

# The gut in Parkinson's disease: new possibilities in treatment of dysfunction

Anton Emmanuel  
*July 2020*



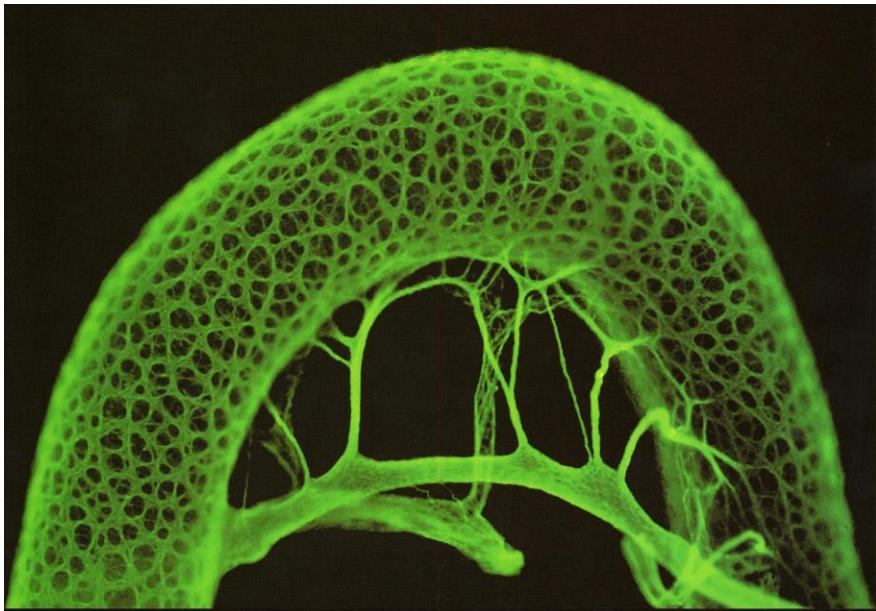
National Hospital  
for Neurology  
& Neurosurgery



