Conflictes d'interès

- Assessories: Gebro, Amgen, Pfizer, Takeda, Abbvie, Abbiotics, Ferring, Janssen, Zambon, PaloBioFarma, Mylan, Biotical.

- Xerrades: Gebro, Amgen, Pfizer, Takeda, Abbvie, Abbiotics, Ferring, Shire, Janssen, Zambon, Salvat, Mayoly, Chiesi, Heel, Mylan, MSD.

- Co-fundador i Director Mèdic: GoodGut Biotech

Trasplantament fecal: Mites i realitats

Xavier Aldeguer
Cap del Servei de l'Aparell Digestiu.
Hospital Doctor Josep Trueta /Institut d'Assistència Sanitària. Girona/Salt. Catalunya.
Co-fundador de GoodGut
Barcelona, 2019

MICROBIOMA HUMANO

Índex

- Concepte de disbiosi.
- Trasplantament fecal, en què consisteix?
- Trasplantament fecal: Evidències
- Trasplantament fecal: Cap on anem?

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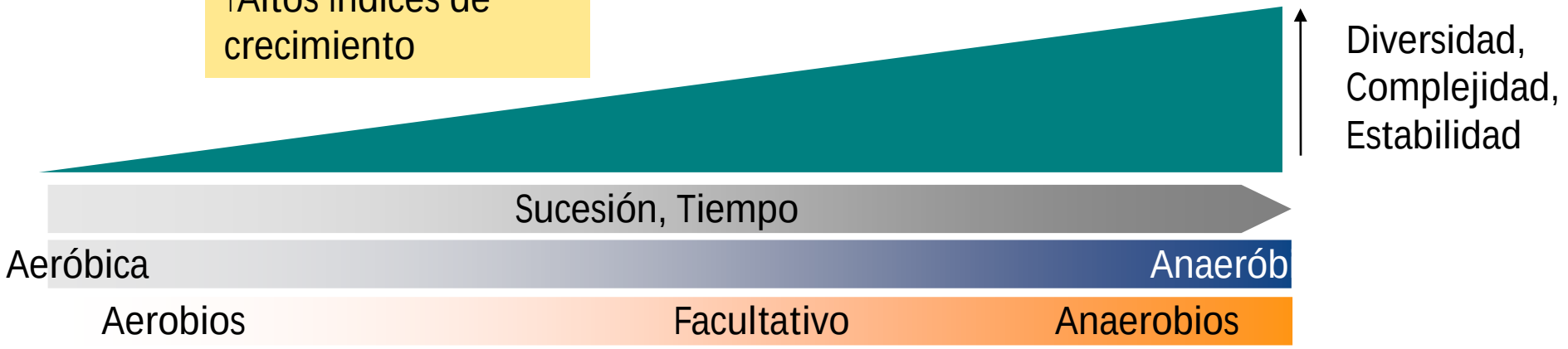
Un poco de ecología

- Colonizadores
- Bacterias generalistas
- Altos índices de crecimiento

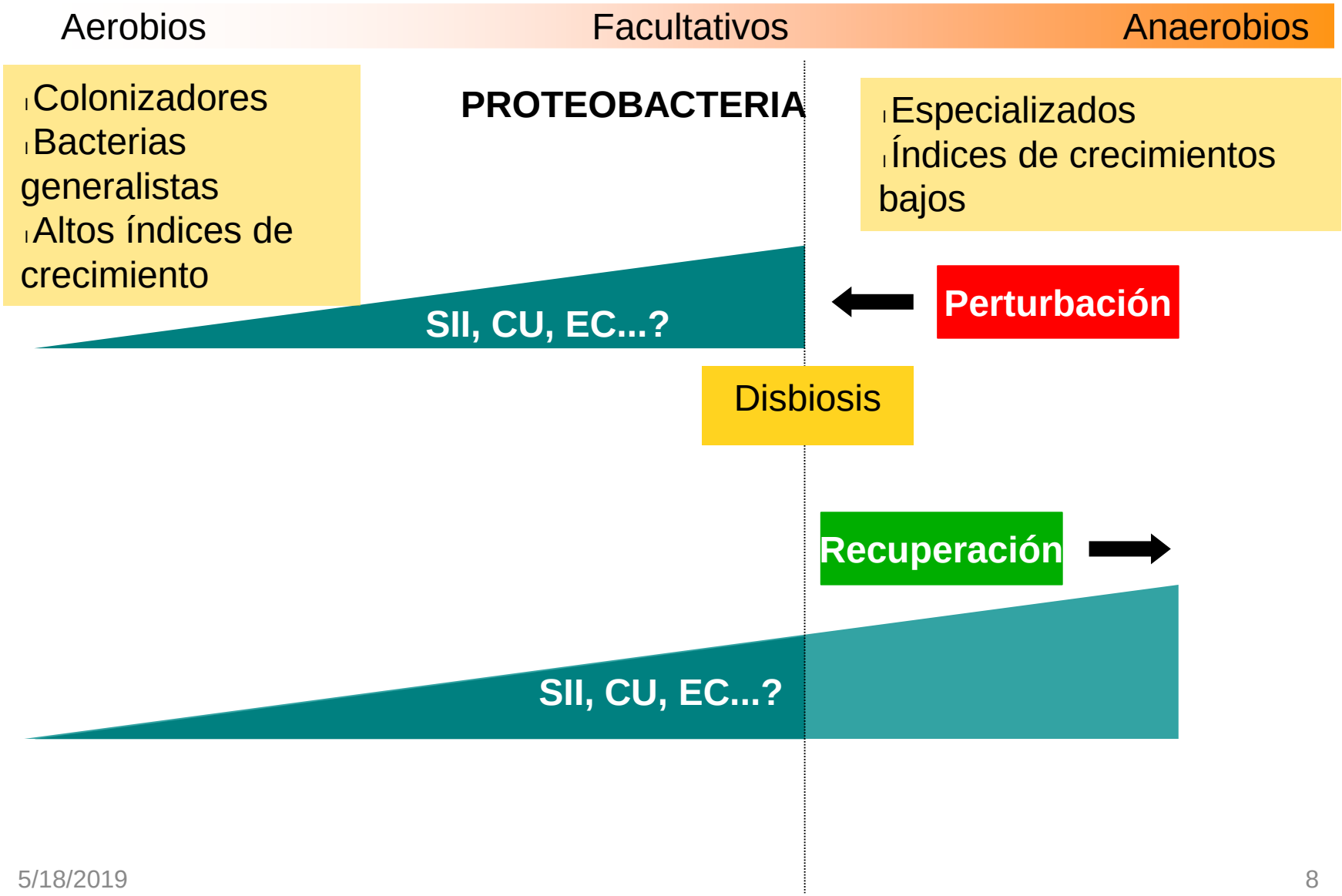
- Especializados
- Índices de crecimientos bajos



- Rico en nutrientes
- Componentes orgánicos de alto peso molecular

- Fermentación
- Componentes orgánicos de bajo peso molecular

Un poco de ecología



Tipos de disbiosis

- Pérdida de bacterias beneficiosas
- Expansión de patobiontes o bacterias potencialmente perjudiciales
- Pérdida de la diversidad microbiana

Charisse Petersen et al
Defining dysbiosis and its influence on host immunity and disease. Cellular Microbiology (2014) 16(7), 1024–1033

