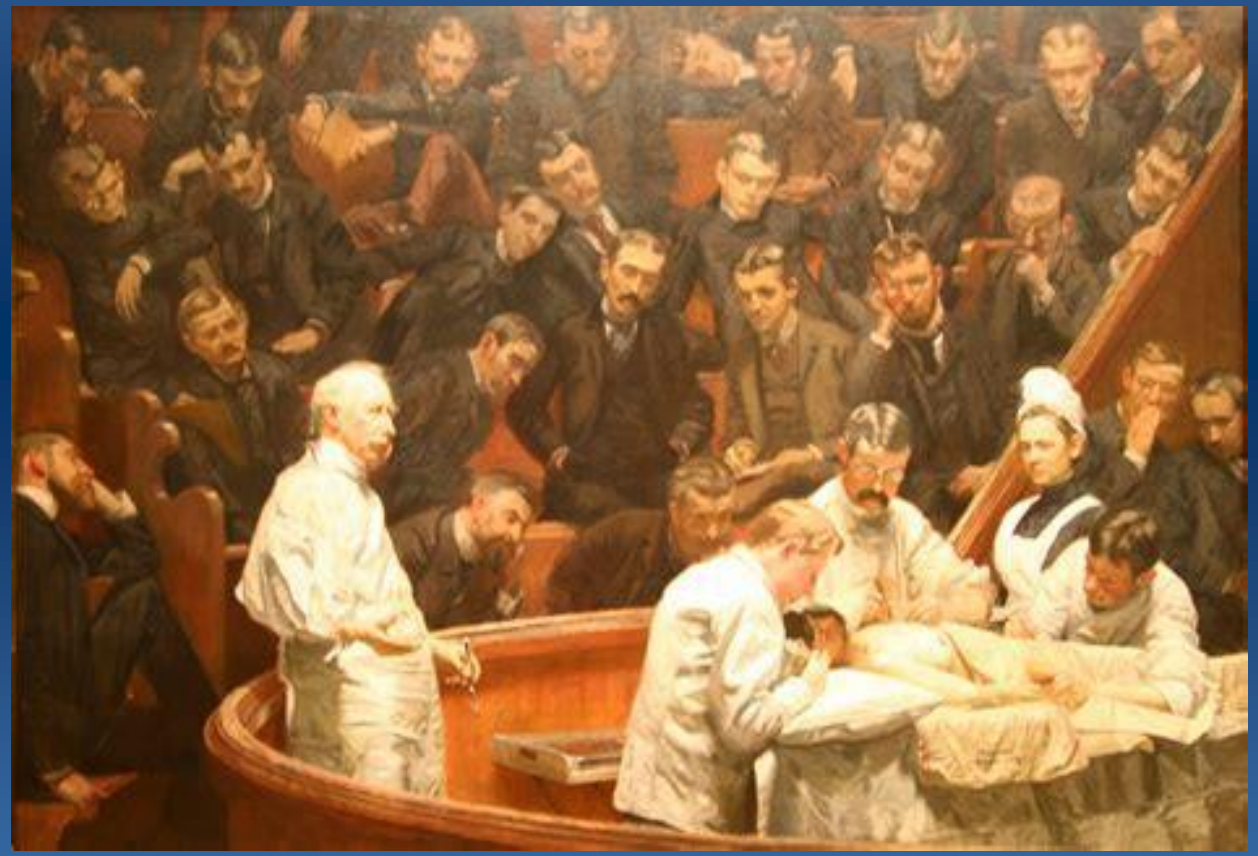
NO DISCLOSURES

How Have We Trained Our Surgeons?



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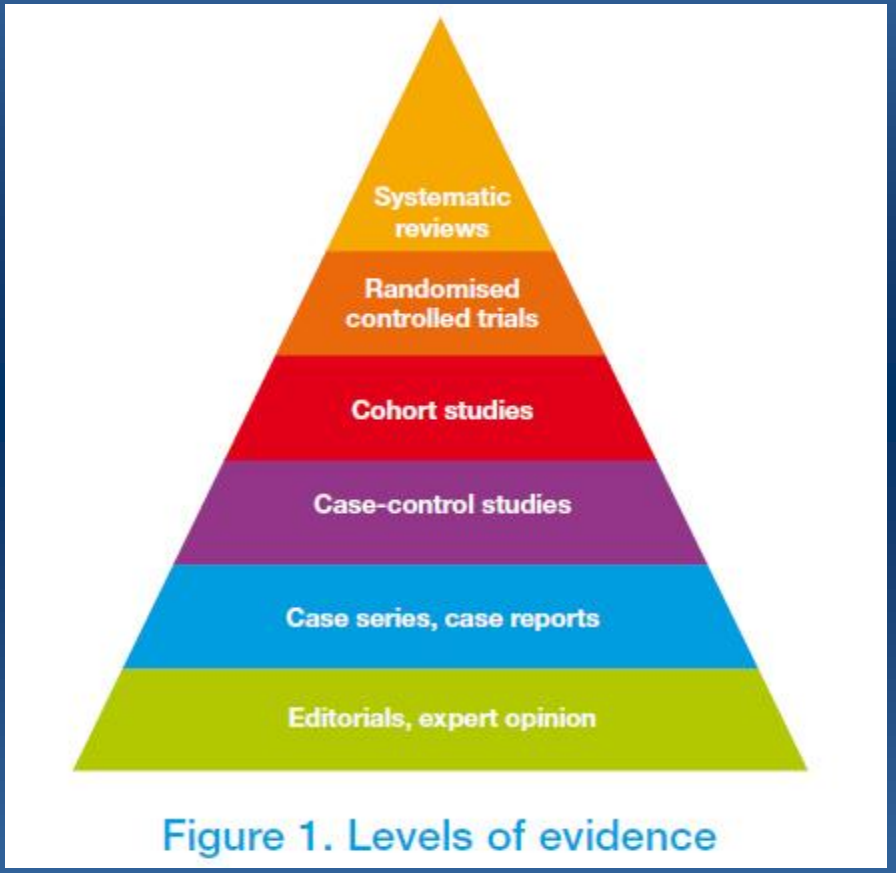
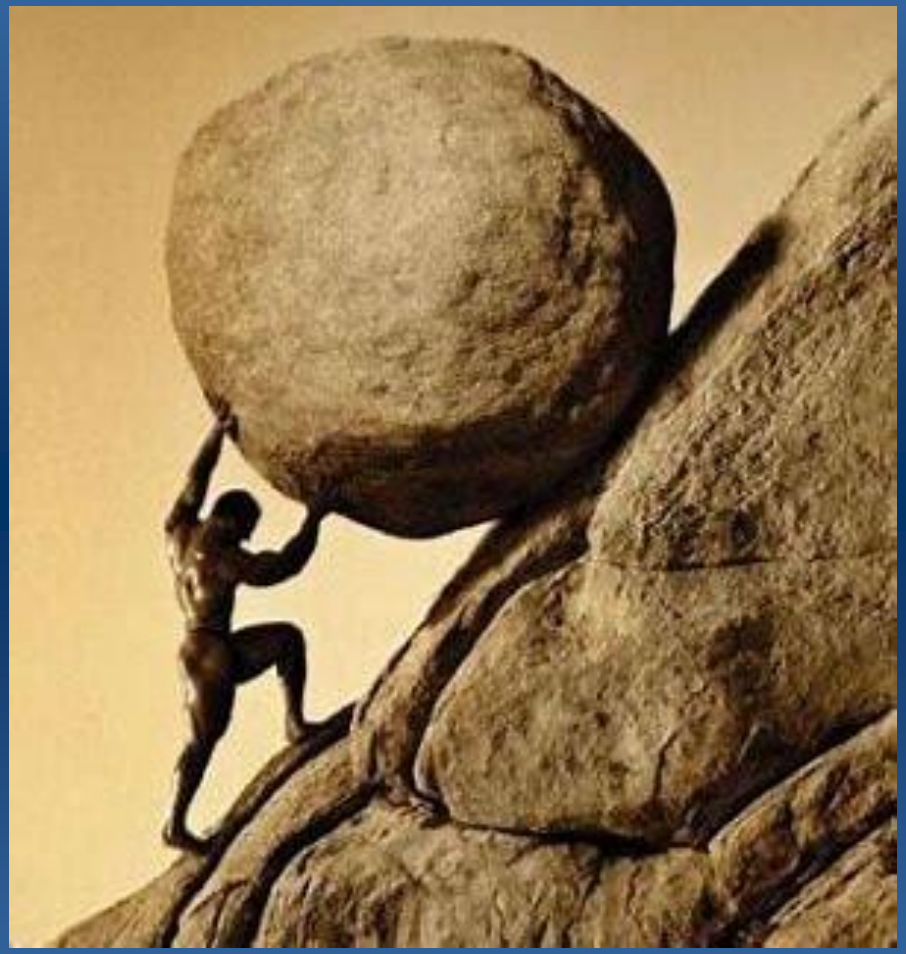


Figure 1. Levels of evidence

“ New therapeutic procedures should be always supported by randomized controlled trials.”

