

# Prise en charge actualisée de la colite aiguë grave (CAG)



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## **Liens d'intérêt :**

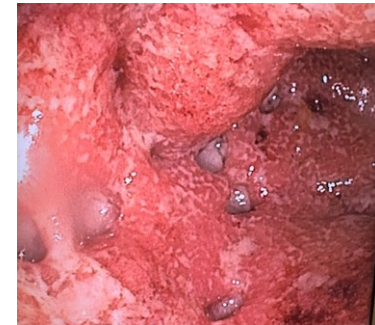
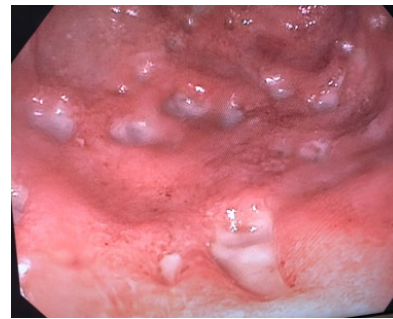
Abbvie, Amgen, Biogen, Celltrion, Ferring, Fresenius-Kabi, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda.

# Disclaimer

- This is a medical education event with the support of Janssen-Cilag NV.
- This presentation represents the opinion of the speaker and not necessarily the opinion of Janssen.
- This presentation may include discussions on off-label use of drugs.

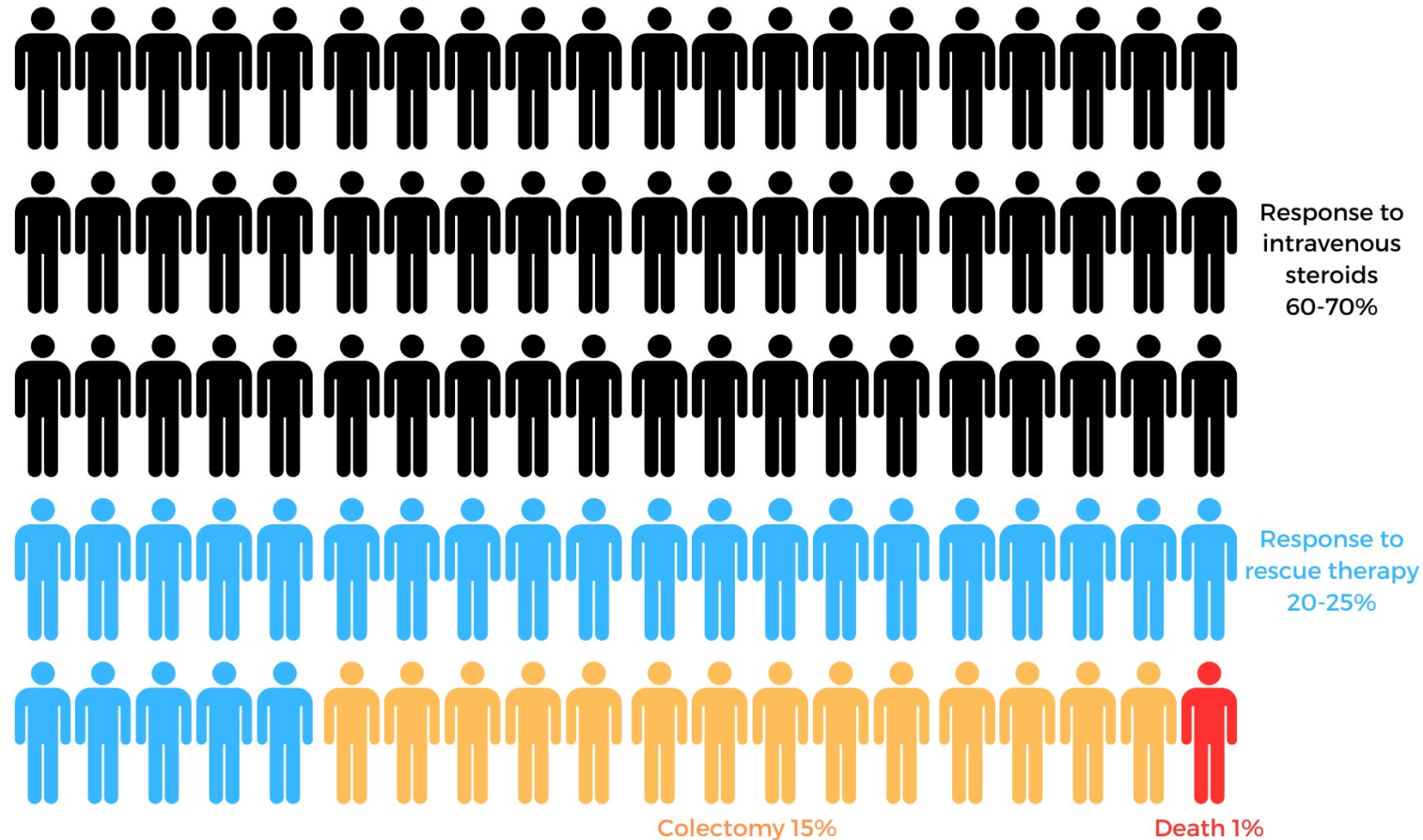
# Colite aiguë grave (de RCH)

- ~25 % des malades
- > 25 % de formes inaugurales
- Identification par les critères modifiés de Truelove & Witts (CRP >30 mg/L)



# Pronostic à court terme de la CAG

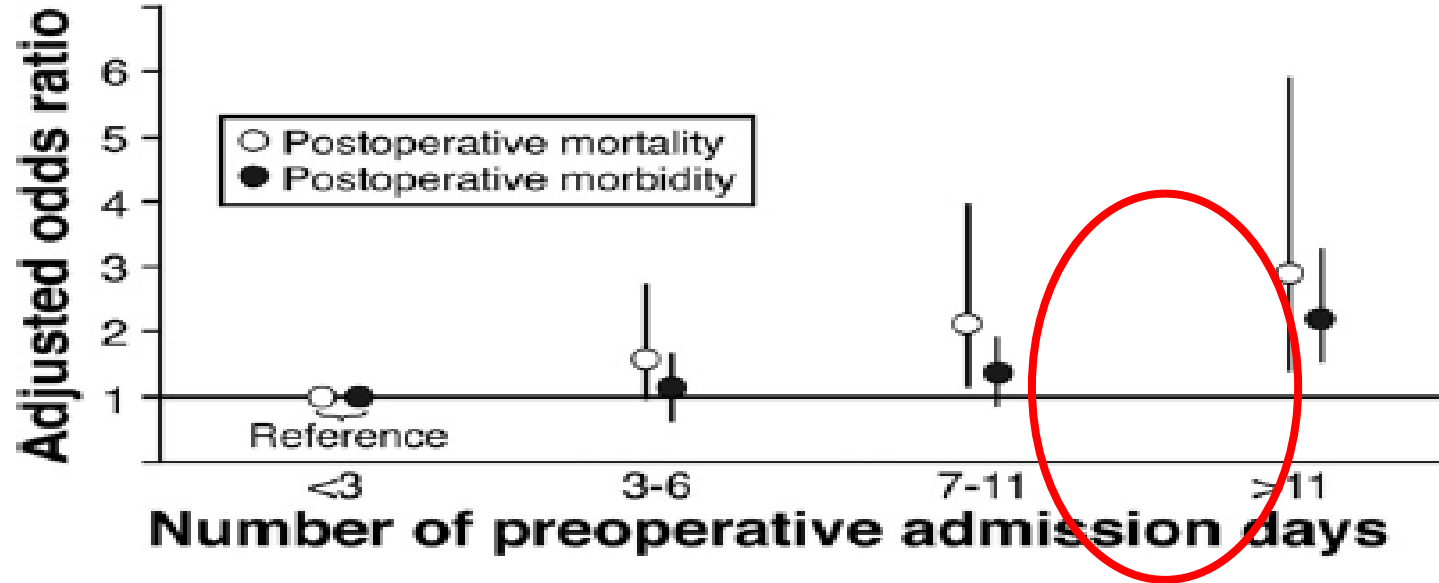
Illustrated short-term outcomes of 100 patients admitted for ASUC



**Message n°1 :**  
**la CAG tue encore !**



# Morbi-mortalité de la colectomie pour RCH selon la durée de l'hospitalisation pré-opératoire



**Message n°2:**

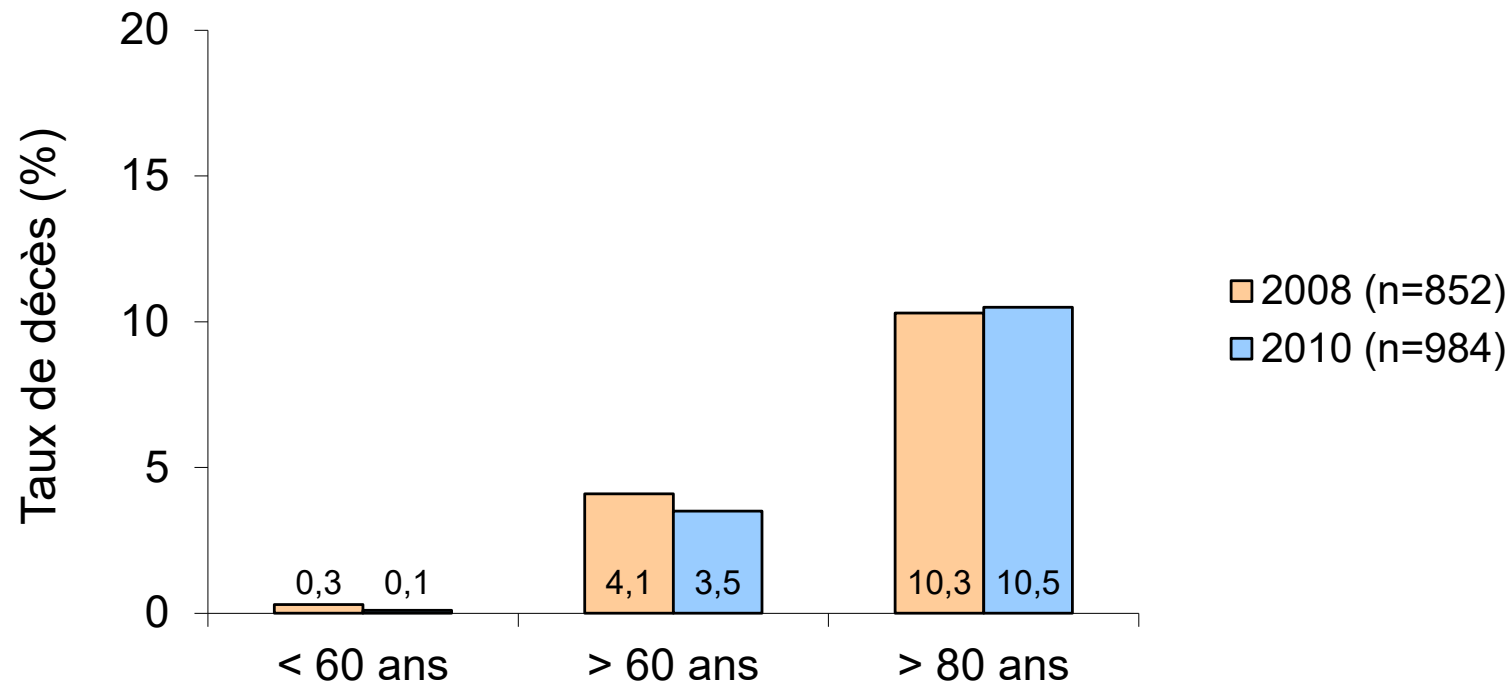
**la prise en charge de la CAG est une  
course contre la montre**