Índice

- Concepte de disbiosi.
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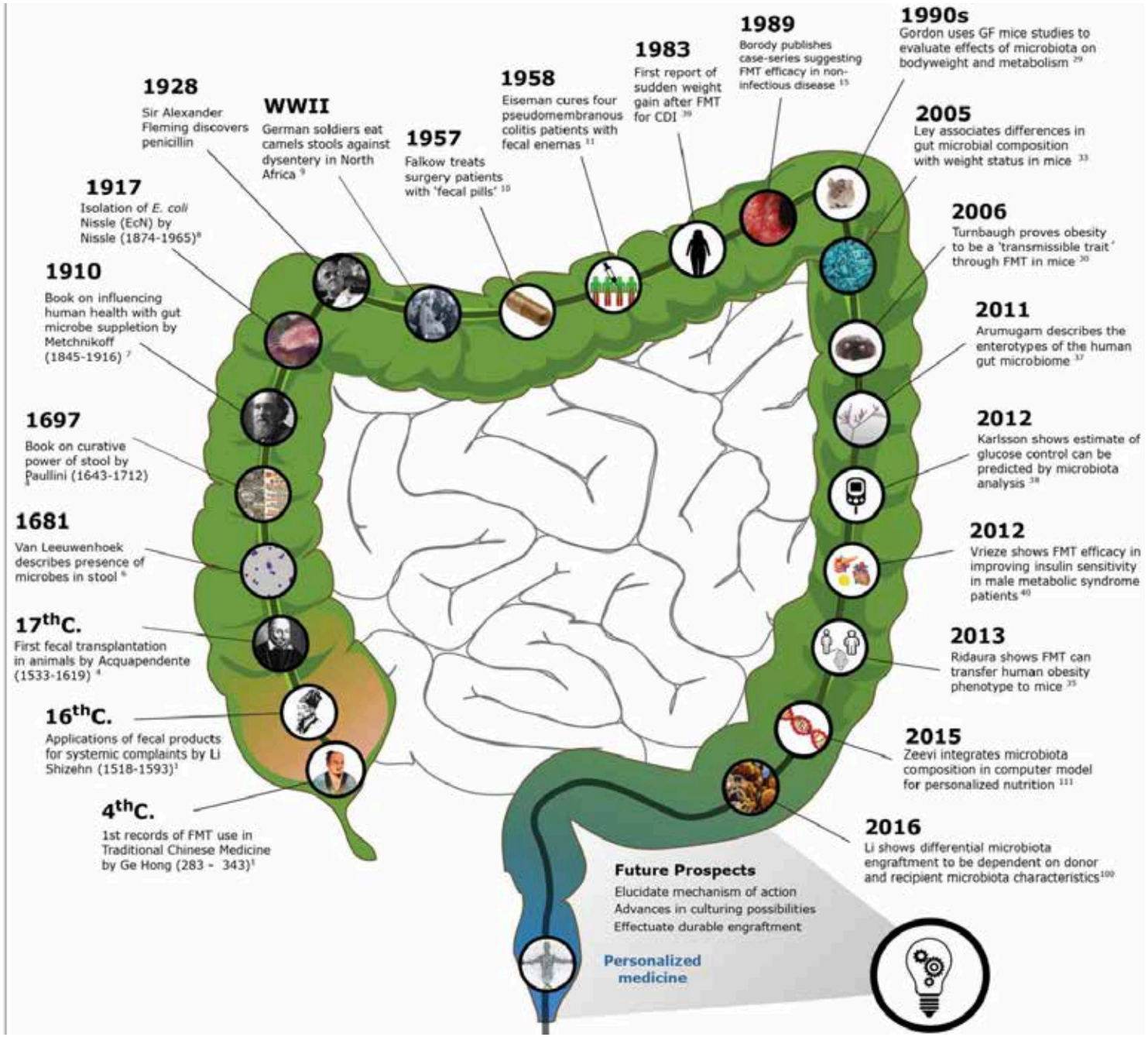
Modulació de la microbiota.
Definicions

Trasplantament fecal: Transferència de la microbiota intestinal d'un donant sa per introduir o re-establir l'estabilitat de la comunitat microbiana en el tub digestiu

Saulnier DM, et al. Curr Opin Biotechnol 2009
Pineiro M, et al. J Clin Gastroenterol 2008
Zatorski H, et al. Front Med 2014


1928
Sir Alexander Fleming discovers penicillin
WWII
German soldiers eat camels stools against dysentery in North Africa [9]
1957
Falkow treats surgery patients with 'fecal pills' [10]
1958
Eiseman cures four pseudomembranous colitis patients with fecal enemas [11]
1983
First report of sudden weight gain after FMT for CDI [39]
1989
Borody publishes case-series suggesting FMT efficacy in non-infectious disease [15]
1990s
Gordon uses GF mice studies to evaluate effects of microbiota on bodyweight and metabolism [29]
2005
Ley associates differences in gut microbial composition with weight status in mice [33]
2006
Turnbaugh proves obesity to be a 'transmissible trait' through FMT in mice [30]
2011
Arumugam describes the enterotypes of the human gut microbiome [37]
2012
Karlsson shows estimate of glucose control can be predicted by microbiota analysis [38]
2012
Vrieze shows FMT efficacy in improving insulin sensitivity in male metabolic syndrome patients [40]
2013
Ridaura shows FMT can transfer human obesity phenotype to mice [35]
2015
Zeevi integrates microbiota composition in computer model for personalized nutrition [111]
2016
Li shows differential microbiota engraftment to be dependent on donor and recipient microbiota characteristics [100]
1917
Isolation of E. coli Nissle (EcN) by Nissle (1874-1965) [8]
1910
Book on influencing human health with gut microbe suppletion by Metchnikoff (1845-1916) [7]
1697
Book on curative power of stool by Paullini (1643-1712)
1681
Van Leeuwenhoek describes presence of microbes in stool [6]
17thC.
First fecal transplantation in animals by Acquapendente (1533-1619) [4]
16thC.
Applications of fecal products for systemic complaints by Li Shizehn (1518-1593) [1]
4thC.
1st records of FMT use in Traditional Chinese Medicine by Ge Hong (283 - 343) [1]
Future Prospects
Elucidate mechanism of action
Advances in culturing possibilities
Effectuate durable engraftment
Personalized medicine

Preparation

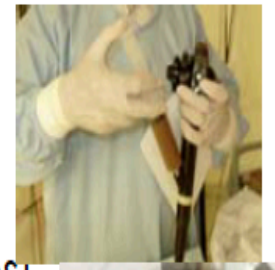
- Recipient:
  - Standard bowel prep required
  - Continue Abx until day before
- Donor:
  - MOM the night before is ok
  - Stool volume: 50-200gm
  - Collected within 6 hrs of procedure
  - Stool should not be refrigerated
  - *Avoid food allergens

Stool Preparation

- Stool is blended with 500cc NS for 1 min until liquid
- Solution is passed through a strainer into an emesis basin
- Drawn up into 60cc syringes
- Solution can be instilled through the scope
- Full colonoscopy to the TI is performed
- Instillation in the TI and right colon

Step 4: Mode of Delivery

- Nasogastric or nasoduodenal tube
  - Uncomfortable
  - Requires radiology
- Retention enemas
  - Variable patient ability to tolerate
- Lower endoscopy
  - Enables examination of mucosa
- Encapsulation
  - Decreased procedure related risk & cost



Aas et al. 2003; Rubin et al 2012; Van Nood 2013; Silverman et al. 2010; Kassam et al 2012; Lee et al 2014;

Efectos adversos TMF

- Menores:
  - Náuseas/vómitos (vía oral)
  - Dolor abdominal
  - Fiebre
  - Distensión abdominal
  - Diarrea/estreñimiento
- Graves:
  - Relacionados con endoscopia
  - Sepsis (puede ser a largo plazo)
  - Brote EII
  - SBI post TMF
- Potenciales:
  - Activación enfermedades crónicas: Plaquetopenia autoinmune, obesidad…
  - Desconocido (CCR…)

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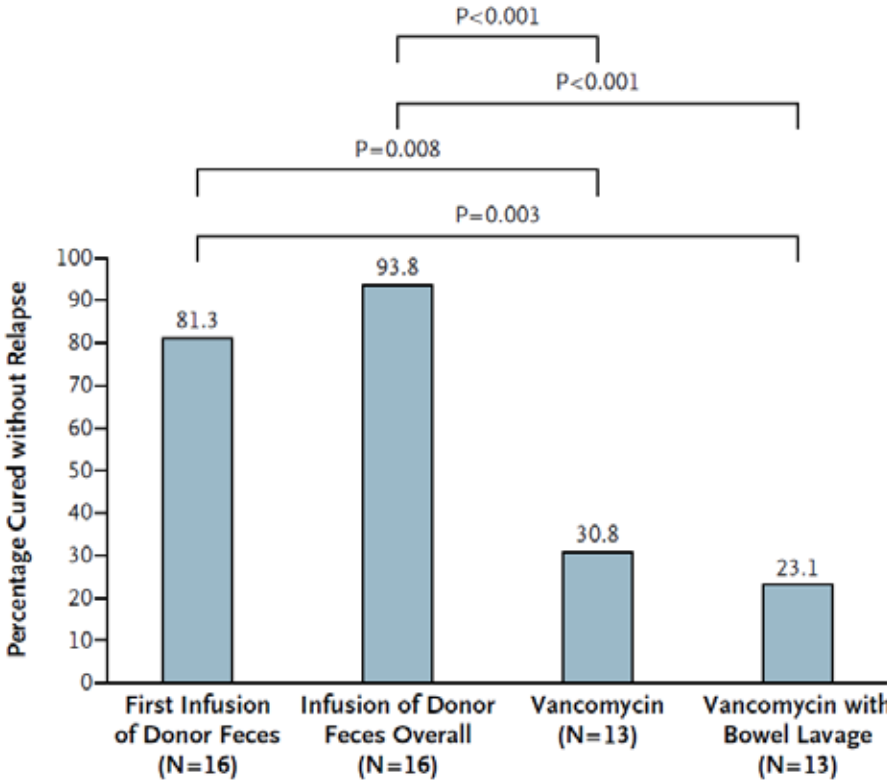
Transplante fecal