A.L. Cochrane, 1989



RANDOMIZED TRIALS CAN NOT BE DONE IN PEDIATRIC SURGERY

- Parents would never consent
- Surgeons would never have equipoise

EQUIPOISE

"the condition in which the physician is indifferent to the therapeutic value of an experimental treatment versus a control"

Charles Fried

EQUIPOISE

Personal equipoise is “overwhelmingly fragile…disturbed by a slight accretion of evidence” favoring one treatment over another

Benjamin Freedman

CLINICAL EQUIPOISE

- Justification to support 2 treatment paths
- No proof of superiority

You don't need personal equipoise to support, participate in or design a trial

INSTITUTIONAL DISCREPANCY TO ESTABLISH CLINICAL EQUIPOISE

Treatment of Empyema

FIBRINOLYSIS

- Had been shown to be superior to chest tube alone

VATS

- Had been shown to be superior to chest tube alone

We were a house divided

VATS v Fibrinolysis for Empyema

Convinced fibrinolysis is effective

Convinced thoracoscopy is better

How can we conduct a study?

- There are no comparative data
- Our assumptions require proof
- A fixed management protocol

If patients are going down 2 pathways regardless, we have an ethical obligation to perform a trial

STUDY POPULATION

Inclusion Criteria

VATS v Fibrinolysis for Empyema

FIBRINOLYSIS

- 12 Fr tube placed by IR or surgery in procedure room
- 4mg tPA in 40ml NS given into tube on insertion and each day for 3 doses

VATS

- Thoracoscopic debridement with chest tube left behind on – 20 cm H_20 suction

London Prospective Trial - 60 pts

VATS v Fibrinolysis w/Urokinase

- No difference in LOS (6 v 6 days)
- VATS more expensive (11.3K v 9.1K)

16% failure rate for fibrinolysis

CMH STUDY RESULTS

Outcomes – 36 pts

	VATS	tPA	P Value
LOS (Days)	6.9	6.8	0.96
O2 tx (Days)	2.2	2.3	0.89
PO Fever (Days)	3.1	3.8	0.46
Analgesic doses	22.3	21.4	0.90
Proc Charges	$11,660	$7,575	0.01

16.6% failure rate for fibrinolysis

VATS v Fibrinolysis

Summary

- No recovery advantages to VATS
- Fibrinolysis is less costly
  - Avoids an operation in the majority

ALL PATIENTS

EMPYEMA

(Loculations or > 10,000 WBC/µL)

↓

12 Fr chest tube with 3 doses of tPA

↓

Drainage decreased without clinical improvement

↓

Ultrasound or CT

↙ ↘

Persistent pleural space disease — **No pleural space disease**

↓ ↓

VATS — **Continue Antibiotics**

VATS v Fibrinolysis for Empyema

AFTER THE TRIAL

102 consecutive patients same protocol

Duration of stay

- All Patients: 7 +/- 3 days
  - Fibrinolysis only: 6.3 +/- 2.0 days
- Fibrinolysis then VATS: 11.8 +/- 4.3 days
  - Mean stay 5.9 +/- 3.7 days after VATS

Avg VATS operative time

- 62 +/- 13 minutes

15.7% failure rate for fibrinolysis

After the Observational Study

Redefining Failure

Sept, 2014 – March, 2019

48 patients

- All Patients –LOS: 6 days (IQR 5, 7.2)

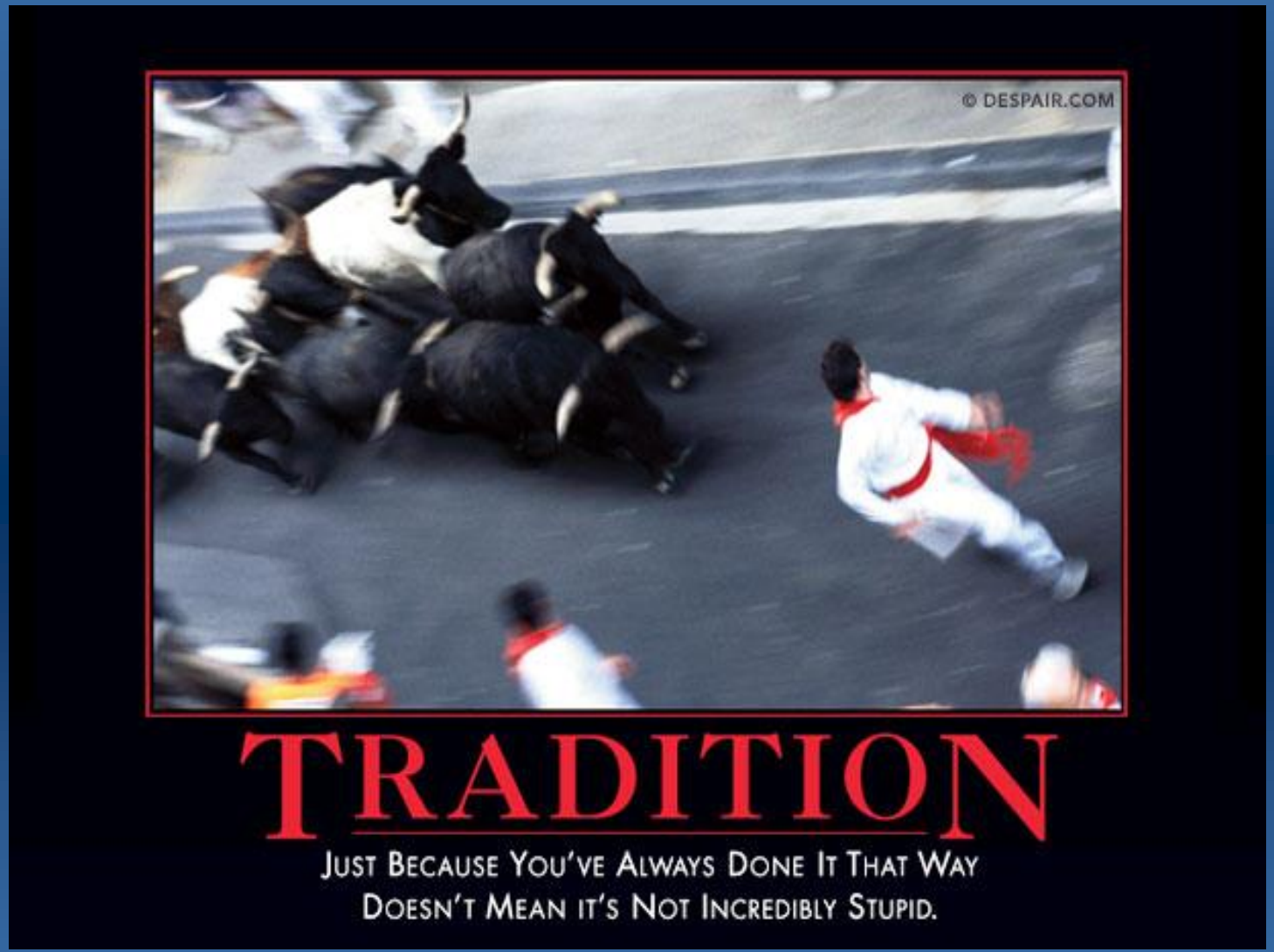
Only 2 patients underwent VATS (4%)

- Both in the first 2 years of the study period

4% failure rate for fibrinolysis

ENEMY OF PRACTICE EVOLUTION

SURGICAL DOGMA


© DESPAIR.COM
TRADITION
JUST BECAUSE YOU'VE ALWAYS DONE IT THAT WAY
DOESN'T MEAN IT'S NOT INCREDIBLY STUPID.

SURGICAL DOGMA

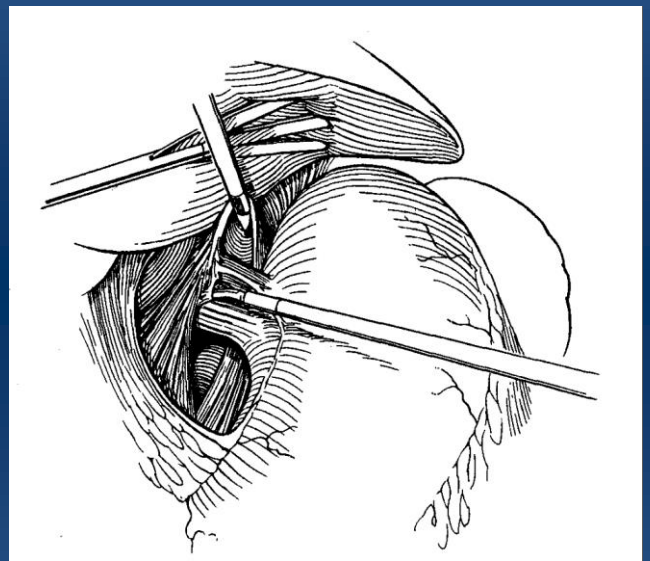


Fig. 2. Laparoscopic view of the esophagogastric junction with the liver retracted.

