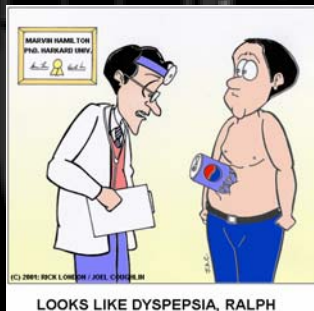


Seen it all:
Gastroenterology in Primary
Care

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Areas of discussion

Dyspepsia
Irritable bowel syndrome
Hepatitis B



Dyspepsia

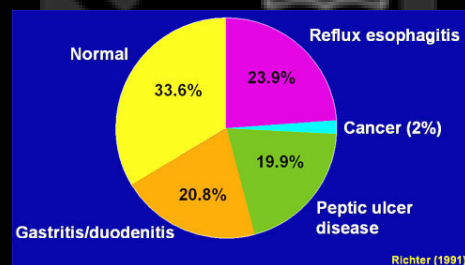
- Discomfort or pain centred in the upper abdomen
 - Associated symptoms:
 - fullness,
 - bloating,
 - early satiety
- ?weight loss ?heartburn included

Epidemiology

- Prevalence is 20-49%
- Scandinavia: dyspepsia developed in 0.8% of subjects without dyspepsia in a 3-month period

Talley NJ et al. *Gastro International* 1991;4:145-60
Locke GR III et al. *Gastroenterology* 1997;112: 1448-56
Talley NJ et al. *Dig Dis Sci* 1995;40:584-9

Causes of dyspepsia



Causes of dyspepsia

Ask about Drugs

NSAIDs,
alendronate
erythromycin
orlistat
acarbose
theophylline

Discriminant value of symptoms

Symptom subgroups and scoring systems correlate poorly with cause.

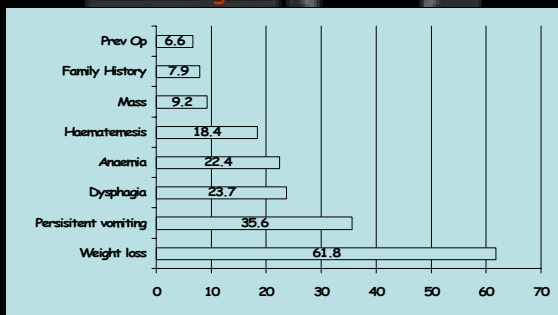
Alarm features (1)

- > 45 years-new onset
- Weight loss >10% of body weight
- Anorexia
- Persistent vomiting
- Rectal bleeding/melaena
- Anaemia
- Abdominal mass/ lymphadenopathy
- Progressive dysphagia or odynophagia

Alarm Features (2)

- Family history of upper GI cancer
- Previous gastric surgery or malignancy
- Previous history of peptic ulcer
- Jaundice

Frequency of alarm symptoms in gastric cancer



American Journal of Gastroenterology 1999;94:2329-2330

Management Strategies

1. Prompt endoscopy & directed treatment
2. Blind empiric antisecretory treatment
3. *H.pylori* test & treat

Prompt endoscopy & directed treatment

- "Gold standard" option
- Little advantage over non invasive strategies if young age and lack of alarm symptoms
- Provide reassurance -but effect not durable

Blind empiric antisecretory treatment

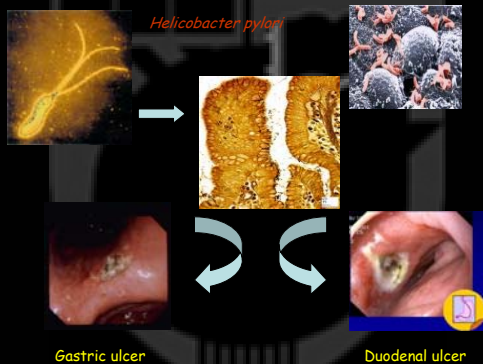
- Possible acid hypersensitivity
- RCT in primary care setting suggests PPI is superior over other Rx
- Chinese trial showed no benefit
- Can promote healing of undiagnosed peptic ulcer, but remains at risk of recurrence once Rx is stopped