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

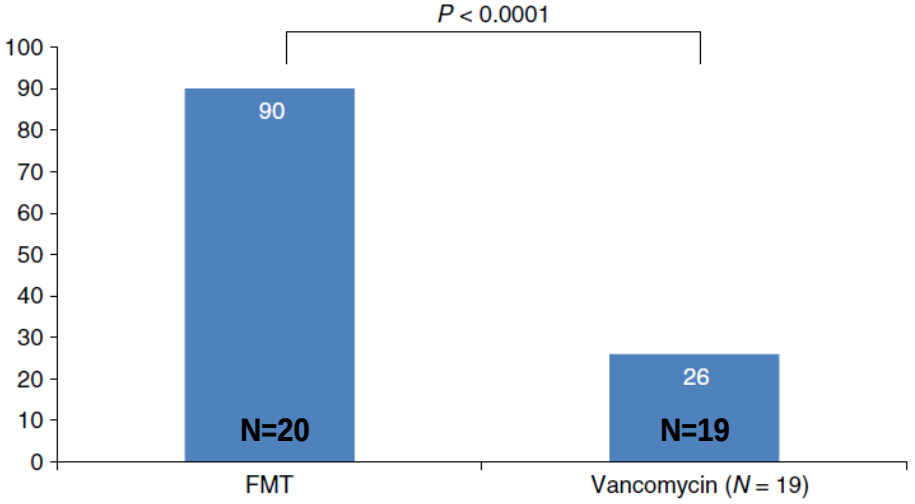
Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.



AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection

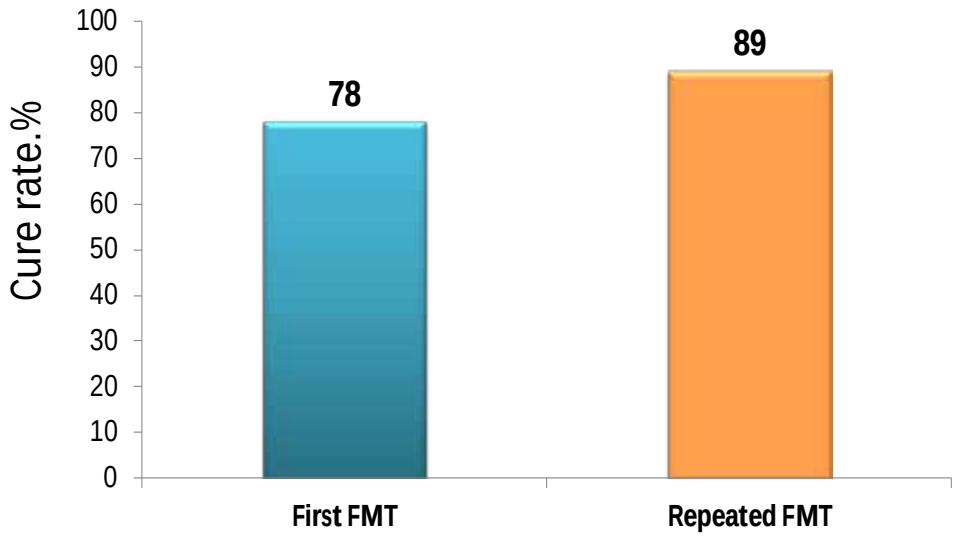
G. Cammarota*, L. Masucci†, G. Ianiro*, S. Bibbò*, G. Dinoi*, G. Costamagna‡, M. Sanguinetti† & A. Gasbarrini*



van Nood E et al. N Engl J Med. 2013 Jan 31;368(5):407-15.
Cammarota G et al. Aliment Pharmacol Ther. 2015 May;41(9):835-43.

Transplante Microbiota Fecal *Clostridium difficile* Recurrente en pacientes con Inmunosupresión prolongada

- A multicenter retrospective series.
- 80 immunosuppressed patients (36 IBD).



- None suffered infections definitely related to FMT.
- Few SAEs or related AEs.
- Patients with IBD did not experience a higher incidence of SAEs or AEs compared with patients IC because of other conditions ($P \leq 0.32$).
- 4 IBD patients had a flare after FMT.

Kelly et al. Am J Gastroenterol 2014; 109:1065–1071

OPEN ACCESS

European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,[1] Gianluca Ianiro,[1] Herbert Tilg,[2] Mirjana Rajilić-Stojanović,[3]

- FMT for **recurrent CDI**: strong recommendation with high quality of evidence
- FMT for **refractory CDI**: strong recommendation, quality of evidence is low.
- FMT for **first episode** CDI is not recommended: insufficient evidence

Cammarota et al. Gut 2017

Protocol Consens SCD

- Pacients adults > 3m esperança vida que presenten una infecció por C diff recidivant després de rebre al menys una pauta antibiòtica:
  - ≥ 10 d ttm amb vancomicina a dosis de ≥125 mg cada 6h
  - ≥ 10 d ttm amb metronidazol a dosis de ≥ 500 mg cada 8 h
- Selecció donant: Descartar malalties transmisibles, Hª familiar CRC o EII, no SII, no fàrmacs excretables femtes
- Preparar TMF i realitzar en menys 6h des de defecació.
- Receptor: Pauta vancomicina curta (5d) i preparació PEG

TMF en Colitis ulcerosa: 3 estudis controlats

	Moayyedi, et al.	Rossen, et al.
Number	70	37
Primary endpoint	Remission: Mayo score ≤ 2 and endoscopic score of 0 at week 7.	Clinical rem. (SCCA ≤ 2) combined with ≥ 1 point decrease in Mayo endo score at week 12.
Route and dose	Retention enema; weekly x 6wks	Naso-duodenal tube; wk 0 and wk 3
Subjects who achieved the primary endpoint	9/38 (24%) FMT vs. 2/37 (5%) controls (p=0.03)	7/23 (30%) FMT vs. 5/25 (20%) controls (p=0.51)
Serious Adverse Events	No difference between groups	2; not felt to be related
Other	7/9 patients in remission received FMT from single donor; Stool from patients with FMT had greater microbial diversity compared to baseline	**Microbiota changes in responders. Control is autologous transplant**

Gastroenteroly 2015

Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

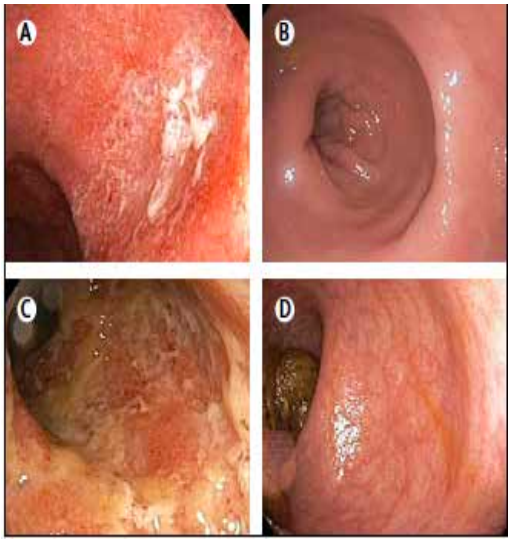
Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

FMT (Colono + enemas) vs Placebo
Dosis intensiva y multidonor (5 enemas / sem)
Primary End Point: Remisión (clca + endosc) o respuesta a la semana 8

	Faecal microbiota transplantation (n=41)	Placebo (n=40)	Risk ratio (95% CI)	p value
Primary outcome				
Steroid-free clinical remission and endoscopic remission or response*	11 (27%)	3 (8%)	3·6 (1·1–11·9)	0·021
Secondary outcomes				
Steroid-free clinical remission†	18 (44%)	8 (20%)	2·2 (1·1–4·5)	0·021
Steroid-free clinical response‡	22 (54%)	9 (23%)	2·4 (1·3–4·5)	0·004
Steroid-free endoscopic remission§	5 (12%)	3 (8%)	1·6 (0·4–6·4)	0·48
Steroid-free endoscopic response¶	13 (32%)	4 (10%)	3·2 (1·1–8·9)	0·016

*Total Mayo score ≤2, with all subscores ≤1, and ≥1 point reduction from baseline in endoscopy subscore. †Combined Mayo subscores of ≤1 for rectal bleeding plus stool frequency. ‡Decrease of ≥3 points or ≥50% reduction from baseline (or both) in combined Mayo subscores for rectal bleeding plus stool frequency. §Mayo endoscopy subscore 0. ¶Mayo endoscopy subscore ≤1, with ≥1 point reduction from baseline.