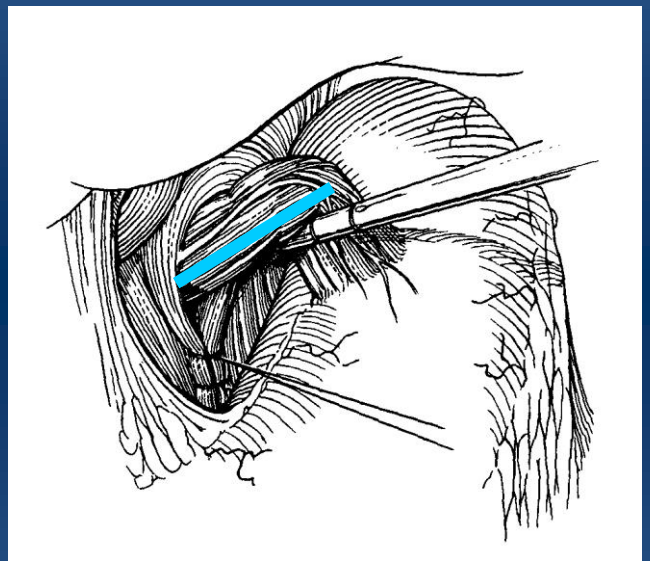
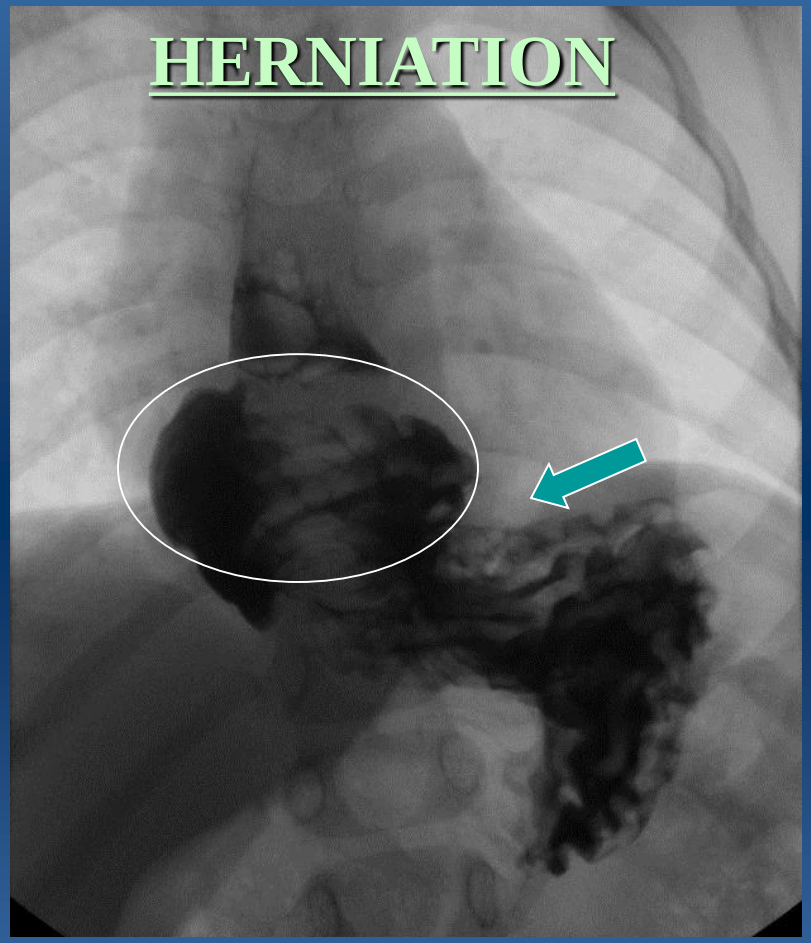
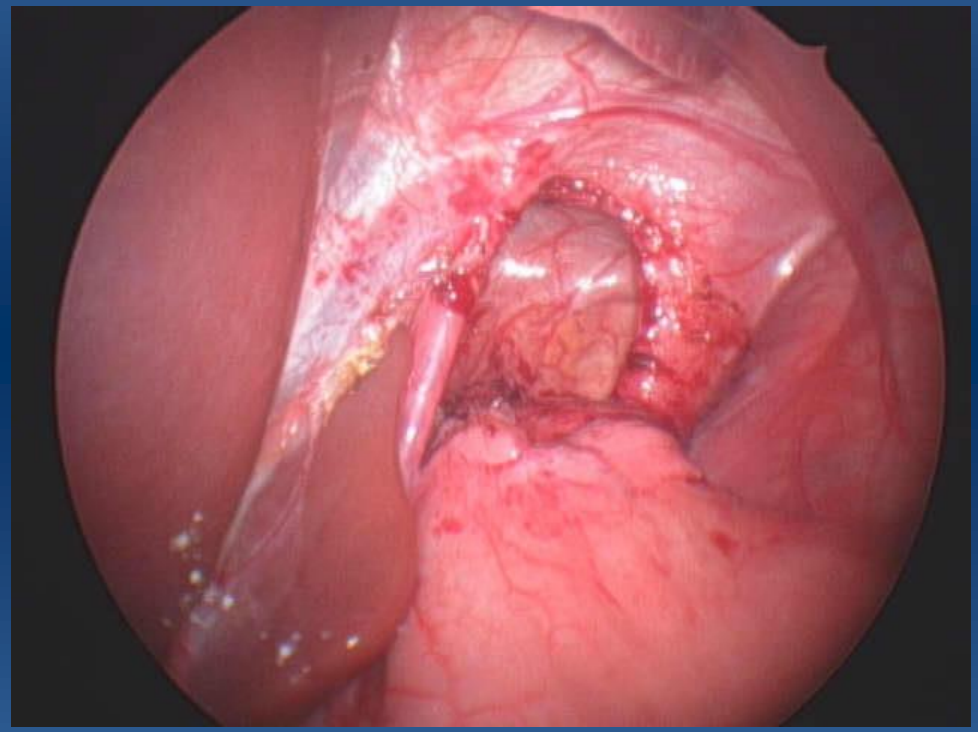


Fig. 4. Approximation of the crura during laparoscopic Nissen fundoplication.

HERNIATION





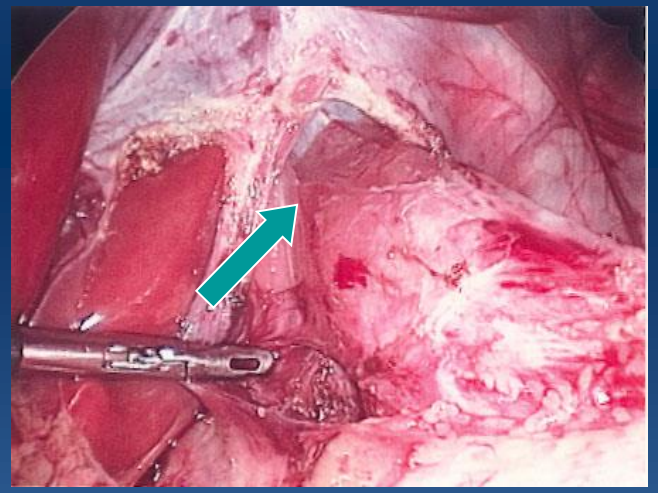
BACKGROUND

- We had begun doing less dissection and placing more stitches and were seeing less herniations – Whit Holcomb

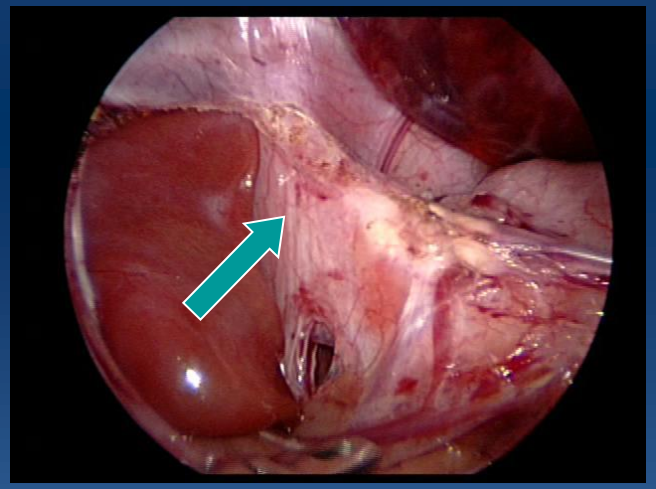
- The UAB group was bipolar on the topic - Keith Georgeson v Mac Harmon

