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TULBURARI FUNCTIONALE DIGESTIVE POSTINFECTIOASE

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RISCURI GASTROENTERITA INFECTIOASA

- **Dupa gastroenterita acuta bacteriana, pana la o treime din pacienti vor avea tulburari functionale gastrointestinale prelungite**

- **O parte din cei afectati vor indeplini criteriile de diagnostic pentru PI-IBS (sindromul de intestin iritabil postinfectios)**

MAGNITUDINEA GASTROENTERITEI INFECTIOASE

- **Diareea infectioasa – una din cele mai frecvente afectiuni in lume:**
  - **1 bilion cazuri / an- la varste < 5 ani**
  - **Un copil are:**
    - **6-7 episoade /an tari in curs de dezvoltare**
    - **1-2 episoade /an tari dezvoltate**
- **Majoritatea indivizilor cu diaree bacteriana acuta se vindeca in mai putin de 5 zile**
- **7-31% vor dezvolta sindrom de intestin iritabil , postinfectios (PI-IBS)**

Epidemiologia diareei infectioase

- **Global in lume:**
  - **Media episoadelor infectioase anuale = 3**
  - **La copii:**
    - **Conditii sanitare precare: 8 episoade in primul an de viata, mai frecvent bacterii, paraziti**
    - **Conditii sanitare bune: episoade mai putine, probabil virale**
- **Anglia:**
  - **1 din 5 persoane pe an are un episod de diaree**
  - **Majoritatea cazurilor sunt neraportate**
  - **La copii mici: predomina infectiile virale**
  - **Infectiile bacteriene (Campylobacter)**
    - **grupa 30-39 ani – 16%**
    - **grupa 1-4 ani – 6,7%**

RISC MARE LA VARSTA MICA

- **UK – studiu enterite cu Campylobacter – incidenta 2 varfuri: 1-4 ani si 15-24 ani**

- **Tari in curs de dezvoltare**
  - **Infectii precoce (<2 ani)**
  - **Incidenta infectiilor simptomatice scade rapid la adult**

IBS - EPIDEMIOLOGIA IN LUME

- **Prevalenta IBS variaza intre 1,1% si 45%, dupa studii populationale in diverse tari**
- **Rata medie a prevalentei – 5-10% pentru multe tari europene, SUA si China**
- **Prevalenta foarte joasa Iran 5,8%, India 4,2%**
- **Tari dezvoltate din Asia – similar tarilor vestice**

- **IBS si Westernizare rapida:**
  - **Ameliorare igiena**
  - **Supraaglomerare**
  - **Stress**
  - **Modificari ale dietei**
- **Exemplu: prevalenta in Singapore in 10 ani de industrializare creste de la 2,3% la 8,6%**
- **Exista diferente**
  - **Intre tarile vestice si din tarile in curs de dezvoltare**
  - **In functie de varsta: grad mai mare de inflamatie la adult .**

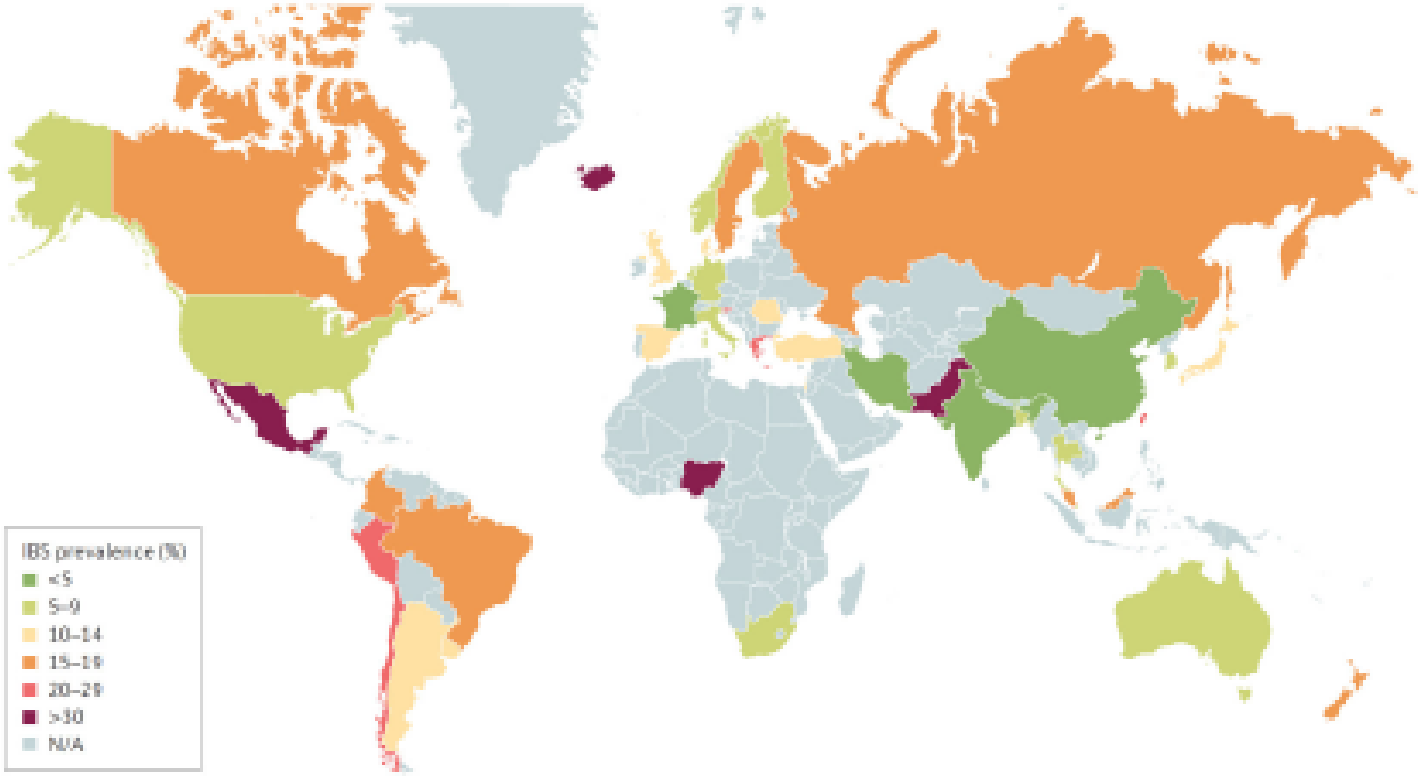


Figure 2. IBS prevalence in population studies around the world

Pooled prevalence data per country are colour-coded. Data from REF. 1 are supplemented by studies from another nine countries (see Supplementary information S1 (table)). IBS, irritable bowel syndrome; N/A, not applicable.

Enck et al, Nat Rev Dis Primers. 2016 ; 2: 16014. doi:10.1038/nrdp.2016.14.

Mecanismele gastroenteritei

- **Diareea infectioasa:**
  - **Creste secretia apoasa + electroliti in intestinul subtire**
  - **Scade absorbtia in intestinul subtire si intestinul gros**
- **Coexista doua mecanisme**
  - **Enterotoxine (Vibrio cholerae, E. coli) – secretie profuza crescuta**
  - **Scaderea absorbtiei intestinale – leziuni de mucoasa provocate de germeni enteroinvazivi (Salmonella, Shigella, Yersinia)**

Infectiile bacteriene invazive

Leziuni celulare

- Stimularea raspunsului imun
- Activarea nervilor enterici
- Activarea celulelor mastocitare

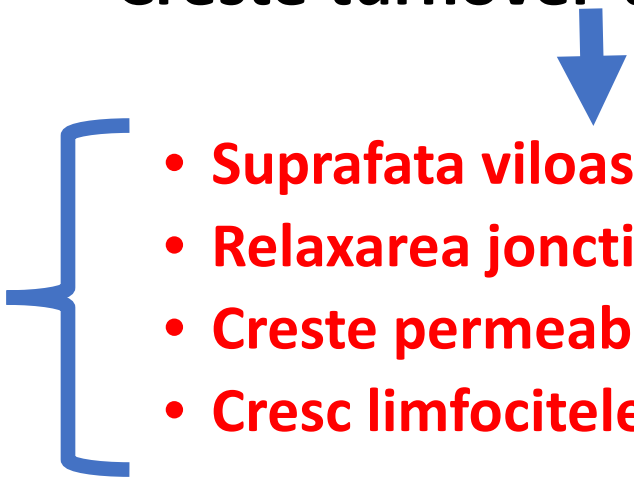
- **Provoaca infiltrat inflamator acut:**
  - Eliberare mediatori proinflamatori
  - Stimulare secretie