Blind empiric antisecretory treatment

- If Hp is uncommon, consider antisecretory alone
- If Hp prevalent, eradicate infection before antisecretory to eliminate ulcer disease

H. Pylori test-and-treat

Advantage:
eliminates underlying ulcer disease



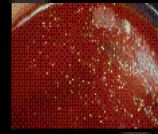
H. Pylori test-and-treat

- Disadvantages:
- 1/3 will remain symptomatic due to unmasking of functional dyspepsia or GERD
 - Most functional dyspepsia not relieved with *Hp* eradication.(NNT 1 in 15)
 - Conflicting results over the efficacy of test& treat over OGDS/PPI

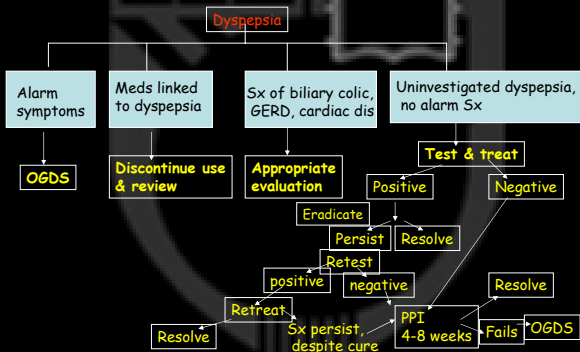
How to test for *H. pylori* Non-invasive



How to test for *H. pylori* Invasive



Treatment algorithm for Dyspepsia



Failed standard therapies

What next?

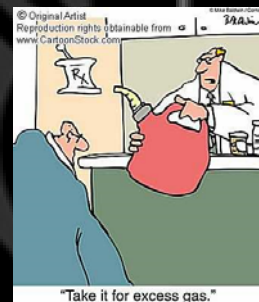
1. Stepping up PPI/H2RA
2. Tricyclic antidepressants
Limited data on efficacy
Treat for at least one month
Low dose 10-25mg nocte
3. Serotonin type 4 agonists eg tegaserod
4. Serotonin type 1 agonists eg sumatriptan
5. Itopride (Ganaton)

Failed standard therapies

Re-evaluate data used to make diagnosis of dyspepsia

Other diseases masquerading as functional dyspepsia

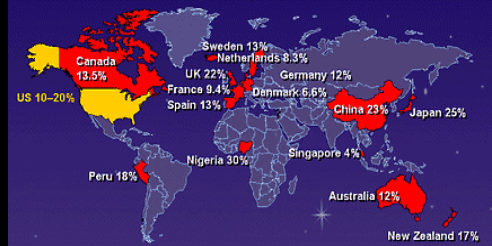
- Occult pancreatic adenocarcinoma
- Lactose intolerance
- Coeliac disease
- Eosinophilic gastroenteritis
- Type II DM
- Crohn's
- Thyroid dysfunction
- Hypercalcaemia
- CTD



Irritable bowel syndrome

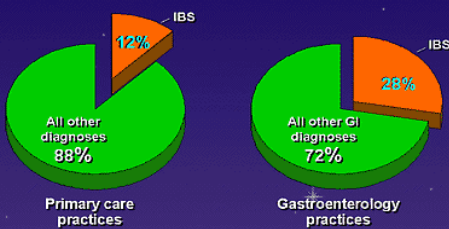
- Benign, chronic symptom complex of altered bowel habits and abdominal pains
- Functional - no organic or structural cause
- Other associated functional disorders:
Functional dyspepsia
Functional anorectal pain
Noncardiac chest pain

World prevalence of IBS



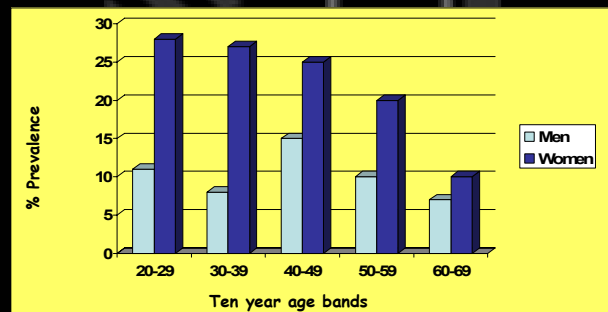
Adapted from Camilleri et al, Aliment Pharmacol Ther 1997; 11: 3
Muller-Lissner et al, Digestion 2001; 64: 200