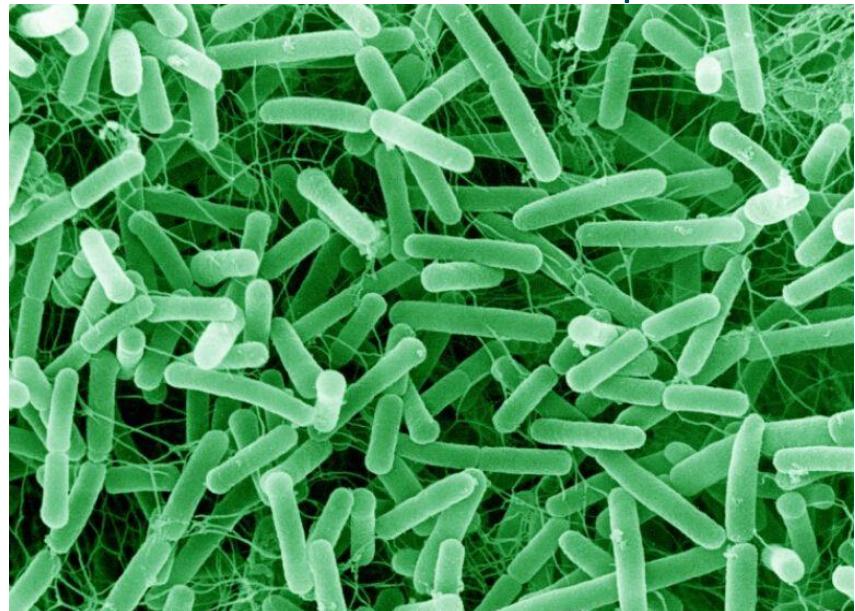


## The human gut

More bacterial cells than human cells



More neurones than the spinal cord



## 63 year old woman

Severe abdominal pain, bloating and nausea

Constipation

Parkinson's disease since age 50 – bradykinesia

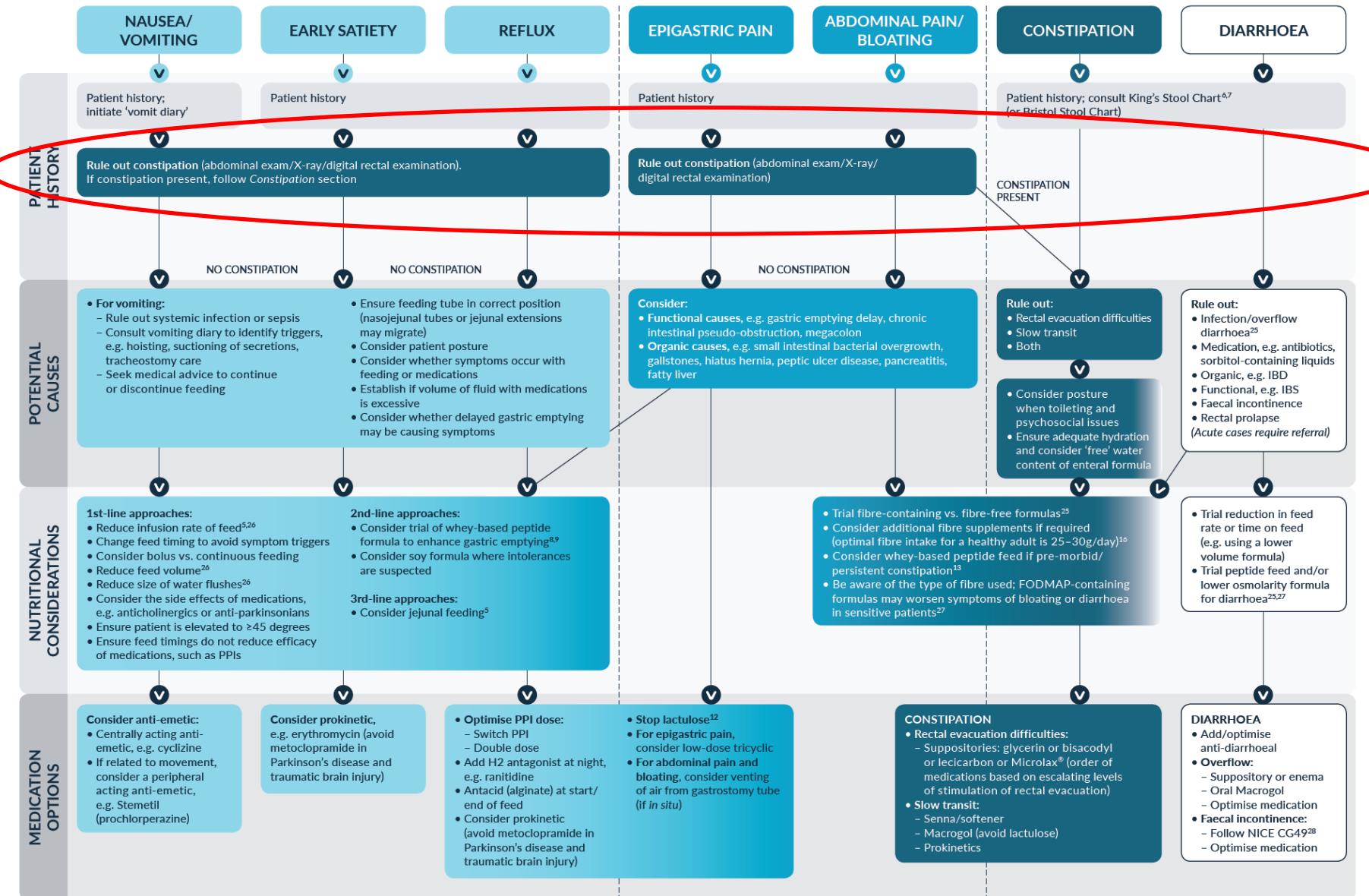
- on L-Dopa
- BMI 19

Two children – one Caesarean, one vaginal delivery

Retired geography teacher

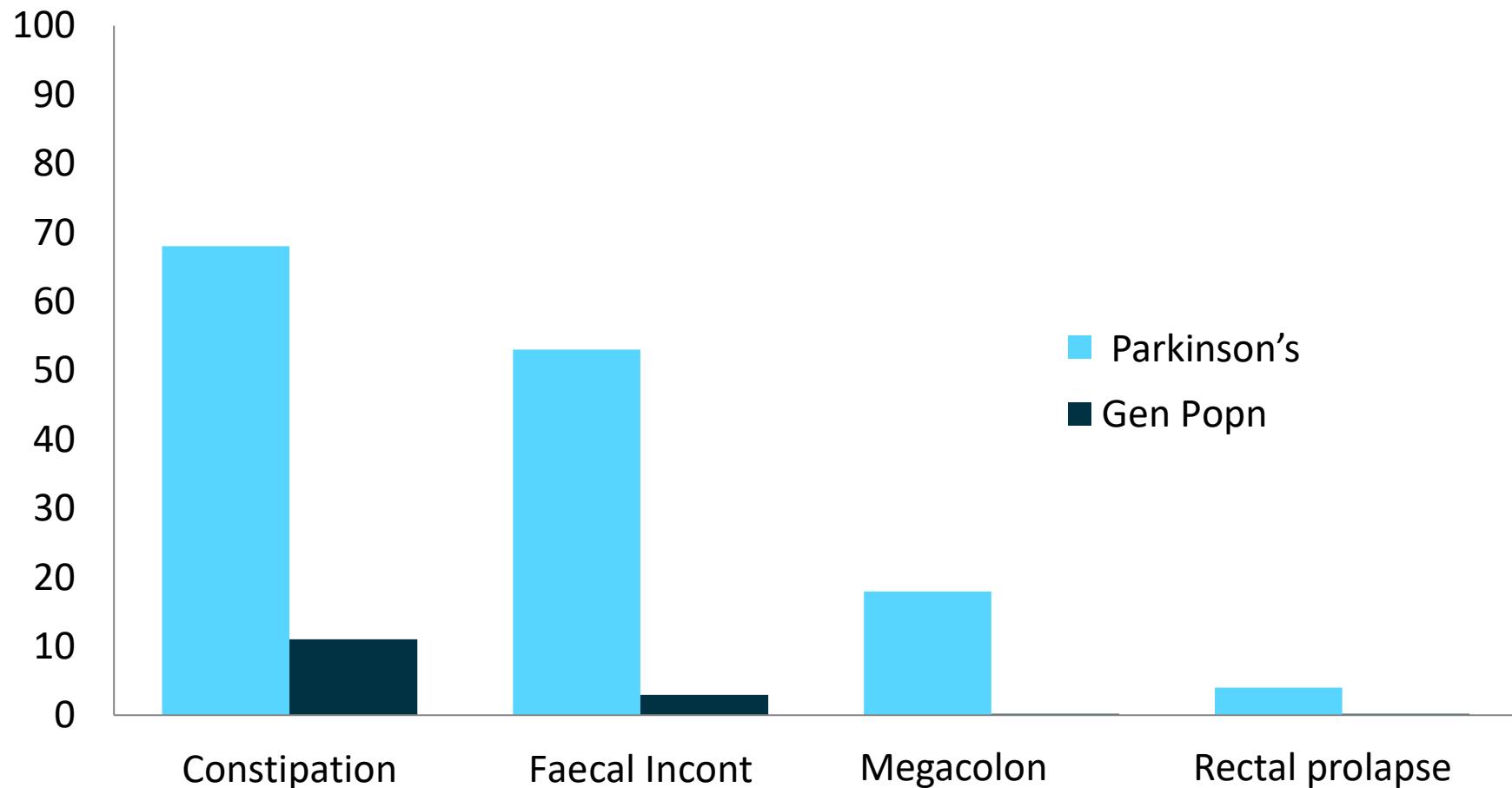
# Involvement goes beyond the bowel

## IDENTIFY GI SYMPTOMS



# Prevalence of neurogenic bowel symptoms

% patients  
with dysfunction



## What's the diagnosis?

Constipation

Slow transit

Pelvic floor problem

IBS

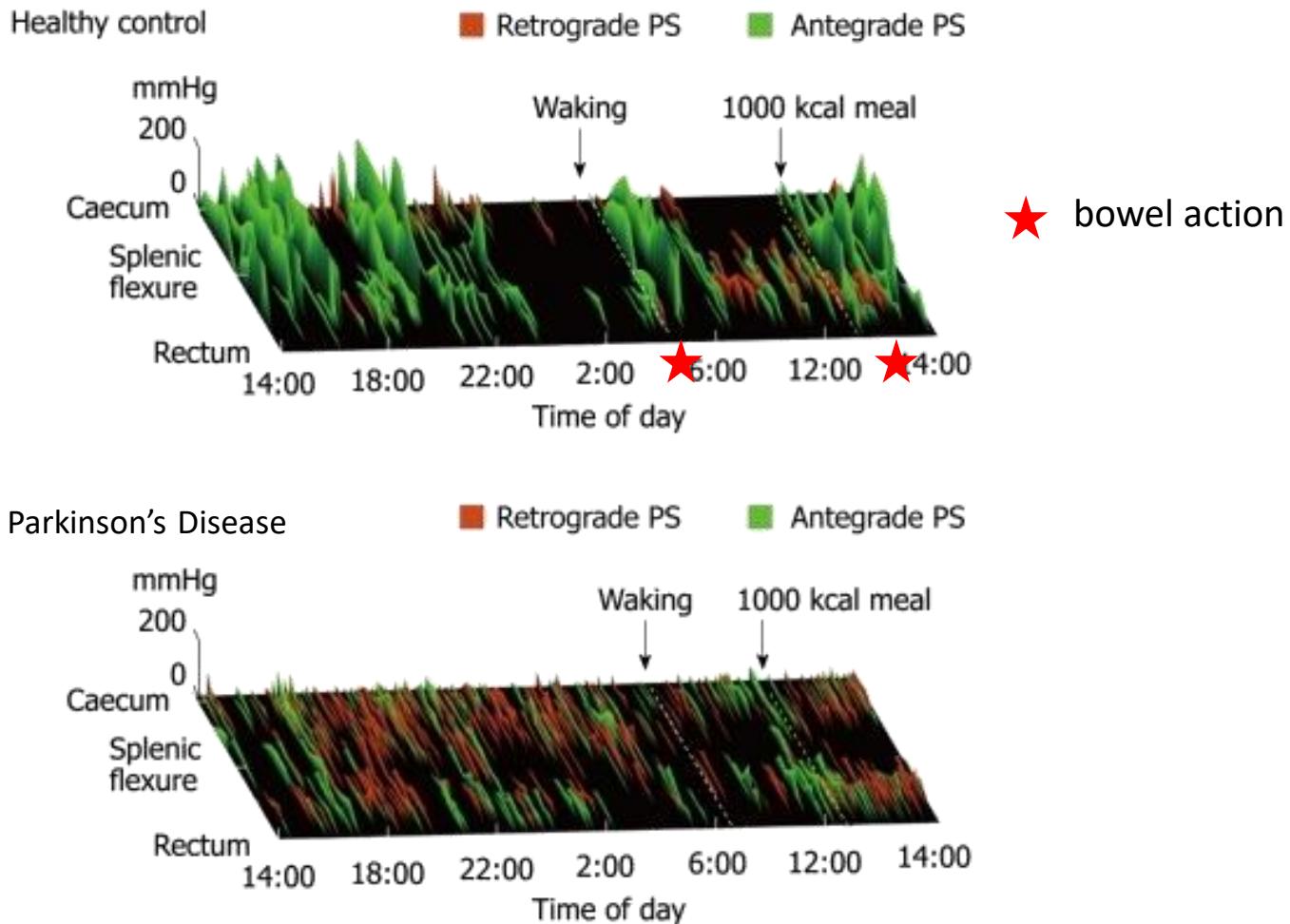
“What does it matter? The solution is Movicol”

“What does it matter? Send her to a surgeon”

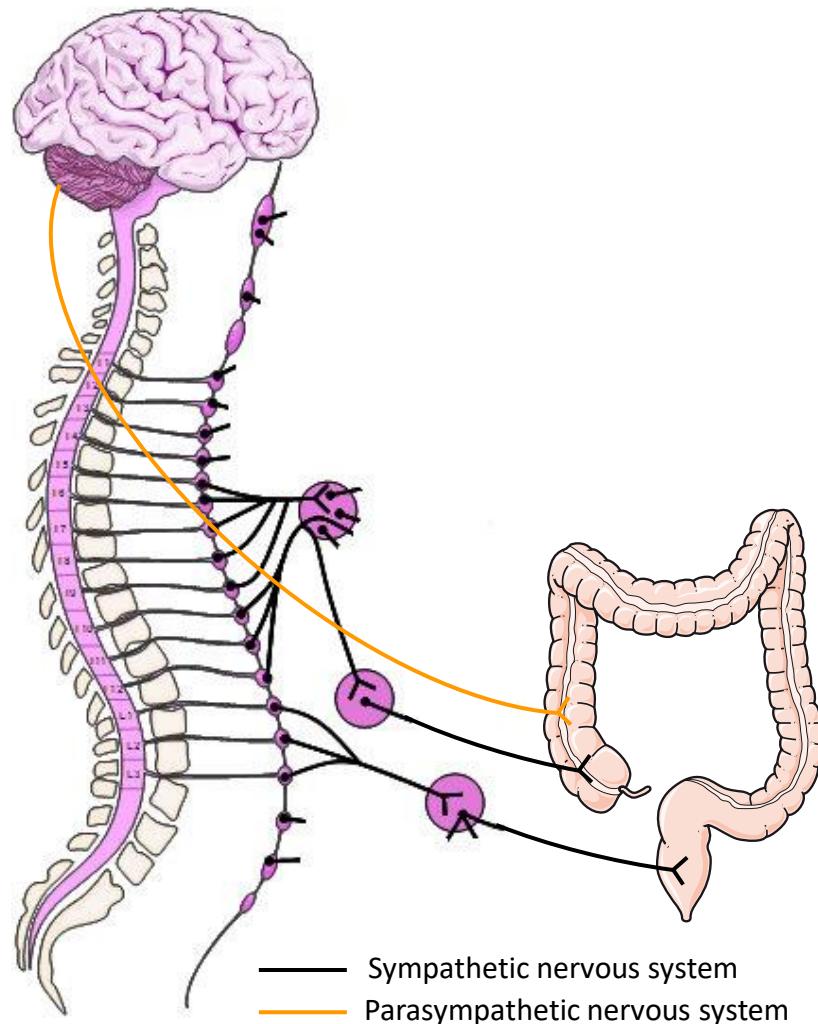
“What does this have to do with Parkinson’s disease”

# Motility

## Healthy vs. Parkinson's

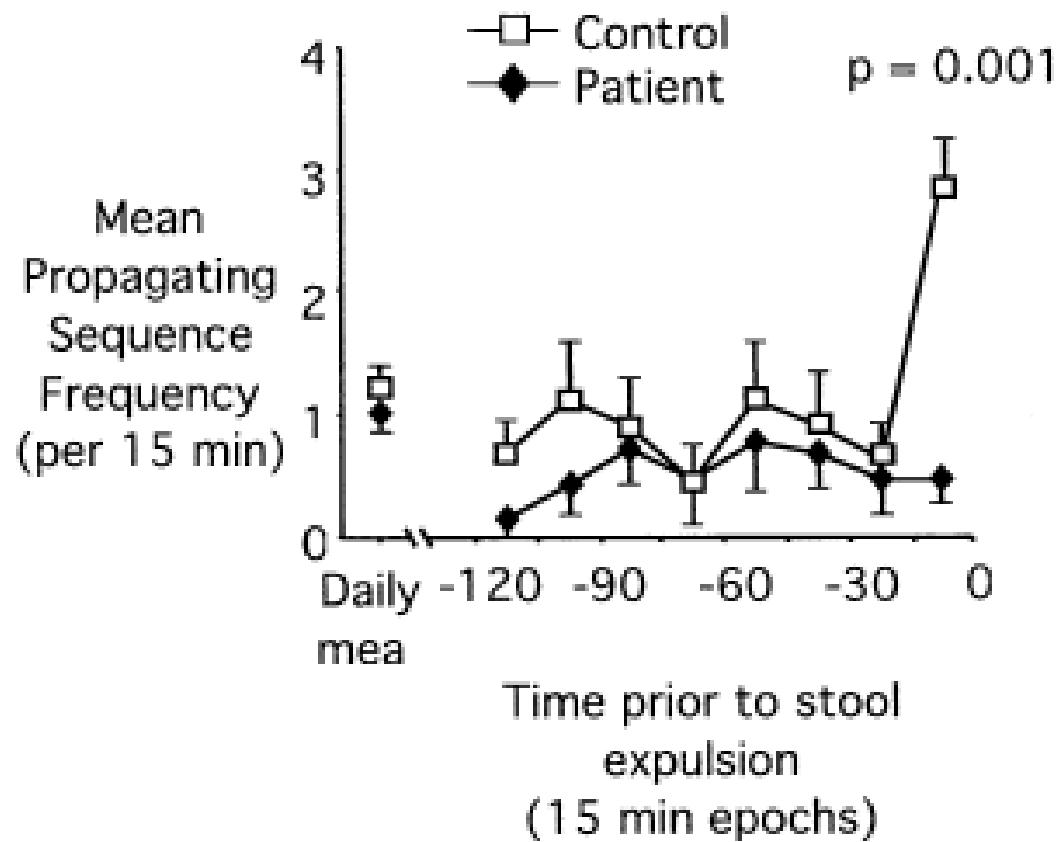


# Regulation of colonic function



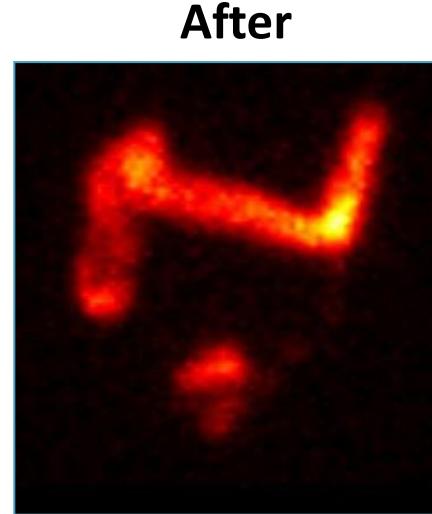
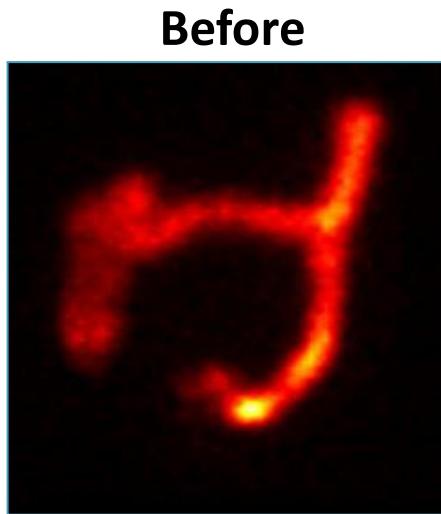
- Two-way interaction between ENS and CNS via sympathetic and parasympathetic nervous system
- So, a number of factors can influence colonic function:
  - Conscious: Behavioural factors<sup>1</sup>
    - e.g. toilet avoidance
  - Unconscious: Emotional distress<sup>2</sup>
  - Hormonal: Increased expression of progesterone receptors<sup>3</sup>

# Relationship of synchronising defaecatory effort with colonic mass movements

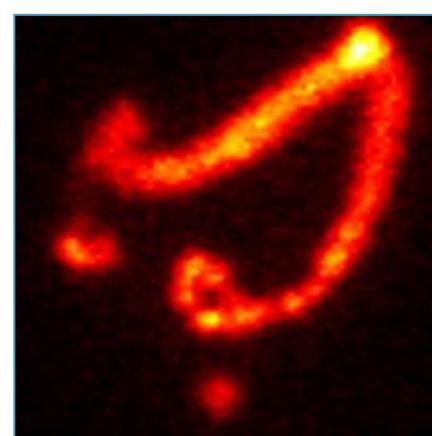
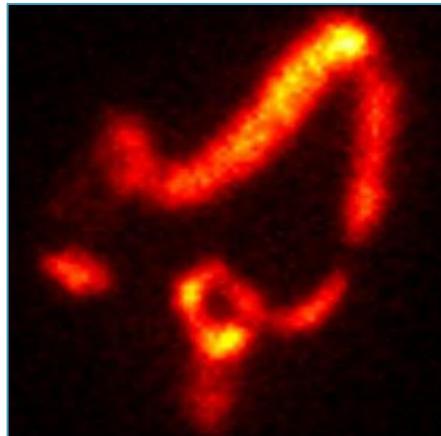


**Scintigraphic study showing defaecation produces a complete emptying of the left colon in healthy subjects, but not in SCI**

**Healthy subject**



**Neurological disorder**



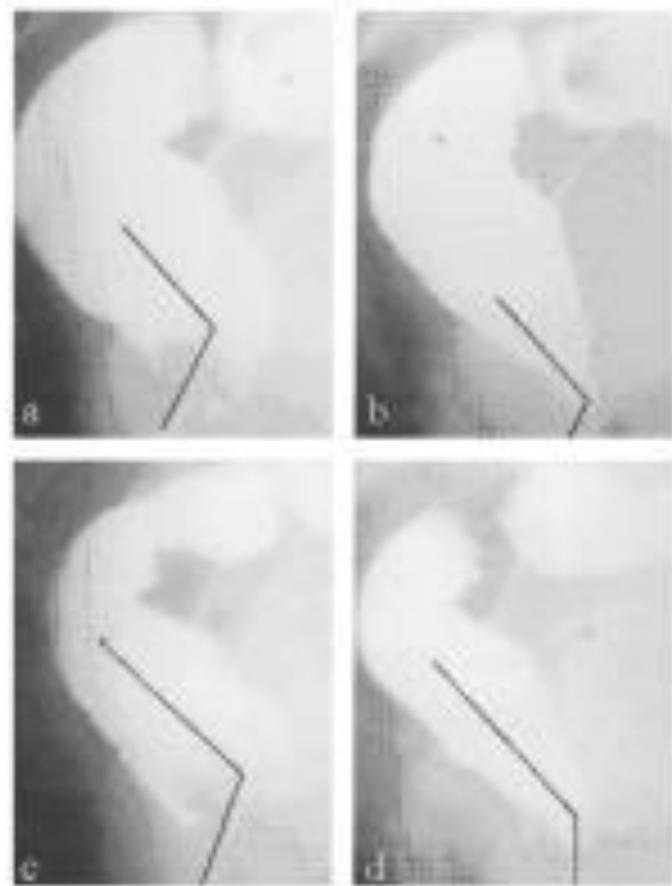
# 63 year old woman with Parkinson's



# Pelvic Floor Dyssynergia – a form of dystonia

Botox injection into puborectalis<sup>1</sup>  
100-150 units

Under ultrasound guidance  
Effect within 72 hours



## Now 66 year old woman with Parkinson's

Evacuation easier, repeat injections 2-3 times/year

3 years later: developed hypertension, started amlodipine

Profoundly constipated

- infrequent urge, hard stool

# 66 year old woman with Parkinson's



# Prucalopride in Neurogenic Bowel Dysfunction

SCI/spina bifida n=13

Multiple sclerosis n= 18

Parkinson's disease n=14

Miscellaneous n=9 (muscular dystrophy, ALS, stroke)