Table 2: **Primary and secondary outcomes at week 8**



Lancet 2017

TMF en Crohn

Suskind et al. IBD 2015	Cui B et al. J Gastro Hepat 2015
• 9 pacientes • Un solo TMF • Sonda nasogástrica • 5/9 in remisión en sem 6 / 12	• 30 pacientes EV refractaria • Un solo TMF • Respuesta clínica 26/30 (86.7%) • Remisión 23/30 (76.7%) en sem 4

Sólo usaron la remisión clínica como patrón de respuesta

Perfil Seguretat TMF en MII

- Efectes adversos Ileus: Vòmits, diarrea, flatulències, distensió
- Transmissió d'infecció:
  - després d'autoadministració de TMF.
  - Infecció greu per Listeria en un pacient amb CU
- Brots:
  - Febre, marcadors elevats i molèstia abdominal post-TMF
  - Pacients amb immunosupresores: 5/36 (14%) amb brot post-TMF

Vermeire S. Gastroenterology 2012
Angelberger S et al. Am J Gastroenterol 2013
Hohmann C et al. N Engl J Med 2014
Iokona C et al. Am J Gastro 2014

TMF: SBI diarrea o mixt vs placebo

Table 1 List of articles included in the review examining the treatment of irritable bowel syndrome with fecal microbiota transplantation

Ref.	Year	Type	*n*	N in regard to IBS	Subcategory		
					IBS-D	IBS-C	IBS-M
Borody *et al*[35]	1989	Letter to the editor	55	Not specified	-	-	-
Andrews *et al*[34]	1992	Case report	1	1	-	1	-
Borody *et al*[27]	2004	Review	6	3	-	3	-
Pinn *et al*[28]	2013	Conference abstract	13	13	9	3	1
Holvoet *et al*[29]	2015	Conference abstract	12	12	-	-	-
Cruz Aguilar *et al*[30]	2015	Conference abstract	9	9	5	4	0
Hong *et al*[31]	2016	Conference abstract	10	10	-	-	-
Syzenko *et al*[32]	2016	Conference abstract	12	12	6	5	1
Mazzawi *et al*[33]	2016	Conference abstract	9	9	-	-	-

Halkjær et al, World J Gastroent

9 Assajos contorlados registrats en l'actualitat en clinicaltrials.gov

TMF i pouchitis

Table 1. Baseline characteristics of patients with pouchitis and outcome after FMT

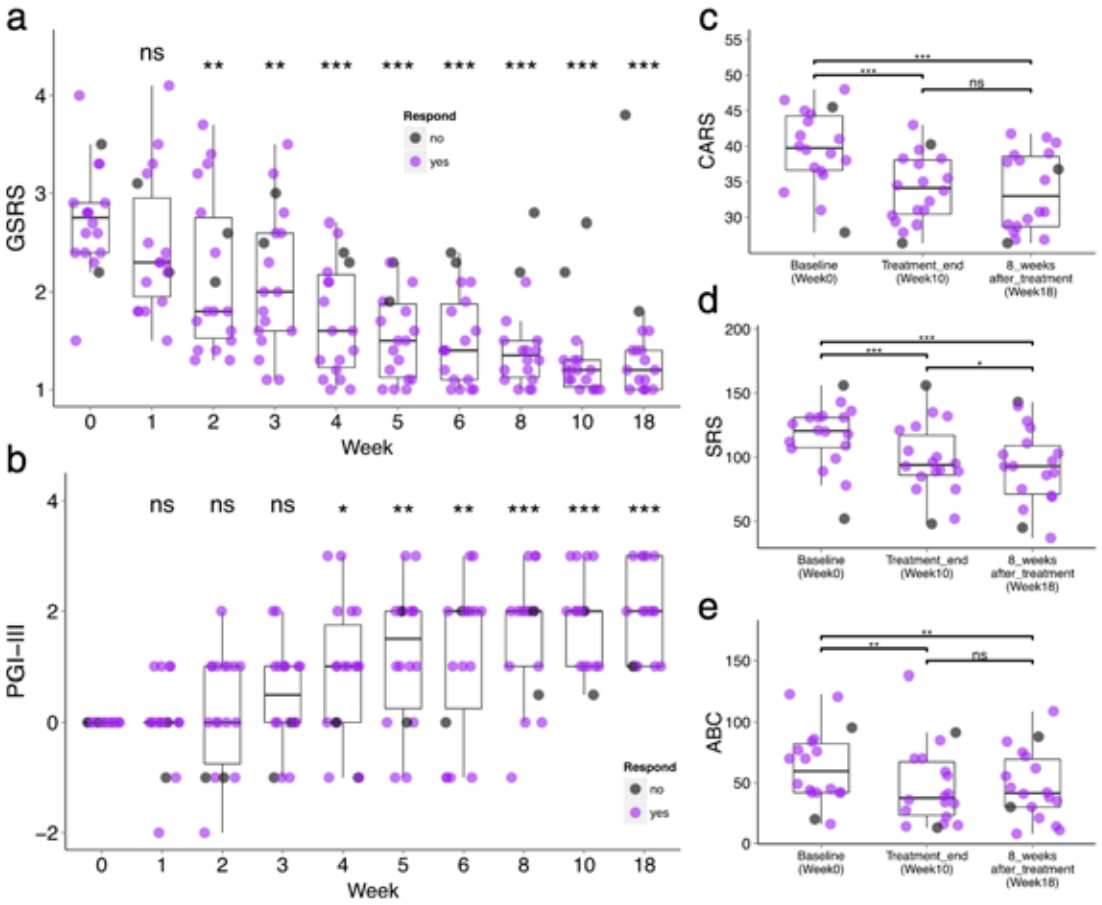
Patient, sex, age (years)	Pouch age (months)	Previous antibiotic treatment	Number of FMTs	PDAI (symptoms+ endoscopy+histology) before first FMT	PDAI (symptoms+ endoscopy+histology) after last FMT	FC before/after last FMT	Outcome/follow-up after last FMT
1. J. M., female, 32	16	Cipro Metro Rifaximin	1	4+4+2=10	2+2+1=5	566/47	Remission for 4 months
2. D. W., female, 38	22	Cipro Metro Rifaximin	3	5+4+3=12	1+0+1=2	479/<15	No improvement after first and second FMT 3 months of remission after third FMT
3. C. G., female, 40	58	Cipro Metro	3	4+2+3=9	0+1+1=3	849/150	Improvement after first and second FMT 3 months remission after third FMT
4. H. F., male, 26	36	Cipro Metro Rifaximin	3	3+4+2=9	0+1+1=2	ND	3 Months remission after third FMT, then relapse occurred
5. T. K., male, 27	96	Cipro Metro Rifaximin	7	4+5+5=14	1+3+3=7	ND	Improvement for 12 months

FC, fecal calprotectin; FMT, fecal microbiota transfer; ND, not determined; PDAI, pouchitis disease activity index.

