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Comparison of Superficial Surgical Site Infection Between Delayed Primary Versus Primary Wound Closure in Complicated Appendicitis

A Randomized Controlled Trial

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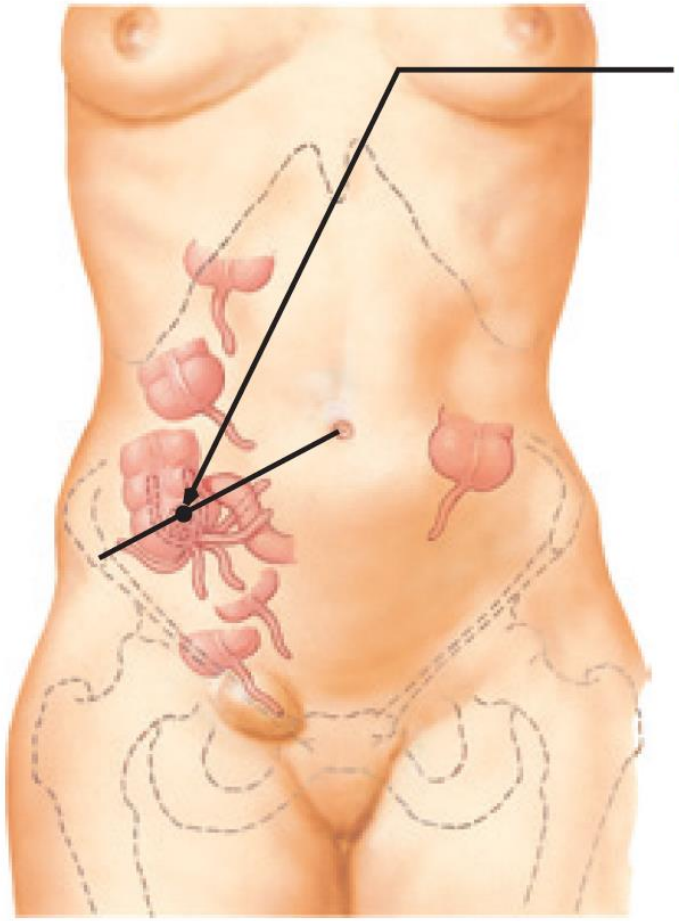
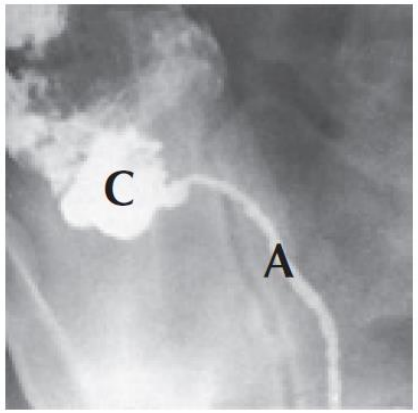
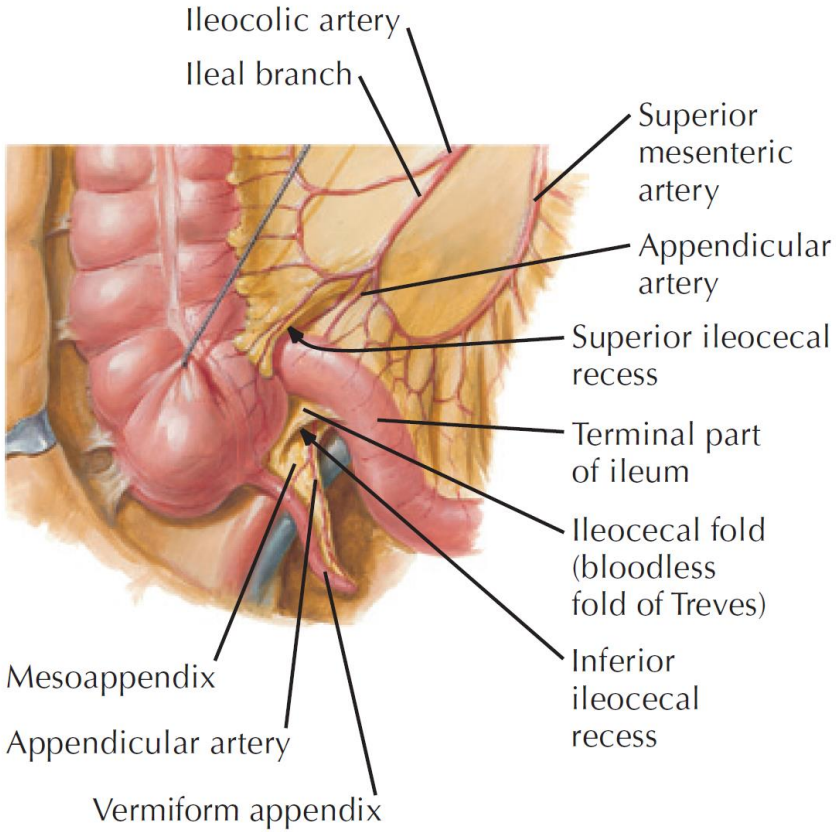
Anatomy

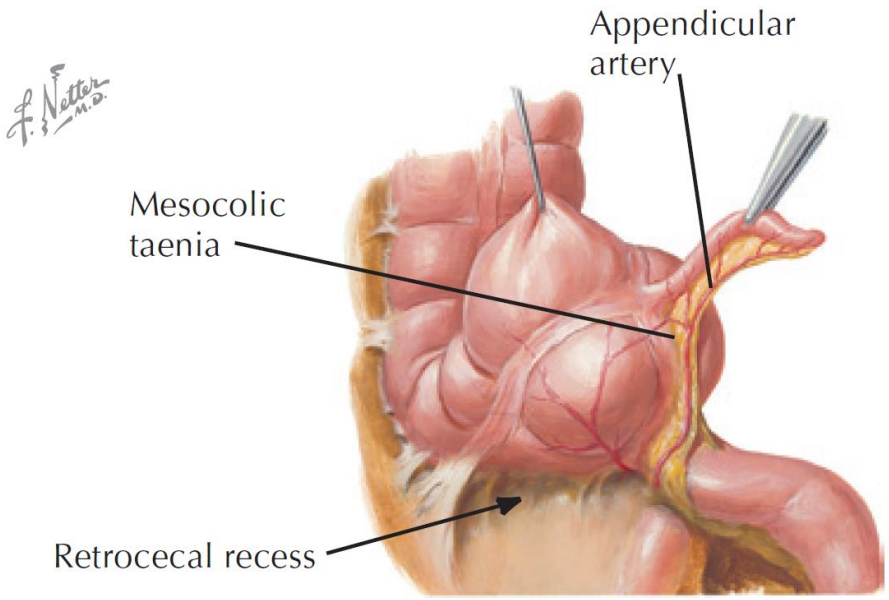




Barium radiograph of unusually long appendix (**A**, Appendix; **C**, Cecum)