Standard doses

All slow transit

## Prucalopride in Neurogenic Bowel Dysfunction

n=54 – no differences between diseases

Stool freq improvement >3/week n=17

Symptom severity VAS pre vs post: 7.3 to 5.9

Bowel care independence n=10

Reduced bowel care time <30mins/day average n=18

Reduced/absent faecal incontinence n=14 of 37

## Parkinson's Disease Constipation

Affects about 95% of PD patients

~30% may be faecally incontinent (esp parous women)

4-times more common than age sex-matched controls

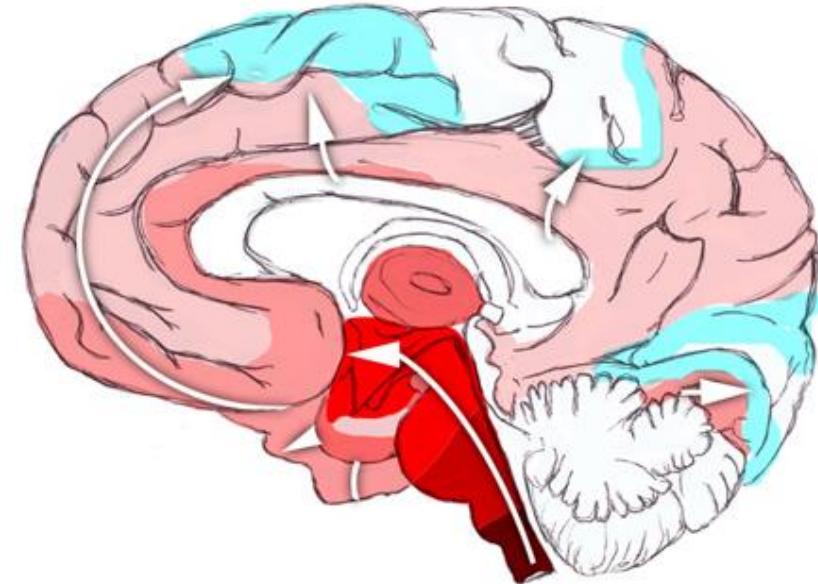
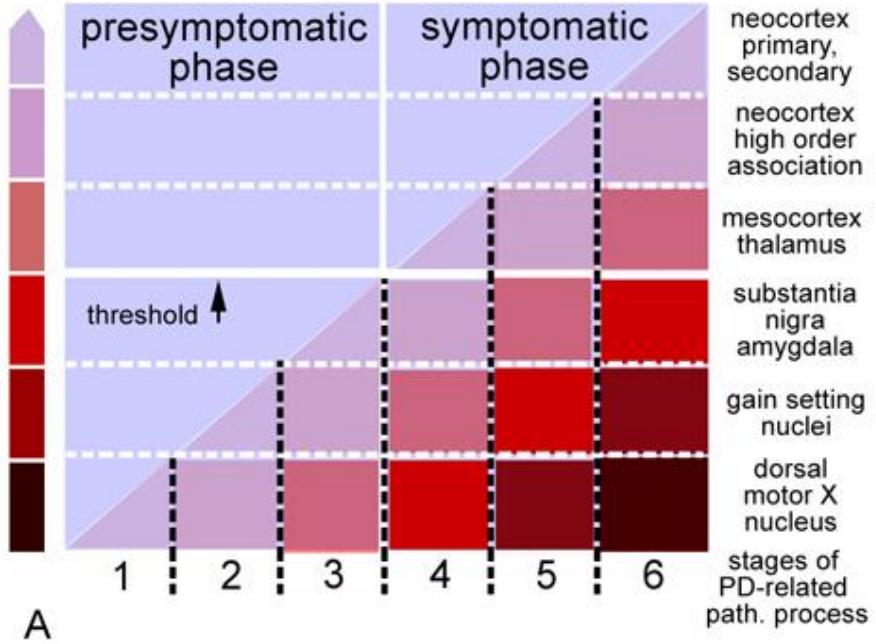
Constipation may predate motor symptoms (Abbott et al Neurology 2011)

Men: constipation = 4x risk: constipation & anosmia = 8x risk

Major complications: severe, but very rare  
- ileus, volvulus, perforation

# Parkinson's Disease

## The Braak Hypothesis and Bowel Function



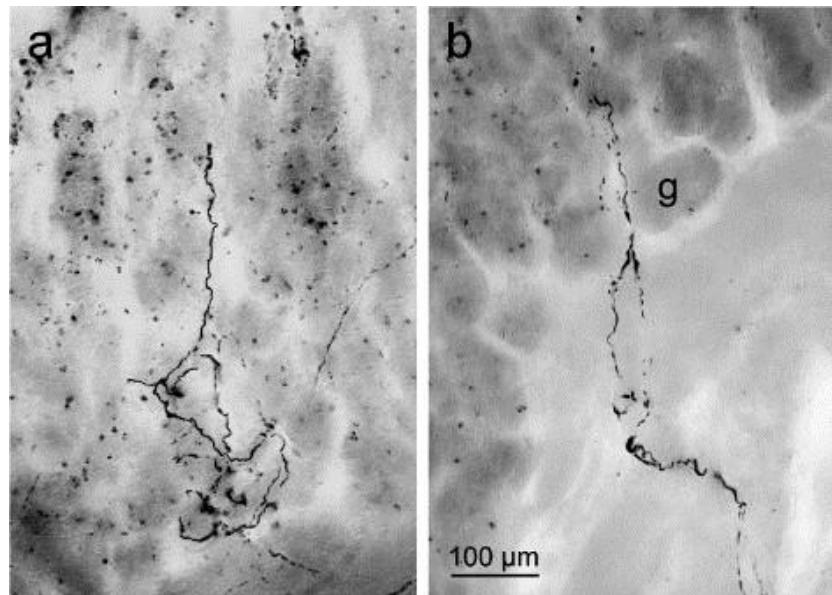
Vagal innervation of gut from oesophagus to colon

⇒ ascending path of neurodegeneration

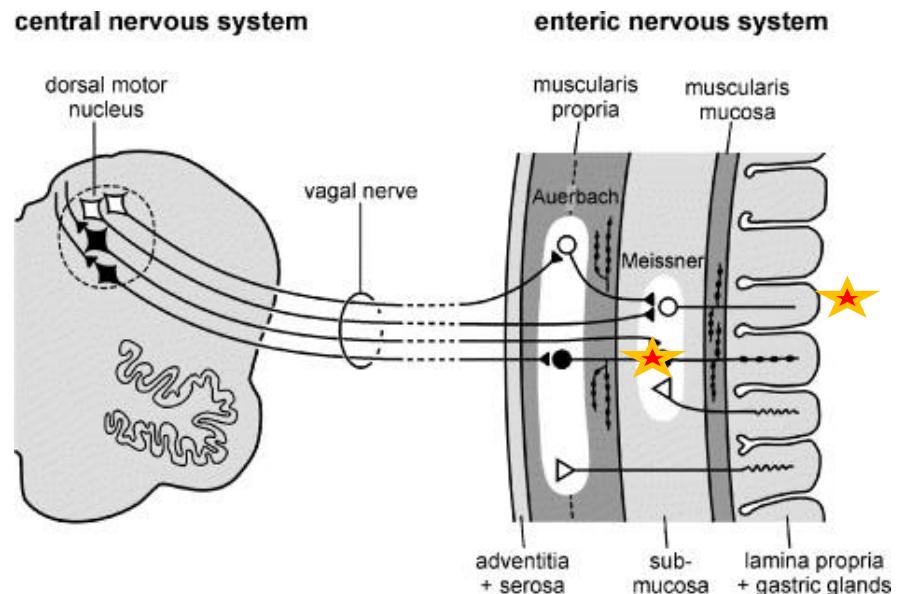
Dorsal motor nucleus of vagus as “departure point” of the disease

# Parkinson's Disease

## The Braak Hypothesis and Bowel Function

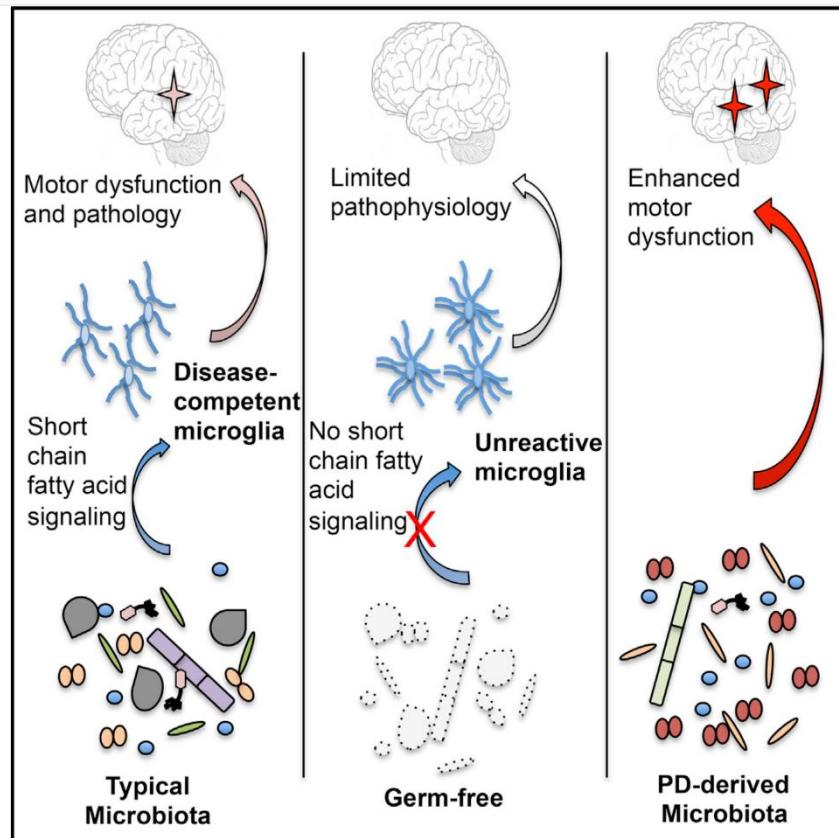


Aggregated axonal  $\alpha$ -synuclein inclusions in the colonic Meissner plexus



Schematic diagram showing the interconnections between the enteric nervous system and brain.

