Intestinal Pseudo-obstruction (Gut Motility Disorders)

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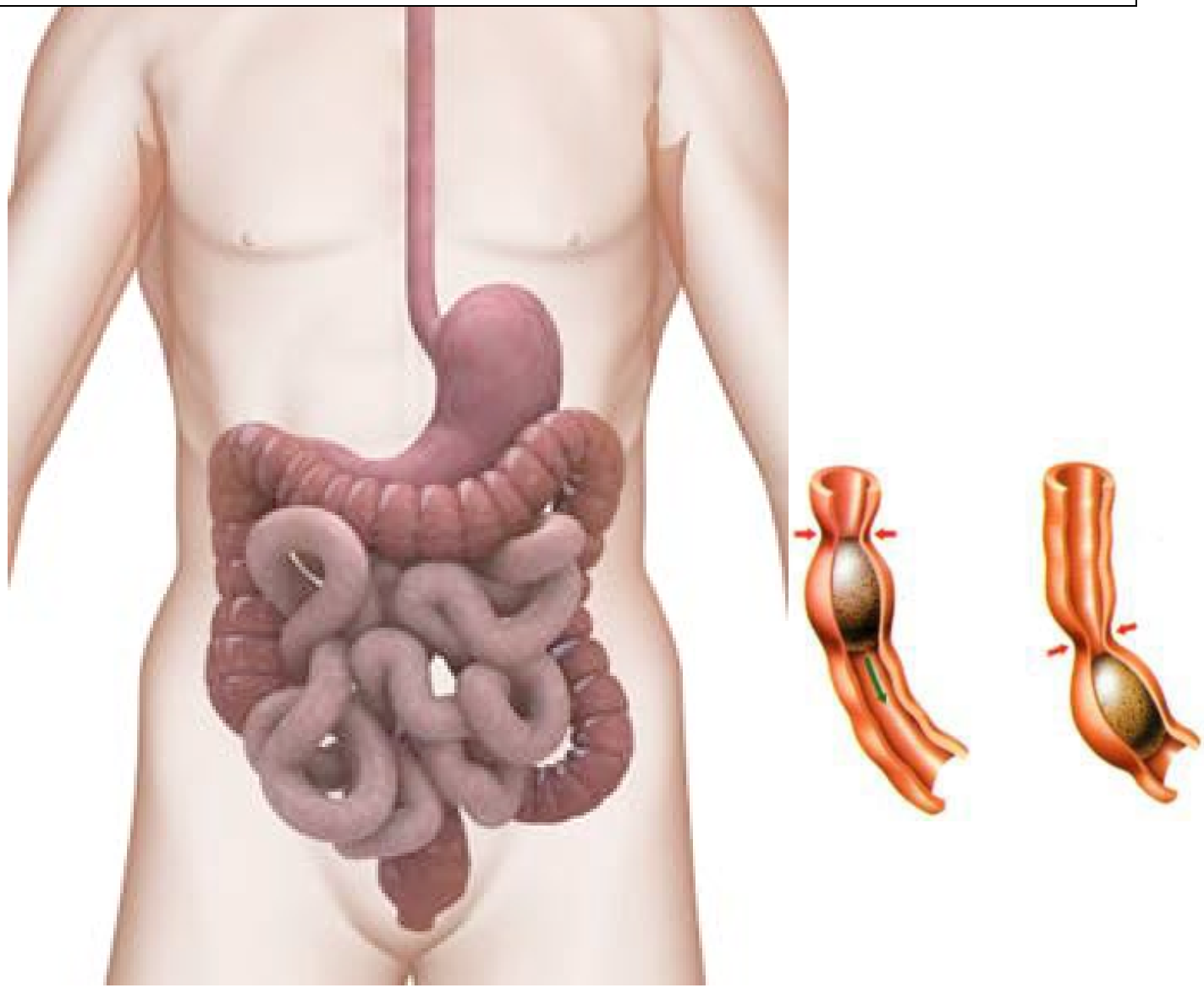
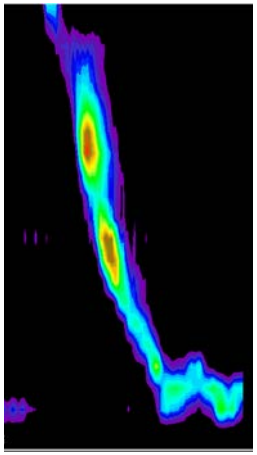
Gastrointestinal Tract