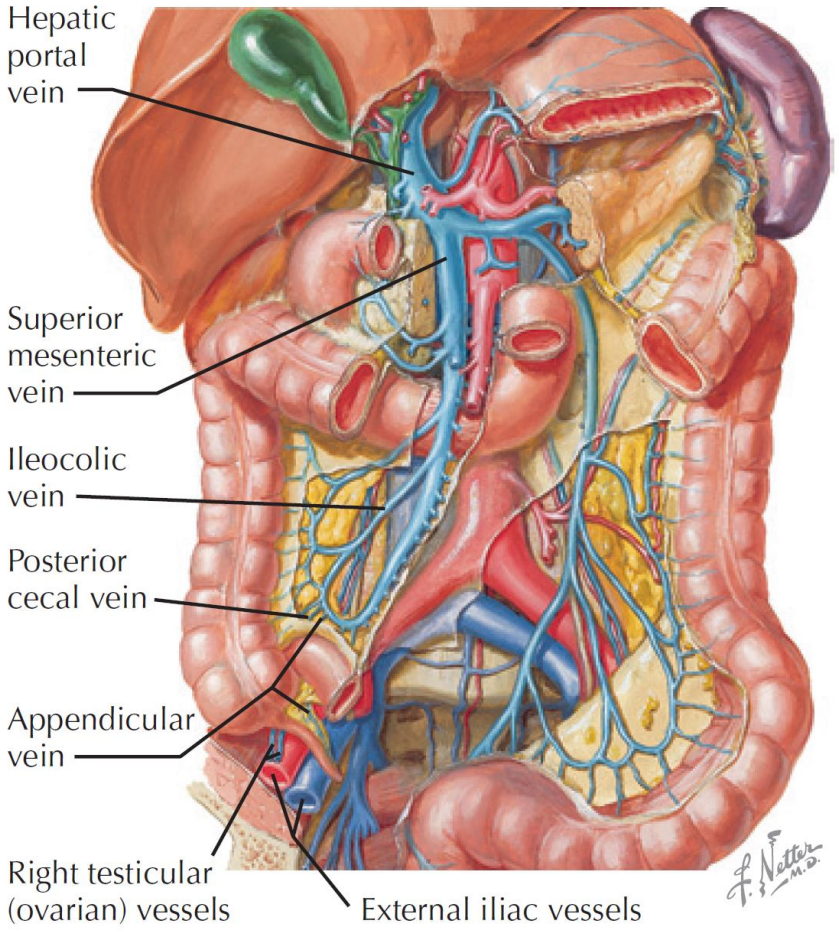
Anatomy



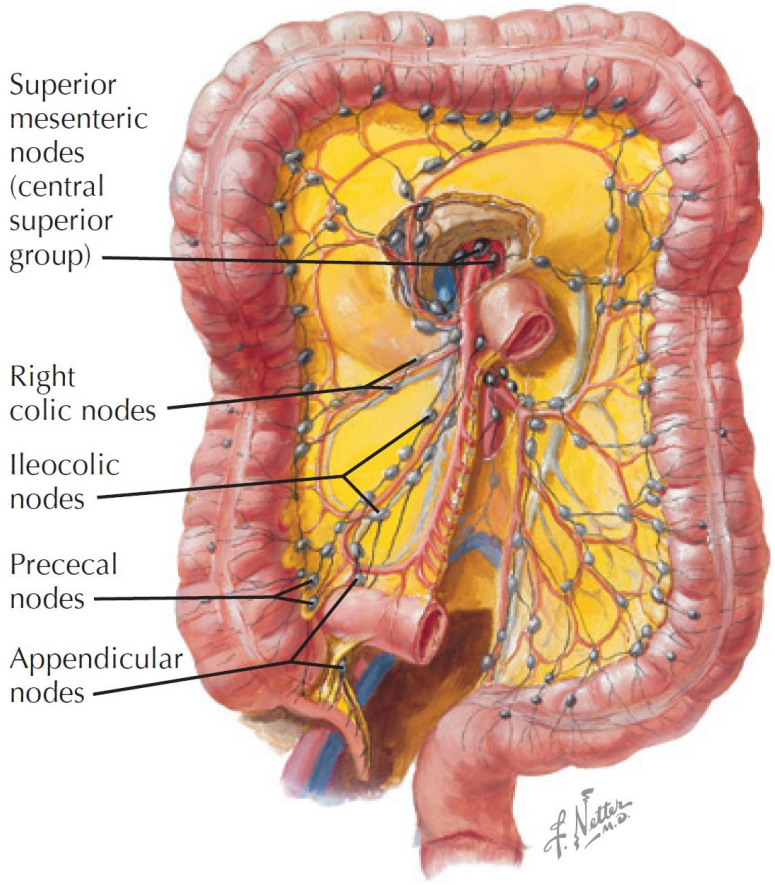


Ileocecal Region and Appendix

Anatomy



Veins of Large Intestine



Lymph Drainage of Large Intestine

Epidemiology

- Occurs in 10% of the population
- Most common abdominal surgical emergency

Pathogenesis in Adults

- Fecalith obstructs the proximal lumen (similar to pathogenesis of acute diverticulitis)
  - Increased intraluminal pressure causes mucosal injury and bacterial invasion.
- Other causes
  - Seeds (sunflower, persimmons), pinworm infection
- Primary pathogens are *Escherichia coli* (most common) and *Bacteroides fragilis*.

Clinical Findings in Sequence

- Initial colicky periumbilical pain (50% of cases)
  - Irritation of unmyelinated afferent C fibers on visceral peritoneal surface
  - Refer pain to the midline
- Fever
  - Very important sign for identifying appendicitis in children with abdominal pain
- Nausea, vomiting, and fever
  - Pain *precedes* nausea and vomiting
- Cutaneous hyperesthesia at level of T12

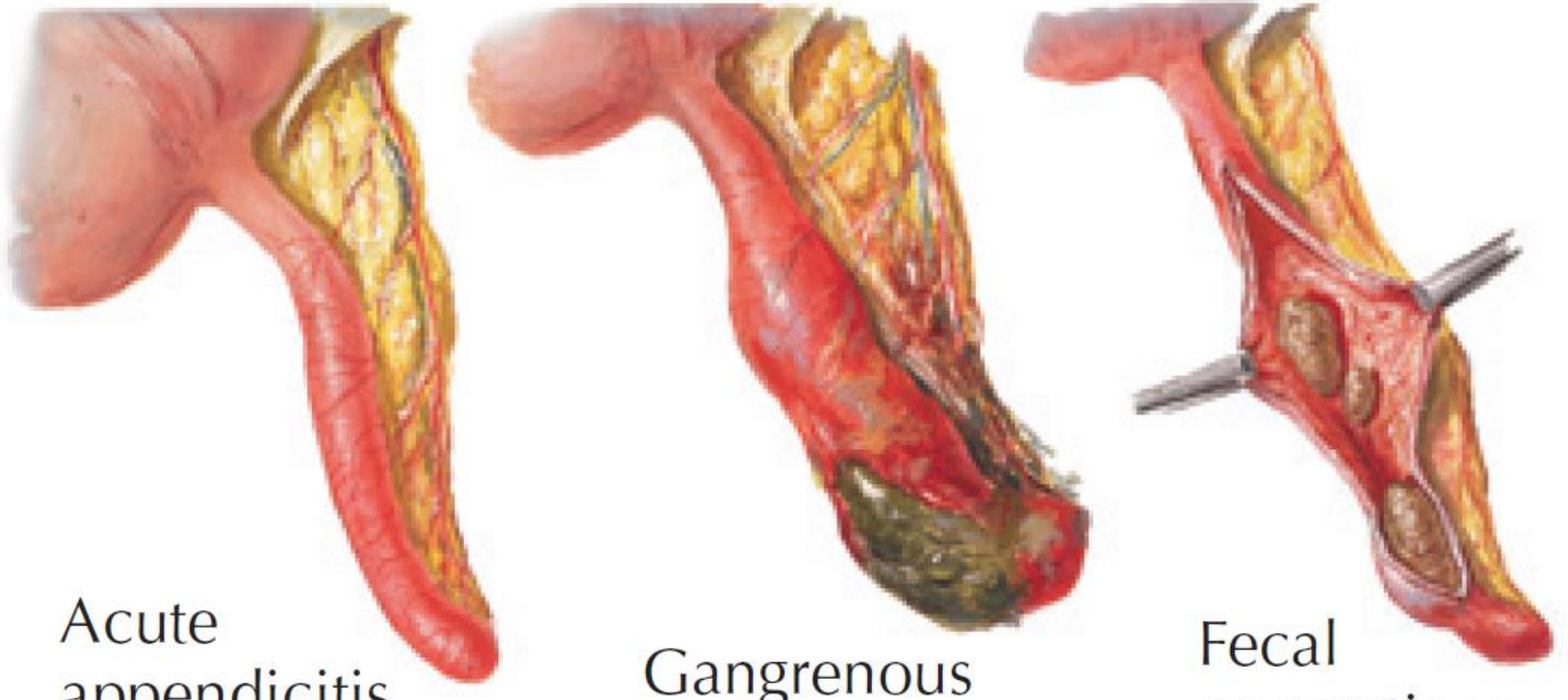
Clinical Findings in Sequence

- Pain shifts to right lower quadrant (RLQ) in 12 to 18 hours.
  - Irritation of Aδ fibers on parietal peritoneum
    - Localizes pain to the exact location
  - Rebound tenderness at McBurney point (Blumberg sign)
  - Pain with right thigh extension (psoas sign)
  - RLQ pain with palpation of left lower quadrant (Rovsing sign)
- Signs of a lower urinary tract infection may occur.
  - Increased frequency, dysuria

Clinical Findings in Sequence

- Laboratory findings
  - Neutrophilic leukocytosis with left shift (90% of cases)
  - Abnormal urinalysis
    - Increased protein, hematuria, pyuria

Acute Appendicitis Classification



Complications

- Periappendiceal abscess with or without perforation
  - Most common complication
  - May develop subphrenic abscess
    - Usually due to *Bacteroides fragilis*
- Pyelophlebitis
  - Infection of the portal vein
  - Danger of portal vein thrombosis
  - Radiograph shows gas in the portal vein.

Complications

- Subphrenic abscess
  - Persistent postoperative fever
  - Diaphragm fixed on the right; right-sided pleural effusion
  - Tenderness over lateral seventh and eighth ribs
  - Diagnosis
    - Ultrasound, CT scan, gallium scan
  - Treatment
    - Extraperitoneal drainage and antibiotics

Diagnosis of Acute Appendicitis

- Clinical examination
- Spiral CT RLQ after Gastrografin enema
  - Sensitivity 90% and specificity 94%
- Plain CT scan with rectal contrast agent
- Ultrasonography
  - Sensitivity 75% and specificity 90%

Treatment

- Appendectomy
- Cefoxitin
  - Given prophylactically perioperatively if perforation suspected