# Human gut microbiota from PD patients induce enhanced motor dysfunction in mice



Gut microbes promote  $\alpha$ -synuclein-mediated motor deficits and brain pathology

Depletion of gut bacteria reduces microglia activation

SCFAs modulate microglia and enhance PD pathophysiology

# Multi-strain probiotics in Parkinson's Disease

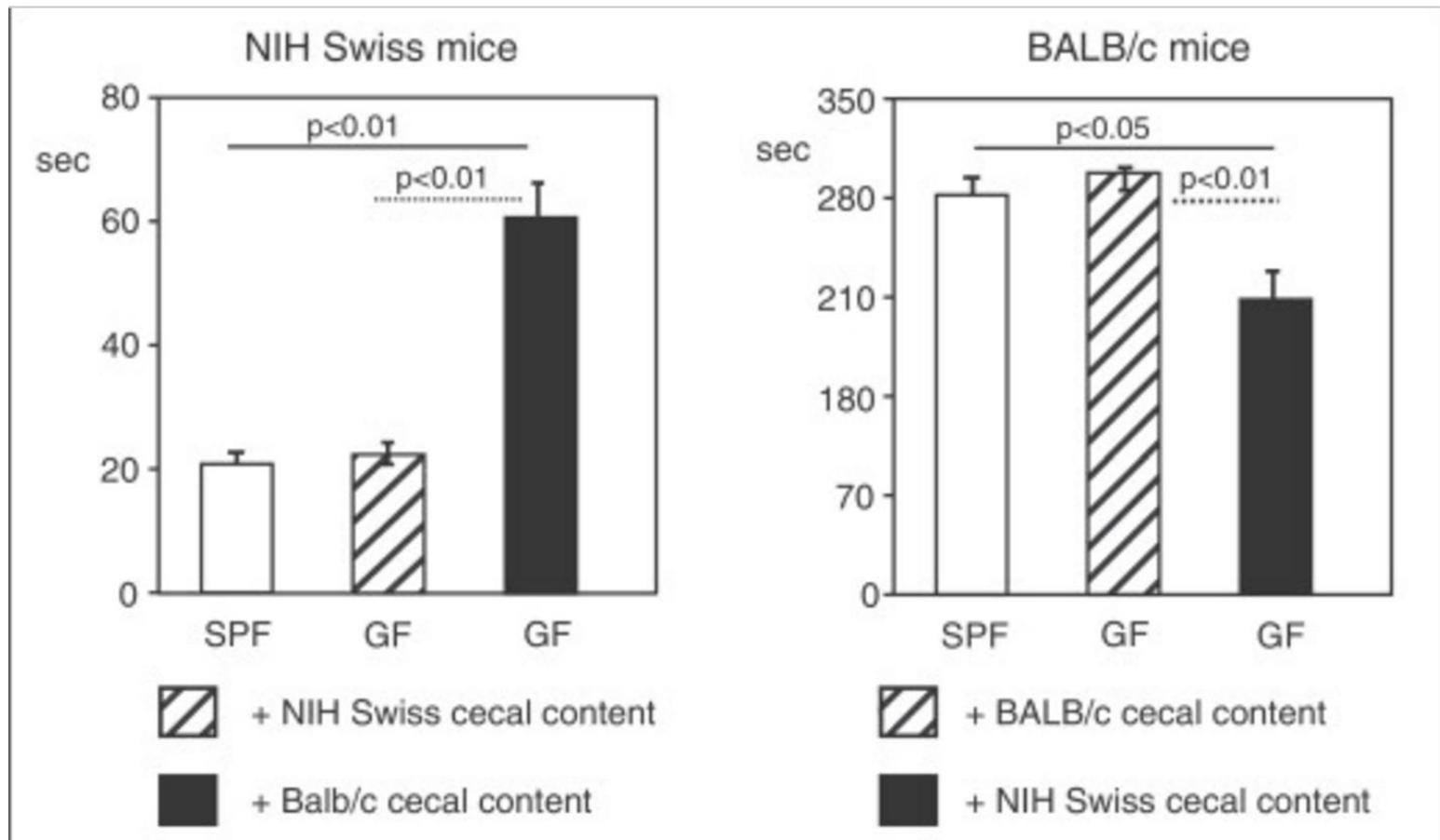
Randomised double-blind, n=120, 4 weeks

Fermented milk with prebiotic fibre and probiotic

| Endpoint                                      | Experimental Group (n = 80) | Placebo Group (n = 40) | P Value |
|---|-----------------------------|------------------------|---------|
| Three or more CBMs in week 3 - 4 (%)          | 58.8                        | 37.5                   | .03     |
| Mean increase in stool consistency*           | 0.7                         | 0.1                    | .018    |
| Mean decrease in use of laxatives, week 3 - 4 | 0.8                         | 0.1                    | .018    |
| Satisfied/very satisfied (%)                  | 55.0                        | 17.5                   | <.001   |
| Likely to continue treatment (%)              | 56.3                        | 30.0                   | .008    |

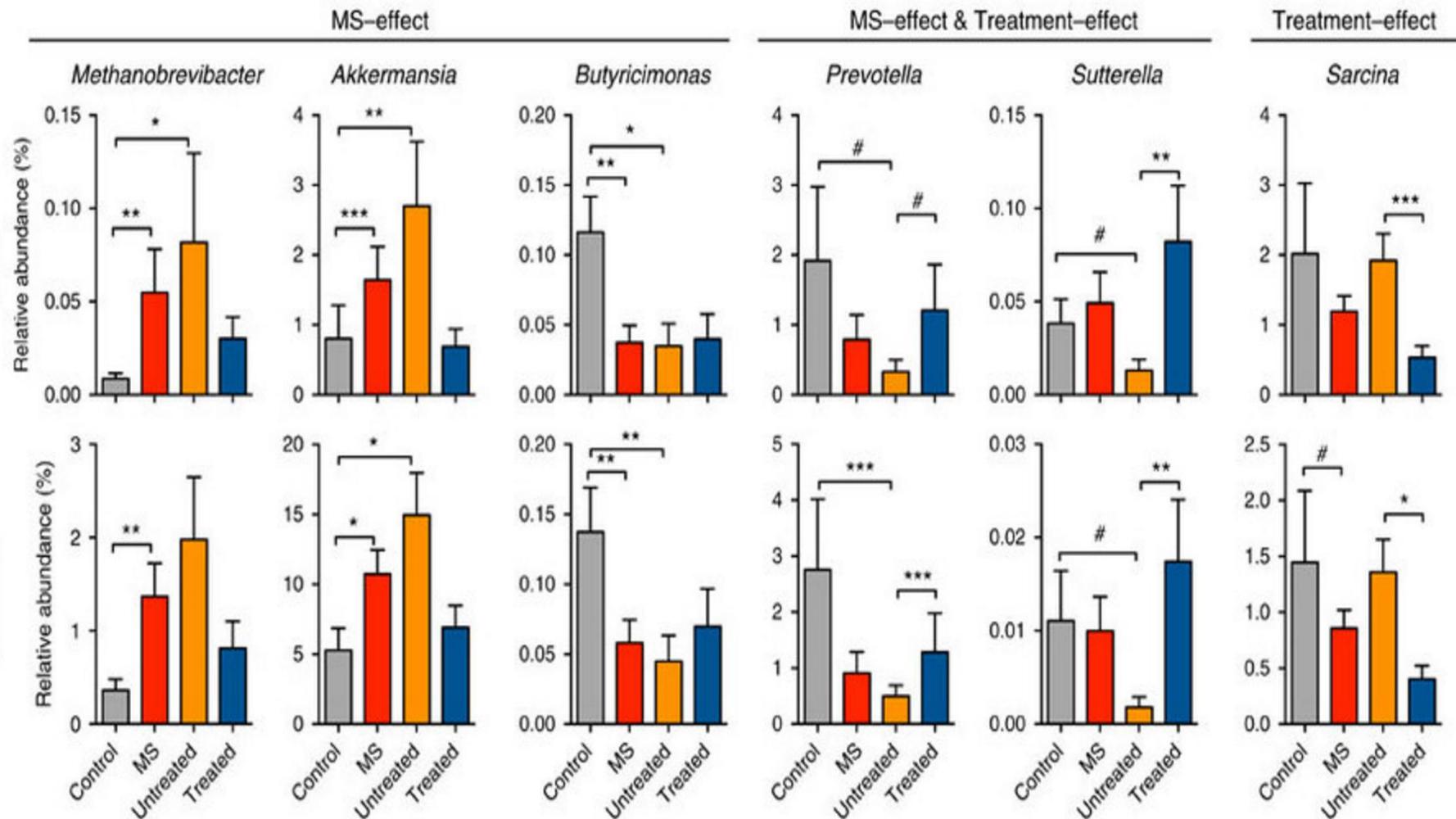
\*Stool consistency, Bristol Stool Form Scale score.

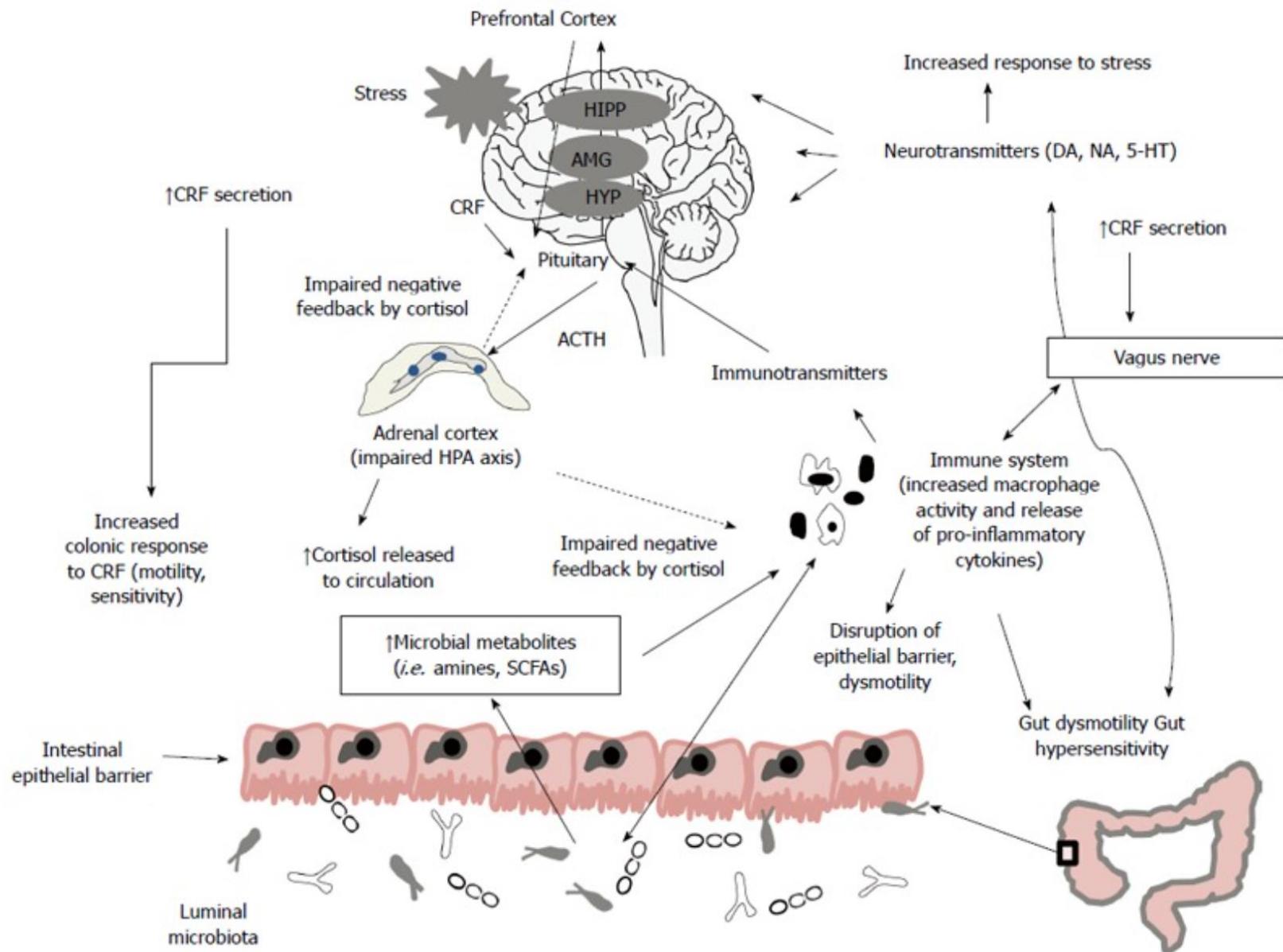
# Faecal microbial transplant transfers behavioural traits



# Microbiome and multiple sclerosis

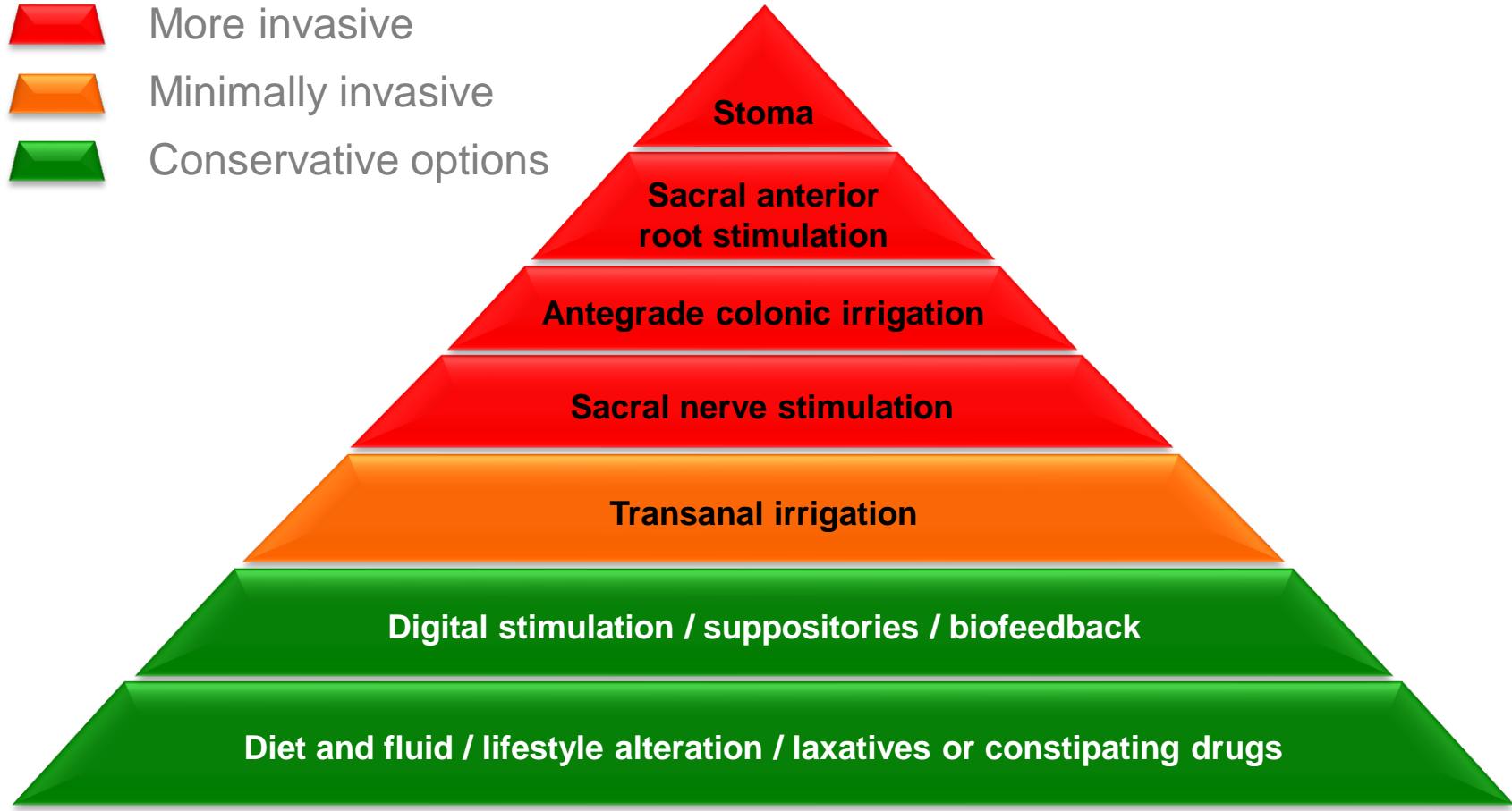
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# Care algorithm in neurogenic bowel dysfunction