# Mortalité de la CAG selon l'âge

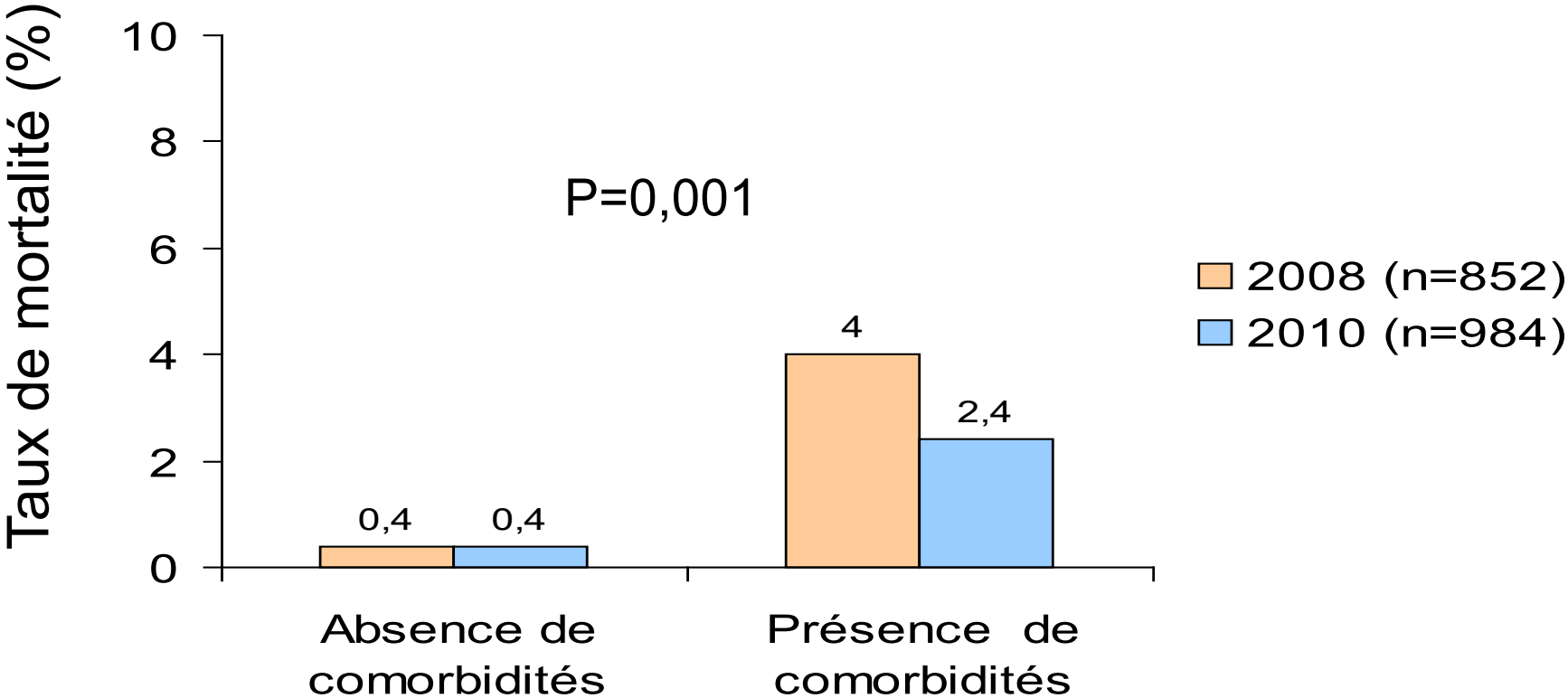
## Audit britannique (2008 et 2010)



Mortalité x 13-28 après 60 ans

# Mortalité de la CAG selon les comorbidités

Audit britannique (2008 puis 2010)



**Message n°3:**

**les objectifs thérapeutiques ne sont pas les mêmes  
pour tous les patients !**

**Objectif n°1 : sauver la vie**

**Objectif n°2 : sauver le colon**

### **Message n°3:**

**les objectifs thérapeutiques ne sont pas les mêmes  
pour tous les patients !**

**Objectif n°1 : sauver la vie  
(surtout s'il est âgé ou fragile)**

**Objectif n°2 : sauver le colon  
(chez tous les autres)**

# Traitement initial de la CAG

## La base

- Corticoïdes i.v.
- Réhydratation
- HBPM

## Les options

- Mise à jeun
- Nutrition artificielle
- AB
- Topiques

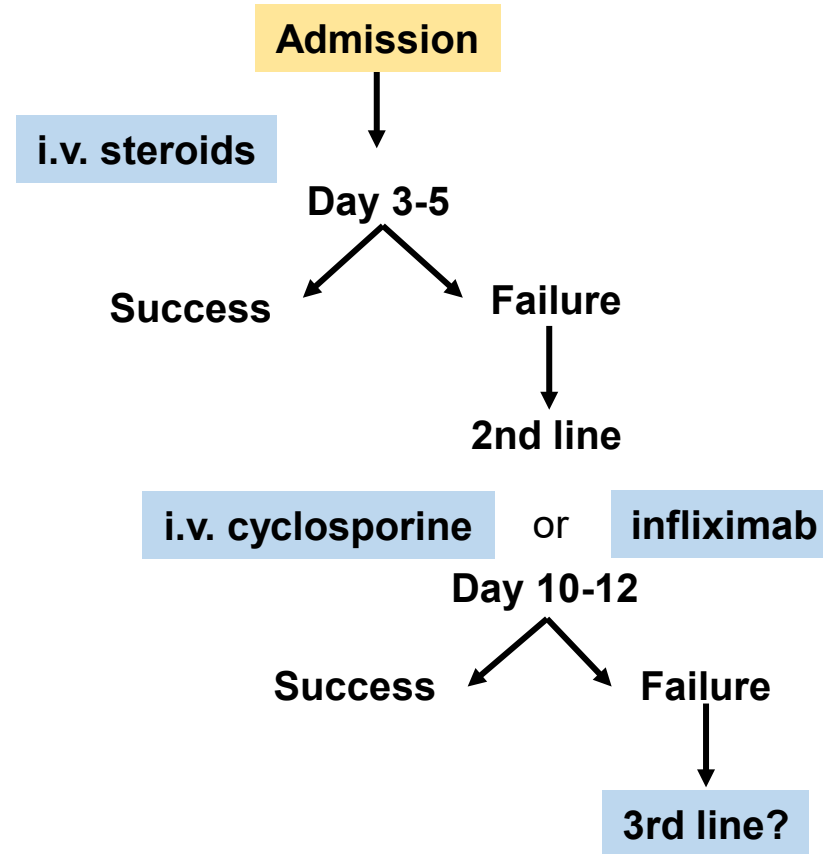
# Indications de colectomie en urgence dans la CAG

Formes compliquées d'emblée (24 % des indications de colectomie dans la RCH) :

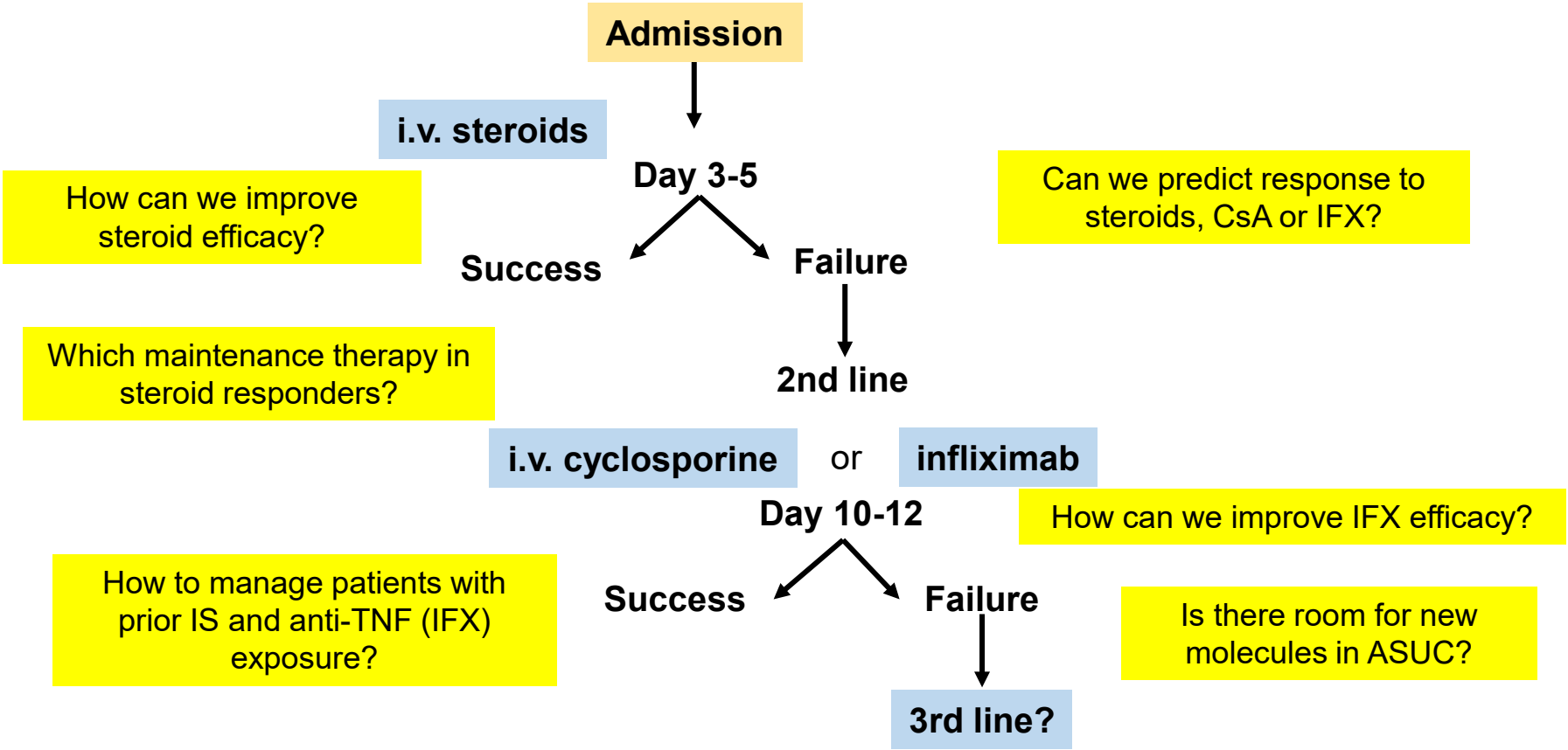
- Perforation/péritonite (4 %)
- Hémorragie massive (10 %)
- Mégacolon toxique (10 %)