INTERVENTIONS

Maximal Mobilization (MAX)



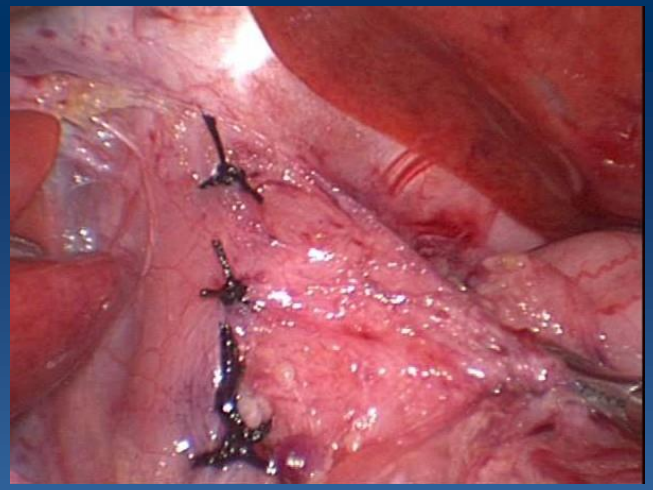
Minimal Mobilization (MIN)



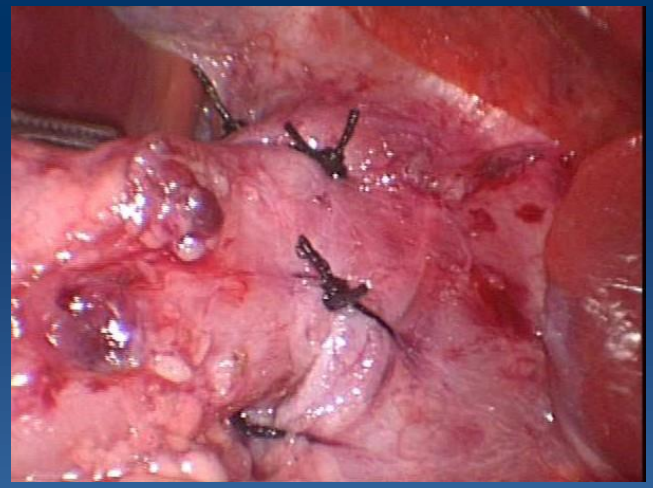
INTERVENTIONS

At Least 4 Esophagocrural Sutures Placed in All Patients

Right Crus



Left Crus



Dissection vs No Dissection

Study Design

- Primary Outcome Variable - Hiatal Hernia
  - 2 centers – CMH and UAB
  - All patients get upper GI study at 1 yr

QUALITY ASSURANCE

- Photograph after dissection to confirm minimal or maximal mobilization
- Photographs were reviewed by participating surgeons at APSA when we reviewed the data
- No patients were removed because photograph didn’t confirm randomization allotment

OUTCOMES

During Study Follow-Up

(16 Months – 3.5 Years)

	MAX (N = 70)	MIN (N = 64)	P Value
Wrap Herniation	30.0%	7.8%	0.002
Re-Operation	18.4%	3.3%	0.006

LONG-TERM FOLLOW-UP

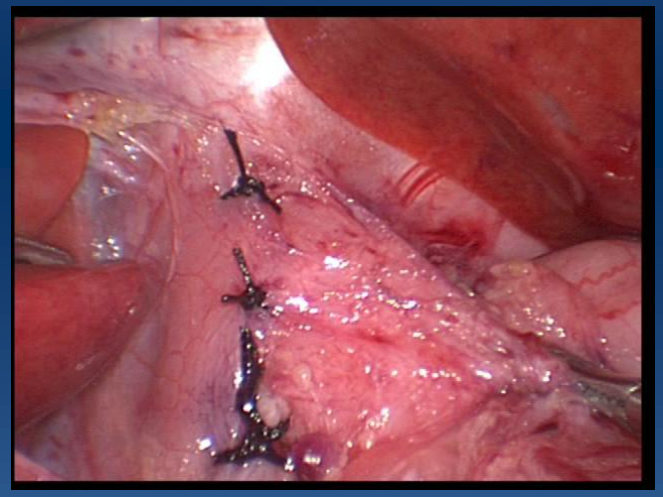
- 122 patients in original study at CMH
  - 67% telephone contact (43 MAX, 39 MIN)
  - 11.5% deceased (4MAX, 10MIN)
  - 21.3% lost to follow-up (14 MAX, 12 MIN)
- Median time to follow-up: 6.5yrs
- Mean age: 8.4 ± 2.8yrs

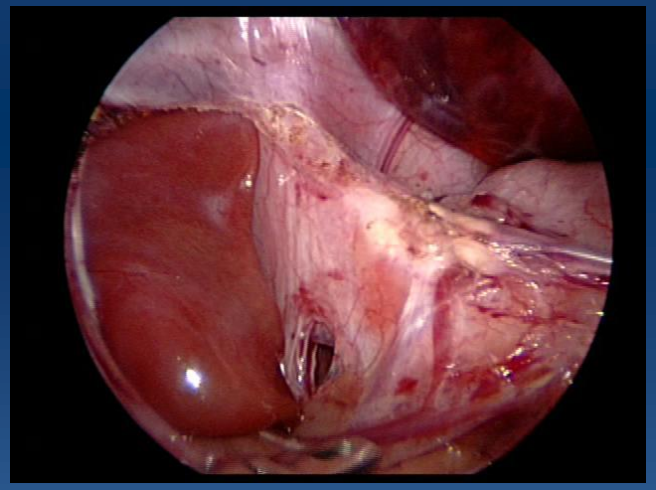
RATE OF POST-OPERATIVE HERNIATION AT 1 AND 5 YRS

	1 yr	5 yr
MAX	12%	37%
MIN	3%	12%
	P=0.01	P=0.01

NISSEN FUNDOPLICATION STUDY #2

Crural Stitches vs No Stitches





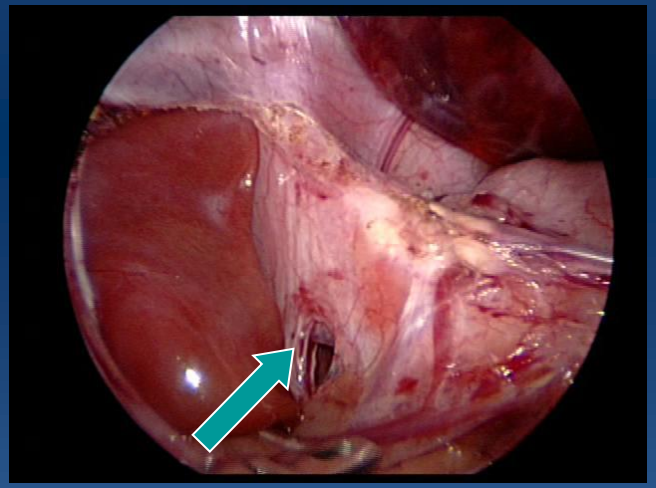
Stitches vs No Stitches

- Randomized 120 patients
- No herniations in either group
  - 1 reoperation for failed fundo in stitch group
- Far shorter operating time with no stitches

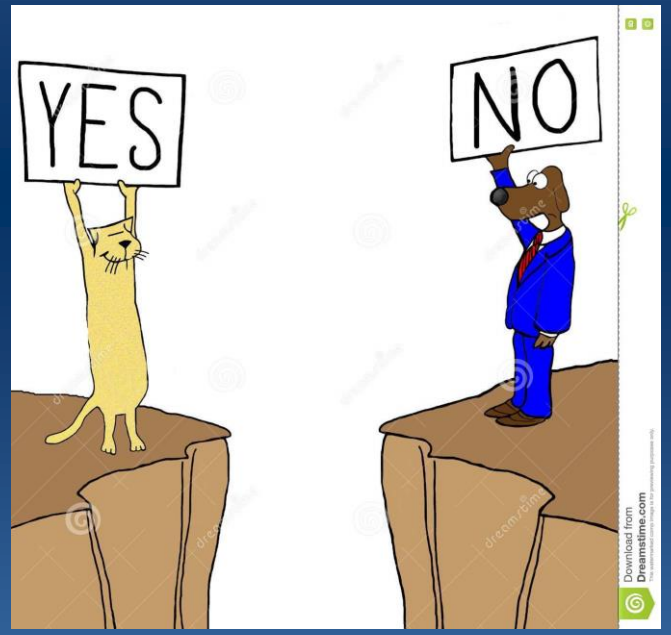
“It was the dissection causing the problem”

Prosp Observational Study

No Crural Stitches



GROUP PRACTICE = CLINICAL EQUIPOISE



PERFORATED APPENDICITIS

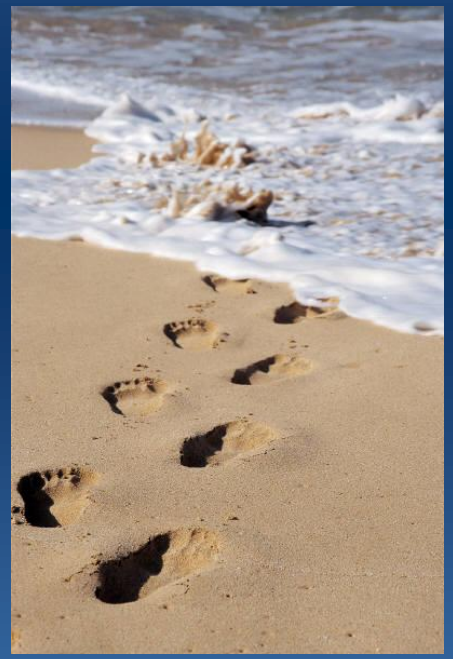
Should we irrigate?