- **Clinic ulceratii, sangerare**

Infectii virale

- Diaree apoasa de scurta durata
- Leziuni tisulare minime

- Ex.: infectia cu Norovirus:
  - Creste turnover-ul enterocitelor si apoptoza



- Suprafata viloasa redusa 50%
- Relaxarea jonctiunilor stranse
- Creste permeabilitatea
- Cresc limfocitele intraepiteliale (nu polinucleare)

Tulburarile intestinale functionale postinfectioase depind de

- Extinderea si distributia inflamatiei
- Durata si varsta (copil, tanar, adult)
- Factori psihologici
- Factori imunologici

Rol microbiota intestinala in IBS

- **Copilul sanatos:**
  - **Difera intre indivizi**
  - **Relativ stabila la aceeasi persoana**
  - **Microbiota instabila in IBS prin:**
    - **Terapie cu antibiotic(in infectia cu salmonella si diareea calatorului)**
    - **Modificari ale dietei**
- **Pacientii care au primit antibiotice:**
  - **simptome intestinale se amplifica de 4 ori la 4 luni dupa tratament**
  - **Folosirea antibioticelor – factor de risc in IBS**

Diareea acuta

- Scade cantitatea de anaerobi
- Acizi grasi cu lant scurt diminuati
- pH crescut

Permit poluarea bacteriana

Tulburari functionale intestinale

Sindromul de intestin iritabil post infectios (PI-IBS)

- **Dupa diareea acuta majoritatea cazurilor se vindeca complet**
- **25% - modificari persistente in functia intestinala**
- **si 7-36% indeplinesc criterii Roma III pentru IBS**

Definitie

- **PI-IBS se caracterizeaza prin**
  - **Debut brutal al simptomelor (diagnostic IBS Roma IV)**
  - **Simptome care apar dupa un episod de GEA infectioasa :**
    - **Diaree**
    - **Varsaturi**
    - **Febra**
    - **Coprocultura pozitiva (anterior)**

Table 1 Diagnostic criteria for irritable bowel syndrome (IBS) according to Rome IV criteria.

Diagnostic criteria for IBS

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria*:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

*criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

IBS subtypes

IBS can be further classified based on predominant bowel habits. IBS subtypes can be only confidently established when the patient is evaluated off medication used to treat bowel habit abnormalities:

- IBS-C: constipation predominant IBS)
- IBS-D: diarrhea predominant IBS
- IBS-M: mixed IBS, where both diarrhea and constipation are present
- IBS-U: unclassified IBS

Example of subtype IBS-C: more than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7.

Incidenta PI-IBS

- **De peste 45 de ani (1962) Chaudry si Truelove au evaluat 130 cazuri IBS din care 26% dupa episod dizenteric**
- **PI-IBS apare dupa infectii bacteriene cu**
  - **Salmonella**
  - **Campylobacter jejuni**
  - **Shigella**

Incidenta variabila: 4-32%

Table 2. Incidence of postinfectious irritable bowel syndrome (IBS).

Study (year)	Duration of follow-up	No. of patients with acute infectious gastroenteritis	Incidence of postinfectious IBS, %
Borgaonkar et al. [9] (2006)	3 months	191	4
Dunlop et al. [11] (2003)	3 months	747	14
Gwee et al. [12] (1996)	3 months	75	27
Gwee et al. [13] (1999)	12 months	94	23
Ilnyckyj et al. [14][a,b] (2003)	3 months	109	4
Ji et al. [15][a] (2005)	12 months	101	15
Marshall et al. [16][a] (2006)	2–3 years	1368	30
McKendrick and Read [17] (1994)	12 months	38	32
Mearin et al. [18][a] (2005)	12 months	467	12
Neal et al. [8] (1997)	6 months	386	6
Neal et al. [1] (2002)	6 years	192	4
Okhuysen et al. [19] (2004)	6 months	97	7
Parry et al. [20][a] (2003)	6 months	128	14
Rodríguez and Ruigómez [21][a] (1999)	12 months	318	4
Stermer et al. [22][a,b] (2006)	6 months	483	14
Thornley et al. [23] (2001)	6 months	188	9

[a] Study with control group.
[b] Study without pathogen identification.

Studii care includ grup de control

incidenta IBS dupa enterite bacteriene acute:
10-15%

- O metaanaliza (2006) – 8 studii Halvorsth et al. –
  - prevalenta IBS = 9,8% dupa gastroenterite infectioase, fata de 1-2% control
- 3 studii – risc PI-IBS la bolnavi cu diareea calatorului
  - Ilnicky et al. (2003) – 109 adulti sanatosi turisti din SUA, Canada in tari in curs de dezvoltare
    - 44% diaree calator, din care 4,2% IBS la 3 luni, fata de 1,6% grup control
  - Okhuysen et al. (2004) – 97 studenti stagiu Mexic 5 saptamani
    - 10% diaree calator, din care 17% IBS la 6 luni
  - Stermer et al. (2006) – 14% IBS dintre bolnavii cu diareea calatorului, fata de 2,4 % grup control

Alte raportari(dupa etiologie)

- **Diverse studii raporteaza**
  - **Incidenta foarte crescuta de PI-IBS = 36% in episod Walkerton – prin infectie severa combinata (C. jejuni + E. coli O157)**
  - **Alta serie – incidenta crescuta = 31% la pacienti spitalizati Boli Infectioase cu forme severe de boala**
  - **Studiu UK – incidenta 7%**
- **PI-IBS asociat cu Shigella**
  - **Tulburari functionale 22,4%, control 7,4%**
  - **PI-IBS 8,1%, control 0,8%**
- **PI-IBS asociat cu Salmonella**
  - **Studiu populatie batrani cu infectie cu Salmonella**
    - **PI-IBS = 31%**
  - **Studiu prospectiv timp de 1 an, risc relativ:**
    - **Dispepsie functionala 5,2%**
    - **PI-IBS 7,8%**
- **PI-IBS asociat cu Campylobacter jejuni**
  - **PI-IBS = 9-13%**