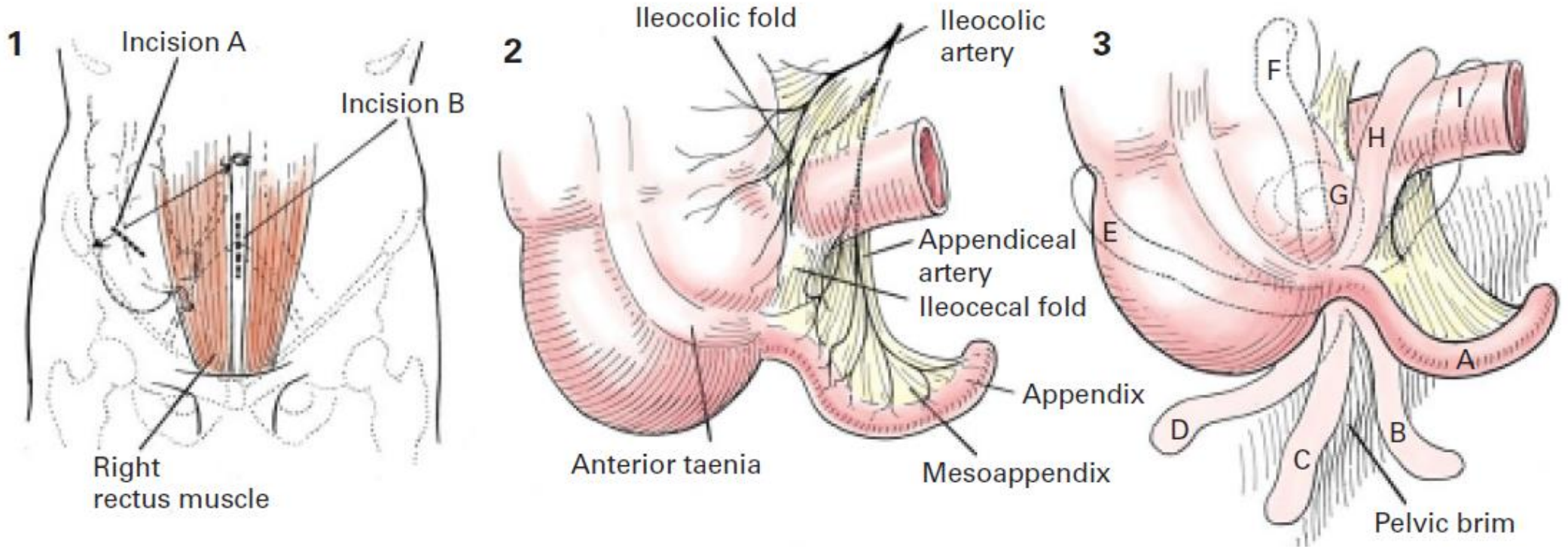
Appendectomy

- **Step 1.** Choice of incision is up to the surgeon. We prefer McBurney
- **Step 2.** Incise the aponeurosis of the external oblique along the lines of its fibers
- **Step 3.** Use a curved Kelly clamp to make an opening on both the internal oblique and the transversus abdominis muscles. Enlarge the opening with the Kelly clamp and insert two Richardson's retractors.
- **Step 4.** If the transversalis fascia is divided together with the flat muscles, occasionally there will be a thick stroma of preperitoneal fat which can be pushed laterally, or sometimes medially, revealing the peritoneum.

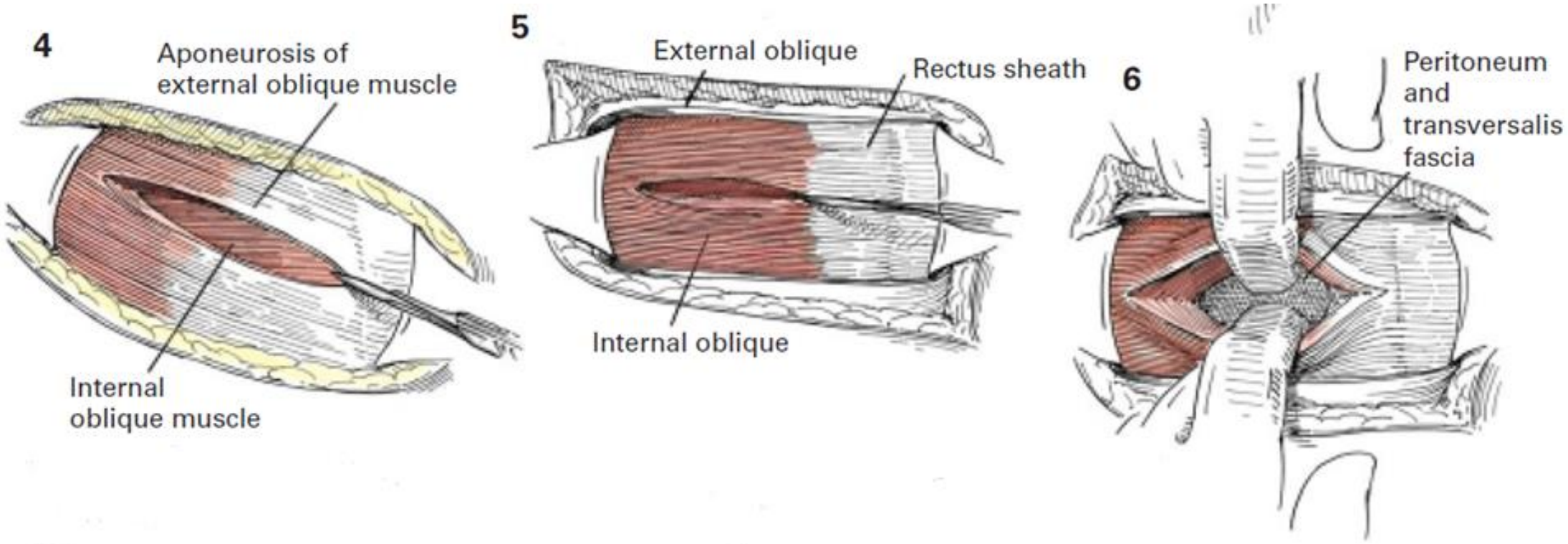
Appendectomy

- **Step 5.** Elevate the peritoneum and, if applicable, the transversalis fascia. Make a small opening in the peritoneum with a knife or scissors, then enlarge it with both index fingers and insert the retractors of your choice
- **Step 6.** Take cultures of the free peritoneal fluid and, using moist gauze, pull the cecum out of the wound. In most cases, the appendix is delivered with the cecum or may be seen.
- **Step 7.** Grasp and study the mesentery of the appendix and reinsert the cecum into the peritoneal cavity. Divide the mesoappendix between clamps