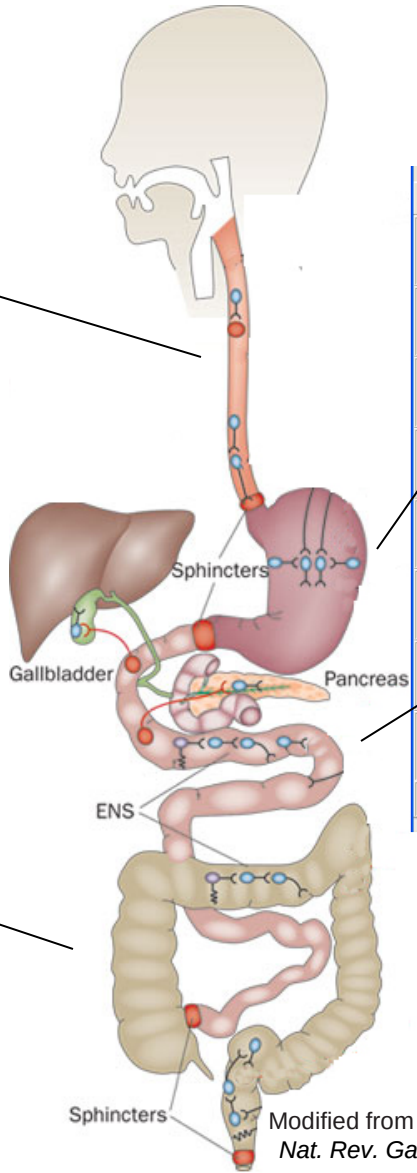
functions dependent on gut motility

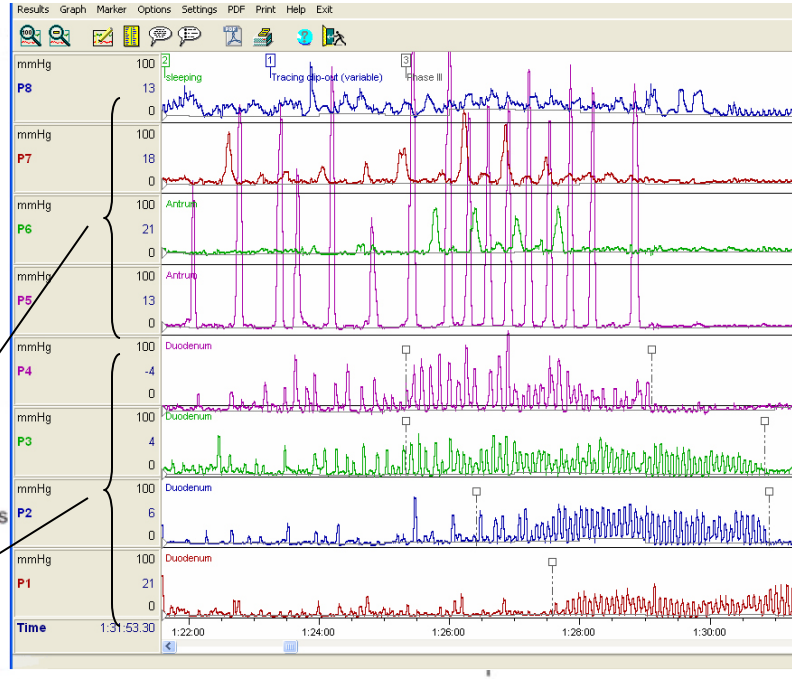


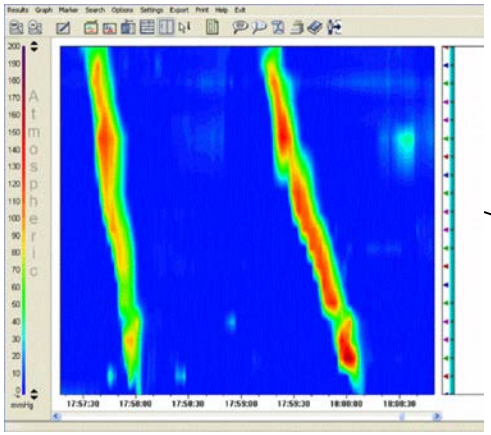
Gut Motility

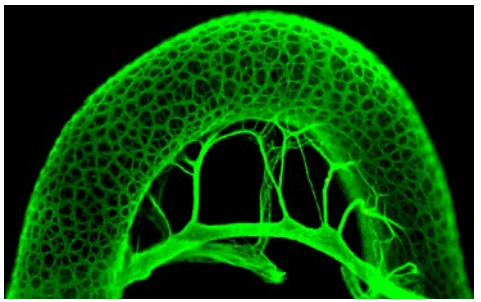