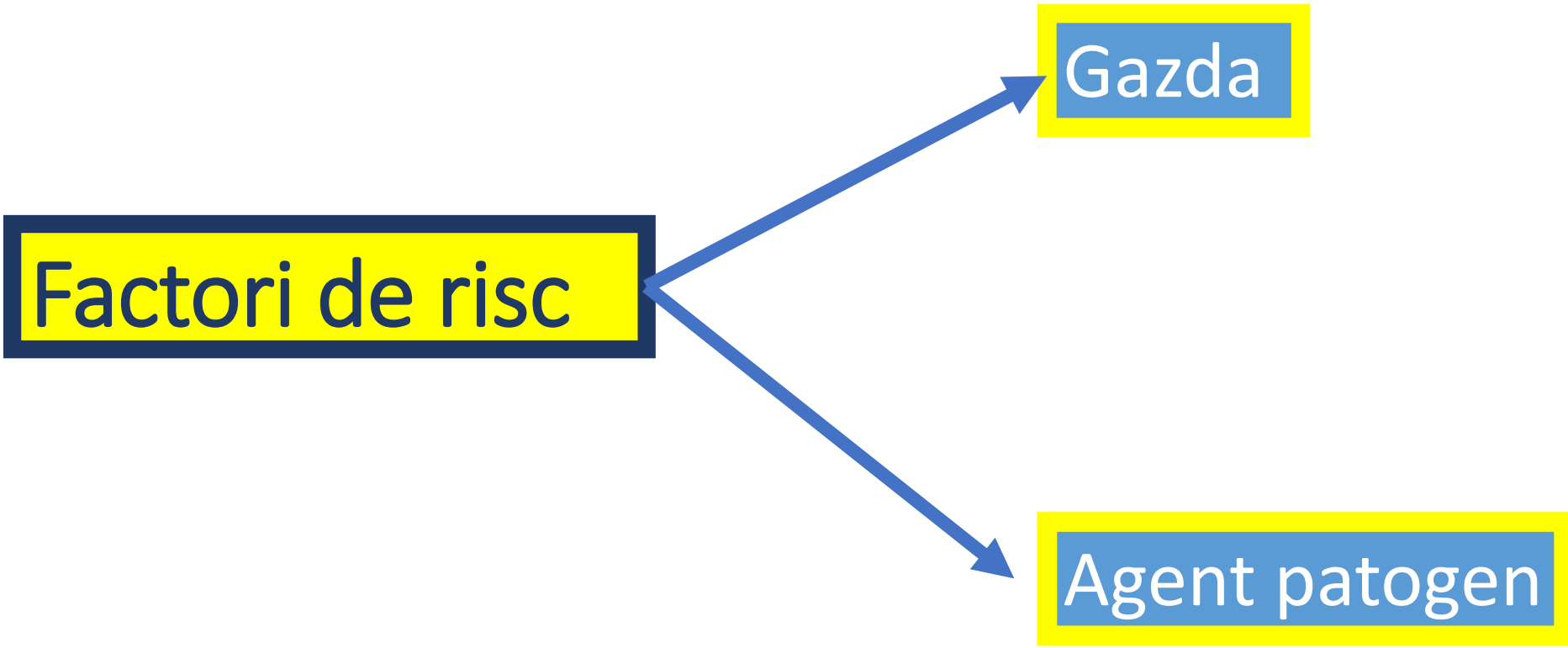
ALTE ETIOLOGII-prevalenta variabila

- PI-IBS poate sa apara dupa infectii cu
  - protozoare
  - paraziti
  - virusi
- Exemple
  - PI-IBS asociat cu infectii cu Trichinella britow – prevalenta 13,9%
  - PI-IBS asociat cu infectii virale – se sugereaza ca ar putea da IBS – fenomen tranzitor, leziuni reziduale putine
    - Studiu episod gastroenterite presupus virale:
      - 107 bolnavi cu GEA
      - 23,6% = PI-IBS la 3 luni
      - 3,4% grup control
  - PI-IBS asociat cu Norovirus
    - Episod diareic de origine alimentara cu Norovirus
      - PI-IBS = 23,6% la 3 luni
      - Control = 3,4%

ETIOLOGII-LOCALIZARE

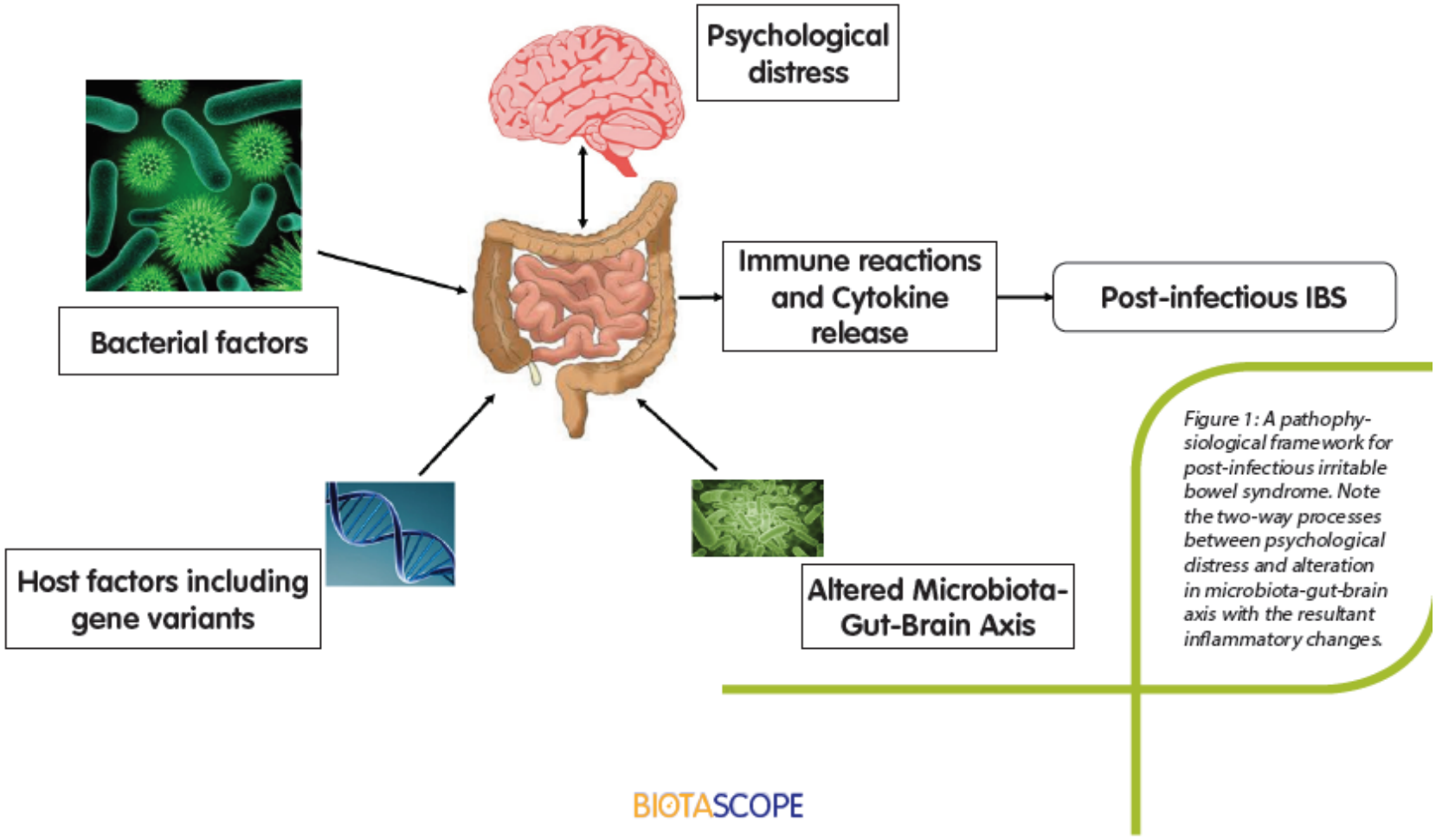
Simptomele postinfectioase par sa indice segmentul afectat:

- **Giardia intestinalis = infectie duodenala – dispepsie postinfectioasa**
- **Shigella – inflamatie colonica distala insotita:**
  - **diaree**
- **Salmonella si C. jejuni – intestin mediu – produce**
  - **dispepsie postinfectioasa**
  - **IBS**


Gazda
Factori de risc
Agent patogen

A. Factori legati de gazda

- **Predispozitie familiala pentru IBS**
  - **Recent se descrie contributie genetica**



Lee et al., Current Gastroenterology Reports · September 2015

FACTORI GENETICI

- **Studiu Walkerton – 3 variante gene candidat pentru PI-IBS**
  - **TLR9**
  - **Cadherina 1 (CDH 1)**
  - **Interleukina 6**
- **Alte studii: TNF alfa, SNP_S (Single mediated polymorphism)**

- **Sex feminin:**
  - **nu exista dovezi privind diferentele in raspunsul imun privind infectia, numar imunocite rectale**
  - **risc crescut PI-IBS: diferente in raspunsul creierului la durere**
- **Factori psihosociali**
  - **Stress puternic**
  - **Anxietate**
  - **Hipocondrie**
  - **Depresie**
  - **Nevroza**
  - **Evenimente amenintatoare de viata**

- **1. PI-IBS la copil**

  - **Tulburarile functionale intestinale postinfectioase sunt frecvente la copil**
    - **Studiu SUA – IBS 14% liceu; 6% gimnaziu**

      Din 88% copii cu coproculturi pozitive infectioase 36% au avut tulburari gastrointestinale functionale fata de martor 11%, mai mare ca la adulti!!!
    - **Sexul feminin nu este factor de risc la copil**

- **PI-IBS la adult**
  - **Varsta mai tanara – risc crescut PI-IBS**
  - **Varsta mai inaintata – factor predictiv pentru incidenta mai mica - risc relativ 0,36 datorita:**
    - **Declin raspuns imun la persoane in varsta**
      - **Au mai putine imunocite in mucoasa rectala**
      - **Limfocite mai putine in lamina propria care raspund la antigene**
      - **Acestea reduc riscul initierii inflamatiei de grad mic**
    - **Adulti protejati de imunitatea capatata in copilarie**

B. Factori legati de agentul patogen

Severitatea si durata infectiei gastrointestinale

- peste trei saptamani – 11,4%, risc de trei ori mai mare.
- in enterita Shigella – infectie peste 14 zile,
  risc 4,6 mai mare comparativ cu durata sub 8 zile