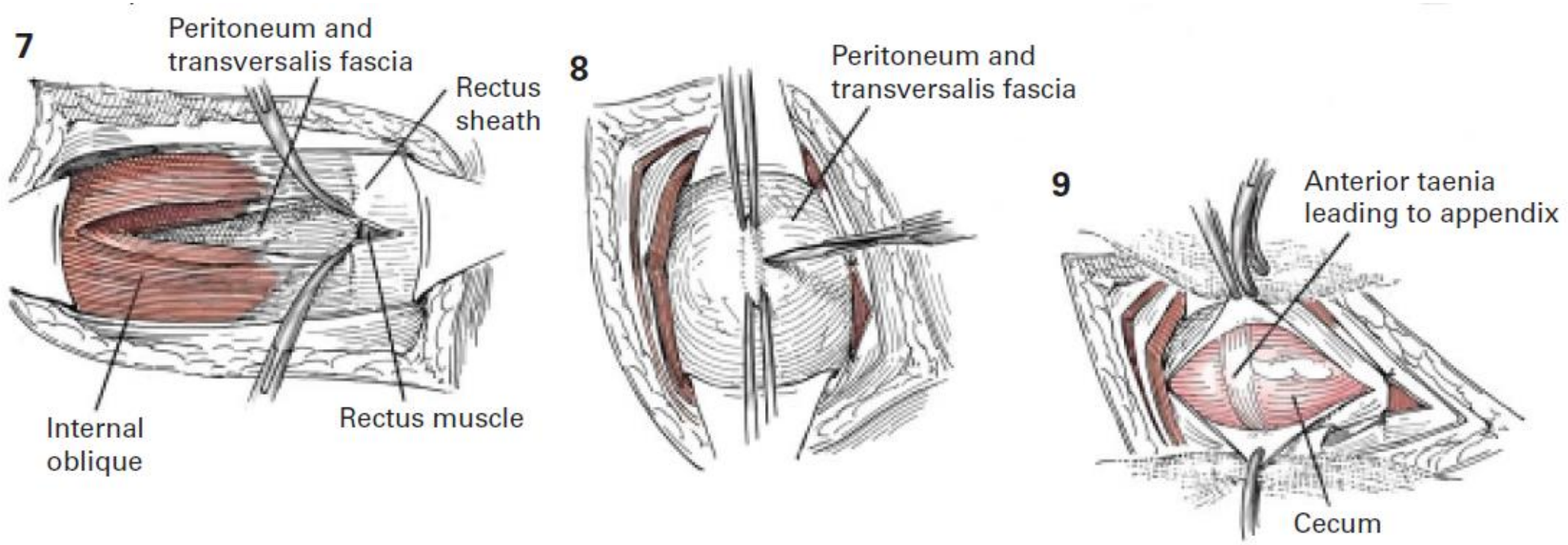
Appendectomy



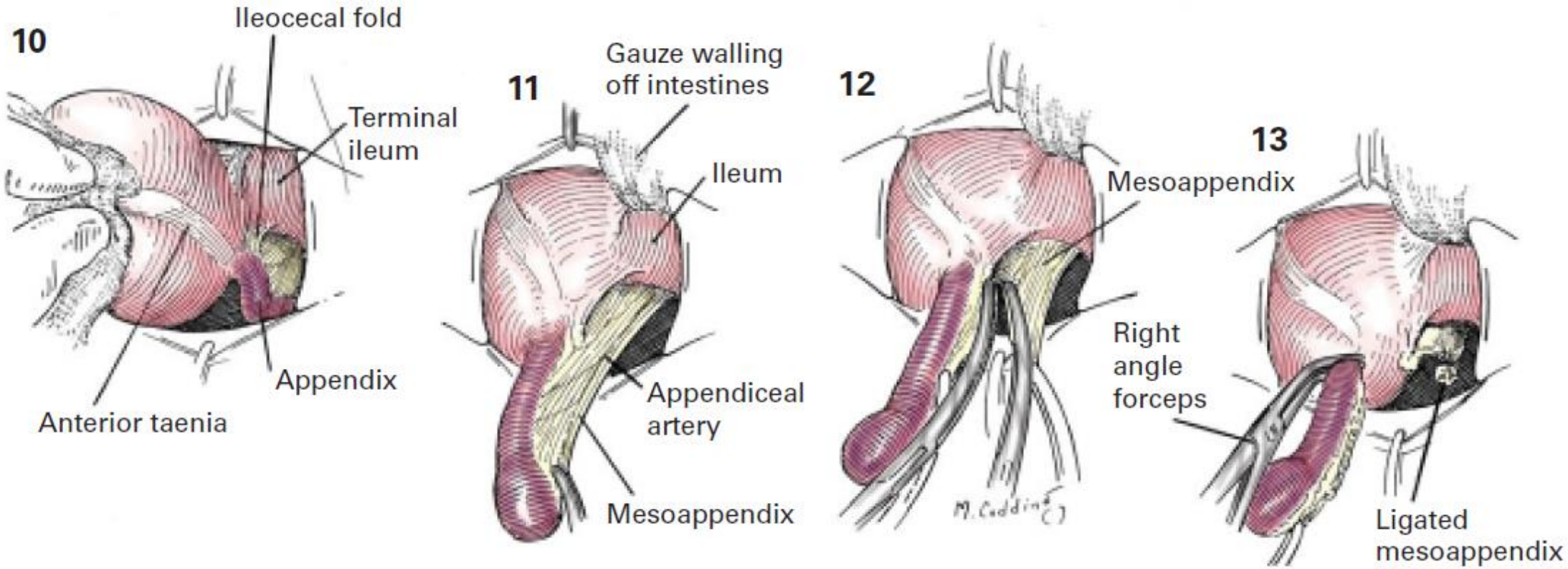
Appendectomy



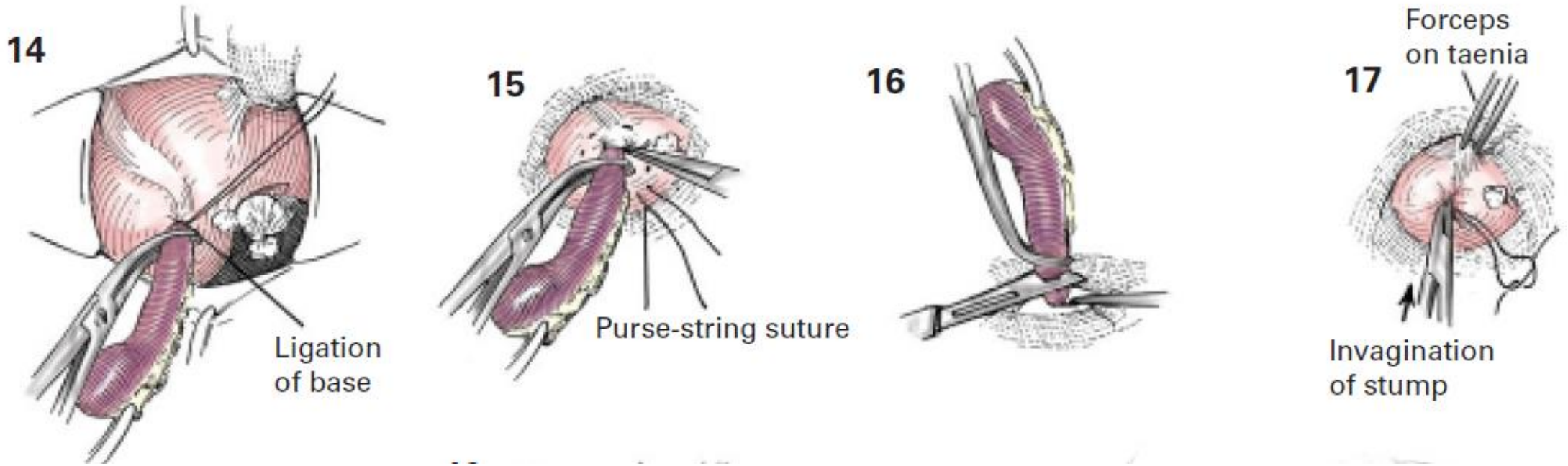
Appendectomy



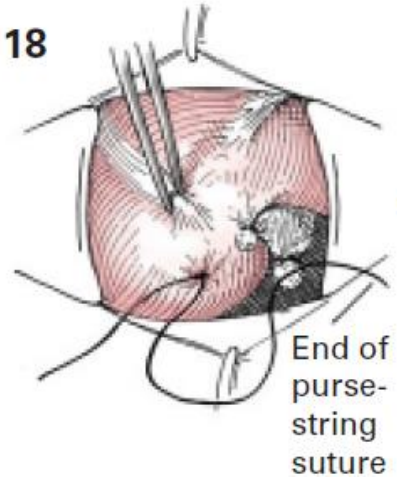
Appendectomy

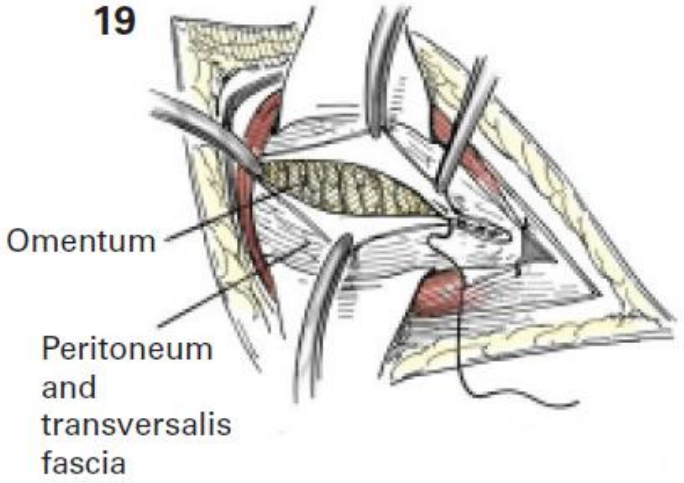


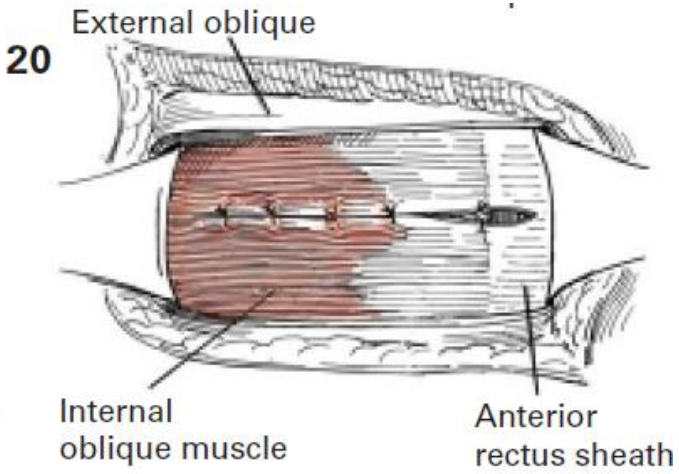
Appendectomy

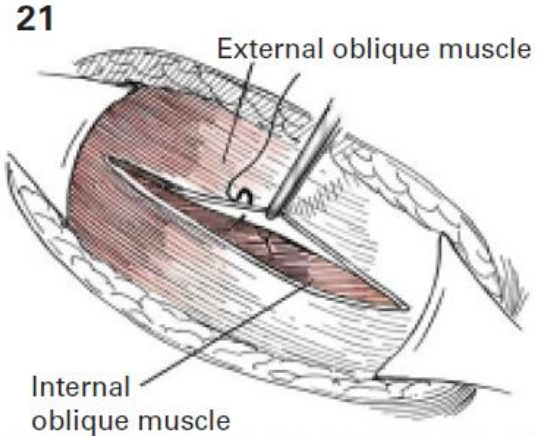


Appendectomy



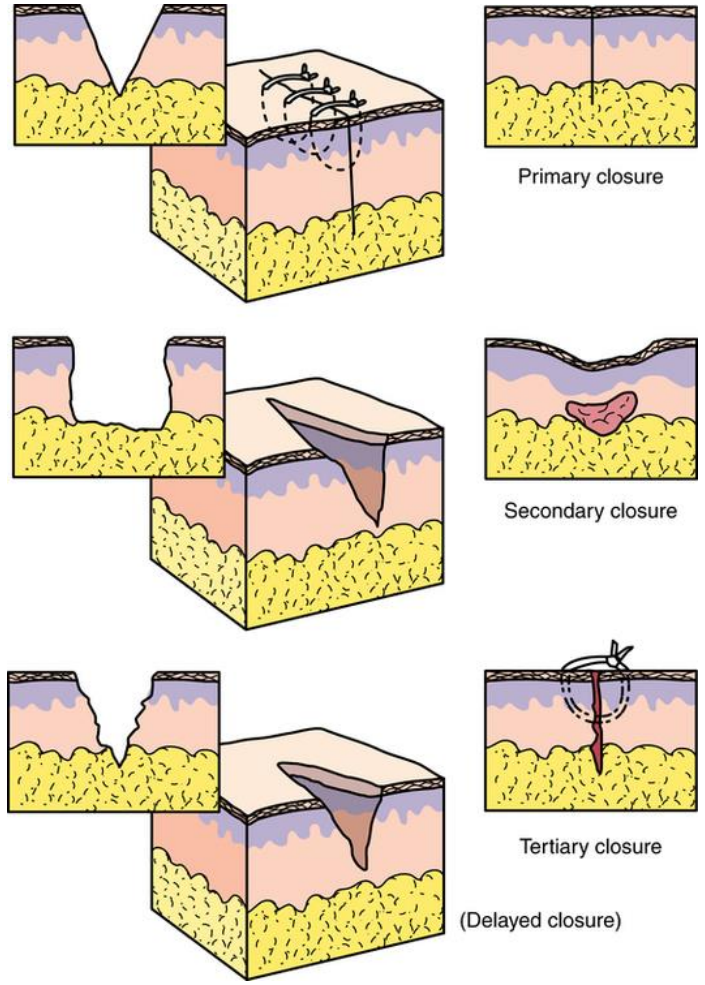






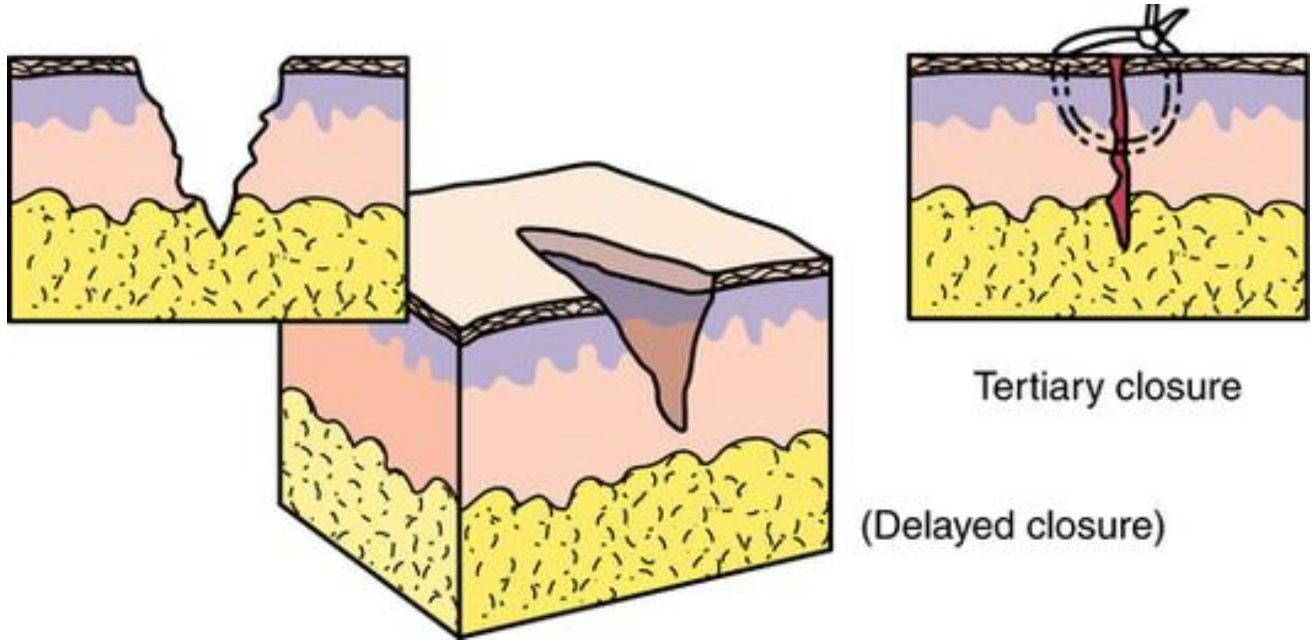
Type of Wound Closure

- Primary closure (PC)
  - Closed wound immediately after operation
- Delayed primary closure (DPC)
  - Closed 3-7 after operation with proper wound care
- Secondary intention or closure
  - Dressing until wound completely healed



Delayed Primary Wound Closure (DPC)

- Introduce since World War I in traumatic wound
- In 24-28 hrs., epithelialization of primary closure dirty incisions
    - Trap bacteria, exudates, clot, and debris



Delayed Primary Wound Closure (DPC)

Delayed Primary Wound Closure (DPC)

Pros of CPC

- Effect in reducing the number of bacteria contamination and colonizing the infection
- Increase local wound resistance, tissue oxygenation, wound blood supply within 3-5 postoperative day
- Incisions closed within 5 days: same strength as primary closure

Cons of DPC

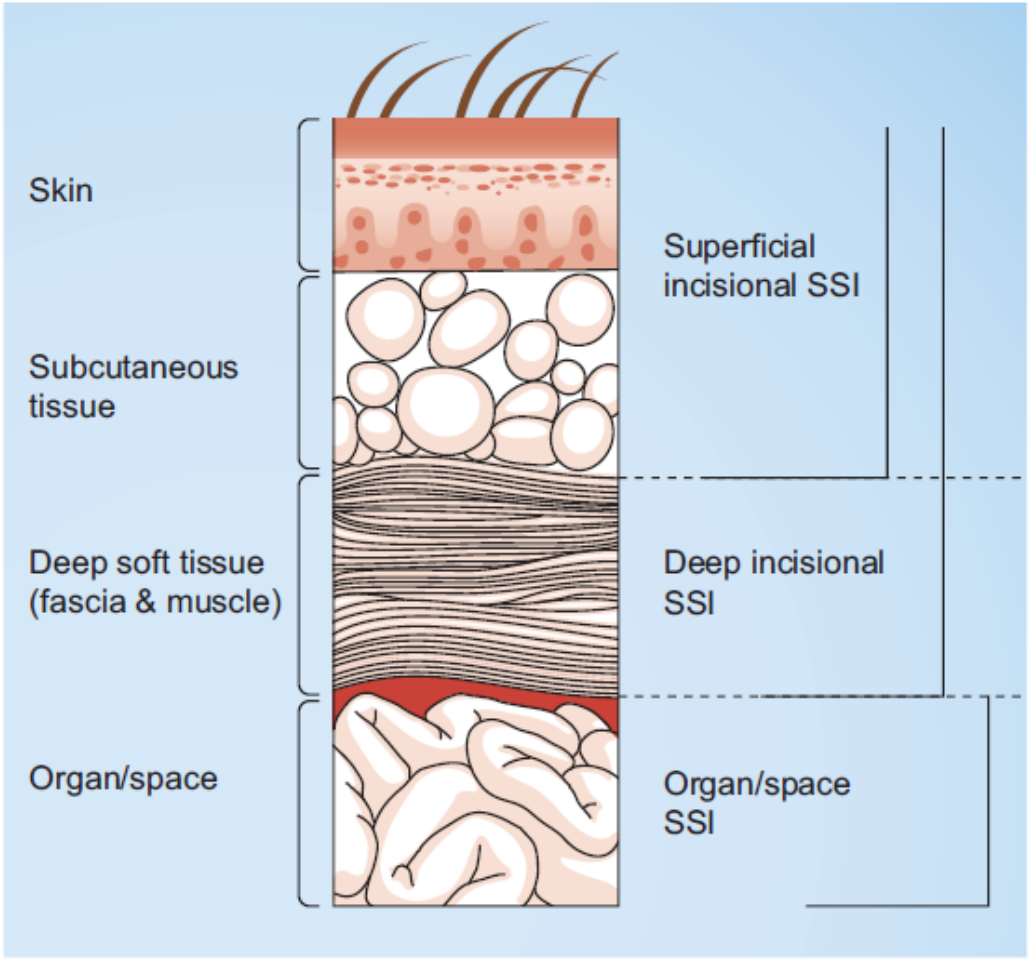
- Daily wound dressing
- Necessitate of resuturing
- Increase pain
- increase length of stay
- Increase cost of treatment
- Considered as invasive intervention

Surgical Site Infections

- Infections occurring within
  - 30 days after a surgical operation
  - within 1 year if an implant is left in place after the procedure)
- Affect either the incision or tissue deep into the operation site

Surgical Site Infections

- Surgical site infections
  - Superficial (involving only the skin or subcutaneous tissue)
  - Deep (involving deep soft tissues of an incision)
  - Organs or body spaces(higher mortality rate and higher costs than superficial SSIs)



Surgical Site Infections