IRRIGATION

“Dilution is the solution to pollution”

NO IRRIGATION

“Macrophages can’t swim”



STUDY POPULATION

Inclusion Criteria

- Under 18 years of age
- Perforated appendicitis at the time of appendectomy
  - Stool in the abdomen
  - Hole in the appendix

Exclusion Criteria

- Severe concomitant process

INTERVENTIONS

Irrigation

- 1 bag of saline attached to the suction/irrigator
  - Minimum irrigation volume of 500cc

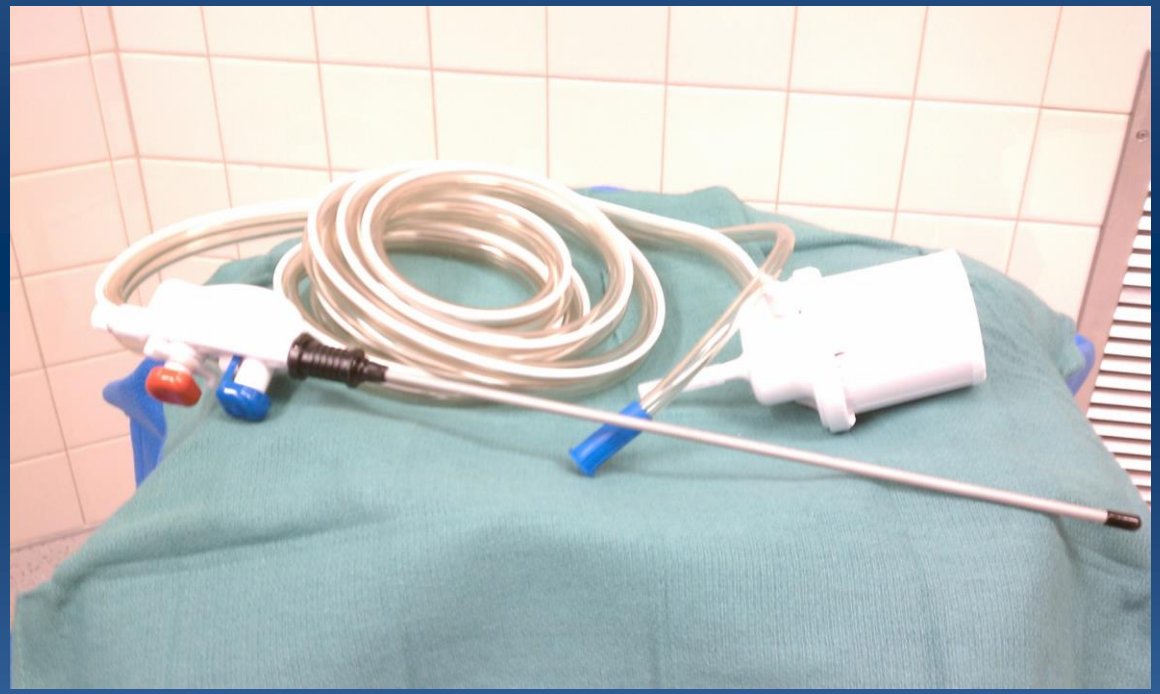
Suction Only

- No bag attached to the suction/irrigator

Battery Powered Suction Irrigator Used in All Cases

STANDARDIZED SUCTION

Battery Powered Suction Irrigator



MANAGEMENT

- One computer order set for both groups
- Standard PCA was utilized for pain control
- Foley catheter placed, no nasogastric tubes
- Once daily dosing of IV ceftriaxone (50 mg/kg) and metronidazole (30 mg/kg)
- When tolerating diet, discharged home to complete 7 day course with oral amoxicillin/clavulanate

RESULTS

Irrigation

- 1 suction patient received irrigation
  - Analyzed with the no irrigation patients
- Mean volume of irrigation was 867 +/- 327 ml
  - Range 500 – 2000 ml

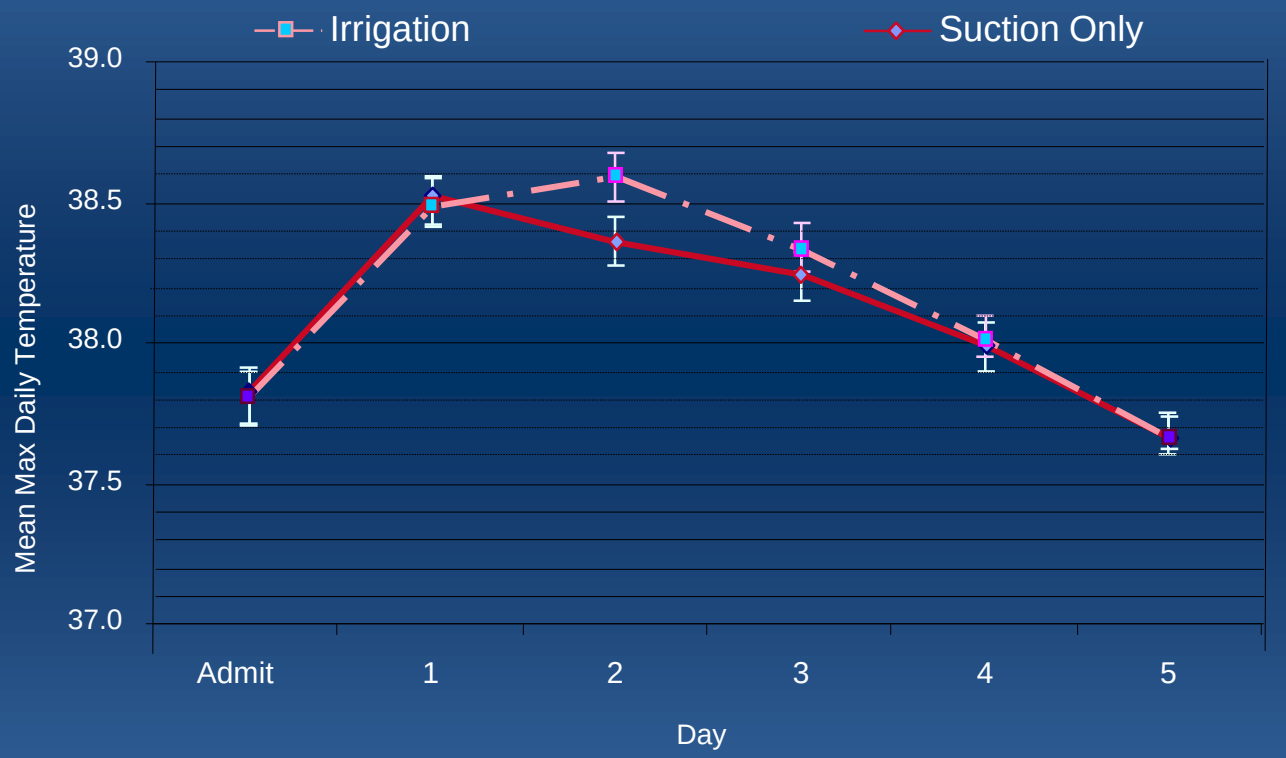
And the results are……..