# Medical management of ASUC



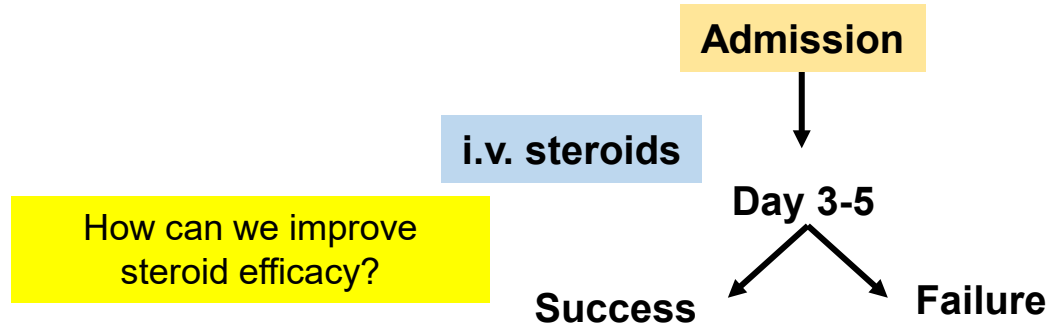
# Medical management of ASUC: pending questions



Adapted from Spinelli A et al, J Crohn's Colitis 2022



# Medical management of ASUC: pending questions





European  
Crohn's and Colitis  
Organisation

# Efficacy of the Truelove regimen (iv steroids)

## 1.1.Statement 1.1.

Intravenous corticosteroids as the initial standard treatment for adult patients with ASUC are recommended, as this treatment induces clinical remission and reduces mortality [EL3]

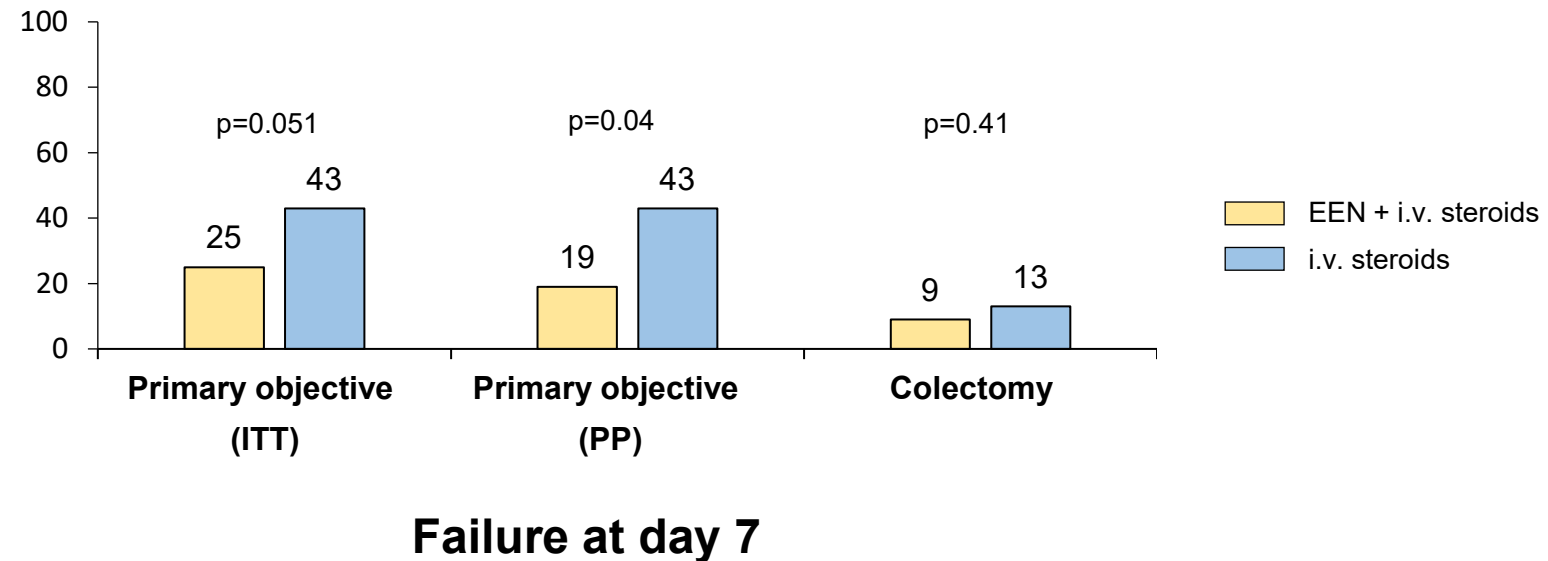
- 60-70% response within 5-7 days <sup>1,2</sup>
- Prediction of steroid failure still day 3 <sup>3,4</sup>:
  - Nb of stools and CRP at day 3 (Oxford index)
  - Colonic dilatation
  - Hypoalbuminemia

1. Truelove S et al, Lancet 1978
2. Turner D et al, CGH 2007
3. Travis S et al, Gut 1996
4. Spinelli A et al, JCC 2022

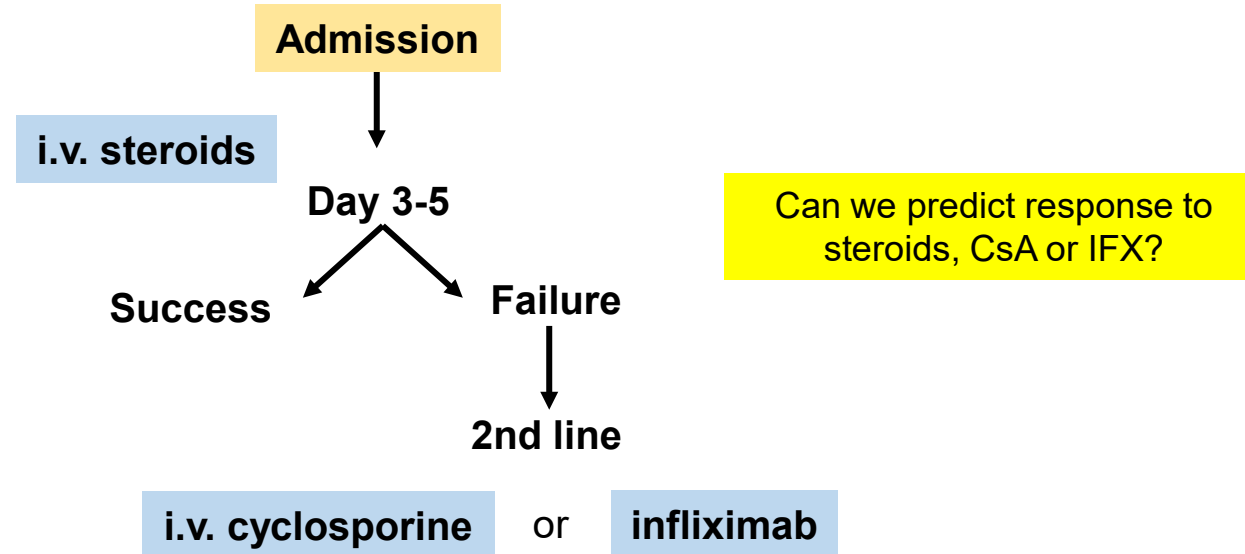
# Steroids + exclusive enteral nutrition vs. steroids alone in ASUC

RCT including 62 patients admitted for ASUC (New Delhi)

Primary objective: steroid failure at day 7



# Medical management of ASUC: pending questions





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Crohn's and Colitis  
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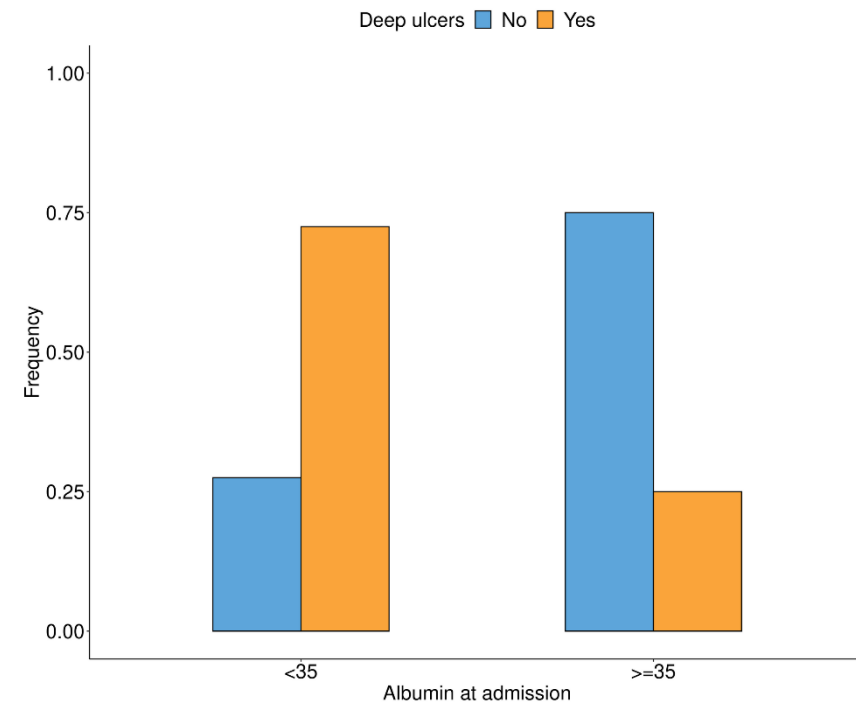
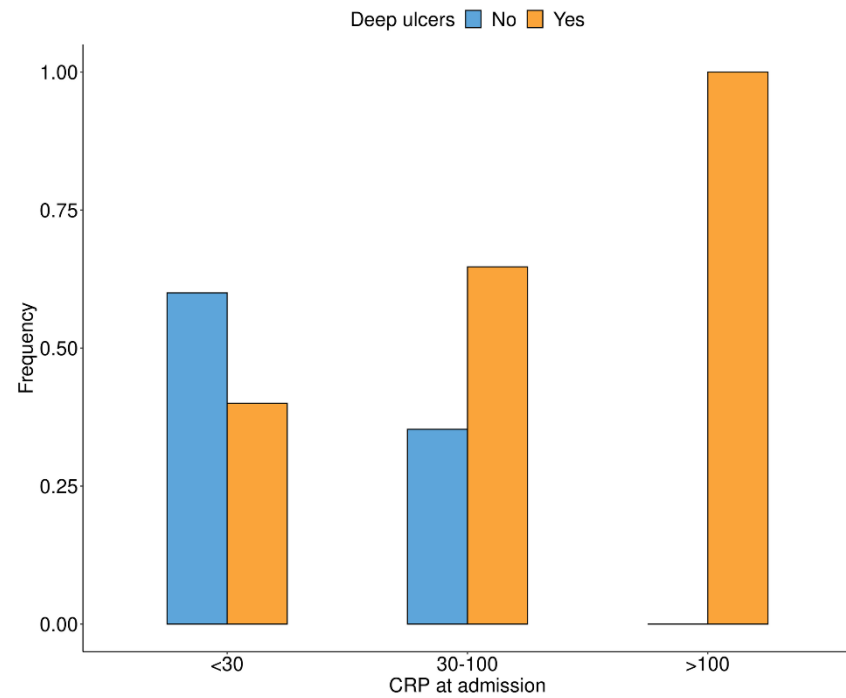
# Simple tools for predicting failure of iv steroids at admission