Stallmach et al AM J Gastro, 2016

TMF i autisme

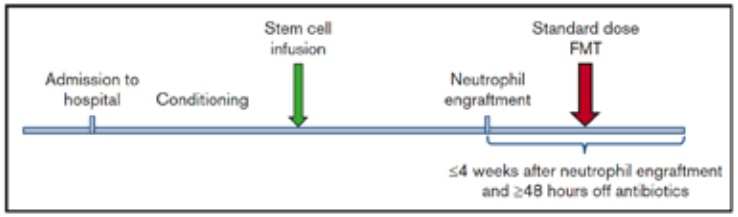
- Estudi en 18 nens entre 7 i 16a



Mejora significativa (80%) de los índices de evaluación autismo (sólo 2 niños con <50% disminución

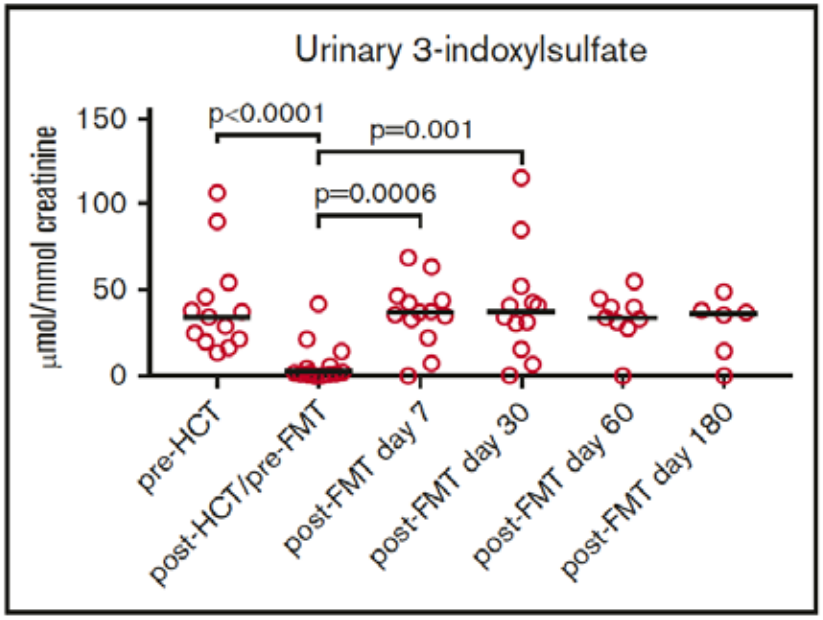
Kang et al, Microbiome 2017

TMF i malaltia empelt contra hoste

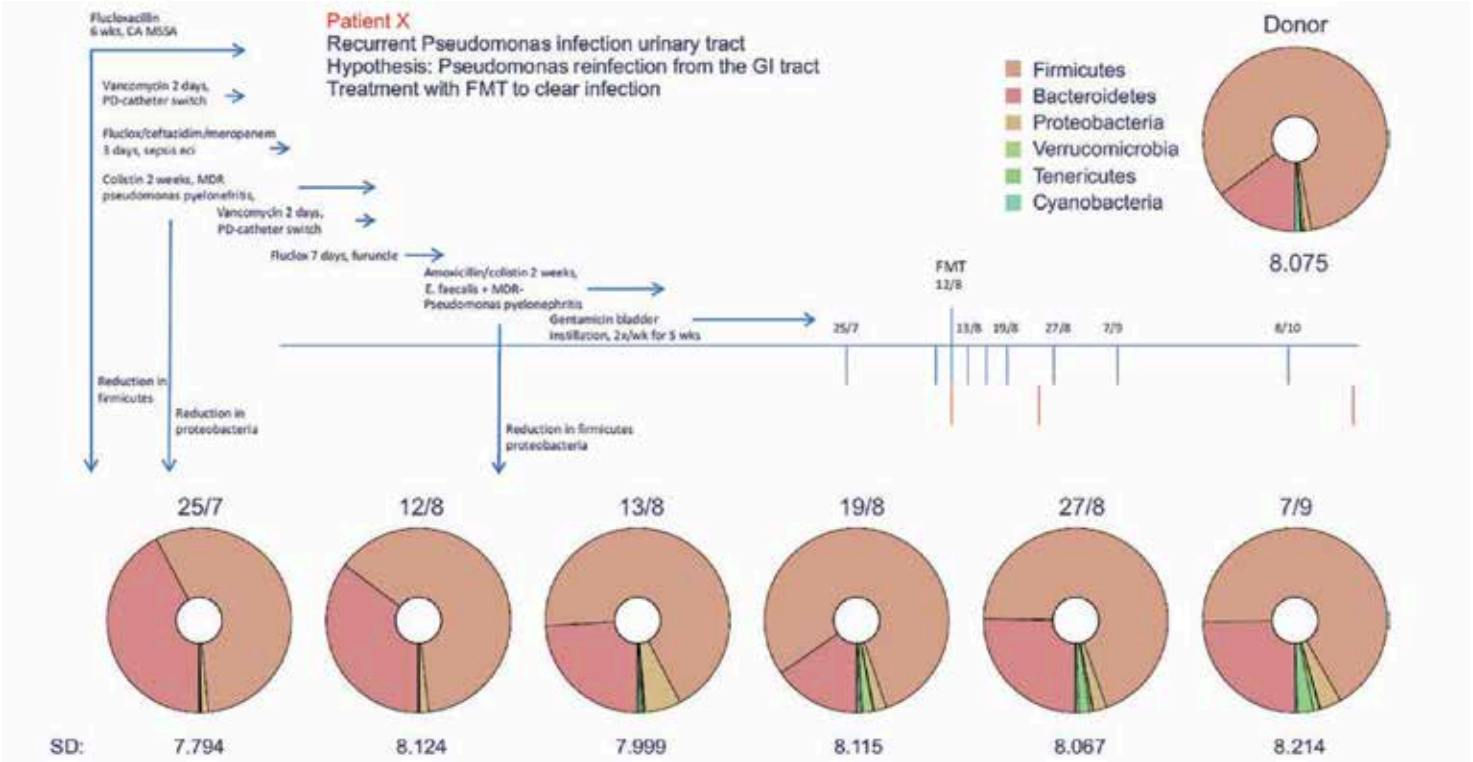


Administración de TMF en forma de càpsulas d'un donant 3º

DeFilipp et al, BloodAdv 2018



TMF per la descolonització de soques multiresistents



Stalenhoef et al, OFID, 2017

Encefalopatia hepática i FMT

18 pacientes
Un solo donante escogido

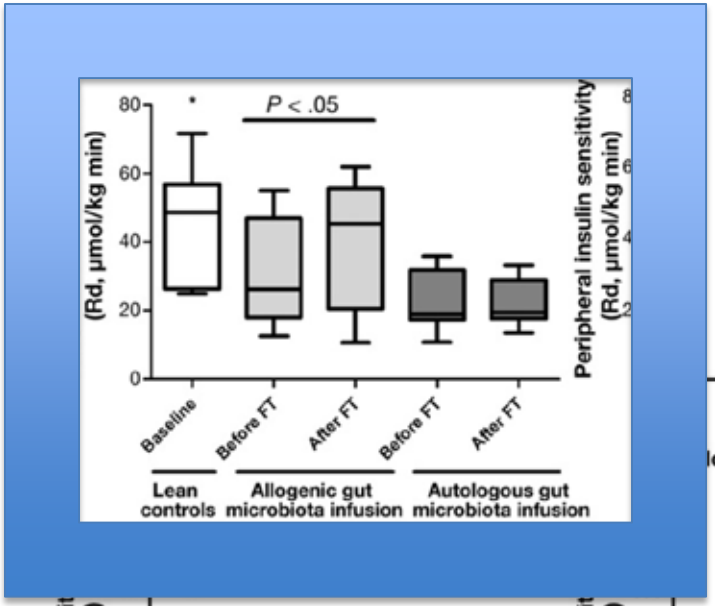
TABLE 2. Clinical Outcomes

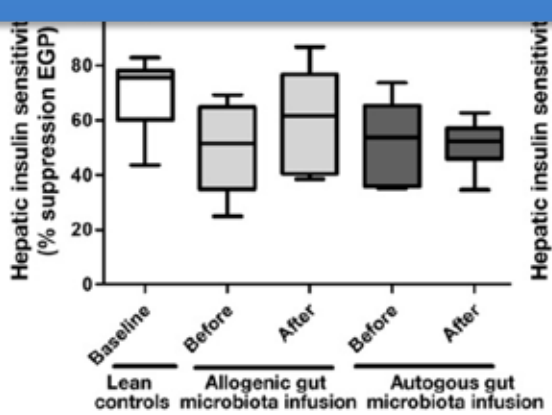
	SOC Arm (n = 10)	FMT Arm (n = 10)	P Value
Patients with SAEs at day 150 (%)	8 (80)	2 (20)	0.02
Total SAEs at day 150*	11	2	0.01
Patients with altered mental status by day 150	[illegible]	[illegible]	[illegible]
Total HE episodes at day 150*	6	0	0.03
Stroop OffTime+OnTime change (day 0 and day 20); positive indicates improvement	−43.5 ± 95.7	29.1 ± 27.9	0.04
PHES score change (day 0 and day 20); negative indicates improvement	0.0 ± 3.1	−3.1 ± 2.1	0.01
MELD score change (day 0 and day 35)	−0.2 ± 2.7	0.1 ± 2.0	0.78
Serum albumin (mg/dL) change (day 0 and day 35)	0.02 ± 0.16	0.00 ± 0.21	0.79
Serum AST (IU) change (day 0 and day 35)	4.4 ± 17.2	−0.6 ± 1.9	0.46
Serum ALT (IU) change (day 0 and day 35)	1.44 ± 9.30	−3.8 ± 6.4	0.18
WBC count (/mm^3) change (day 0 and day 35)	0.22 ± 0.47	0.20 ± 0.91	0.95
Hemoglobin (g/dL) change (day 0 and day 35)	0.40 ± 0.65	0.0 ± 1.0	0.29