complex regional patterns







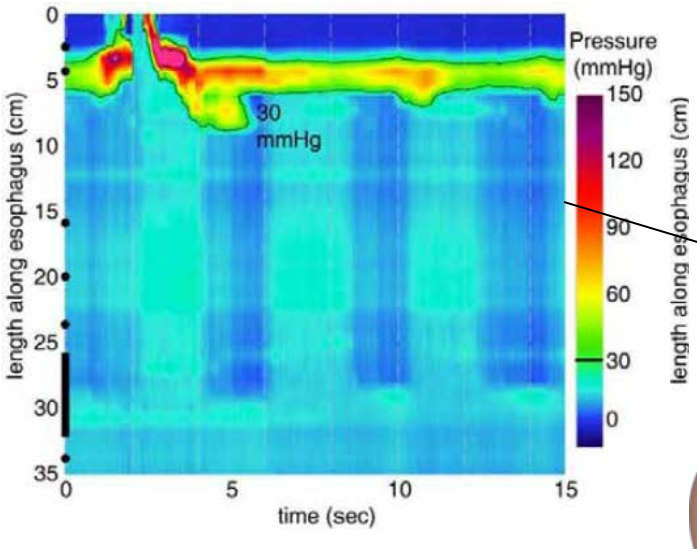


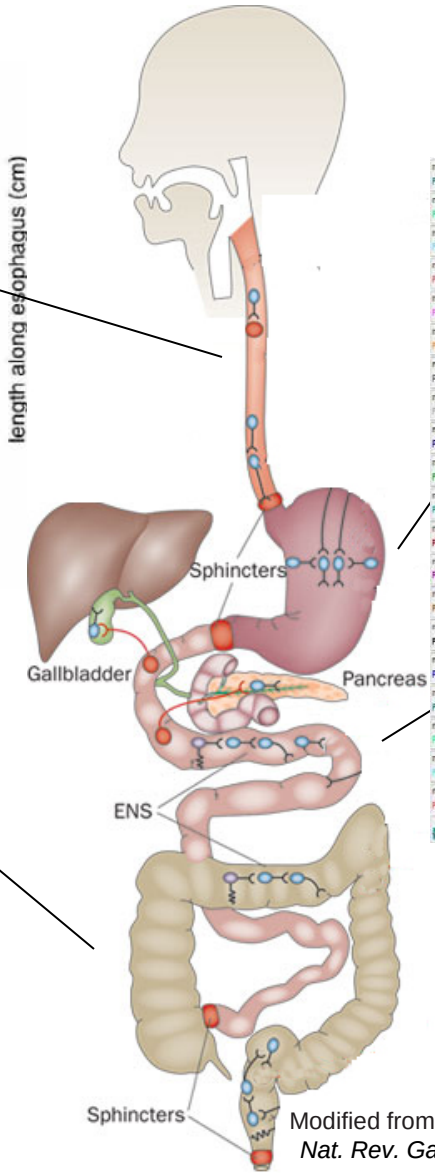


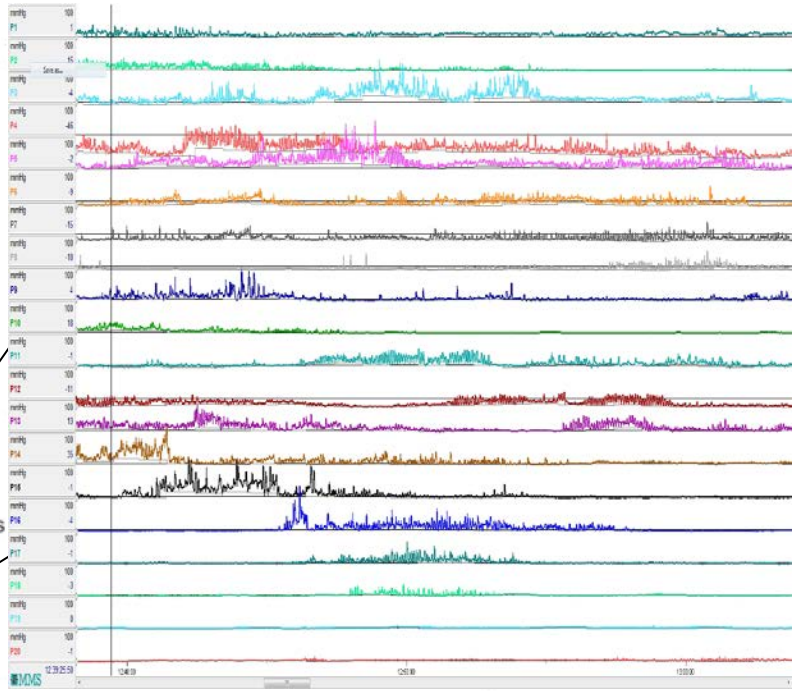
Modified from Furness, J. B. (2012)
Nat. Rev. Gastroenterol. Hepatol.