## ADMIT-ASC score (at admission):

- CRP  $\geq$ 100 mg/L 1 pt
- Albumin  $\leq$ 25 g/L 1 pt
- UCEIS  $\geq$ 7 2 pts
- UCEIS  $\geq$ 4 1 pt

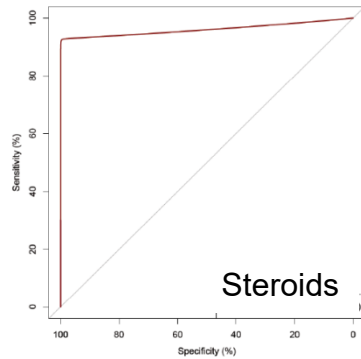
Score	Discovery (Oxford)		Combined validation		Total	
	N	Response %	N	Response %	N	Response %
0	3 (2.3%)	100%	8 (4.7%)	100%	11 (3.6%)	100%
1	60 (45.8%)	61.7%	88 (51.2%)	75.0%	148 (48.8%)	69.6%
2	40 (30.5%)	22.5%	51 (29.7%)	54.9%	91 (30.0%)	40.7%
3	18 (13.7%)	16.7%	22 (12.8%)	18.2%	40 (13.2%)	17.5%
4	10 (7.6%)	0.0%	3 (1.7%)	0.0%	13 (4.3%)	0.0%

# Relationship between CRP, albumin and deep ulcerations in UC



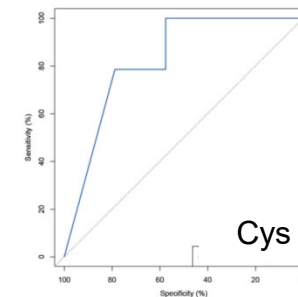
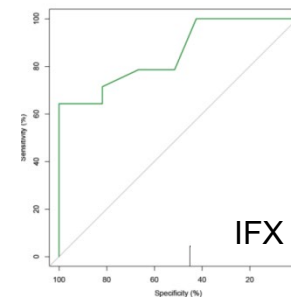
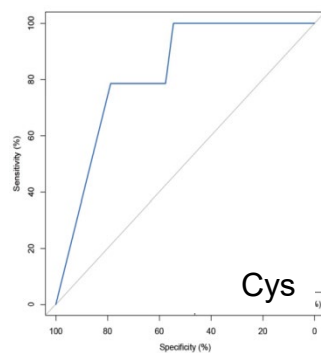
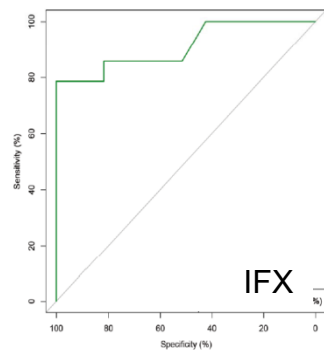
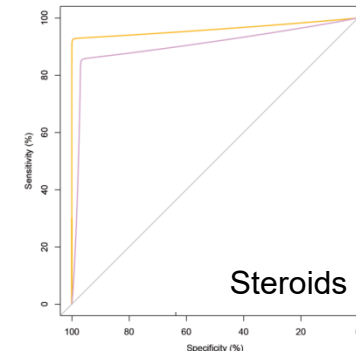
# Prediction of drug response in ASUC by deep learning

Discovery cohort (n=47)



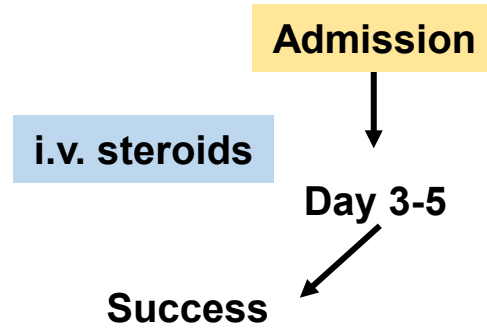
Algorithm combining 9 colonic microRNAs + 5 routine biologic factors

Validation cohort (n=29)





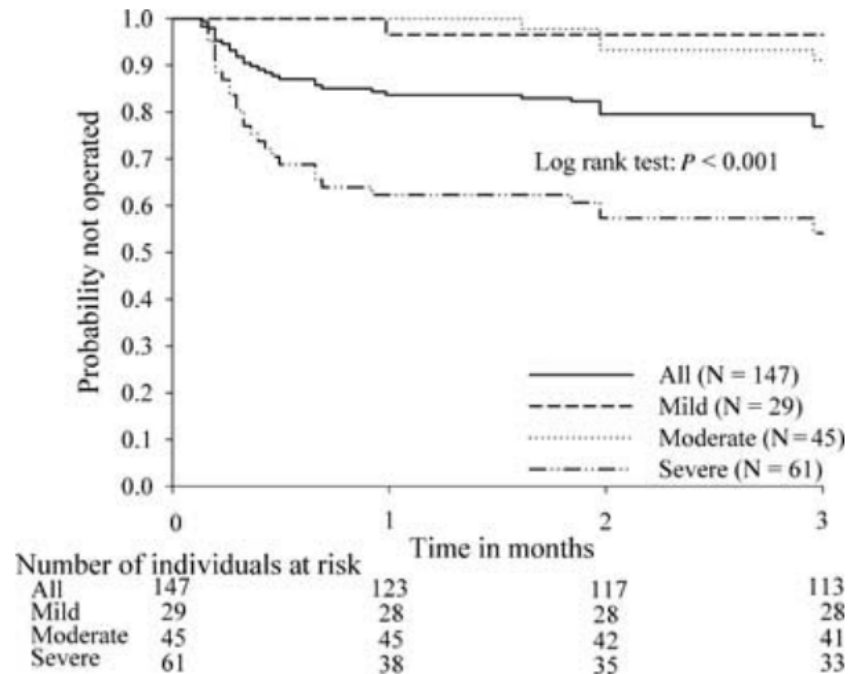
# Medical management of ASUC: pending questions



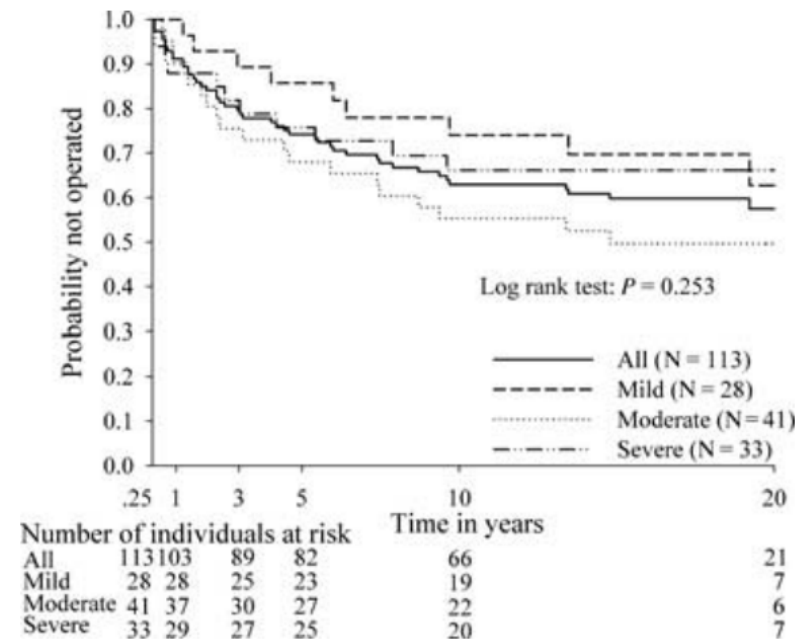
Which maintenance therapy in  
steroid responders?

# Long-term disease course after a first episode of ASUC

Cohort from Orebrö (Sweden) 1975-82



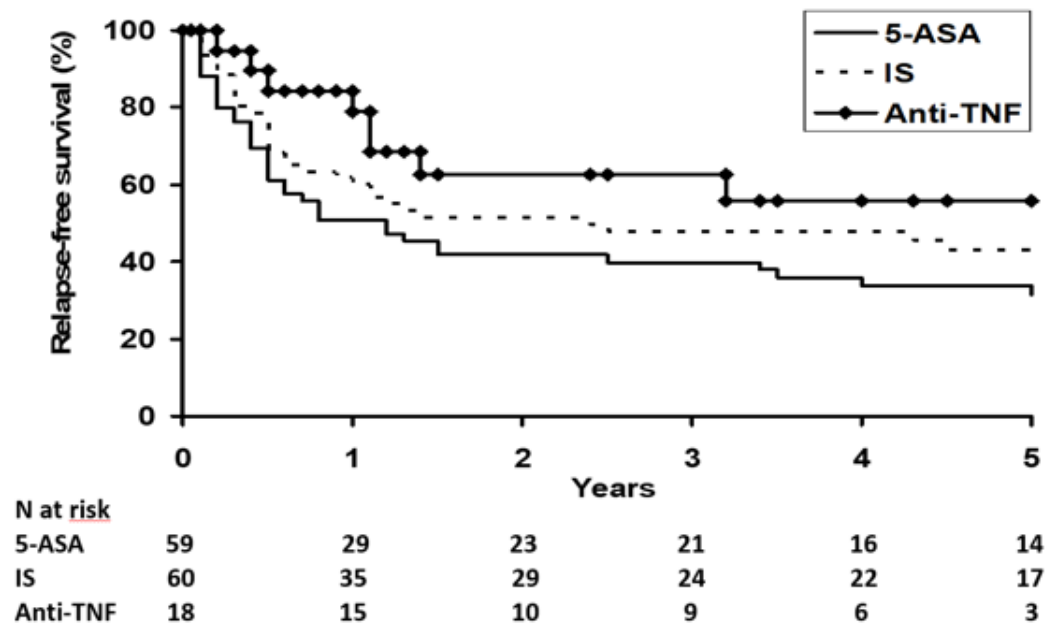
**Short-term survival off colectomy (0-3 months)**



**Long-term survival off colectomy (beyond 3 months)**

# Which maintenance therapy in steroid-responders?

Multicenter cohort from Paris (2006-2017)  
142 pts with ASUC responding to iv steroids