  Durata sub o saptamana – riscul creste doar de 2 ori

ROLUL ENTEROTOXINELOR

Toxicitatea infectiei

- **Patogeni care secreta toxine: Campylobacter jejuni, E. coli enterotoxigen, E. coli O 147 producator shiga-toxina**
- **Supernatantul din cultura de Campylobacter jejuni determina toxicitatea in vitro**
- **Riscul de dezvoltare a tulburarilor gastrointestinale este de 12,8 comparativ cu cei fara toxina**

Natura germenului influenteaza riscul:

- **Infectii Campylobacter, Shigella determina leziuni de mucoasa mai severe si durata mai mare de boala fata de Salmonella**
  - **4,2% PI-IBS infectie Campylobacter**
  - **2,6% PI-IBS infectie Salmonella**
- **Studiu Zanini (Italia) – GEA Norovirus**
  - **13% dezvolta PI-IBS**

Particularitatea inflamatiei in PI-IBS

- **1. Cresterea numarului limfocitelor – limfocite T**
  - **Colon – IBS**
  - **Rect – PI-IBS**
- **2. Hiperplazia celulelor enterocromafine (CE)**
  - **La om – dupa infectie C. jejuni**
  - **La soarece – dupa infectie Trichinella spiralis**
  - **Cresterea nivelului 5HT (serotonina) postprandial**
    - **5HT – actiune secretorie, prokinetica → scaun diareic PI-IBS**

INFLAMATIE-COMPONENTA IMUNA

- **3. Cresterea numarului de celule mastocitare**
    - **Ileon terminal – infectie Shigella, bolnavi IBS-D**
    - **Rect – bolnavi PI-IBS**
  - **Mastocite – sursa mediatori: proteaze, histamina, serotonina**
- **4. Eliberare citokine pro inflamatorii**
  - **IL-6, IL-8, TNFα, IL-1β**

Cauzele inflamatiei persistente a mucoasei in PI-IBS

- **De ce inflamatia la unii pacienti persista si la altii nu?**

Factori predispozanti pentru raspunsul inflamator exagerat si prelungit

1. Genetici

- **Proportie mare dintre bolnavii cu IBS au crescut polimorfismul heterozigotilor TNFα G/A**

Table 1 Mucosal cellular changes, genes, cytokines (serum & mucosal), and permeability changes in selected bacterial, parasitic, and unspecified pathogen related PI-IBS

Pathogen	Mucosal cellular changes	Genes	Serum cytokines	Permeability	Mucosal cytokines
Bacterial					
Campylobacter jejuni	1. ↑ rectal EC cells, ↑ LP T lymphocytes[27] 2. ↑ rectal EC cells, ↑ LP CD3, CD8 T lymphocytes, ↑ CD8 IELs, ↑ calprotectin-ir cells[31]	1. ↑ *CCL11, CCL13, Calpain 8, GABRE*; ↓ *NR1D1, GPR161*[33] 6 months postenteritis, not PI-IBS	1. ↑ PBMC TNF-α, no difference IL-10, IL-1β; ↑TNF-α rs1800629[33] 2. No difference in IL-18, INFγ polymorphisms[36]	1. ↑ 0–6 h L/M ratio (initially, 12 weeks) not PI-IBS)[31] 2. ↑ 3–6 h Cr^{51} EDTA excretion (initially, 6 months) postenteritis, not PI-IBS[33]	1. No differences in IL-10, TNF-α and IL-1β[33]
Mixed infections	-	1. ↑*TLR9* (rs 5743836), *IL6* (rs206986), *CDH1*(rs16260)[11]	1. ↑ PBMC TNF-α, IL-1β, IL-6, LPS-stimulated IL-6[73]	1. ↑ L/M ratio[71]	1. ↑ rectal mucosal IL-1β[72]
Shigella	1. ↑ Ileal MC, ↑ NSE, substance P, 5-HT-ir nerve fibres[65] 2. ↑ 5-HT-ir EC cells, PYY-ir EC cells, IELs, CD3, CD8 lymphocytes, MC, CD68 cells; ↓ Calprotectin-ir macrophages[66]	-	-	-	↑ Terminal ileal and rectosigmoid IL-1β[65]
Parasitic					
Giardia lamblia	1. ↑ PI-IBS/FD: ↑ CCK-ir cells, ↓EC cells; no difference in duodenal 5-HT or 5-HIAA[58]	-	-	-	-
Unspecified	1. ↑ MC PAR_2 mRNA expression by PI-IBS supernatants[74] 2. ↓ colonic mucosal PAR_4, unchanged PAR_2 expression[75] 3. ↑ EC cells, ↑ LP T lymphocytes. No difference in IELs & MC[76] 4. ↑ mean chronic inflammatory cells in PI-IBS[77]	-	1. TNF-α (G/A, high producer) more prevalent in IBS (both PI and non-PI-IBS) compared to controls. No differences in IL-10 genotype[78]	1. ↑ 0–3 h Cr^{51} EDTA excretion[80]	-

MC: Mast cells; LP: Lamina propria; EC: Enterochromaffin cells; IELs: Intraepithelial lymphocytes; PBMC: peripheral blood mononuclear cell; PAR: Protease activated receptor.

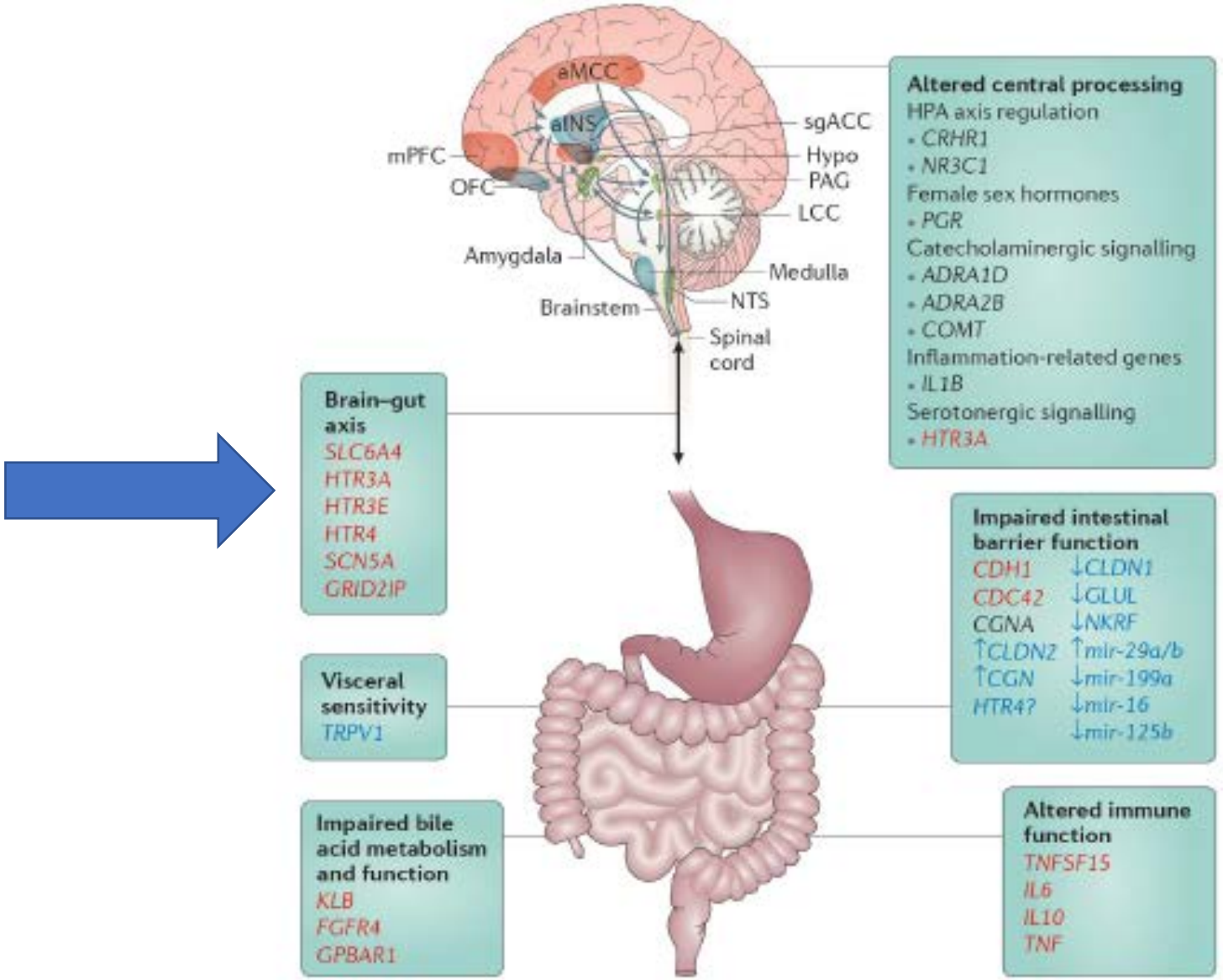


Figure 6. Summary of the genetic findings associated with different pathophysiological mechanisms underlying IBS