Prevalence of IBS diagnosis in primary care and gastroenterology practices



Mitchell and Drossman, Gastroenterology 1987; 92: 1282

Distribution by age and gender



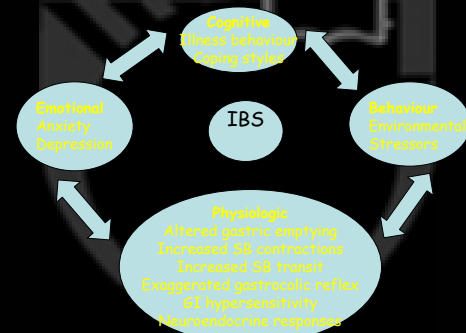
In Malaysia.....

Prevalence of IBS in young adult Malaysia: a survey among medical students

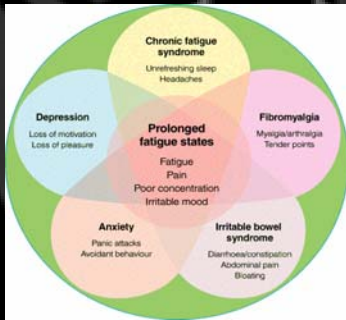
- Prevalence rate 15.8%
- Women > Men
- Constipation-predominant IBS- 77.4%
- Higher prevalence of psychological & psychosomatic sx
- Minority sought medical treatment

YM Tan et al, J Gastroenterol Hepatol 2003

Aetiology & Pathophysiology



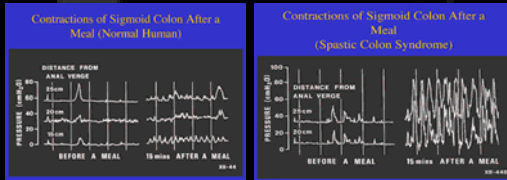
Extraintestinal manifestations



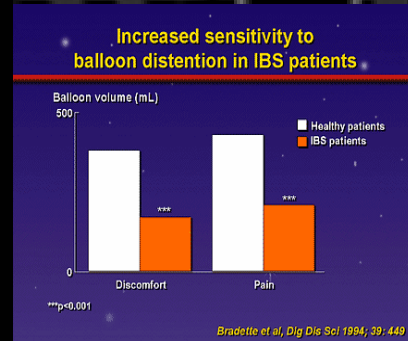
Pathophysiology of IBS

- Altered motility
- Visceral hypersensitivity
- Central hyperresponsiveness
- Prior gut infection

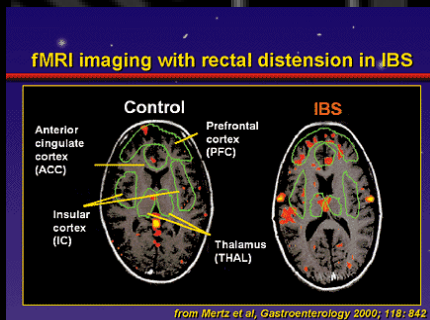
Altered motility



Visceral hypersensitivity



Altered pain perception



Brain-Gut interaction

Painful Visceral Sensation

Activation of sympathetic spinal afferents

Haemostatic visceral responses
Assoc with vagal responses
Eg satiety, nausea

Efferent responses assoc with visceral perception
Modulate intensity of afferent input

Post-infective IBS

- Acute GI infective episode
- Viral or bacterial
- Sx of gastroenteritis subside but Sx of IBS emerge
- Low grade inflammation present in subset
- Biggest predictor of subsequent IBS following enteric infection is adverse life event /psychological stress

Pathophysiology of infectious IBS

1. Accelerated gut transit
2. Increase rectal sensitivity
3. Increased intestinal permeability
4. Increased number of lymphocytes