-  More invasive
-  Minimally invasive
-  Conservative options



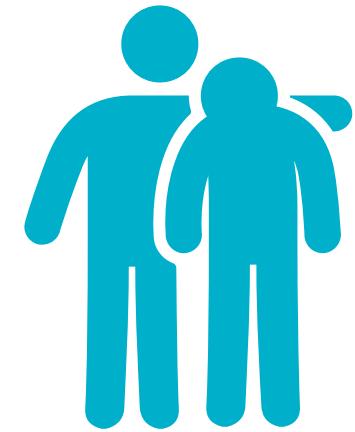
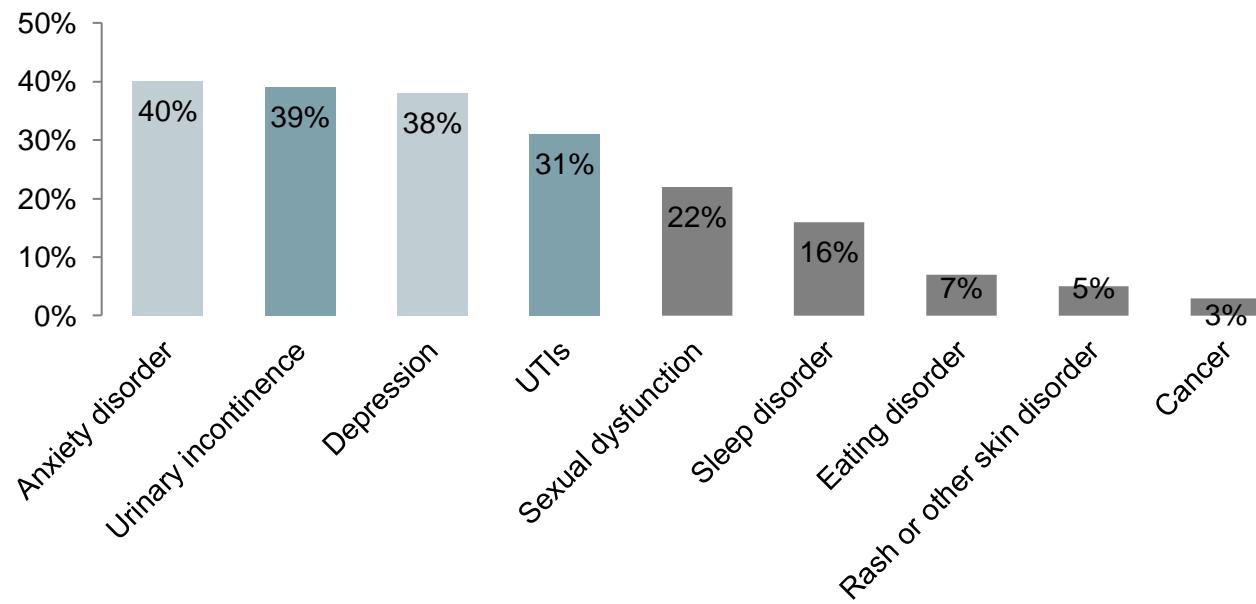
## Faecal accidents and the unpredictability of bowel movements are the biggest bowel issues for neurological patients

|   | Total    | Spinal Cord Injury (SCI) | Multiple Sclerosis (MS) | Anorectal malformation (ARM) | Parkinson's disease |
|---|----------|--------------------------|-------------------------|------------------------------|---------------------|
| Total                                       | 317      | 73                       | 86                      | 38                           | <b>23</b>           |
| Fecal accidents                             | 55 (17%) | 19 (26%)                 | 14 (16%)                | 7 (18%)                      | <b>6 (26%)</b>      |
| Urgency/unpredictability of bowel movements | 62 (20%) | 14 (19%)                 | 20 (23%)                | 10 (26%)                     | <b>6 (26%)</b>      |
| Chronic constipation                        | 57 (18%) | 9 (12%)                  | 15 (17%)                | 5 (13%)                      | <b>9 (39%)</b>      |
| Pain or discomfort                          | 68 (21%) | 8 (11%)                  | 18 (21%)                | 6 (16%)                      | <b>4 (17%)</b>      |
| Time spent on toilet                        | 20 (6%)  | 9 (12%)                  | 5 (6%)                  | 1 (3%)                       | <b>6 (26%)</b>      |

(showing top 5 results, other results <4%)

# Many experience mental health challenges and urinary problems alongside their bowel issues.

Anxiety and depression are among the most experienced conditions by people suffering from bowel issues, along with urinary incontinence and closely followed by UTIs



# Patients find that bowels are controlling their lives, not the other way around



*"I would have an accident about once a quarter, but I was scared all of the time. If I had a good four months and no accident, I would think 'This is the calm before the storm'."*

JAKE, US



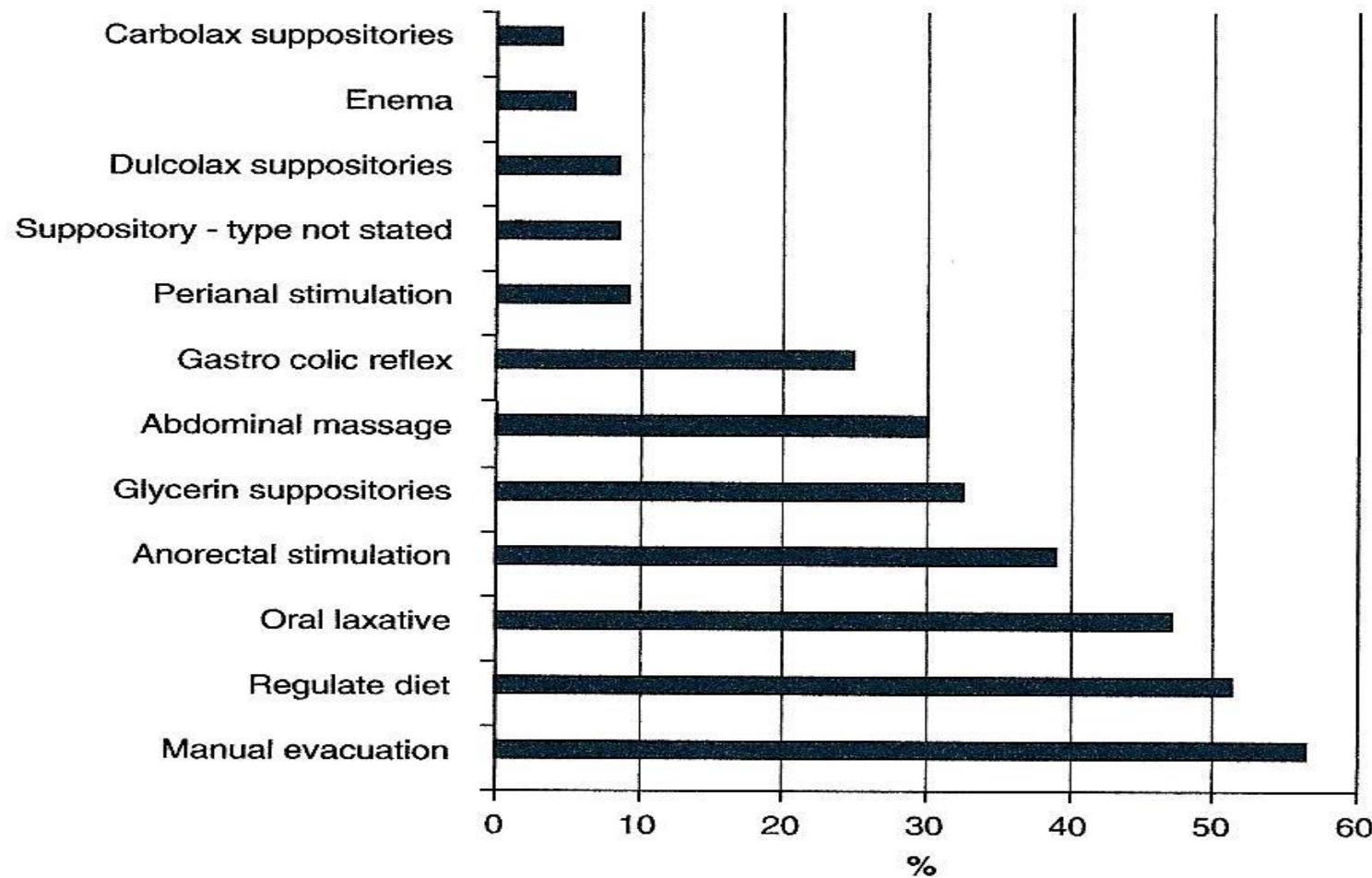
# 2 week diary at initial assessment

#### Irritable Bowel Syndrome — Diarrhea Predominant (IBS-D) Symptom Event Log

The purpose of this Event Log is to collect some information about your bowel movements. After EVERY bowel movement, please fill out the Date and Time, and answer all of the following questions on that row. Please see the example provided in the first row.

# Bowel management after SCI in community settings

Interventions used for bowel care (multiple responses possible)



## Effect of exercise

- Several other studies link exercise with reduced risk
  - Community survey of 1,699 Japanese
  - >4h /day walking reduces risk OR 0.46(0.2-1.0)
    - Nakaji et al *Eur J Nutr* 2002;**41**(6):244-8
- One RCT of exercise in IBS-C
  - 56 IBS randomised to usual care or 12 weeks exercise programme
  - Recruitment low (18%)
  - Primary endpoint : QOL showed no change
  - Significant improvement in constipation
    - Daley et al *Int J Sports Med* 2008;**29**(9):778-82

## Effect of fluid intake

Severe water restriction reduces stool weight

- RCT in volunteers reducing fluid intake from 2500ml to <500ml
- Results: Stool weight fell from 1,290 to 940 g/wk, p<0.05

Klauser et al *Z Gastroenterol* 1990;28(11):606-9

No evidence of benefit with additional water if already well hydrated:

- RCT of 108 children with CC randomised to:
  - No change
  - 50% increase in fluid intake with water
  - 50% increase in total fluid intake as soft drinks
- Results: No change in stool frequency or consistency