2. Microbiota

- **Alterarea microbiotei in IBS**
  - **Date indirecte – proteaze fecale crescute de origine bacteriana in IBS-D**
  - **Proteazele cresc sensibilitatea viscerala (la soarece) via PAR 2 (receptor 2 protease activator)**

CRESTEREA SENSIBILITATII VISCERALE

- **3. Cresterea numarului de celule mastocitare**
  - **Dovada – crescute la om in IBS**
  - **Situate langa nervii aferenti**
  - **Corelate cu severitatea durerii**

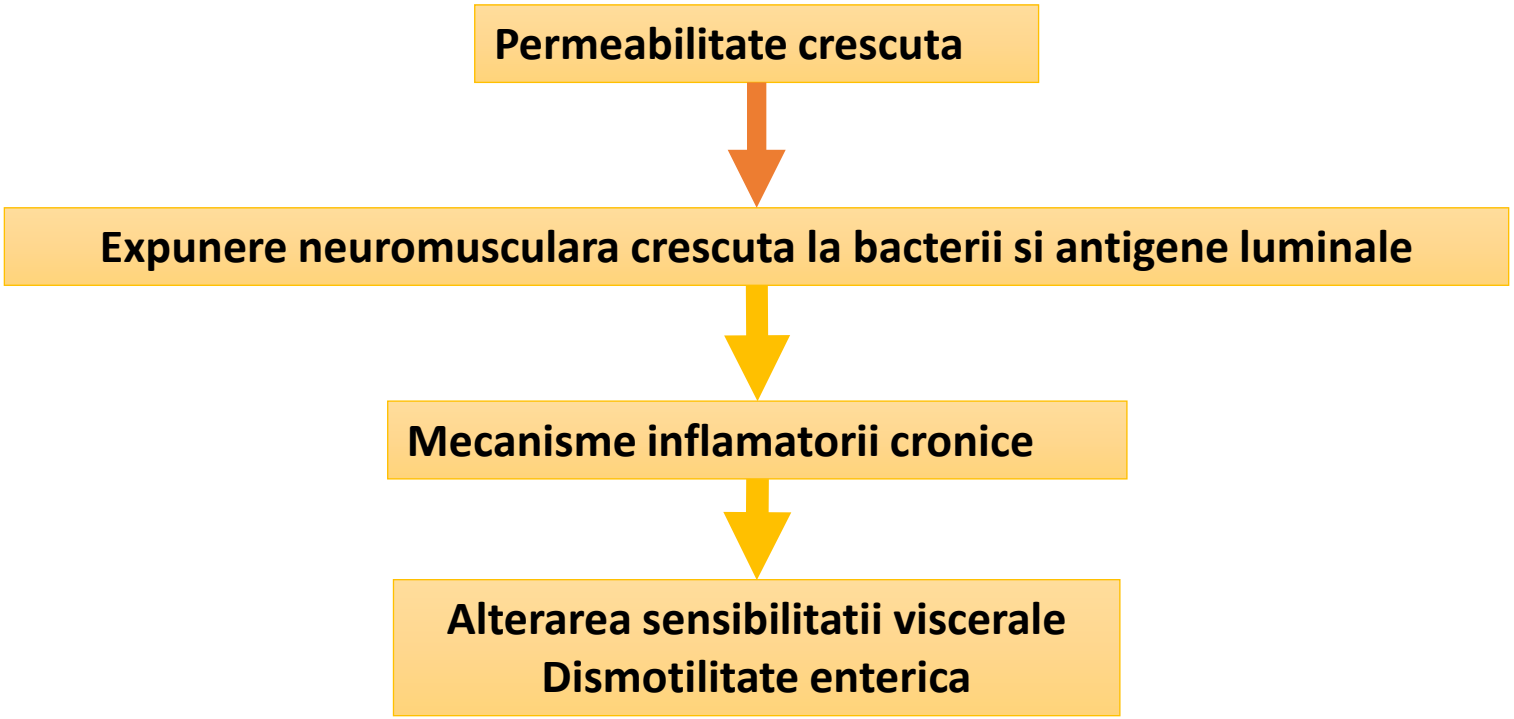
- **Sursa de proteaze – cresc sensibilitatea viscerala**
- **Sursa mediatori (histamina, serotonina) – excita nervi senzoriali enterici – creste sensibilitatea viscerala (soarece)**

Caracteristici fiziopatologice

- **1. Cresterea numarului celulelelor inflamatorii**
  - **a. Hiperplazia celulelor enterocromafine**
  - **b. Creste numarul de limfocite T intraepiteliale si lamina propria**
- **2. Eliberare de citokine (LT)**
  - **In PI-IBS eliberare citokine proinflamatorii IL-1β**
  - **Inflamatia joaca rol important in PI-IBS**

Simptomele in PI-IBS au origine si perpetuare prin factori imunologici.

- **3. Permeabilitate intestinala crescuta**
  - **Lactuloza / manitol ↑ (urina)**
    - **Marshall et al. (2004) – epidemie hidrica GEA cu C. jejuni + E. coli O157:H7**
    - **Permeabilitate intestinala crescuta la 35% PI-IBS si 13% control (fara IBS)**