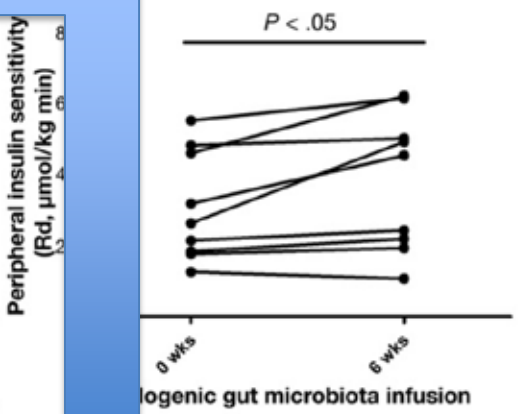
Bajaj et al, Hepatology, 2017

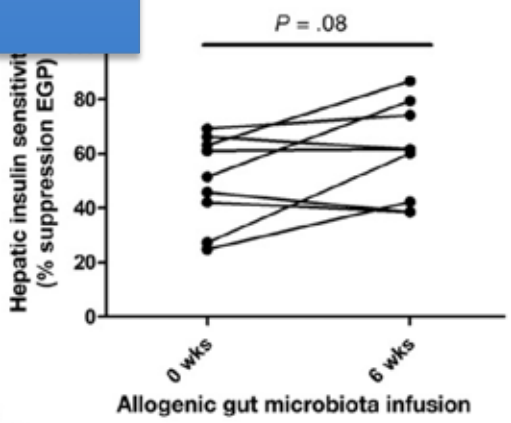
TMF i malalties metabòliques

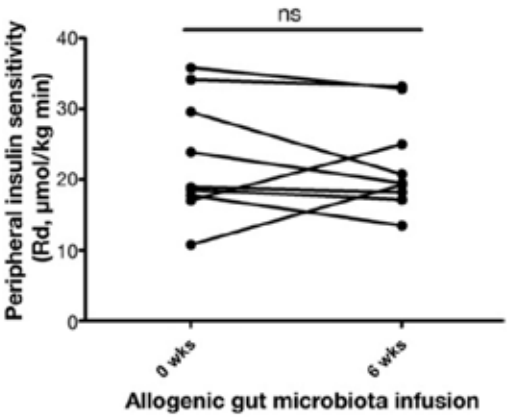
TMF de donantes delgados vs autólogo

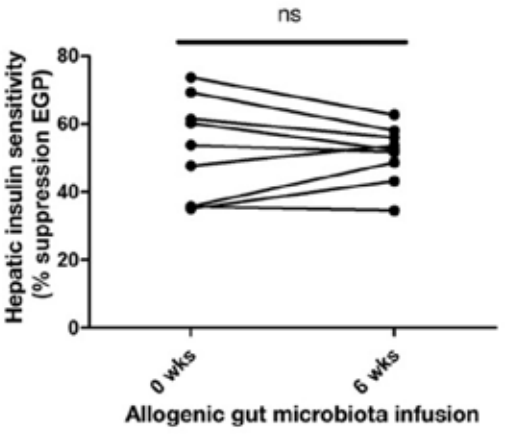












Vrieze et al Gastroenterol 2012

Índex

- Concepte de disbiosi.
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La abundancia y filogenia cepas del donante son la clave de que el TMF se consolide
Algunas especies del paciente receptor no desaparecerán y puede ser previsible
¿Valoración conjunta del perfil paciente y donante : “matching”?

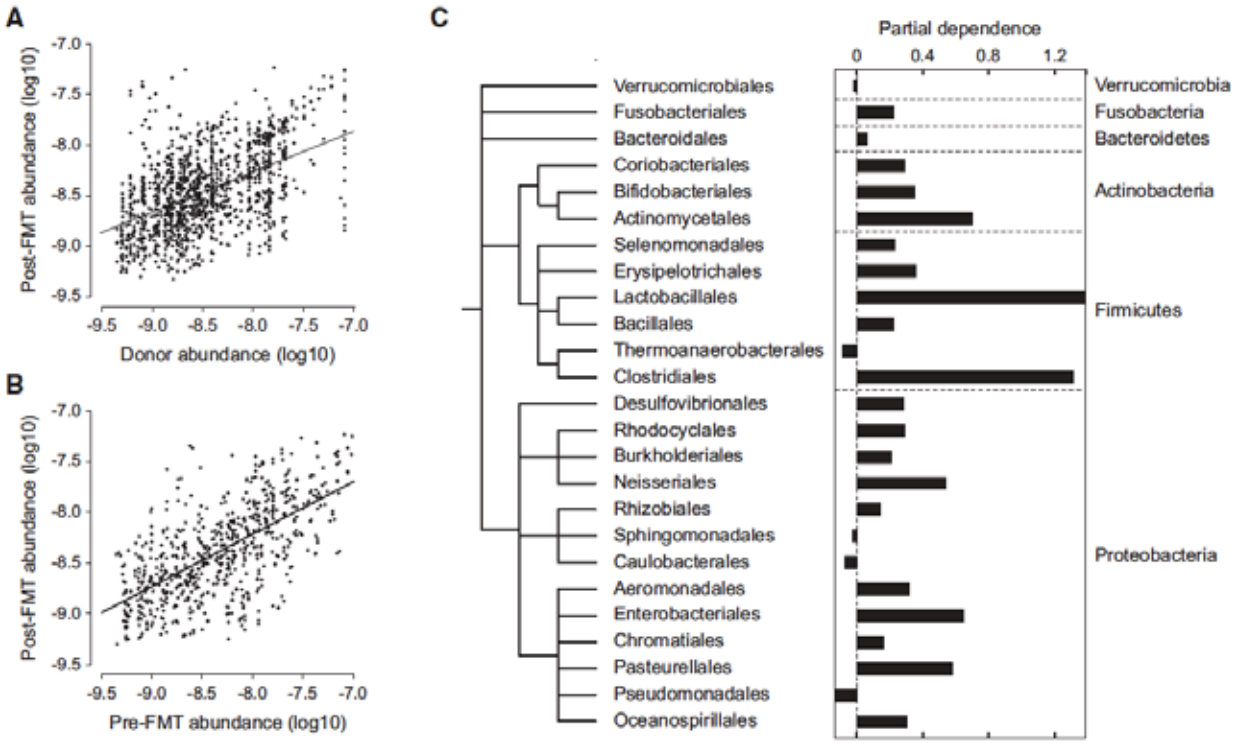
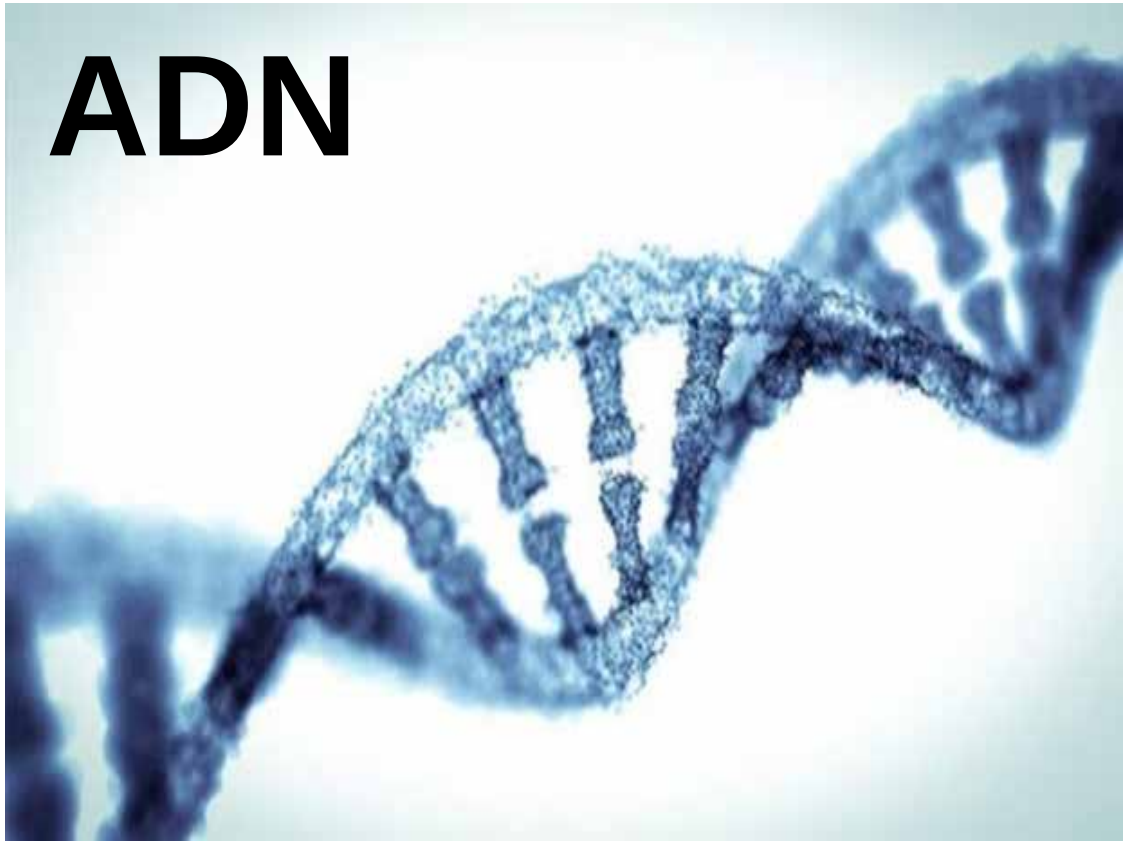