RESULTS

Outcomes

	No Irrigation (n = 110)	Irrigation (n = 110)	P Value
Abscess (%)	19.1%	18.3%	1.0
Op Time (mins)	38.7 +/- 14.9	42.8 +/- 16.7	0.06
Initial PO's (dys)	2.6 +/- 1.5	2.5 +/- 1.3	0.70
Reg Diet (hrs)	3.4 +/- 1.7	3.5 +/- 1.5	0.63
Narcotic Doses	11.4 +/- 5.4	11.6 +/- 6.3	0.76
Days of Stay	5.5 +/- 3.0	5.4 +/- 2.7	0.93
Charges ($K)	48.1 +/- 20.1	48.1 +/- 18.2	0.97

TEMPERATURES

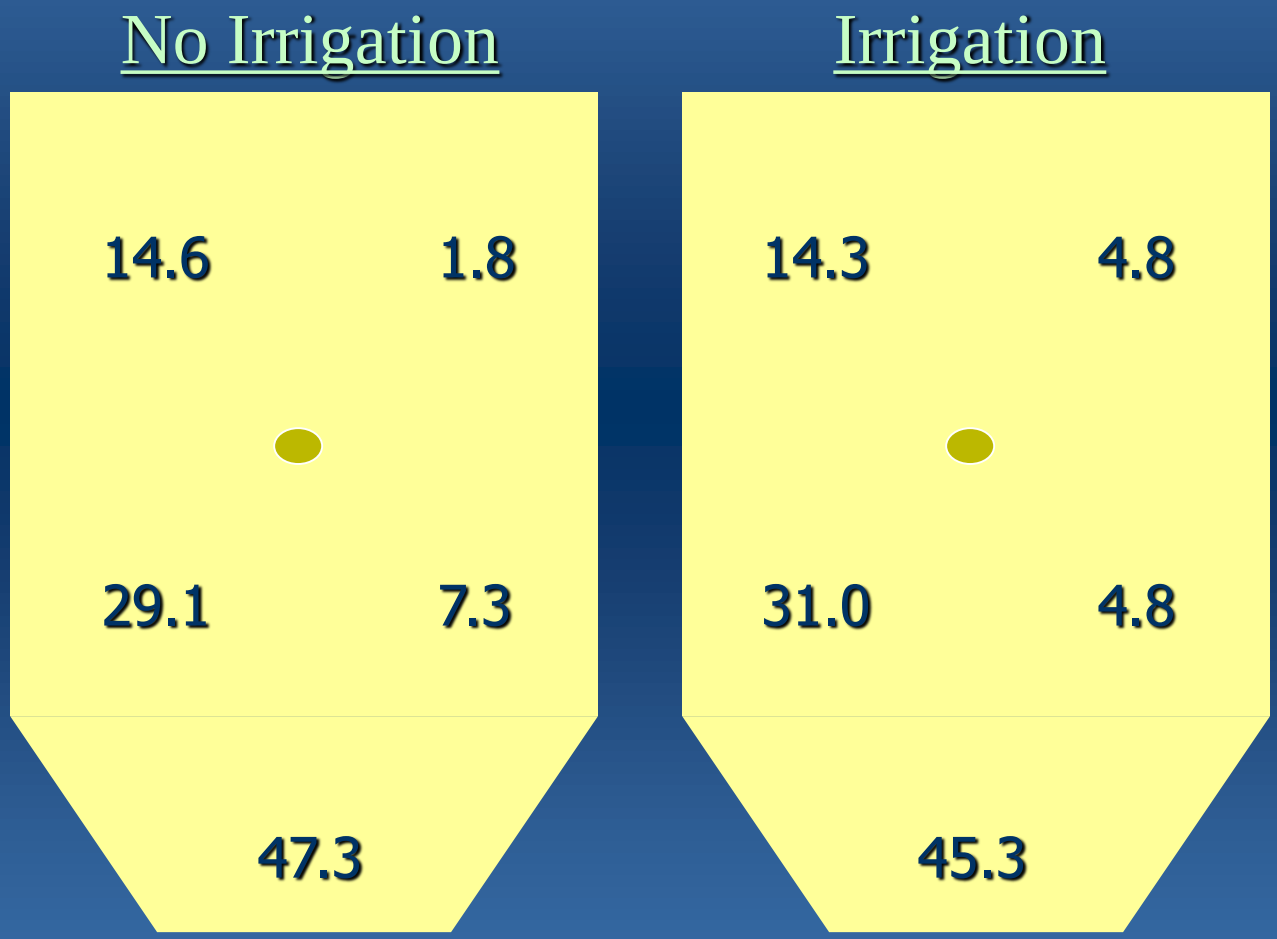


RESULTS

Outcomes of Patients with Postoperative Abscess

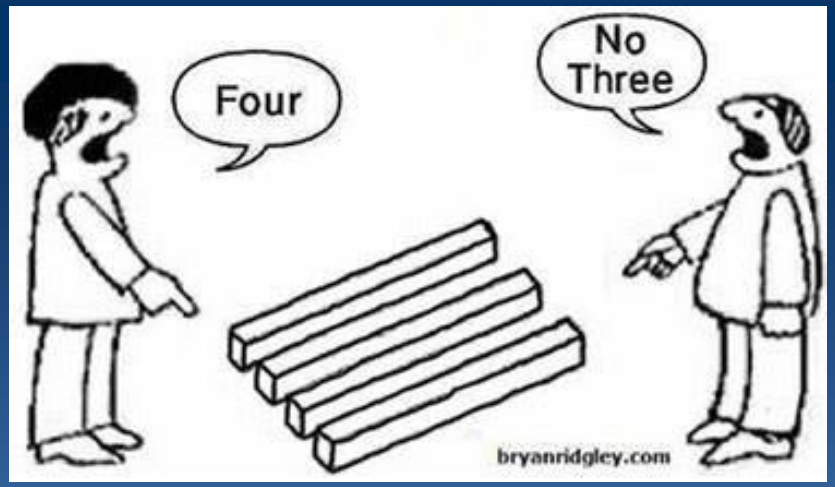
	No Irrigation (n = 21)	Irrigation (n = 20)	P Value
Drain Placed (%)	52%	40%	0.54
Days of Drainage	2.3 +/- 2.2	1.8 +/- 2.8	0.58
Days of Stay	8.7 +/- 4.4	9.4 +/- 3.8	0.56
Reg Diet (hrs)	19.5 +/- 3.9	21.4 +/- 8.6	0.37
Days Home Health	10.4 +/- 4.5	13.0 +/- 7.4	0.20
Charges ($K)	28.3 +/- 22.7	24.6 +/- 13.8	0.54

LOCATION OF ABSCESSES



CONCLUSION

Irrigation = Suction Alone



HOW CAN WE INVESTIGATE DURING INNOVATION?

PROGRESSION OF INNOVATION

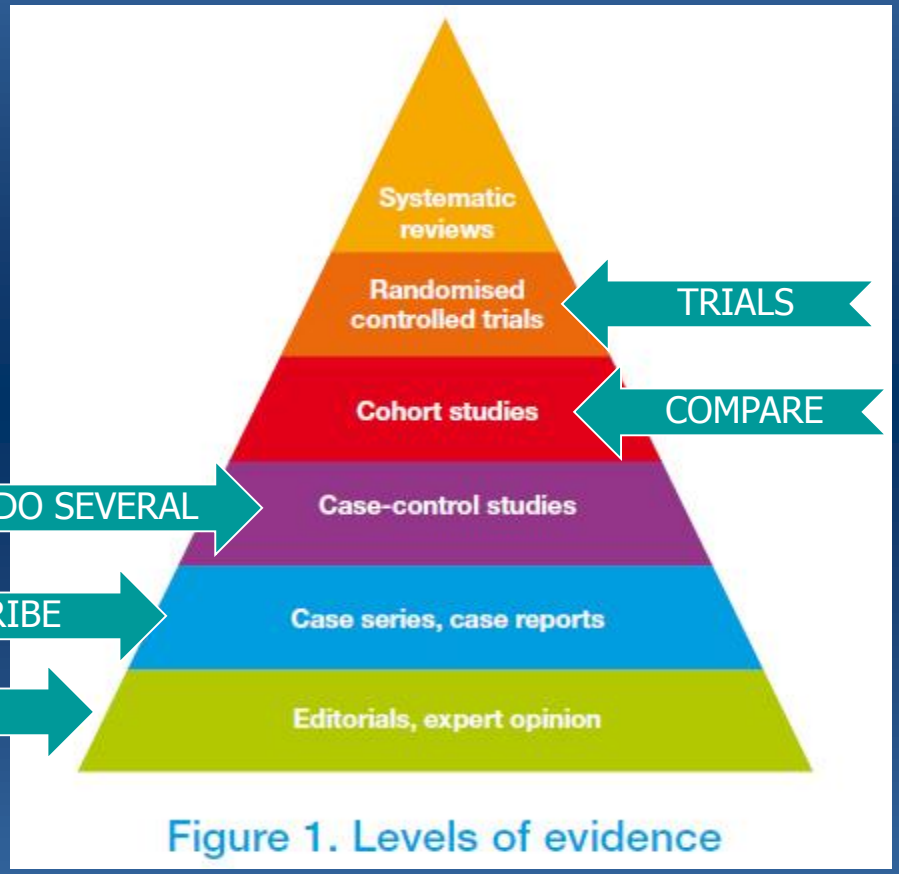


Figure 1. Levels of evidence


VS

Acceptance of Laparoscopy

- Cholecystectomy, splenectomy, nephrectomy, adrenalectomy, fundoplication, others
  - Same operation - no laparotomy
  - Shorter LOS, shorter convalescence, improved patient satisfaction, improved cosmesis, improved visualization/ease of operation

Disruptive Innovation

WHAT'S THE PROBLEM?