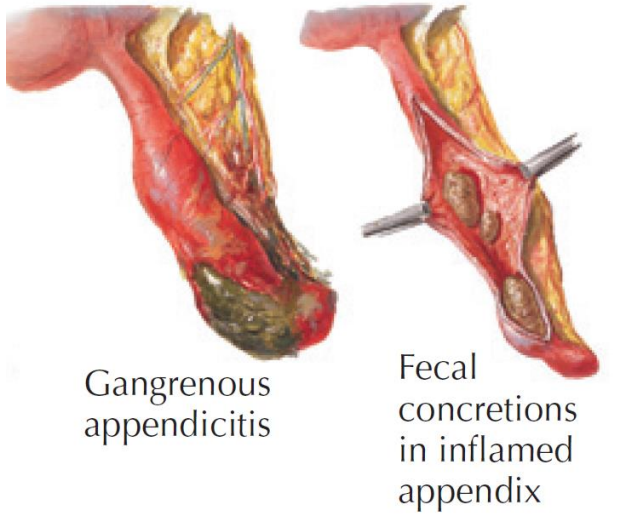
- A wound is considered infected (CDC definitions)
  - The isolation of pathogens from an aseptically obtained culture of fluid or tissue from the wound
  - Purulent drainage from the incision, with or without laboratory confirmation of infection
  - Local signs and symptoms of infection such as erythema and warmth
  - Diagnosis of wound infection by the surgeon.

Surgical Site Infections

- The second most frequently reported nosocomial infections and account for 22% of all healthcare-associated infections
- The most common nosocomial infection, accounting for 38% of healthcare-associated infections among surgical patients
- Develop in 2–5% of the 16 million patients undergoing surgical procedures in the USA each year
- Associated with a 2- to 3-fold increased risk of death, and a 60% increased risk of requiring a postoperative intensive care unit stay.
- Length of hospital stay is increased by 7–12 days, the patient is five-times more likely to require readmission, and direct healthcare costs are increased by at least US$5000.

Surgical Site Infection in appendectomy

- Most common complication after appendectomy
  - Esp. in complicated appendectomy
  - After both patient and healthcare provider
- In Thailand: about 20,000 ruptured appendicitis per year
  - Rate of wound infection: 10-50%
    - More nursing care
    - Length of stay
    - Decrease quality of life
    - Increase both direct and indirect cost
  - High impact to our society



Surgical Site Infection in appendectomy

- Pathophysiology
  - Microbe related: degree of contamination, virulence of bacteria
  - Host defense mechanism: immunocompromised
  - Operative related: prolonged hospital stay, use of drain

Research Question

- Dose delayed primary wound closure after appendectomy in adult with complicated appendicitis with right lower quadrant wound incision reduce postoperative superficial incisional surgical site infection compare to primary wound closure?