Spiller et al Gut 2000;47:804
Rodriguez et al. BMJ 1999;318:565

Diagnosis of IBS

Rome II criteria

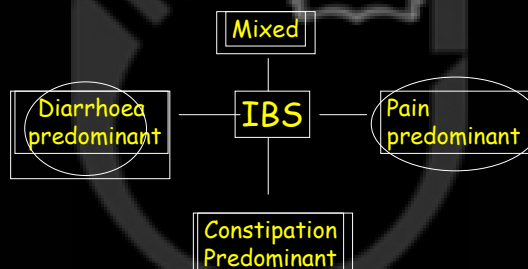
- 12 or more weeks of continuous or recurrent abdominal pain or discomfort

Plus at least 2 of the following

- Relieved by defaecation
And/or
- Associated with change in stool frequency
And/or
- Associated with stool appearance

Drossman et al. Gut 1999;45:1-81

Subtypes of IBS



Red Flags

- Anaemia
- Fever
- Family History of CRC or IBD
- Positive FOBT
- New onset of symptoms over age 50
- Nocturnal symptoms
- Persistent diarrhoea or severe constipation or rec
- Rectal bleeding
- Weight loss
- Palpable abdominal or rectal mass

Management of IBS



A strong patient-physician relationship
Repeated reassurance of no serious disease

Dietary recommendations

Limit caffeine, alcohol and fat



No association between IBS and food intolerance

Pain-predominant IBS Drug Therapy

- Antispasmodics - mebeverine
- Tricyclic antidepressants- amitryptilline
- 5 HT4 agonist- Tegasarod*

* Approved for short term control in♀ by FDA

Jailwala et al. Ann Int Med 2000;133:136-147
Steinhart et al. Int j Psychiatry Med 1981;11:45-57

Diarrhoea Predominant Drug Therapy

- Loperamide (immodium)- slows transit
- Cholestyramine- bile acid sequestrant
- 5HT3 antagonist (Alosetron*, riodansetron)

*In females only

Camilleri et al. Arch Int Med 2001;161:1733-40
Jailwala et al. Ann Int Med 2000;133:136-147

Constipation Predominant Drug Therapy

- Fiber Supplementation
- Laxatives
- 5HT4 agonist-Tegaserod (*Zelmac*)

Cann et al. Gut 1984;25:168-73
Kamm et al. Am J Gastroenterol 2005;100(2):362-72

Gas/ Bloating Drug Therapy

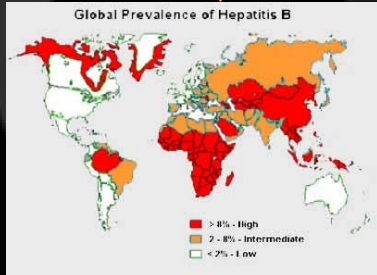
Dietary modification
Antispasmodics

Chronic Hepatitis B
Preventable and Now Treatable



Epidemiology

More than 300 million carriers worldwide
 ~ 500 000 to 1.2 million die annually from HBV related complications



Hepatitis B virus

- Double stranded DNA virus (hepadnaviruses)
- 8 genotypes (A to H)
- Prevalence of genotypes varies geographically



How hepatitis is spread

INFECTION SOURCE	TRANSMISSION PROBABILITIES		
	B virus	C virus	
	Definitely	Rarely	Suspected
Between family members	B		
Job exposure to blood	B C		
Needle-stick injuries	B C		
IV drug use (shared needles)	B C		
Transfusions	B C		
Hemodialysis	B C		
Orally		B C	
Sexually	B		C
Anal/oral sex	B		C
Mother to child at birth	B		C
Body piercing	B C		
Acupuncture/tattooing	B C		
Recreational cocaine	B C		

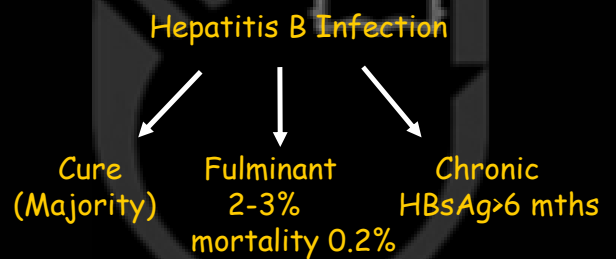
Who should be tested?