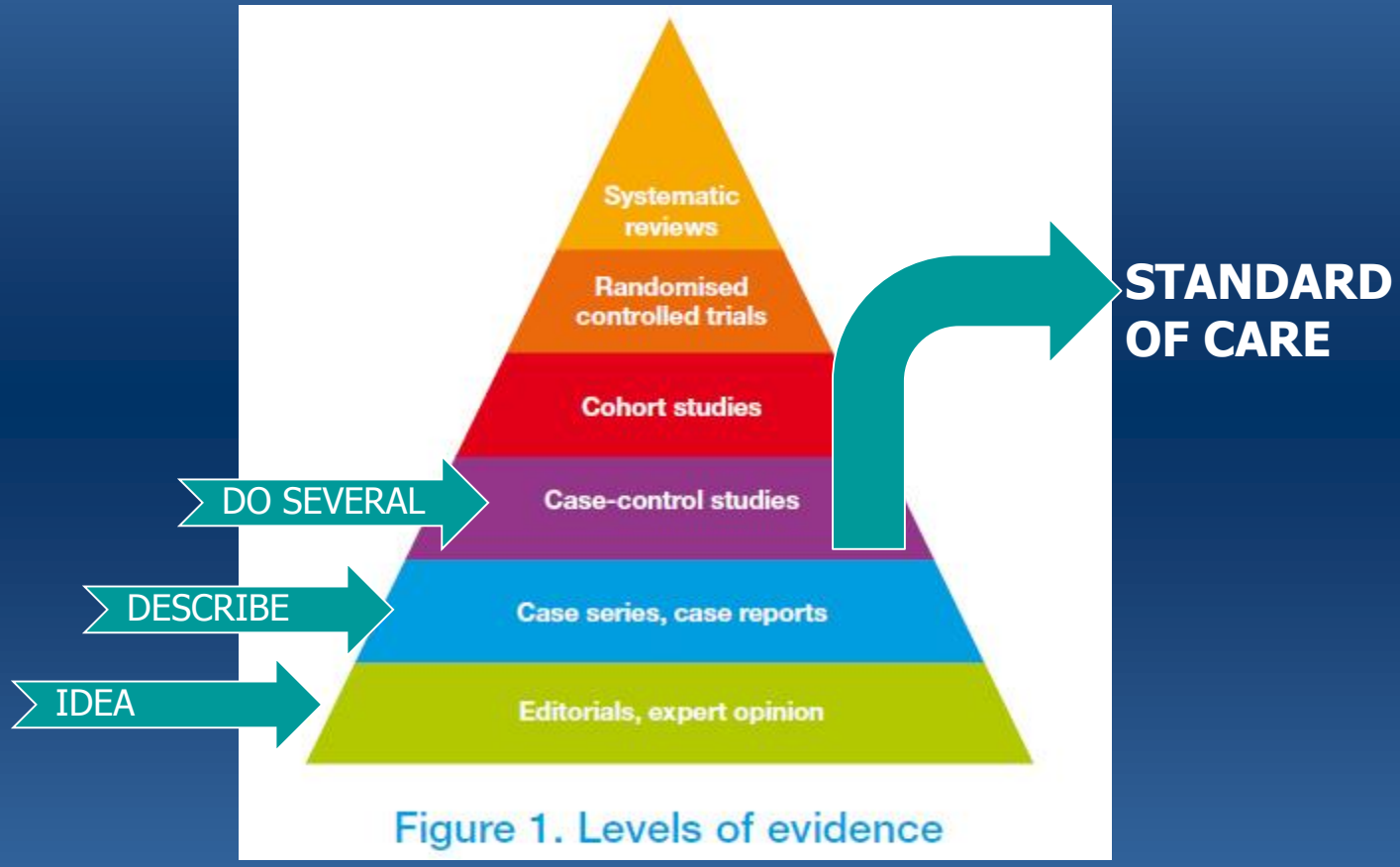


Figure 1. Levels of evidence

Subconscious Maleficence

Practi[illegible] harm of patients

Subconscious Maleficence

- Extra-intracranial artery bypass for stroke
  - Over 1000 cases by 1978
  - RCT in 1985 – then gone
- Arthroscopic debridement for osteoarthritis
  - Case series and cohort comparisons led to 650,000/yr in US by 1996
  - Trial in 2002 – no benefit over placebo

Subconscious Maleficence

- Colectomies for epilepsy
- Anglechik ring for GERD
- Reimplants for low grade VUR
- Nephrectomy/splenectomy trauma
- Jejunoileal bypass for obesity
- Swan Ganz catheters

How Do We Prevent Becoming Tomorrow's Example?

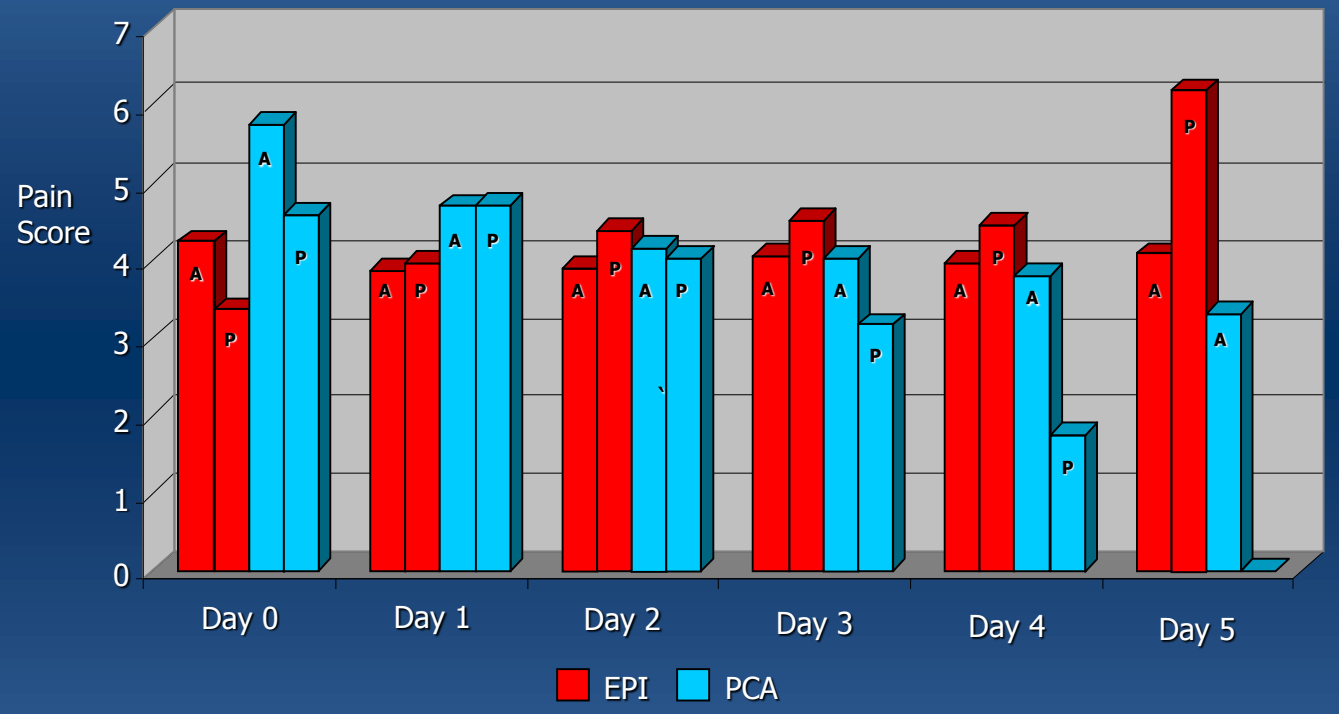
Investigate with the launch of new treatments