Research Objectives

- **Primary objective**
  - To compare the rate of **postoperative superficial incisional surgical site infection** in complicated appendicitis between primary and delayed primary wound closure

Research Objectives

- **Secondary objective**
  - To compare **postoperative pain score at day 1 and 3** after appendectomy between primary and delayed primary wound closure
  - To compare **quality of life at postoperative day 3 and 30** after appendectomy between primary and delayed primary wound closure
  - To do **cost-utility analysis** between primary and delayed primary closure in complicated appendicitis

Multicenter parallel RCT

Conducted from November 2012 to February 2016, across 6 hospital in Thailand

- Thammasart University
- Ramathibodi hospital
- Chonburi hospital
- Pathum Tani hospital
- Lampang hospital
- Surin hospital

Inclusion Criteria

- Age > 18 year +
- Have appendectomy with right lower quadrant incision
- Providing informed consent

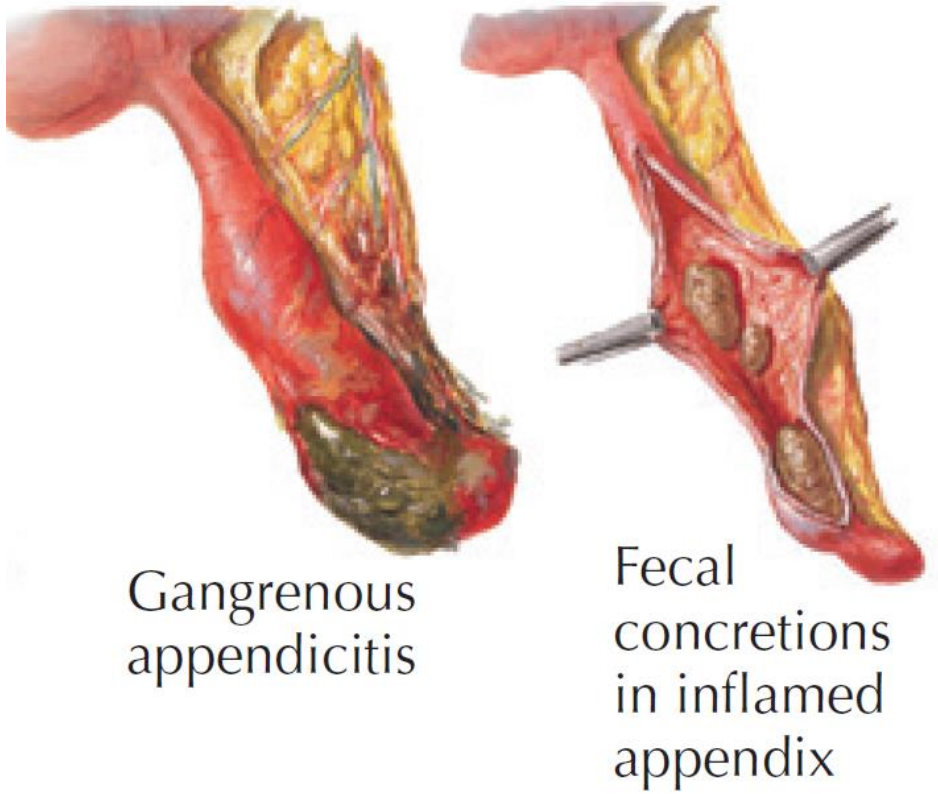
Exclusion Criteria

- Pregnancy
- Immunocompromised host
  - HIV infections
  - ESRD
  - Autoimmune diseases
  - Cirrhosis with ascites
  - Taking immunosuppressive drugs
  - Morbid obesity (BMI > 40 kg/m2)

Operative Criteria

for Complicated Appendicitis

- Gangrenous appendicitis
  - Erythematous or swelling of appendix
  - Appearance of necrotic wall (dark, grayish color)
- Ruptured appendicitis
  - Erythematous or swelling of appendix
  - Appearance of hole in an appendix
  - Rupture of appendix during a procedure
  - Appearance of frank pus



Randomization

- Ratio 1:1
- **Stratified block randomization based on study site**
- Vary block size of 4 to 6
- Sequence generation: independent statistician
- Allocation concealment: sequential sealed opaque envelope
  - Open: met intraoperative criteria
  - Before skin closure

Blinding

- Primary outcome
  - Not blinded
  - Standard operative procedure for measure outcome
- Research assistant
  - Secondary outcome (pain, recovery time, quality of life, cost)
  - Blinded

Interventions

- Appendectomy and wound closure were done by surgical staff or surgical residents under supervision
- PC : wound closed immediately after the operation using nonabsorbable monofilament suture or stapler
- DPC : wound was left open twice daily saline-soaked gauze , and closed on operative day 3 to 7 using the same suture as PC

Co-intervention

- **Use of antibiotics** : Pre/Post operative IV ATB until BT was < 37.8℃ for 2-3 days, then switched to oral ATB for 7-10 days
- **Postoperative pain control :** IV Opiod (morphine 3-5 mg or pethidine 25-50 mg) as requested every 4 hours, switching to paracetamol or NSAIDs after oral diet
- **Wound dressing and care**
- **Closed Suction Drain**

Outcome

Primary Outcome

- Superficial surgical site infection
  - CDC criteria

Secondary Outcome

- Postoperative pain: Visual analog scale (100 mm scale)
- Recovery time

  Times to return to normal activities (day)

  Times to return to work (day)
- Quality of life

  EQ5D (5 scale)---- convert to Thai utility scores
- Costs

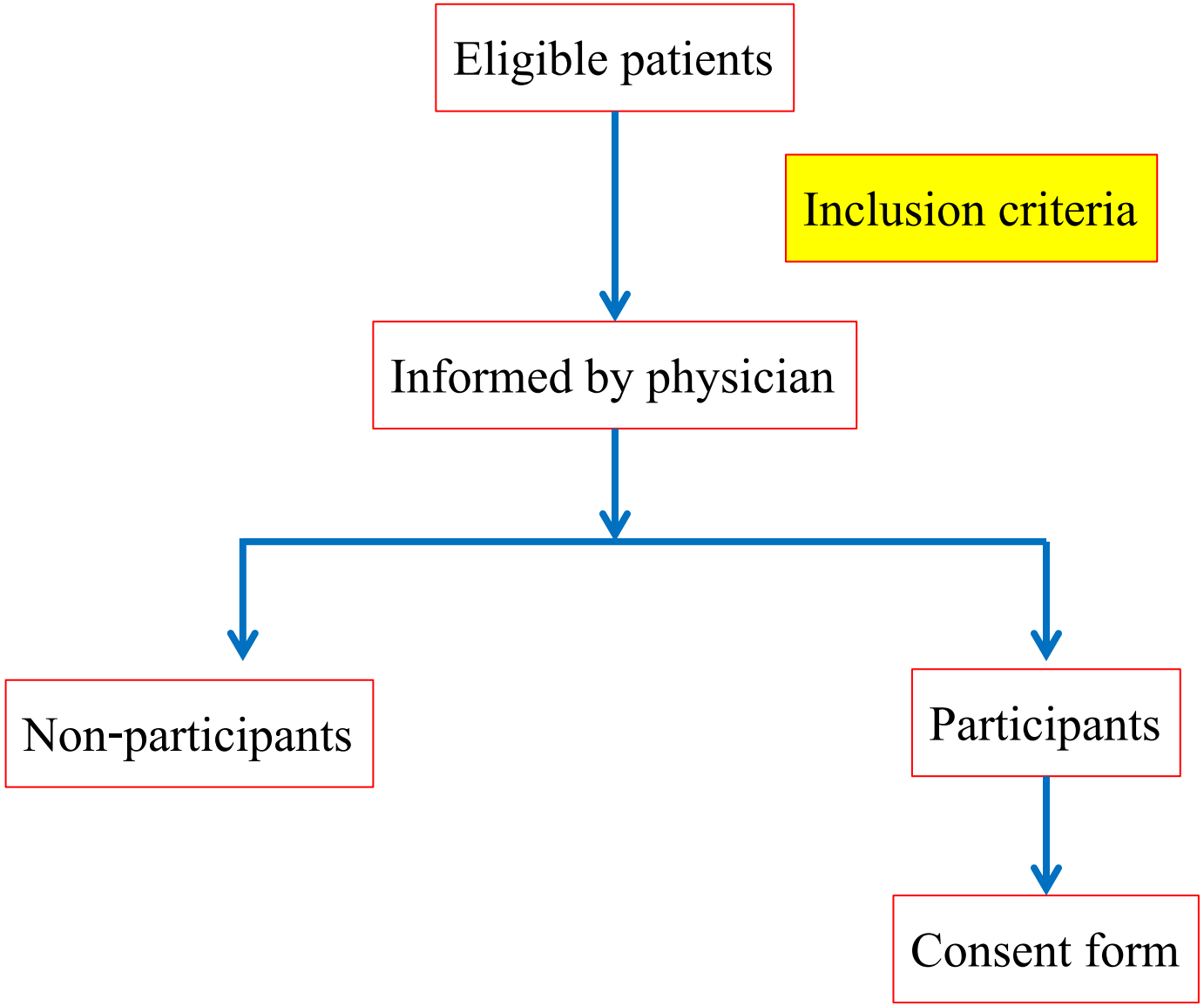
  Direct medical cost: assume equal except cost of wound care (dressing and resuture)