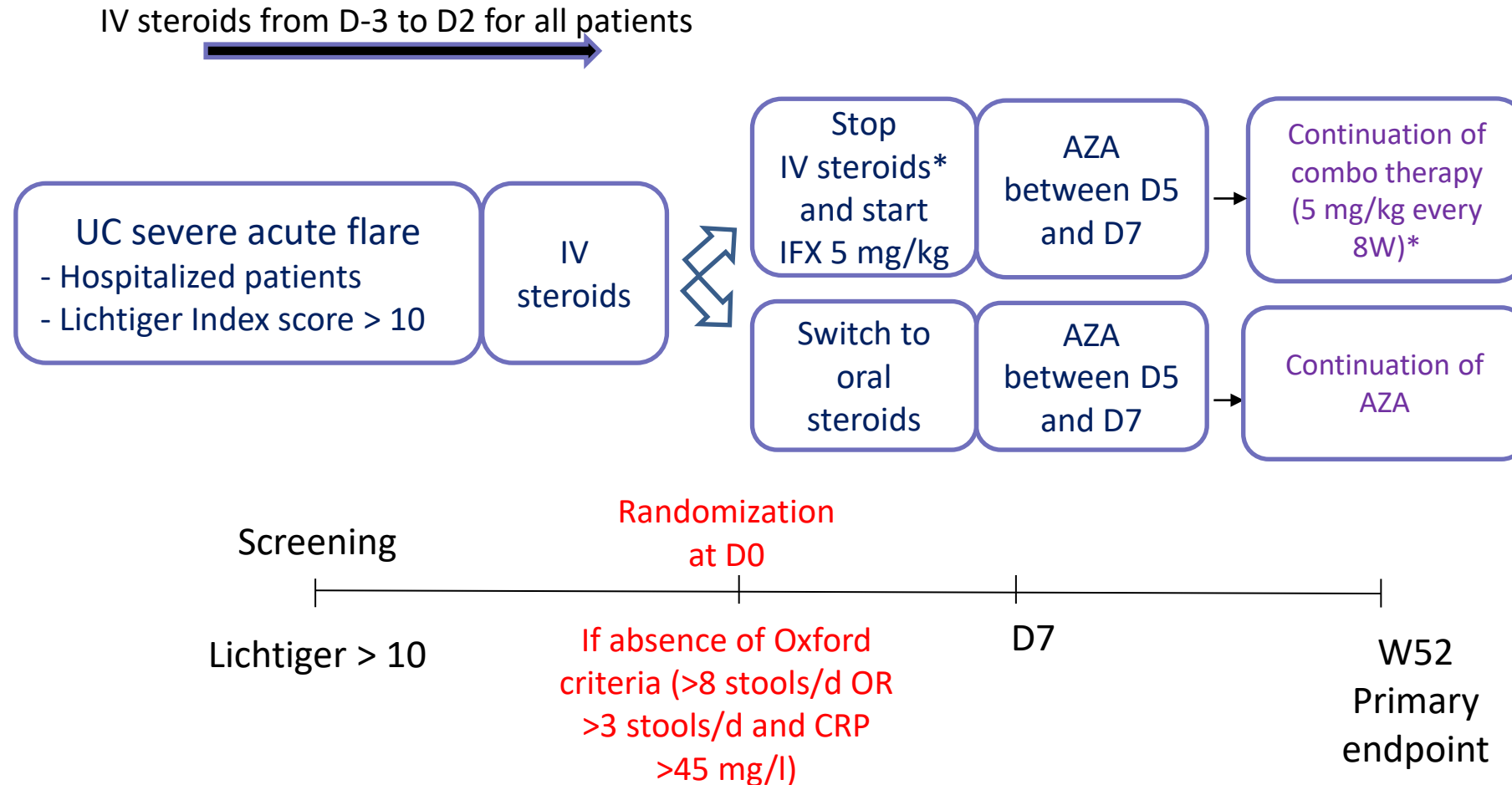
Relapse-free survival

## French recommendations on UC:

- Very low level of evidence
- According to prior treatment exposure:
  - None: 5-ASA is an option
  - Other cases: azathioprine and/or biologics

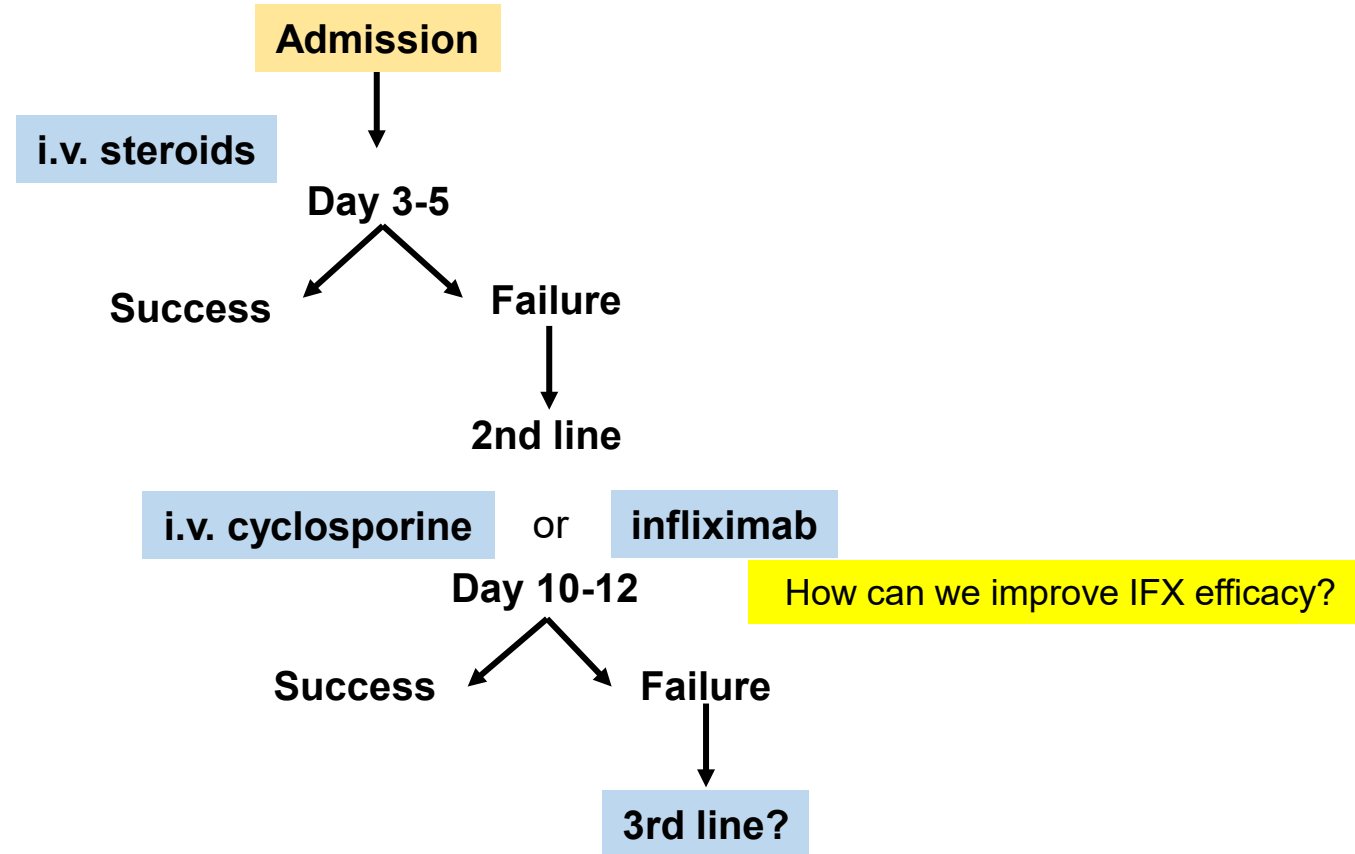
Salameh R et al, Aliment Pharm Ther 2020  
Amiot A et al, HGOD 2022

## Study design

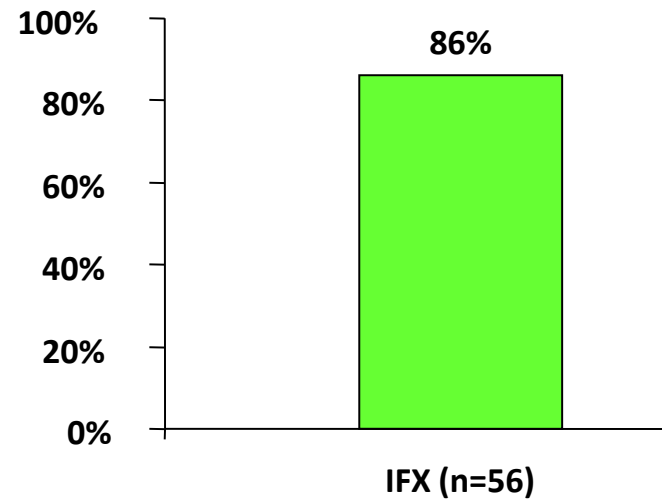


\* Oral steroids are permitted up to day 7

# Medical management of ASUC: pending questions



# Response at D7 to one single 5mg/kg IFX infusion in ASUC

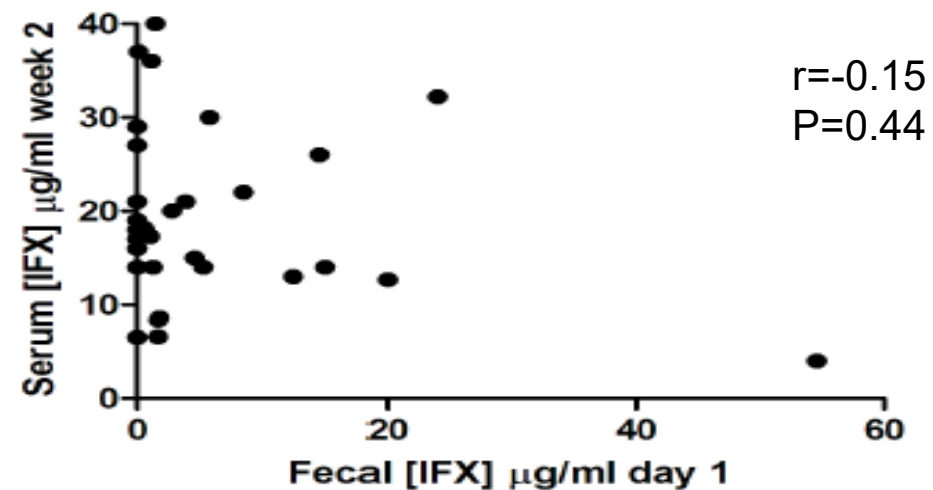


Response: Lichtiger score < 10 and decrease  $\geq 3$  points as compared to baseline



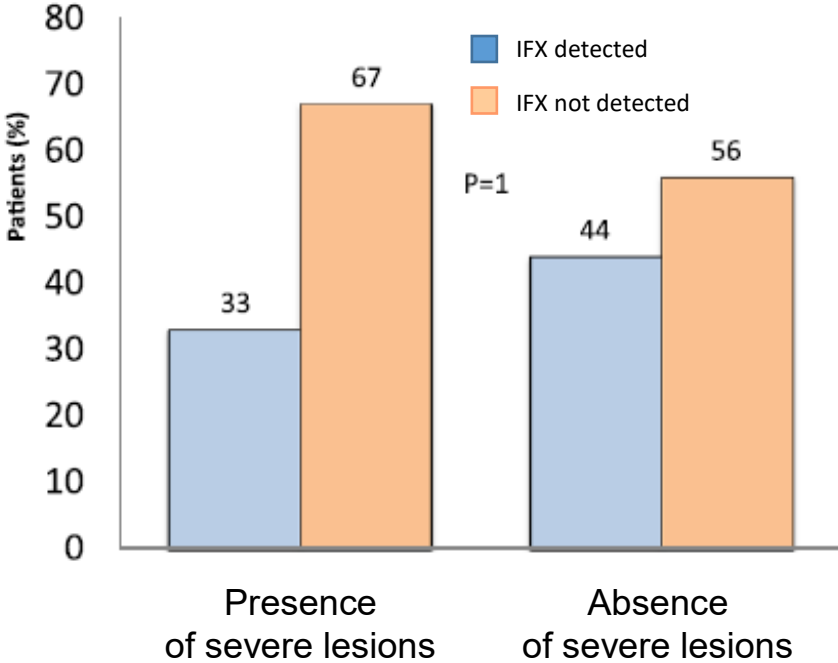
# Significance of infliximab fecal loss?