Figure 5. The Abundance and Phylogeny of Bacterial Species are the Strongest Determinants of Bacterial Engraftment
(A) The abundances of mg-OTUs in the donor are strongly correlated with their abundances in the post-FMT patient.
(B) The abundances of mg-OTUs in the patient are strongly correlated before and after FMT.
(C) The partial dependence of engraftment on each taxonomic order, reflecting the orders' marginal effects on the probability of engraftment in the reduced model. Orders are arranged on the bacterial taxonomy, with phylum labels on the right.

Smillie et al, Cell Host & Microbiome, 2018

Identificando donantes: Firmas microbiológicas

¿Cómo podemos evaluar las especies que componen la microbiota de nuestro colon si no somos capaces de cultivarlas todas?

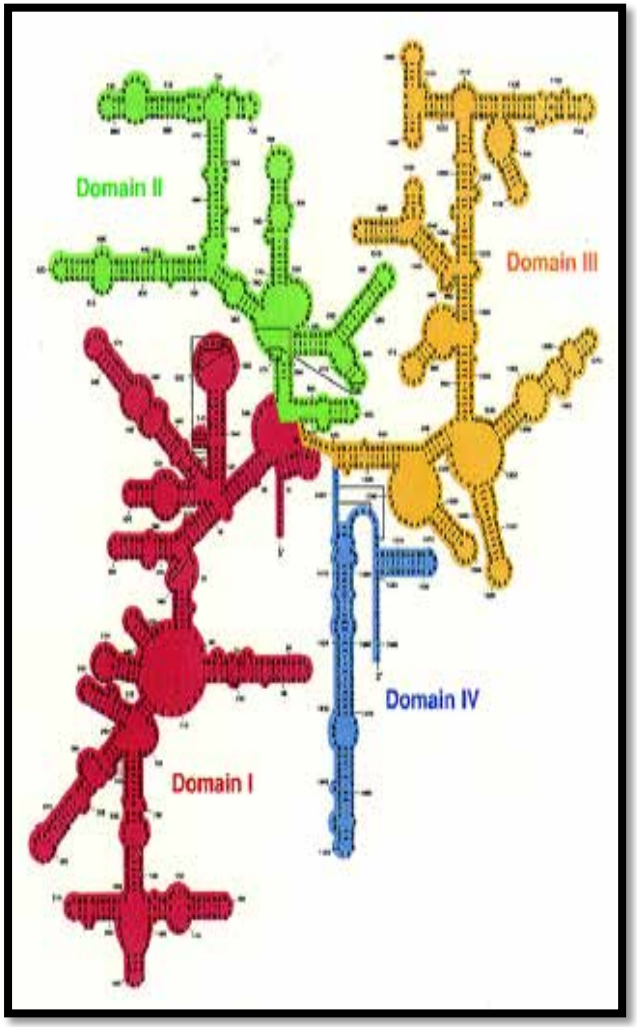


Métodos moleculares para estudiar la diversidad

16S RNA ribosómico, un buen marcador filogenético

- Universal
- Función idéntica y estructura (secuencia) conservada
- Fácilmente comparable
- Cronómetro evolutivo

16S rRNA



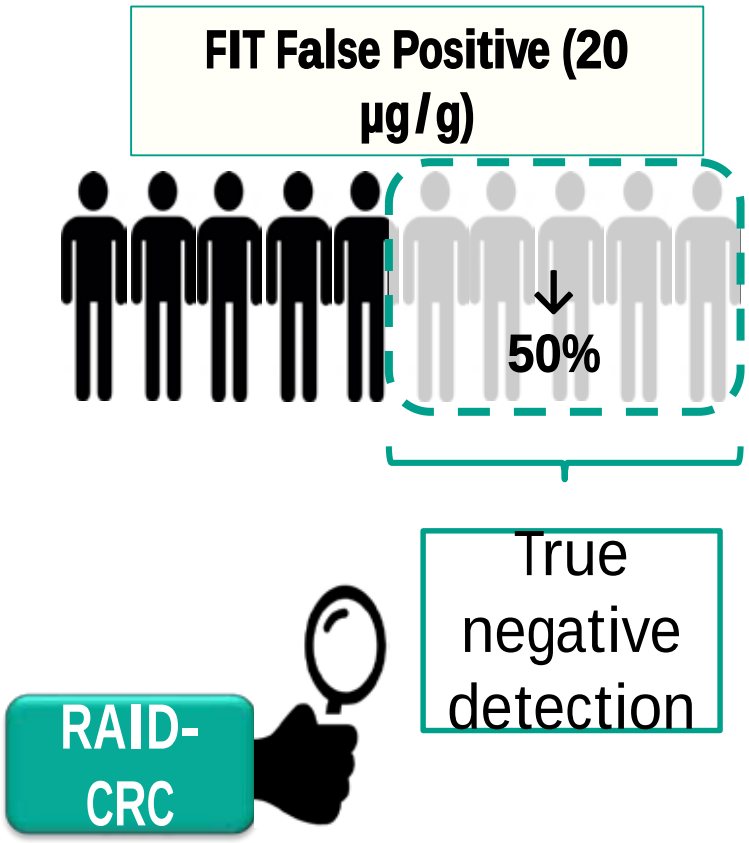
GOODGUT

Enhancing digestive health

RAID-CRC

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RAID-CRC (using FIT100)				
Precancerous lesion	50	91	40	94
Colorectal cancer	93	87	55	99
Advanced neoplasia	76	91	72	92
RAID-CRC (using FIT50)				
Precancerous lesion	59	90	43	95
Colorectal cancer	94	85	51	99
Advanced neoplasia	80	90	70	94
FIT100 (this study)				
Precancerous lesion	62	81	28	95
Colorectal cancer	98	75	42	99
Advanced neoplasia	84	81	59	94
FIT50 (this study)				
Precancerous lesion	76	76	28	96
Colorectal cancer	100	71	38	100
Advanced neoplasia	91	76	55	96
FIT100[46,47]				
Precancerous lesion	28	93	13	97
Colorectal cancer	78	92	2	99
Advanced neoplasia	30	93	15	97

FIT100 (20 µg haemoglobin/g of faeces); FIT50 (10 µg haemoglobin/g of faeces); PPV, positive predictive value; NPV, negative predictive value.



Alimentary T&P, Apr 2019

Diagnóstico diferencial con RAID-Dx

N= 84

Valores de sensibilidad y especificidad obtenidos para el diagnostico diferencial del Síndrome del Intestino Irritable y las enfermedades inflamatorias intestinales mediante el RAID-Dx y la calprotectina (punto de corte 50 µg/g).

Resultados SII *vs* EII	RAID-Dx	Calprotectina (50 µg/g)
Sensibilidad (%)	88.2	51.5
Especificidad (%)	89.2	92.2
Valores predictivos positivos (%)	79.0	80.9
Valores predictivos negativos (%)	94.3	74.6

RAID-Monitor: Activity Monitoring

RAID-Monitor: Digestive disease activity

Sensitivity and specificity values for preliminary RAID-Monitor and Calprotectin (pre-determined cut-off 250 µg/g) when analysing the same cohort diagnosed of Crohn's disease (n=34) and ulcerative colitis (n=70).