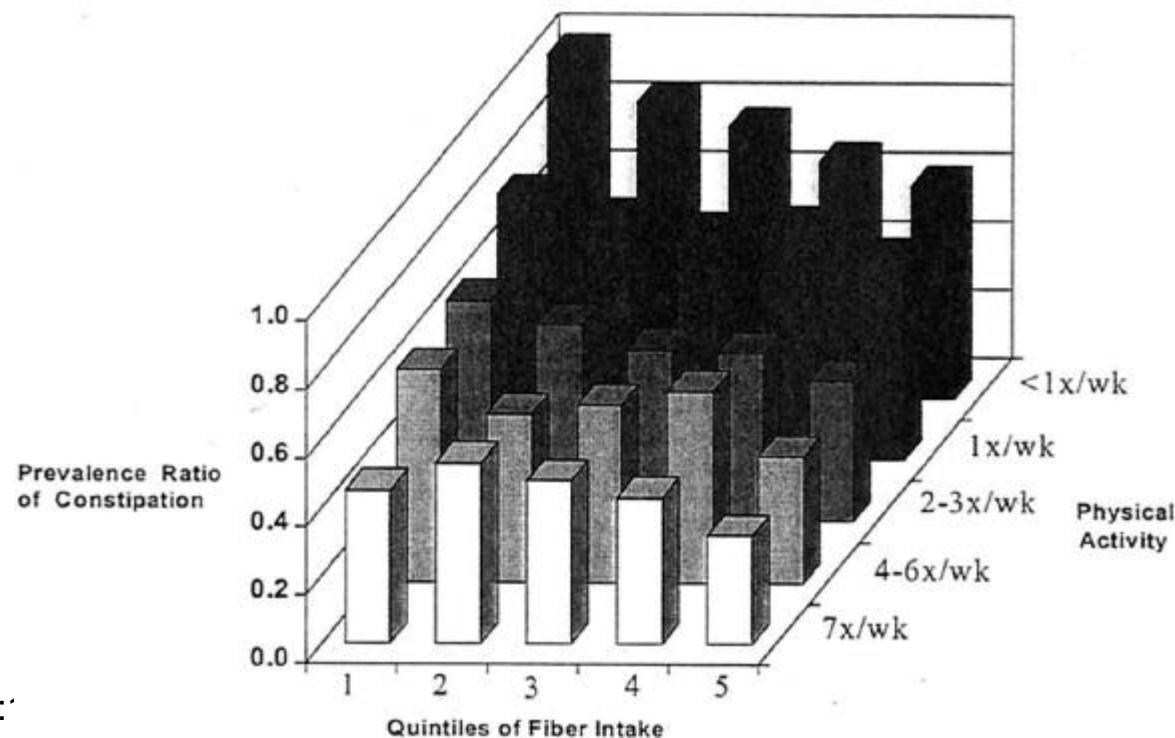
Young et al *Gastroenterol Nurs* 1998;21(4):156-61

## Effect of diet

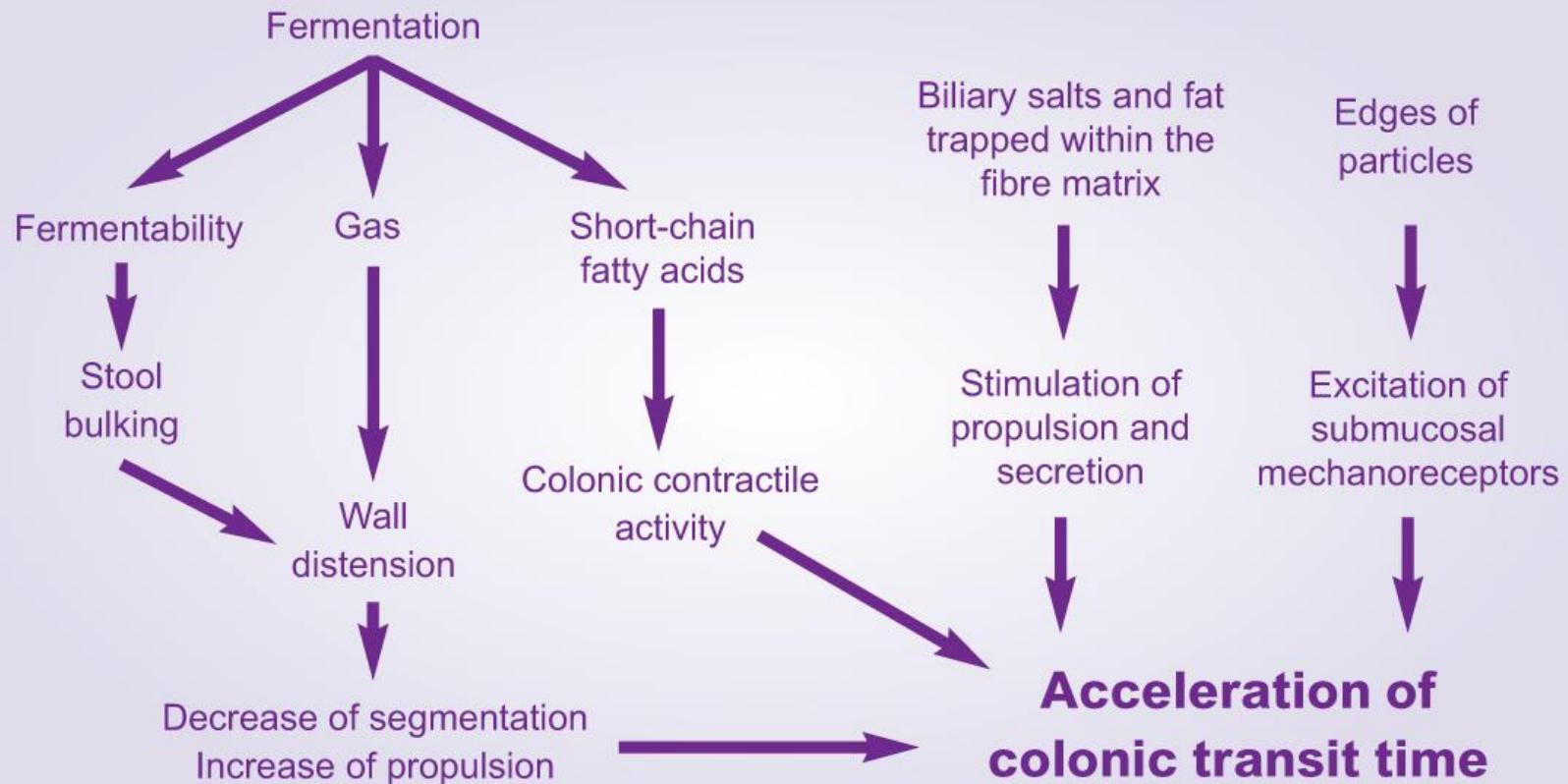
Nurses Health Study: 62,036 women aged 36-61 years  
3327 (5.4%) constipated ( <3 BM/wk)

Risk factors: Younger, lower BMI

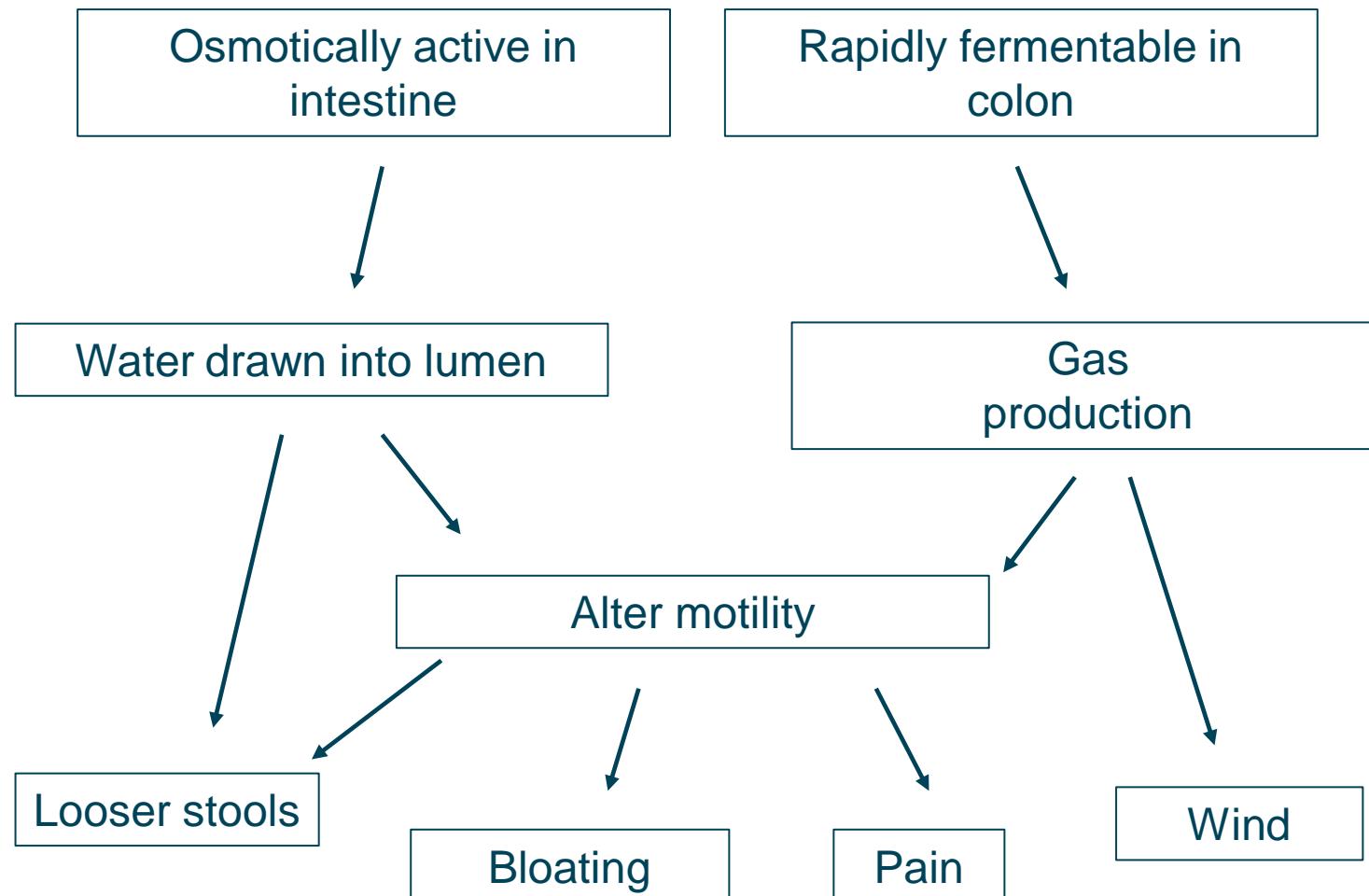
Protective factors: High fibre intake, regular exercise,  
coffee drinking, smoking, alcohol intake >7.7gm/day



# Not all patients benefit from increasing fibre intake

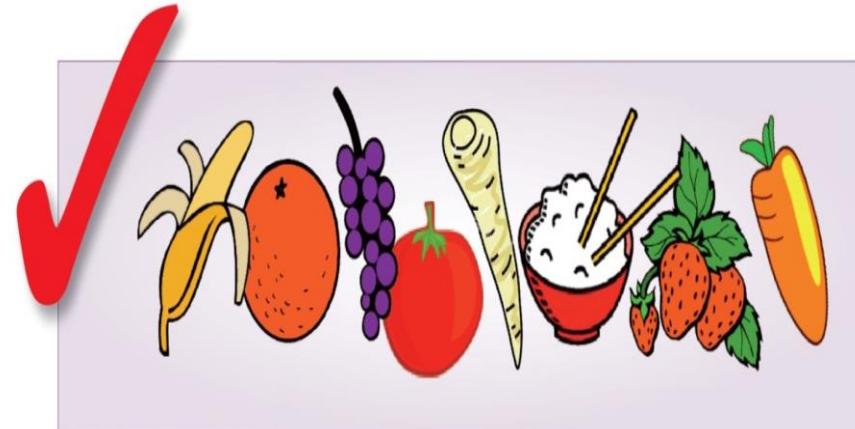


# FODMAPs: defined by function not biochemistry



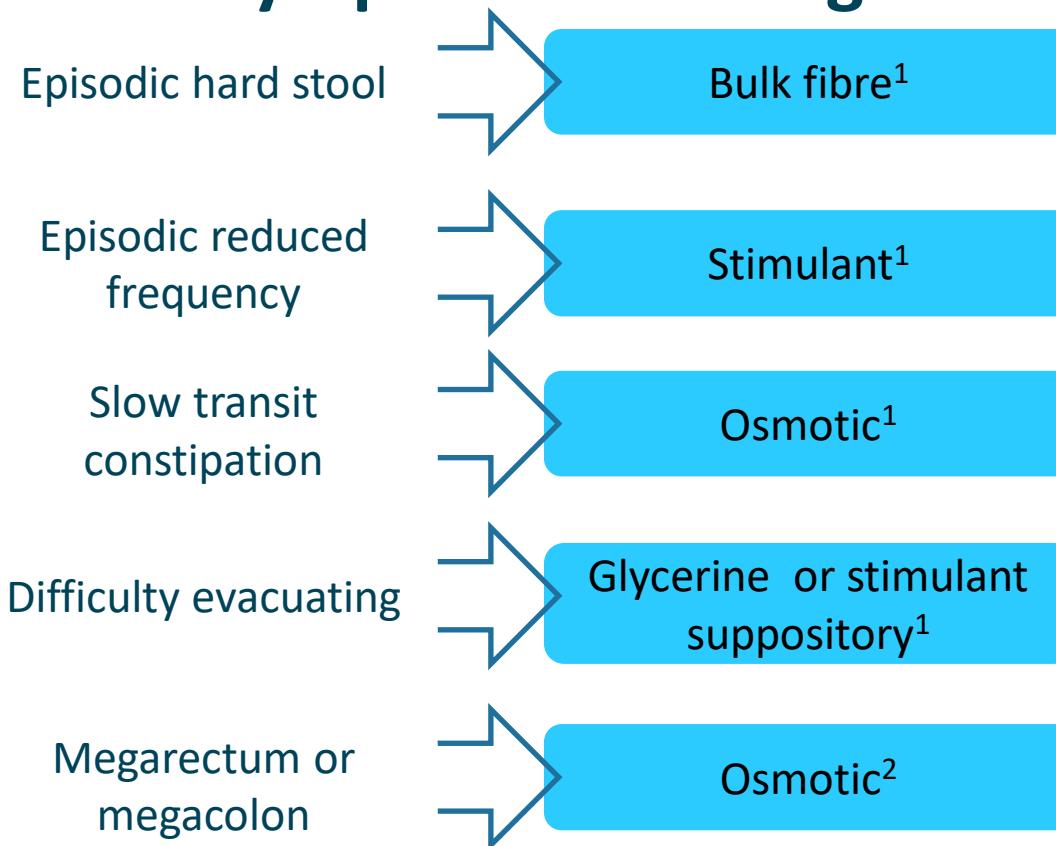
# Low FODMAPS vs Standard diet

| Symptom                   | Group    | Improved   | P*     |
|---------------------------|----------|------------|--------|
| Bloating                  | Standard | 17/35 (49) | 0.002  |
|                           | FODMAP   | 32/39 (82) |        |
| Abdominal pain/discomfort | Standard | 20/33 (61) | 0.023  |
|                           | FODMAP   | 29/34 (85) |        |
| Flatulence/wind           | Standard | 14/28 (50) | 0.001  |
|                           | FODMAP   | 33/38 (87) |        |
| Diarrhoea                 | Standard | 18/29 (62) | 0.052  |
|                           | FODMAP   | 30/36 (83) |        |
| Constipation              | Standard | 10/22 (45) | 0.161  |
|                           | FODMAP   | 10/21 (67) |        |
| Nausea                    | Standard | 4/14 (29)  | 0.04   |
|                           | FODMAP   | 10/15 (67) |        |
| Energy levels             | Standard | 11/30 (37) | 0.042  |
|                           | FODMAP   | 20/32 (63) |        |
| Composite score           | Standard | 19/39 (49) | <0.001 |
|                           | FODMAP   | 37/43 (86) |        |