Correlation fecal [IFX] day 1 and serum [IFX] week 2



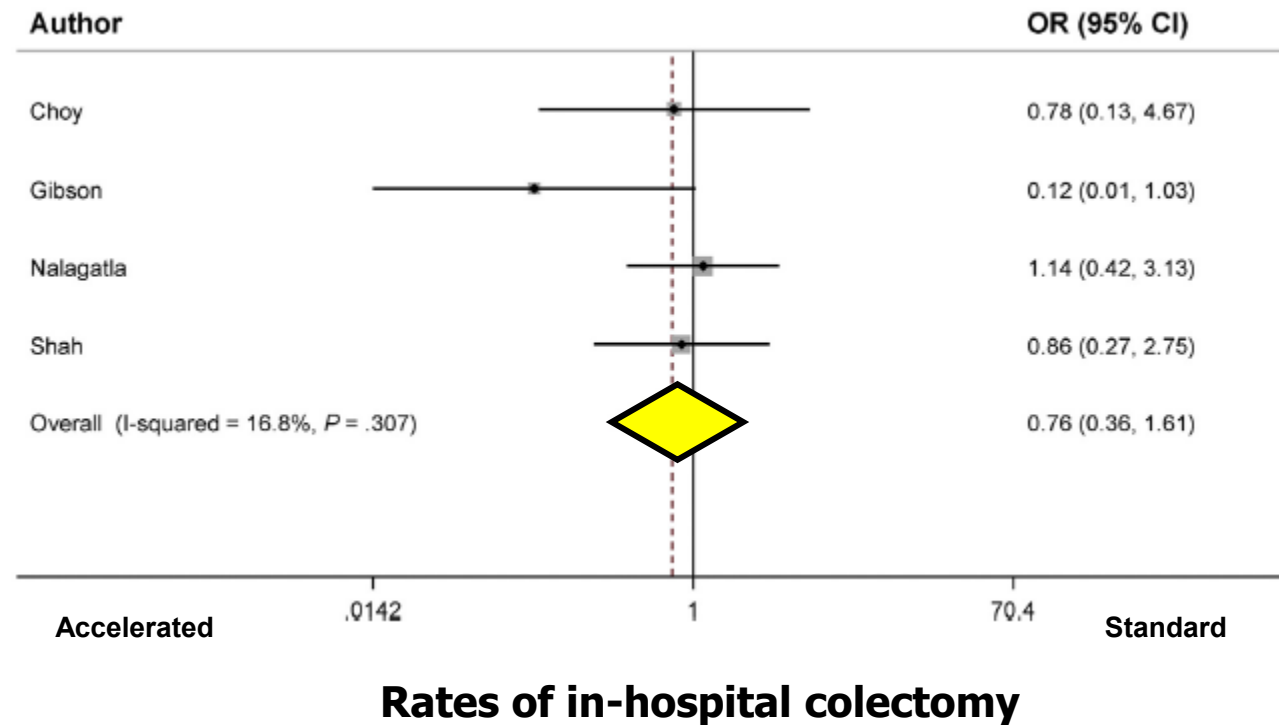
Brandse JF et al. Gastroenterology 2015

Detection of IFX in the stool



Poullenot F et al, Dig Liv Dis 2018

# Towards an intensified IFX induction in ASUC?





# Benefit of an accelerated IFX regimen?

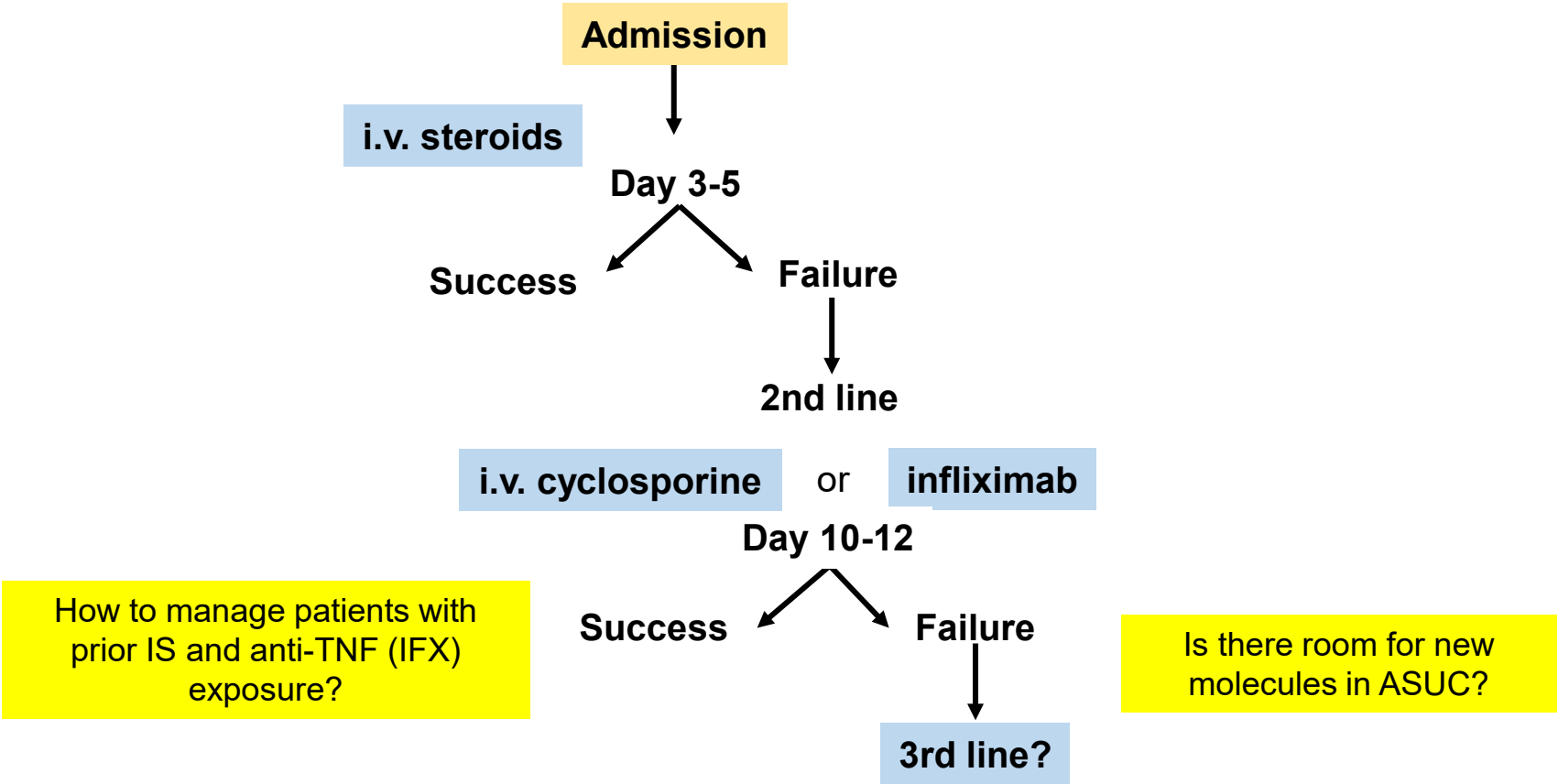
## 1.3.Statement 1.3.

There is currently insufficient evidence to determine the optimal regimen of infliximab rescue therapy in patients with ASUC refractory to corticosteroid therapy [EL4]

2 ongoing trials:

- PREDICT-UC (NCT02770040): n=138  
IFX 10mg/kg at w0-1 vs 5mg/kg at w0-1-3 vs standard IFX
- TITRATE (NCT03937609): n=120  
IFX regimen based on dashboard model with PK vs. standard IFX