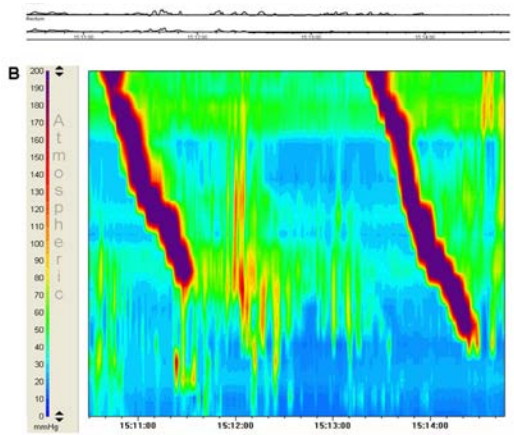
Gut Motility Disorders

failure of gut neuromusculature









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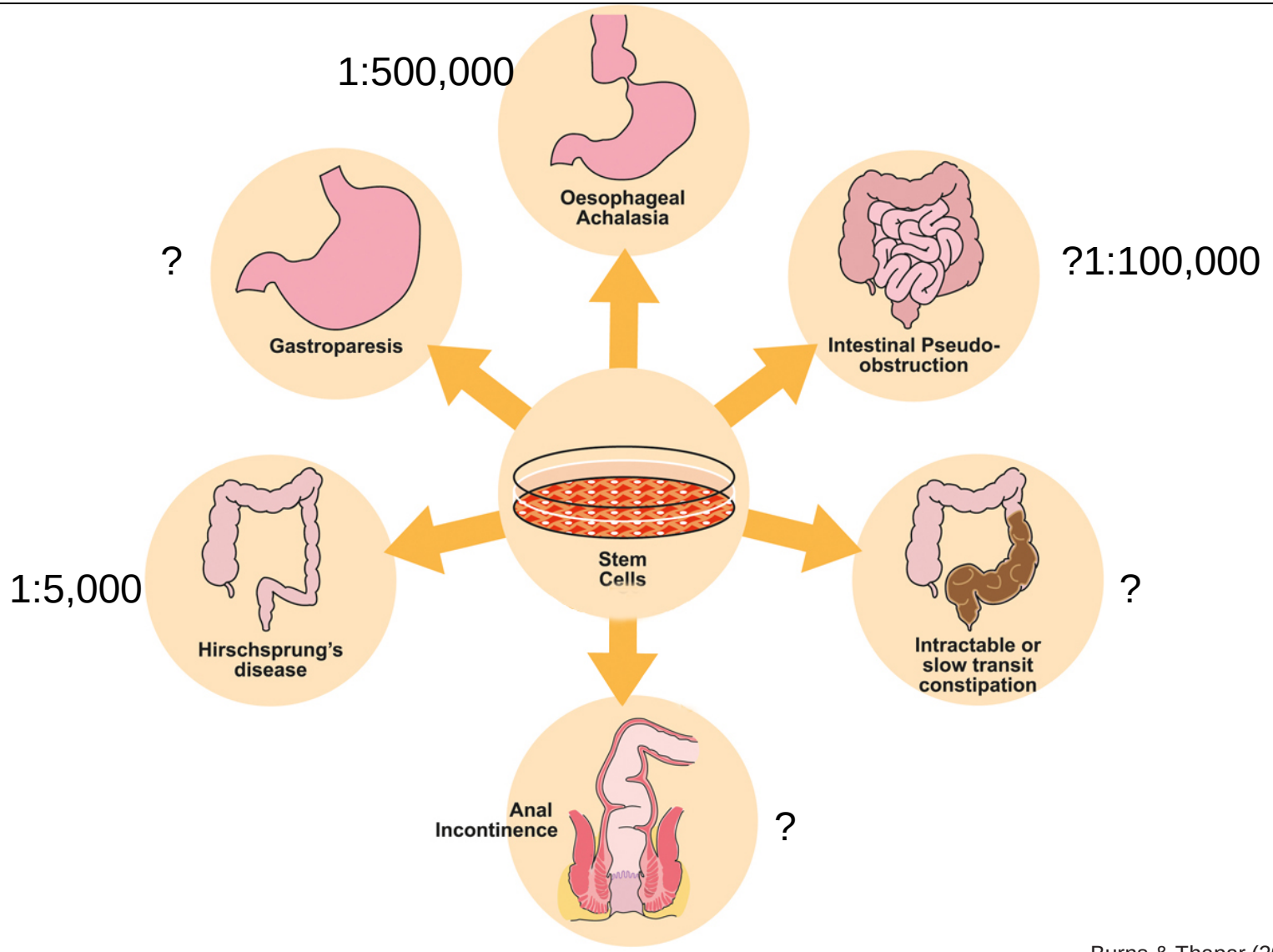
Nat. Rev. Gastroenterol. Hepatol.