n=82, unclear duration

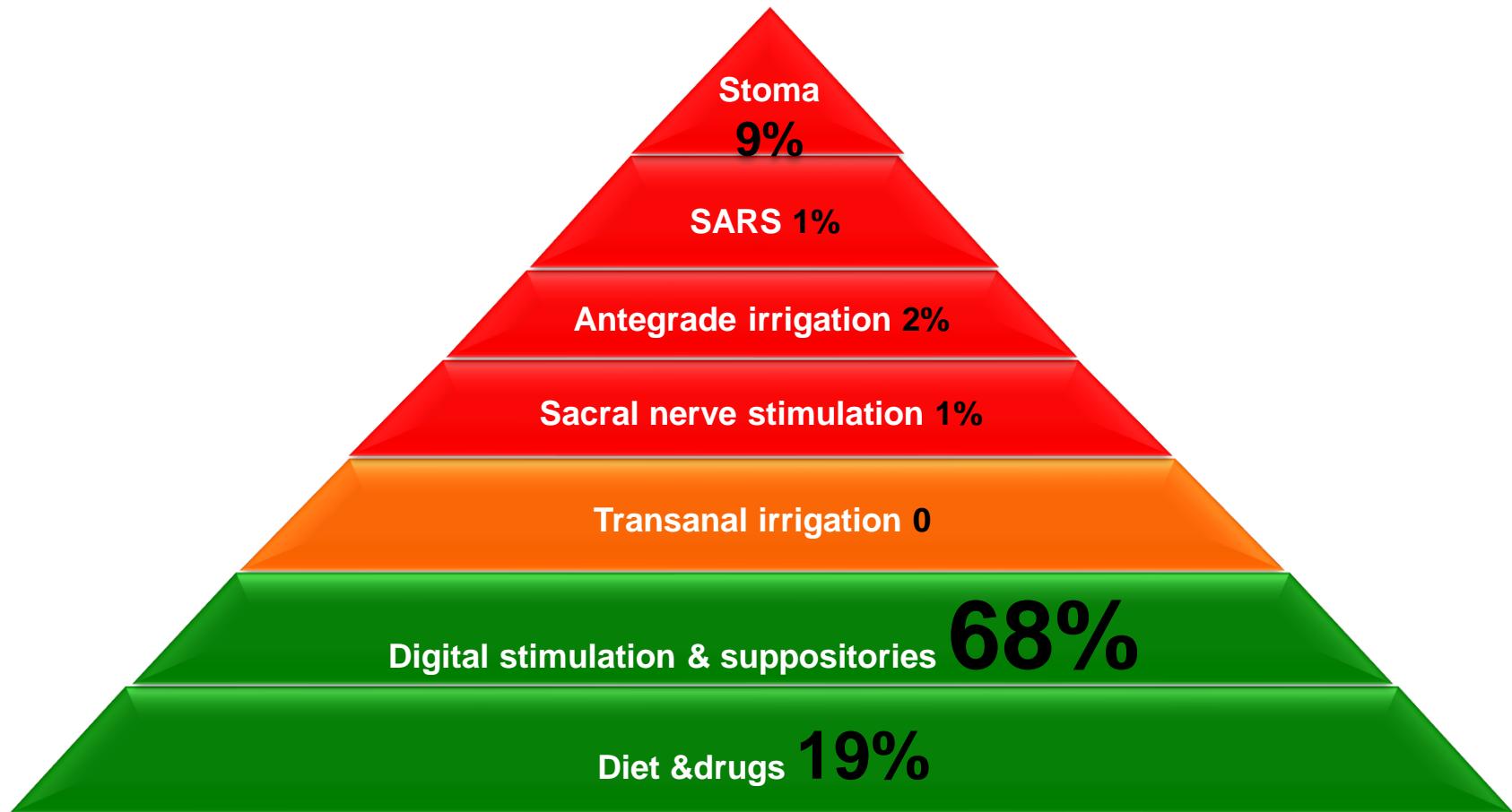
# Summary: Tailoring laxatives to the patient, based on their symptoms and diagnosis



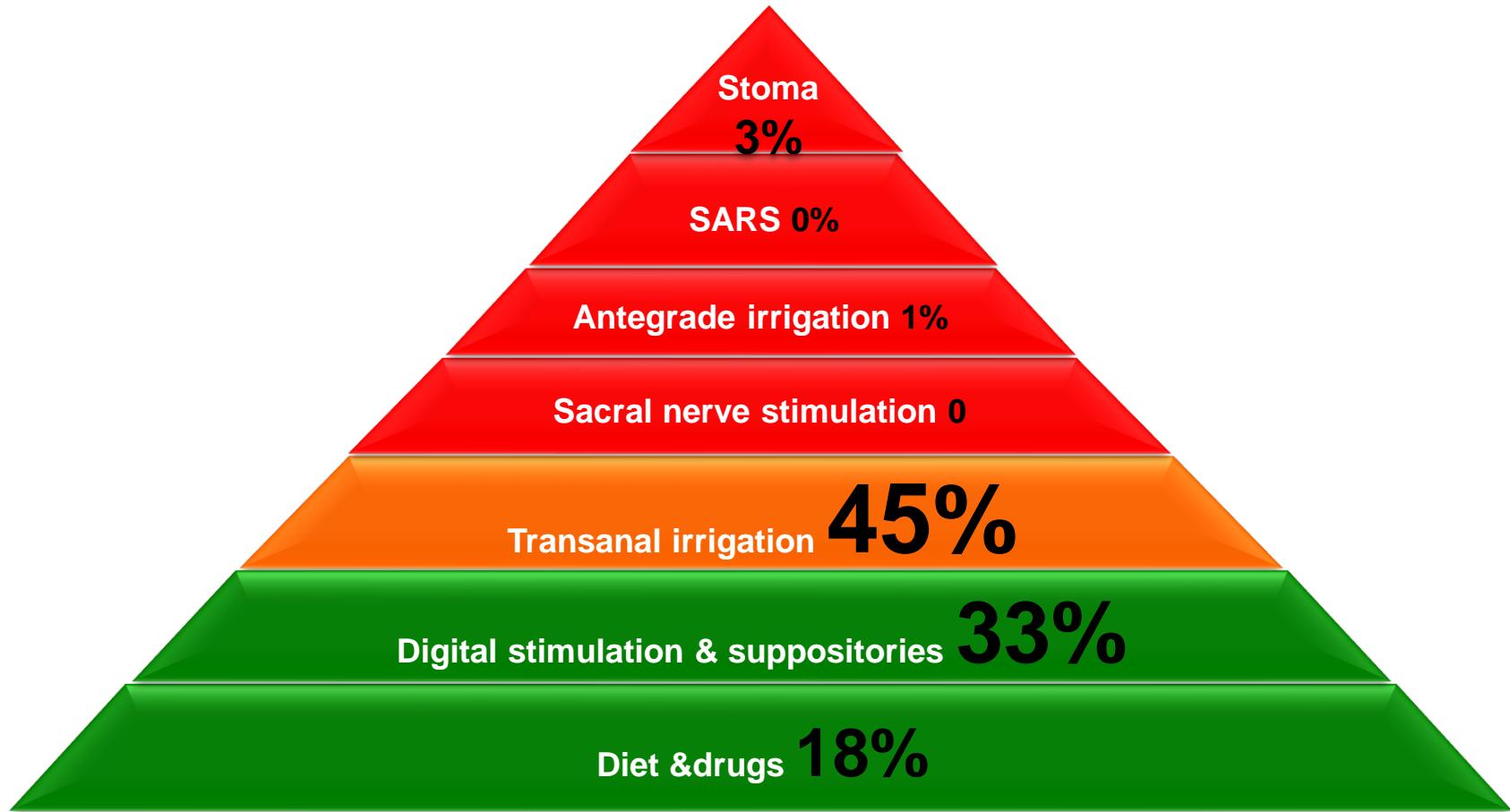
If no improvement:

- Increase dose<sup>1</sup>
- Rational combination e.g.
  - Stool softener and stimulant laxative<sup>3,4</sup> or
  - bulking agent<sup>1</sup>