# Medical management of ASUC: pending questions



Adapted from Spinelli A et al, J Crohn's Colitis 2022



**Vedolizumab**

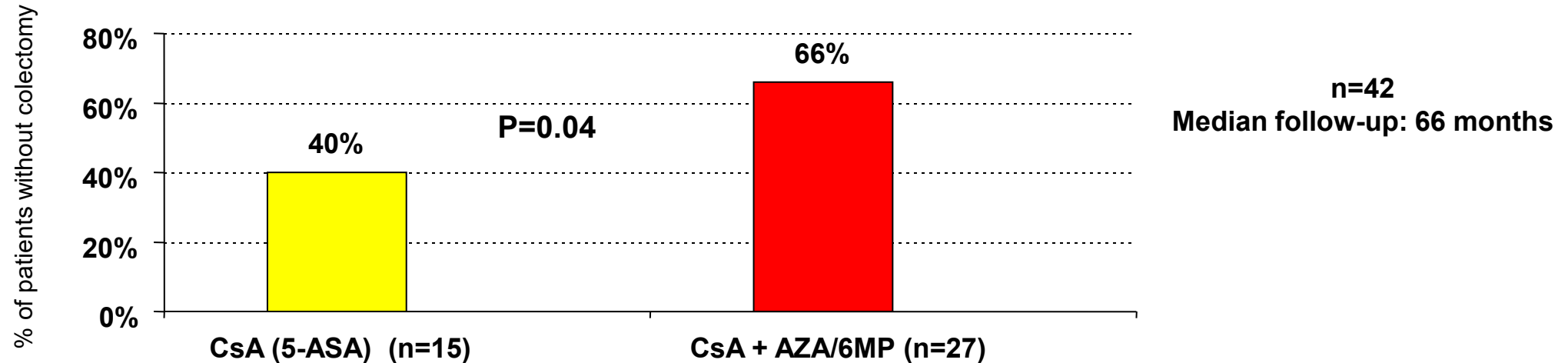
**JAK inhibitors**

**Anti-TNF**

**Anti-IL12/23 &  
anti-IL23 p19**

**S1P modulators**

# Conventional bridging strategy using CsA in ASUC



**Rates of survival without colectomy at 18 months**

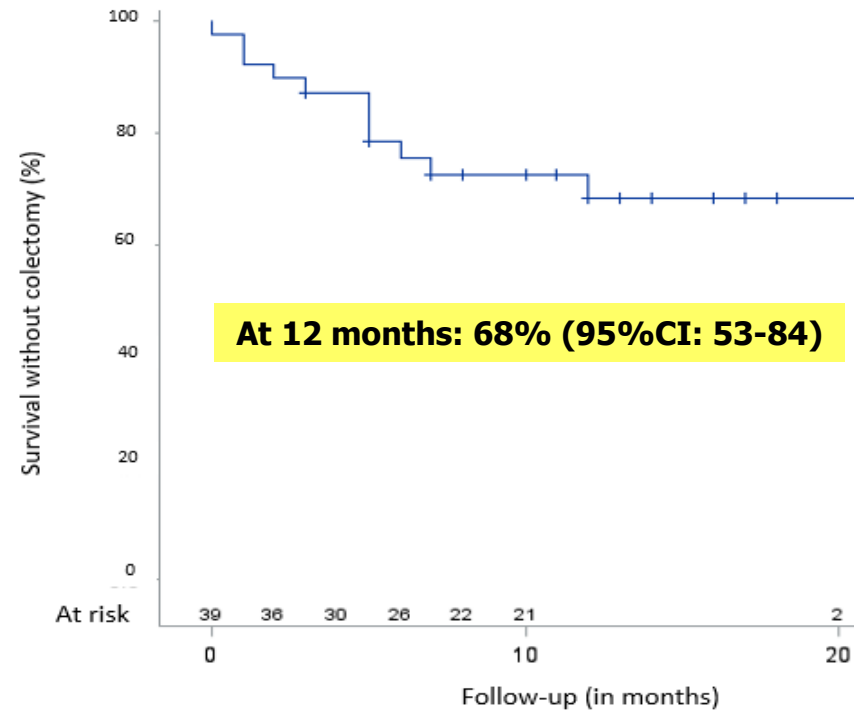
# New bridging strategies in (A)SUC

Absence of controlled data

- Calcineurin inhibitor/vedolizumab (anti-TNF failure):

Studies	Patients	Response rate (avoidance of colectomy)	CI95%
8	156	69%	61-76

# Bridge CsA-vedolizumab in severe UC: long-term survival without colectomy



**Safety:**  
No death  
4 SAEs  
3 kidney failures  
1 *Campylobacter colitis*



# New bridging strategies in (A)SUC

Absence of controlled data

- Calcineurin inhibitor/vedolizumab (anti-TNF failure):

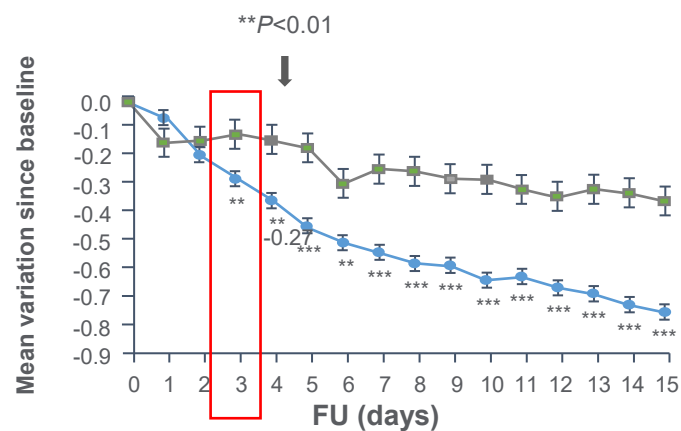
Studies	Patients	Response rate (avoidance of colectomy)	CI95%
8	156	69%	61-76

- Calcineurin inhibitor/ustekinumab (prior anti-TNF and vedolizumab failures):

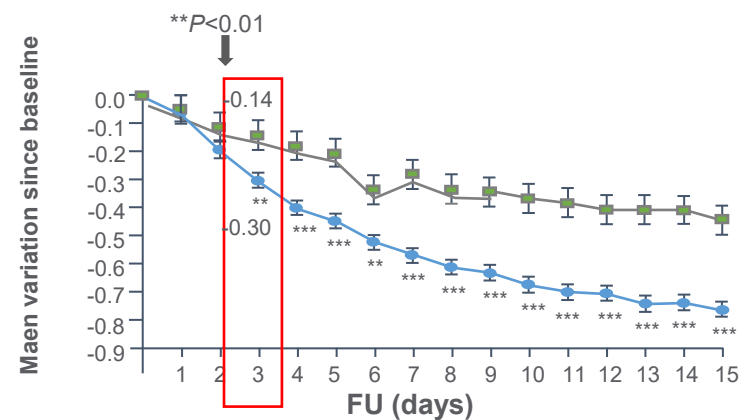
100% response in 13 patients from 3 studies (1, 2 and 10 cases)

# Tofacitinib acts since day 3

## Stool frequency



## Rectal bleeding

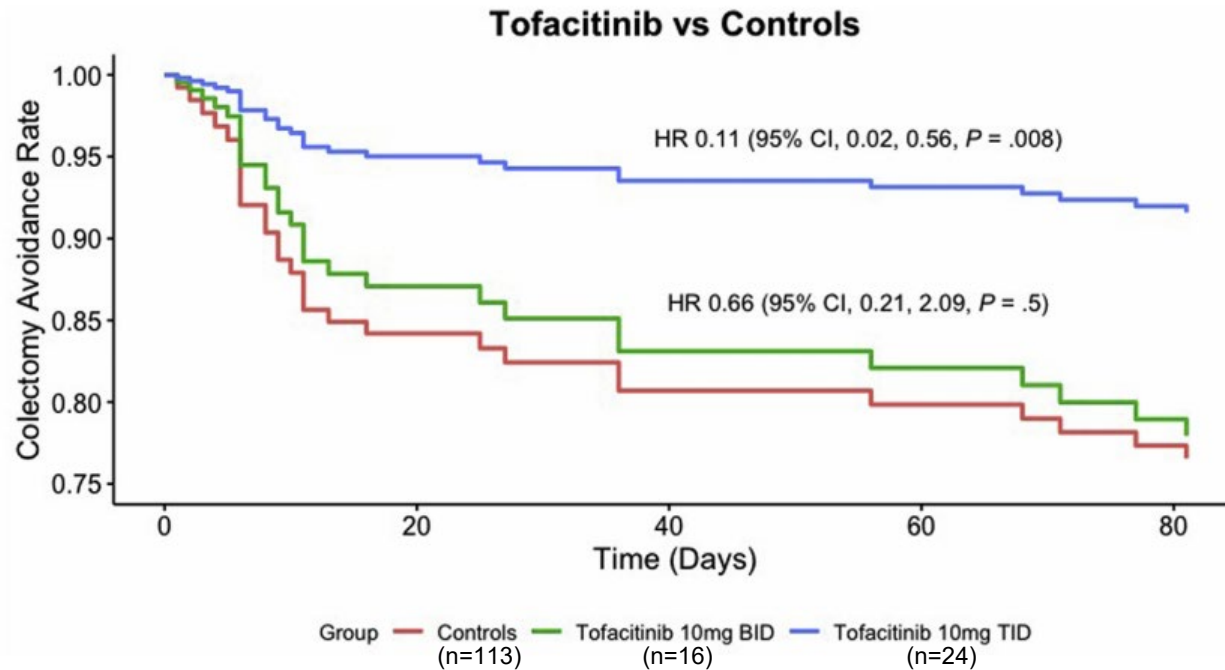


■ Placebo  
● Tofacitinib 10 mg BID



# Tofacitinib for treating refractory ASUC?

Monocenter retrospective experience (University of Michigan)  
40 patients compared with 'controls' having standard management



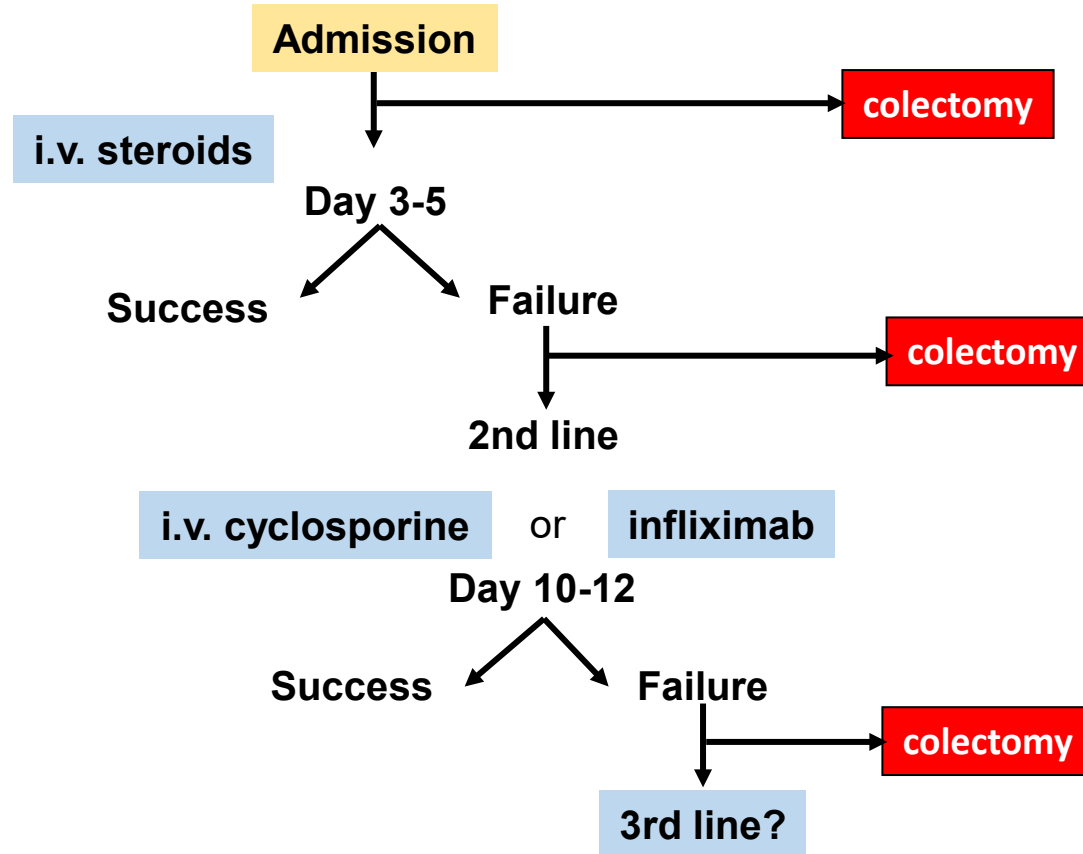
## Safety:

No death  
4 C diff infections  
1 opportunistic infection  
No MACE or VTE

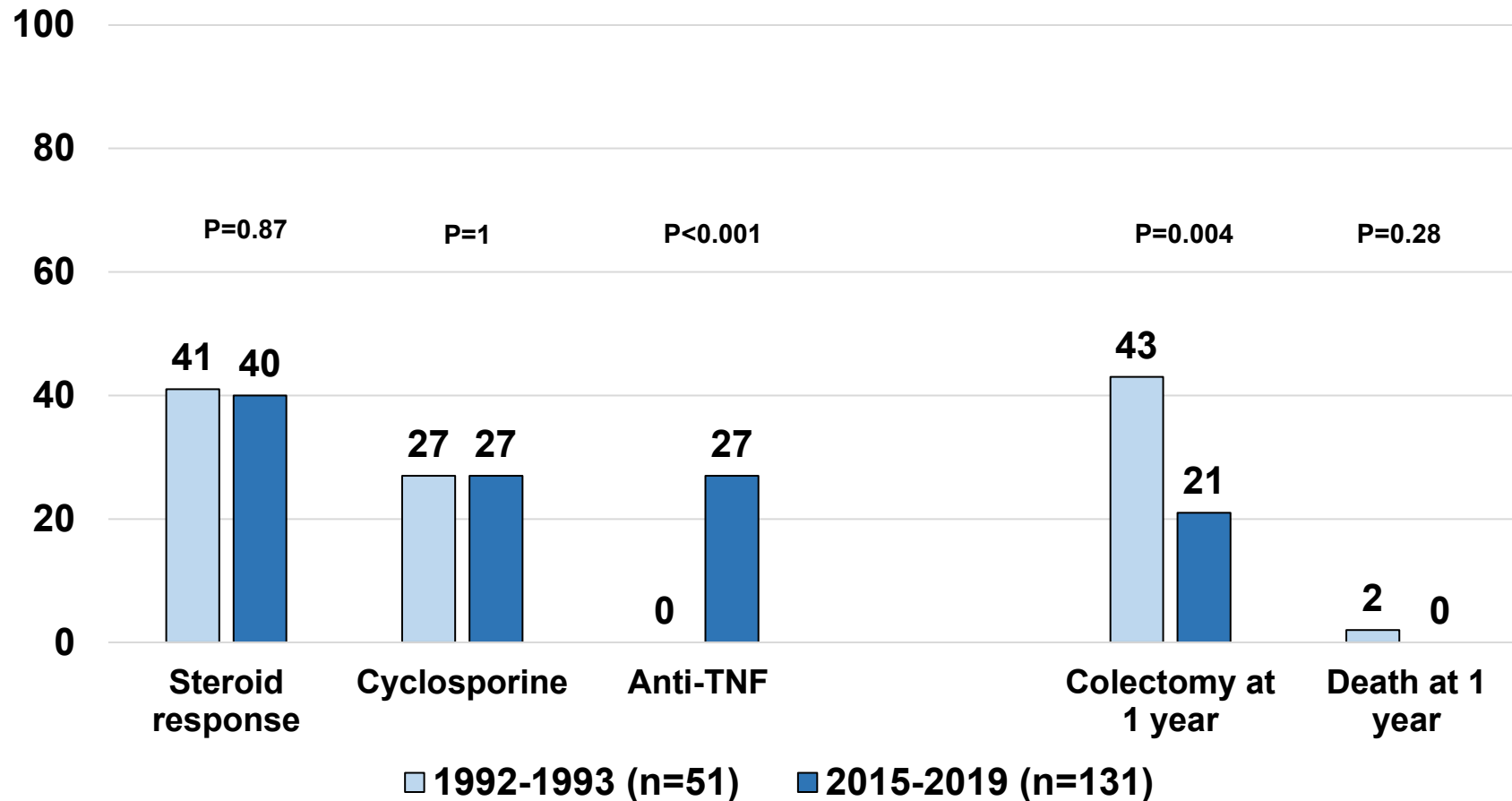
# Benefit of JAK inhibitors in ASUC?

- 1 small series with upadacitinib: 5/6 successes
- 2 ongoing trials:
  - TRIUMPH (NCT04925973): prospective cohort  
n=26 (Canada)  
Tofacitinib 10x2/d  
Endpoint: clinical response at day 7
  - TOCASU (NCT05112263): open-label randomized trial  
n=96 (India)  
Cyclosporine iv vs tofacitinib (10x3/d for the first 3 days and 10x2/j thereafter)  
Endpoint: failure at day 7 and day 98

# Management of ASUC



# Historical changes in the management of ASUC: the Oxford experience

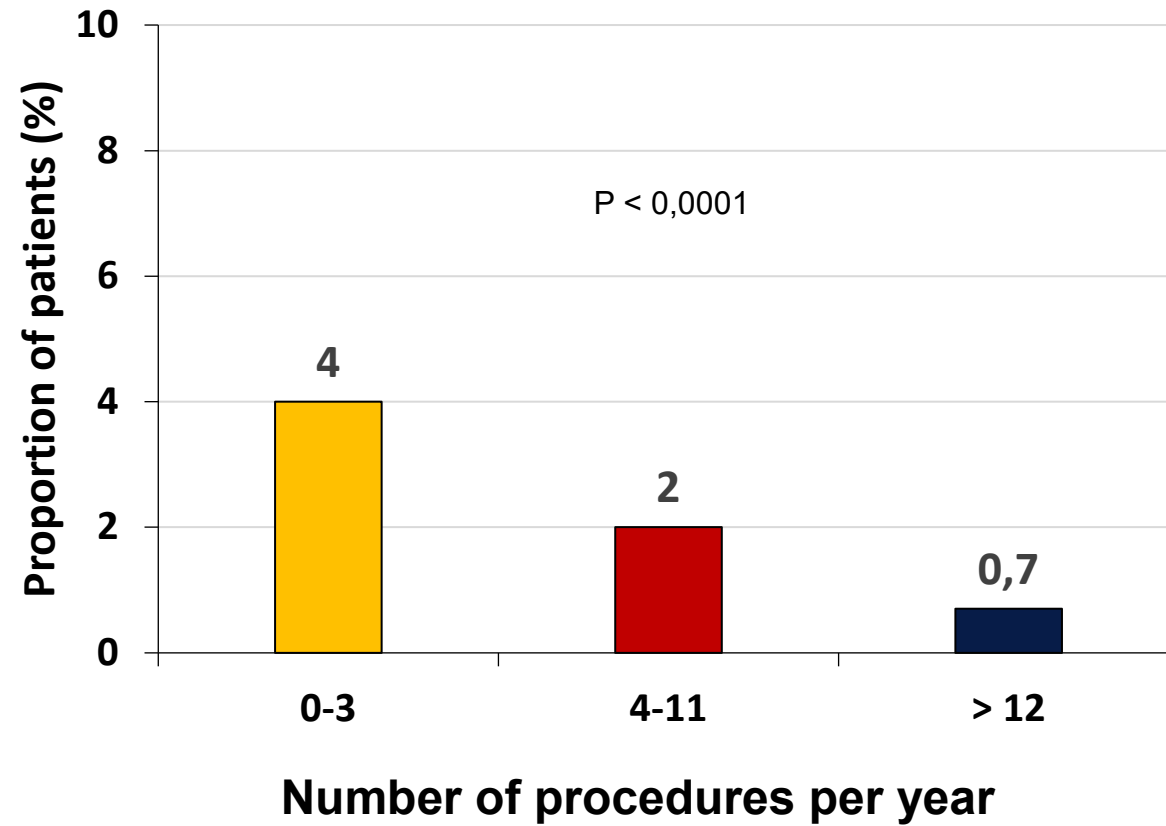


# **Laparoscopic colectomy has become the gold standard in UC**

Meta-analysis: 11 studies / 607 patients

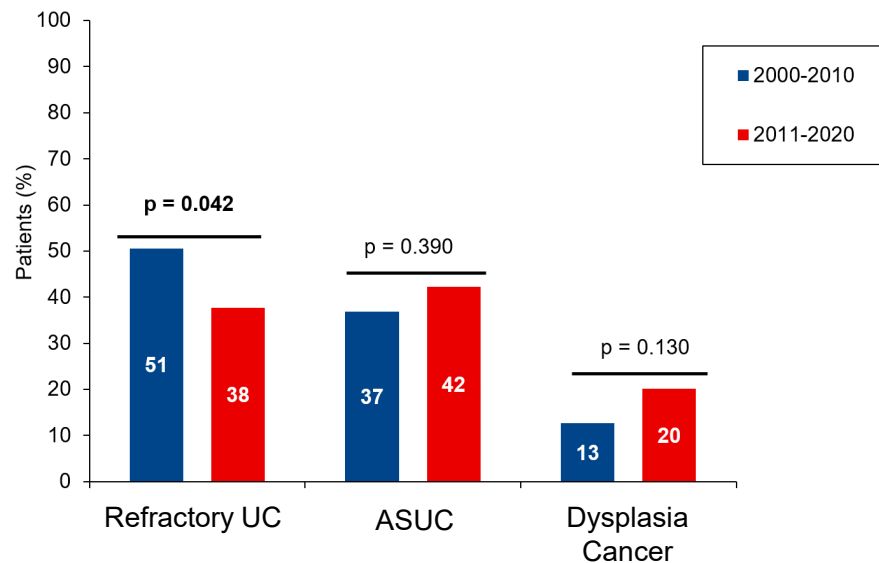
- No difference on postoperative morbidity
- Shorter hospital stay after laparoscopic approach: 2.66 days less
- Faster recovery after laparoscopic approach: 1.96 day less

# Colectomy mortality according to center volume



# Evolution of colectomy in UC since 2000

Two-center retrospective cohort (2000-2021): 286 surgeries



	2000-2010	2011-2020	p
Preoperative biologic exposure	50.6%	<b>74.9%</b>	<0.001
Laparoscopy	47.7%	<b>81.4%</b>	<0.001
Laparoscopy converted	3.5%	4.5%	
Median interval since last biologic (d):	34	<b>24</b>	0.001
Median postoperative duration (d):			
All	19	14	0.109
Refractory UC	13	<b>9</b>	0.021
Rate of severe complications	12.6%	<b>5.5%</b>	<b>0.038</b>
Mean number of infectious complications	0.46	0.31	0.070
Rate of mortality at D30	2.3%	1%	0.391

# Factors associated with postoperative mortality in UC

Registry from New-York state (USA)  
UC surgeries 2000-2006, 2007-2013

## 30-day mortality rate:

- Elective colectomy 0.6%
- Nonelective colectomy 12.9%

## Factors associated with 30-day mortality (n=5,297 surgeries)

Factors	OR (CI95%)	p
Age (10-yr increments)	1.88 [1.65-2.18]	< 0.001
Renal failure	3.00 [1.73-5.24]	< 0.0001
2007-2013 period (vs 2000-2006)	1.82 [1.19-2.62]	0.002
Days from admission to surgery (>4)	1.03 [1.00-1.04]	0.01
Minimally invasive approach	0.13 [0.05-0.36]	< 0.001
High volume center ( $\geq 15$ /yr)	0.24 [0.08-0.54]	0.002



# Take-home messages on ASUC

- ASUC death rates remains 1% in Western countries.
- Early identification of steroid refractoriness, close monitoring by gastroenterologists/surgeons in experienced centers and early introduction of rescue treatments (CsA, IFX, colectomy) are crucial to decrease ASUC morbidity and mortality.
- Salvage colectomy should be discussed at each therapeutic step and not be delayed especially in elderly/frail patients.
- IFX and CsA have close efficacy and safety results.
- New therapeutic perspectives must be further evaluated.



# Long-term complications of IPAA for UC

Type and frequency of long-term (>30 days) postoperative complications