Paediatric Gastrointestinal Motility Disorders

rare, diverse and challenging



Burns & Thapar (2014)
Nature Reviews Gastro Hepatol

Chronic Intestinal Pseudo-obstruction

Failure of function of the small intestine

- Symptoms/signs of small intestinal obstruction but no mechanical cause
- Dilated small intestine with fluid levels

Paediatric Intestinal Pseudo-obstruction
natural history and prognosis

In infants CIPO appears to have a particularly severe course
- 60%–80% requiring parenteral nutrition and
- 10%–25% dying before adulthood Mousa et al. Dig Dis Sci 2001

Faure et al. Dig Dis Sci 1999
Muto et al. JPS 2014

Soh et al. JPS 2015

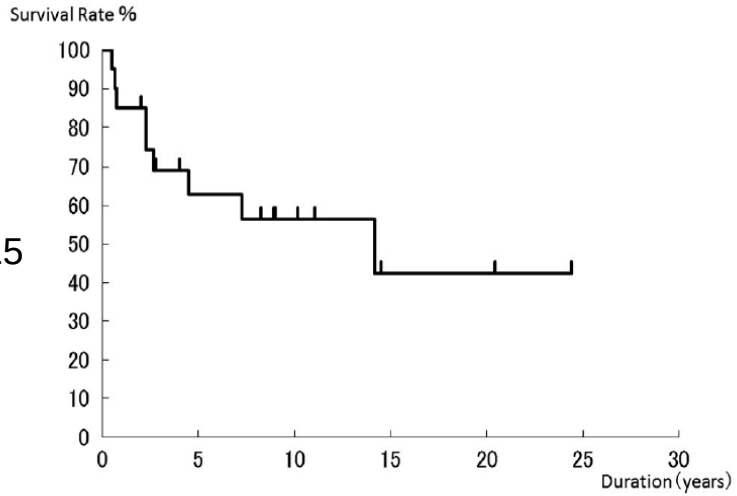
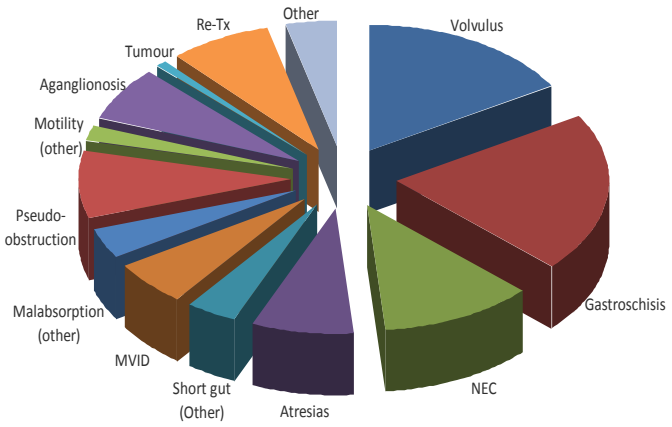


Fig. 1. The survival rates of MMIHS obtained from 19 patients using the Kaplan–Meier method. The five- and ten-year survival rates were 63 and 57%, respectively.

Intestinal transplantation



Paediatric Intestinal Pseudo-obstruction

Great Ormond Street Hospital data pre-2012

Delayed referral and/or diagnosis

- 11.3 years

Repeated unnecessary abdominal surgeries

- 3-5 surgeries before referral to tertiary centre

Poor feed tolerance

- ~100% on parenteral nutrition

Complications (morbidity, hospitalisation days, mortality)

- 90 days a year in hospital, 20-30% mortality, PN related complications

Poor quality of life

Paediatric Intestinal Pseudo-obstruction

Epidemiology

North America - NASPGHAN Survey

- 100 infants are born in the United States every year with CIPO
- incidence of approximately 1 per 40,000 live births
- Equal sex incidence

Japan - Nationwide survey

- children younger than 15 years of age the prevalence of 3.7 in one million children (1 in 270,000 children)
- 56.5% developed CIPO in the neonatal period
- Equal sex incidence

Vargas et al JPGN 1988
Muto et al. JPS 2014

Paediatric Intestinal Pseudo-obstruction

Pharmacotherapy

- Anticholinesterase inhibitors
  - Neostigmine, Pyridostigmine, Donepezil
- $5HT_4$ Receptor Agonists
  - (Cisapride, Tegaserod withdrawn)
  - Prucalopride
  - TD-5108
- Motilin Agonists / Ghrelins
- Octreotide
- Cannabinoids
- Opioid Receptor Antagonists
- Chloride Channel Activators
  - Lubiprostone
- Guanylate Cyclase Receptor Agonists
  - Linaclotide
- Antibiotics

Paediatric Intestinal Pseudo-obstruction

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- gonists
- Activators
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- ate Cyclase Receptor Agonists
  - Linaclotide
- Antibiotics

Not tested in Children
Variable Efficacy
Unacceptable extra-intestinal Side Effects

Paediatric Intestinal Pseudo-obstruction
Management

- Nutrition to preserve growth and development
  - Enteral feeds
  - PN
- Limit symptoms & improve quality of life
  - Medical Rx
  - Surgery
  - Psychology
- Prevent complications
  - Sepsis
  - Bacterial Overgrowth