# Management of neurogenic bowel dysfunction 2007



# Management of neurogenic bowel dysfunction 2017



# PRESSURE CONSTANT

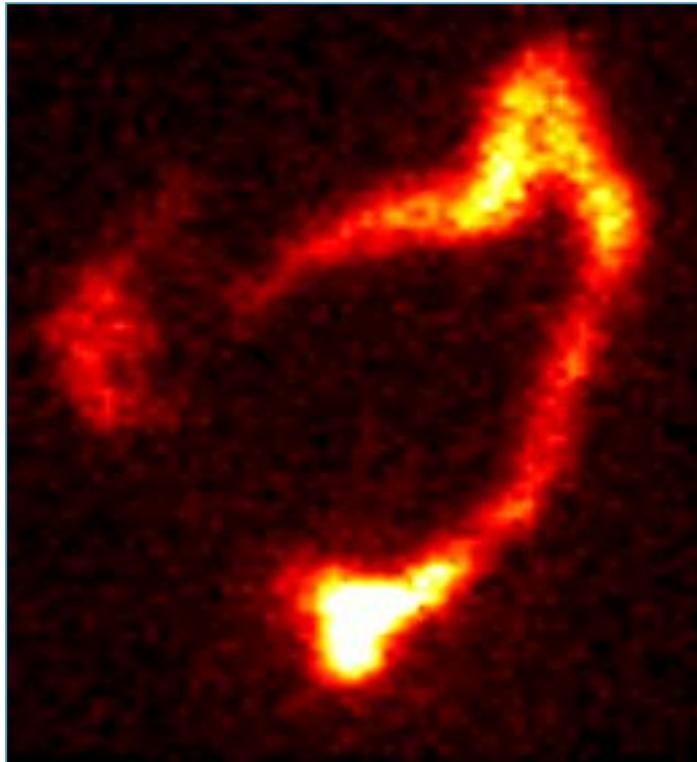


# PRESSURE VARIABLE

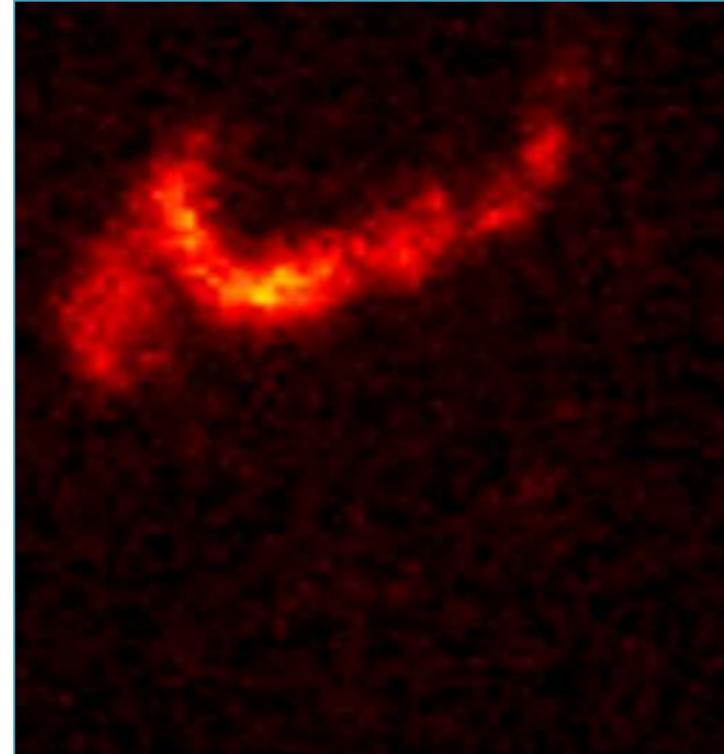


# Transanal irrigation

**Before irrigation**

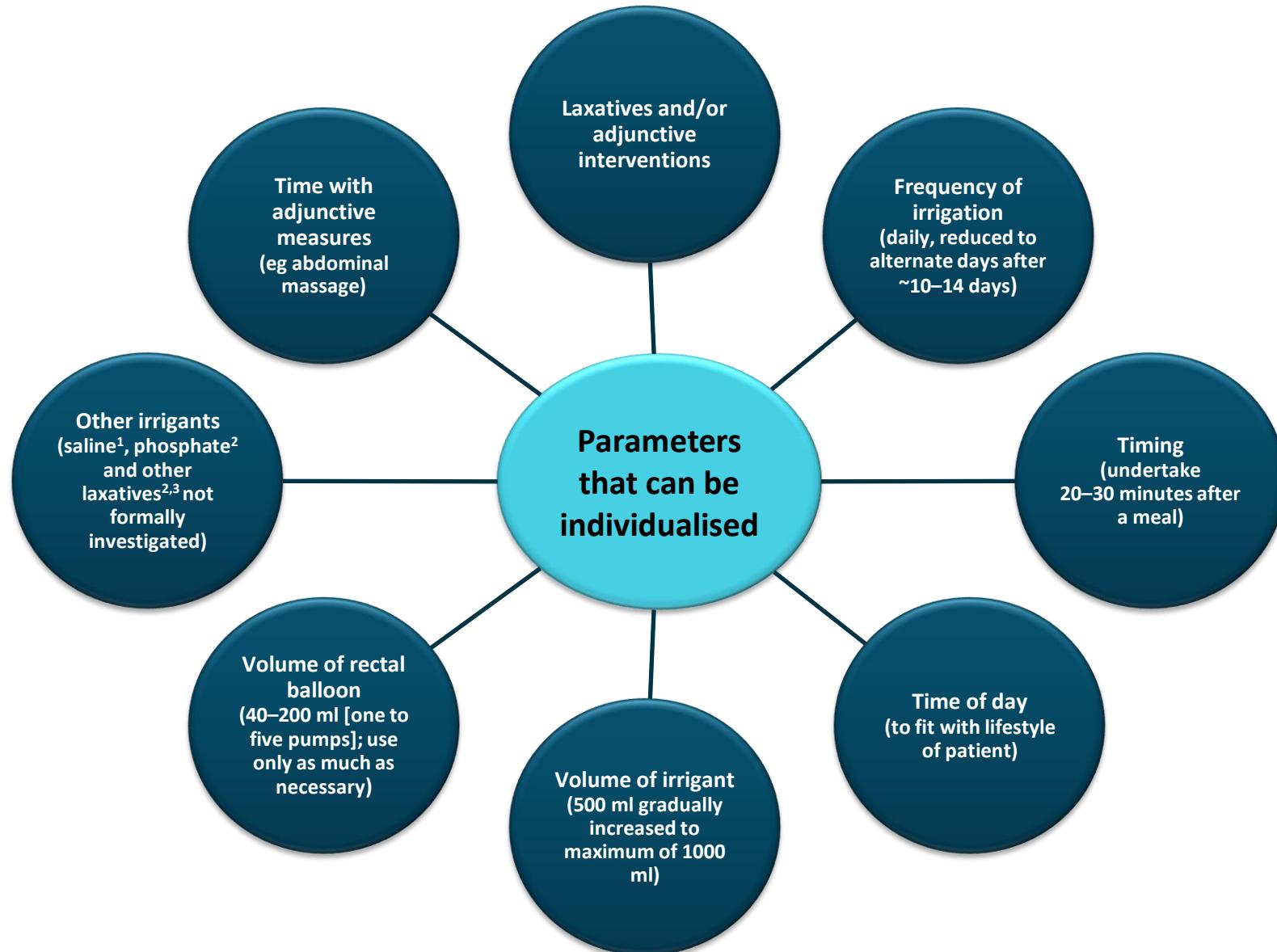


**After irrigation**

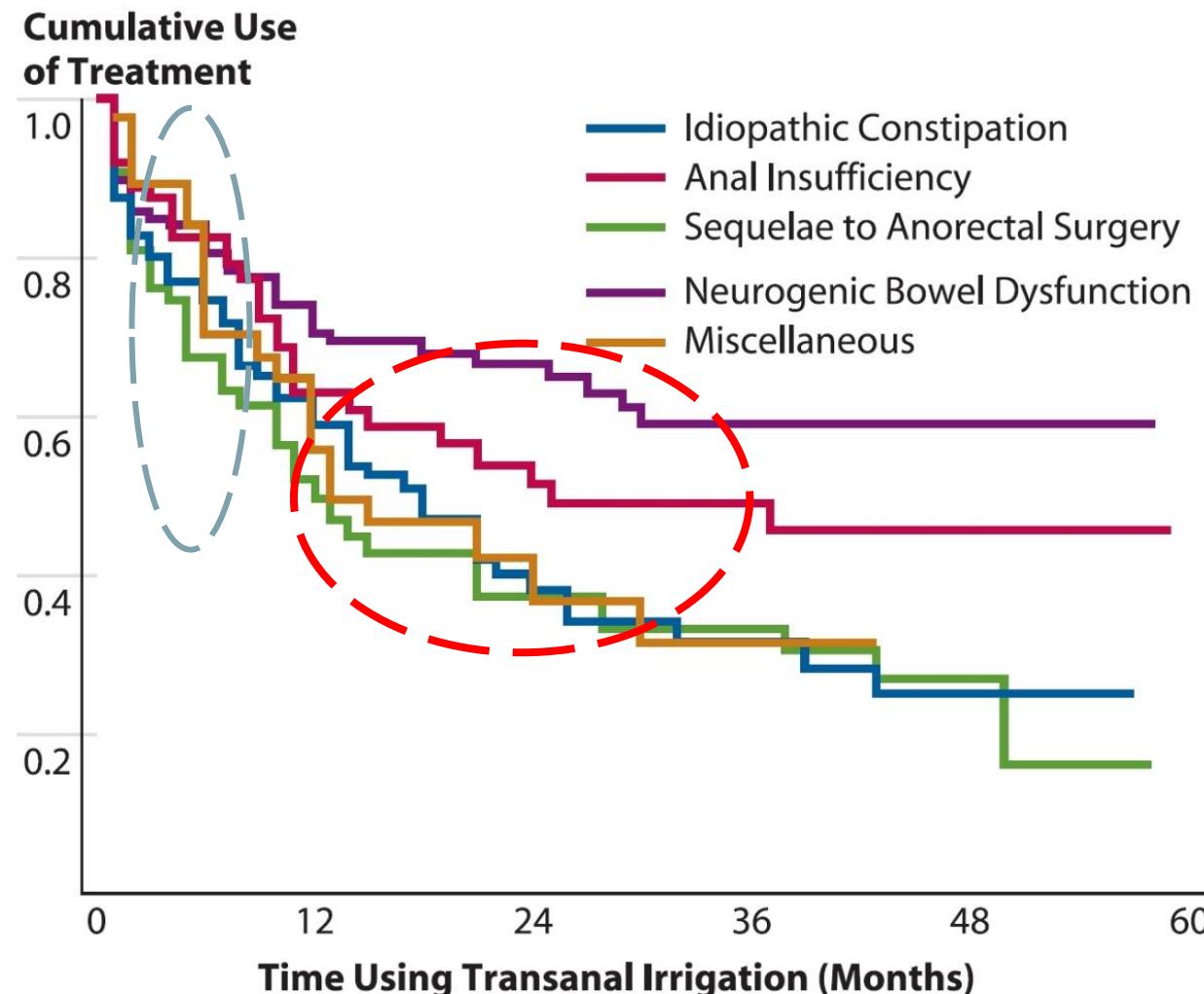


Anterior view of the  $^{111}\text{In}$ -labeled bowel content before washout (A) and after (B): the colon is empty up to the left colic flexure

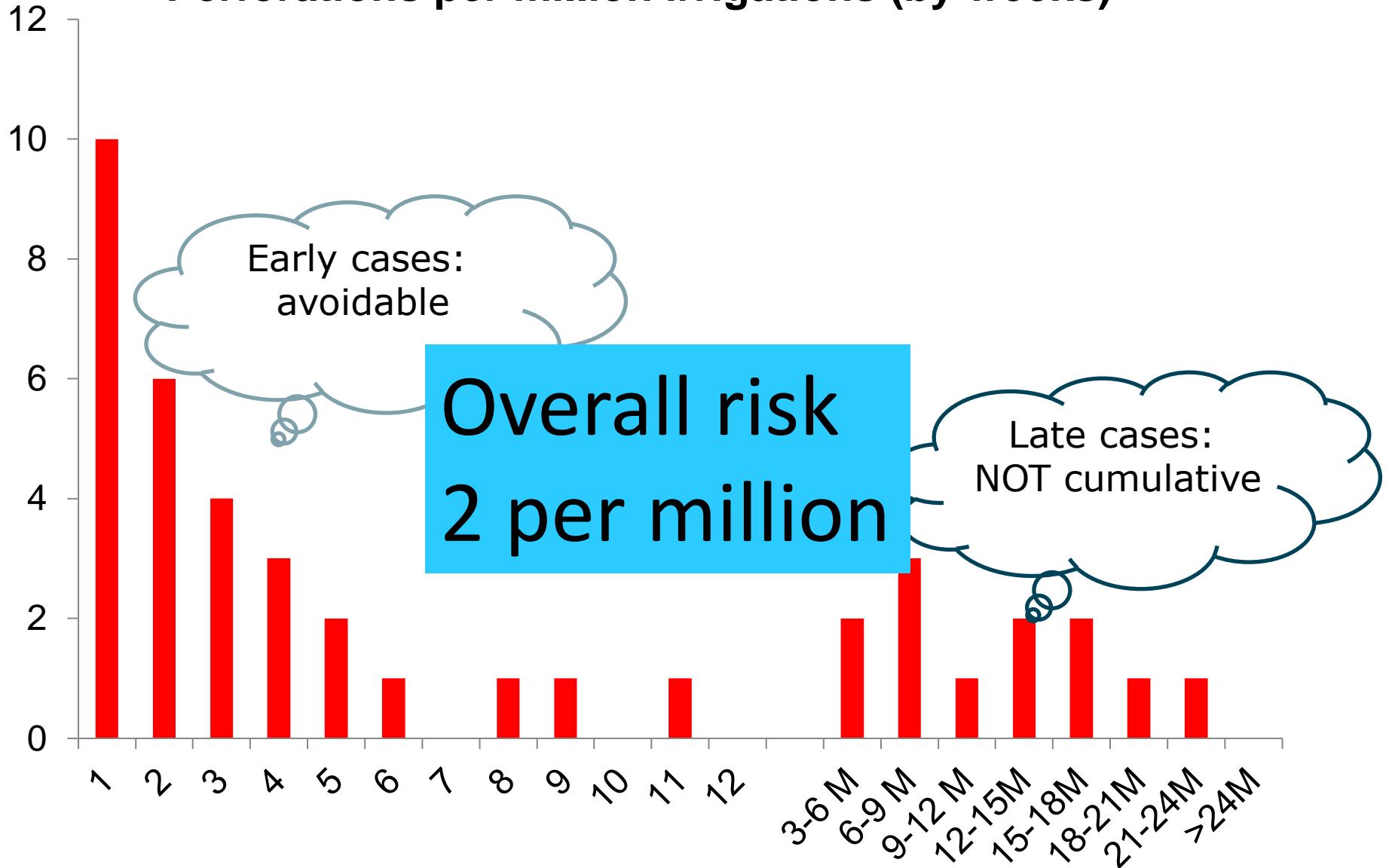
Christensen P et al. Dis Colon Rectum 2003; 46:68-76



# Adherence with transanal irrigation



## Perforations per million irrigations (by weeks)



# April 2018: NICE appraisal

## 1 Recommendations



Next &gt;

- 1.1 The case for adopting Peristeen for transanal irrigation in people with bowel dysfunction is supported by the evidence. Peristeen can reduce the severity of constipation and incontinence, improve quality of life and promote dignity and independence.
- 1.2 Peristeen may not be suitable for all people with bowel dysfunction. It may take several weeks before a person is comfortable with using Peristeen, and some people may choose to stop using it. Peristeen is therefore most effective when it is offered with specialist training for users, carers and NHS staff, and structured patient support.
- 1.3 Cost modelling for Peristeen is uncertain, but it is likely that Peristeen provides additional clinical benefits without costing more than standard bowel care.



# Work done by Physiology Unit team



## Aspire

SUPPORTING Spinal Injured  
PEOPLE



PARKINSON'S<sup>UK</sup>  
CHANGE ATTITUDES.  
FIND A CURE.  
JOIN US.