- **4. Malabsorbtie saruri biliare**

- **5. Intoleranta la lactoza – mai frecventa la copil**

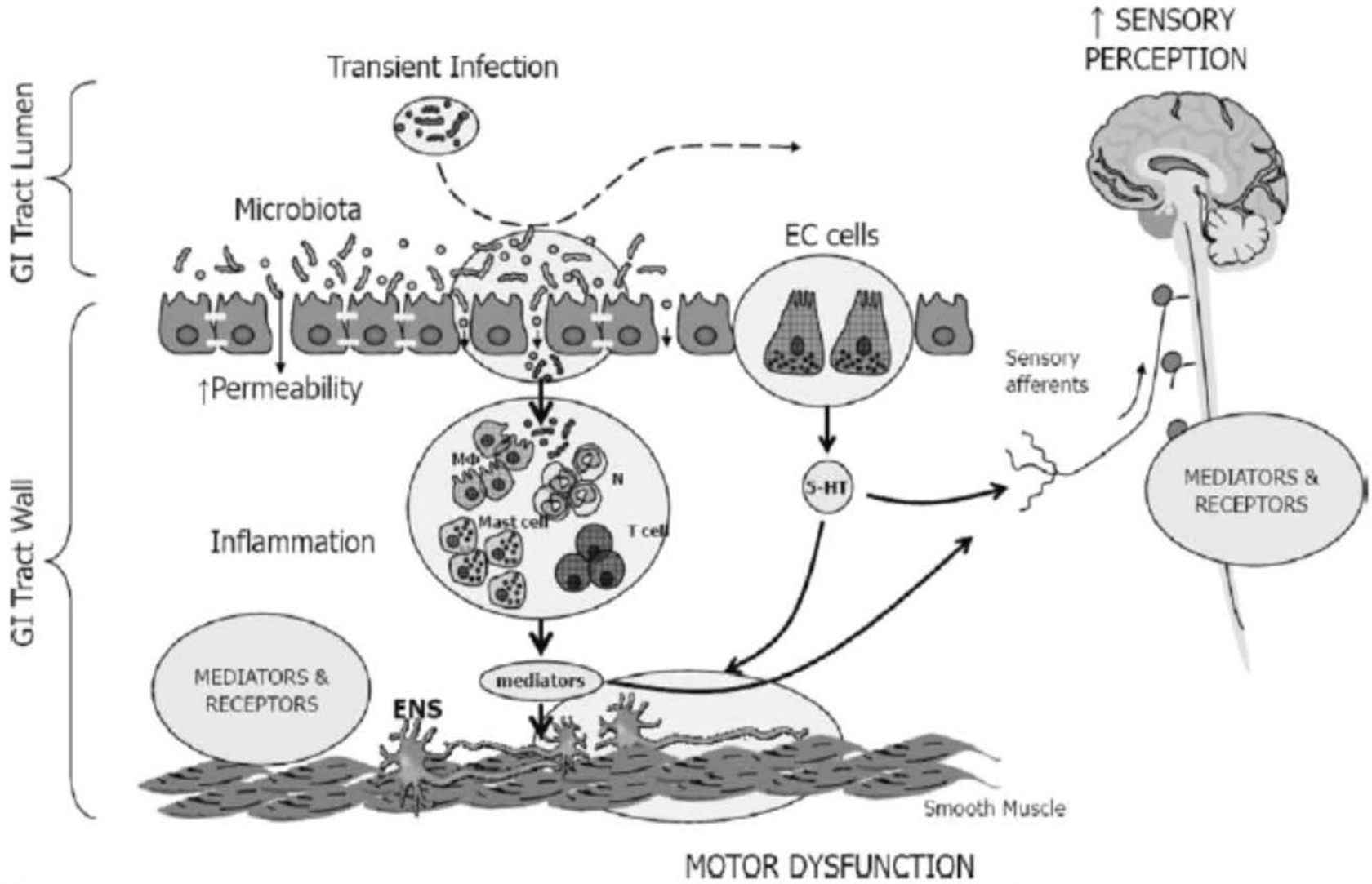
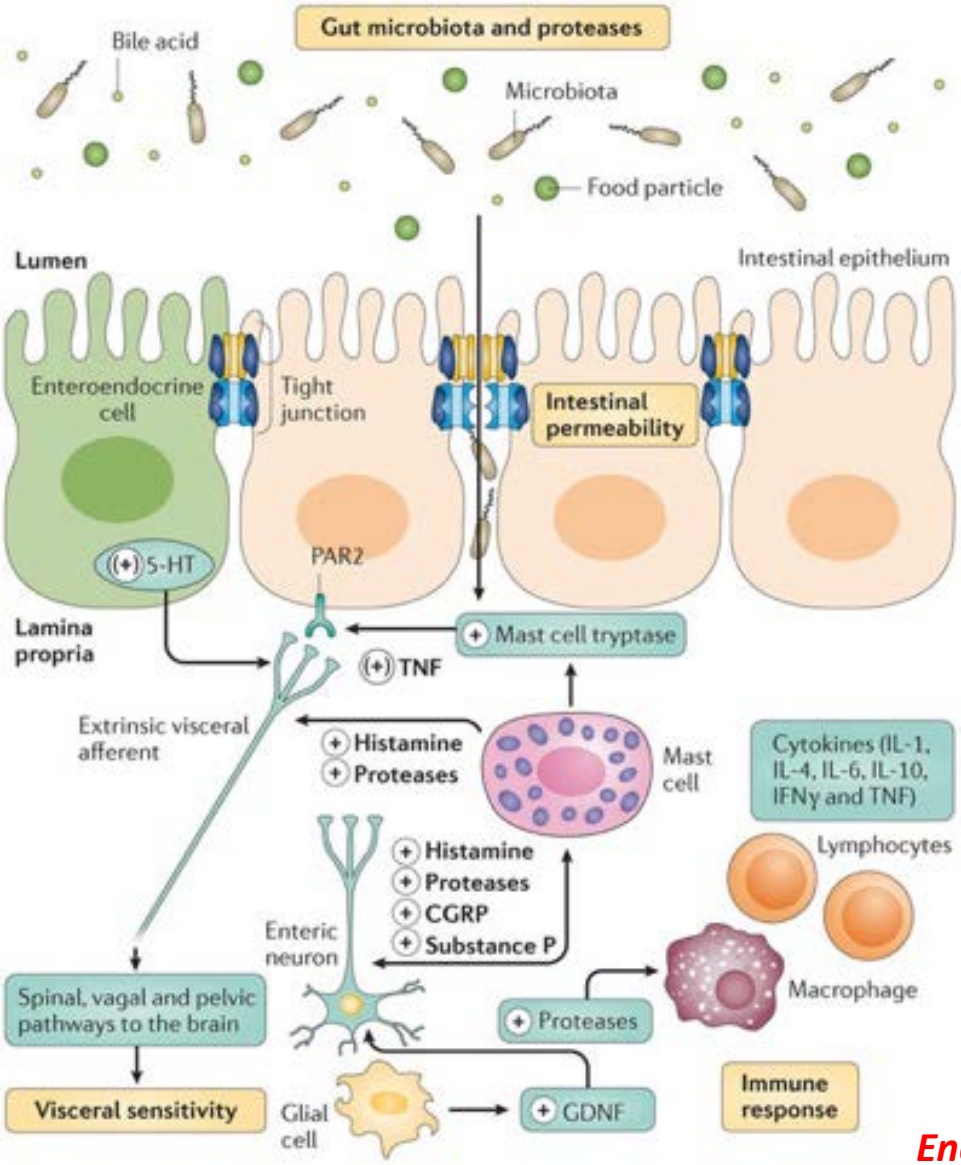


FIG. 1. Working hypothesis on the putative pathogenetic mechanisms of PI-IBS. A transient infectious gastroenteritis leads to the persistence of a mild inflammatory response (T cells and mast cells) and enterochromaffin cell hyperplasia as well as increased mucosal permeability. Inflammatory cells release mediators (eg, histamine, proteases, and cytokines) and enterochromaffin cells release serotonin (5-HT). These mediators affect the enteric nervous system (ENS) and smooth muscle activity, leading to intestinal motor dysfunction. Interaction of these mediators with sensory afferents evokes increased sensory perception.