- Persons born in endemic areas
- Homosexuals
- IVDU
- Patients on dialysis
- HIV patients
- Pregnant women
- Family, household and sexual contacts of HBV infected persons

Clinical manifestations

- Incubation 60-180 days
- Variable clinical spectrum
- Asymptomatic
- Mild anicteric illness
- Acute disease with jaundice
- Fulminant hepatitis
- Extrahepatic-vasculitis, nephritis, arthritis and PAN

Prognosis



Risk factors for chronicity

1. Childhood acquisition
 - 90% in childhood infection
 - 1-5% in adults
2. Males
3. Congenital or acquired immunodeficiencies

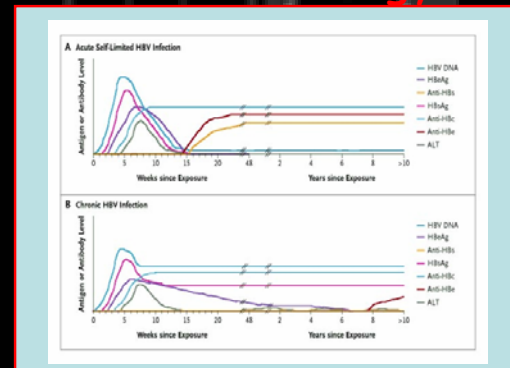
Evaluation

- History & Examination-risk factors
- Lab: FBC, LFT, Coag, HBV serology
- Exclude other causes of liver disease
- Alpha fetoprotein
- USS abdomen

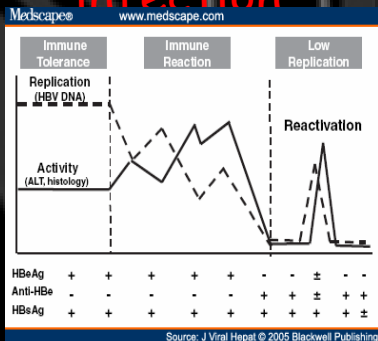
HBV serology

- HBsAg-detectable 2-8 week before jaundice
- HBV DNA
- HBeAg
- Anti HBs
- Anti HBc (IgM)

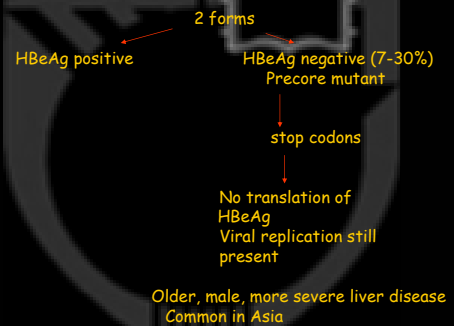
HBV Serology



Phases of HBV infection



Chronic HBV



Prevention

- Safe and effective vaccine in 1980s
- Routine vaccination of newborns in endemic areas
- Decline in chronic HBV and HCC



Who should be treated?

- Rx delayed for 3-6 months in newly diagnosed HBeAg + patients
- ALT higher >2X ULN
- HBV DNA >10⁵ copies/ml
- Liver biopsy with necroinflammatory score of 4

Why should we treat?

To improve survival and decrease risk of hepatocellular carcinoma

Liaw et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease, NEJM 2004;351:1521-1531

Licensed Treatment



LAMIVUDINE



ADEFOVIR



ENTECAVIR



PEG INF α-2A



STANDARD IFN

1. Lau et al, NEJM 2005
2. Marcellin et al, NENM 2004
3. Marcellin et al, NEJM 2003
4. Hadziyannis et al, NEJM, 2003
5. Chang et al, NEJM, 2006
6. Lai et al, NEJM, 2006

Advantages & Disadvantages of HBV therapies

IFN	LAMIVUDINE	ADEFOVIR	ENTECAVIR
Sub-cut injection	Oral	Oral	Oral
Finite	Long duration	Long duration	Long duration
10MU x3/wk(std)	100mg od	10mg od	0.5mg od
180mcgx1/wk(P EG)	150mg od (HIV)		1mg od(LAM-R)
25%(+) / 63%(-) suppression HBVDNA	36%(+) / 72%(-)	21%(+) / 51%(-)	67%(+) / 90%(-)
No resistant mutants	Resistant muts 15-30% yr1 70% yr5	Resistant mut 0% yr1 18% yr4	????
Side effects++		Nephrotoxic	Carcinogenic in rodents