Performance	Crohn's Disease		Ulcerative colitis	
	RAID-Montior	Calprotectin	RAID-Monitor	Calprotectin
Sensitivity (%)	91.7	83.3	88.2	76.2
Specificity (%)	89.5	84.2	87.5	70.8
Positive predictive value (%)	84.6	76.9	83.3	65.6
Negative predictive value (%)	94.4	88.9	91.3	81
False inactive reduction (%)	66.6		50	

RAID-Monitor compared to calprotectin is able to detect endoscopic activity **reducing in 66.6% the false inactive CD patients and 50% in the false inactive UC.**

Cápsulas

Pros:

- Evita una prueba invasiva y anestesia
- Menos coste
- Sin preparación intestinal

Cons;

- Motilidad
- Píldoras grandes
- Muchas píldoras
- Dosis desconocida

TMF 2.0: consorcios de Microbiota (“heces artificiales”)

- Hasta hoy sólo tenemos datos sobre productos originados biológicamente, no hay datos de suspensiones realizadas sintéticamente

1.- RBX2660: 87,1% sobre recurrencia rCDI

- Objetivo 1º falló pero objetivos 2arios (mejora signif. sobre placebo de uno de los grupos)

2.- SER 109 :

- 30 pacientes
- 86,7% Cura rCDI
- No efectos adversos destacables

Cli Infect Dis Dubberke 2018
Khanna et al J Infect Dis 2016

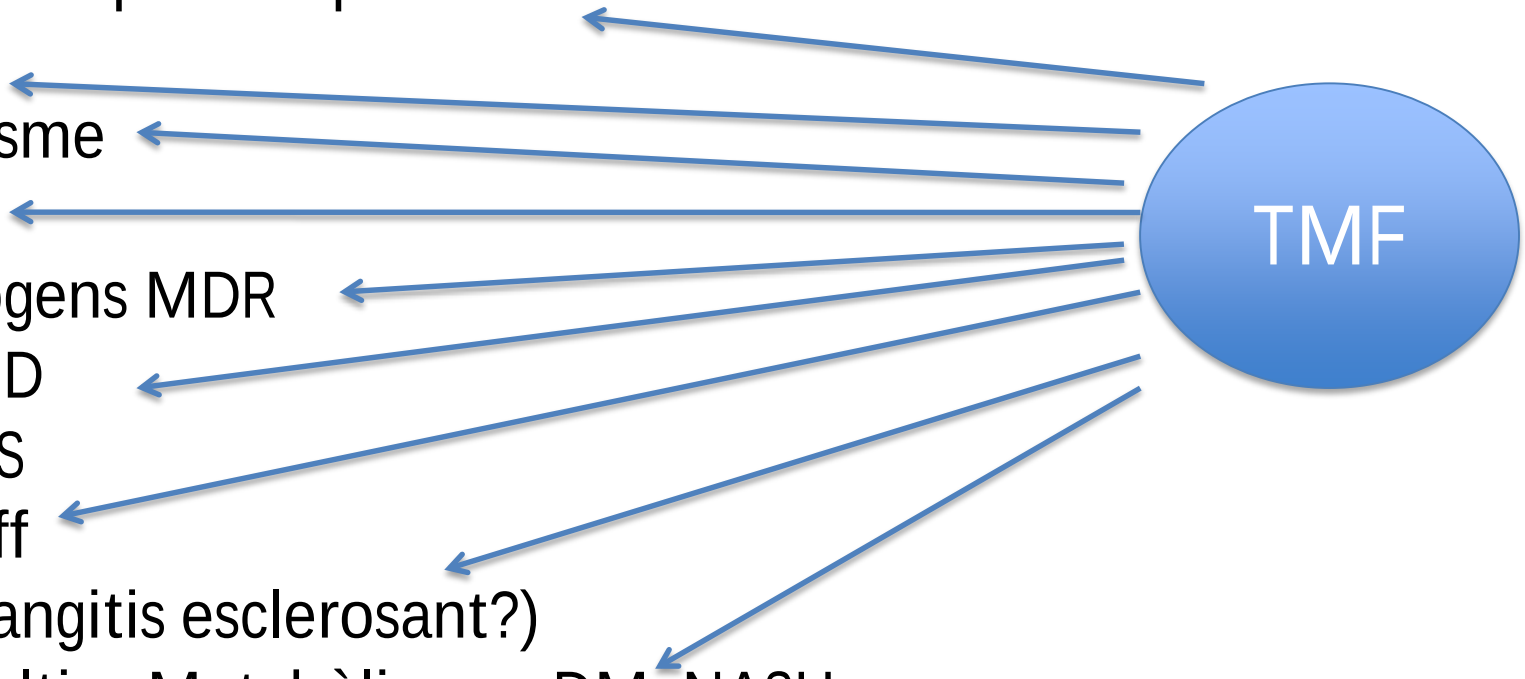
Gap entre investigadores básicos microbiota y clínicos: ¿Microbiomólogo ? (1)

- Continua puesta al día en investigación sobre microbiota
- Conocimiento sobre alteraciones disbióticas en enfermedades GI y extra GI
- capacidad interpretación del perfil microbiota
- Aplicación de investigación microbioma en práctica clínica
- Experto en modulación microbiota (pre-pro bióticos, TMF..)

Misssatges a retenir (1)

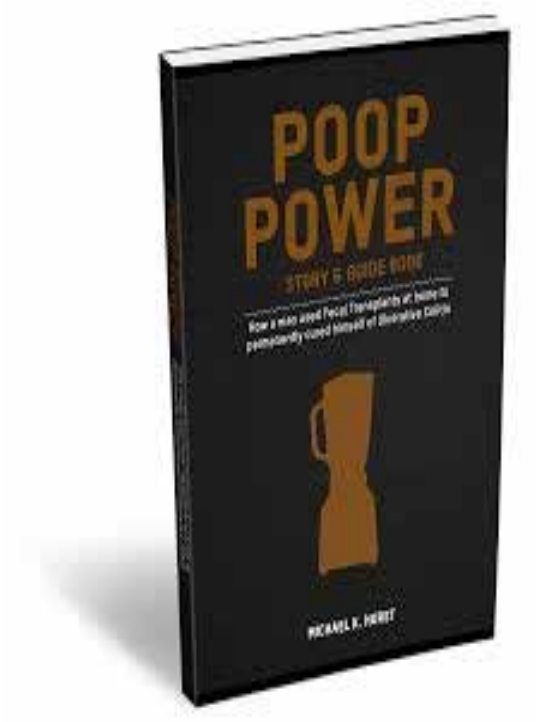
Indicacions FMT: de la investigació a la clínica

- Encefalopatia hepàtica
- CU
- Autisme
- SII
- Patògens MDR
- GVHD
- MetS
- C Diff
- (Colangitis esclerosant?)
- Malalties Metabòliques: DM, NASH

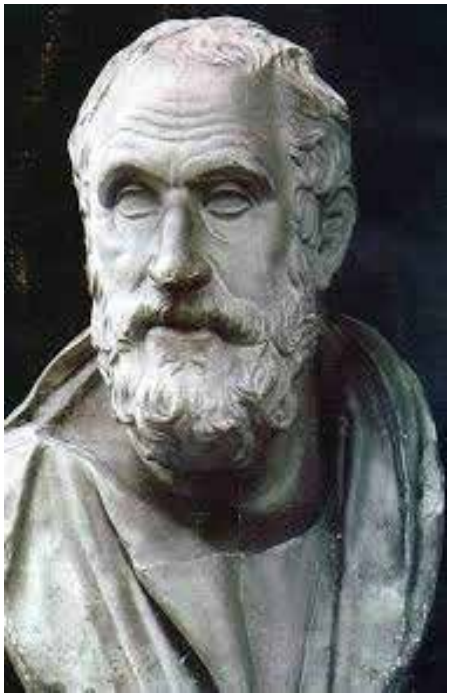


Missatges a retenir (2)

- Protocols futurs adaptats a les indicacions i perfils de pacients
- Marcadors clínics i microbiològics de predicció de resposta: Signatures microbiològiques
- L'ús de femtes encapsulades poden impulsar el TFM i mantenir el seu efecte en malalties cròniques
- TMF 2.0: Suspensions artificials
- Trasplantament tisular vs intervenció farmacèutica
- Desenvolupament de bancs de femtes i centres experts en TMF
- Concept de microbiomòleg


POOP
POWER
STAY'S INSIDE NOW
MICHAEL K. HURST

Hipòcrates



Tota malaltia s’inicia als budells

Gràcies!

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