FIZIOPATOLOGIA INTESTINULUI IRITABIL



Enck, Nature Rev DP 2016

Mecanisme patogenice – particularitati dupa etiologie

CAMPYLOBACTER JEJUNI

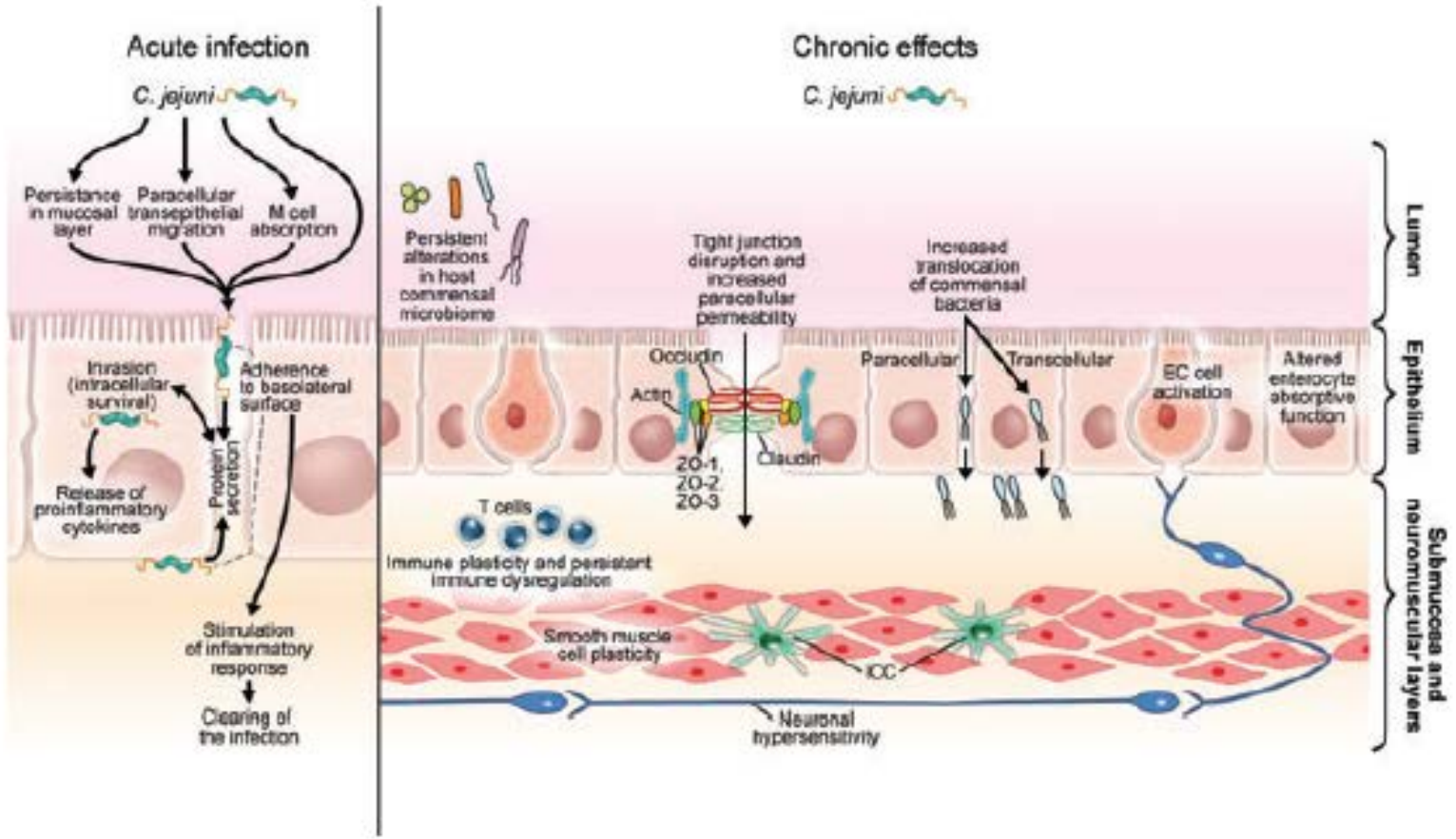


Figure 1 *Campylobacter jejuni* acute effects and mechanisms for postinfectious irritable bowel syndrome. Acute virulence of *C. jejuni* depends upon factors including adherence to basolateral surfaces, protein secretion, invasion, and intracellular survival. These and other putative virulence factors can stimulate host-inflammatory response and release of cytokines. Subsequent induction of innate and humoral immune response results in clearing of infection. Chronic gastrointestinal manifestations as seen in PI-IBS may result from number of luminal and epithelial factors including persistent alterations in commensal gut microbiota, dysregulation of tight junction function and increased commensal translocation, Enterochromaffin cell activation, and altered enterocyte absorptive function. This can further result in persistent immune dysregulation and neuromuscular excitability.

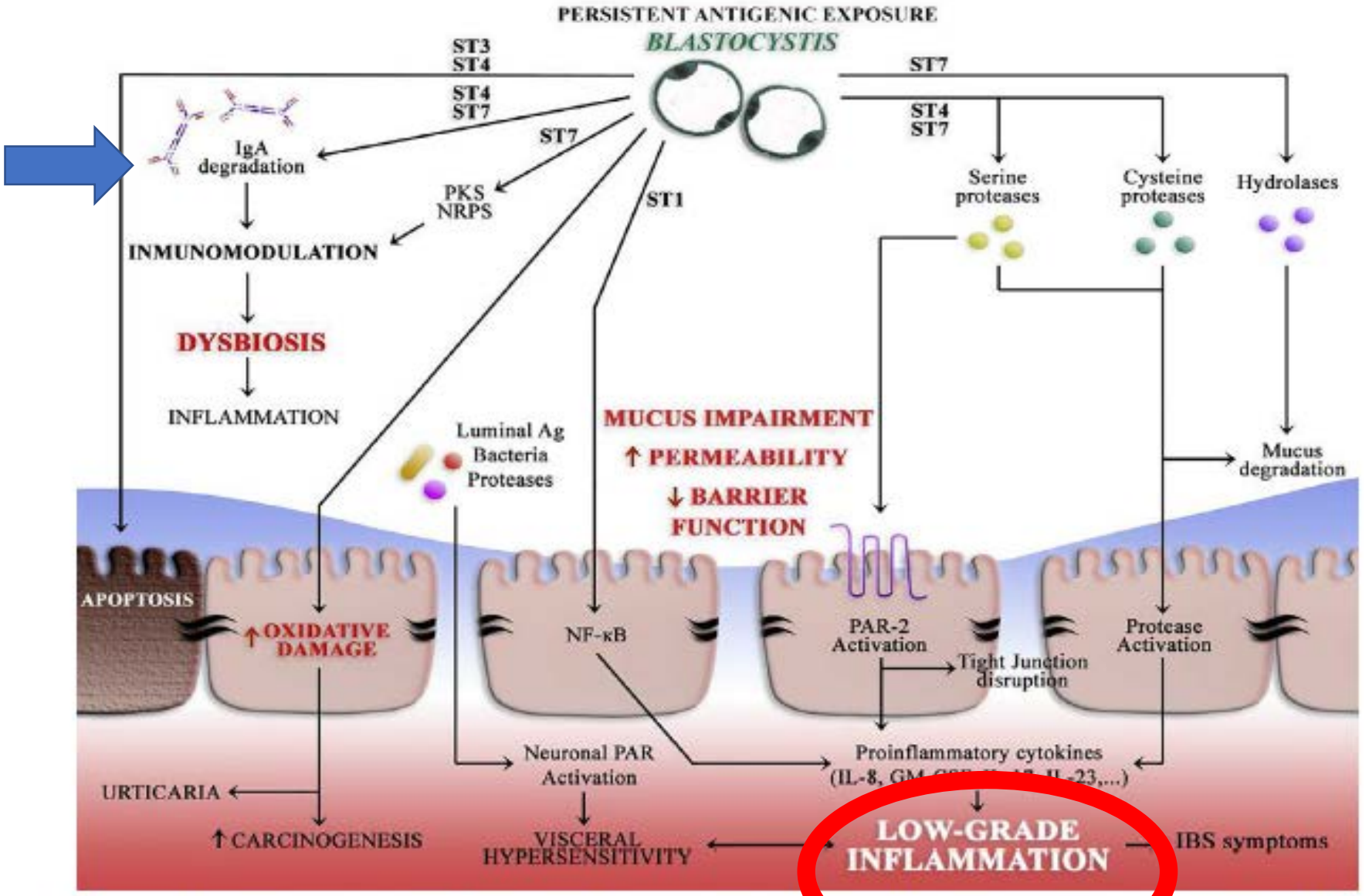


Fig. 1. Overview of the physiopatological effects of *Blastocystis* on the intestinal mucosa and de nstrated mechanisms in relation t ecific subtypes (ST1, ST3, ST4 y ST7) [1,2,7,66–75,77]. IgA, immunoglobulin A; IL-8, interleukin 8, IL-17, interleukin 17; IL- terleukin 23; GM-CSF nulocyte-Macrophage Colony-Stimulating Factor; NF-κB, nuclear factor kappa B; PAR, protease-activated receptor; PKS, polyketide synth Ribosomal polyketide synthase.

Diagnostic pozitiv

- **Diagnosticul stabilit pe baza simptomelor:**
  - **Majoritatea pacientilor cu PI-IBS îndeplinesc criteriile simptomatice ROMA pentru IBS-D**
  - **Pana la o treime dintre bolnavi au**
    - **Constipatie**
    - **Balonare**
    - **Mucus in scaun**
    - **Tulburari intestinale mixte (diaree, constipatie)**

Table 1 Diagnostic criteria for irritable bowel syndrome (IBS) according to Rome IV criteria.

Diagnostic criteria for IBS

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria*:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

*criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

IBS subtypes

IBS can be further classified based on predominant bowel habits. IBS subtypes can be only confidently established when the patient is evaluated off medication used to treat bowel habit abnormalities:

- IBS-C: constipation predominant IBS)
- IBS-D: diarrhea predominant IBS
- IBS-M: mixed IBS, where both diarrhea and constipation are present
- IBS-U: unclassified IBS

Example of subtype IBS-C: more than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7.

Diagnostic diferential

- **Poluare bacteriana intestinala (SIBO)**
- **Malabsorbtie carbohidrati (intoleranta la lactoza)**
- **Malabsorbtie acizi biliari**
- **Boli inflamatorii intestinale – colita ulceroasa**
- **Infectii enterice**
- **Neoplazii la adult**

Tratamentul IBS

- **Terapia este o necesitate substantiala, deoarece lipseste un tratament eficient in IBS**
- **Tratamentul consta**
  - **1. terapie medicamentoasa**
  - **2. dieta low-FODMAP**
  - **3. transplant fecal de microbiota in IBS + IBD sau constipație rebelă**

Tratamentul IBS

- **Tratamentul actual recomandat de British Institute for Health and Care Excellence**

Strategii non-dietetice

- **1. Terapii farmacologice**
  - **Linia I – antispastice, laxative, antimotilitate, loperamid**
  - **Linia II – antidepresive triciclice**
- **2. Terapie psihologica**
- **3. Probiotice**

Strategii dietetice

- **Ghid 2015 NICE (National Institute for Clinical Evidence) pentru strategia dietetica IBS = "low FODMAP diet"**

1. Terapie medicamentoasa

Table I. Drug therapy in PI-IBS.