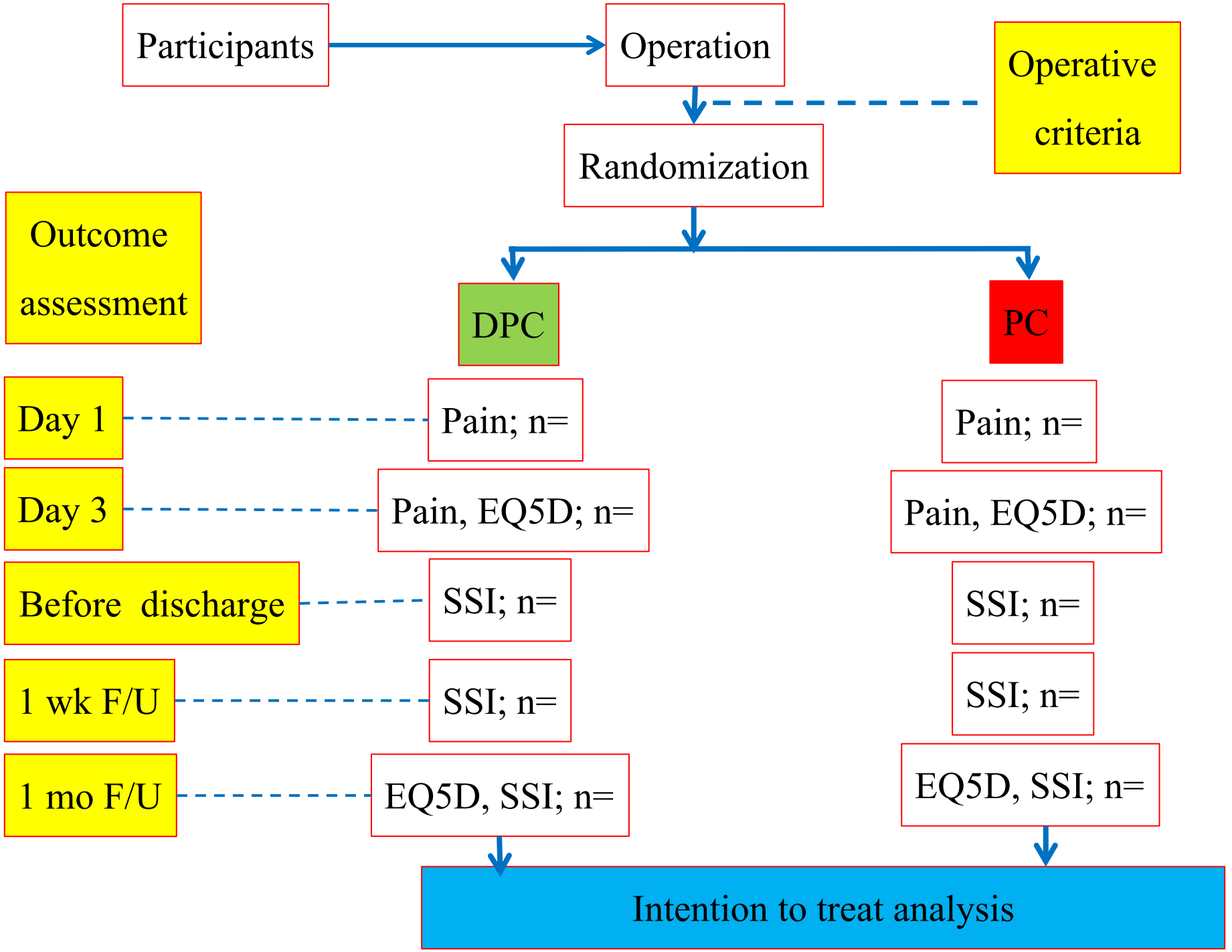
  Direct non-medical cost and indirect cost: interview

Dimension		UK	Thai
Constant		0.081	0.202
Mobility	Level 1	0	0
	Level 2	0.069	0.121
	Level 3	0.314	0.432
Self care	Level 1	0	0
	Level 2	0.104	0.121
	Level 3	0.214	0.242
Usual activities	Level 1	0	0
	Level 2	0.036	0.059
	Level 3	0.094	0.118
Pain/discomfort	Level 1	0	0
	Level 2	0.123	0.072
	Level 3	0.386	0.209
Anxiety/Depression	Level 1	0	0
	Level 2	0.071	0.032
	Level 3	0.236	0.11
N3		0.269	0.139

Utility from EQ-5D

Patient's flow




Participants
Operation
Operative criteria
Randomization
Outcome assessment
DPC
PC
Day 1
Pain; n=
Pain; n=
Day 3
Pain, EQ5D; n=
Pain, EQ5D; n=
Before discharge
SSI; n=
SSI; n=
1 wk F/U
SSI; n=
SSI; n=
1 mo F/U
EQ5D, SSI; n=
EQ5D, SSI; n=
Intention to treat analysis

Sample Size

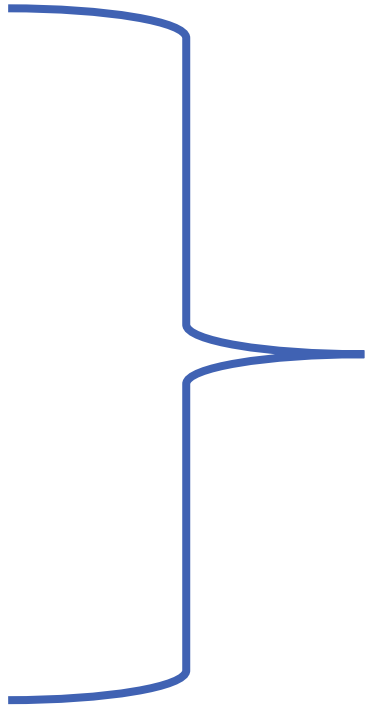
- **The pool superficial SSI rate in DPC was 29.5%** (95% CI : 14.8%,29.5%)
- Type I error : 0.05 (2-side)
- Power : 0.80
- Ratio : 1:1
- Test for difference (2-sides)
- Side of detectable = 10%, suggesting a total of 570 patients (285 each group)
- Taking into account loss to follow up of 5%, **600 patients were set as target**

Statistical Analysis

- Intention to treat analysis
- Primary outcomes
  - Binary regression analysis with or without adjusted variable
  - Protocol violation : Per-protocol, as-treated, counterfactual
  - Imputed data
- Secondary outcomes
  - Mixed linear regression model
- Cost-utility analysis
  - Incremental cost-effectiveness ratio (ICER)

RESULTS

- Multicenter parallel RCT conducted from November 2012 to February 2016
- All patients : 607 patients
  - 126 Thammasart University
  - 92 Ramathibodi hospital
  - 117 Chonburi hospital
  - 30 Pathum Tani hospital
  - 170 Lampang hospital
  - 72 Surin hospital



Randomization

DPC = 304

PC = 303

Baseline Characteristics of Patients

Characteristics	DPC (n = 304)	PC (n=303)
Age, year, mean	46 (18.0)	45 (18.1)
Sex, number(%)		
Male	155 (51)	169 (56)
Female	149 (15)	134 (44)
BMI, kg/m^2, mean(SD)	23.4(4.31)	23.4(4.34)
Smoking, number (%)	45 (15)	51 (17)
ASA classification, number (%)		
Class I + II	266 (89)	257 (85)
Class III+IV	34 (11)	44 (15)
Diabetes, number (%)	31 (10.3)	20 (6.7)
Hypertension, number (%)	55 (18.2)	60 (20)
Symptom onset, h, mean (SD)	37.7 (1.0)	37.7 (1.1)