-Prosp observational if the leap is disruptive

- Comparative study if equipoise exists

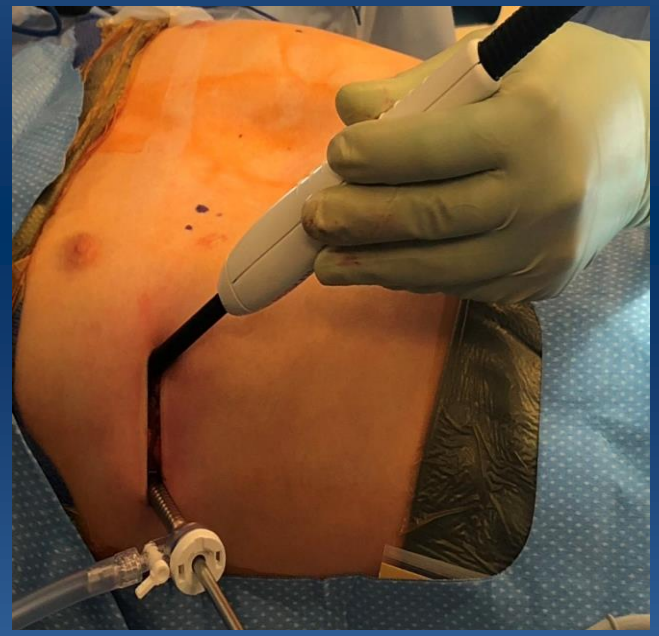
PECTUS EXCAVATUM

Epidural v PCA RCT

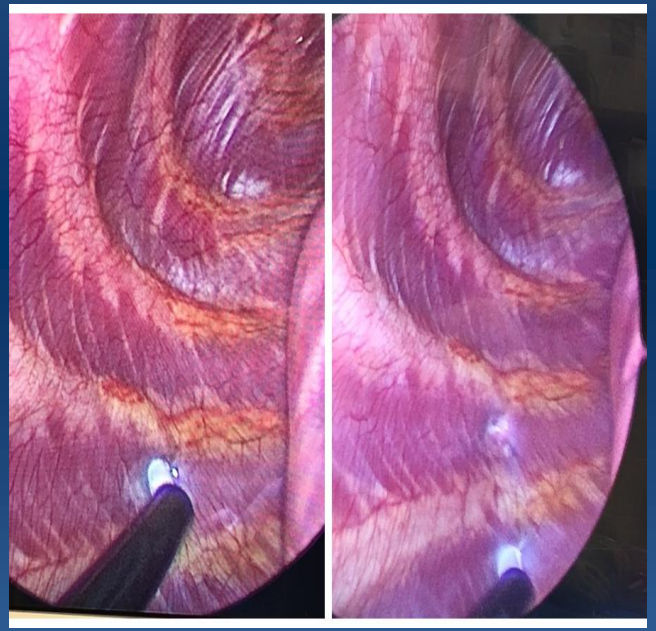


A = AM Pain Score **P = PM Pain Score**

CRYOABLATION



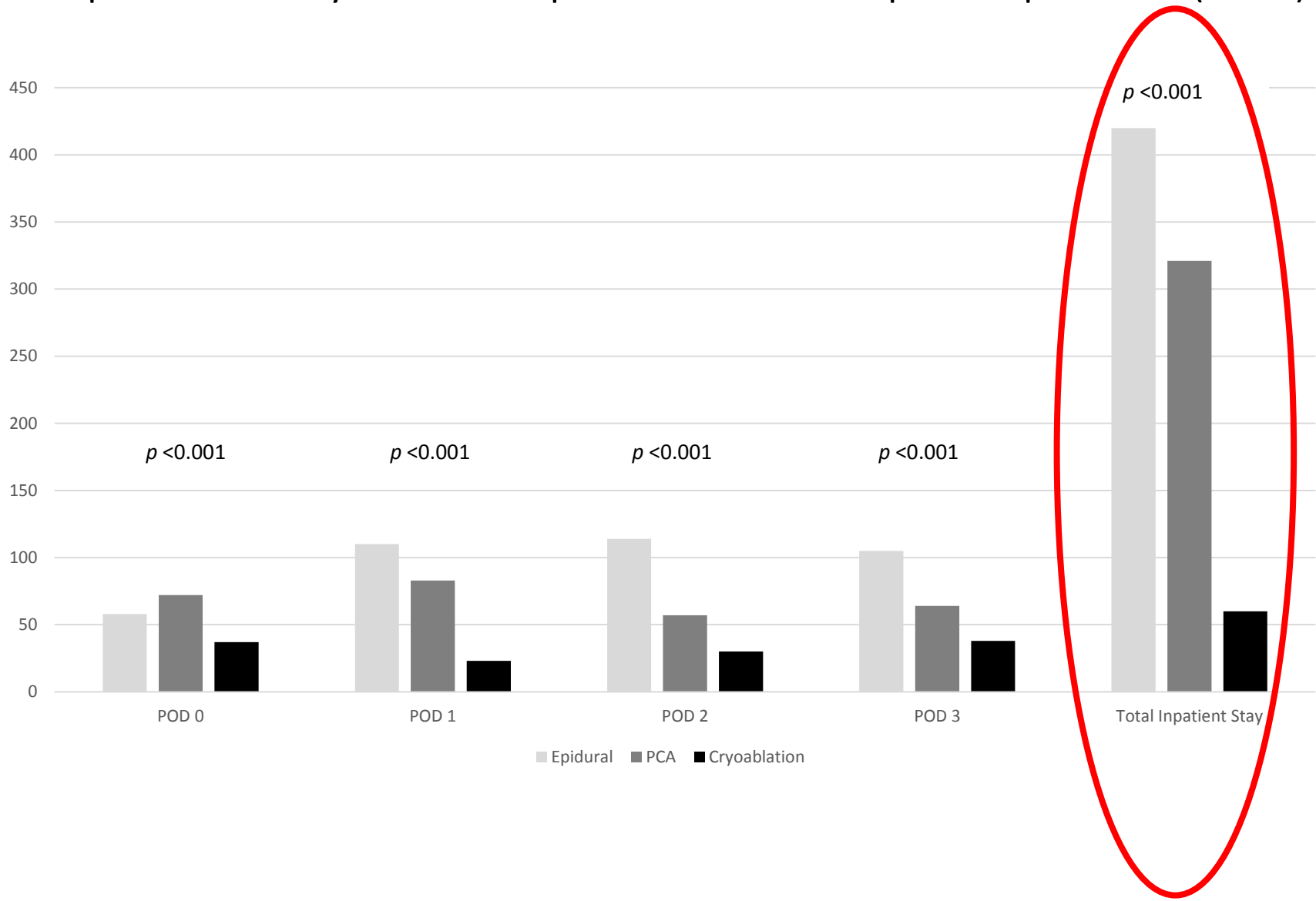
CRYOABLATION



EPI v PCA v Cryo

	Epidural (n=32)	PCA (n=33)	Cryoablation (n=35)	*p*-value
Gender, Male (%)	90.6	93.9	82.4	0.2
Age (yr)	15 [14, 16]	14 [13,16]	16 [14, 17]	*0.02**
Height (m)	1.8 [1.7, 1.8]	1.7 [1.7, 1.8]	1.7 [1.7, 1.8]	0.46
Weight (kg)	56.6 [52, 61.6]	56.1 [48, 58.4]	57.1 [50, 64]	0.24
Correction Index (%)	30 [37, 30]	30 [30, 40]	35 [30, 47]	*0.01**
Time to only oral pain meds (hr)	71.1 [50.4, 82.7]	66.6 [50, 70]	20.9 [11.6, 28.4]	*<0.01**
Length of stay (d)	4.3 [4.1, 5.1]	4.2 [3.4, 5.2]	1 [1, 1.3]	*<0.01**

Comparison of Daily and Total Inpatient Median Morphine Equivalents (MME)



tPA in Abdominal Abscesses Associated with Appendicitis

New Therapy (tPA)

↘

Compare to Standard

↓

IRB said “do more”

↙

New becomes Standard

RESULTS

Drainage Outcomes

	Saline (n = 32)	tPA (n = 30)	P Value
Post Drain LOS	3.3 +/- 1.3	4.5 +/- 1.6	0.002
Total Days of Stay	6.4 +/- 4.0	7.1 +/- 3.8	0.49
Days of Drain	3.5 +/- 3.6	4.6 +/- 2.4	0.17
Drain Total (ml)	128 +/- 160	204 +/- 166	0.06

RESULTS

Downstream Outcomes

	Saline (n = 32)	tPA (n = 30)	P Value
Healthcare visits	5.2 +/- 2.3	5.9 +/- 2.3	0.24
Day of IV abx	15.6 +/- 4.0	16.8 +/- 5.0	0.30
Recurrent abscess	2 (6%)	6 (20%)	0.22
Med Charges ($K)	4.1 +/- 2.6	6.5 +/- 3.1	0.002

tPA in Abdominal Abscesses Associated with Appendicitis

New Therapy (tPA)

↘

Compare to Standard

↓

Worse outcome with more expense

↙

Standard Remains

Center for Prospective Trials

- Initiated in 2006
  - Randomized Trials
    - 18 Published
    - 2 Completed
    - 2 Enrolling
  - Prospective Observational Studies
    - 6 Published
    - 2 Completed
    - 6 Enrolling

Lesson Learned

Lessons Learned

Lessons Learned

“Don’t be too timid about your actions, all life is an experiment. The more experiments you make the better”

Ralph Waldo Emerson

As long as you are collecting the data