Chronic Intestinal Pseudo-obstruction

Challenges

- Rare
  - need for national/international registries
  - collaboration
- Lack of clarity
  - aetiopathogenesis
  - diagnostic criteria
  - classification
- Lack of uniformity
  - available expertise
  - diagnostic protocols
  - management strategies

gut environmental factors

cell signalling pathways

transcription factors

intracellular molecules

Table 1 | Role of molecules produced by the gut mesenchyme or epithelium in ENS development

Secreted ligand	Role in ENCCs	Phenotype of mouse ENS after perturbation	Evidence for role in Hirschsprung disease
GDNF (mesenchymal)	Prom… differ…	…ch[146]	Yes[148]
Endothelin-3 (mesenchymal)	Promotes proliferation and migration;	*Edn3*$^{+/-}$: normal enteric neuron density[150]	Yes[9,152]
ECE1 (mesenc…			
Neurotrophin-3 (mesenchymal…			
Sonic hedgeho… (epithelial)			
Indian hedgeh… (epithelial)			
BMP2 and BM… (mesenchymal…			
Netrin (epithel…			
Semaphorin 3… (mesenchymal…			
Neurturin (mesenchymal…			
GGF2			

Abbreviations: BM… system; GDNF, gli…

Table 2 | Role of cell-surface molecules expressed by ENCCs in ENS development

Cell-surface molecule	Role in ENCCs	Phenotype of mouse ENS after perturbation	Evidence for role in Hirschsprung disease
RET	Signal…	…ach[165]	Yes[10]
GFRA1	GPI linked GDNF receptor[36]	*Gfra1*$^{+/-}$: normal ENS[2]	Yes[167]
GFRA2			
ET-BR			
TrkC			
PROKR1, PROK…			
ErbB2			
ErbB3			
DCC			
Notch			
PTCH1			
β1-integrin (Itβ1…			
L1-CAM			
PSA-NCAM			
N-Cadherin			
Neuregulin-1			

*Ednrb$^{s/s}$: s is a hy… ENS, enteric nervou… not determined; PR…

Table 3 | Transcription factors and cofactors expressed by ENCCs and their role in ENS development

Transcription factor	Role in ENCCs	Phenotype of mouse ENS after perturbation	Evidence for role in Hirschsprung disease
Sox10	Progen… Phox2…	…aganglionosis[17,191] …nosis[53,192]	Yes[189–191]
Sox8	Acts with Sox10, maintains progenitors[55]	*Sox8*$^{-/-}$ or *Sox8*$^{+/-}$: increases severity and penetrance of *Sox10*$^{+/-}$ phenotype[55]	ND
Foxd3	Reg…		
Phox2b	Pro…		
Hand2	Pro… sub…		
Ascl1 (Mash1)	Pro… sub…		
Pax3	Act…		
AP-2 family	ap2…		
Sox2	Exp…		
Zeb2 (Zfhz1b, SIP1)	Spe…		
Hlx	Pro…		
TCF4	Inte…		
Hoxb5	Ind…		
HIPK2	Pos…		

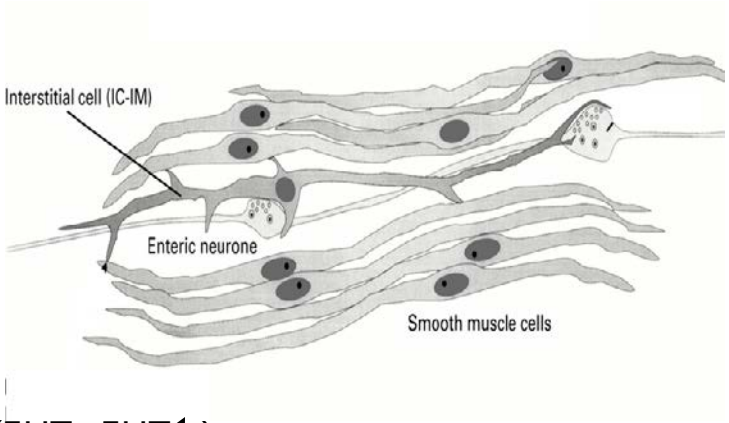
Abbreviations: AP-2, acti… ND, not determined; RET…

Table 4 | ENCC intracellular molecules, neurotransmitter-related molecules and dietary factors involved in ENS development