DRUG	EFFECTS	DISADVANTAGES
Opiates (codeine, loperamide)	- inhibit rapid transit and secretion - improving stool consistency	- less effective in controlling pain in irritable bowel syndrome
Anticholinergic agent (antispasmodics)	- reduce intestinal the activity of smooth muscle	
Tricyclic antidepressants	- anti-histaminic, anti-muscarinic, serotonin reuptake inhibition - reduce pain, nausea and diarrhea in IBS	
5HT3-antagonists (Alosetron)	- slows colonic transit - improves stool consistency and frequency in D-irritable bowel syndrome	- never been tried specifically in post-infective irritable bowel syndrome - severe constipation, rarely ischemic colitis
5HT4 agonists (Tegaserod, Prucalopride)	- stimulates colonic transit patients with constipated irritable bowel syndrome - softens the stool consistency - increases the frequency of bowel movement - reduces the symptoms of bloating	
Cholestyramine	- useful in diarrhoea due to bile salt malabsorption - very effective in PI—IBS	- poorly tolerated owing to its unpleasant taste in its current formulation
Antibiotics (Doxycycline, Ciprofloxacin, Flagyl, Neomycin, Rifaximin)	- small intestinal bacterial overgrowth (SIBO) - effective on both diarrhea and constipation IBS - improves the gastrointestinal symptoms	
Probiotics	- restore the intestinal microbiota - improvement of postinfectious irritable bowel syndrome in animal models	

Terapii antiinflamatorii

- **Dovezi recente subliniază inflamația mucoasei de grad mic in IBS, incercându-se trialuri de terapii antiinflamatorii**

- **Trial 3 saptamani prednisolon in PI-IBS**
  - **Fara efect pe simptome**
- **Studii privind folosirea mesalazinei care are proprietati antiinflamatorii**
  - **Beneficii la bolnavii cu IBS:**
    - **scade durerea,**
    - **scade activitatea proteolitica,**
    - **modifica flora intestinala**
- **Trial recent randomizat cu mesalazina: reduce numar celule mastocitare si amelioreaza simptomele**

Postinfectious Irritable Bowel Syndrome

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Antagonisti ai receptorilor 5-HT3 – alosetron, ondansetron

- **S-au citat efecte adverse: constipatie severa, colita ischemica**
- **5-HT – serotonina → celule enterocromafine**

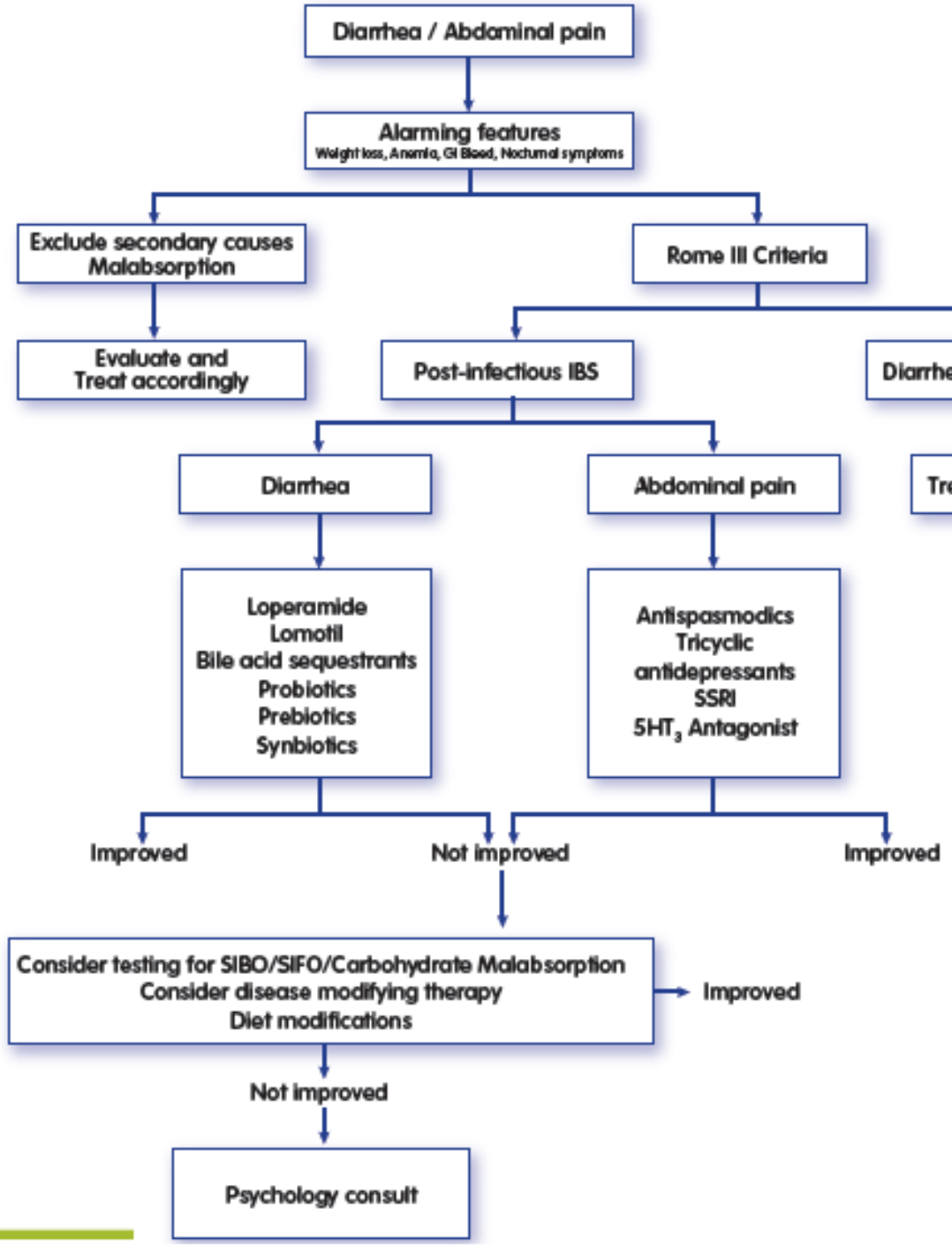

Figure 2: A diagnostic and management algorithm for post-infectious irritable bowel syndrome. #Exclusion of secondary causes is based on the presence of alarm features (older age, unintended weight loss, nocturnal symptoms, anemia, blood in stools, and family history of intestinal cancers) but conditions that mimic IBS-D should also be considered and these include small intestinal bacterial overgrowth, carbohydrate malabsoprtion and less commonly inflammatory bowel disease. @ If high index of suspicion for malabsorption, then this should be tested and consider conditions including tropical sprue and bile acid diarrhea.
**Disease-modifying therapies may include anti-inflammatory agents, e.g. corticosteroids and mesalazine, and anti-serotonergic agents, e.g. ondansetron.*

Prognostic

- **Riscul de PI-IBS scade in timp dupa infectie. Bolnavii pot spera la vindecare lenta, graduala**
- **Studii recente sugereaza ca simptomele pot persista ani cu ameliorare treptata**
  - **Studiu Walkerton – prevalenta PI-IBS scade de la 28% la 15,4% dupa 8 ani**
  - **Metaanaliza Thabane – declin OR pentru PI-IBS de la 7,6 la 3 luni la 3,8 la 36 luni**
    - **7,6 la 3 luni**
    - **5 la 6 luni**
    - **6,4 la 12 luni**
    - **3,8 la 36 luni**

CONCLUZII

- GEA I este acceptata ca factor etiologic in IBS
- Fiziopatologia PI IBS este legata de predispozitii genetice si persistenta anomaliilor de mucoasa (inflamatie intestinala de grad mic, reactii immune postinflamatorii, citochine,hiperplazia celulelor enterocromafine si mastocitare, interactiuni axa intestine-creier).
- Managementul bolii este dificil si complex(medicamentos, dietetic, psihologic)

Pana incerci sa definesti o notiune, ea isi schimba semnificatia sau apar notiuni si viziuni noi