Table 5. Comparison of Interferon, Lamivudine, and Adefovir Dipivoxil in HBeAg-Positive Chronic Hepatitis B

Parameter	Interferon (untreated)	Lamivudine (placebo)	Adefovir dipivoxil (placebo)
	12-24 wk	52 wk	48 wk
Serum HBV DNA level (IU)	37 (17)	44 (16)	21 (9)
Serum HBV DNA log ₁₀ reduction	Not available	Not available	3.52 log (0.55)
HBeAg loss (%)	33 (12)	32 (11)	24 (11), 44 at 72 wk
HBeAg seroconversion (%)	18*	15-18 (4-6), 50 at 5 yr	12 (6), 23 at 72 wk
HBeAg loss (%)	11-26 at 5 yr in white patients	Insignificant data	Insignificant data
ALT normalization (%)	23*	41-72 (7-24)	48 (16)
Histological improvement (%)	Poor data	49-56 (23-25)	53 (25)
Development of resistance (%)	No	14-32, increasing to 69 at 5 yr	3.6 at 2 yr
Durability of response after HBeAg seroconversion (%)	80-90 at 4-8 yr	77 at 37 mo	Not available
Defined treatment course	Yes	Unclear	Unclear
Safety	Poor	Same as placebo	Same as placebo
Tolerability	Poorly tolerated	Well tolerated	Well tolerated
Dosing regimen	5 MU/3d or 10 MU 3 times wk for at least 16 wk (injection)	100 mg once daily (oral)	10 mg once daily (oral)
Cost/mo. (\$)†	1420	260**	450**

NOTE: All data are at 1 year unless otherwise stated.
 HBsAg, hepatitis B e antigen; HBV, hepatitis B virus; HBeAg, hepatitis B surface antigen; ALT, alanine aminotransferase; MU, million units; LLD, lower limit of detection.
 *Interferon and lamivudine, hybridization assay (LLD, 10³ copies/mL); adefovir, polymerase chain reaction assay (LLD, 400 copies/mL).
 †Difference between treated and untreated.

NIHCE recommendations



- PegIFN alfa-2a as initial Rx in adults (Both HBeAg+ and HBeAg-)
- Adefovir as second line after unsuccessful IFN Rx, relapse, poor tolerability to IFN Rx
- Adefovir should not be normally given before LAM Rx
- Adefovir to be used alone or in combination with Lamivudine in cases of LAM resistance

NIHCE Guidelines, NHS (UK), Feb 2006

Entecavir vs Lamivudine

A comparison of Entecavir and Lamivudine for HBeAg + in Chronic Hep B. Chang et al NEJM March 9, 2006



Entecavir 0.5mg vs LAM 100mg

- Higher histologic improvement (72% vs 62%)
- Higher virologic improvement (67% vs 36%)
- Higher biochemical improvement (68% vs 60%)
- Higher seroconversion (21% vs 18%, NS)
- No viral resistance

Entecavir vs Lamivudine

A comparison of entecavir and Lamivudine for HBeAg - in Chronic Hep B. Lai et al NEJM March 9, 2006



Entecavir 0.5mg vs LAM 100mg

- Higher histologic improvement (70% vs 61%)
- Higher virologic improvement (90% vs 72%)
- Higher biochemical improvement (78% vs 71%)
- Higher seroconversion (21% vs 18%, NS)
- No viral resistance

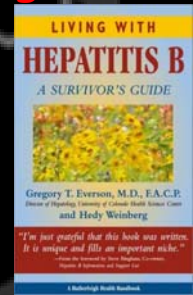
Monitoring of Patients



- USS and alfa fetoprotein every 6 months in high risk:
 Males >45 yrs
 Cirrhosis
 Family hx of HCC
- Inactive carriers- LFT

Counseling

- Abstinence from alcohol
- Prevention of sexual transmission
- Perinatal transmission
- Vaccination of household members



Summary

- Effective prevention with vaccination programmes
- Entecavir and PEG IFN Rx for treatment naïve patients
- Consider adefovir and ? entecavir in relapses or treatment failures with IFN and LAM (in combination)
- Patient education
- Strategy for screening health care workers and rapid post exposure prophylaxis