Factor	Role in ENCCs	Phenotype of mouse ENS after perturbation	Evidence for role in Hirschsprung disease
Intracellular molecule			
SPRY2		…achalasia[19]	ND
KIF26A	Negative regulator of RET signalling[20]	*Kif26A*$^{-/-}$: enteric neuronal hyperplasia with megacolon[20]	ND
Phactr4	Promotes migration[214]	*Phactr4*$^{humdy/humdy}$ (missense mutation): decrease in NOS neuron density in the colon[214]	ND
KIF-1 binding protein (KIAA1279/KBP)	ND	ND	Yes[65]
Pten	Inhibits migration and proliferation[29]	*PTEN* cKO: hypertrophy and hyperplasia of the ENS; fatal intestinal pseudo-obstruction[21]	ND
Small GTPases	Promote migration, proliferation, neurite extension[26]	*Cdc42* and Rac1 cKO: lack of colonization of the distal intestine[142]	ND
microRNAs	Promote differentiation[215]	*Dicer* cKO: apoptosis of ENCCs by E17[216]	ND
Tcof1/Treacle	Promotes survival[54]	*Tcof1*$^{-/+}$: reduced number of NCCs and a delayed and prolonged migration of ENCCs[54]	ND
Protein kinase Cζ	Promotes cell polarity, axon formation, migration[88]	ND	ND
BBS	Promotes migration[217]	ND	Yes[23]
Neurotransmitter-related molecule			
Norepinephrine transporter	Promotes development and survival of neuronal subtypes[99]	*NET*$^{-/-}$: reduction of 5-HT and calretinin neurons and total enteric neuron number[99]	ND
Sodium-dependent action potentials	Promotes neuronal differentiation of neuron subtypes[83]	ND	ND
Serotonin	Promotes differentiation[100]	*Tph2*$^{-/-}$: reduction of dopaminergic and total enteric neuron number[100]	ND

Neuro-immune interactions

role in gastrointestinal symptoms/disease



Ye et al
2008 J Cell Mol Med

Smyth et al
2013 Plos One

Serotonin ($5HT_3$, $5HT_4$)

PAR 1,2 and 4

Histamine 1-4

CAM 1

IL-4

IL-13

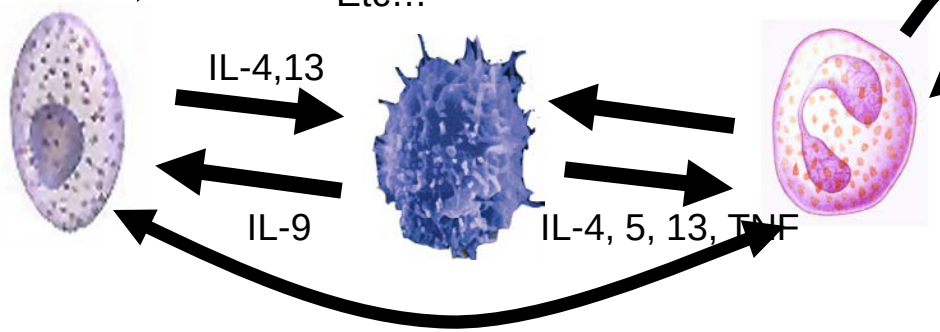
Etc…

CGRP
Substance P
Acetylcholine
Noradrenaline

IL-9
IL-4
IL-13
Etc…

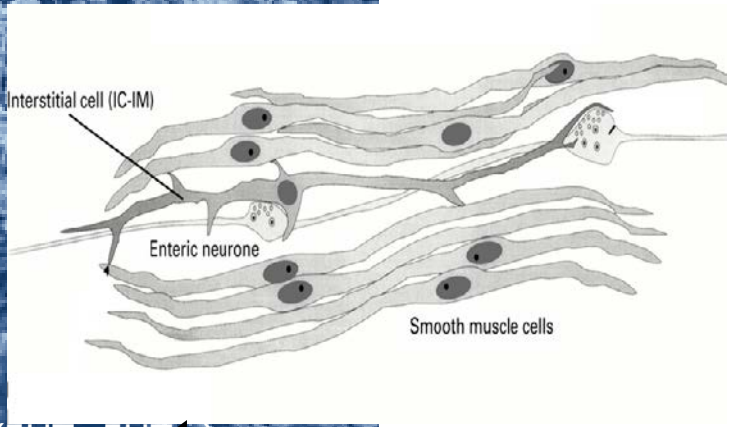
Eotaxin
Substance P
Acetylcholine

Leukotrienes
MBP
Etc…



Neuro-immune-microbiome interactions

role in gastrointestinal symptoms/disease



Ye et al
2008 J Cell
Mol Med

Smyth et al
2013 Plos
One

The Gut Microbiota

Serotonin ($5HT_3$, 5HT$_P$)