Baseline Characteristics of Patients

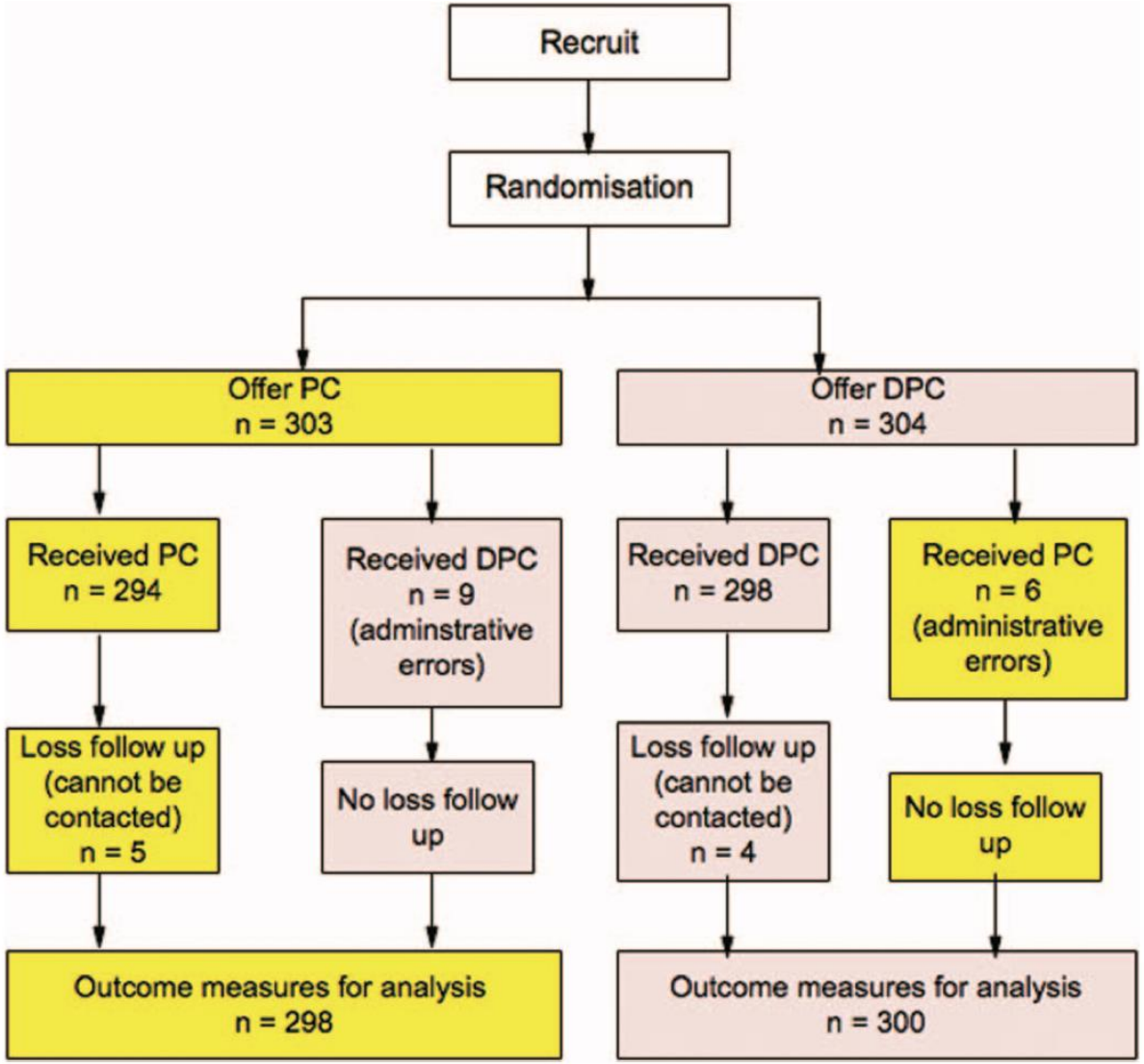
Characteristics	DPC (n = 304)	PC (n=303)
White blood cell count, cell/mm^3, mean (SD)	15561 (4965)	15790 (4979)
Body temperature, ℃ , mean (SD)	37.7 (1.0)	37.7 (1.1)
Fever, number (%)		
≧ 37.8 ℃	142 (47)	148 (49)
＜ 37.8 ℃	159 (53)	154 (51)
Preoperative utility, median (IQR)	0.68 (0.34,0.80)	0.68 (0.34,0.80)
Operative time, min, median (IQR)	47 (14,74)	51 (18,78)
Operative time classification, number (%)		
≦ 75 percentile	232 (77)	222 (74)
＞ 75 percentile	68 (23)	80 (19.2)
Used of drain, number (%)	62 (20.6)	58 (19.2)

Baseline Characteristics of Patients

Characteristics	DPC (n = 304)	PC (n=303)	Total
Severity, number (%)			
Gangrene	**76** (25)	**72** (34)	148
Ruptured	**228** (75)	**231** (76)	459
Intraoperative rupture	**23** (7.6)	**20** (6.6)	43
Visible wound contamination, number (%)			
Exudative Fluid	81 (27)	87 (29)	
Plus	118 (39)	108 (36)	
Feculent material	38 (13)	38 (13)	

- All Superficial SSIs were treated by open dressing with/without re-suture and were cure in 2 months
- None of them died

Consort Flow Diagram



Primary Outcomes : Superficial SSI

- Loss Follow up 9 patients
- Of 598 patients, 52 patients had superficial SSIs with the rate of 8.7 %, of these diagnosis in 7-10 days
- DPC group with SSI, 5 patients had the appearance of purulent drainage (2 P.aeruginosa,1 negative culture, 2 with no culture

TABLE 2. Comparison of Superficial SSI Rates Between PC and DPC Using Different Approaches

Approach	DPC	PC	RR (95% CI)	RD (95% CI)	*P*
ITT					
n	300	298	0.74 (0.44, 1.25)	−0.027 (−0.071, 0.019)	0.258
Rate (%, 95% CI)	10 (6.6, 13.3)	7.3 (4.4, 10.3)			
PP					
n	294	289	0.80 (0.47, 1.36)	−0.019 (−0.065, 0.026)	0.411
Rate (%, 95% CI)	9.5 (6.2, 12.9)	7.6 (4.6, 10.7)			
AT					
n	303	295	0.88 (0.52, 1.48)	−0.011 (−0.56, 0.034)	0.632
Rate (%, 95% CI)	9.2 (5.9, 12,5)	8.1 (5.0, 11.3)			
IV					
n	294	293	0.72 (0.32, 1.12)	−0.027 (−0.076, 0.019)	0.243
Rate (%, 95% CI)	10.1 (6.6, 13.8)	7.4 (4.4, 10.3)			
IV (with adjusted variables)					
n	276	282	0.66 (0.30, 1.01)	−0.036 (−0.083,0.011)	0.118
Rate (%, 95% CI)	10.7 (7.0, 14.1)	6.9 (4.1, 9.8)			

Secondary Outcomes

TABLE 3. Comparisons of Length of Stay, Recovery Times, Postoperative Pain and Costs of Treatment Between PC and DPC Groups Based on ITT Approach

Outcomes	DPC n	DPC $\bar{X}$ (95% CI)	PC n	PC $\bar{X}$ (95% CI)	MD (95% CI)
Length of stay, day	304	4.4 (4.1, 4.6)	302	4.3 (4.0, 4.6)	−0.1 (−0.5, 0.3)
Return to normal activities, day	271	3.8 (3.4, 4.3)	273	3.6 (3.2, 4.1)	−0.2 (−0.8, 0.4)
Return to work, day	265	9.0 (7.5, 10.1)	267	7.7 (6.2, 9.1)	−1.3 (−3.4, 0.8)
Postoperative pain, VAS					
Day 1	301	61 (59, 63)	299	62 (59, 64)	0.3 (−2.5, 3.0)
Day 3	292	29 (27, 31)	295	29 (27, 31)	
QoL, utility scores					
Day 3	300	0.53 (0.51, 0.55)	299	0.54 (0.52, 0.56)	0.02 (−0.01, 0.04)
Day 30	289	0.78 (0.77, 0.80)	287	0.79 (0.77, 0.81)	
	N	Median (IQR)	N	Median (IQR)	Median difference (95% CI)
Costs of treatment, Baht*					
Added direct medical costs†	304	3033 (2733, 3333)	302	1200 (900, 1500)	−1833 (−1884, −1781)
Direct nonmedical costs					
Informal care (during admission)	274	1050 (600, 1800)	271	1050 (600, 1800)	0 (−133, 133)
Informal care (during recovery)	272	450 (0, 1650)	272	300 (0, 1200)	−150 (−440, 140)
Transportation	274	300 (100, 800)	271	300 (100, 600)	0 (−80, 80)
Indirect costs					
Income lost‡	265	2100 (600, 3000)	267	2100 (900, 3000)	0 (−266, 266)
Total costs	248	6398 (4343, 8558)	250	4305 (2750, 6100)	−2083 (−2756, −1410)

Dressings, re-suture

*Analysis using quantile regression analysis.
†Added direct medical costs from DPC were 1833 Baht (1361 Baht for dressing changes [189 Baht/times, 2 times/d for 3.6 days], and 472 Baht for re-suture).
‡Minimum wages of 300 Baht/d in Thailand was used.

Discussion

- Rate of SSI between CPC and PC
  - Superficial SSI rate was 2.7% lower in PC than in DPC, although this was not significant
- Length of stay, recovery time, postoperative pain, and QoL
  - Were not significantly different
- Less cost in PC
  - Total costs were about 2083 Baht/ case lower in PC than DPC

Discussion

- Four approaches were applied to test the robustness of the results : ITT, PP, AT, counterfactual method
  - **Intention to treat**
    - least bias because preserves the original random allocation but may be bias if there is protocol violation and loss to follow up
    - RD 2.7% which may be biased away fromm null because protocol violations were higher in PC than DPC
  - **Pre-protocol and As-treated** analysis more relevant than ITT in assessing the actual effects on interventions received
    - Pre-protocol : selection bias
    - As-treated: observation studies (randomization broke)
  - **IV regression** is applied to estimate what the intervention effect would have been **(ex. Counterfactual effects)** if patient who would have been assigned to PC actually received DPC

Discussion

- The results confirm findings of the previous systematic review and meta-analysis, which demonstrated similarly lower superficial SSI in PC than in DPC groups

Siribumrungwong *et al. World Journal of Emergency Surgery* 2014, **9**:49
http://www.wjes.org/content/9/1/49

WORLD JOURNAL OF EMERGENCY SURGERY

REVIEW Open Access

A systematic review and meta-analysis of randomised controlled trials of delayed primary wound closure in contaminated abdominal wounds

Discussion

- 52 superficial SSI , 26 patients had wound cultures after opening the wound
- 2/3 were gram-negative positive bacteria
- 5 of these were resistant strains >> 2 P. aeruginosa, 2 multidrug-resistant E coli, and 1 ESBL
- Resistant organisms could have been seeded during wound care or have developed during hospitalization

Cost-effectiveness

- PC saved 2083 Baht/case over DPC
- ICER = [cost(A) – cost(B)/QALY(A) – QALY(B)]
- With increase cost with no benefit and QALY gain
- **PC was more cost-effectiveness than DPC**

Impact of Studies

- PC saved 2083 Baht/case over DPC
- 65,729,098 population in mid 2015
- Estimated incidence
  - Appendicitis of 14/10000 pop/ year
  - 92020 appendectomy/ year
- With 18.2% = complicated appendicitis
  - 16748 complicated appendicitis/ year
  - Apply PC in every case: save 34,886,084/ years

Pitfall of Studies

- Patients were randomized to receive DPC or PC to balance unknown and known risk factors of superficial SSI ex. BMI, diabetes, ASA classification, operative time, and degree of contamination

Conclusion

- PC was not different comparing to DPC in adults with complicated appendicitis (gangrenous and ruptured) with lower costs