PAR 1,2 and 4

Histamine 1-4

CAM 1

IL-4

IL-13

Etc…

CGRP
Substance P
Acetylcholine
Noradrenaline

IL-9
IL-4
IL-13
Etc…

otaxin
ubstance P
cetylcholine

Leukotrienes
MBP
Etc…

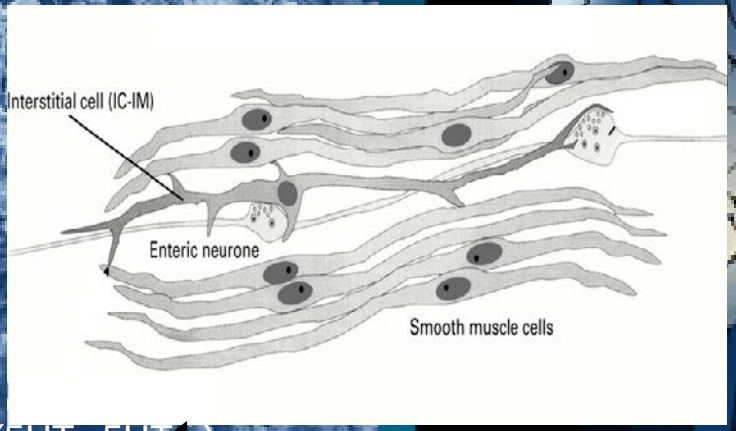
IL-4,13

IL-9

IL-4, 5, 13, TNF

Eotaxin
IL-3
IL-5
GM-CSF

Neuro-immune-microbiome-brain interactions
role in gastrointestinal symptoms/disease



Ye et al
2008 J Cell
Mol Med

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The Gut Microbiota

Serotonin ($5HT_3$, 5HT$_P$)

PAR 1,2 and 4

Histamine 1-4

CAM 1

IL-4

IL-13

Etc…

CGRP
Substance P
Acetylcholine
Noradrenaline

IL-9
IL-4
IL-13
Etc…

Eotaxin
Substance P
Acetylcholine

Leukotrienes
MBP
Etc…

IL-4,13

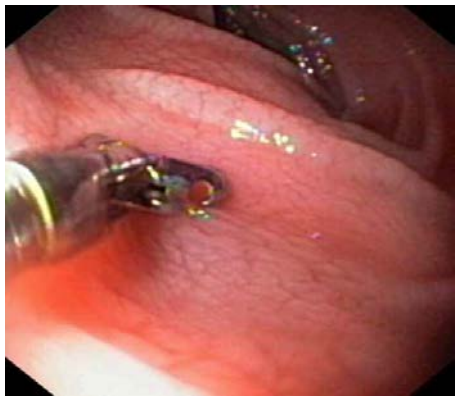
IL-9

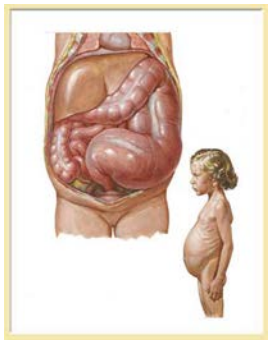
IL-4, 5, 13, TN

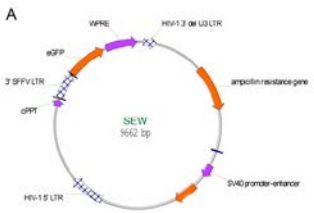
Eotaxin
IL-3
IL-5
GM-CSF

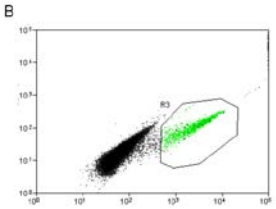
Human studies

In vivo transplantation of post-natal neural stem cells

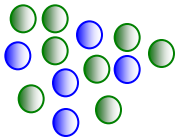


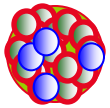


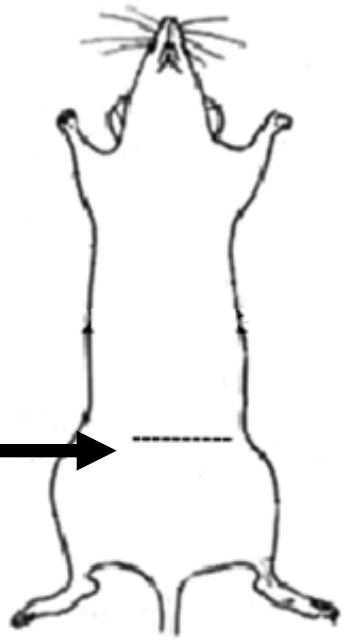




Dissociation into single cells

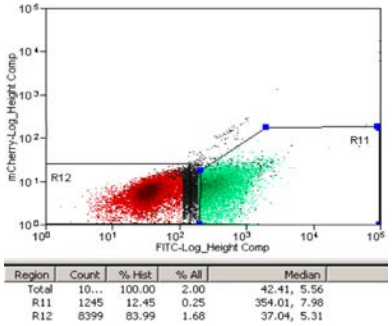






Rag2^{-}*/γc*$^{-}$*/C5*$^{-}$ mouse

p75^{NTR}



Natarajan et al,
Neurogastroenterol Motil
2014


Thank You